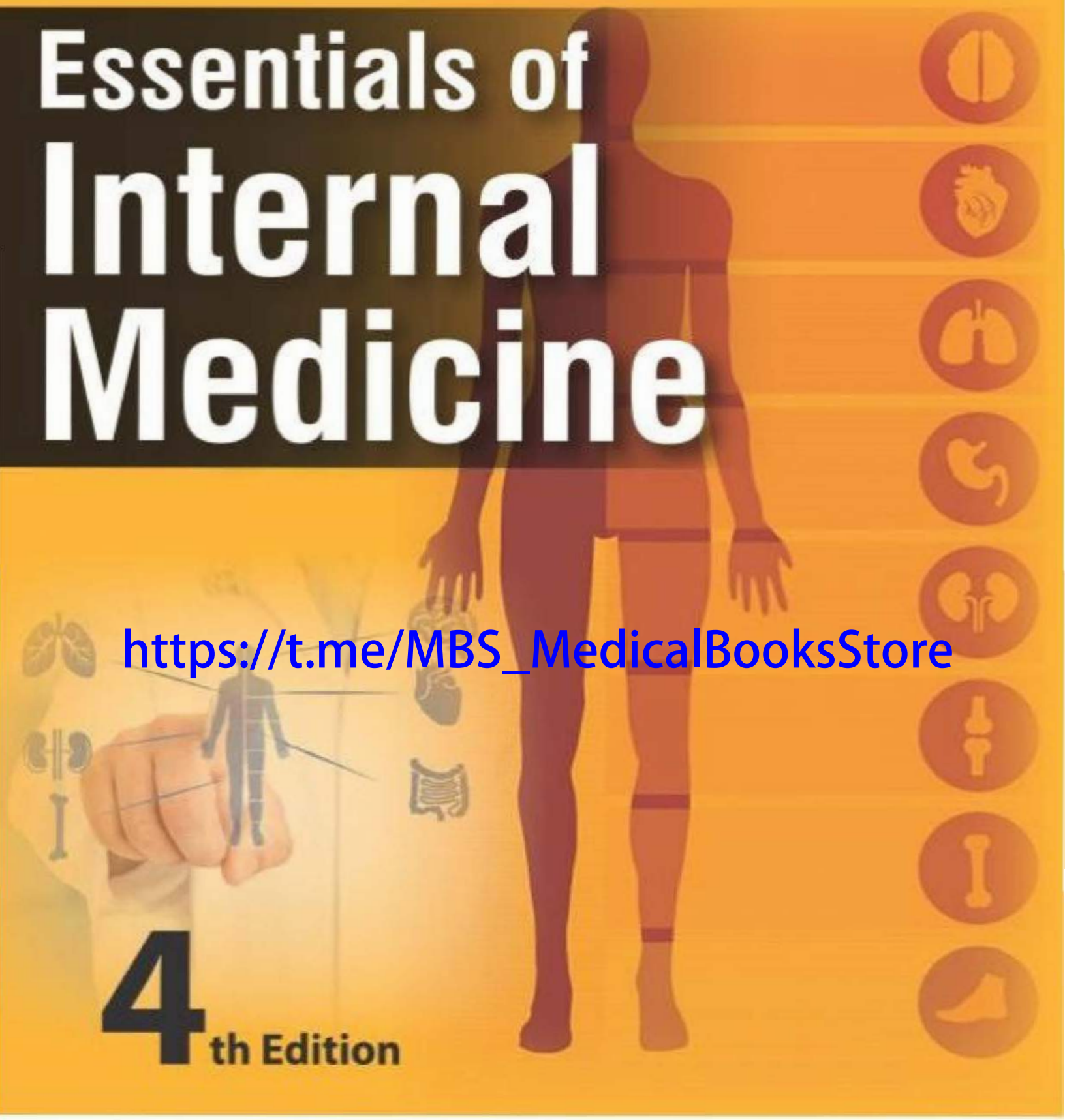
Essentials of Internal Medicine



4th Edition

Ardhendu Sinha Ray
Abhisekh Sinha Ray

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Essentials of
INTERNAL MEDICINE

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Fourth Edition

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Essentials of Internal Medicine

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Dedicated to

Memory of my parents
Late Sital Prasad Singha Roy
and
Late Namita Singha Roy

Preface

When we envisioned this book *Essentials of Internal Medicine,* our primary aim was to develop a compelling basic textbook in internal medicine which would provide a solid understanding of the pathophysiology of diseases, help in the development of strong clinical acumen in approach of common clinical syndromes and make one confident about management of different diseases of various organ-systems. In this fourth edition, *Essentials of Internal Medicine*, we have followed the same core principles that inspired us in our approach to the last three editions. We are grateful to our students and colleagues, for their encouraging words and constructive criticisms. As per the feedback, suggestion and comments we have received, cardiology, nephrology, neurology, and respiratory sections of the book have been thoroughly updated in this edition. New chapters on general physical examination and examinations of different systems like neurology, respiratory, gastrointestinal are added. Revised and improved fourth edition contains all essential points of internal medicine in a student-friendly format.

We believe, this book will continue to be a useful companion to the undergraduate students as well as postgraduate trainees.

Your feedback and suggestions are welcomed.

Ardhendu Sinha Ray
Abhisekh Sinha Ray

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CARDIOVASCULAR SYSTEM

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- Congenital Heart Diseases
- Cardiomyopathy
- Tachyarrhythmias
- Ischemic Heart Diseases

Chapter 1

Electrocardiogram

INTRODUCTION

An electrocardiogram is a graphical record of the change in membrane potential generated during cardiac muscle depolarization and repolarization.

The ECG records the depolarization (stimulation) and repolarization (recovery) potentials generated by atrial and ventricular myocardium and spread all over body.

This electric signals are detected by means of electrode (called lead) attached to the extremities and chest wall and are amplified and recorded on a (millimeter) graph paper.

The graph paper is divided into 1 mm^2 grid-like boxes. Since the universal ECG paper speed is 25 mm/sec, the smallest 1 mm horizontal division corresponds to 0.04 second with heavier line at interval of 5 small square which is equal to 0.2 second. Vertically the ECG graph measure the amplitude of a specific wave 1 mV = 10 mm with standard calibration.

The conventional ECG is recorded by 12 lead of which 6 are extremity limb lead and 6 are precordial or chest lead.

Out of 6 limb leads. Three are bipolar lead [lead-I, lead-II, lead-III] and three are unipolar (aVR, aVL, aVF).

Bipolar leads are

- **Lead-I** → Left arm potential – Right arm potential
- **Lead-II** → Left leg potential – Right arm potential
- **Lead-III** → Left leg potential – Left arm potential.

Unipolar limb leads are—aVR, aVL and aVF.

In these unipolar leads potential of right arm, left arm and left leg are recorded against 'zero' potential which is made within machine by joining the lead of all four limb and passing it through in resistance.

Standard six precordial lead are V_1 – V_6. These are unipolar lead and one electrodes is placed on the following position and the second electrode is zero potential.

- V_1 on 4th intercostal space just right of sternum.
- V_2 on 4th intercostal space just left of sternum.
- V_3 on midway between V_2–V_4.
- V_4 on midclavicular line on 5th space.
- V_5 on anterior axillary line on the same plane of V_4.
- V_6 on midaxillary line on the same plane of V_4 and V_5.
- V_7 on posterior axillary line on the same plane of $V_4V_5V_6$.
- V_8 on posterior scapular line on the same plane of $V_4V_5V_6V_7$.

In case of dextrocardia precordial leads are placed on the corresponding position on the right side of the chest and are called V_2R to V_6R respectively.

ESOPHAGEAL LEADS

Apart from these leads there is special lead called esophageal lead where the recording electrode is placed in esophagus 27 cm down from incisor teeth for recording of the potential from the posterior aspect of heart.

Standard ECG has the following wave and P, Q, R, S, T and U wave, and the following interval PR, QRS and QT interval (Figs 1.1 and 1.2).

During examination of ECG we have to look for following point. (1) **Heart rate**, (2) **rhythm**, (3) **electrical axis of QRS complex**, (4) **P-wave**, (5) **P-R interval**, (6) **Q-wave**, (7) **QRS complex**, (8) **ST-segment**, (9) **Q-T interval**, (10) **T-wave** and (11) **U-wave**.

HEART RATE

It can easily be calculated from an ECG by counting the number of small square in between two consecutive R-wave. And dividing 1500 by the number of small square

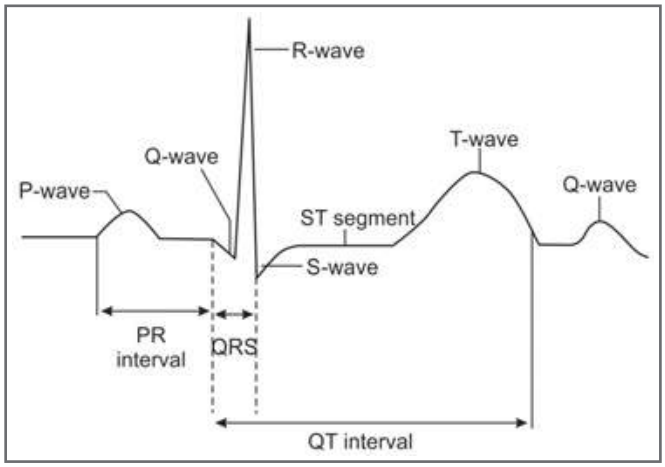


Fig. 1.1: Normal ECG

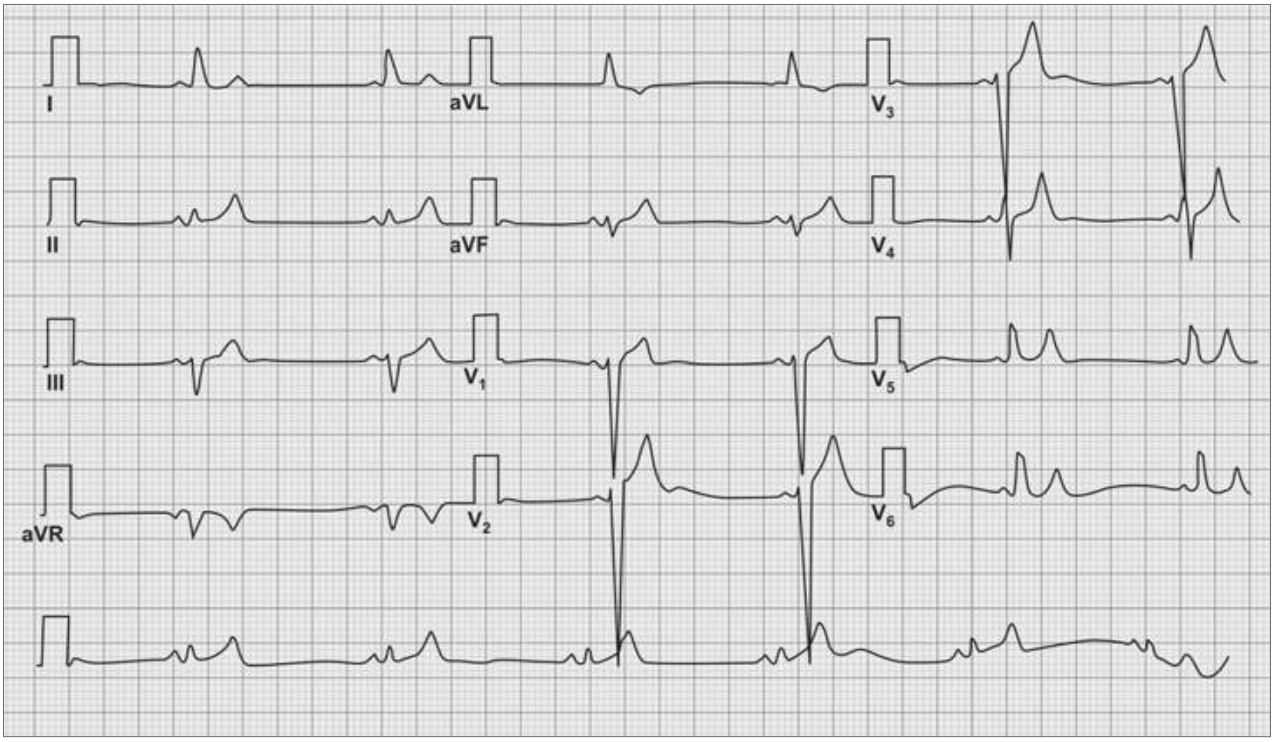


Fig. 1.2 : Sinus bradycardia

in between two R-wave we get the heart rate. 1500 comes from the fact that the paper speed of all ECG machine is 25 mm/sec. So in one minute 1500 small square (25 × 60 = 1500) comes out from the machine.

RHYTHM

If the R-R interval is equal in the rhythm strip (lead-II) and the QRS complexes are preceded by 'P'—then it is called "**regular sinus rhythm**". The R-R interval sometime may vary slightly which is called sinus arrhythmia (which is the respiratory variation of heart rate).

AXIS OF QRS COMPLEX

The axis of an ECG means the direction of the mean electrical vector of QRS complex. It is determined from extremity lead. In Enthovean concept the heart is located at the center of a triangle formed by joining right arm, left arm and left leg (Fig. 1.3).

In unipolar limb lead the heart is located at the center like Figure 1.6. If we simplify Figure 1.4 like Figure 1.5 and if we superimpose Figure 1.6 over Figure 1.5 we get the hexaxial picture (Fig. 1.7) which is very clumsy. Out of these six axis, we take only two mutually perpendicular leads one is **lead-I** and the other is **aVF** (Fig. 1.8) for determination of QRS axis.

POSITIVITY OF THE LEADS

As the depolarization wave runs from SA node and move towards apex (downward and to the left) the left hand side of lead-I is considered positive and the lower half of aVF is considered positive and the upper half aVF is negative and right side of lead-I negative, then the simplified picture come out like Figure 1.8.

Degree of each lead and the extent of normal axis, left axis and right axis deviation is determined by an international convention Figure 1.9.

- Left hand side of lead-I is 0°
- Right hand side of lead-I is ± 180°
- Lower half of aVF is + 90°
- Upper half of aVF is – 90°
- **Normal axis** – 30° to + 110° (Fig. 1.10)
- **Left axis** – 30° to – 90° (Fig. 1.10)
- **Right axis** + 110° to + 180° (Fig. 1.10)
- **Indeterminate axis from** – 90°–180° (Fig. 1.10).

Now in a given ECG for determination of mean axis of QRS complex, we have to consider the mean deflection of QRS from the isoelectric line by summation of deflection of QRS complex in lead I and aVF.

For example (Fig. 1.11), suppose in lead-I the summation of deflection of QRS complex in positive and is equal to 6 small square and in lead aVF it is 5. Small square on the

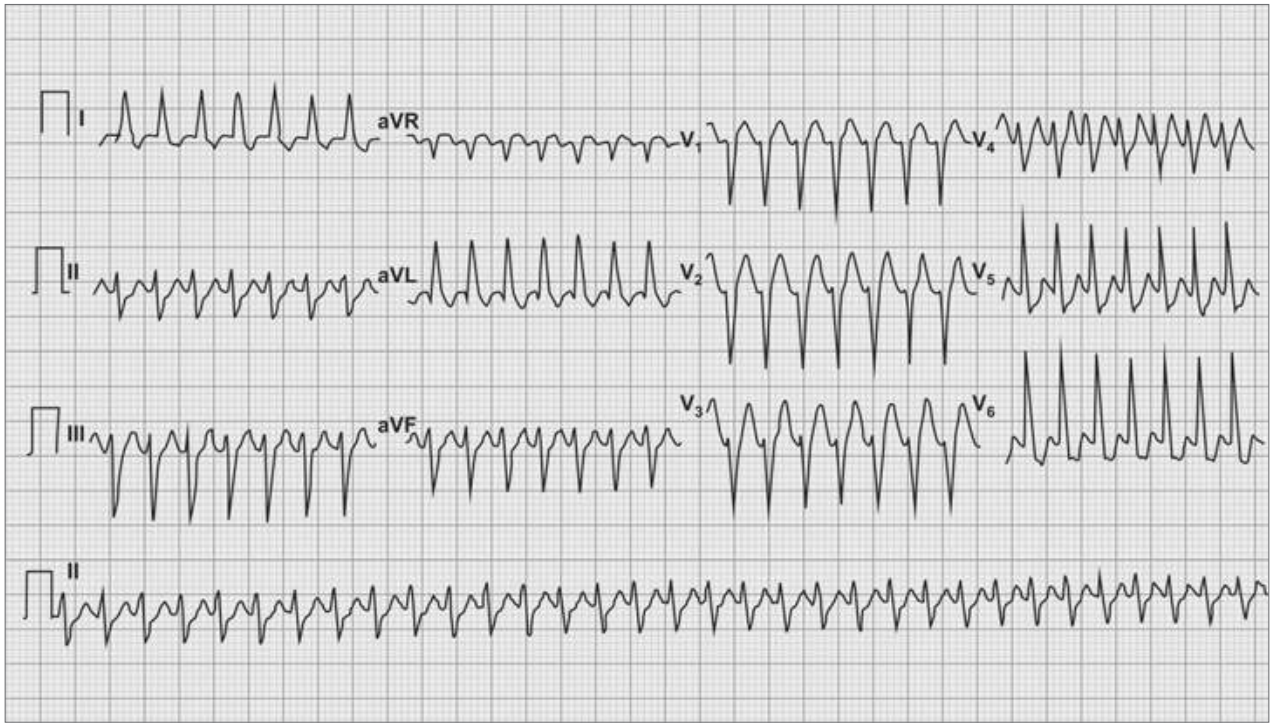


Fig. 1.3: Thin complex tachycardia

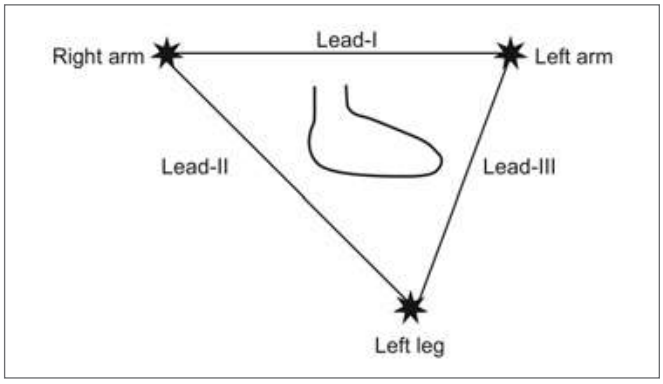


Fig. 1.4: Bipolar limb lead

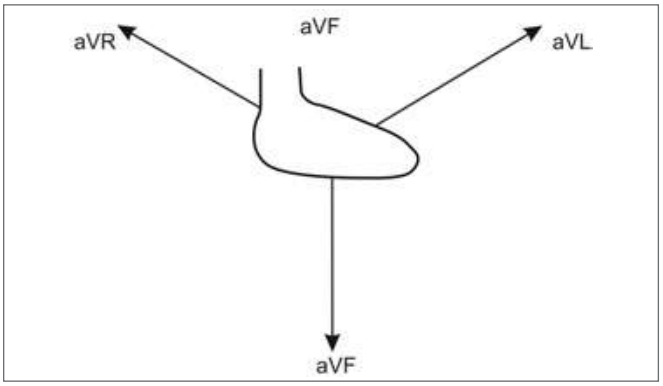


Fig. 1.6: Unipolar limb lead

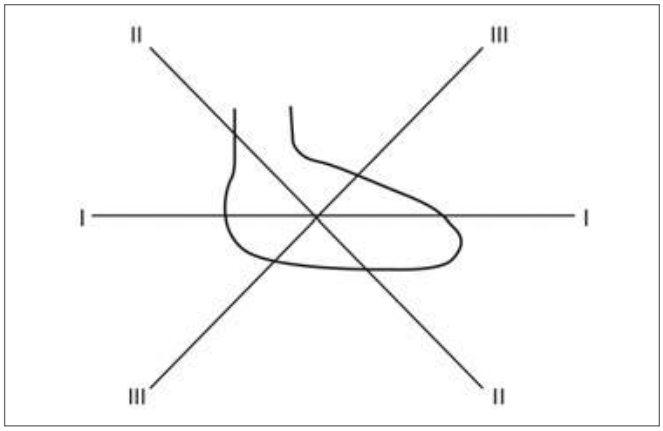


Fig. 1.5: Simplified bipolar limb lead

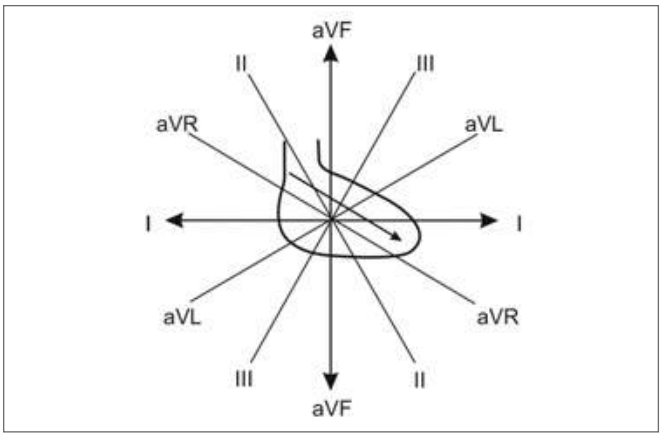


Fig. 1.7: Simplified bipolar limb lead superimposed on unipolar limb lead

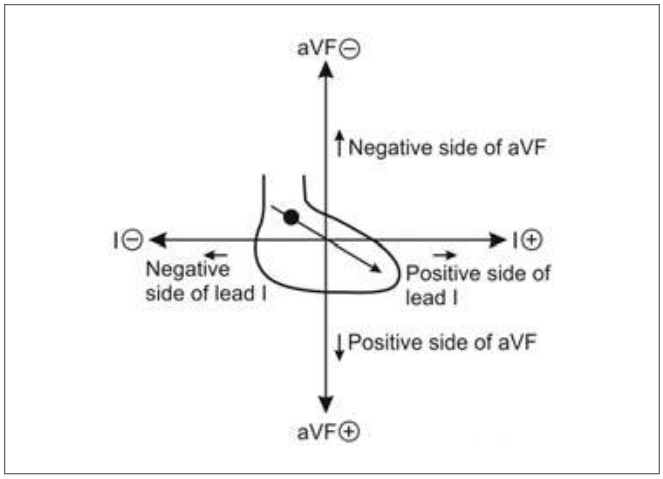


Fig. 1.8: Simplified diagram from hexaxial system

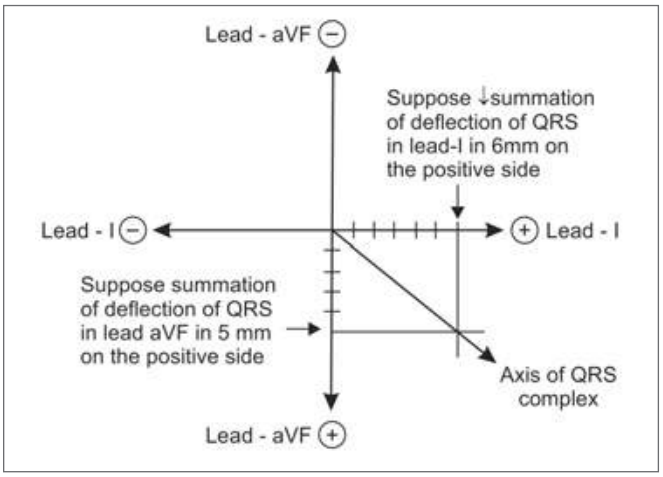


Fig. 1.11: Example of normal axis deviation

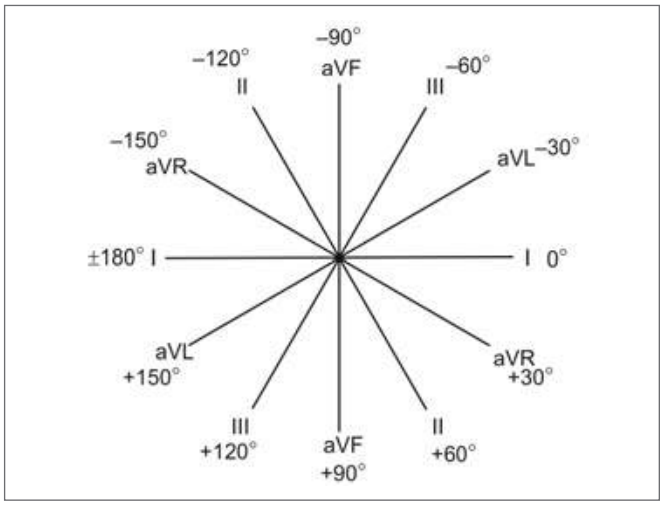


Fig. 1.9: Degree of each lead is allotted by international convention

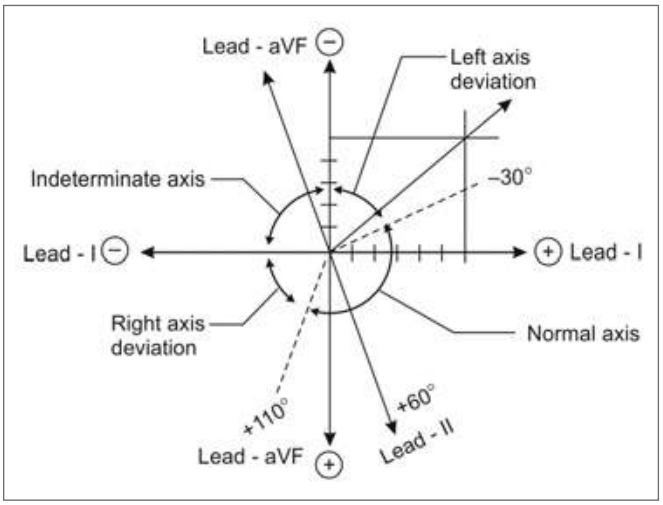


Fig. 1.12: Determination of left axis deviation with the help of lead II`

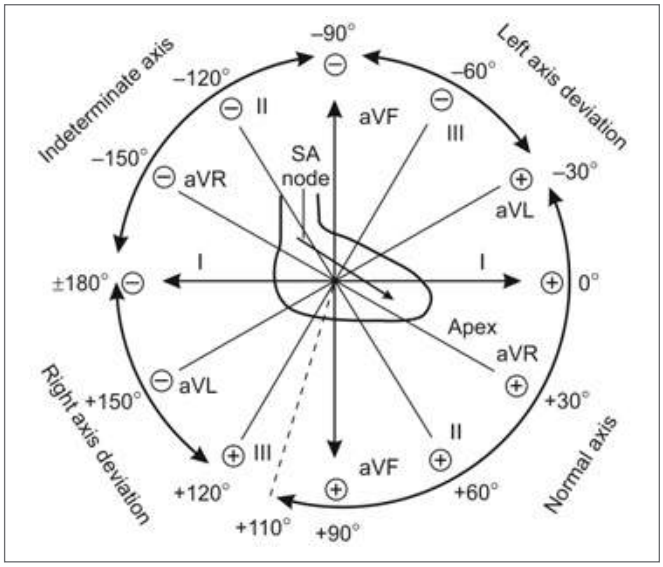


Fig. 1.10: Hexaxial lead with allotted degree and axis deviation

positive side then we have to give a mark 6 mm away from the center on lead-I and 5 mm away from the center on lead aVF on the positive side of the lead (Fig 1.11) and we have to draw perpendicular at that point on lead-I and aVF respectively. The meeting point of this two perpendiculars is in the left lower quadrant joined with center with a line. This line is the mean electrical axis of the QRS complex (Fig. 1.11).

If in the second example (Fig. 1.12) suppose the summation of deflection of QRS in aVF is negative we have to give point on the negative side of aVF lead and the summation deflection of QRS complex in lead-I is positive then the meeting point of the perpendicular on lead-I and aVF is in the left upper quadrant. Then the picture will be like Figure 1.12. Now in such condition whether actual left axis deviation have occured is to be determined by examining lead-II. As perpendicular on lead II at the center is –30°. If the summation of QRS in lead-II is positive then although the QRS axis has rotated upwards but it has not

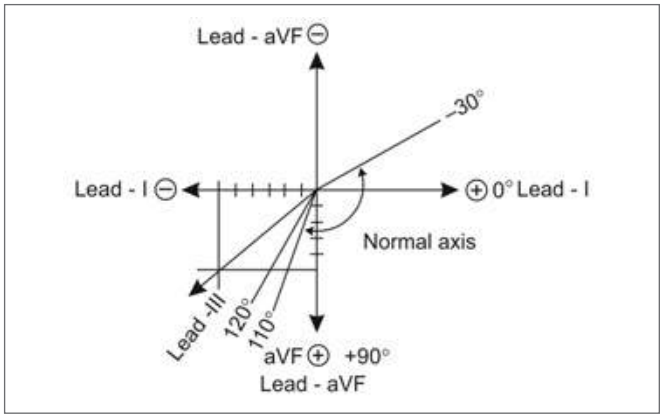


Fig. 1.13: Determination of right axis deviation

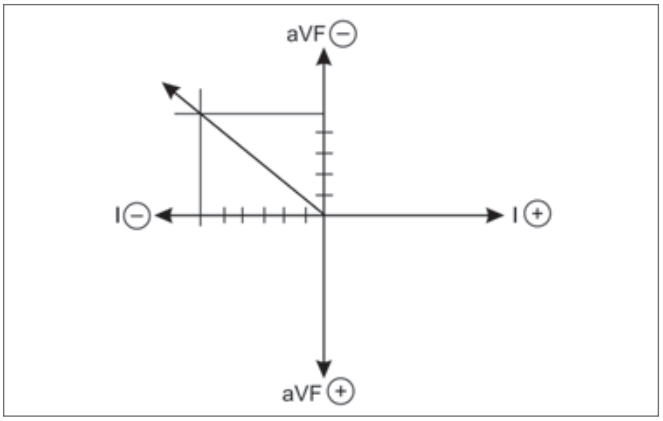


Fig. 1.14: Example of indeterminate axis

crossed above –30°, i.e. although the QRS axis has rotated leftward but it is within the limit of normal axis (–30°). If the summation of QRS deflection is negative in lead-II. The mean QRS vector has rotated upward and beyond –30° and left axis deviation has taken place.

Suppose the summation of QRS deflection in aVF is positive but in lead-I it is negative then the picture will be like Figure 1.13. Then the meeting point of the perpendiculars are in the lower right quadrant. In this condition whether there is true right axis deviation is present to be determined by compairing the height of R-wave in aVF and lead-III. If the complexes in aVF is taller than lead-III then the mean QRS axis is closer to +90° and it is within normal axis, but if the complex in lead-III is taller than aVF then it is considered that the electrical axis is closer to 120° so right axis deviation is present.

If in both lead-I and aVF the summation of QRS deflexion is negative then the meeting point of the perpendiculars would be like Figure 1.14 in the right upper quadrant. This type of axis deviation is called, **indeterminate axis** or **north-west axis** which is rarely seen in congenital heart disease where there is hypertrophy of the extreme superolateral wall of the both ventricle.

P-WAVE

It is due to depolarization of atria and in normal ECG P-wave is upright is lead-II negative in aVR and biphasic in V_1. Ascending limb of P is due to right atrial depolarization and the descending limb of P is due to left atrial depolarization.

- **Abnormalities in P-wave**
  - **Absent P-wave**—In atrial fibrillation, instead of P-wave there will be an uneven baseline with varying R-R interval (Fig. 1.15).
  - **Tall peaked P-wave in lead-II**—It is called "P-pulmonale", where the height of P-wave is more

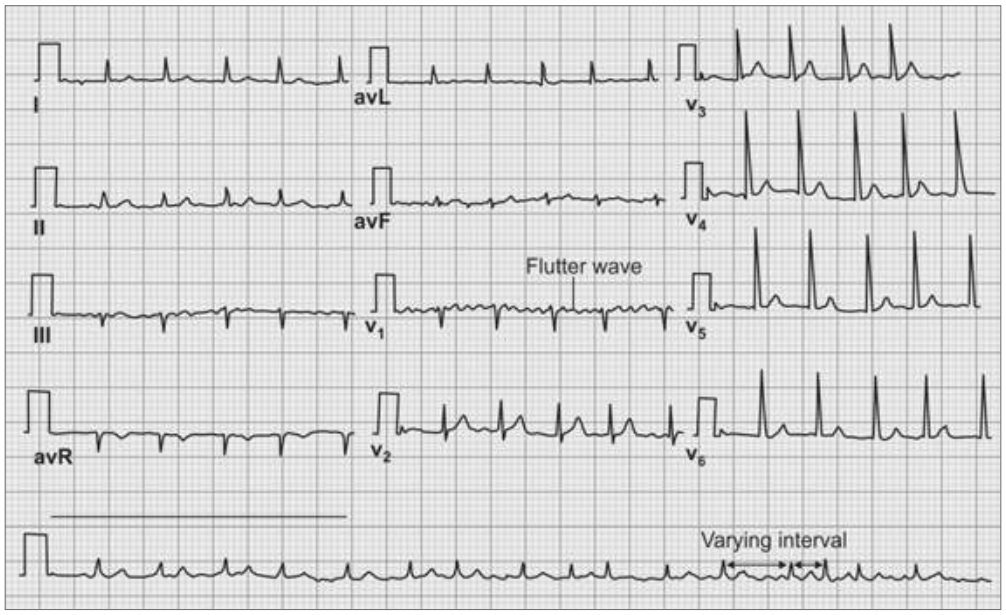


Fig.1.15: Atrial flutter with fibrillation

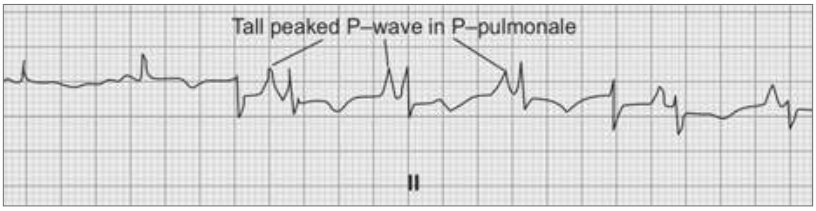


Fig. 1.16: P-pulmonale

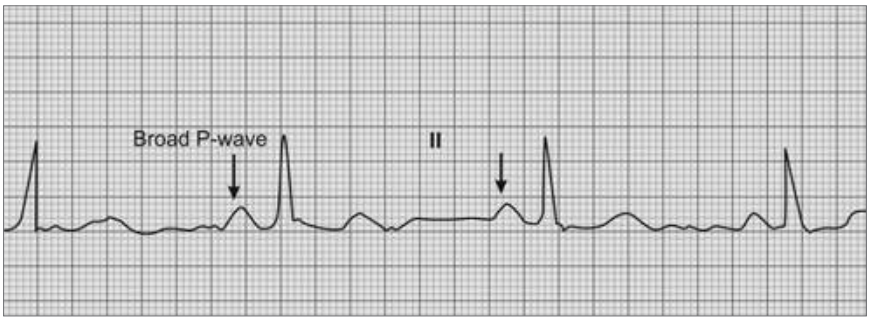


Fig. 1.17: P-mitrale

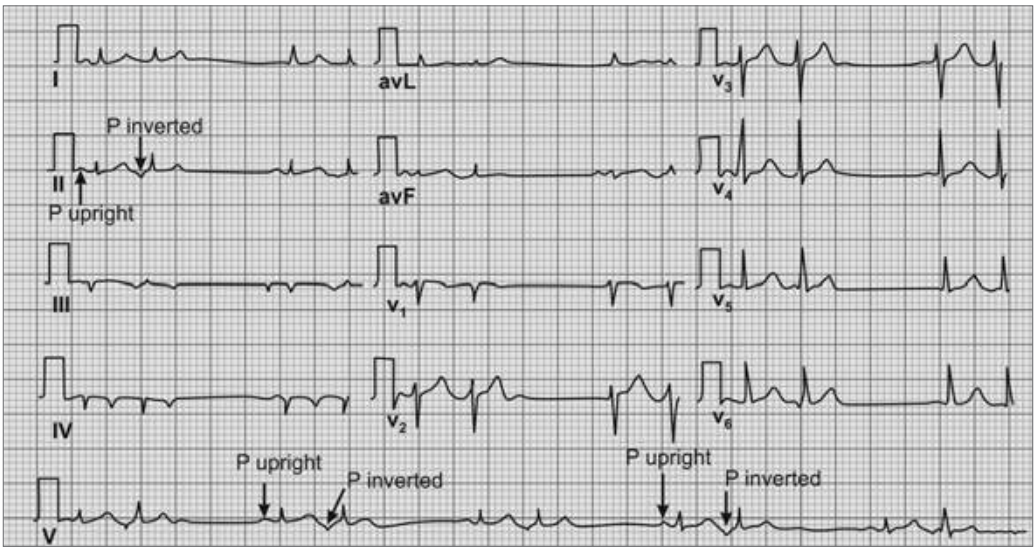


Fig. 1.18: High junctional rhythm

than 2 mm and is due to right atrial hypertrophy (Fig. 1.16).

- **Broad with notched P-wave in lead-II**— It is called P-mitrale. P-wave is more than 2 mm broad seen in left atrial hypertrophy. The notch may or may not be present (seen in mitral stenosis) and usually there is deep negative P-wave in V_1 (Fig. 1.17).
- **Shaw tooth P-wave with fixed R-R interval** —Seen in atrial flutter (Fig. 1.15).
- P-wave with different configuration seen in MAT (multifocal atrial tachycardia) (Fig. 1.18).

P-R INTERVAL

It is the time interval between beginning of atrial depolarization to beginning of ventricular depolarization normally it ranges from 0.12–0.2 sec (3–5 small division of the paper).

Short P-R interval < 0.12 sec is seen in WPW and LGL syndrome (Figs 1.19. and 1.20).

It is due to the presence of aberrant conduction pathway known as **bundle of Kent** which bypasses AV node. If the bundle of Kent end in cardiac musculature it will produce **WPW syndrome** and if the bundle of Kent ends in His bundle it will produce **LGL syndrome**.

In **WPW syndrome**, there will be short P-R interval and QRS will start just after P-wave but as the initial part of ventricular depolarization spread through musculature, it will produce a slow gradual upstroke in the initial part of QRS but the later part of ventricular depolarization takes place through His bundle and the conducting tissue so the

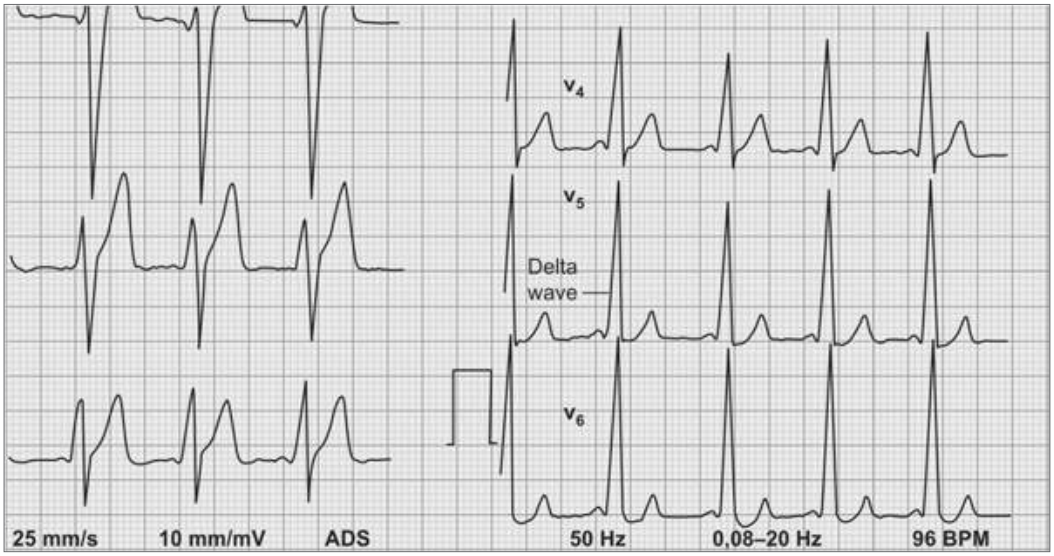


Fig. 1.19: WPW syndrome with short P-R interval with delta wave

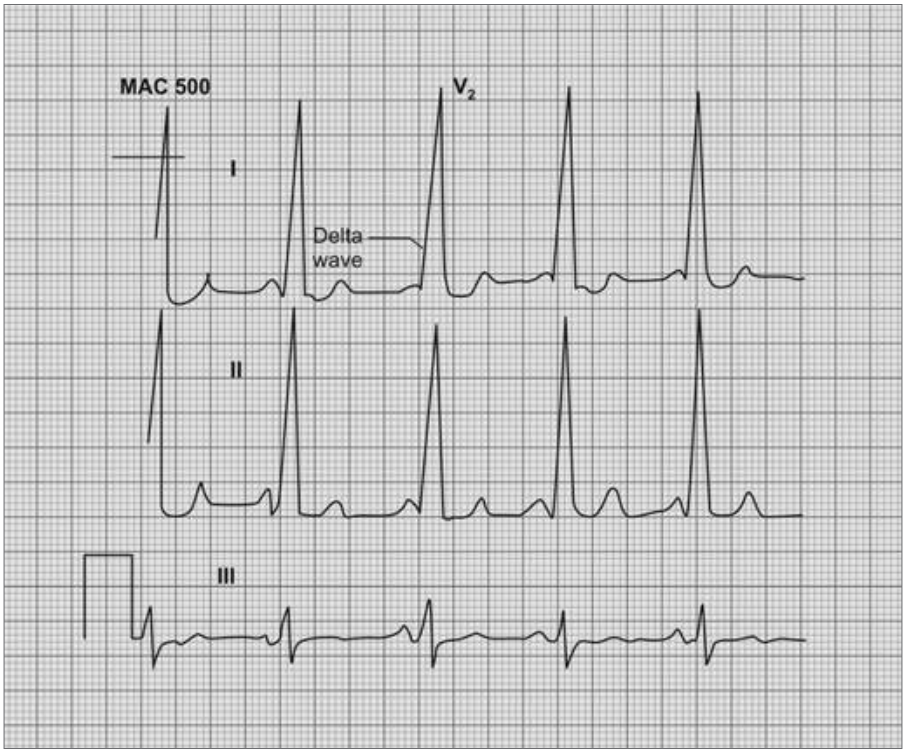


Fig.1.20: WPW syndrome with short P-R interval with delta wave

later part of QRS will be sharp. This initial slow upstroke in QRS is called **delta wave** (Figs 1.20 to 1.22).

In **LGL syndrome** there will be also short P-R interval and QRS will start just after P-wave as the bundle of Kent reenter His bundle after bypassing AV node (Figs 1.23A and B).

- The ventricular depolarization will start just after atrial depolarization. Creating a sharp upstroke of QRS.

Long P-R interval—Seen in 1st degree heart block.

1st degree heart block—In this condition all the atrial depolarization wave is conducted to ventricle but with some delay in AV node due to long refractory period. In this condition P-R interval is >0.2 second or greater than 5 small square (Fig. 1.40).

2nd degree heart block—In this condition not all atrial depolarization wave is conducted to ventricle. There is some drop of beat (impulse) in the AV node. Depending

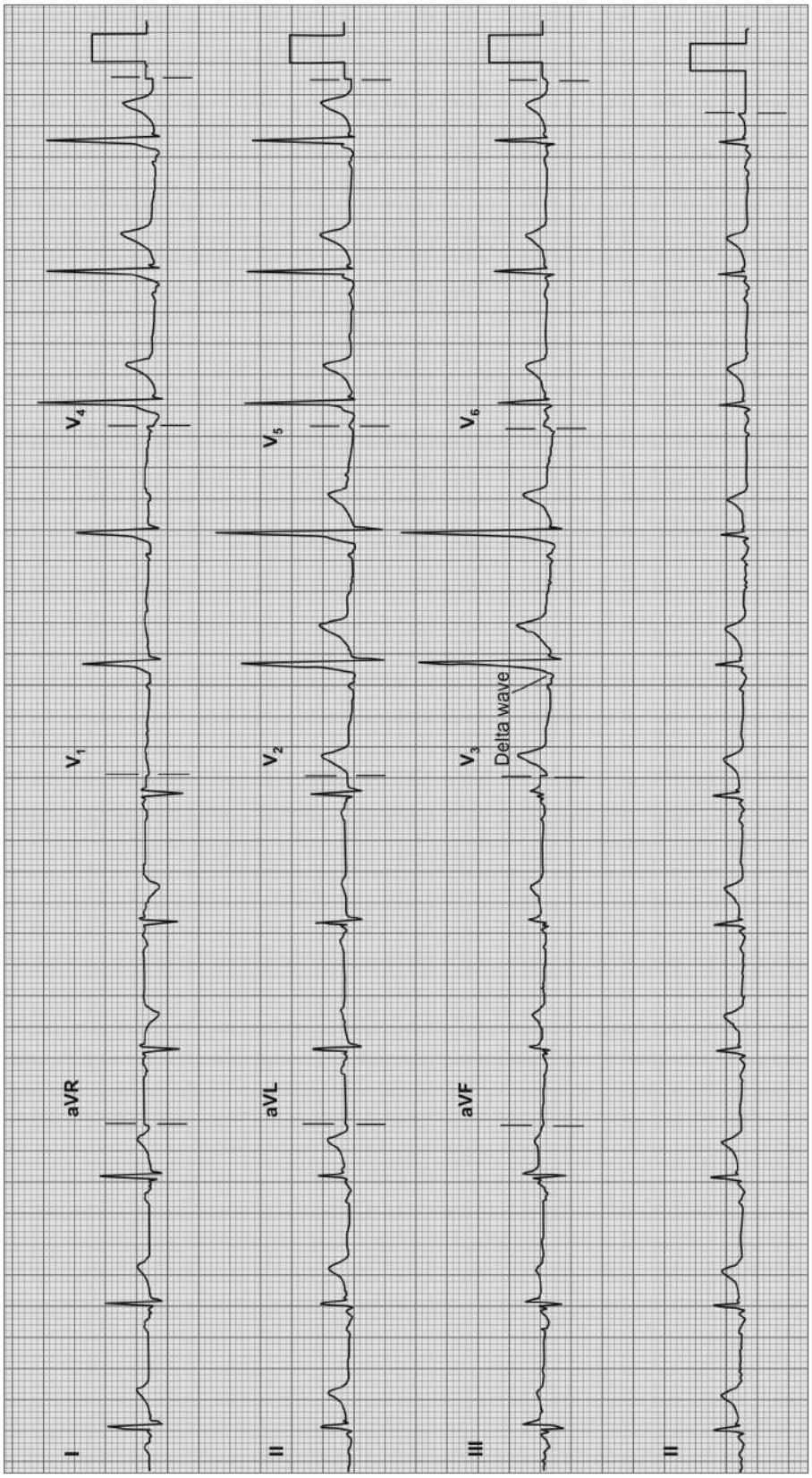


Fig. 1.21A: Dx: WPW syndrome

Clues: Short P-R interval and delta waves are obvious in the precordial leads. This tracing illustrates that not every lead will have a short P-R interval and a delta have in WPW syndrome if the delta wave is isoelectric in that lead (see lead-I specially). RVH should accompany RAD and S-waves in the left precordial leads, which this tracing does not have

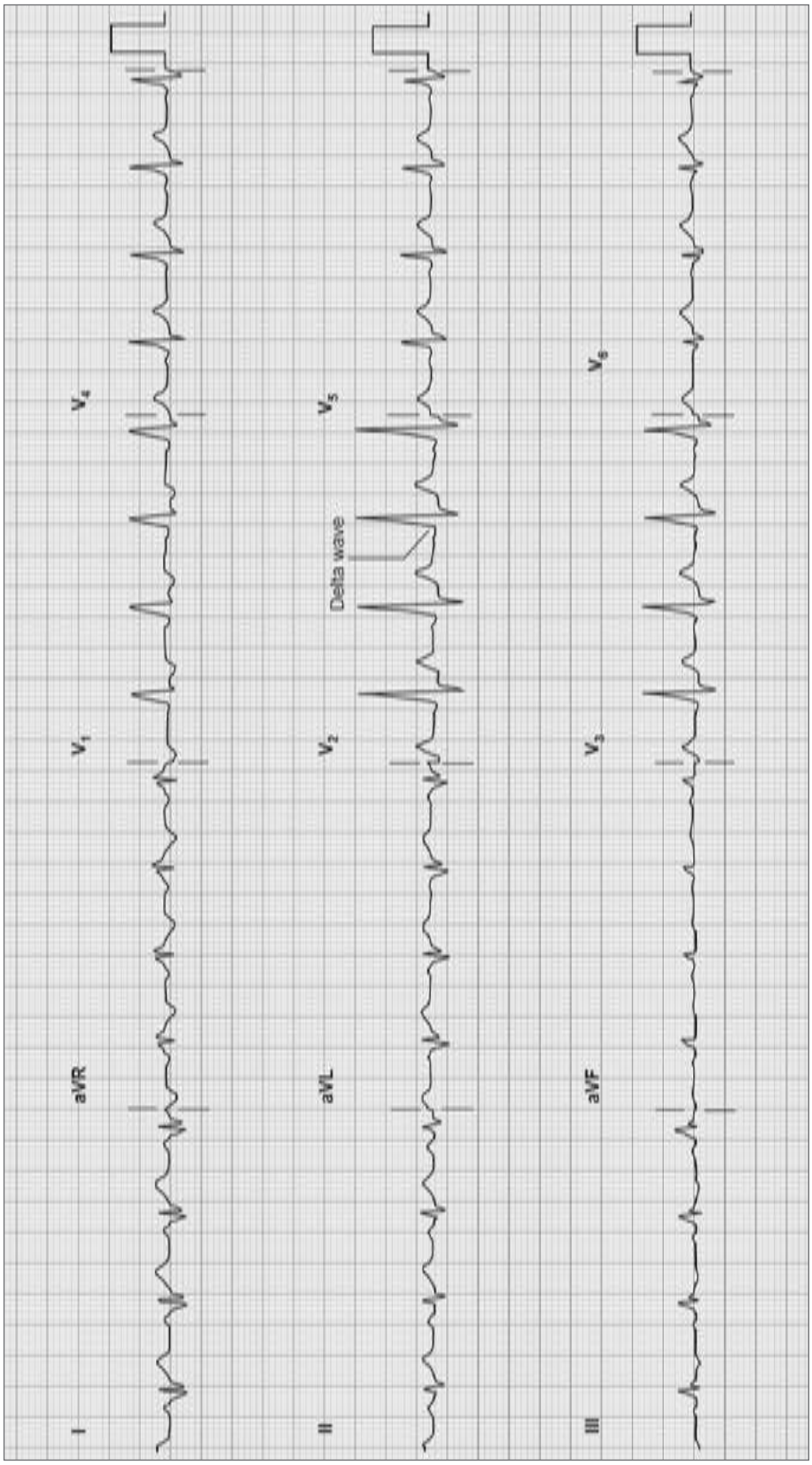


Fig. 1.21B: Dx: WPW syndrome

Clues: At first glance, it appears to be posterolateral MI with pathologic Q-waves in lead-I and aVL. However, the P-R interval is short in the precordial leads and slurred upstroke of typical delta wave is present. This delta wave is directed from the patient's left to right, registering as a negative delta wave in lead-I and aVL, simulating lateral wall MI. In lead-II, the P-R interval is normal and no delta wave is seen because the delta wave is isoelectric in that lead

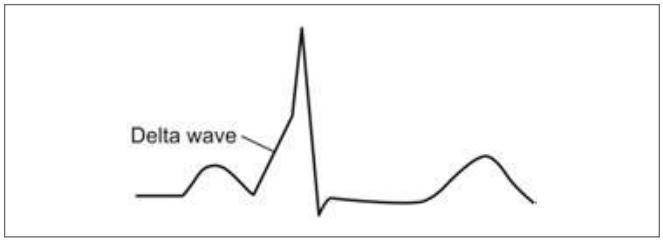


Fig. 1.22: WPW syndrome

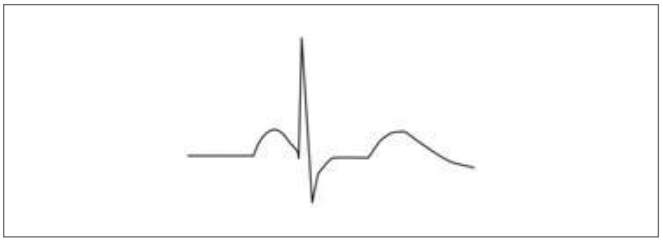


Fig. 1.23A: LGL syndrome

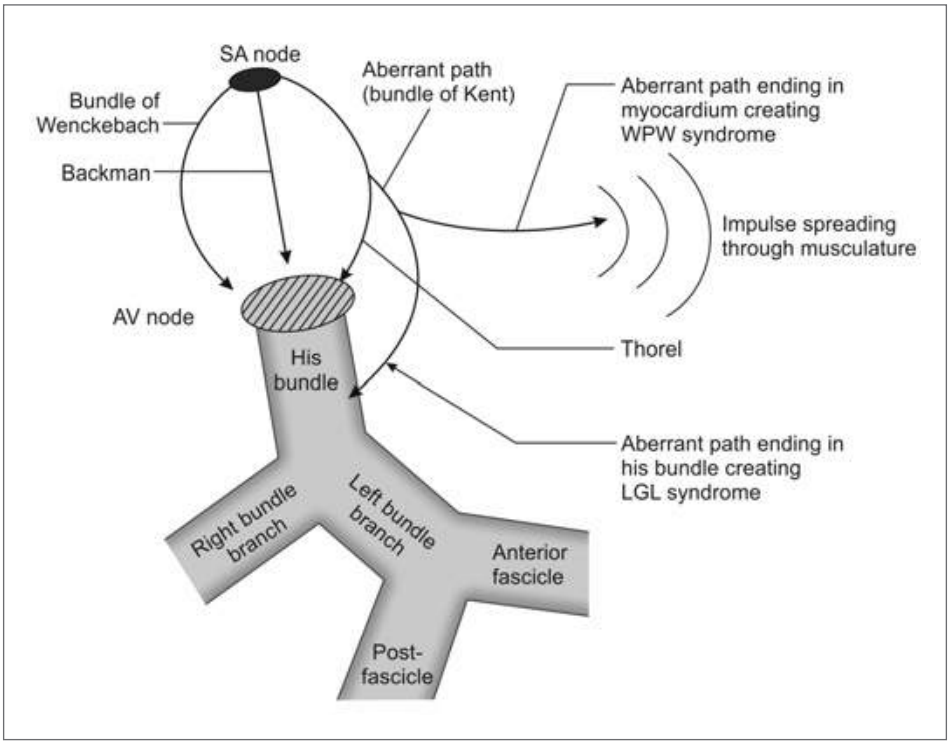


Fig. 1.23B: Schematic diagram of the conducting tissue of heart with aberrant path (bundle of Kent)

on the dropping fashion of ventricular depolarization it is subdivided into Mobitz type-I and type-II.

Mobitz type-I block (Wenckebach block)—In this condition there is gradual prolongation of P-R interval in the successive beat followed by a drop of QRS complex (ventricular depolarization) following a P-wave, called Mobitz type-I block Figure 1.24.

Mobitz type-II block—In this condition due to disease or ischemia AV node cannot conduct all depolarization wave to ventricle. There is a fixed block in AV node and every 2nd or 3rd or 4th atrial depolarization wave is blocked in the AV node. Accordingly they are called 2 : 1, 3 : 1 or 4 : 1 heart block.

Complete heart block (Fig. 1.25)—In complete heart block none of the atrial impulse is conducted to ventricle. All atrial depolarization wave in blocked at AV node and the ventricle is excited from a focus anywhere from the lower part of the conducting system (AV node, His bundle, bundle branch, anterior or posterior, fascicle, Purkinje's fiber) or from ventricular musculature.

QRS INTERVAL

It is the time taken for ventricular depolarization. Normal interval is 0.1–0.12 second. If it is more than 0.12 second or 3 small square then either LBBB or complete RBBB in present.

Q-T INTERVAL

It is the total time of ventricular depolarization and repolarization and is measured from onset of Q-wave to end of T-wave.

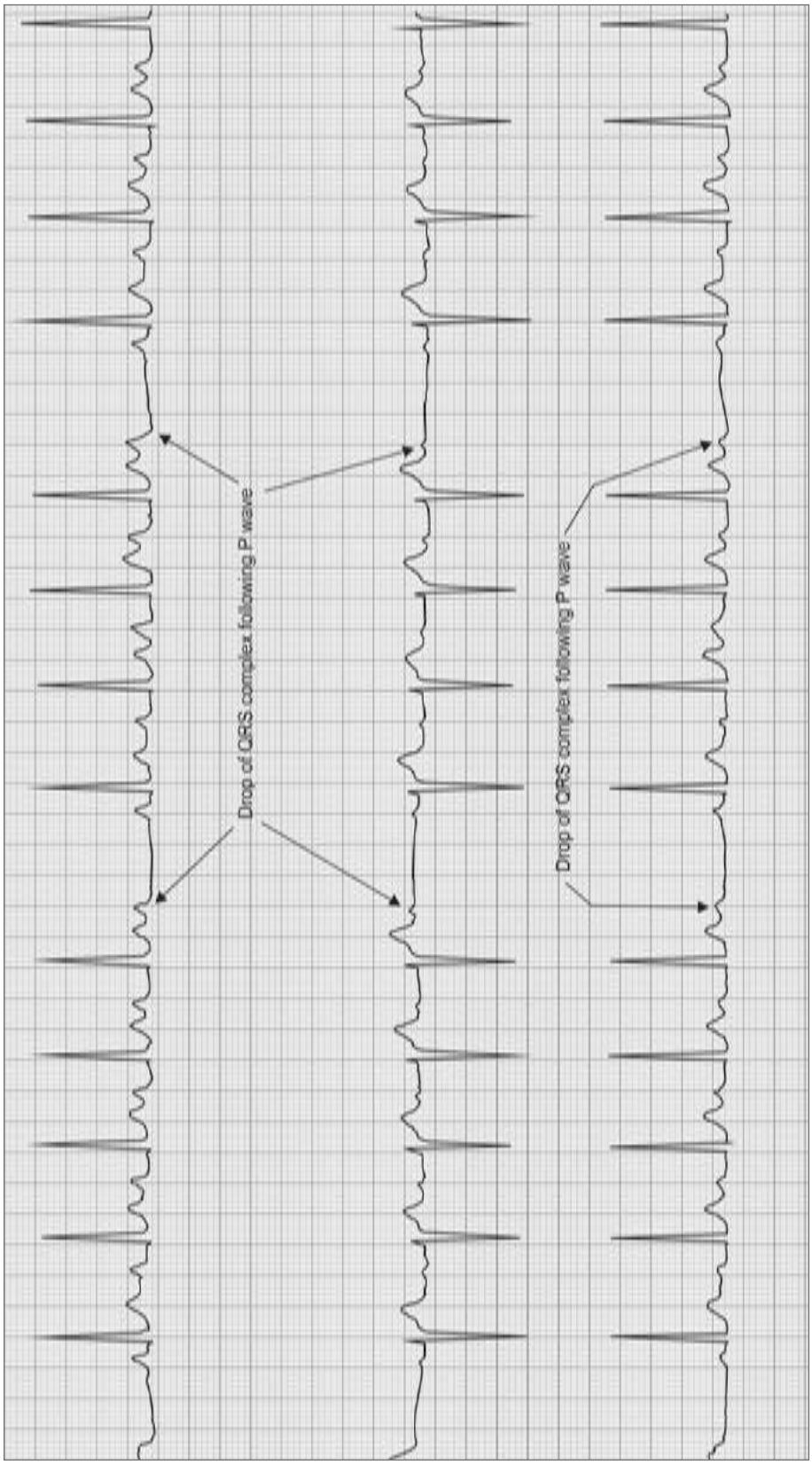


Fig. 1.24: In these three channel rhythm strips, P-waves occur regularly at a rate of about 85/min. Occasionally, the P-waves failed to result in a QRS. Prior to that, the P-R interval progressively lengthens; a typical type-I 2nd degree AV block

Dx: Type-I 2nd degree AV block (AV Wenckebach phenomenon)

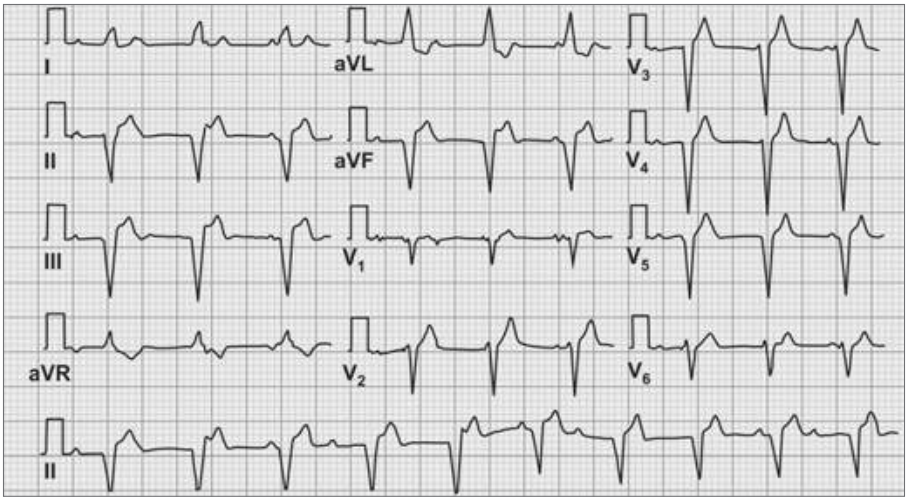


Fig.1.25: Complete heart block with AV dissociation

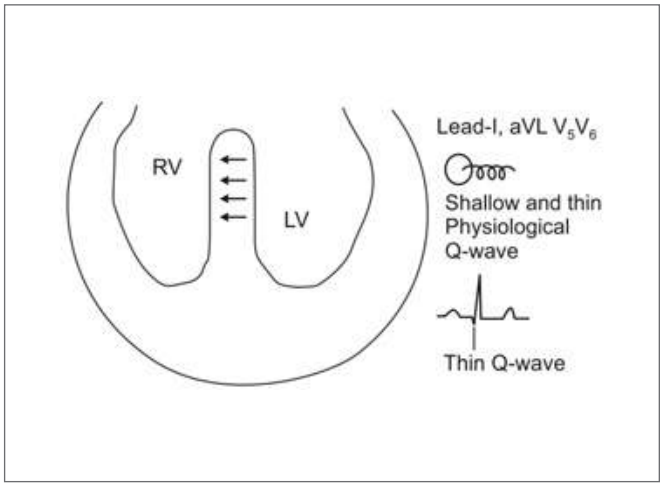


Fig. 1.26A: Physiological Q-wave. In the septal wall electrical vector moves away from the lead-I, aVL V_5, V_6 creating physiological Q-wave is the lead I, aVL, V_5, V_6. It is called physiological Q-wave

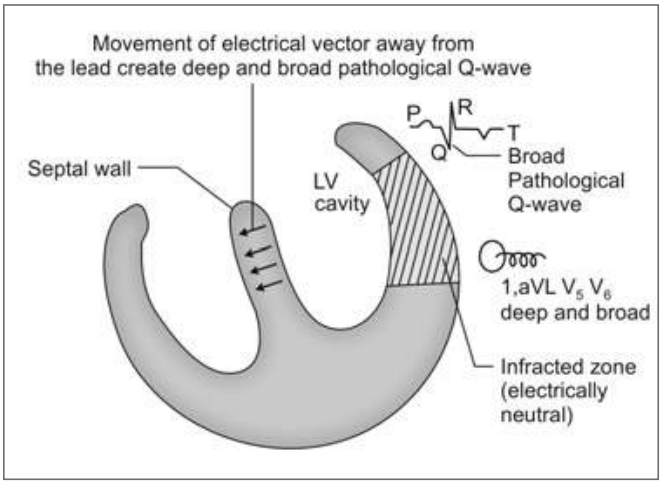


Fig. 1.26B: In postmyocardial infarction state, lead facing the infarcted wall (which is electrically neutral) actually looks towards the opposite wall where the electrical vector moves away from the corresponding lead creating a broad and wide Q-wave

Q-T interval varies with heart rate and must be corrected (called QT_C). The normal QT_C is 0.42 second in men and 0.43 second in female. Person with prolong QT are susceptible to ventricular **ectopic beat and arrhythmia**.

Q-WAVE

It is the first negative deflection in the QRS complex.

Physiological Q-wave (Fig. 1.26A): In normal ECG it is seen in the left-sided chest lead V_5, V_6, and aVL and lead-I which is due to intraventricular septal depolarization. venticular septum is the first structure to depolarize during ventricular depolarization. As the septal depolarization vector moves from left to right (moves away from the lead) which originates from a twig from left bundle branch creating Q-wave in the left-sided lead-I, aVL, V_5, V_6 (Fig. 1.26A).

Criteria for physiological Q-wave

- Thin Q-wave less than one small square duration.
- Depth of Q-wave less than 1/3rd of the following R-wave.

Pathological Q-wave: In postmyocardial infarction state Q-wave is seen in the lead facing the wall of infarction.

The respective lead looks towards the opposite wall of the ventricular cavity (through the infarcted zone which is electrically neutral) where the electrical vector moves away from the corresponding lead creating Q-wave (Fig. 1.26B).

Criteria for pathological Q-wave—

- Must be more than 1 small square width.

- Depth of Q is more than 1/3rd of the following R wave.

In anteroseptal wall infarction Q-wave is seen in lead V_2–V_4 (Figs 1.39, 1.42 and 1.43).

In anterolateral wall infarction Q-wave is seen in lead V_4–V_6, aVL and lead-I.

In inferior wall infarction Q-wave is seen in lead-II, III and aVF (Figs 1.40 to 1.44).

R-WAVE

From the height of R-wave we can have an idea about ventricular hypertrophy.

Criteria of **LVH**, —**R taller than 25 mm in V_5/V_6**

RV_5 /RV_6> 25 mm or RV_6 + SV_1 > 35 mm (Figs 1.27 and 1.28).

Criteria of **RVH is R > S in V_1**

QRS COMPLEX

From QRS complex we can conclude about bundle branch block.

In **right bundle branch block (RBBB)** (Figs 1.29 to 1.33) we see RSR' pattern in V_1 lead. The initial positive

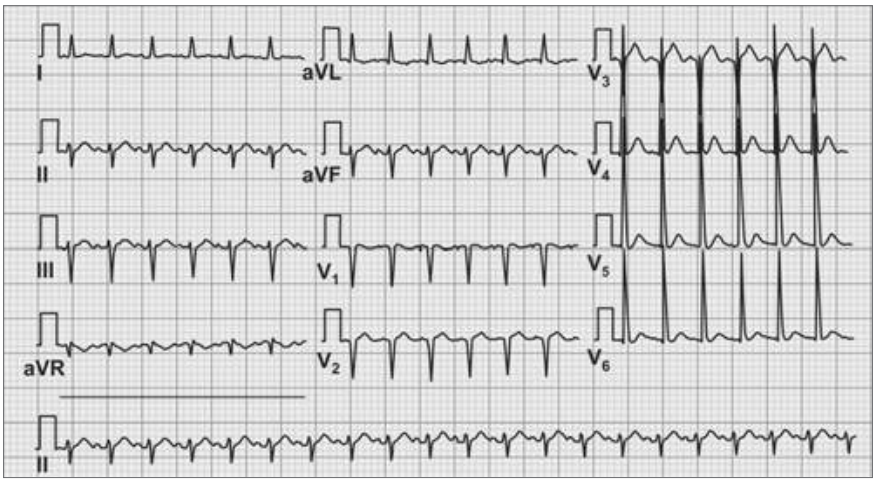


Fig.1.27: LVH with left axis deviation

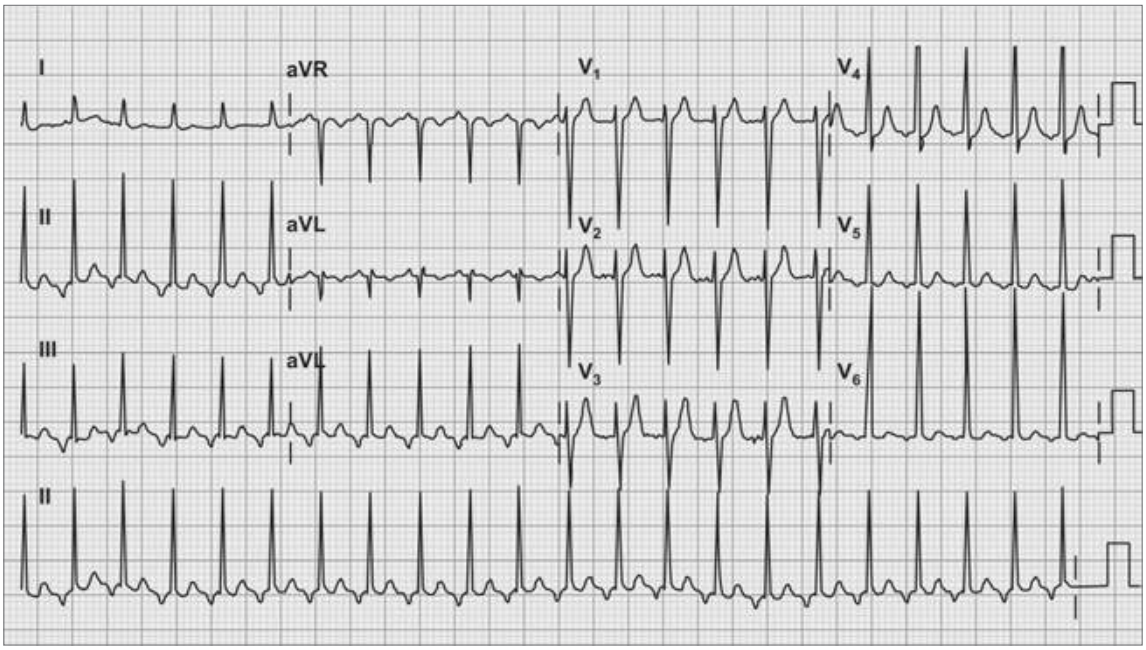


Fig.1.28: Narrow QRS tachycardia at a rate of 129/min. The P-waves are inverted in the inferior leads, suggesting either junctional rhythm or low atrial rhythm. The P-R interval of 120 milliseconds favors junctional tachycardia. Voltage criteria and ST-T changes favor LVH is present

Dx: 1. Probable junctional tachycardia
2. LVH

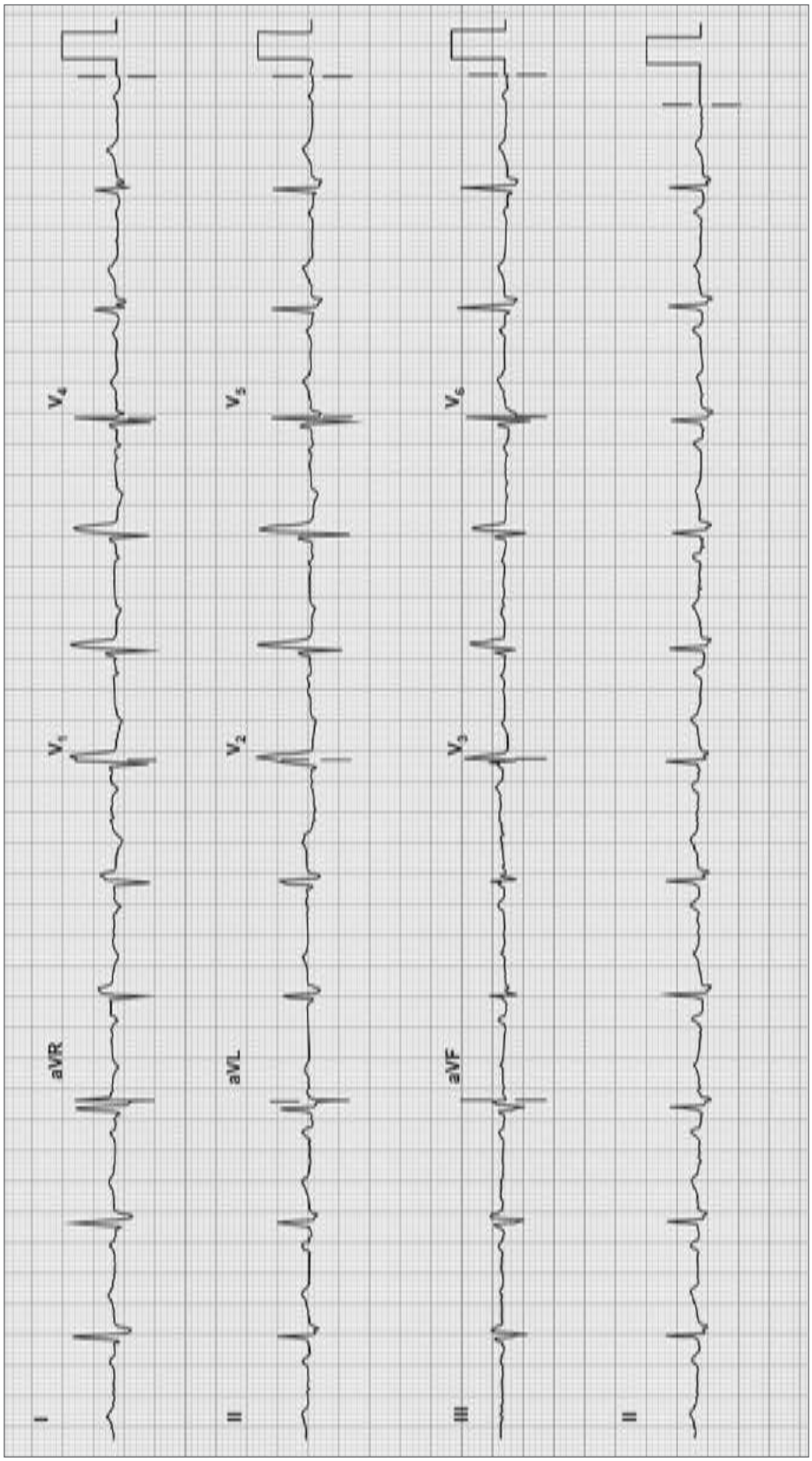


Fig.1.29: An example of typical RBBB

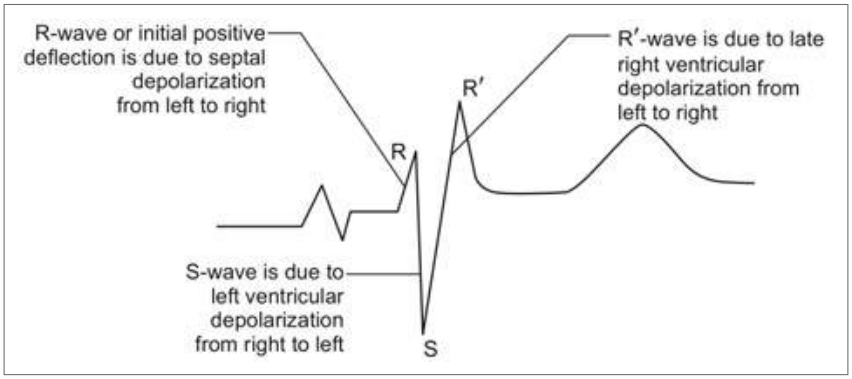


Fig.1.30: Right bundle branch block (RSR' pattern in V_1)

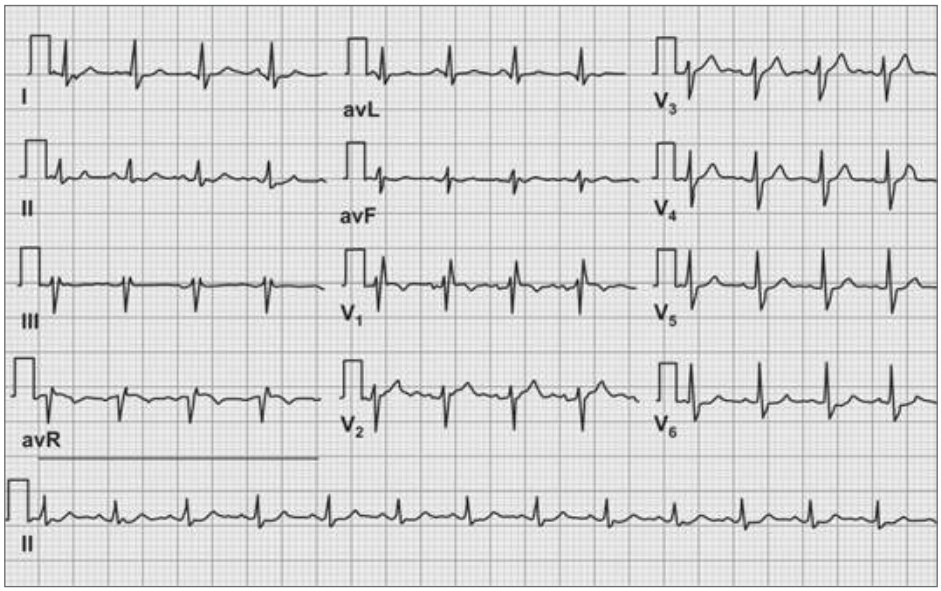


Fig. 1.31: Right bundle branch block

R-wave in V_1 is due to septal depolarization which occurs from left to right. Where the vector is running towards the lead. Then left ventricle is activated and the S-wave is due to left ventricular depolarization which occurs from right to left vector running away from the lead. After that right ventricle is depolarized from left to right creating a R-wave.

The late positive vector, i.e. R-wave is due to late right ventricular depolarization which produces right ward vector. In this situation when the duration of QRS is less than 12 second (< 3 small division), it is called incomplete RBBB and when the duration of QRS is more than 0.12 second (> 3 small division) it is called complete RBBB.

In left bundle branch block (LBBB) (Figs 1.34 to 1.36)

In the left sided lead (V_5, V_6, aVL and lead-I). There will be no Q-wave at the beginning as the septal depolarization in LBBB occurs from right to left (instead of normal left to right). So it will produce a initial positive R-wave followed by a notch or a short duration negative wave which is due to right ventricular depolarization vector (which moves towards right, away from in V_5, V_6) (Fig. 1.36) and in the late part of QRS there is a positive deflection which is due to late depolarization of left ventricle where vector moves towards left creating a late positive deflection in V_5, V_6.

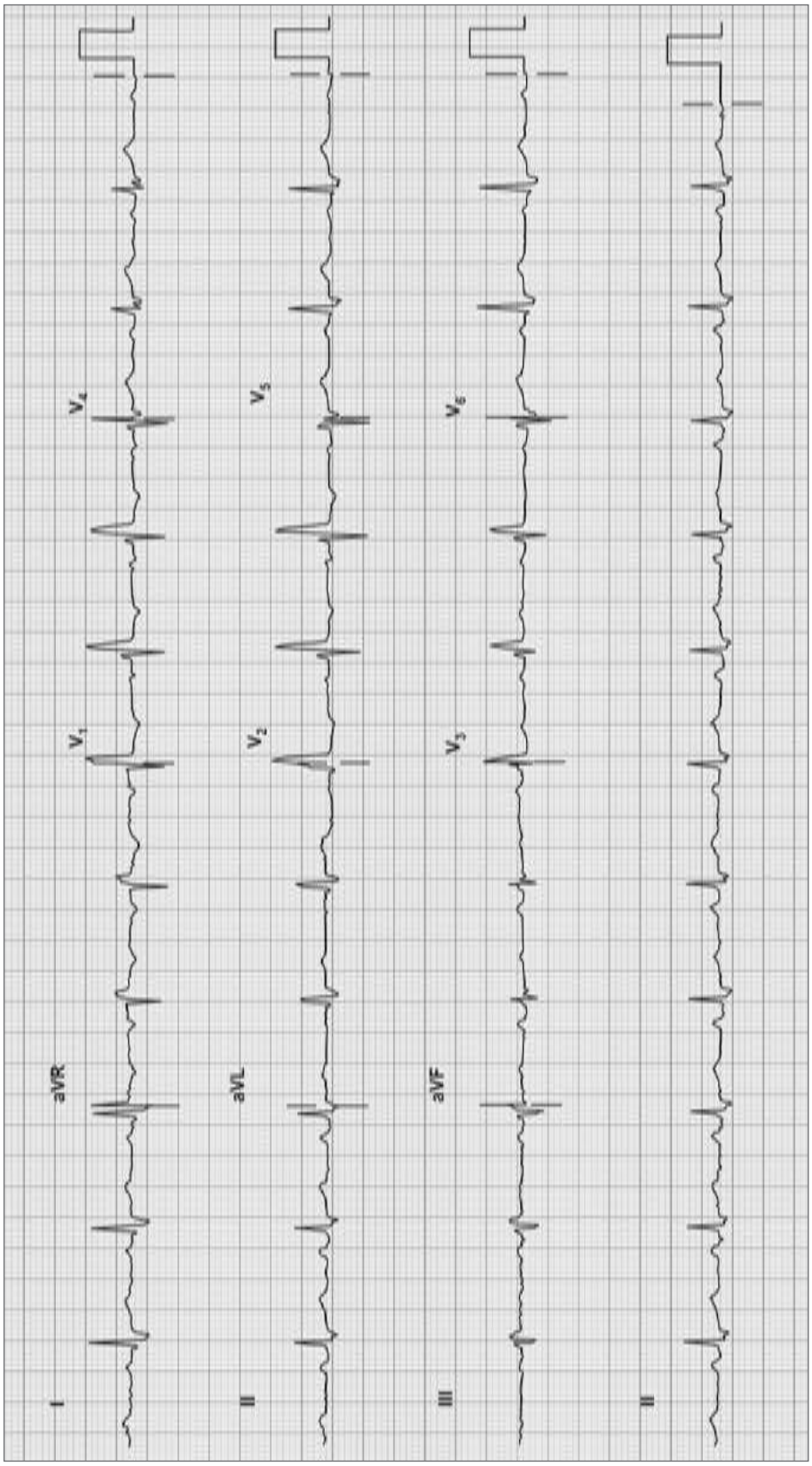


Fig. 1.32: An example of typical right bundle branch block

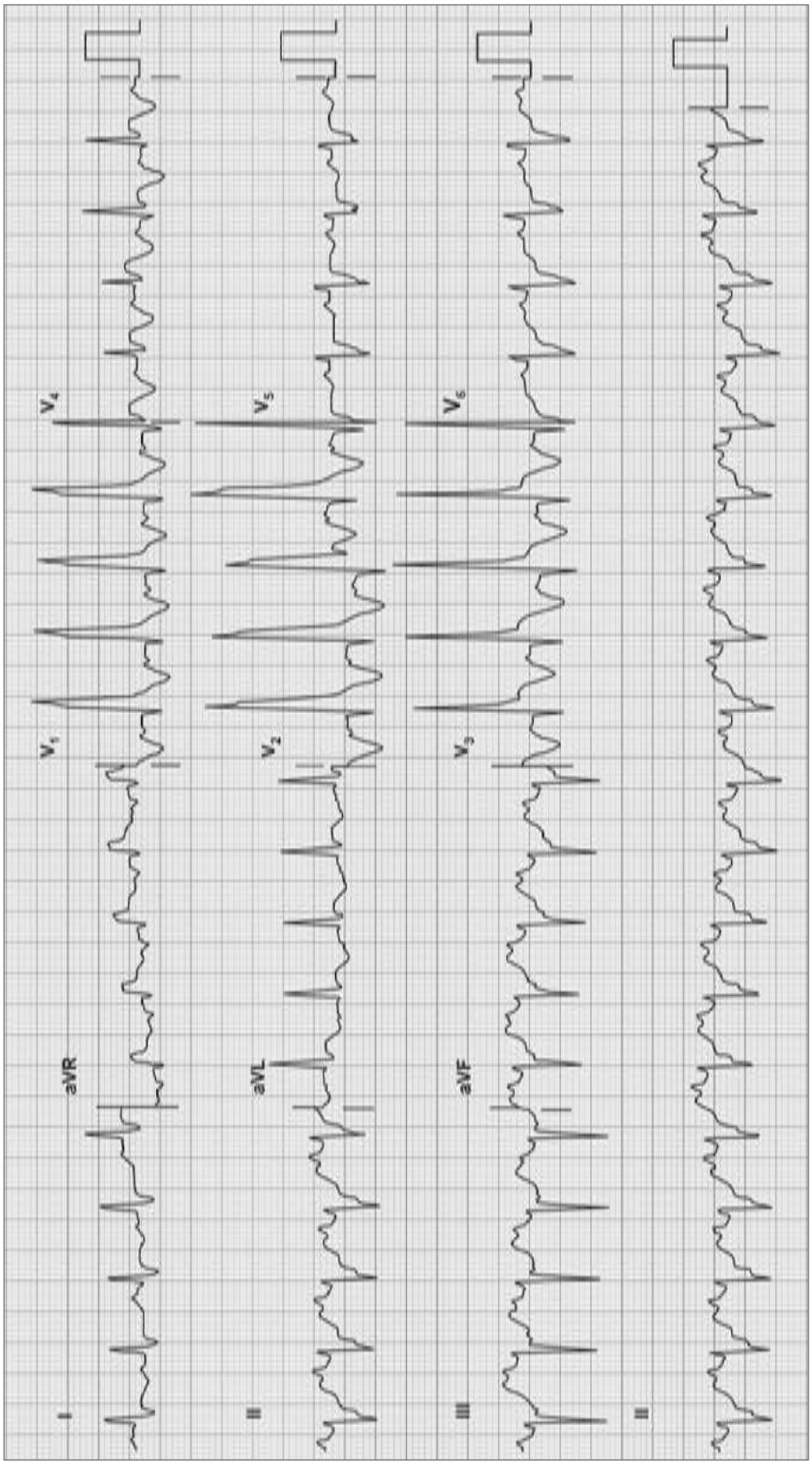


Fig. 1.33: RBBB (RSR' in V_1 and slurring of S-wave in lead-I) and left axis deviation (negative QRS in aVF and II reflect BIFB. Acute anteroseptal STEMI is present (deep Q with ST elevation and inverted T in V_2 V_3 V_4)

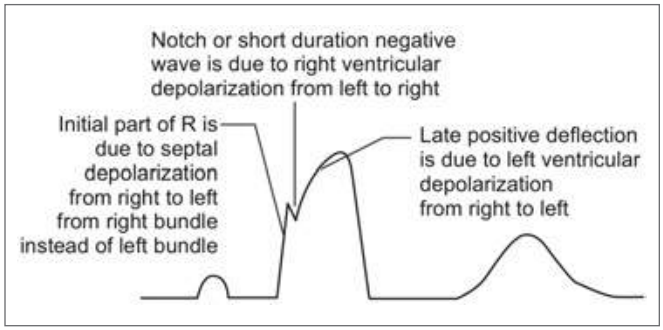


Fig. 1.34: Broad and notched QRS complex of right bundle branch block

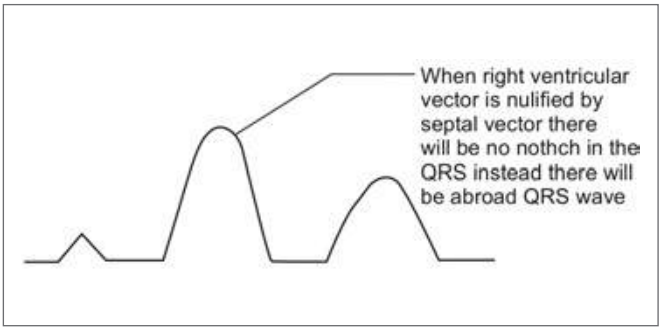


Fig. 1.35: LBBB broad or wide QRS complex of right bundle branch block

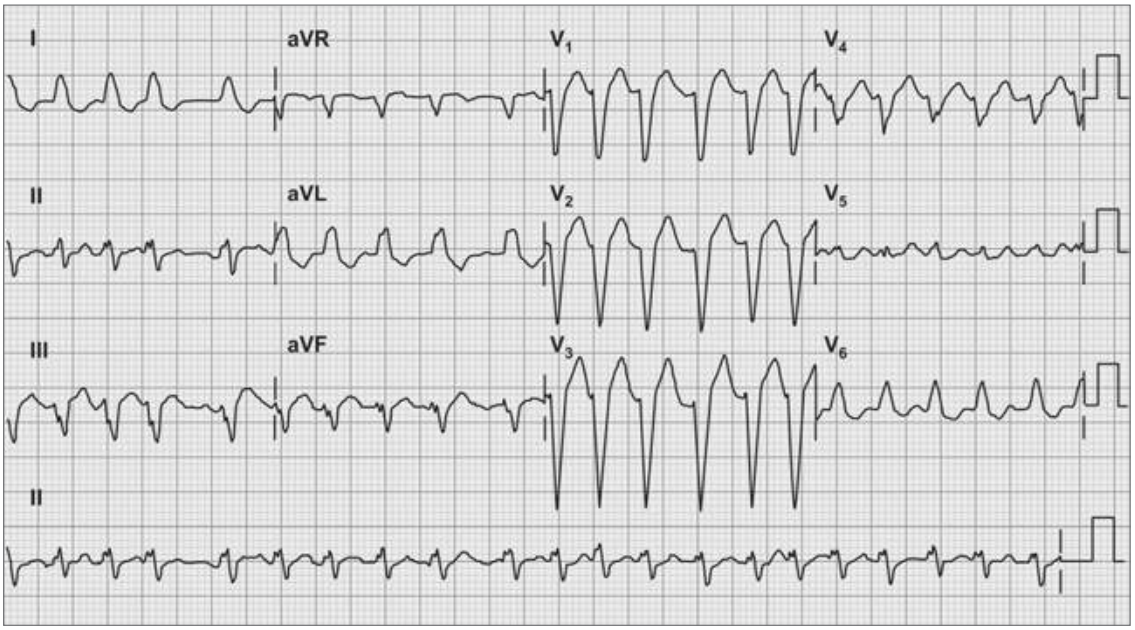


Fig. 1.36: Irregularly irregular rhythm at a rate of 129/min with no definite P-waves indicating atrial fibrillation. The QRS is wide and has a typical LBBB pattern. If the rate is faster one could easily be mistaken the tracing for a run of VT.
Dx: 1. Atrial fibrillation with a ventricular response of 129/min
2. LBBB

ST-SEGMENT

ST-segment gives us information about ischemia and infarction.

In STEMI (ST-elevated myocardial infarction) there will be elevation of ST-segment with convexity upward which incorporate T-wave within it and is seen in the early hours of STEMI (Fig. 1.37) but as the times passes (Fig. 1.38)—The following changes in ECG gradually appear

- The ST-segment gradually comes down
- T-wave gradually become inverted
- Deep and wide Q-wave gradually appear
- Height of R gradually comes down (Fig. 1.38).

All these four changes begins to appear simultaneously or sequentially within few hours after the onset of acute myocardial infarction (Figs 1.40 to 1.43).

Reciprocal change—In STEMI the lead facing the opposite wall of infarction usually have ST-segment depression which is called reciprocal changes. In case of inferior wall infarction. ST elevation is seen in II, III, aVF but reciprocal changes (ST-depression) are seen in V_2, V_3 and V_4. In true posterior wall infarction reciprocal changes are seen

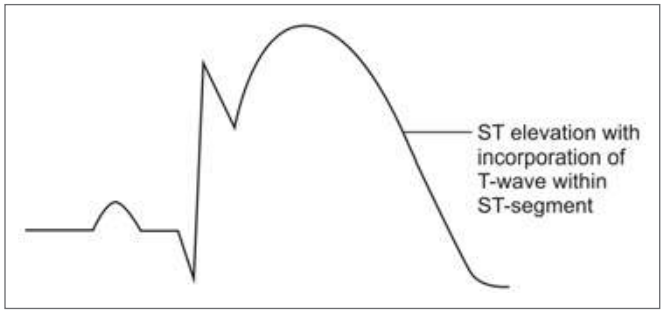


Fig. 1.37: Early stage of STEMI

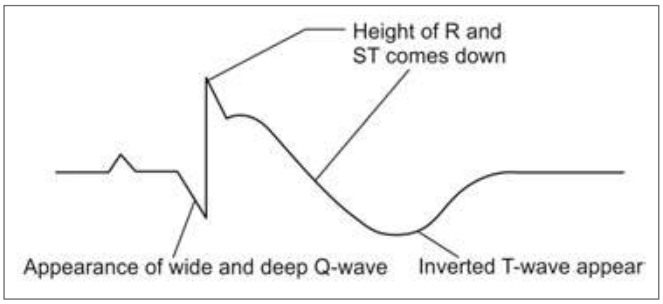


Fig. 1.38: Late stage of STEMI

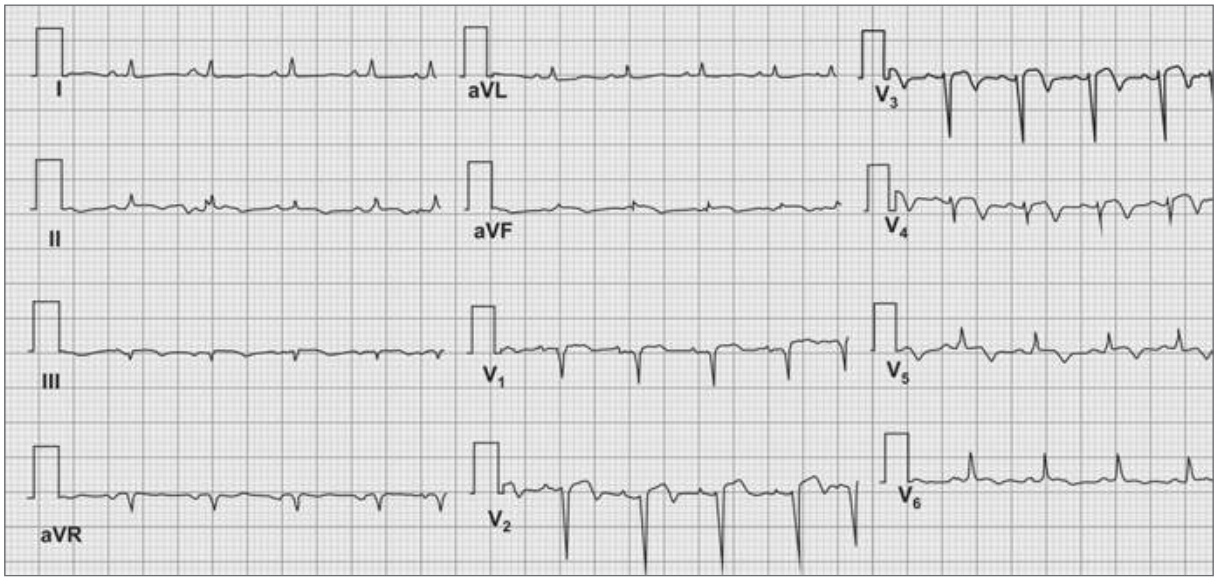


Fig. 1.39: STEMI (involving anteroseptal wall)

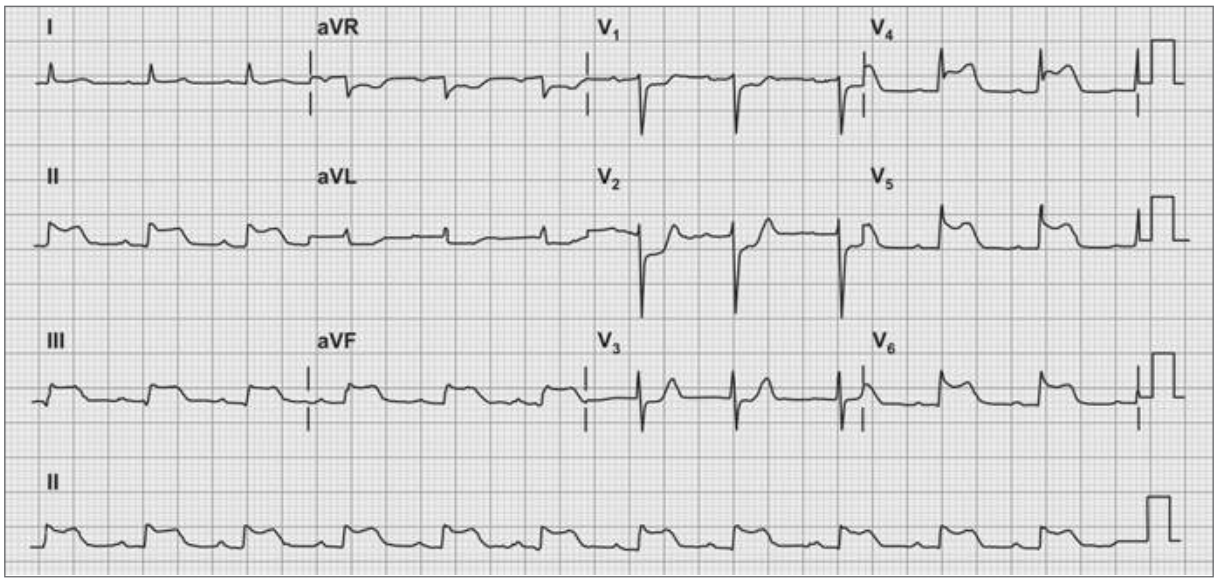


Fig. 1.40: Sinus rhythm at 66/min with 1st degree AV block.

ST elevation in inferolateral leads with horizontal ST depression in V_1–V_3 is diagnostic of STEMI of inferoposterolateral wall. ST is reciprocally depressed only in aVL, not in lead-I indicating RV is not involeved and the culprit lesion must be not in proximal RCA but either **RCA not proximal or circumflex coronary artery**

Dx: 1. Sinus rhythm with 1st degree AV block; 2. STEMI of inferoposterolateral wall

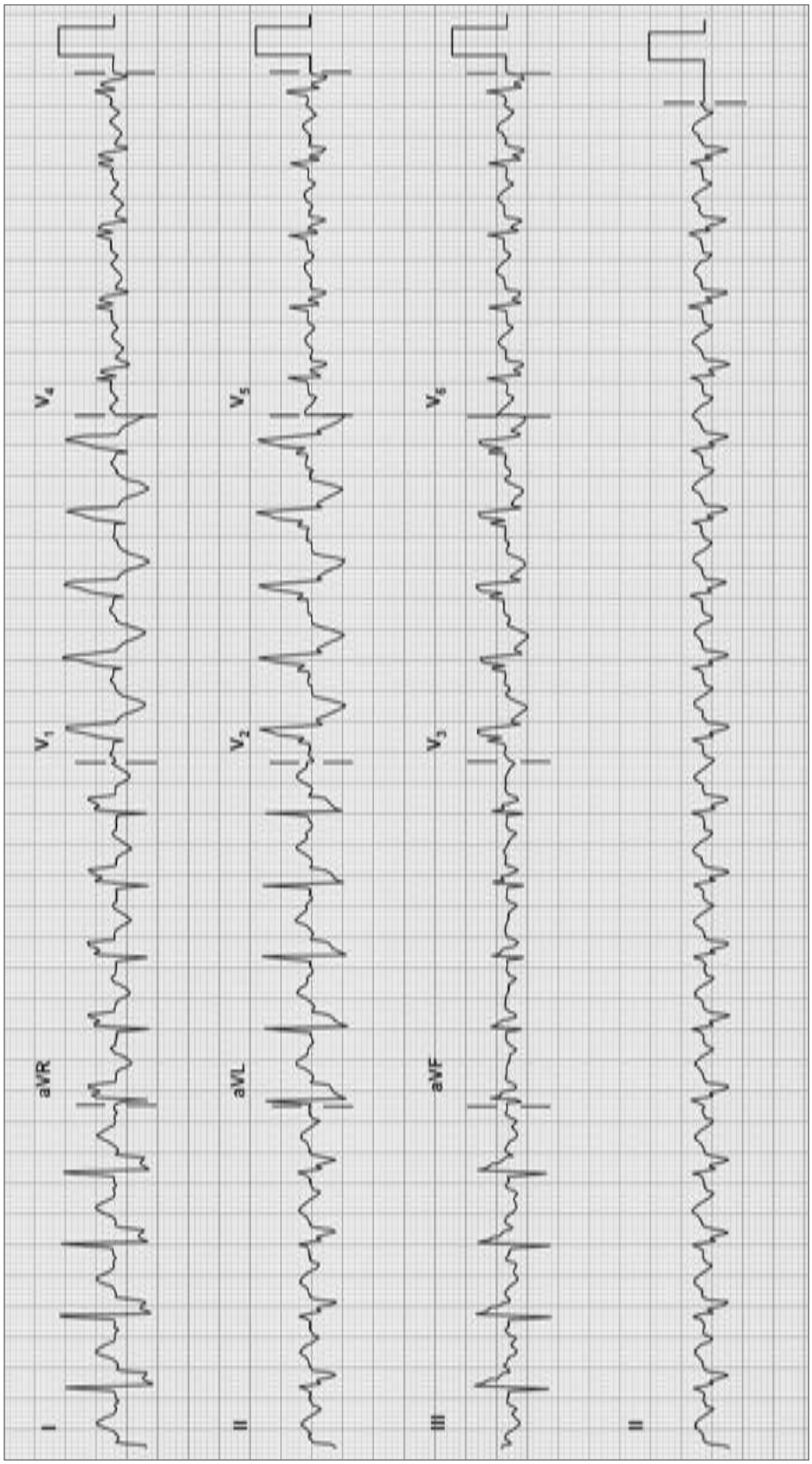


Fig. 1.41: The 'sawtooth' pattern of atrial flutter is obvious in the rhythm strip of lead-II. The flutter rate is somewhat slow at 240/min. Antiarrhythmics are well-known to slow the flutter rate down to 200/min very easily. Complete RBBB is also present. Q-waves in lead-III aVF indicate inferior infarct as well

Dx: 1. Atrial flutter with 2:1 AV conduction
2. RBBB
3. Inferior wall myocardial infarction (MI), probably old

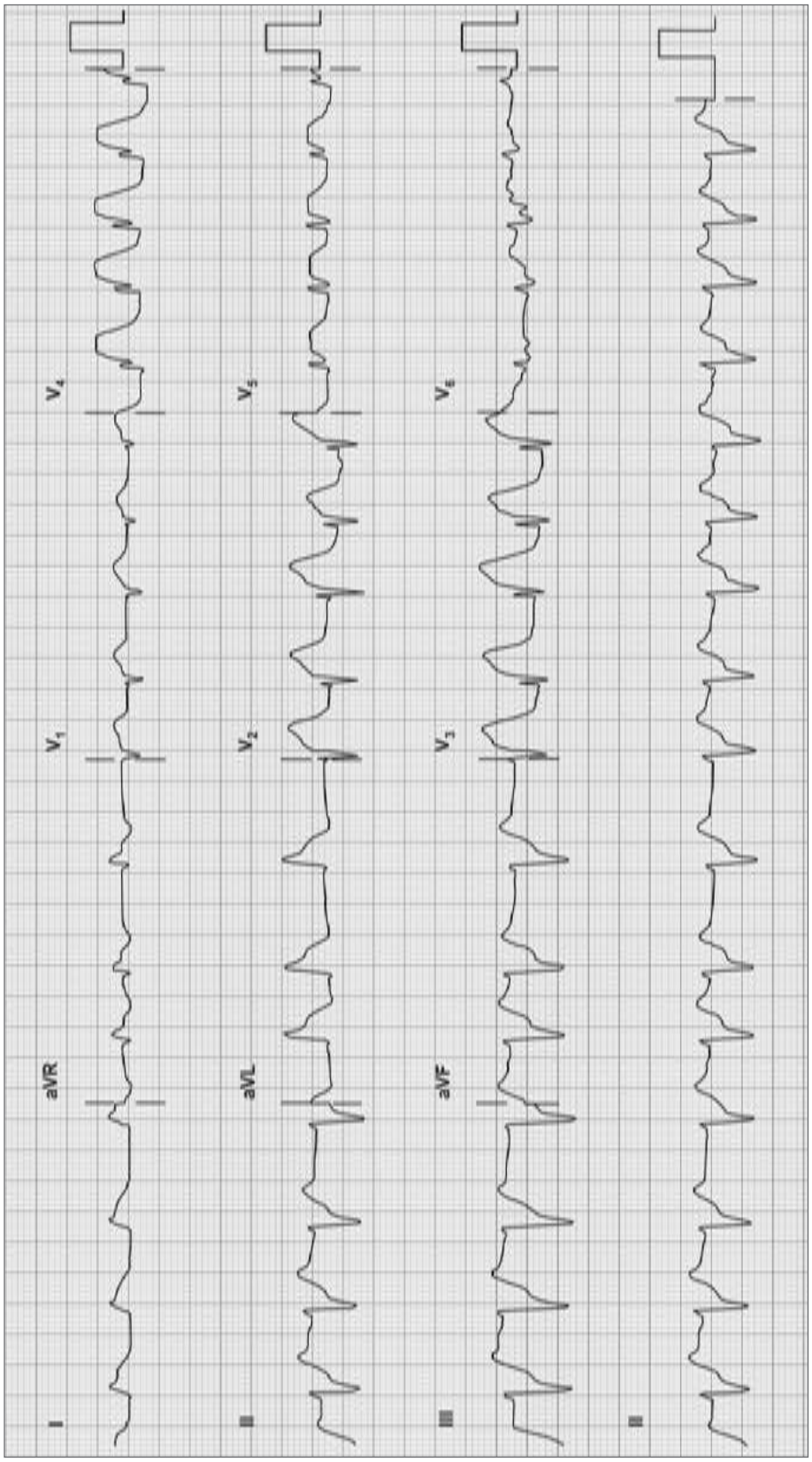


Fig. 1.42: Irregularly irregular rhythm with no visible P-waves indicates atrial fibrillation. Significant, coved ST elevation in the precordial leads as well as in lead-I and aVL indicate acute extensive anterior myocardial infarction (MI). Lead-I and aVL represents high lateral wall which often is perfused by diagonal branch which takes off very proximaly in LAD. Therefore infarction pattern involving precordial lead-I and aVL means the culprit lesion is in the proximal LAD. If lead-I and aVL are not involved, the lesion is in the LAD not proximal. If only lead-I and aVL are involved without precordial leads, the lesion is in the diagonal branch. The ST depression in the inferior leads is the reciprocal change of the ST elevation in aVL

Dx: 1. Atrial fibrillation with a ventricular response of 85 min
2. Acute, extensive anterior infarct

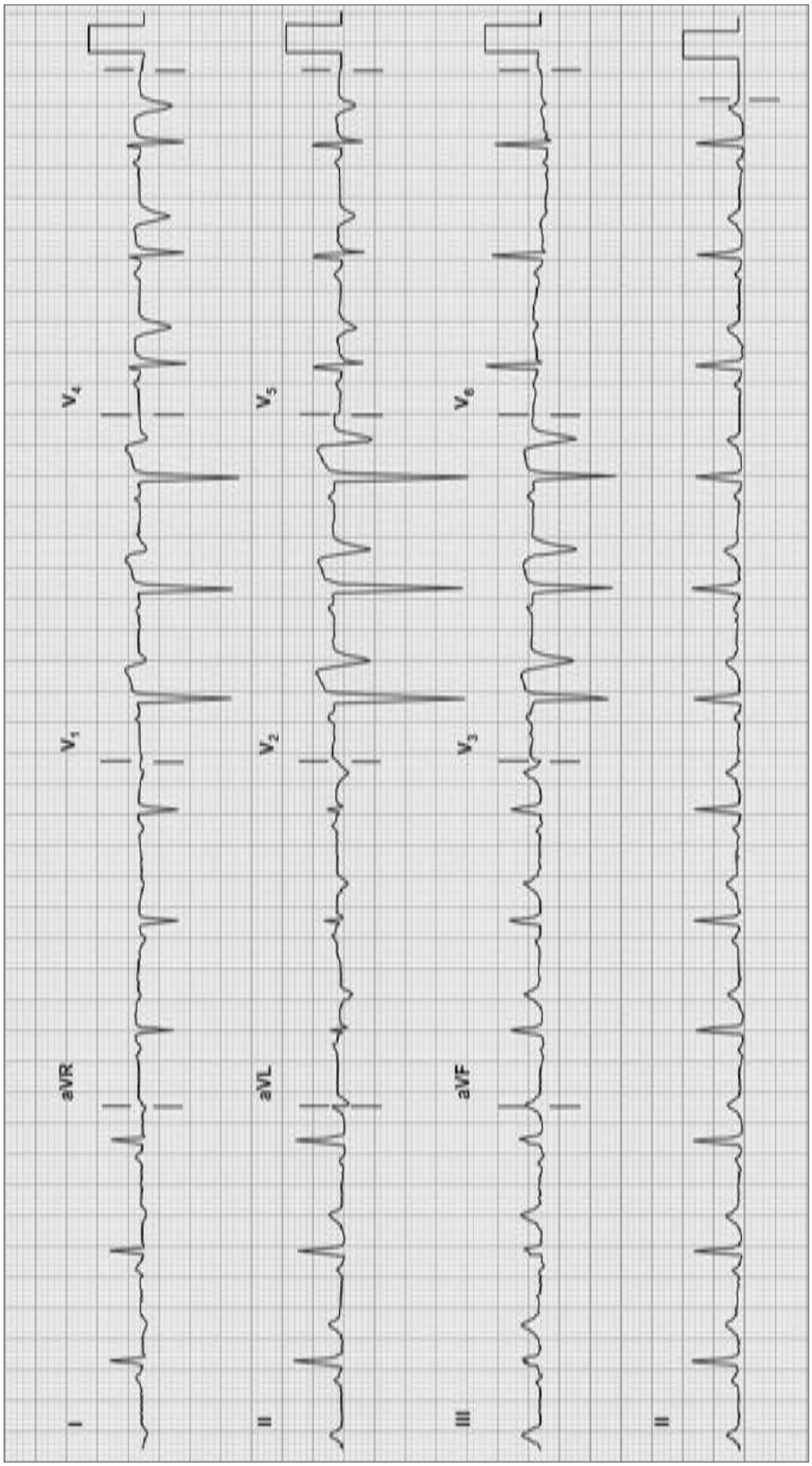


Fig. 1.43: Normal sinus rhythm at a rate of 74/min. QS pattern in the right precordial leads with a slight elevation of the ST-segment and a terminal T-wave inversion reflect recent AMI

Dx: 1. Normal sinus rhythm

2. Recent anteroseptal infarct of some duration

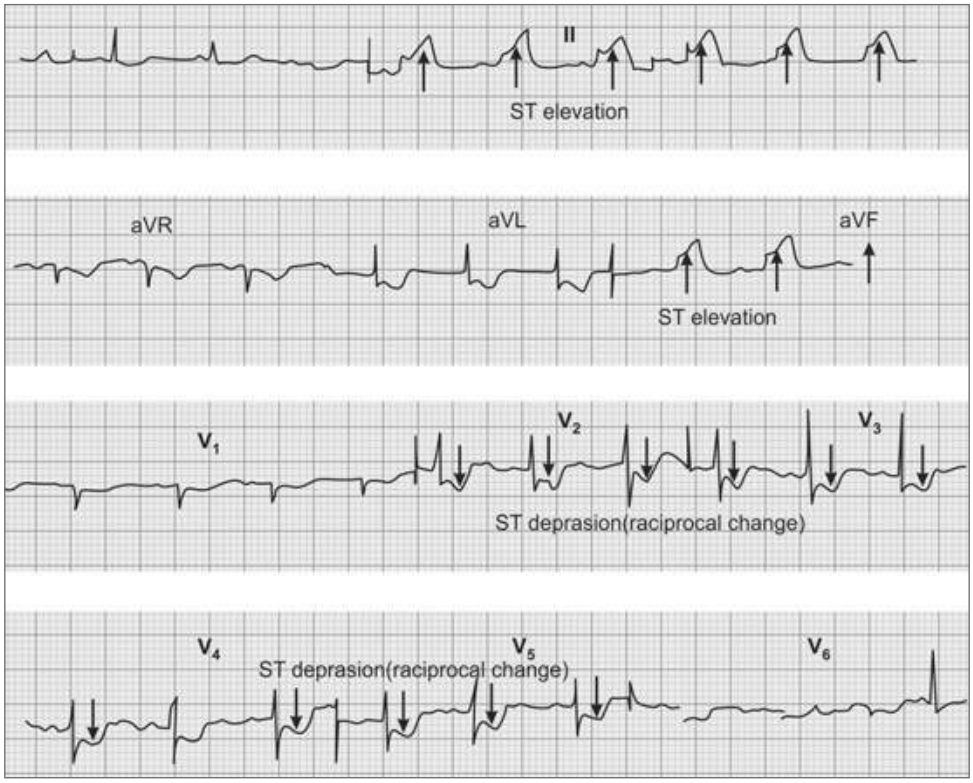


Fig. 1.44: Inferior wall STEMI with reciprocal changes in the anterior wall

in V_2,V_3 and V_4. In anteroseptal wall infarction reciprocal changes are seen in lead-II, III aVF.

In non-ST elevated myocardial infarction (NSTEMI)—Three changes are seen—

- Depression of ST-segment (<1 mm).
- Transient elevation of ST-segment (<20 minutes duration).
- Deep isometric inversion of T-wave (Figs 1.45 and 1.52).

In myocardial ischemia, three classic changes are seen in ST-segment not associated with chest pain.

The ischemic changes in ST-T segment are—

- Down slopping of ST-segment with inversion of T-wave (Fig. 1.46). With unequal length of the ascending and descending limb of T-wave (sensitivity 95%).
- Horizontal depression of ST-segment > 2 mm and longer >2 small division (Fig. 1.47). Sensitivity (80–85%).
- J point is the junction of end ventricular depolarization and beginning of ventricular repolarization.
- Upslopping ST-segment (Fig. 1.48) is also seen in ischemia but sensitivity is (60–65%).

Rarely there may be elevation of ST-segment with convexity downward and present in the adjacent leads seen in pericardial diseases (Figs 1.49A and B). Also called early repolarization.

T-WAVE

Tall peaked T-wave commonly seen in two conditions—(a) *hyperkalemia* and (b) *early stage of acute myocardial*

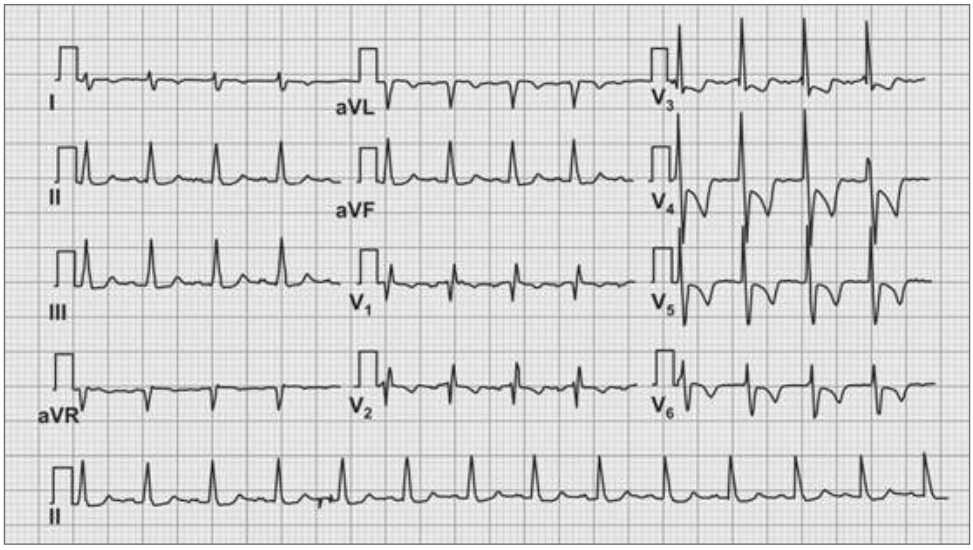


Fig. 1.45: Deep isometric inversion of T-wave is V_4, V_5, V_6 suggestive of NSTEMI

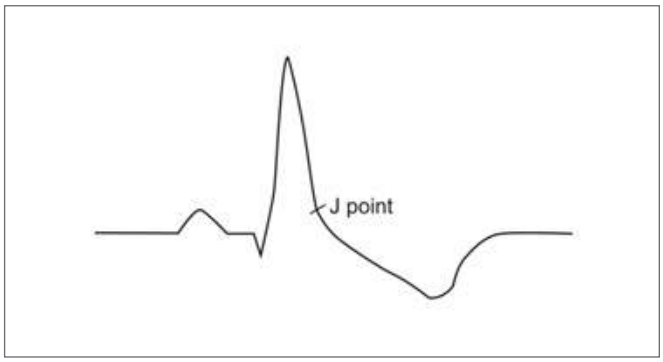


Fig. 1.46: Down slopping ST with inversion of T-wave seen in ischemia with unequal length of the ascending and descending limb of T-wave

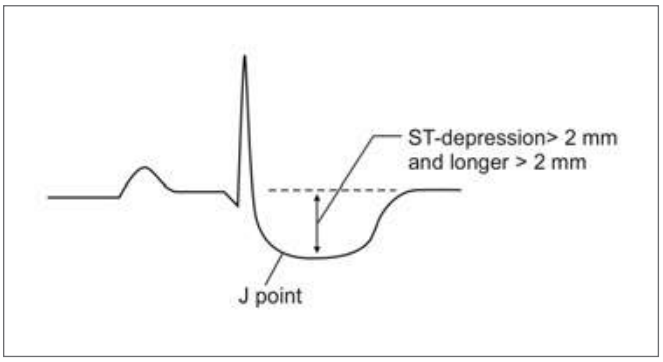


Fig. 1.47: Horizontal depression of ST-segment seen in ischemia

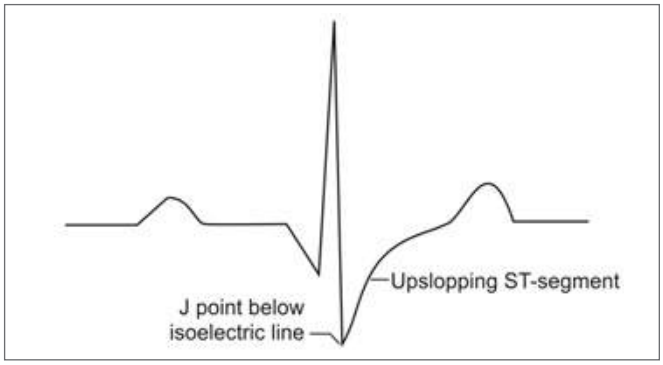


Fig. 1.48: Upslopping ST-segment seen in ischemia

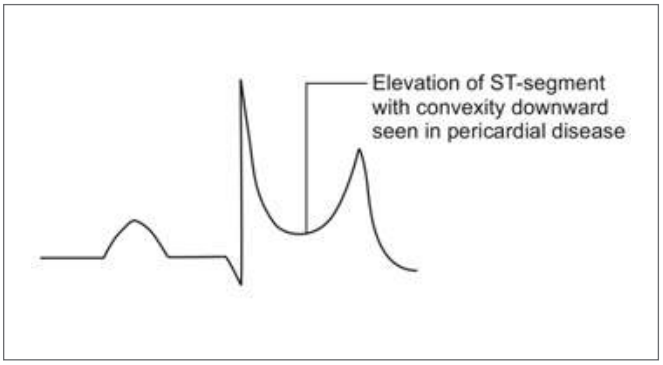


Fig. 1.49A: Elevated ST with convexity downward known as early repolarization seen in pericardial disease and may be seen as a normal varient

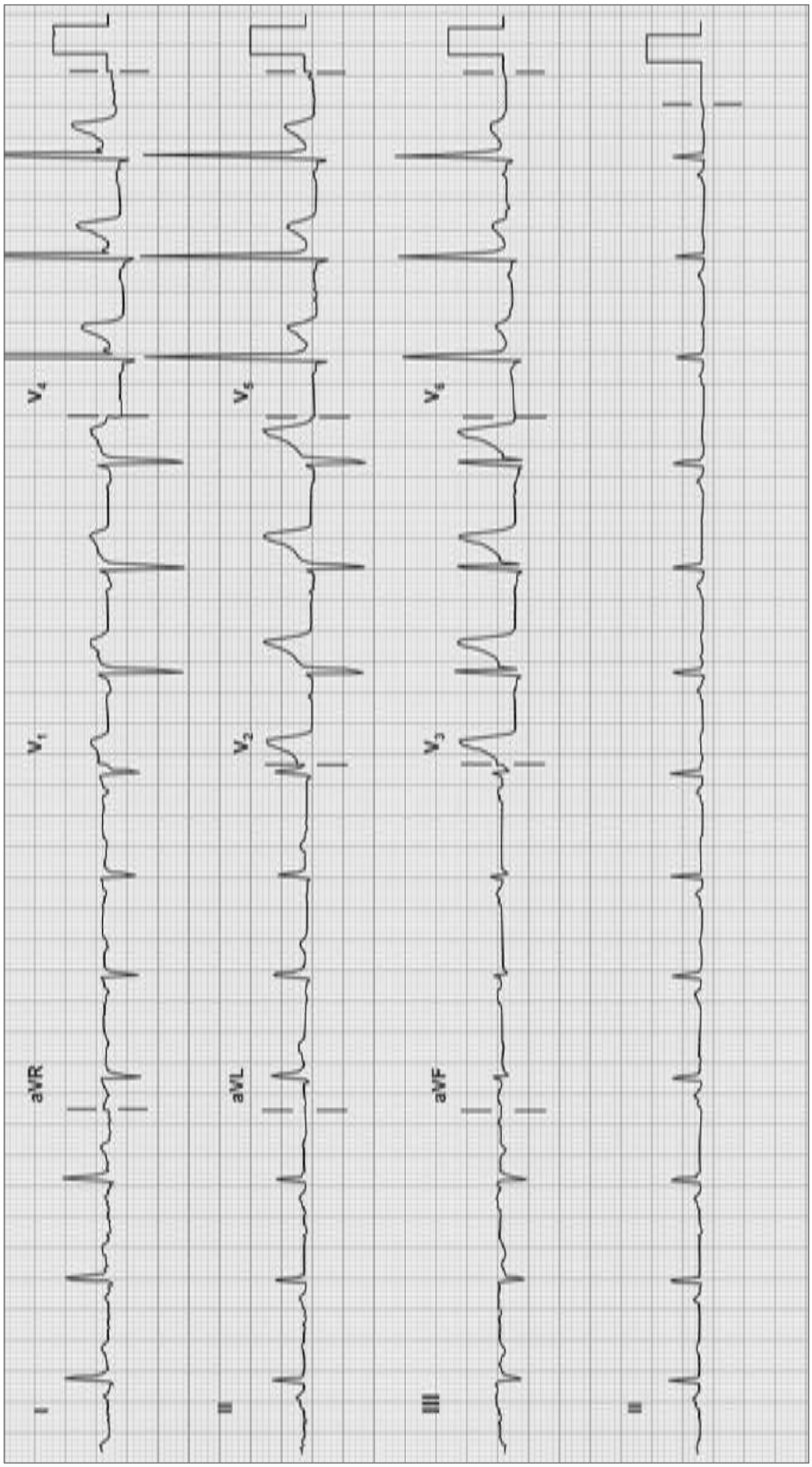


Fig. 1.49B: Normal sinus rhythm at a rate of 80/min. QRS voltage for LVH is present. There is about 4 mm ST elevation in V_3–V_4, and to a lesser degree in other precordial leads. The notching in the junction in V_4 and upward concavity of the ST-segment are all diagnostic of early repolarization pattern as a normal variant. The PR-segment is slightly depressed which is also part of this condition. Sometimes these findings may be mistaken for an acute MI or pericarditis

Dx: 1. NSR
2. LVH by voltage
3. Early repolarization pattern as a normal variant

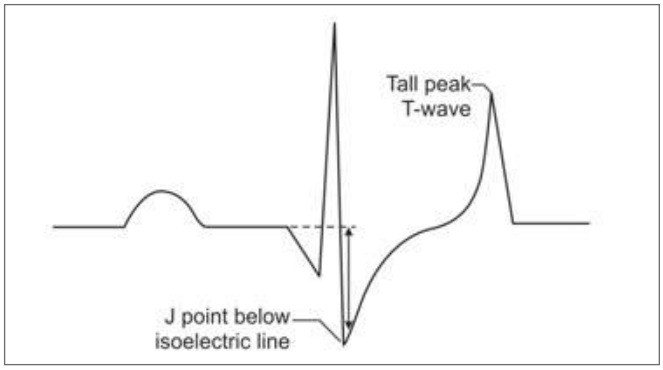


Fig. 1.50: Tall peaked T-wave with J point below isoelectric line seen in hyperkalemia (P-R interval is considered isoelectric line)

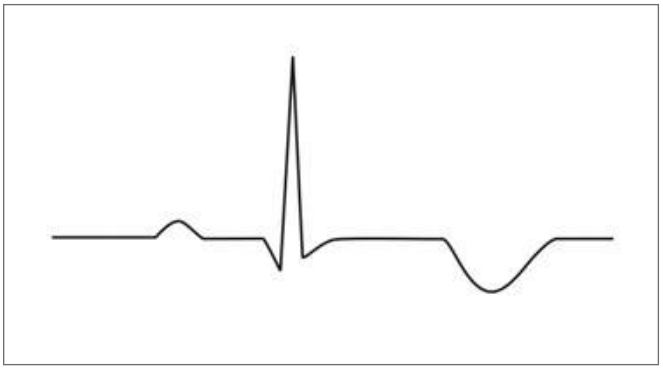


Fig. 1.52: Isometric inversion of T-wave seen in NSTEMI and UA ascending and descending limb of T-wave are of equal length

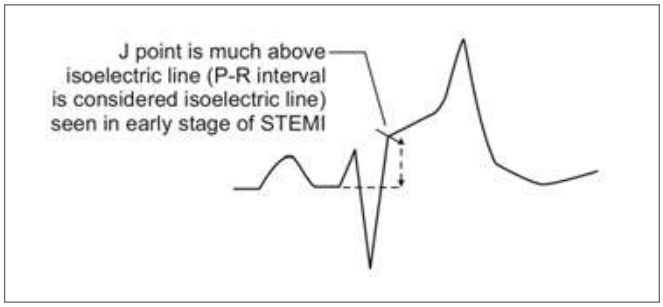


Fig. 1.51: Tall peaked T-wave with 'J' point above isoelectric line (P-R interval) seen in very early stage of acute myocardial infarction

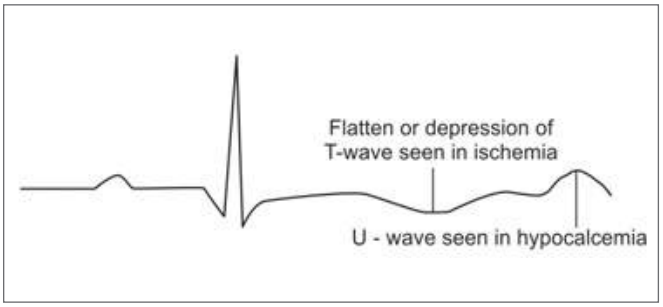


Fig. 1.53: Flattening or depression of T-wave without chest pain seen in chronic ischemia

infarction STEMI. The differentiating point between these two conditions are—

a. In case of hyperkalemia the J point is much below the isoelectric line (Fig. 1.50).
b. In case of early stage acute myocardial infarction the 'J' point in much above the isoelectric line (Fig. 1.51) followed by tall peaked T wave.

Isolated inversion of T-wave may be seen in (a) NSTEMI (non-ST elevated myocardial infarction and (b) old infarction or ischemia (Figs 1.45 and 1.52).

U-WAVE

It is rare and is due to repolarization of conducting tissue of heart. It is prominent in hypocalcemia (Fig. 1.53).

Chapter 2

Rheumatic Fever

- Acute rheumatic fever (ARF) is an acute immunologically mediated multisystem inflammatory disease that follows an episode of GrA streptococcal pha-ryngitis after an interval of few weeks.

- Anticident pharyngitis may be asymptomatic at times
- Any strain of GrA streptococcal appears to be particularly associated with risk of rheumatic fever, perhaps due to a well-developed highly antigenic capsule
- Rheumatic fever rarely develops following an infection by streptococci at other sites like skin
- It only occurs in 3% case of Gr-A streptococcal pharyngitis
- It is postulated that a series of repeated streptococcal infection is necessary to prime the immune system prior to final infection that have caused the disease

Pathogenesis

- It is strongly suspected that acute rheumatic fever is a hypersensitivity reaction induced by Gr-A streptococci
- It is proposed that antibody directed against M protein of Gr-A streptococci cross reacts with normal connective tissue protein present in heart, joint, brain, skin and other tissue due to molecular mimicry
- Hypersenstivity phenomenon is supported by the fact that—
  1. Streptococci cannot be demonstrated from the site of inflammatory lesion
  2. Symptom typically developes 3–4 weeks after infection

Diagnosis

- No specific diagnostic test is available for diagnosis of ARF.
- The diagnosis is therefore a clinical one but requires supportive evidence from microbiology and immunology.
- **Jones criteria** was proposed in 1944, later on updated Jones criteria was published in 1992 and now WHO criteria is followed for clinical diagnosis of acute rheumatic fever.
- 5 major criteria and minor criteria
  - **Major jones criterias**
    - Pancarditis (40–60%)
    - Migratory polyarthritis (75%)
    - Sydenham's chorea (<10%)
    - Subcutaneous nodule (<10%)
    - Erythema marginatum (<10%).
  - **Minor jones criterias**
    - Clinical
      - » Fever (39.5°C)—95%
      - » Polyarthralgia.
    - Laboratory criteria
      - » Elevated acute phase reactant—ESR
      - » Elevated leukocyte count.
    - ECG
      - » Prolonged PR interval >0.2 second.

PLUS

- Supportive evidence of previous Gr-A streptococcal infection within 45 days—
  - Positive throat culture (present in 25–40% of patient)
  - Rapid antigen detection test for Gr-A streptococcus
  - Rising or elevated ASO titer or other streptococcal antibody.
  - Recent scarlet fever.
    - To fulfil Jones criteria
      - » **2 major criteria**.
      - » **1 major + 2 minor criteria with evidences of anticident streptococcal infection are required**. If the 3 antibody tests are negative the diagnosis should be seriously reconsidered.

CARDITIS

Younger the patient more in the chance of carditis. Overall 40–60% of ARF patients have evidence of carditis.

When acute rheumatic fever affects child at 3 years of age 90% of then develop carditis whereas when acute rheumatic fever develops in patient at 15 years of age 30% of them have carditis.

- Mitral valve is usually involved and second one is the aortic valve. Isolated aortic valve involvement is very rare.

- Usually over years as a result of recurrent episode of rheumatic endocarditis leaflet thickening, scarring and calcification lead to either stenotic or regurgitant lesion or both of mitral or aortic valve

- Rheumatic pericarditis may lead to fibrin deposit, serous effusion leading to pericardial calcification but does not lead to constrictive pericarditis.

Features of Carditis

- **Breathlessness** is the most common symptoms is due to heart failure or pericardial effusion.
- **Palpitation or chest pain** is due to pancarditis or pericarditis.
- **Tachycardia** is due to atrial fibrillation or sinus tachycardia.
- **Cardiomegaly** is due to pericardial effusion or heart failure.
- **Features of congestive cardiac failure**—Pulsatile neck vein, pedal edema and hepatomegaly as of manifestations chronic heart failure.
- **S_1 is soft**.
- **S_3 gallop** may be present over apex.
- **Murmur of MR**—95% of the patients of acute rheumatic carditis have **MR murmur**.
  - **Murmur of AR** is present in a quater of them who have **murmur of MR**.
  - 5% of patients have murmur of **isolated pure AR**. **Mitral stenosis murmur** in a patient with acute rheumatic carditis is due to inflamed valve cusps and is known as **Carey-Coombs murmur**.
- **Pericardial friction rub and small effusion are due to pericarditis**.
- **Increased PR interval** greater than 0.2 second (1°st degree heart block) may be present.
- **Second degree of AV block** (Mobitz—type II) seen rarely.

MIGRATORY POLYARTHRITIS

It is seen as typical migratory polyarthritis.

- **Polyarthritis affects 70% of cases in Western countries**. In India it affects only 30–50% patients.
- **Younger the patient more is the chance of developing the arthritis**.
- **Affects knee, ankle, wrist, elbow and hip joint** over a period of hours to days in asymmetric manners. Rheumatic polyarthritis usually do not involve small joint of hands and feet and spinal joint.
- **Joints are painfull swollen and tender, appear quickly last for few hours to days disappear spontaneously to reappear in other joints leaving no residual joint deformity**.
- **Aseptic monoarthritis may be a presenting feature**.

SYDENHAM'S CHOREA (ST VITUS DANCE) (PRESENT IN10% CASES)

Commonly occurs in the absence of other manifestation of ARF it may be restricted to one side (hemichorea).

- **It is 3–4 times more common in female.**
- **It is a late manifestation.**
- **Involves head, tongue and upper extremity.**
- **Usually have the longest latent period** of onset may be several months (~ 6 month) in most of the cases.
- Many patients who appear to have only chorea may **present several decades later with evidence of typical RHD**.
- It has a selflimiting course of 4–6 weeks.
- **There is no definitive diagnostic test** for Sydenham's chorea and the diagnosis is by way of exclusion. That is why all patients with Sydenham's chorea should receive secondary prophylaxis for prevention of recurrent attack of rheumatic fever even if they do not appear to have rheumatic heart disease.

SUBCUTANEOUS NODULE (PRESENT IN 10% CASES)

Seen as small (0.5–2 cm) nontender and mobile lump.

- **It is mostly a late manifestation**—Appears around 2–3 weeks after the onset of rheumatic fever and lasts for 2–3 weeks.
- **Subcutaneous nodule present over extensor aspect** of joint in forearm (elbow) and behind ear (occiput) usually with long standing RHD and usually rare in patient with initial attack.

  Patients with subcutaneous nodule are usually associated with carditis.

ERYTHEMA MARGINATUM (PRESENT IN 10% CASES)

- **It is an early manifestation** predominantly seen over the trunk rare on limb and never on face.
- **Considered to be more specific** than other variety of skin manifestation known to be extremely rare in Indian.
- **The rash is faintly reddish, evanescent not raised** above the skin, nonitchy, starts as a red spot with a pale center, rapidly increasing in size to qualace with adjacent spot to form a serpiginious outline and fades away within 2–3 hours.

Differential Diagnosis of Rheumatic Fever

- *Juvenile arthritis.*
- *Collagen vascular disorder*—SLE and RA.
- *Acute arthritis due to virus*—Rubella, pervovirus, HBV and herpes.

- *Hematological disorder*—Sickle cell disease and leukemia.
- *Poststreptococcal* reactive arthritis.

Treatment

Supportive and symptomatic treatment

Supportive treatment

a. **Rest**—Specially for carditis patient.
b. **Salt poor, high calorie, high protein, diet supplemented with vitamins and minerals**.
   Salt restriction is not necessary in patient without CCF.
c. **In management of chorea**—Assurance and protection from self-injury.
   In severe forms carbamazepine, sodium valproate for 1–2 weeks.
   Use of IVIG is controversial.

Symptomatic treatment—In selecting a suppressive drug (salicylate/steroid) for an individual patient, the guidelines are

- **Patient without carditis**—Aspirin is preferred.
- **Carditis without CCF**—Steroid or aspirin may be used (steroid is preferred).
- **Carditis with CCF**—Steroid is mandatory.
  - *Aspirin*—80–100 mg/kg/day in 4 divided doses in children. In adult 4–8 g/day in 4–5 divided doses.
  - Full dose is given for 2 weeks and then reduced to 60–70 mg/day for further 4 weeks.
  - Blood salicylate level should be 20–25 mg/dL.
  - Naproxen 10–20 mg/kg/day has a good symptomatic response.
  - *Steroid*—Use of steroid is controversial. In pediatric age group
    - Patient >20 kg body weight 1–2 mg/kg/day. Maximum 80 mg/day for 3 weeks followed by 50 mg/day for 1 week followed by 40 mg/ day for 1 week then reduction is 5 mg/week till it is finished.
    - Patient <20 kg body weight. Initial dose is 30 mg divided 6 hourly for 4–6 weeks reduced in similar fashion.

Antistreptococcal antibiotics

Primary and secondary prevention

Primary prevention

- Penicillin is the drug of choice.
  But 10-day course of oral cephadroxil/ cephalexin is superior to 10 day course of oral penicillin.
  5 day oral cephalosporins is comparable to 10 days oral penicillin in eradication of Gr A streptococcus from pharynx.
  Phenoxymethyl penicillin—500 mg BD for 10 days.
  Amoxicillin—500 mg TDS for 10 days.
  Benzathin penicillin—1.2 MU IM single dose.
- Appropriate antibiotic therapy started up to 9 days after the onset of acute streptococcus pharyngitis is effective in primary prevention.
- Erythromycin is used when patient is allergic to penicillin.

Secondary prevention

- Benzathine penicillin G 1.2 MU 4 weekly recommended in USA, but in endemic area with high-risk cases and in special circumstances 3 weekly regimen is recommended.
- Oral prophylaxis is discouraged due to non-adherence and failure of therapy even with optimal adherence.
- Sulfar-containing drugs is contraindicated in pregnancy.
- Prophylaxis should continue even after valve surgery or prosthetic valve implantation for life-long.
- Patient with history of rheumatic carditis or Sydenham's chorea are at high-risk patient for recurrence.
- *Duration of secondary prophylaxis*

1.	**Patient without proved carditis**	5 years after last attack or up to 21 years of age which ever is longer
2.	**Patient with mild MR or healed carditis**	10 years after last attack or 21 years of age whichever is longer
3.	**More severe valvular disease**	Lifelong/for 10 years/ up to 40 years of age
4.	**Valve surgery**	Lifelong

Primary prevention

1.	Benzathene penicillin G	6 lac <27 kg 12 lac >27 kg	IM	Single dose
2.	Penicillin V	Child—250 mg bd/tds Adolescent—500 mg bd/tds	Oral	For 10 days
3.	Erythromycin (patient allergic to penicillin)	40 mg/kg/day in 2–4 divided doses or 250 mg bid	Oral	For 10 days

Secondary prevention

1.	Benzathene penicillin	1.2 MU at 3 weeks interval	IM
2.	Penicillin V	250 mg bid daily	PO
3.	Sulfadiazine (not used in primary prevention)	0.5 G <27 kg daily 1 G >27 kg daily	PO
4.	Erythromycin (patient allergic to penicillin)	250 mg bid daily	PO

Chapter 3

Infective Endocarditis

DEFINITION

Infection and proliferation of microorganism with formation of vegetation on the heart valve (native or prosthetic) or on mural endocardium (on the low pressure side of VSD where it is damaged by aberrent jet or an intracardiac devices) **is called infective endocarditis**.

An analogous process involving arteriovenous shunt, arterioarterial shunt (PDA) or coarctation of aorta is called **infective endarteritis**.

VEGETATION

Vegetation is a mass composed of platelet—fibrin and microcolony of microorganism with scant inflammatory cell.

Site of Formation

- **Damaged or normal heart valve** (native).
- **Prosthetic heart valve**.
- **Low pressure side of IVS** at the site of VSD where the mural endocardium damaged by aberrent jets.
- **Foreign bodies** like intracardiac devices (leads of pacemaker/defibrillator).
- **Arterioarterial/arteriovenous shunt or coarctation** of aorta leading to endarteritis.

TYPES OF ENDOCARDITIS

It is classified according to temporal evolution of the disease into two types:

1. **Acute infective endocarditis**—It is a hectically febrile illness rapidly damages cardiac structure with hematogenous seedlings at extracardiac site and if untreated leads to death within few weeks.
   Common causative agents
   - **β-hemolytic streptococci**
   - **Staphylococci (coagulase positive)**
   - **Pneumococci.**
2. **Subacute infective endocarditis**—Causes structural damage very slowly (if at all), rarely causes metastatic infection, gradually progressive, unless complicated by major embolic event or ruptured mycotic aneurysm.
   Common causative agents
   - ***Streptococcus viridans***
   - **Enterococci**
   - **HACEK group of organism**
   - **Coagulase negative staphylococci**.

Etiology

1. Native valve is usually affected by—
- *Streptococcus viridans*—50–60% (involve damaged valve), source—oral
- *Staphylococcus aureus*—10–20% (source—skin) involve both, normal and damaged valve
- *HACEK group of organism*—Source—URTI (involve damaged valve)
- *Streptococcus bovis*—GI polyp or colonic tumor
- *Enterococci*—Source—Genitourinary tract
- *Nosocomial*—Route of entry is either intravascular catheter and wound, UTI [25% cause of valvulitis] Diagnosed by transesophageal echocardiography

2. Prosthetic valve—
- When develops vegetation within 2 months of operation either by intraoperative contamination or postoperative bacteremia by the causative agent like
  1. Coagulase negative *Staphylococcus*
  2. *Staphylococcus aureus*
  3. Facultative gram-negative bacilli
  4. Diphtheroids
  5. Fungi
- When prosthetic valve develops vegetation within 2–12 months of implantation causative agents are same but with delayed onset
- But when it is delayed >12 months—It is community acquired and infectious agents are similar to native valve endocarditis

3. Transvenous-prosthetic pacemaker lead/defibrillator lead when develop vegetation within 7 days—It is usually by nosocomial infection—same as prosthetic valve.
Most common agent**—***Staphylococcus aureus*** and ***coagulase negative staphylococcus***

4. IV drug abusers—*Staphylococcus aureus.* Affects right side of heart

Other Bacteria in IV Drug Users

- **Pseudomonas**
- **Bacillus**
- **Candida**
- **Lactobacillus**
- **Diphtheroids**
- **Polymicrobials**

Pathogenesis

- Endothelial injury by low velocity jets or low pressure site of cardiac structural lesion allows either direct infection by virulent organism *(Staphylococcus aureus)* or formation of NBTE (nonbacterial thrombotic endocarditis)
- NBTE subsequently serves as site of bacterial attachment during transient bacteremia, except *Staphylococcus aureus* which can directly attach to intact endocardium or subendocardial exposed tissue. NBTE occurs in AS, MR, AR, VSD and complex congenital heart disease or in hypercoagulable state as in **marantic endocarditis** seen in dying patient of endocarditis
- **Libman-Sacks endocardities** seen in SLE and in APLA syndrome where hypercoagulability is a feature
- Organism resistant to microbicidal activity of serum and platelet, proliferate and stimulate the surrounding tissue to release or itself release procoagulant which leads to further deposition of platelet-fibrin causing propagation of vegetation
- Receptors of the bacteria that help in attachment with the injured endocardium or thrombi are—
  1. Fibronectin receptor of gram-positive bacteria
  2. Clumping factor of Staphylococcus
  3. Dextran of Streptococcus
- Organism enmeshed in platelet-fibrin vegetation proliferate to form dense microcolonies in which > 90% of microorganisms are **metabolically inactive, thus resis- tant to antibiotic**

Clinical Manifestation

Mechanism

- Cytokine production from damaged intracardiac structure.
- Embolization of the vegetation fragment leading to infection and infarction.
- Tissue damage due to circulatory immune complex.

Clinical Feature

General manifestation (due to cytokines)

- **Fever** (80–90%), **chills** and **sweating** (40–70%)
- A**norexia, malaise, weight loss** (25–50%)
- **Myalgia, arthralgia** (15–30%), **back pain** (7–15%)
- Clubbing.

Systemic manifestation

Cardiovascular manifestation (directly due to micro-organism)

- **Incompetence murmur** (80–85%)—Mostly MR murmur. Others are VSD, AR, AS murmur.
- **CCF** (30–50%) It is due to
  - Myocarditis
  - Valvular dysfunction
  - Intracardiac fistula.
- **Varying degree of AV block**—It is due to extension of perivalvular abscess arising from mitral valve or noncoronary cusp of aortic valve to nearby AV node or bundle of His.
- **Acute myocardial infarction**—It is due to embolization of coronary artery by vegetation.
- **Perivalvular abscess** causing intracardiac fistula.

Immunological manifestation seen in (2–15% cases and are nonembolic)

They are as follows

- **Osler's node**
- **Rheumatoid factor**
- **Glomerulonephritis**
- **Roth's spot**.

Risk of embolization is high in three conditions

- Endocarditits caused by *Staphylococcus aureas*
- Vegetation > 10 mm diameter
- Vegetation involving mitral valve.

Suppurative peripheral embolic manifestation can involve many organs but mainly

- **Skin** (microabscess)
- **Spleen** (splenomegaly)
- **Kidney** (flank pain, hematuria)
- **Skeletal muscle**
- **Meninges** (purulent or aseptic meningitis)
- Stroke due to cerebrovascular emboli
- Intracranial hemorrhage due to hemorrhagic infarct or rupture mycotic aneurysm.

Nonsuppurative peripheral manifestation are

a. Subungual hemorrhage
b. Osler node
c. Janeway lesion
d. Conjunctival hemorrhage
e. Seizure, embolic stroke, intracranial hemorrhage (due to hemorrhagic infarct or ruptured myotic aneurysm).

Manifestation Related to Predisposing Factor

- **IV drug users** have involvement of tricuspid valve which is manifested by
  - Faint murmur
  - **Cough**
  - **Pleuritic chest pain**

  - **Pyopneumothorax**
  - **Nodular pulmonary infiltrates**.
- **Transvenous pacemaker/defibrillator** lead associated SABE may have overt or cryptic symptoms and signs and are marked by comorbid illness results in **fever, minimal murmur, pulmonary symptoms** due to septic emboli.
- **Prosthetic valve endocarditis**—Those who have **early onset** (within 60 days)—they lack in peripheral manifestation. Typical symptoms are marked by comorbidity associated with surgery. **Late onset** features are paravalvular infection causing valvular dehiscence, regurgitant murmur, heart block and CCF.

INVESTIGATION OF INFECTIVE ENDOCARDITIS

- **Blood culture**—Reveals typical microorganism for infective endocarditis from
  - Two separate blood cultures drawn 12 hours apart.
  - All of the three blood cultures.
  - Majority of four.
  - More positive blood cultures with the first and the last drawn at least 1 hour apart.

  Causes of Negative Blood Culture
  - Prior antibiotic exposure.
  - Pyridoxal requiring streptococci (abiotropic streptococci).
  - HACEK group of organism or when endocarditis is caused by *Bartonella quintana* or *henselae* or *Tropheryma whipplei*—Cause indolent culture negative afebrile endocarditis.
- **Echocardiography**—
  - TEE (transesophageal echo)—If negative almost exclude endocarditis but may have to be repeated within 7–10 days with optimal multiplanner technique.
  - TTE (transthoracic echo)—Less informative.
- **Cardiac catheter and coronary angio**—In older individuals who are to undergo surgery.
- **Laboratory investigations**—
  - **Complete blood count** for anemia (present in 90%), leukocytosis (present in 30%).
  - **ESR**—Elevated in more than 90% cases.
  - **Rheumatoid factor** present in 50% patient.
  - Circulating **immune complex** detected in (65–100%) patients.
  - **Complement**—Decreased (in 5–40%) patients.
  - C-reactive protein (CRP)—Increased.
  - Urine RE—Microscopic hematuria present in (30–50%).

Diagnosis

Duke's criteria (for diagnosis of infective endocarditis).

Major criteria

- **Positive blood culture**
- **Evidence of endocardial involvement**
  - By transesophageal echocardiography
  - Clinical—New valvular regurgitation murmur.

Minor criteria

- **Predisposing factor**
  - Previous heart disease (congenital or MR)
  - IV drug abusers.
- **Fever >100.4°F**
- **Vascular phenomenon**
  - Major arterial embolization
  - Septic pulmonary infarction
  - Mycotic aneurysm
  - Intracerebral hemorrhage
  - Conjunctival hemorrhage
  - Janeway lesion.
- **Immunological phenomenon**
  - Osler's node
  - Roth's spot
  - Glomerulonephritis
  - Positive rheumatoid factor.
- **Microbiological evidence** of positive blood culture not meeting major criteria.
  - Presence of 2 major or 1 major and 3 minor or 5 minor criteria allows a clinical diagnosis of definitive endocarditis.
  - Presence of 1 major and 1 minor or 3 minor criteria indicates possible endocardits.

Treatment

Definitive treatment

- **Streptococci**
  - *Penicillin susceptible (any one of the followings)*—
    - Penicillin G 2–3 MU IV 4 hourly for 4 weeks.
    - Penicillin G 2–3 MU IV 4 hourly for 2 weeks and gentamicin 3 mg/kg IV od for 2 weeks.
    - Ceftriaxone 2 g IV od for 4 weeks.
  - *Relatively penicillin resistant streptococci*
    - Penicillin G 4 MU IV 4 hourly for 4 weeks and gentamicin 1 mg/kg IV tds for 2 weeks.
    - Vancomycin 15 mg/kg IV bd for 4 weeks.
  - *Total penicillin-resistant streptococci or Abiotropic species*
    - Penicillin G 4 MU IV 4 hourly and gentamicin 1 mg/kg IV tds → Both for 6 weeks.
    - Vancomycin → 15 mg/kg IV bd over 1 hour for 4 weeks.
- **Enterococci**
  - Penicillin 4 MU IV 4 hourly and gentamicin 1 mg/kg IV tds → Both for 4–6 weeks.
    Or

  - Ampicillin 2 g IV 4 hourly and gentamicin 1 mg/kg IV tds) → Both for 6 weeks.
    Or
  - Vancomycin 15 mg/kg IV bd and gentamicin 1 mg/kg IV tds → Both for 4–6 weeks.
- **Staphylococcus—**
  - Methicillin susceptible (native valve) (any one)—Nafcillin/oxacillin—2 g IV 4 hourly for 4–6 weeks.
    Or
  - Cefazolin 2 g IV tds for 4–6 weeks.
    Or
  - Vancomycin 15 mg/kg IV bd for 4–6 weeks.
  - Methicillin resistant staph. (native valve)
  - Vancomycin 15 mg/kg IV bd for 4–6 weeks.
  - Methicillin susceptible *Staph.* (prosthetic valve)—
  - Nafcillin/oxacillin 2 g IV 4 hourly for 6–8 weeks. and gentamicin 1 mg/kg IV 8 hourly for 2 weeks and rifampin 300 mg tds po for 6–8 weeks.
  - Methicillin-resistant Staph. (prosthetic valve)—Vancomycin 15 mg/kg IV bd for 6–8 weeks and gentamicin 1 mg/kg IV 8 hourly for 2 weeks and rifampicin 300 mg tds po for 6–8 weeks.
- HACEK Group (any one)
  - Caftrioxone 2 g IV od for 4 weeks.
    Or
  - Ampicillin 2 gm IV 6 hourly and salbactum 1 G IV 6 hourly → Both for 4 weeks.

Preventive treatment

- **Oral cavity, esophagus and respiratory tract procedure**—
  - *Patient nonallergic to penicillin (any one of the following)—*
    - Amoxycillin—3 g PO 1 hour before the procedure.
      Or
    - Ampicillin—2 g IV 1 hour before the procedure.
  - *Patient allergic to penicillin (any one of the following)—*
    - Clarithromycin (500 mg PO 1 hour before the procedure).
      Or
    - Cephalexin/cephadroxyl (2 g PO 1 hour before the procedure).
      Or
    - Clindamycin (600 mg PO 1 hour before the procedure)/clindamycin 600 mg IM/IV 1 hour before the procedure.
    - * Patient unable to take oral medication—Cephazolin (1 g IV ½ hour before the procedure).
- **Genitourinary and GI tract procedures**—
  - *High-risk patients*—To be given ½ hour before the procedure.
    - Patient nonallergic to penicillin— Ampicillin (2 g IV) and gentamicin (1.5 mg/kg IV).
    - Patient allergic to penicillin— Vancomycin (1 g IV) and gentamicin (1.5 mg/kg IV).
  - *Moderate risk patients—*
    - **Patient nonallergic to penicillin**— Ampicillin (2 g IV ½ hour before the procedure).
      Or
    - Amoxycillin (2 g PO 1 hour before the procedure).
    - **Patient allergic to penicillin**— Vancomycin (1 g IV—infused over 1–2 hour and completed within ½ hour of the procedure).

INDICATIONS FOR SURGERY

Relative Indication

- Moderate to severe CCF due to valvular dysfunction.
- Unstable/obstructed orifice of prosthetic valve.
- Uncontrolled infection despite optimal antibiotic therapy.
- Endocarditis caused by brucella, fungus, pseudomonas.
- Prosthetic valve endocarditis (PVE) caused by *Staph. aureus.*
- Relapse of PVE after optimal therapy.
- Fistula formation to the pericardial sac.

Absolute Indication

- Perivalvular extension of infection.
- Myocardial abscess.
- Intracardiac fistula.
- Poorly responsive *Staphylococcus aureus* in native valve endocarditis (NVE) (mitral/aortic).
- Relapse of NVE after optimal antibiotic therapy.
- Large (>10 mm) hypermobile vegetation.
- Endocarditis caused by resistant enterococci or gram-negative bacilli.

Chapter 4

Valvular Heart Disease

MITRAL STENOSIS

Mitral stenosis (MS) is the most common complication of acute rheumatic fever. Female : Male ratio 2:1.

- **Mitral valve apparatus is composed of**
  - Valve leaflets.
  - Valve annulus.
  - Chordae tendinae.
  - Papillary muscles.
  - Myocardium to which the papillary muscles are attached.

All components of mitral valve may be involved in rheumatic process.

ETIOLOGY OF MITRAL STENOSIS

Major Causes

- **Rheumatic fever** (predominant cause 98%)
  40% of all RHD have pure MS
  40% of all RHD have MS with MR
  Rest are associated with other valvular abnormalities.
- **Congenital** (mitral valve stenosis and cor triatriatum).
- **Rare causes**
  - Senile calcification of valve annulus.
  - SLE.
  - Rheumatoid arthritis.
  - Infective endocarditis—Ball-valve thrombus.
  - Associated with ASD in **Lutembacher syndrome**.
  - Malignant carcinoid.
  - Mucopolysaccharidosis of Hunter-Hurler phenotype.
  - Amyloid, Fabry disease and Whipple's disease.
  - Methyserzide therapy.
  - Congenital diaphargm.
  - Cor triatriatum.
  - Left atrial myxoma.

PATHOLOGY OF MITRAL STENOSIS

Fibrosis resulting from acute rheumatic fever causes fusion of mitral valve apparatus over 2–12 years time:

- **Commissural fusion** (30%)
- **Cuspal fusion** (15%)
- **Chordal fusion** (10%)
- **Rest are combined**.
  - *Commissural*—Valve cusp fuse at their edges.
  - *Cuspal*—Fibrous obliteration, revascularization, thickening and rigidity of cusp.
  - *Chordal*—Fusion, thickening and shortening of the structures.

All these changes lead to typical funnel-shaped appearance. Shaped like fish mouth with calcium deposition over the leaflets and ring.

Progressive thickening, fibrosis, and calcification may be due to—

- Smouldering rheumatic activity or
- Constant trauma by turbulant flow initiated by deformed valve leads to progressive thickening fibrosis and calcification of valve apparatus.

PATHOPHYSIOLOGIC COURSE OF MITRAL STENOSIS

Latent period is at least a decade or more from acute rheumatic fever to develop severe MS. Symptoms commonly commence at 3rd and 4th decade.

In tropics and underdeveloped area, disease progresses very rapidly and present in early adolescent.

Once a patient of MS become symptomatic seriously the disease progresses continuously to death within 2–5 years.

GRADING OF MITRAL STENOSIS

Normal cross-sectional area of valve orifice 4–6 cm^2

- **Mild MS** have valve orifice = <2 cm^2
- **Moderately severe MS** have valve orifice ≅ 1.0–1.5 cm^2
- **Critical MS** valve orifice – <1 cm^2.

PATHOPHYSIOLOGY OF MITRAL STENOSIS

- In case of mild MS, the blood can flow from LA to LV only if propelled by abnormally elevated LA to LV pressure gradient (hemodynamic hallmark of MS).
- In critical MS, the LA pressure is approximately 25 mmHg to maintain normal COP (cardiac output).
- Elevated LA pressure leads to increased pulmonary venous pressure resulting in increased pulmonary

capillary wedge pressure which ultimately results in decreased compliance of lung and exertional dyspnea.

Combination of mitral valve disease and atrial inflammation secondary to RHD leads to:

- LA dilation.
- Fibrosis of LA wall.
- Disorganization of LA muscle bundle.
- Entry of atrial muscle sleeve into the opening of pulmonary vein.

All these factors lead to:

- Disparity in conduction velocity.
- In homogenous refractory period which ultimately leads to **atrial fibrillation** resulting either from ectopic focus or from reentry.

CAUSES OF PULMONARY HYPERTENSION IN MITRAL STENOSIS

- Passive backward transmisston of LA pressure.
- Reflex pulmonary arterial constriction (reactive pulmonary hypertension).
- Interstitial edema surrounding pulmonary vascular bed.
- Organic obliterative changes in pulmonary vasculature. Severe pulmonary hypertension results in pulmonic regurgitation, RV enlargement secondary TR and right heart failure.

CLINICAL FEATURES OF MITRAL STENOSIS

History

Most patients remain asymptomatic when valvular obstruction remains mild or in case of moderate obstruction with slight increase of LA–LV pressure gradient.

Principal Symptoms

- Dyspnea—
  - It is due to reduced lung compliance.
  - Patients with critical obstruction to left atrial emptying are NYHA class-III dyspneic and generally have orthopnea and at risk of developing Frank pulmonary edema precipitated by any condition which will increase the flow across the AV valve (exercise, emotional stress, respiratory infection, atrial fibrillation, tachyarrhythmia, pregnancy).
- **Cough and wheeze** —It accompanies dyspnea.
- **Hemoptysis**—It is due to
  - *Rupture of pulmonary* **bronchial venous connection** secondary to pulmonary venous hypertension.
  - *Blood-stained sputum* complicating chronic bronchitis, bronchopneumonia, and lobar pneumonia.
  - *Pinkish frothy sputum* characteristic of pulmonary edema due to rupture of alveolar capillary when left atrial failure develop.
  - *Pulmonary infarction* from pulmonary embolism is a late complication of MS associated with leg veins thrombosis.
  - *Anticoagulation overdose*.
- **Chest pain**—
  - 15% of MS patients have chest pain indistinguishable from angina.
  - Causes of chest pain—
    - Right ventricular hypertension
    - Coincidental coronary atherosclerosis
    - Coronary arterial embolization.
- **Thromboembolism**—Thrombus formation occurs in left atrial appendage
  - 10–20% of MS patients suffer from systemic thromboembolism with atrial fibrillation.
  - 10–15% of thromboembolism patients die and responsible for 25% of all fatalities in MS.

  Precipitating factor of thromboembolisms
  - Atrial fibrillation
  - Decrease COP
  - Increase age
  - Underlying infective endocarditis.

  Site of embolism—
  - Cerebral.
  - Coronary.
  - Sudden death may be caused by obstruction of mitral orifice outlet by large pedunculated thrombus.
- **Infective endocarditis**—Rare in isolated MS.
  - More common in milder form of MS and MR than in severe MS.
- **Other symptoms**
  - *Compression of recurrent laryngeal nerve* causing hoarseness of voice by dialated LA, pulmonary artery and tracheobroncheal lymph node known as Ortner's syndrome.
  - *Features of RVF—*
    - Pulsatile neck veins
    - Hepatomegaly
    - Edema
    - Ascites
    - Hydrothorax (in extreme case).

Signs

- **Mitral facies**
  - Pinkish pimple patches on the cheeks.
  - Differential diagnosis—Cushing, thyrotoxicosis, SLE and alcoholism.
- **Arterial pulse**
  - Low/normal volume (low volume pulse indicates severe MS) may be irregular due to associated atrial fibrillation.
- **JVP**
  - Prominent a-wave in patient with sinus rhythm.

- In atrial fibrilation → a wave disappears only one crest, i.e. prominent V or CV pattern when associated with TR.

- **Apex**—
  - Inconspicuous LV.
  - Tapping S_1 suggestive of still pliable anterior leaflets.
  - Apex may be of RV type in severe RVH.
  - Diastolic thrill at the apex (better palpable with the patient in left lateral recumbant posture).
- **Palpable P_2/diastolic shock over left 2nd ICS**.
- **RV lift on left parasternal region** also suggestive of RVH/left atrial enlargement.
- **Auscultation**—
  - *S_1*—Generally short, sharp, accentuated due to fibrosis of cusp and incomplete filling of LV.
  - *Loud P_2* — Loud P_2 with closely split S_2 due to reduced compliance of pulmonary vascular bed which shortens the hangout time interval of pulmonary valve.

  Finally S_2 becomes single and accentuated.
  - *Other signs of pulmonary hypertension*—
    - Nonvalvular pulmonary ejection sound (click)
    - Systolic murmur of TR
    - Graham Steell murmur of PR
    - S4 originating from RV.
  - *Diastolic murmur*—
    - ***It is a low pitch middiastolic rumbling murmur with a presystolic accentuation, commensing immediately after OS. Best heard at the apex with the bell of stethoscope, patient in left lateral position and the breath held at the end of expiration provided the patient is in sinus rhythm.*** If atrial fibrillation is present with MS, the auscultatory finding of MS is ***middiastolic rumbling murmur with variable intensity 1st heart sound. Presystolic accentuation of the murmur will be absent.***
    - Murmur is accentuated by mild exercise or in any condition which increases the transmitral valve pressure gradient.
    - ***The duration, and not the intensity of the murmur is a guide to the severity of MS.***
    - In mild MS middiastolic and late diastolic/ presystolic component of murmur are not continuous. There may be a gap in between mid and late diastolic murmur.
    - In severe MS, the murmur is hollow diastolic.
  - *Opening snap (OS)*
    - Mechanism of production of OS—It is due to sudden tensing of mitral valve leaflets after the valve cusp has completes its opening excursion. During downward depression of mitral cusp from upward position to downward position at the beginning of ventricular diastole.
    - Most readily audible at expiration at or medial to cardiac apex following A_2 with the diaphragm of the stethoscope.
  - **OS is indicative of**
    - MS is organic
    - Significant MS.
  - **Loud OS signifies**
    - High LA–LV pressure gradient.
    - Valve cusp are still pliable and not calcified.
    - Severe AR, MR, SABE, AF and atrial failure are absent.
    - MS is readily amenable to surgery.
  - **Differential diagnosis of middiastolic murmur of MS**
    - Carey Coombs murmur of acute rheumatic fever.
    - Austin Flint murmur of AR.
    - Flow murmur of severe MR, VSD and PDA.
    - Left atrial myxema.
    - Diastolic flow murmur through tricuspid valve in ASD.

Severity of MS is indicated by
a. Short A_2–OS gap
b. Long duration of delayed diastolic murmur

  - Dynamic auscultation—Sudden standing and resultant reduction of venous return lower LA pressure and widen the A_2–OS interval. This is useful in distinguishing an A_2–OS combination from a split S_2 which narrows on standing.

Investigations

- **ECG**—Changes in MS are
  - **Evidence of LA enlargement in lead-II, as wide notched P-wave (P. mitrale)**.
  - In lead-V_1 → **Biphasic** P-wave with >1 small square duration and deapth.
  - Features of RVH in V_1.
- **X-ray**—Evidence of MS.
  - **LA enlargement** as a double contour at the right border of heart (specially if associated with MR) and prominent LA appandages at the left border.
  - **Enlargement of pulmonary artery** appears as fullness of plumonary bay at the left border in PA view.
  - **LA enlargement** is also evident by C-shaped indentation over barium swallow esophagus in left lateral view.
  - **RVH** is demonstrated by
    - Apex is much above the diaphragm.
    - Diminution of retrosternal space in left lateral view with slight increase in transverse diameter of heart which is boot-shaped due to upturn apex.

Peasant's wooden boot with upturn toes—Coeren-saboot appearance of cardiac silhouette.
- **Karley's B-line**
  - Dense short horizontal line commensing from periphery at the costophrenic angle due to thickened intralobular septa.
- **Karley's A line—**Straight dense line about 4 cm in length running towards the hilum from periphery (in severe long-standing mitral stenosis).
- Evidence of **pulmonary hemosiderosis**.
- Evidence of **pulmonary edema (rarely)**.
- Bat's wing-shaped opacity spreading from hilum.
- Evidence of **parenchymal calcification**.
- Evidence of **mitral valve calcification** (retrosternal location at the level of 4th ICS).
- Deviation of left main and upper lobe bronchus.
- Prominent upper lobe pulmonary vein.
- Hilar arterial prominence.
- Peripheral prooning of blood vessel.

- **Echocardiography**
  - *M-Mode echo shows*
    - Thickened, calcified and stenotic mitral valve
    - LA enlargement
    - Restricted valve casp movement.
  - *2D echo shows*
    - LA thrombus.
    - Restricted motion and doming of valve leaflets.
    - Valve orifice size measurement.
    - Detection of valve—calcification and thickening of subvalvular apparatus with fusion and retraction of chordae.
    - LV contractility.
  - *TEE* gives superior image of mitral valve and LA thrombus.
  - *Doppler* study shows—Functional status of LA, LV, RV can be assessed and quantification of the severity of MS.
  - Estimate pulmonary artery wedge pressure.
  - Assessment of any other valve anomaly.

CARDIAC CATHETER

To rule out CAD in patient with chest pain.

Management

Medical therapy

1. **Penicillin prophylaxis** for acute rheumatic fever and infective endocarditis.
2. **Restriction of fluid and Na^+ intake**.
3. **Oral loop diuretics** (frusemide with potassium-sparing diuretic).
4. **Digitalis in patient with AF**—To slow the ventricular rate and also in patient with right ventricular failure. β-blockers or non-DHP CCB can also be used.
5. **Warfarin** for 1 year in patient with systemic/pulmonary embolization.
6. **Medical/electrical cardioversion** of AF should be attempted if AF is of recent origin and LA is not husely dialated.

Surgical management

Indications of surgery in MS

1. **Symptomatic patient** with moderate to severe MS (valve size < 1.0 cm^2/m^2 body surface or 1.5 cm^2).
2. **Mild MS** *but symptomatic* with ordinary activity.
3. **Complication**—Development of embolism.
4. **Patient's symptom cannot be controlled** only by medical therapy.
5. **Pregnancy with MS** whose previous pregnancy was symptomatic.
6. **PHTN**—Pulmonary arterial SBP >60 mm after exercise and >50 mm at rest.
   Mean pulmonary capillary wedge presure >25 mm.
   Valvotomy is not recommended for entirely asymptomatic patient or when mitral valve orifice is >1.5 cm^2.

Operative procedure

- **Mitral valvotomy**—Unless contraindicated should be done in all symptomatic patients with isolated MS of orifice size is <1.5 cm^2.
  Two techniques
  - **Percutaneous mitral balloon valvotomy (PMBV)**—Short and long-term results are similar to those of surgical valvotomy.
  - **Surgical valvotomy**—Opening of valve commissure, loosening of any subvalvular fusion of papillary muscles and chordae with removal of deposition of calcium and left atrial thrombus.
    Mortality is about 2%.
    About half of the patients after surgical mitrals valvotomy require reoperation by 10 years.
- **Mitral valve replacement (MVR)**—Is required
  - In MS (orifice <1 cm^2).
  - NYHA class-III symptomatic despite optimal medical therapy.
  - When MS is associated with significant MR or whose valve in severly disorganized by PMBV or prior operative manipulation should have valve replacement.
    Operative mortality is 6% and 10 years survival is about 70%.

AORTIC REGURGITATION

AORTIC REGURGITATION CAUSED BY

1. Primary aortic valve disease
2. Aortic root dilation.

Causes of Aortic Valve Disease

- Rheumatic heart disease.
  - Puckering of valve cusp due to infiltration of cusp by fibrous tissue.
  - Commissural fusion prevent proper apposition.
- Calcific AS in elderly is the most common cause of AS with AR.
- Infective endocarditis
  - Destruction or perforation of valve leaflet.
  - Vegetation interfering with proper apposition of cusp.
- Iatrogenic
  - Catheterization.
  - Percutaneous aortic balloon valvotomy.
  - Radiofrequency catheter ablation.
- Bicuspid aortic valve.
- Large VSD.
- Membraneous subaortic stenosis.
- Myxomatous degeneration of aortic valve.
- Structural deterioration of bioprosthetic valve.

Causes of Aortic Root Disease

- Degenerative aortic dilation (age-related)
- Ankylosing spondylitis, RA, SLE, Crohn's disease
- Psoriatic and other seronegative spondyloarthritis
- Systemic HTN
- Dissecting aortic aneurysm
- Cystic medial necrosis (Marfan)
- Aortic dilation secondary to bicuspid valve
- Osteogenesis imperfecta
- Syphilitic aortitis
- Appetite-suppressant drug.

PATHOPHYSIOLOGY OF CHRONIC AORTIC REGURGITATION

- In chronic AR, blood is ejected into comparatively high pressure aorta which results in left ventricular hypertrophy along with dilation due to increase EDV.
- In compensated AR there is sufficient wall thickening so that the ratio of wall thickness : cavity radius remains normal.
- In long-standing chronic AR with increasing severity over time wall thickening fails to keep peace with the hemodynamic load and the end systolic wall stress rises. At this point after load mismatches results in declining of systolic function and EF falls.
- Left ventricular mass is greatly increased often greater than 1 kg. Severe chronic AR has the largest EDV of all heart diseases.
- Regurgitant flow may exceed 20 L/min in severe cases, so that LV output reaches about 25 L/min.
- LV function—Due to decompensation of LV function and reduction of LV compliance, LV end diastolic pressure rises which leads to rising LA, PCWP, RV and RA pressure which at first occurs during exercise later at rest. It leads to fall in EF causing pulmonary congestion.
- Myocardial ischemia is due to
  - Increase in LV wall tension.
  - Increase in LV mass.
  - Decrease in coronary blood flow in diastole as DBP is less than normal.

Clinical Features

History

Patients remain asymptomatic when patients are in compensated state but LV gradually enlarges.

Most patients develop symptoms in 4th or 5th decade only after considerable cardiomegaly and myocardial dysfunction have developed.

Principal symptoms

- Dyspnea—On exertion.
- Orthopnea.
- PND.
- Palpitation—Usually during exertion and lying down posture.
- Pain chest—Due to pounding of heart against chest wall.

Out of these symptoms, dyspnea develops early and rest are the late features which are more prominent with stress, exertion and tachycardia.

These complaints are present for many years before the symptoms of overt LVF develops.

Past history

- Past history of rheumatic fever, SABE may be there.
- Features of RA, SLE, ankylosing spondylitis may be present.

Peripheral signs of AS

The following peripheral signs are seen in chronic AR due to increased pulse pressure—

- **Lighthouse sign**—Alternate blanching and flushing of forehead.
- **Ladolfi sign**—Change in pupil size with cardiac pulsation.
- **Müller sign**—Pulsation of uvula.
- **De Musset's sign**—Head nodding with carotid pulsation.
- **Corrigan's sign**—Dancing carotid in neck.
- **Suprasternal pulsation**—Visible.
- **Locomotor brachialis**—Visible brachial artery pulsation.
- **Bisferiens pulse**—More commonly palpable in brachial and femoral artery than carotid artery. In this condition

percussion wave and dicotic wave are separately palpable also known as "double kicking pulse".
- **Wide pulse pressure**—Korotkoff 's sound often persists up to zero even though intraarterial pressure rarely falls below 30 mmHg.
- **Water hammer pulse (high volume collapsing pulse)**—Pulse pressure greater than 60 mm Hg. Diastolic blood pressure usually less than 60 mm Hg.
- **Prominent digital arterial pulsation**.
- **Quincke's sign**—Visible capillary pulsation at finger nail and lip.
- **Rosenbach sign**—Pulsation of liver.
- **Gerhardt sign**—Pulsation of spleen.
- **Traube's sign**—Also known as pistol shot sound—A booming systolic and diastolic sound heard over femoral artery.
- **Duroziez's sign**—Systolic murmur heard over the femoral artery when it is compressed proximally and a diastolic murmur when it is compressed distally.
- **Hill sign**—Popliteal SBP 60 mm or more higher than brachial SBP.

Palpation

- **Apex heaving LV type** (forceful and ill-sustained) appear with features of LV enlargement.
- **Systolic retraction** over left parasternal region.
- **Systolic thrill** at the base of the heart (aortic area) which is also palpable at suprasternal notch or over carotid artery called '**carotid shudder**' (due to increased flow through carotid artery in systole).

Auscultation

- **Soft S_1**.
- **S_2 may be absent or single or exhibit narrow paradoxical splitting**.
- **A_2 is soft or absent in valvular AR but A_2** may be normal or rarely may be accentuated in aortic root disease.
- **P_2 may be obscured** by early diastolic murmur.
- **Systolic ejection sound** (click) may be present due to abrupt distension of aorta by augmented stroke volume.
- **S_3 gallop** reflects increased EDV of left ventricle or may be a feature of LV dysfunction who are candidate for surgical treatment.
- **S_4 may be audible in late stage of AR with severe LV dysfunction**.
- **A high pitch decrescendo, blowing early diastolic murmur starting immediately after A_2, best heard at left 3rd ICS parasternal region (neoaortic area) with radiation towards apex with the diaphragm of stethoscope and the patient in sitting posture leaning forward with the breath held at the end of expiration (when the AR is due to primary valve defect)**.
- **When the AR is due to aortic root dilation the same murmur radiates along the right sternal border**.
- The murmur may be holodiastolic and may have a rough quality in severe AR.
- **When murmur have musical quality (cooing dove murmur)** it indicates eversion or perforation of aortic cusp.
- **The severity of regurgitation correlates better with the duration rather than intensity of the murmur. The greater the severity of the AR, shorter the length of the murmur**. In long-standing severe AR the late diastolic component is abolished *due to equilibration of LV pressure and aortic pressure*.
- **An enjection systolic flow murmur radiating to carotid** (but more high pitched and less rasping than murmur of organic AS) **may be heard associated with a systolic thrill due to increased flow through aortic valve in systole**.
- **A functional mid and late diastolic apical rumble known 'Austin Flint murmur'** may be heard in severe AR in presence of normal mitral valve due to impinging of aortic reflux jet on the aortic leaflet of mitral valve (absence of OS and loudness differentiate it from organic MS).
- **Dynamic auscultation**—Murmur of AR may be accentuated by increasing the afterload as in equating posture, with leaning forward and isometric exercise.

Laboratory Investigations

- **ECG**
  - Left axis deviation.
  - LVH.
  - LV strain pattern—ST depression with upright T or more commonly inverted T with down-slopping ST segment.
  - Q wave in I, AVL, V_3–V_6 with small R-wave (precordial) leads due to LV diastolic overload.
  - ECG is not a accurate predictor of cardiac weight.
- **Chest X-ray**
  - In acute AR—Minimum cardiac enlargement.
  - In chronic AR—Marked cardiac enlargement with downward and outward shifting of apex.
    Apex may be displaced below diaphragm.
    Left lateral view shows encroachment in the posterior mediastinum by LV.
  - Calcification of aortic valve—Specially in com- bined AS with AR.
  - Linear calcification in the wall of aorta — Specially in syphilitic aortitis and degenerative aortic diseases.
  - Dilation of ascending aorta (unfolding of aortic arch)—Specially in aortic root disease.

Echocardiography

- **M-Mode echo identify**
  - Cause of AR
  - Thickening of valve cusp

  - Presence of congenital abnormality like bicuspid valve
  - Presence of prolapse of the valve cusp
  - Presence of vegetation and dilation of aortic root.
- **2-D echo quantify**
  - LV–EDV
  - LV–ESV
  - Ejection fraction
  - Venticular mass.
- **TEE** (transesophageal echocardiography) gives more detailed information about
  - LV size
  - Regurgitant blood volume
  - Presence of vegetation.
- **High frequency fluttering of anterior leaflet of mitral valve due to impingement of regurgitant blood even in mild AR is an important echo sign** but is not seen in rheumatic involvement of mitral valve as the valve is rigid.
- **Doppler**—Most sensitive and accurate noninvasive technique for detecting mild AR, regurgitant flow, orifice size, progression of regurgitation and its effect on ventricle, ejection fraction and timing of surgical intervention.

Radionucleotide imaging is necessary for

Accurate noninvasive assessment of severity of AR by allowing determination of regurgitant fraction and of the LV/RV stroke volume ratio. Usually radionucleotide imaging is only done when—

- Echo resolution is suboptimal
- Discrepancy between clinical and echo finding.

MRI

- Accurate measurement of the regurgitant volume and regurgitant orifice size.
- Most accurate noninvasive technique for detecting LV mass and LV end diastolic volume.

Management

- **Medical therapy**
  - All patients with AR of any severity should receive prophylaxis for infective endocarditis.
  - Asymptomatic patients with mild to moderate AR and normal or minimal increase in cardiac size require no therapy but should be followed up clinically and by echo every 12–24 months.
  - Patients with mild to moderate AR and patients with severe AR but normal EF and mild ventricular dialation may engage in aerobic exercise.
  - Asymptomatic patients with chronic severe AR and normal LV function should be examined 6 monthly.
  - Patients with severe AR having limitation of cardiac reserve and evidence of decreased LV function should not engage in vigorous exercise.
  - Systemic arterial diastolic hypertension, if present, should be treated (because it increases the regurgitant flow) with nifedipine and ACEI. (β-blocker should be used with great caution).
  - Atrial fibrillation and bradyarrhythmia are poorly tolerated and should be treated if possible.
  - Vasodilator therapy—Chronic AR with significant volume overload and increased EDV should be considered for vasodilator therapy with hydralazine, nifedipine or ACE.
    Chronic medical therapy may be necessary for the patient who refuses surgery or considered inoperable due to serious comorbid condition. Chronic medical therapy consists of agressive management of heart failure and vasodilator therapy with
    - Diuretic
    - Salt restriction
    - ACEI or nifedipine (vasodilator).
    - Digoxin.
- **Surgical therapy**—Since severe symptoms (NYHA class III or IV) and left ventricular dysfunction with an ejection fraction less than 50% are independent risk factor for poor postoperative survival, surgery should be carried out in NYHA class-II patient before severe left ventricular dysfunction has developed.
  - *Indications for surgery*
    - Symptomatic chronic severe AR
    - Poor exercise tolerance
    - EF less than 50%
    - LV EDD more than 70 mm
    - LV ESD more than 50 mm.
  - *Operative procedure*
    - Annuloplasty for primary aortic root disease. Two procedures
      - » Encircling suture of the aorta
      - » Subcommissural annuloplasty.
    - Excision of a part of aorta with replacement by a graft or prosthetic valve in case of aneurysmal dilation of aorta.
    - AVR (aortic valve replacement) in severe AR, if it is due to primary valve disease.

AORTIC STENOSIS

Types of Aortic Stenosis

There are three types of aortic stenosis present depending on to anatomical site

- **Valvular**
  - Congenital
  - Rheumatic
  - Degenerative.

- **Supravalvular**
  - Hourglass constriction of aorta
  - Membranous—Diaphragm in the aorta.
- **Subvalvular**.

Valvular

- **Congenital**
  - *Unicuspid*—Aortic valve produces severe obstruction in infancy.
  - *Bicuspid aortic valve* have abnormal architecture causes turbulent flow which traumatises the valve cusp resulting in fibrosis and calcification.
    It may be stenotic due to commissural fusion.
  - Tricuspid valve cusps are unequal in size with commissural fusion.
- **Acquired**
  - Rheumatic valvular AS usually with mitral valve involvement
    - It is mostly associated with AR or mitral valve disease.
  - Degenerative—Leading cause of AS in developed countries.
    - Two types
      - » Atherosclerotic
      - » Calcific
      - » Rare causes are
        - ▫ Rheumatoid involvement of cusp
        - ▫ Ochronosis with alcaptonuria.

Supravalvular

- Hourglass constriction (most common)—It is associated with marked thickening and disorganization of tunica media of aorta produce a constricting annular ridge at the superior margin of the sinus of Valsalva.
- Membranous type—Result of fibrous or fibromuscular semicircular diaphragm with a small central opening stretched across the lumen of the aorta.

Subvalvular

- Static obstruction—due to fibromuscular band.
- Dynamic obstruction—HOCM (hypertrophic obstructive cardiomyopathy).

Pathophysiology of Aortic Stenosis

In adult obstruction usually develops and progresses gradually.

This form of chronic progressive AS is well-compensated by LVH maintaining stroke volume for many years.

Late in the course of AS, left ventricular aortic pressure gradient, stroke volume, COP all decline resulting in PHTN and RVH.

LVEDV remains normal until late but LV mass increases due to concentric hypertrophy of left ventricle.

- Mild stenosis : Valve orifice size—1.5–2 cm^2.
- Moderate stenosis : Valve orifice size—1–1.5 cm^2.
- Severe stenosis : Valve orifice size—less than 1 cm^2.
- Critical stenosis : Valve orifice size—less than 0.8 cm^2.

Cardiac output is often within normal limit in most of the patients of severe AS in resting condition but often fails to rise during exercises.

Clinical Features of Aortic Stenosis

History

There is a long latent period for onset of symptoms. Manifestations most commonly commence at the 5th decade in congenital and rheumatic AS whereas 7th–9th decade in degenerative AS.

Cardinal manifestations are—

- **Angina** (seen in 66% of critical AS) is due to—
  - Decreased oxygen supply—
    - Due to decreased BP
    - Due to increased LVEDP.
  - Increased demand of O_2 due to increased LV mass.
- **Syncope** is due to—
  - Decreased cerebral perfusion, specially during exercise.
  - Malfunction of baroreceptor mechanism.
  - Vasopressor response due to greatly increased LV systolic pressure during exercise.
  - Ventricular fibrillation causing graying out spell or dizziness.
  - Transient AV block.
- **Exertional dyspnea**.
- **Heart failure**.

Dyspnea may be associated with PND and orthopnea, pulmonary edema reflecting varying degree of pulmonary HTN.

Marked fatiguability, debilitation, peripheral cyanosis are not prominent until late stage of the disease.

Survival curve shows that interval from the onset of the symptom to the time of death is approximately—

- 2 years with heart failure
- 3 years with syncope
- 5 years with angina.

Infective endocarditis is more common in younger with mild valvular disease but less common with old people with rock-like calcific aortic stenosis.

Physical Examination

- **Palpation—Outside precordium**
  - **Pulsus parvus et tardus**—Slow and low rise pulse.
  - **Systolic thrill** felt most prominent over carotid producing carotid shudder.
  - **Simultaneous palpation of apex and carotid** reveals a lag in the later.
  - **Pulsus alternans**—Suggests left ventricular dysfunction.

- **Jugular venous pulse**—Prominent a-wave reflecting diminished RV compliance consequent to pulmonary hypertension and hypertrophy of septum.

Due to pulmonary hypertension secondary RVF and TR develop for which 'C V' or 'V' wave may seen in neck venous pulse.

- **Palpation of precordium**
  - **Apex**
    - Usually normal in position but may be shifted down and out which forceful and well-sustained.
    - Systolic thrill best appreciated when patient in upright position leans forward during full expiration. Palpated most readily in 2nd ICS on right side of sternum or suprasternal notch and is frequently transmitted to carotids (carotid shudder).
  - **Features of RVH and RVF**
    - Right parasternal heave
    - Engorged pulsatile neck veins (earliest)
    - Pedal edema
    - Hepatomegaly } Late feature
    - Ascites. }

Auscultation of Aortic Stenosis

- S_1—Normal or soft.
- S_4—Prominent due to vigorous atrial contraction and partially closed mitral valve during presystole.
- **S_2**—
  - S_2 may be single due to inaudibility of A_2.
  - A_2 may be inaudible due to immobility caused by calcification of valve cusps.
  - P_2 is burried in prolonged ejection systolic murmur.
  - Prolongation of LV systole causes overlapping of A_2 with P_2 or there may be reverse splitting.
- **Aortic ejection click**—Due to sudden halting of upward movement of aortic valve—heard 0.06 second after S_1.
- **Ejection systolic murmur of AS is low pitch, rough and grasping in character**—Best heard at the base of the heart on right 2nd ICS close to sternum and breath held at the end of expiration, with the diaphragm of the stethoscope and well-transmitted to the carotids. The high-pitched component may be transmitted to the apex (**Gallavardin's** phenomenon) comes in differential diagnosis of murmur of MR.

  In patient with severe aortic stenosis but with pre serve COP, the murmur is of grade III/IV whereas in severe aortic stenosis with heart failure and low COP the murmur is relatively soft and brief.
- **More severe is the stenosis**.
  - More prolonged is the murmur of AS
  - Peaks later in systole.
- **Dynamic auscultation**—Murmur of valvular AS is augmented by squatting and reduces in intensity during starting of Valsalva maneuver and on standing.

Investigations ofAortic Stenosis

- Doppler echocardiography for diagnosis and assessment of aortic stenosis and LV function every yearly in symptomatic patients and at 2–5 years interval in asymptomatic patients with a mild to moderate AS.
- Cardiac catheterization—When AS is associated with coronary artery disease and when there is discrepancy between the clinical picture and echocardiographic finding.

Management of Aortic Stenosis

- **Medical management**—In patient with severe AS (<1 cm^2).
  - Avoid strenuous physical activity even in asymptomatic stages.
  - Avoid dehydration, low COP and hypovolemia.
  - β-blocker and ACEI are safe in asymptomatic patient used for CAD or HTN.
  - Nitroglycerine may be used for angina.
  - Statin (atorvastatin or rosuvastatin) is beneficial for degenerative calcific AS.
- **Surgical treatment of AS**—(mortality <1%)

  Indications
  - When orifice size is less than 1 cm^2.
  - Symptomatic AS.
  - Aneurysmal dilation of aortic root in moderate AS.
  - When hypotensive response to exercise develops in AS with left ventricular dysfunction.

Valvoplasty can be done in small number of selected patients.

- In children—In noncalcified congenital AS who commonly have bicuspid valve—two types of procedure.
  - Commissural incision under direct vision (mortality less than 1%).
  - Balloon aortic valvoplasty when valve orifice area >0.8 cm^2. The development of regurgitation and restenosis after 10–20 years requires reoperation or valve replacement.
- In adult—Aortic valve replacement (AVR) is recommended.

MITRAL REGURGITATION

Abnormality of any one of the five components of mitral valve apparatus may cause MR. But the major causes of MR are

1. Rheumatic endocarditis
2. Mitral valve prolapse
3. Infective endocarditis
4. Cardiomyopathy
5. Ischemic heart disease.

- **Other rare causes are**
  - Endocardial cushion defect

- Calcification of mitral annulus
- Carcinoid
- Collage vascular disorder
- Trauma.

- **Acute MR**—
  - Papillary muscle rupture (post-MI)
  - Endocarditis
  - Trauma
  - Rupture chordal/flail leaflet (MVP).
- **Chronic MR**—
  - Myxomatous MVP
  - Rheumatic (33%)
  - Endocarditis
  - Annular calcification
  - Congenital
  - HOCM
  - DCM.

Irrespective of cause, severe mitral regurgitation (MR) is most often pro- gressive, since enlargement of LA places tension on the posterior mitral leaflet pulling it away from the mitral orifice, thereby aggravating valvular dysfunction.

Similarly LV dilatation (LVEDD >6 cm) increases the regurgitation which in turn enlarges LA and LV further causing chordal rupture resulting in a vicious cycle hence it is said that, mitral regurgitation begets mitral regurgitation.

PATHOPHYSIOLOGY OF MITRAL REGURGITATION

In MR the volume of the regurgitant blood varies directly with LV systolic pressure and size of the regurgitant orifice. But later it is profoundly influenced by extent of LV dilatation.

- Normally ejection fraction rises in severe MR and in presence of normal LV function. Even a modest reduction in ejection fraction (EF) reflects significant dysfunction.
- V-wave in the LA pressure pulse in usually prominent with rapid Y descent.
- In chronic MR there is often increase in LV compliance so that LV volume rises with little elevation of diastolic pressure. The cardiac output is usually not affected but reduced in seriously symptomatic patient.
- In severe cases as much as 50% of total LV stroke volume regurgitates with each beat. Qualitative and clinically useful estimate of the severity of MR is made by the degree of LA opacification after injection of contrast material in LV or by color Doppler.
- Patient with acute MR usually have normal or reduced LA compliance with marked pulmonary congestion and edema.
- Patient with long-standing chronic severe MR usually have marked increase in LA compliance and are at the opposite end of the spectrum. These patients usually complain of severe fatigue and exhaustion secondary to low COP. AF is invariably present.

CLINICAL FEATURES OF MITRAL REGURGITATION

Symptoms

1. **In chronic severe MR**
   - Fatigue.
   - Exertional dyspnea.
   - Orthopnea.
   - Right-sided heart failure or its other presentation may be found where MR is associated with pulmonary vascular disease or marked PHTN.
2. **In acute severe MR**
   - LV failure with acute pulmonary edema is the common presenting feature.
3. **Physical finding**—
   a. *General examination*
      - BP—Normal.
      - JVP—Prominent a-wave in patient with sinus rhythm and marked PHTN.
      - Prominent v-wave in patient with MR with TR.

   b. *Systemic examination*—
      - Laterally displaced apex.
      - Palpable systolic thrill at the apex in 25% patients.
      - Hyperdynamic apex with brisk systolic impulse.
      - Left parasternal thrust and diastolic knock over pulmonary area due to pulmonary hypertension.

   c. *Auscultation*—
      - Soft S_1 buried (in murmur).
      - Wide splitting of S_2.
      - Low-pitched S_3 due to sudden tensing of papillary muscle, cordae tendinae and valve leaflet.
      - ***Pansystolic blowing murmur of grade 3 or 4 intensity found at the apex radiating to axilla, best heard during expiration with the bell of the stethoscope in case of dysfunction of anterior cusp of mitral valve.***
      - *In case of primary involvement* ***of posterior mitral leaflet, or ruptured chordae the regur- gitant jet strikes LA wall adjacent to aortic root; hence the murmur is transmitted to base of the heart*** *and in these cases it may be confused with murmur of AS.*
      - In MVP the murmur usually commences at late systole after a midsystolic click.
      - A middiastolic rumble over mitral area due to increase in flow across the mitral valve during first rapid filling phase of diastole may be heard. S_4 is audible in patient with acute severe MR who are in sinus rhythm.
      - In case of ruptured cordae the murmur has **cooing dove quality called Seagull murmur**.
      - In case of flail leaflet the murmur may have musical quality.

INVESTIGATIONS OF MITRAL REGURGITATION

1. **Chest X-ray**—Enlargement of LA and LV but later LA enlarges massively and forms double contour on the right border of cardiac silhouette in chest X-ray (PA).
2. **ECG**—Shows features of
   - LA enlargement
   - RA enlargement
   - Atrial fibrillation
   - LV hypertrophy.
3. **Echocardiography**
   - Color flow Doppler is most accurate for diagnosis of MR.
   - 2D echo can identify the etiology.
   - LA is usually enlarged and exhibits increased pulsation.
   - LV may be hyperdynamic.
   - Mitral valve calcification and LV dyskinesia in ischemic MR.
   - Ruptured chordae, flail leaflet in post-AMI mitral regurgitation can easily be detected in echo.
   - Coarse erratic motion of involved leaflet in infective endocarditis can be seen.

TEE (transesophageal echocardiography)—Provides greater detailing.

MANAGEMENT OF MITRAL REGURGITATION

Medical Therapy (Table 4.1)

- Rest.
- Reduced NaCl intake.
- Enhanced NaCl excretion by diuretic.
- Vasodilator (nitrates) increase cardiac output by lowering BP and reducing regurgitant flow.
- Digitalis to slow ventricular rate.

IV GTN or nitroprusside reduces afterload thereby reduces the volume of regurgitant flow in acute severe MR with AMI.

- **ACE inhibitors** in ischemic MR.
- **Anticoagulant** and tight elastic stocking to reduce venous thrombi and pulmonary embolism.
- Prophylaxis for endocarditis should be given.

INDICATIONS OF SURGERY

1. **In severe MR** whose limitations do not allow full time employment or the performance of normal household activities despite optimal medical management.
2. **In asymptomatic MR with progressive LV dysfunction** with LVEF <60% and end systolic cavity dimension on echo >45 mm.
3. **In asymptomatic patient when PHTN or atrial fibrillation are present**.

Procedure

1. **Mitral valve replacement with prosthesis** is indicated where the valves are markedly deformed, shrunken, with calcified leaflet secondary to rheumatic fever.
2. **Mitral valvoplasty or annuloplasty** is indicated in patient with—
   a. Severe annular dilation.
   b. Flail leaflet.
   c. MVP (mitral valve prolapse).
   d. Ruptured chordae.
   e. Infective endocarditis.
      - MVR (mitral valve replacement) carries operative risk ~ 6%.
      - Valvoplasty or annuloplasty caries operative risk ~ 3%.
      - Thromboembolic or hemorrhagic complications occur with mechanical prosthesis requires replacement by bioprosthesis.

Table 4.1: Concise conservative medical therapy for valvular heart disease

		Symptoms control		Long-term therapy
A.	Mitral stenosis	1. β-blocker 2. Non-DHP CCB 3. Digoxin 4. Cardioversion for new onset AF may be tried 5. Diuretic for HF	For rate Control in AF	1. Penicillin prophylaxis for RF 2. Warfarin for AF or thromboembolism
B.	Mitral regurgitation	1. Diuretic for HF 2. Vasodilator therapy for acute MR with nitrate, ACEI 3. Counterpulsating aortic balloon for acute MR (in AMI)		1. Warfarin for AF or thromboembolism 2. Vasodilator for HTN
C.	Aortic stenosis	1. Diuretic for HF		1. Nil
D.	Aortic regurgitation	1. Diuretic and vasodilator, for HF ACEI and nitrate		1. Vasodilator for HTN

Chapter 5

Heart Failure

DEFINITION

Heart failure (HF) is a *pathophysiological condition in which heart is unable to pump adequate amount of blood required by the metabolizing tissue of the body or can do so with elevated ventricular filling pressure.*

CAUSES OF HEART FAILURE

A. Primary factor—
   a. Ischemic heart diseases (responsible for 75% cases)
   b. Hypertensive heart diseases
   c. Cardiomyopathy
   d. Congenital
   e. Valvular.

B. Precipitating factor

Precipitating factor places an additional load on a myocardium which is chronically overburdened. Such a patient usually have a compensated heart failure in normal condition with little cardiac reserve. The additional load imposed by the precipitating factor results in further deterioration of cardiac function and the patient develops overt sign and symptom of heart failure

Factors that precipitate acute heart failure in a case of compensated chronic heart failure

1. Arrhythmia
2. Dietary excess
3. Silent myocardial infarction
4. Accelerated hypertension
5. Discontinuation of heart failure therapy
6. Systemic or pulmonary infections
7. Anemia
8. Medication that worsen heart failure
   a. CCB—Verapamil, diltiazem
   b. β-blocker
   c. NSAID
   d. Antiarrhythmic agent (class-I agent and sotalol)
   e. Anti-TNF antibody
9. Alcohol
10. Pregnancy
11. Acute valvular insufficiency (MR)

STAGES OF HEART FAILURE

- **Stage A**—Patients are at high-risk for developing HF but have no structural disorder or signs and symptoms of the heart failure. Patients with HTN, CAD, DM, cardiotoxins, dyslipidemia are in this group.
- **Stage B**—Patients have a structural disorder of heart but have never developed signs and symptoms of HF. (patients with previous MI, LV diastolic dysfunction, asymptomatic valvular or congenital heart diseases).
- **Stage C**—Patients with past/current symptoms of HF, associated with underlying structural heart diseases. (patients with known structural heart diseases with shortness of breath, fatigue, reduced exercise tolerance).
- **Stage D**—Patients have end-stage heart diseases and require specialized treatments strategy such as mechanical circulatory support, continuous inotropic infusions, cardiac transplantation or hospice care.

  NYHA (New York Heart Association) **functional classification** of dyspnea primarily gauges the severity of symptoms in patients who are in stage C and D heart failure.
  - *NYHA class-I*—Patients with cardiac disease but ordinary physical activity do not cause undue fatigue or dyspnea, palpitation or angina (without limitation of physical activity).
  - *NYHA class-II*—Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest but ordinary physical activity causes fatigue, dyspnea, palpitation and angina.
  - *NYHA class-III*—Patients with cardiac disease have marked limitation of physical activity and less than ordinary, physical activity cause fatigue, dyspnea, palpitation and angina.
  - *NYHA class-IV*—Patients with cardiac disease who are unable to carry out any physical activity without discomfort. Symptoms of heart failure may be present even at rest.

FORMS OF HEART FAILURE

Heart failure is classified in various ways:

- Systolic failure/diastolic failure

- Forward failure/backward failure
- High output failure/low output failure
- Acute failure/chronic failure
- Right-sided failure/left-sided failure.

Systolic Failure Same as Forward Failure

Inability of the ventricle to contract normally and expel sufficient amount of blood.

Causes

IHD, MI and cardiomyopathy.

Clinical features of left ventricular systolic failure

Inadequate COP resulting in weakness, fatigue, exercise in tolerance and other symptoms of hypoperfusion.

Diastolic Failure Same as Backward Failure

The ventricle is unable to relax and/or fill normally and adequately (increase resistance to ventricular filling).

Causes

- Constrictive pericarditis
- Restrictive cardiomyopathy
- Hypertrophic cardiomyopathy
- Cardiac tamponade.

Clinical features of

- *Left ventricular diastolic failure*
  - Orthopnea
  - PND.
- *Right ventricular diastolic failure*
  - Increase jugular venous pressure
  - Pedal edema
  - Congestive hepatomegaly.

High Output Failure

Causes

- Hyperthyroidism
- Arteriovenous fistula
- Anemia
- Pregnancy
- Beriberi
- Paget's disease.
  [Arteriovenous O_2 concentration difference will be below normal (35–50 mL/L)].
- Cardiac output may not recede below the lower limit in normal condition but it will be below the lower limit during exercise.

Low Output Failure

Causes

- Ischemic heart disase, DCM, hypertension and VSD
- Normal COP → 2.5–3.5 L/min/m^2
- At rest—Within normal limit
  At exercise—Fail to increase adequately.

Acute Heart Failure

Sudden fall in cardiac output.

[Sudden fall in systolic blood pressure and sudden decrease in COP lead to **systemic hypotenstion without pedal edema**].

Causes

- Sudden development of large MI.
- Rupture of chordae tendineae.
- Accelerated hypertension (acute left heart failure).
- Massive pulmonary embolism (acute right heart failure).

Chronic Heart Failure

Gradual fall in cardiac output.

Causes

- DCM.
- Multivalvular heart disease that affects slowly due to salt, H_2O retention.
  [Arterial pressure well-maintained with accumulation of water in extravascular space leading to edema].

Right Heart Failure

Causes

- Cor pulmonale.
- Congenital valvular pulmonary stenosis.
- Pulmonary hypertension, secondary to pulmonary emboli.

Clinical features

- Edema, elevated venous pressure and hepatomegaly.

Left Heart Failure

Causes

- MI, cardiomyopathy, hypertension and AS.

Clinical features

- Dyspnea
- Orthopnea

- Pinkish frothy sputum
- Cyanosis
- Basal rales due to pulmonary congestion
- S_3 gallop.

Causes of right heart failure secondary to left heart failure

- Pulmonary hypertension.
- Salt-water retention.
- Muscle bundle composing both the ventricles are continuous.
- Both ventricles share a common wall.
- Biochemical changes that occur in left heart failure involve and impair the function of right ventricle and cause right heart failure.

Backward Failure Same as Diastolic Failure

When the ventricle fails to fill normally.

Causes

- HOCM
- Constrictive pericarditis
- Restrictive cardiomyopathy
- Cardiac tamponade.

Forward Failure Same as Systolic Failure

When the ventricle cannot discharge normally.

Causes

- Myocardial infarction
- AS
- Cardiomyopathy.

In backward failure pressure in atria rises, resulting in increase release of ANP which causes retention of Na^+ and water, leading to transudation of fluid in interstitial space of lung. In forward failure salt-water retention is due to decrease in renal perfusion causing excessive proximal and distal tubular Na^+ and water absorption through activation of RAAS system.

CLINICAL FEATURES OF HEART FAILURE

Symptoms

- **Dyspnea and orthopnea**
  - **Dyspnea**—Severity of dyspnea correlates with the functional NYHA classification. It is due to interstitial pulmonary edema which causes activation of receptor in the lung result in rapid shallow breathing, and increase fatigue of respiratory muscle due to imbalance of O_2 demand and supply to respiratory muscle.
  - **Orthopnea**—Dyspnea in recumbent position. It is a late manifestation of HF than exertional dyspnea due to redistribution of fluid from leg and abdomen to thorax causing increase in pulmonary capillary pressure combined with elevation of diaphragm.
- **Cough**.
- **Paroxysmal nocturnal dyspnea**—Severe shortness of breath and cough that generally occurs at night during sleep although when metabolic demand is minimum. It is caused by
  - Depression of respiratory center during sleep.
  - Due to reduced pulmonary compliance from interstitial pulmonary edema.
  - Due to redistribution of blood from leg and abdomen to cardiopulmonary circuit in recumbent posture.
- **Cheyne-Stokes respiration is due to—**
  - Decreased sensitivity of respiratory center to $PaCO_2$.
  - Increased circulation time from lungs to brain in atherosclerotic and hypertensive patient.
- **Fatigue and weakness is due to low COP**.
- **Abdominal symptoms**—Due to congested liver and portal hypertension.
  - Anorexia
  - Nausea
  - Abdominal pain and fullness.
- **Cerebral symptoms**
  - Confusion.
  - Difficulty in concentration and impairment of memory, headache, insomnia and anxiety.

Signs

- **General—**
  - **Hypotension**—Acute heart failure results in systolic hypotension (reflecting reduced stroke volume). But DBP will rise due to peripheral vasoconstriction.
  - **Edema**—Pitting bipedal edema—due to increased venous pressure. Presacral edema seen in bedridden patient.
  - **Cyanosis**—Sequelae of acute LVF.
  - **Sinus tachycardia** due to compensatory sympathetic drive.
  - **Pulsus alternans** due to LVF.
  - **Pulsus pervus** feeble pulse due to low stroke volume.

(Other causes of pulsus alternans—Cardiomyopathy, hypertension, IHD and following extrasystole)

  - *Increase systemic venous pressure (normal <8 cm of H_2O) and positive abdominojugular reflux. Neek venous pressure may be normal at rest but may become abnormally elevated for 15 second with sustained (<10 sec) pressure over abdomen.*
    - Giant cv-waves indicate the presence of tricuspid regurgitation.
  - **Extremity may be cold, pale and diaphoretic**.
  - **Jaundice**—Increase in conjugated and unconjugated bilirubin due to impairment of hepatic function secondary to hepatic congestion and hepatocellular hypoxia associated with centrilobular atrophy of liver.

- **Cardiac cachexia is due to**
  - Increased TNF.
  - Increased BMR.
  - Anorexia, nausea, vomiting (due to central cause, chronic digitalis intoxication and congestive hepatomegaly).
  - Diminished absorption from intestine due to intestinal congestion.
  - Protein losing enteropathy (usually in right heart failure).

- **Systemic signs**

CVS—

- **Apex is usually shifted downward and outward** and palpable over 6th or 7th intercostal spaces and well-sustained.
- **S_3 (protodiastolic gallop)** is audible and some time palpable over apex in patient with volume overload and tachycardia.
- **S_4 is usually present** with diastolic dysfunction and is not a specific indicator of heart failure.

Lungs

- **Dull percussion note over base of both lung** is due to hydrothorax. Pleural effusion most commonly seen in biventricular failure. Pleural effusion in HF is usually bilateral but when unilateral, it is frequently on right side.
- **Pulmonary rales or crepitations** is due to transudation of fluid from pulmonary capillary into alveoli. It is frequently absent in chronic heart failure due to increased lymphatic drainage of alveolar fluid.
- **Expiratory wheeze** is usually found in acute heart failure.

Abdomen

- **Hepatomegaly** is an important sign. Usually liver is tender and may pulsate in systole if TR is present. Ascites usually a late sign and is due to impairment of venous drainage.
- **Jaundice** is due to hepatic dysfunction is also a late sign.

DIAGNOSIS OF HEART FAILURE

Table 5.1: Framingham's criteria

	Major criteria		Minor criteria
1.	PND	1.	Extremity edema
2.	Neck vein distension	2.	Night cough
3.	Increased venus pressure (>16 cm of H_2O). Normal ≤8 cm	3.	Dyspnea on exertion
4.	Positive abdominojugular reflux	4.	Hepatomegaly
5.	Cardiomegaly	5.	Pleural effusion

Contd...

6.	Basal rales	6.	Vital capacity is reduced to two-third of normal
7.	Acute pulmonary edema	7.	Tachycardia > 120/min
8.	S_3 gallop		

Common Criteria

Weight loss >4.5 kg over 5 days of treatment.

- **To establish the heart failure → 1 major + 2 minor criteria are required**.
  - **Investigations (in a patient of heart failure)**
    - Complete hemogram
    - Urine analysis
    - Serum electrolytes including Ca^{2+} and Mg^{2+}
    - BUN (blood urea nitrogen) and creatinine
    - Blood sugar (fasting and postprandial)
    - LFT (liver function test)
    - TSH and free T_4.
    - Both BNP and N-terminal pro-BNP are sensitive marker for heart failure, false-positive elevation are associated with—
      - » Right heart failure
      - » CRF
      - » Elderly person
      - » Women.
- **12 lead ECG for MI, arrhythmia and LVH**.
- **Chest X-ray** (PA view) for heart size, pulmonary vasculature and PHTN.
- **2D echo** with Doppler study or EF, RWMA and structural disease.
- **Cardiac catheterization** with angiography (in patient with IHD and heart failure).

MANAGEMENT OF CHRONIC HEART FAILURE

TREATMENT OF STAGE A (PATIENT AT HIGH-RISK OF DEVELOPING HEART FAILURE)

- Control of systolic and diastolic hypertension.
- Treatment of hyperlipidemia.
- Avoidence of patient behavior that may increase the risk of heart failure (smoking, alcohol and illicit drug use).
- ACEI in patient with a history of atherosclerotic vascular diseases, DM, HTN and associated cardiovascular risk factor.
- Control of ventricular rate in patient with supraventricular tachyarrhythmias.
- Treatment of thyroid disorders.
- Periodic evaluation for signs and symptoms of heart failure.

ACC/AHA guideline does not force for lifestyle interventions to prevent HF including exercise, salt restriction or routine use of nutritional supplement.

TREATMENT OF STAGE B (PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION WHO HAVE NOT DEVELOPED SYMPTOMS)

The goal of therapy is to reduced risk and also to minimize the rate of progression of heart failure.

- ACE inhibitors.
- β-blockers.
- Valve replacement or repair for patients with hemodynamically significant valvular stenosis or regurgitation.
- Regular evaluation for signs and symptoms of heart failure.

PLUS

- Measures taken in stage A heart failure.

TREATMENT OF STAGE C (PATIENTS WITH LV DYSFUNCTION WITH CURRENT/PRIOR SYMPTOMS)

- Diuretic.
- ACE inhibitors.
- β-blockers (unless contraindicated).
- Aldosterone antagonist—Spironolactone/eplerenone when EF < 35% who are symptomatic despite standard antifailure therapy (diuretic, β-blocker and ACEI).
- Combination of hydralazine with isosorbide dinitrate.
- Digitalis.
- Withdrawal of drugs known to adversely effect the clinical status of patients (NSAIDs, antiarrhythmic drugs and CCB).
- Immunization with influenza and pneumococcal vaccine may be encouraged.

PLUS

- Measures taken for patients in **stage A** and **stage B** heart failure.

In contrast with the recommendation for stage B patients the guidelines support the use of moderate sodium restriction as well as daily measurement of weight.

The patient should not engage himself in heavy labor or exhaustive sports.

TREATMENT OF STAGE D (PATIENTS WITH REFRACTORY END-STAGE HEART FAILURE)

- Meticulous identification and control of fluid retention.
- Continuous intravenous inotropic support.
- Aortic counterpulsating balloon therapy specially in acute VSD and MR.
- Hospice care.
- Cardiac transplantation/assisted mechanical device.

PLUS

- Measures taken for the patient of **stage A**, **stage B** and **stage C** heart failure.

TREATMENT OF DIASTOLIC (DYSFUNCTION) FAILURE

The major management strategies are

- Control of hypertension.
- Control of ventricular rate in patient with ventricular fibrillation.
- Use of diuretic to control pulmonary congestion.

THERAPEUTIC MEASURES OF HEART FAILURE

- **Activity**—Heavy exercise is contraindicated. Routine moderate exercise is recommended.
- **Diet**—Restriction of Na 2–3 g/day, fluid <2 L/day.
- **Diuretics**—Diuretics is the cornerstone in the management of HF.
  - Acute heart failure is treated by loop diuretics like furosemide, torsemide, bumetanide. Chronic heart failure is treated by thiazide.
  - Treat diuretic resistance by
    - IV administration of diuretics.
    - Use of >2 diuretics in combination (furosemide + metolazone).
    - Use of short-term dobutamine/dopamine to increase the renal blood flow.
  - Weigh the patient daily to select and adjust the dose of diuretics.
- **ACE inhibitor**—Indicated in all patients with left heart dysfunction or left heart failure and it increases life expectancy.

Contraindications of ACEI—
- Angioneurotic edema
- Anuric renal failure
- Creatinine >3 mg/dL
- K^+ >5.5 mmol/L
- Bilateral renal artery stenosis
- Pregnancy
- Hypotension

Enalapril—5–40 mg/day, ramipril—1.25–20 mg/day.
- Use ARB who develops angioedema or cough with ACE inhibitor [losartan/valsartan/irbesartan/candesartan/telmisartan/olmesartan]

Combination of ACEI with ARB is probably better than ACEI Alone.

- **β-blockers**—It is the only drug that reduces the morbidity and mortality associated with heart failure and increases life expectancy.

- Used in all NYHA Class-II and III patients with systolic heart failure
- Use together with ACE inhibitor and diuretic
- Metoprolol—To start with 12.5 mg/day slow release form gradually increase the dose over 4 weeks to reach a target dose of 200 mg/day
- Bisoprolol : 1.25–10 mg/day
- Carvedelol : 3.125–50 mg/bid

- **Digitalis—**In patient with left ventricular systolic heart failure along with diuretic, ACE inhibitor and β-blocker, digitalis can be added. Specially useful in patient with acute heart failure with AF.

Contraindications of β-blocker
- Bronchospasm
- Bradycardia (<60 bits/min)
- Advance heart block and PR interval >0.2 S
- Basal rales >10 cm above diaphragm

Dose—0.25 mg/day (0.125 mg/day in old patient).

- **Sympathomimetics**
  - **Dobutamine**
    - 2.5–10 μg/kg/min
  - **Dopamine**
    - 1–2 μg/kg/min causes renal and mesenteric vasodilation.
    - 2–10 μg/kg/min causes β_1 receptor stimulation but little tachycardia.
    - >10 μg/kg/min causes α_1 receptor stimulation with elevation of DBP. Peripheral vasoconstriction. Constant infusion leads to receptor downregulation so intermittent sympathomimetics therapy is advised.

SPECIAL MEASURES FOR CHRONIC HEART FAILURE

- **Hydralazine and Isosorbide dinitrate** combination in patient who are intolerant to ACE inhibitor. [Hydralazine—37.50 / ISDN—10 one tab tid.
- **Spironolactone** (25–50 mg/day).
  Eplerenone 25–50 mg/day specially in NYHA class-IV heart failure patient.

- Do not use CCB for treatment of hypertension or angina as it has a negative ionotropic effect

- **Antiarrhythmic therapy**—Is not recommended for patient with asymptomatic/nonsustained ventricular arrhythmia.
  - **Class-I antiarrhythmic**—Should be avoided except in life-threatening condition.
  - **Class-III antiarrhythmic**—Specially amiodarone, have no negative inotropic and proarrhythmic effect and may be used not for prevention of sudden death but for treatment of supraventricular arrhythmia. It also improves the success of electrical cardioversion.
- **Implantable cardiac defibrillator (ICD)** are highly effective in treatment of sustained VT or VF. They have also shown to reduce the incidence of sudden death, when they are implanted prophylactically in mild to moderate HF (NYHA-II and III).

5. **Phosphodiasterase inhibitor**—
   - *Levosimendan*—12 μg/kg loading dose followed by 0.1–0.2 μg/kg/min continuous infusion.
   - *Milrinone*—50 μg/kg loading dose followed by 0.25–0.75 μg/kg/min continuous infusion.

   These two agents stimulate myocardial contractility with systemic and pulmonary vasodilation. They reverse the major hemodynamic abnormality associated with HF.

- **Device therapy**—Patient of symptomatic HF (NYHA class III and IV stage) despite optimal therapy with QRS duration >120 mg require **biventricular pacing** for cardiac resynchronization to stimulate both the ventricle simultaneously and improve the ejection fraction.

ACUTE DECOMPENSATED HEART FAILURE WITH PULMONARY EDEMA

Acute decompensated left heart failure with pulmonary edema are medical emergency. LV dysfunction leads to pulmonary congestion and systemic hypoperfusion.

Cardiogenic shock is characterized by systemic hypoperfusion due to severe depression of cardiac index [<2.2 (L/min) m_2] and sustained systolic arterial hypotension <90 mmHg inspite of raised PCWP >18 mm Hg.

Leading causes of acute decompensated HF and pulmonary edema are the following—

- **Silent myocardial infarction** (most common) with or without VSD, chordal rupture, ventricular free wall rupture.
- **Accelerated hypertension**
- **Cardiomyopathy**
- **Endocarditis**
- Cardiac tamponade
- **Tachyarrhythmia**

At this stage, three basic hemodynamic determinants should be searched for—
- Elevated LV filling pressure
- Depressed cardiac output
- Increase systemic vascular resistance.

Depending on these factors patients are divided into four categories—
- **Profile A (warm and dry)** (normal LV filling pressure with normal perfusion)—They are not congested, have normal tissue porfusion, their symptoms are due to hepatic or pulmonary disease or myocardial ischemia and should be treated accordingly.
- **Profile B (warm and wet)** (elevated LV filling pressure wih normal perfusion)—These patients present with acute pulmonary edema. Treatment of elevated filling pressure with diuretics and vasodilators are required to reduce LV filling pressure.

Contd...

Contd...

- **Profile C (cold and wet)** (elevated LV filling pressure with decreased perfusion)—They have pulmonary congestion, reduced cardiac output and elevated systemic vascular resistance. They are treated by intravenous ionotropic agent with vasodilator property, e.g. dobutamine, low dose dopamine, milrinone. These drugs increase the myocardial contractility and decrease the peripheral resistance thereby increase the cardiac output.
- **Profile L (cold and dry)** (normal or low LV filling pressure with decrease tissue perfusion)—They should be carefully evaluated by right heart catheterization for elevated LV filling pressure. If LV filling pressure <12 mm Hg a cautious trial of blood volume expansion by normal saline should be tried.

Therapy may not be successful if profound RV dysfunction or cardiorenal syndrome develops which is the usual cause of death in hospital (approx 25%).

- **Acute AR or MR**
- **Severe AS or MS**
- **Aortic dissection**
- **Pulmonary embolism**
- **β-blocker or CCB overdose**
- Hyperglycemia and ketoacidosis
- Pregnancy
- Dietary excess
- **Infection**.

Management

- **Clinical features**
  - Aggravation or rapid onset dyspnea at rest
  - Tachypnea
  - Tachycardia
  - Pulsus alternans
  - Cyanosis
  - Hypotension
  - Wheeze/ronchi
  - Rales
  - S_3, S_4 gallop.
- **Laboratory investigation**
  - **Hypoxia** in arterial blood gas.
  - **Chest X-ray**—Kerley's B line and loss of distinct vascular margin.
  - **Echo and color Doppler for determination of ejection fraction and structural heart disease**.
  - **Increase N-terminal pro-BNP**—Diagnostic of heart failure.
  - **Measurement of PCWP** (pulmonary capillary wedge pressure) to differentiate high pressure from normal pressure pulmonary edema.
  - **Measurement of systemic vascular resistance**.

Treatment

Management of acute decompensated heart failure with pulmonary edema.

1st line of management

- **Oxygen** by nasal catheter or by intratracheal intubation as needed.
- **Nitroglycerin**—0.4 mg × 3 dose by S/L route.
- **Injection furosemide**—0.5–1.0 mg/kg IV.
- **Injection morphine**—2–4 mg/IV.

Every effort should be made to identify the precipitating factor that leads to the development of acute decompensated heart failure to guide further therapy.

2nd line of management (guided by blood pressure)

- If SBP >100 mm Hg injection nitroglycerine—10–29 μg/min IV infusion.
- If SBP = 70–100 mm Hg with sign and symptoms of shock, injection dopamine—5–15 μg/kg/ min IV infusion.
- If SBP = 70–100 mm Hg without sign and symptoms of shock, injection dobutamine—2–20 μg/kg/min infusion.
- If SBP <70 mm Hg with sing and symptoms of shock, injection norepinephrine 0.5–30 μg/min IV infusion.

  It should be started with very low dose then gradually titrated upward to maximum dose up to 15 μg/min to maintain systolic BP >90 mm Hg.

3rd line of management (guided by etiology)

- Identify and treat reversible cause like
  - **Severe HTN**—By nitroprusside/nitroglycerine—IV infusion.
  - **AMI**—By coronary angiography followed by angioplasty or CABG.
  - **AMI with MR/VSD**—Intraaortic balloon pump followed by surgical repair.
  - **AMI with LBBB**—Three chamber pacemaker implantation. One lead in atrium, second lead in right ventricle and the third one for simultaneous depolarization of left and right ventricle to be placed in coronary sinus. In this way resynchronization of both ventricle is done to maximize the cardiac output.
  - **Avoidence of the offending agent**.
  - Appropiate management of tachyarrhythmia AFSVT, VT, VF.

Drugs Used for Acute Decompensated Heart Failure

- **Diuretics**
  - Furosemide—40 mg Bid
  - Torsemide—20 mg Bid

  - Hydrochlorthiazide—25 mg OD
  - Metolazone—5 mg OD/BD.
- **Intravenous vasodilators**
  - Nitroglycerin—20–200 μg/min
  - Nitroprusside—10–350 μg/min
  - Nesiritide—2 μg/kg → 0.03 μg/kg min.
- **Intravenous isotropic agent**
  - Dobutamine—1–2 μg/kg/min → 10 μg/kg/min. Chronic infusion over 72 hour develops tachyphylaxis require higher dose.
  - Milrinone—50 μg/kg/min bolus followed by 0.1– 0.75 μg/kg/min.
  - Levosimendan—Bolus 12 μg/kg → 0.1–0.2 μg/kg/min.
- **Intravenous vasoconstrictor**
  - Dopamine—5–15 μg/kg/min
  - Epinephrine—0.5–50 μg/kg/min
  - Phenylephrine—0.3– μg/kg/min
  - Vasopressin—0.05–0.4 U/min.
- **Mechanical and surgical intervension**
  - Intraaortic balloon counterpulsation.
  - Percutaneous and surgically implanted LV-assisted devices.
  - Cardiac transplantation.

Chapter 6

Hypertension

DEFINITION

Elevation of systolic or diastolic blood pressure above the normal range is called hypertension. In 92–94% patients no cause could be found out after extensive investigation and is called **essential hypertension** and in the remaining 6–8% patients hypertension is secondary to diseases of the kidney or other endocrine organ and is called **secondary hypertension**.

Classification (according to JNC-7)

	SBP	DBP
Normal	<120	<80
Prehypertension	120–139	80–89
Stage–I	140–159	90–99
Stage–II	>160	>100

Classification of BP based on current European guideline

	SBP mmHg	DBP mmHg
Optimal	<120	<80
Normal	120–129	80–84
High normal	130–139	85–89
Grade–1 HTN (mild)	140–159	90–99
Grade–2 (moderate)	160–179	100–109
Grade–3 (severe)	≥180	≥110
Isolated systolic HTN	≥140	<90

- **Labile hypertension**—*Those persons whose BP sometimes but not always is in the hypertensive range are called labile hypertensive.*
- **Malignant hypertension**—*When hypertension causes papilledema, deteriorating renal function and encephalopathy—it is called malignant hypertension. The DBP is usually in stage–II (DBP >130 mm Hg) with retinal hemorrhage and exudate.*
- **Accelerated hypertension**—*Defined as significant recent increase over previous level of hypertension associated with vascular damage on fundoscopic examination but without papilledema.*
- **Orthostatic hypotension**—It is *defined by a fall of systolic pressure >20 mm Hg or diastolic pressure >10 mm Hg is response to assumption of upright posture from a supine posture within 3 minutes. There should also be lack of compensatory tachycardiac seen in autonomic insufficiency in patient with diabetes and Parkinson's disease.*
- **Isolated systolic hypertension**—It is defined as *SBP >140 mm Hg and DBP <90 mm Hg and staged appropriately*. Systolic blood pressure increases steadily with age by contrast diastolic blood pressure tends to decline from about the age of 50–60 years. As a consequence most person older than 60 years (75–80% in this age group) have isolated systolic hypertension.

TYPES OF HYPERTENSION

1. **Primary (essential)**—90–94%
2. **Secondary**—6–10%.
   - Etiology of secondary hypertension
     a. **Renal hypertension**—
        - Renoparenchyma (2–3%)
        - Renovascular (1–2%).

     b. **Endocrine hypertension**—
        - Primary hypereldosteronism (0.3%)
        - Cushing (0.1%)
        - Pheochromocytoma (0.1%)
        - OCP induced (0.5–1%).

Table 6.1: Blood pressure measurement techniques

	Method	Notes
1.	In-office–Length and width of the cuff should be 80% and 40% of arm circumference respectively	Two readings, 5 minutes apart, sitting on chair after 10 minutes relaxation. Confirm elevated reading in contralateral arm. Systolic leg pressure is usually 20 mm higher than systolic arm pressure
2.	Ambulatory BP monitoring	1. Indicated for evaluation of white coat hypertension
3.	Patient self-check	2. Absence of 10–20% decrease in BP during sleep may indicate increase CVD risk 3. Provides information on response to therapy 4. May help to improve adherence to therapy and is useful for evaluating *white coat hypertension* 5. To assess patient with resistant hypertension 6. To assess adequacy of 24 hour BP-control

Signs and Symptoms

Symptoms related to

1. Elevated BP
2. Hypertensive vascular disease
3. Underlying disease in secondary hypertension.

Symptoms (related to increased BP)

- Patient may be asymptomatic.
- Occipital headache (early morning)—most common presentation.
- Dizziness, palpitation and easy fatiguability.
- Impotence.

Symptoms due to hypertensive vascular disease

- Epistaxis.
- Hematuria.
- Blurring of vision due to retinal changes.
- Weakness/dizziness due to transient cerebral ischemia.
- Angina pectoris.
- Dyspnea—Due to CCF/ischemic heart diseases.

Symptoms related to underlying disease

- Polyuria
- Polydypsia
- Muscle weakness
- Cramps/tetany

} Secondary to hypokalemia in primary hyperaldosteronism

- Weight gain
- Emotional lability
- Episodic headache

} Cushing's disease

- Palpitation
- Diaphoresis
- Postural dizziness
- Tremor, pallor/flash, nausea, vomiting.

} Suggest pheochromocytoma

Signs

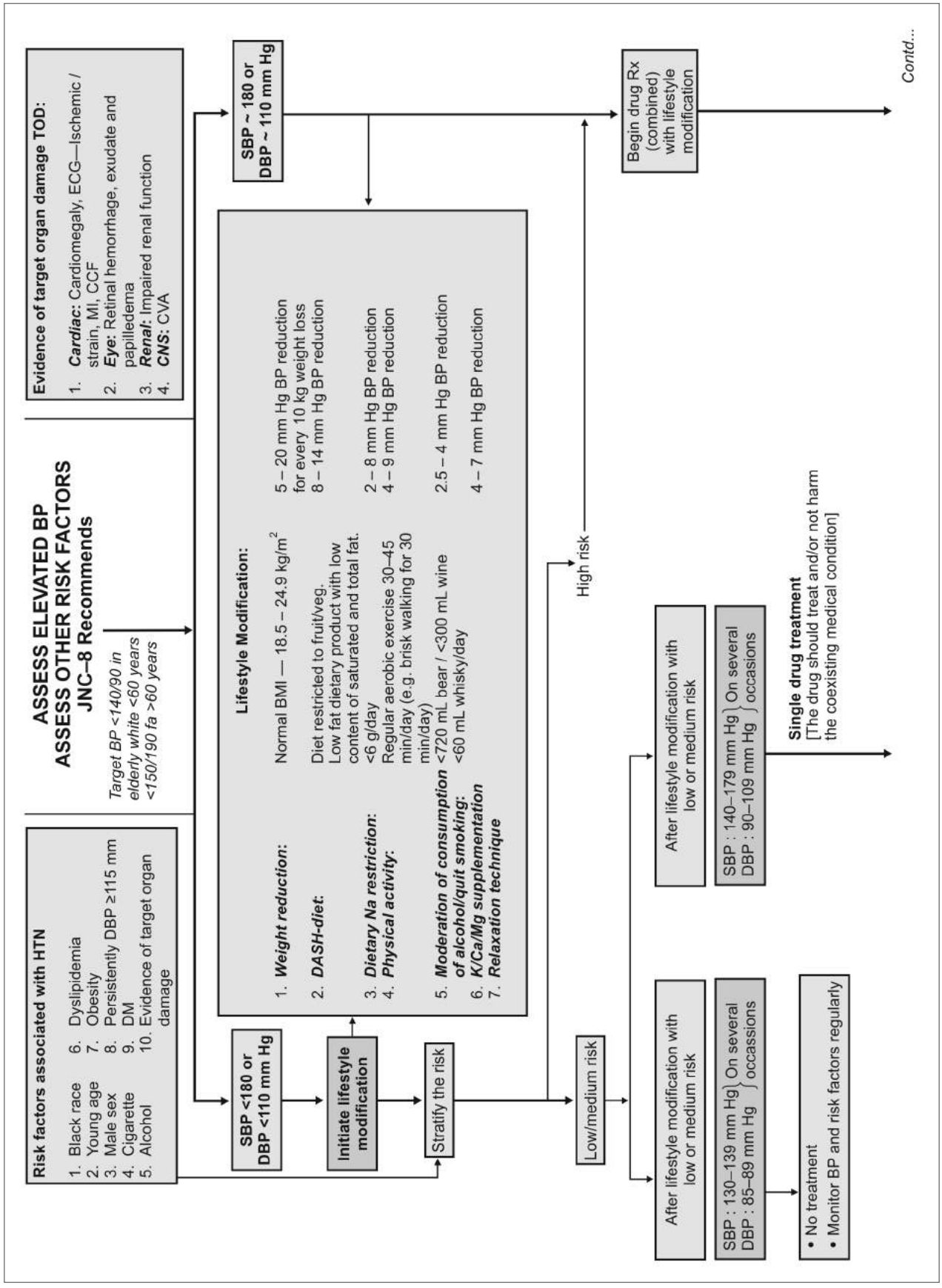
- Moon facies
- Truncal obesity

} Suggest Cushing's

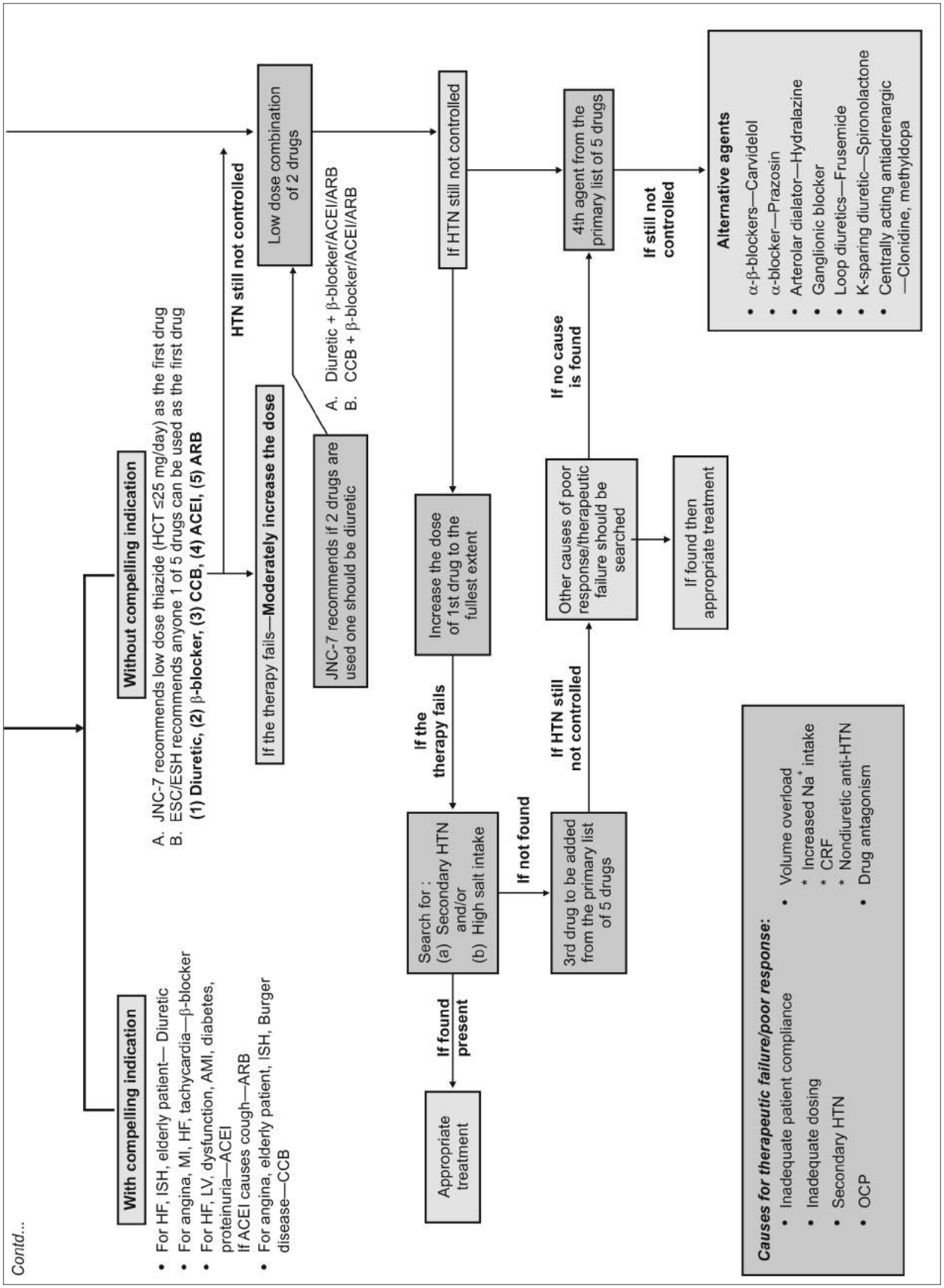
- Muscular development in upper limb out of propor- tion than that of lower limb—coarctation of aorta.
- Rise in DBP when the patient goes from supine to erect posture—essential hypertension.
- Fall (in absence of antihypertensive drug) of DBP on sudden standing from supine posture → secondary hypertension.
- Height and weight—ideal BMI 18.5–24.9 kg/m^2 (every 10 kg fall in weight cause fall in SBP by 5–20 mmHg.)
- Pulse—
  - Whether palpable in all peripheral sites or not.
  - When any radioradial/radiofemoral delay is present → Suggest Takayasu disease/coarctation of aorta.
- Neck vein—Engorgement or pulsation of neck vein is a indicator of right ventricular functional status.
- Edema.
- **Fundoscopic examination**—
  - Detailed fundoscopic examination for hemorrhage exudate and papilledema.
- Detail examination of CVS including auscultation of heart, palpation and auscultation of carotid artery. Evidence of LVH, LVF should be searched for. Search for murmur over midline of trunk, palpable collateral vessel (from coarctation of aorta) should be done.
- Palpation of abdomen for polycystic kidney.
- Auscultation of abdomen and flanks for any murmur of renal artery stenosis/coarctation of aorta. [Important for patient with hypertension below 30 years of age].
- Femoral arterial pressure should be recorded.

Investigations

- Blood sugar, urea, creatinine, Hb, PCV and cholesterol.
- Urine—RE and ME for pus cell, RBC, epithelial cell, cast and protein, glucose and blood.
- Serum electrolyte—K^+ and Na^+.
- ECG and USG of KUB.



Flowchart 6.1: Management of essential hypertension


Contd...
With compelling indication
For HF, ISH, elderly patient— Diuretic
For angina, MI, HF, tachycardia—β-blocker
For HF, LV, dysfunction, AMI, diabetes, proteinuria—ACEI
If ACEI causes cough—ARB
For angina, elderly patient, ISH, Burger disease—CCB
Without compelling indication
A. JNC-7 recommends low dose thiazide (HCT ≤25 mg/day) as the first drug
B. ESC/ESH recommends anyone 1 of 5 drugs can be used as the first drug
(1) Diuretic, (2) β-blocker, (3) CCB, (4) ACEI, (5) ARB
HTN still not controlled
If the therapy fails—Moderately increase the dose
JNC-7 recommends if 2 drugs are used one should be diuretic
A. Diuretic + β-blocker/ACEI/ARB
B. CCB + β-blocker/ACEI/ARB
Low dose combination of 2 drugs
If HTN still not controlled
4th agent from the primary list of 5 drugs
If still not controlled
Alternative agents
α-β-blockers—Carvidelol
α-blocker—Prazosin
Arterolar dialator—Hydralazine
Ganglionic blocker
Loop diuretics—Frusemide
K-sparing diuretic—Spironolactone
Centrally acting antiadrenargic —Clonidine, methyldopa
If no cause is found
Other causes of poor response/therapeutic failure should be searched
If found then appropriate treatment
If HTN still not controlled
3rd drug to be added from the primary list of 5 drugs
If not found
If the therapy fails
Increase the dose of 1st drug to the fullest extent
Search for : (a) Secondary HTN and/or (b) High salt intake
If found present
Appropriate treatment
Causes for therapeutic failure/poor response:
Inadequate patient compliance
Inadequate dosing
Secondary HTN
OCP
Volume overload
* Increased Na+ intake
* CRF
* Nondiuretic anti-HTN
Drug antagonism

Additional
- TC and DC
- Electrolyte—Ca^{+2} and PO_4^{-3}
- Total lipid profile
- TSH
- Chest X-ray
- Echocardiography.

Special screening for secondary hypertension
1. **Renovascular disease**
   a. ACEI radionuclide renal scan (isotope renal scan).
   b. Renal duplex Doppler flow study.
   c. MRI and angiography.
   d. Renal vein renin study.
2. **Pheochromocytoma**
   – 24 hour urinary assay for creatinine, metanephrine and catecholamines.
3. **Cushing's**—Serum cortisol assay.
   – Overnight dexomethasone suppression test for serum cortisol (normal <5 μg/dL).
   – 24 hour urine cortisol (normal <100 μg) and creatinine.
4. **Primary aldosteronism**
   – Plasma aldosterone—Renin activity ratio—High.

TREATMENT OF HYPERTENSION

Hypertension is the most common condition seen in primary care and leads to myocardial infarction, stroke, renal failure and death if not detected early and treated appropriately. Patients want to be assured that blood pressure (BP) treatment will reduce their disease burden.

There is strong evidence to support treating hypertensive persons aged 60 years or older to a BP goal of less than 150/90 mmHg and hypertensive persons 30 through 59 years of age to a diastolic goal of less than 90 mmHg; however, there is insufficient evidence in hypertensive persons younger than 60 years for a systolic goal, or in those younger than 30 years for a diastolic goal, so JNC-8 recommends a BP of less than 140/90 mmHg for those groups based on expert opinion. The same thresholds and goals are recommended for hypertensive adults with diabetes or nondiabetic chronic kidney disease (CKD) as for the general hypertensive population younger than 60 years. There is evidence to support initiating drug treatment with an (1) angiotensin-converting enzyme inhibitor, (2) angiotensin receptor blocker, (3) calcium channel blocker, or (4) thiazide-type diuretic in the nonblack hypertensive population, including those with diabetes. In the black hypertensive population, including those with diabetes, (a) a calcium channel blocker or (b) thiazide-type diuretic is recommended as initial therapy. There is moderate evidence to support initial or add-on receptor blocker in persons with CKD ACEI or ARB as to improve kidney outcomes.

- Drugs used for treatment of hypertension
- Drugs (ABCD)
  A. ACEI → Enalapril → 2.5–40 mg/day
     Ramipril → 1.25–20 mg/day
     Quineapril → 5–80 mg/day
     ARB → Losartan 25–50 mg OD/BD
     Telmisartan 40–80 mg
     Olmesartan 20–40 mg
  B. β-blocker → Metoprolol 25–200 mg/day
     Atenolol → 25–100 mg/day
     Bisoprolol → 5–10 mg/day
     Nebibolol → 5–10 mg/day
  C. CCB → Diltiazem—30–90 mg QID nifidipine 20 mg TDS
     Amlodipine—2.5–10 mg/day; verapamil 40–240 mg/day
  D. Diuretic—Frusemidc 40–80 mg
     Thiazide → 12.5–25 mg/day
     Indapamide → 2.5 mg/day
     Metolazone → 2 mg/day

MALIGNANT HYPERTENSION

It is a syndrome associated with an abrupt increase in blood pressure. Clinically associated with **progressive retinopathy** (arteriolar spasm, hemorrhages, exudate and papilledema), **deteriorating renal function** (proteinuria, microangiopathic hemolytic anemia) and **encephalopathy**.

The a*bsolute level of BP is not as important as its rate of rise*.

Pathologically it is associated with—(a) **diffuse necrotizing vasculitis**, (b) **arteriolar thrombi** and (c) **fibrin deposition in arteriolar wall**.
- Less than 1% of all hypertensive patients (both essential and secondary) developed malignant hypertension.
- Average age of diagnosis is 40.
- Male predominate over female.
- With effective antihypertensive therapy life expec- tancy greater than 5 years is not uncommon.

CLINICAL FEATURES OF MALIGNANT HP

1. **Manifestations of hypertensive encephalopathy** are, e.g. *headache, vomiting, visual disturbances including transient blindness, paralysis, convulsion, stupor and coma.*

   These manifestations are due to spasm of cerebral vessel and cerebral edema.
2. **Cardiac decompensation** resulting in *heart failure*.
3. **Rapidly declining renal function**.

   Exact pathogenesis of malignant hypertension is not known.

   Two separate pathology are observed
   – Diffuse necrotizing vasculitis.
   – Generalized arteriolar fibrinoid necrosis of the walls of small arteriole (which can be reversed by timely antihypertensive therapy) contribute to the other associated signs and symptoms.

PATHOPHYSIOLOGY OF MALIGNANT HTN

- Cerebral vasodilation due to marked elevation of blood pressure causes loss of autoregulation of cerebral blood flow and produces cerebral encephalopathy.
- Elevated level of plasma renin and aldosterone are responsible for vascular damage.
- Microangiopathic hemolytic anemia is the cause of deterioration of renal function.

Table 6.2: Drugs used in treatment of hypertension with indication and contraindication

Class of drugs	Compelling indication	Compelling contraindication
Diuretic	HF, ISH and elderly person	Gout
β-blocker	Angina, AMI and tachyarrhythmia	Asthma, COPD and heart block
ACEI	HF, LV dysfunction, AMI and diabetic nephropathy	Pregnancy, hyperkalemia, bilateral renal artery stenosis, serum creatinine >3 mg%
Calcium antagonist	Angina, elderly person and ISH	Heart block, heart failure
ARB	Same as ACEI and ACEI-induced cough and angioneurotic edema	Same as ACEI

Drugs for Treatment of Hypertensive Emergencies

Although blood pressure should be lowered rapidly but overaggressive lowering of BP may precipitate cerebral ischemia or infarction.

The initial goal of therapy is to lower the BP by 25% within minutes to 2 hour or the BP in the range of 160/100–110 mmHg. This can be done by—(a) nitroprusside, (b) labetolol and (c) nicardipine (d) nitroglycerin.

In malignant hypertension without encephalopathy the goal BP can effectively be achieved with frequent dosing of short-acting oral agent like **captopril, clonidine** and **labetolol**.

Parenteral Drug for Hypertensive Emergencies

- **Hypertensive encephalopathy**—Nitroprusside—2–10 μg/kg/minutes IV for 10 minutes. Nicardipine—5–15 mg IV titrated by 2.5 mg/hour. Labetolol—20 mg IV over 2 minutes then 40–80 mg at 10 minutes interval up to maximum 300 mg total.
- **Malignant HTN**—Labetolol, nicardipine, nitroprusside, enalaprilat—0.625–1.25 mg IV over 5 minutes 6–8 hourly.
- **Stroke**—Nicardipine, labetolol and nitroprusside.
- **AMI/UA**—Nitroglycerine—5–200 μg/min, nicardipine, labetolol and esmolol.
- **LVF**—Nitroglycerine, enalaprilat and loop diuretic.
- **Preeclampsia**—Hydralazine—10–50 mg IV at 30 minutes interval.
  Methyl dopa
  Labetolol—100 mg bd
- **Adrenergic crisis**—Phentolamine and nitroprusside.
- **Aortic dissection**—Nitroprusside, esmolol and labetolol.

INAPPROPRIATE HYPERTENSION/ (SECONDARY HYPERTENSION)

DIAGNOSTIC FEATURES THAT FAVOR

Inappropriate HTN

- Age of onset of HTN <20 years or >50 years.
- BP >180/110.
- Poor response to therapy despite good compliance.
- Evidence of target organ damage at diagnosis—
  - Fundoscopy—Showing retinopathy of grade II or higher grade.
  - Serum creatinine >1.5 mg%.
  - Cardiomegaly.
  - LVF.

Features Indicative of Secondary HTN

- Unprovoked hypokalemia.
- Abdominal bruit.
- Variable blood pressure at different limb with tachycardia, sweating and tremor.
- Family history of renal disease.

CAUSES OF SECONDARY HYPERTENSION

- **Renal**—
  - *Renoparenchymal diseases*—
    - AGN (acute glomerulonephritis)
    - Chronic nephritis
    - PCKD (polycystic kidney disease)
    - Diabetic nephropathy
    - Hydronephrosis.
  - *Renovascular diseases*—
    - Renal artery stenosis (arteriosclerosis and fibromascular dysplasia).
    - Internal vasculitis.
  - Renoprival.
  - Renin-producing tumor.
- **Endocrine**—
  - Acromegaly
  - Hypothyroid
  - Hyperthyroid
  - Hyperparathyroid.
  - Adrenal—
    - **Cortical**—Cushing's syndrome, Conn's syndrome, CAH (congenital adrenal hyperplasia).
    - **Medullary**—Pheochromocytoma.

  - Extraadrenal—Chromaffin tumor.
  - Carcinoid tumor.
  - Exogenous hormone—OCP (oral contraceptive pill), glucocorticoid, mineralocorticoid, erythropoietin, tyramin-containing food, sympathomimetic (nasal decongestant, NSAID, MAO inhibitor, cocaine).
- **Coarctation of aorta**
- **Pregnancy-induced hypertension**
- **Stress**
- **Obstructive sleep apnea**
- **Increased intravascular volume**.

History

- **Age**— <20 year >50 year.
- **Onset**—Abrupt onset.
- **Family history**—Positive.
- **History of therapeutic failure**.
- **History of headache, palpitation, nausea, vomiting, chest pain, nervousness, tremor coming in episodic manner**—Pheochromocytoma.
- **History of atherosclerotic disease**—Smoker, worsening of renal function with history suggestive of recurrent flush pulmonary edema—renovascular HTN.
- **History of OCP and other drugs**.
- **History of diabetes**.
- **History of chronic renal disease** (e.g. oliguria, polyuria and hematuria).

Examination and Investigation

Features of renovascular hypertension

- Abdominal bruit
- Advanced fundal change
- Deterioration of renal function with ACEI.

Basic investigations
- Captopril-enhanced renal scan.
- Duplex-Doppler renal artery flow study.
- MR-angio of renal arteries and kidney with gadolinium enhancement.

Special investigation features are as follows
- Low sodium and low potassium with high renin.
- Secondary hyperaldosteronism.
- Moderate proteinuria.
- Serum creatinine >1.5 mg%.
- >1.5 cm difference in kidney size on USG.
- MR-angio/CT-angio for evaluation of renal blood flow.
- Ratio of renal vein renin with IVC renin >1.5. or If the ischemic kidney liberates 1.5 times higher renin as evidence by renal vein renin study then benefit will be obtained from surgical intervention on the ischemic kidney.

  Care to be taken to prepare the patient properly before renal vein blood sampling by discontinuing renin suppressing drugs.
  - β-blocker for 10 days
  - ACE inhibitor for 1 day
  - Restriction of sodium intake for 4 days.

Features of renoparenchymal hypertension

Clinical features—Enlarged kidney (bimanually palpable and ballotable kidney seen in PCKD and hydronephrosis).

Investigations
- Urine analysis—RBC, WBC, cast, proteinuria, increase in specific gravity.
- Serum creatinine >1.5 mg%.
- USG (Diagnostic of PCKD, hydronephrosis and granular contracted kidney)—Contracted kidney with increase cortical echogenicity with loss of corticomedullary differentiation—suggestive of renoparenchymal disease.
- Isotope renogram.
- Renal biopsy.

Features of pheochromocytoma-associated hypertension

Clinical features
- Sweating, palpitation, pallor, weight loss, tremor, arrhythmia, headache, anxiety, nausea and vomiting.
- May be associated with MEN2B and neuro- fibromatosis.
- Orthostatic hypotension.
- Sudden paroxysmal hypertension.
- Palpable adrenal mass (rarely).

Investigations
- Estimation of free catecholamine in blood and urine.
- Metanephrine concentration in plasma and urine (most sensitive).
- VMA in urine.
- CT/MRI, PET scan—For detection of adrenal tumor.
- MIBG (metaiodobenzyl guanidine) scan for determination of source of catecholamine/for ectopic source.
- Catecholamine estimation in adrenal venous sampling.

FEATURES OF COARCTATION OF AORTA

- **Suzman sign**—Pulsation over the inferior angle of scapula.
- **Differential cyanosis** (upper half of body is red while leg and toe are cyanosed) with PDA.
- **SBP difference** in arm and leg >20 mm Hg.
- **Bruit over aorta**.

Investigations

- X-ray chest—'3' sign—Notching of ribs due to coarctation.
- Aortogram—Diagnostic.
- Echo/CT.
- Doppler.
- CT angio/MR angio is diagnostic (by noninvasive method).

FEATURES OF CUSHING'S SYNDROME

- Typical clinical features—Moon facies, acne and truncal obesity.
  - Investigations
    - 24 hours urine cortisol below 100 μg rules out Cushing's.
    - Overnight dexamethasone suppression test—Measurement of plasma cortisol at 8 AM. After administration of 1 mg dexamethasone at bed time—plasma cortisol below 5 μg/dL, rule out Cushing's.
- High dose dexamethasone suppression of plasma cortisol.
- Late night salivary cortisol is also a sensitive and convenient screening test.
- CT/MRI of abdomen and pituitary.
- Petrosal venous sampling—For ACTH.
- Adrenal venous sampling—For cortisol.

FEATURES OF CONN'S SYNDROME (PRIMARY HYPERALDOSTERONISM)

Causes

- Adrenal adenoma (60–70%)
- Bilateral adrenal hyperplasia
- Adrenal carcinoma
- Ectopic malignancy (ovarian arrhenoblastoma).

Clinical Features

- Headache.
- Muscle weakness, tetany, muscle cramp, fatigue, polyuria and polydipsia.
- Diastolic hypertension.
- Glucose intolerance.

Investigations to Establish Conn's Syndrome

- Increase sodium, decrease potassium, decrease rennin and increase aldosterone in serum.
- Serum aldosterone >555 p mol/L.
- Aldosterone : Renin ratio remains high (>30 : 1).
- ECG—Cardiomegaly, LVH, U-wave (in ECG), arrhythmia and ventricular ectopic.

Investigation to Determine the Side of Tumor

- High resolution CT/MRI to determine the side of adrenal tumor because surgical removal of unilateral tumor reduces arterial blood pressure.
- Bilateral adrenal venous sampling for measurement of plasma aldosterone for differentiating unilateral from bilateral primary aldosterone.

Chapter 7

Congenital Heart Diseases

ATRIAL SEPTAL DEFECT (ASD)

- **Anatomically ASD are of four types**
  - **Osteum primum type** (AV septal defect/ endocardial cushion defect) the defect located adjacent to atrioventricular valve either of which may be deformed and regurgitant. Common in Down's syndrome associated with VSD.
  - **Osteum secundum type**—Osteum secundum type of defect is **10 times more common than osteum primum type**.
    This is the most common type of ASD located at fossa ovalis (associated with fetal alcohol syndrome) midseptal in location and should not be confused with patent foramen ovale.
    This type of defect is due to—
    - Either due to excessive resorption of septum primum.
    - From deficient growth of septum secundum.
    - May be associated with total anomalous pulmonary venous connection (TAPVC).
  - **Sinus venosus type**—Located high in atrial septum near the entry of superior vena cava associated with anomalous pulmonary venous connection from right lung to superior vena cava or right atrium.
  - **Coronary sinus** defect.

PATHOPHYSIOLOGY OF ASD

In any type of ASD the degree of left to right shunt depends on

- Size of the defect.
- Relative diastolic feeling property (diastolic compliance) of both ventricle.
- Any condition causing decreased left ventricular compliance, e.g. systemic HTN, cardiomyopathy and MI.
- Any condition causing increased LA pressure— MS and MR.

HEMODYNAMIC ALTERATION

- Left to right shunt through ASD occurs at very minor pressure difference; hence silent on auscultation.
- RA receives additional amount of blood (apart from SVC or IVC) from LA. So, there is enlargement of RA in size.
- This increased amount of blood when passes through normal-sized tricuspid valve produce a **delayed diastolic murmur (DDM)** which is audible at left lower sternal border.
- RV also enlarges in size and due to passage of large volume of blood through normal size pulmonary orifice, a **pulmonary ejection systolic murmur is produced**.

  The P_2 component of second sound is delayed due to excess blood flow through pulmonary valve both during inspiration and expiration causing wide fixed splitting of S_2 without any change in the gap between A_2 and P_2 during inspiration and expiration.

Clinical Features

- The degree of symptoms and the age of its appearance is related to the size of ASD.
- Large ASD (pulmonary flow/systemic flow >2) may cause CCF and failure to thrive in an infant.
- Undetected ASD without significant shunt pulmonary flow/systemic flow >1.5 probably causes symptom in adulthood.

Symptoms

- Patients are generally asymptomatic except physical under development.
- Mild effort intolerance is present.
- Frequent chest infection usually develop with large size ASD.
- CCF is rare.
- Beyond 4th decade
  - Atrial arrhythmias may develop

– PAH usually seen
– Bidirectional or right to left shunt may be present.

Patient of high altitude due to hypoxemia develop PHTN at younger age.

In older age group left to right shunt increases due to reduced compliance of left ventricle.

Other Examination

- Parasternal impulse (due to RVH).
- Palpable systolic thrill in left 2nd space due to increased flow through pulmonary artery.
- Mild to moderate cardiac enlargement. Apex—RV type.
- S_1 is normal or accentuated due to loud tricuspid component.
- **S_2 is widely split** and **the split is fixed without respiratory variation**. P_2 is accentuated and widely transmitted along left sternal boarder upto apex.
- **Ejection systolic murmur** of grade III or less, over the left 2nd and 3rd interspace (flow murmur through pulmonary artery), may be transmitted all over the chest.
- **DDM at the left lower sternal boarder** (tricuspid flow murmur due to excess flow).
- **Presence of pansystolic murmur** at apex in a patient with ASD suggest—
  – Osteum primum type defect (other features are left axis deviation in ECG > –30° associated with MR, TR and VSD).
  – Floppy mitral valve (along with ASD).
  – Rheumatic MR (right axis deviation in ECG).
  – ASD with a cleft in the mitral valve.

X-ray features are as follows

- Mild to moderate cardiomegaly.
- RAH.
- RVH.
- Fullness of pulmonary bay due to prominent main pulmonary artery.
- Relatively small aortic kunckle (hypoplastic aortic kunckle).
- Plethoric lung field (pulmonary plethora is due to increased flow through pulmonary circuit). Vascularity diminishes if PHTN develops.

ECG features are

- **Ostium secundum type**
  – Right axis deviation.
  – RVH.
  – RSR´ in V1. rSr´ is right preordial lead suggest RV outflow tract enlargement.
- **Osteum primum type**
  – Left axis deviation in ECG. Counter clockwise rotation of heart and RV conduction defect.
- **Sinus venosus ASD**
  – Atrial ectopic with 1st degree heart block.

Echocardiography

Shows the size of the chamber and the defect can be measured.

Complications

Development of pulmonary arterial HTN, rare below the age of 20 years, recognized by disappearance of systolic and diastolic murmur and appearance of a constant loud pulmonary ejection click and loud P_2. Second heart sound remains to be wide and fixed split (without respiratory variation).

Treatment

- **Medical management**
  – Treatment of chest infection
  – Treatment of infective endocarditis
  – Treatment of SVT
  – Treatment of CCF.
- **Surgical management—**Risk of operation is very low and even patients are operated above 40 years of age.
  Ideal age for operation is between 2–5 years.
  The defect is closed by a—
  – Decron patch/patch of pericardium
  – Direct suturing.

  Using heart lung bypass, the operation may be done below 2 years of age by application of hypothermia causing CAC (complete arrest of circulation).

VENTRICULAR SEPTAL DEFECT (VSD)

MORPHOLOGY OF VSD

VSD constitute about 27% of all CHD either singly or in combination with other anomalies.

- Ventricular septum can be divided in four parts
  – Inlet.
  – Onlet.
  – Trabecular.
  – Small membranous part lying just below the aortic valve.
- VSD can be classified into 3 main categories.
  – **Muscular VSD**—Bordered entirely by myo- cardium, can be trabecular, inlet or outlet in position/location.
  – **Membraneous VSD (90%)**—Most common type of VSD.
    It often have inlet, outlet or trabecular extension and bordered in part by fibrous continuity between leaflets of AV valve and aortic valve.
  – **Doubly committed subarterial VSD**—Situated in outlet septum. Common in Asian patient.
    Bordered by fibrous continuity between aortic and pulmonary valve.

PATHOPHYSIOLOGY OF VSD

- **Restricted VSD**—Produce significant pressure gradient between LV and RV.
  Pulmonary/aortic/systolic pressure ratio is <0.3. Small shunt (pulmonary/systemic flow <1.4).
- **Moderately restricted VSD** Pulmonary/aortic systolic pressure ratio is <0.66.
  Moderate shunt (pulmonary : systemic flow = 1.4–2.2 : 1)
- **Large (nonrestricted) VSD**
  Pulmonary/aortic systolic pressure ratio is >0.66. Large shunt (pulmonary systemic flow >2.2).
- **Eisenmenger VSD**—Right to left shunt.
  Aortic/pulmonary/systolic pressure ratio is 1 : 1.
  Pulmonary/systemic flow is <1 : 1.

Natural History and Hemodynamics

Restrictive VSD cause very little hemodynamic alteration and may close spontaneously in late childhood and sometimes in early adult life.

Moderately restrictive/nonrestrictive VSD cause shuting of blood from LV to RV across ventricular septum.

The flow of blood from LV to RV starts very early in systole even before closure of AV valve (S_1) and continue throughout the systole—even after closer of aortic valve (S_2) as LV pressure is still higher than RV pressure.

So a pansystolic murmur starting before S_1 ends beyond A_2 completely masking it (A_2).

The shunted blood from LV almost directly enter the pulmonary artery because both ventricle is contracting simultaneously.

An ejection systolic murmur is heard over pulmonary region due to increased flow of blood through the pulmonary artery.

In the background of pansystolic murmur at VSD site, pulmonary ejection systolic murmur cannot be well-recognized. But it can be recognized as selective transmission of ejection systolic murmur to the left 2nd space where its ejection character can be recognized.

Increased pulmonary flow causes delayed loud P_2 with wide variable split of S_2.

Increased blood flow through the pulmonary circuit produces pulmonary plethora on X-ray.

Increased pulmonary flow produces left heart volume overload.

Left atrial enlargement produces parasternal thrust. Accentnated S_1 usually not appreciated at the bed side. Early A_2 is due to decrease LVET (left ventricular ejection time).

Increased flow across mitral valve produces a *functional delayed diastolic murmur (differential diagnosis of murmur of MS)*.

Complications and Prognosis of VSD

- **Restrictive VSD**—Spontaneous closer, no hemodynamic burden.
  - High-risk of endocarditis.
- **Perimembranous defect and doubly committed VSD**—
  - Progressive AR.
  - Later development of subaortic and subpulmonary stenosis.
- **Moderately restrictive VSD**
  - LA, LV, dilation and dysfunction.
  - Increase pulmonary vascular resistance.
- **Nonrestricted VSD**
  - Progressive rise in pulmonary vascular resistance starting early in life.
  - Eisenmenger's syndrome develop at later stage.

Clinical Features in Pediatrics

- **Restrictive VSD**—Present with murmur in the neonatal age group only when pulmonary vascular resistance falls.
- **Large nonrestrictive VSD**—Present at a later age due to equalization of pressure of both ventricle obviates the generation of pansystolic murmur.
  - Presents with breathlessness, congestive heart failure and failure to thribe at 2nd and 3rd month of life.
  - Pulmonary ejection murmur due to increased flow through pulmonary artery.
  - Middiastolic mitral rumble due to increased flow through mitral orifice.

Clinical Features in Adults

- **Small restrictive VSD** are asymptomatic.
  On examination—A harsh, high frequency pansystolic murmur usually grade 3/6–4/6 with maximal intensity at the left sternal boarder on left 3rd or 4th ICS.
- **Moderately restrictive VSD**—Presents with dyspnea usually triggered by atrial fibrillation.
  Apex—Displaced down and outward.
  Pansystolic murmur of grade 3/6–4/6 with a apical diastolic rumble and S_3 due to increased flow through mitral valve.
- **Large nonrestrictive VSD with Eisenmenger**—
  Central cyanosis, clubbing with pedal edema due to RVF.
  Sign of pulmonary hypertension—Right ventricular heave—
  - Palpable and loud P_2.
  - Right-sided S_4.
  - Pulmonary ejection click.
  - Soft ejection systolic murmur.
  - High pitch early diastolic murmur of pulmonary regurgitation (**Graham steell murmur**).

Investigations

ECG

- The congenital right ventricular hypertrophy disappears slower than normal.

Small restrictive VSD have normal ECG tracing.
Moderately restrictive/Nonrestrictive VSD—

- Evidence of LA, LV volume overload and distension.
- Deep Q, Tall R, Tall T, LV enlargement.
- Wide bifid/notched LA enlargement.
- Following repair there may be features of RBBB.

Chest X-ray

- Reflects the magnitude of the shunt and degree of pulmonary vascular resistance.
- Heart size is enlarged with LV type enlargement.
- Pulmonary plethora.
- Hypoplastic aorta.
- LA - enlargement.
- In small/restrictive VSD pulmonary vasculature is normal.
- A moderate size shunt causes signs of left ventricular dilation with some pulmonary plethora.

Echocardiography

Identify

- The location, size and hemodynamic consequence of VSD.
- Presence of associated AR and/ or LVOT obstruction.
- Mitral valve motion.
- Presence of pulmonary stenosis/RVOT obstruction.
- Presence of pulmonary hypertension.

Cardiac catheterization is to be done for

- Measurement of pulmonary arterial pressure.
- Therapeutic percutaneous closure of VSD specially in muscular VSD.

Assessment of Severity

- **Small restrictive VSD**—Pansystolic murmur with normal S_2 (P_2-normal intensity, normally split S_2). Absence of DDM over apex.
- **Very small VSD**—Ejection systolic murmur (small VSD acts as stenosing valve).
  Functional systolic murmur that disappear when the patient grows up.
- **Short ejection systolic murmur**
  - RVOT obstruction. Soft P_2 but delayed. Widely split variable S_2.
  - Large nonrestrictive shunt. Loud and delayed P_2 with wide variable split.
- **PHTN (P_2 loud / accentuated)**
  - Hyperkynetic—Pansystolic murmur with thrill widely split—variable S_2 and mitral DDM.
  - Obstructive—Thrill absent. S_2 is closely split. No mitral DDM. No thrill or parasternal impulse.

Complications and Fate

- CCF—Develops around 30–40 years of age.
- Infective endocarditis—It is the most common congenital lesion producting SABE.
- Subvalvular pulmonary stenosis.
- PHTN.
- AR due to prolapse of right coronary/noncoronary cusp.
- Spontaneous closure—90% by 3 years.

Treatment

Medical management

- Control of CCF—by diuretic and ACEI in child to buy time prior to surgery for diminution of size or spontaneous closer.
- Treatment of repeated chest infection.
- Prevention and treatment of anemia.
- Prevention and treatment of infective endocarditis.

Surgical management

Indications

- CCF in early childhood and not responding to treatment.
- Large (left to right) shunt (Qp/Qs >1.4).
- Associated pulmonary stenosis.
- Associated pulmonary HTN (>50 mm Hg).
- Increased LA/LV size.

Relative Indications

- Associated AR.
- History of recurrent endocarditis.
- Early surgical intervention is done at 3–9 months of age.
- In presence of evidence of PHTN (>50 mm Hg) surgery is done at 2 years of age.
- In presence of evidence of CCF which is refractory to medical treatment surgery is done at 1 year of age.

Interventional Options and Outcomes

- Direct suturing.
- Patch (Dacron) repair is preferred. It has the following advantages like—
  - High closure rate.
  - Low perioperative mortality.
  - Patch leak is uncommon and seldom needs reoperation.
- Right atrial approach is preferred to right ventriculotomy (complication RBBB).
- Device closure by cardiac catheter, is useful in muscular VSD and perimembranous VSD.
- Eisenmenger syndrome is contraindication of surgery.
- Yearly check up is necessary after surgery of with VSD *with other complications*.

Complications of Surgery

Risk of complication is <2% in surgery
- Complete heart blocks
- Bifascicular blocks
- RBBB
- Residual VSD or incomplete closer.

FALLOT'S TETRALOGY (TOF)

The four components of the defect in TOF:
- Obstruction of right ventricular outflow tract.
- Outlet VSD.
- RVH.
- Overriding of aorta (<50%).

The fundamental abnormalities are abnormal anterior and cephaloid deviation of outlet septum in respect to trabecular septum.

The dominant site of obstruction of right ventricular outflow tract is usually at the subvalval level of pulmonary valve but sometime the whole right ventricular outflow tract may be atretic.
- **Associated abnormality**
  - Right sideed aortic arch (25%).
  - The origin of anterior descending (anterior interventricular) artery is from right coronary artery.
  - Absence of pulmonary valve.

PATHOPHYSIOLOGY OF TOF

In the absence of alternative source of pulmonary blood flow the degree of cyanosis is directly proportional with—
- Severity of right ventricular outflow tract obstruction
- Level of systemic vascular resistance.

EPIDEMIOLOGY OF TOF

- TOF accounts for 75% of all congenital cyanotic heart disease >2 years of age.

NATURAL HISTORY OF TOF

Progressive hypoxemia is the most prominent feature in the first few years of life. Survival into adult life with palliation or correction is possible.

HEMODYNAMIC ABNORMALITY OF TOF

- Physiologically pulmonary stenosis causes concentric RVH.
- Then the right ventricular pressure is greater than aortic pressure then right to left shunt appear to decompress RV.
- With increase in severity of PS greater will be the shunt, but the intensity of systolic murmur (which is due to PS) will decrease.
- As the systolic pressure difference between two ventricle is very low, VSD remains silent (no murmur at the site of VSD).
- Right to left shunt is also silent as there is insignificant pressure difference between RV and aorta.
- As RV is effectively decompressed by VSD, CCF never occur unless the patient is associated with other abnormality like—anemia, infective endocarditis, HTN, unrelated myocarditis, AR and PR.

CLINICAL FEATURES OF TOF

- Patient may become symptomatic anytime after birth. Neonates as well as infants may face anoxic spell. Cyanosis may be present from birth or may appear later.

Symptoms of TOF

1. **Dyspnea on exertion (DOE)**—The most common symptoms is DOE (dyspnea on exersion) and exercise intolerance.
2. **Squatting**—It is the most common congenital lesion where squatting is noted. During exercise the systemic resistance fall so more amount of blood from right ventricle is shunted to aorta and thereby flow through pulmonary artery fall further and this cause increase in cyanosis and increase in dyspnea. Squatting increases the systemic resistance which diverts blood from aorta to pulmonary artery and results in improvement of cyanosis.
3. **Anoxic spell**—Mostly occurs after wakeing up from sleep or after exersion—child starts crying and become dyspneic, bluer than before and may become unconscious or *convulsion may develop*. Frequency of anoxic spell may vary from once in a few day to multiple attacks in a day.

Signs of TOF

- Cyanosis
- Clubbing
- Neck vein with prominent a-wave.

CVS

- Normal-sized heart.
- Mild parasternal impulse.
- Systolic thrill over pulmonary artery present in less than 30% patient.
- Normal S_1.
- Single S_2, the audible sound is A_2.
  Delay in P_2 due to RVOT obstruction.
  P_2 is reduced in intensity and is due to decrease pulmonary pressure.
  Late and soft P_2 is generally inaudible in TOF since aorta is somehow anteriorly displaced.

- Ejection systolic murmur in left 2nd ICS which usually ends before S_2 and is due to pulmonary stenosis.
- Constant aortic ejection click due to dilated aorta.
- In constant pulmonary ejection click due to valvular PS.

X-ray

- Normal-sized heart with features of RVH (upturn apex, absence of main pulmonary artery segment gives the heart boot shape (Coeur-en-sabot).
- Aorta is enlarged and in 30% cases right-sided which is diagnosed by concave impression on right side of trachea.
- Pulmonary fields are oligemic.

ECG

- Right axis deviation
- Feature of RVH
- T-wave is inverted in right precordial lead
- P-pulmonale may be present.

ECHO

Can identify the followings:
- Overriding of aorta
- RVH
- RVOT obstruction
- VSD.

COMPLICATIONS OF TOF

- Anoxic spell which are potentially fatal.
- Anemia may complicate the disease and may predispose CCF.
- Very prone to develop infective endocarditis.
- Neurological complication are frequent and is due to paradoxical embolism.
  - Venous thrombosis develop in leg vein due to sluggish circulation and polycythemia which may dislodge and pass via VSD from right side to left side and ultimately embolize in cerebral vessel causing cerebral abscess is called **paradoxical embolism**.
    Brain abscess presents with headache, convulsion, vomiting with or without fever and neurological deficit.

Management

Treatment actually consist of:
- Symptomatic treatment
- Palliation
- Curative surgery.

Symptomatic treatment

- Correction of anemia and other complicating factor that may precipitate CCF.
- Management of anoxic spell
  - Squatting.
  - Humidified 100% O_2 by mask.
  - Morphine – 0.1–0.2 mg/kg IV.
  - Correct acidosis by IV infusion $NaHCO_3$.
  - Propranolol 0.1 mg/kg IV during cyanotic spell and 0.5 –1 mg/kg every 4–6 hourly as maintenance dose.
  - Vasopressor—Methoxamine may be used IM or IV.
- Management of arrhythmia—
  - Medical or catheter ablation.

Palliation

3 types of operative treatment usually done.
- **Blalock-Taussig shunt (preferred method)** Anastomosis of subclavian artery with pulmonary artery. Anastomosis is made with a goretex graft, usually done on the opposite side of aortic arch.
- **Potts shunt**—Descending aorta is anastomosed with pulmonary artery.
- **Waterston's shunt**—Ascending aorta is anastomosed with right pulmonary artery.

  These 3 operations are usually done to prolong the life and to increase the exercise tolerance.

Indications of Surgical Intervention

- **Children**—
  - Symptomatic infants are now repaired at any age.
  - Asymptomatic infants are repaired in the first 6 months of age.
    - This is done by transannular patch for enlargement of RVOT.
    - Balloon valvuloplasty of RVOT and pulmonary artery is preferred in prematurity and marked hypoplasia of pulmonary artery.
- **Adult (unoperated)**—Surgical repair is still recommended as the results are gratifying.
- **Adult (palliative)**—Seldom intended as a permanent strategy as palliated patients are at increased risk of cyanosis and erythrocytosis (from gradual shunt stenosis or development of pulmonary hypertension).
- **Adult (repaired)**—The following situation may warrant reoperation.
  - Residual VSD (with shunt >1.5 : 1)
  - Residual pulmonary stenosis
  - Severe pulmonary regurgitation
  - Rapid enlargement of RVOT aneurysm
  - Significant AR—aortic root diameter >55 mm
  - Progressive left ventricular dilatation.

  Curative surgery—Consist of closing the VSD and resecting the RVOT obstruction.

PATENT DUCTUS ARTERIOSUS (PDA)

INTRODUCTION OF PDA

Patent ductus arteriosus, derives from the left 6th primitive arch and connects the proximal left pulmonary artery to descending aorta just (5–10 mm) distal to left subclavian artery.

It is present in fetal life but functional closure of the duct occurs shortly after a term birth due to vaso-constriction whereas anatomical closure from intimal proliferation and fibrosis takes several weeks afterbirth to complete.

PDA are present in 5–10% of term infants. Females predominate over males as M : F = 1 : 3.

TYPES OF PDA

PDA are categorized according to the degree of left to right shunt which is determined both by the size and length of the duct and the difference between systemic and vas- cular resistance as follows—

- **Silent**—Tiny PDA detected only by nonclinical measure (e.g. Echo).
- **Small**—Continuous murmur common, Qp/Qs <1.5 : 1 (pulmonary flow : systemic flow).
- **Moderate**—Continuous murmur uncommon Qp/Qs = (1.5–2.2): 1.
- **Large**—Qp/Qs >2.2 : 1.
- **Eisenmenger's**—Continuous murmur absent, substantial pulmonary hypertension, differential cyanosis and hypoxemia is present.

NATURAL HISTORY OF PDA

PDA is common in preterm infants and delayed spontaneous closure of PDA may be anticipated if the infant does not succumb to other problem.

Full-term infant—Sometime full-term newborn have PDA because of relative hypoxia which contribute to vasodilatation of the duct. These include

1. Infant born at high altitude.
2. Congenital malformation causing hypoxia.
3. Malformation in which the PDA supply systemic circulation such as hypoplastic left heart syndrome. Interrupted aortic arch and aortic coarctation.

CLINICAL FEATURES OF PDA

- **Most preterm infant** (birth weight <1.5 kg) have a PDA of which 1/3rd is large enough to cause significant cardiopulmonary deterioration.
  - *On examination*
    - Bounding peripheral pulse
    - Precordial pulsation
    - Multiple episode of apnea and tachycardia.
    - *Hepatomegaly*
      - On auscultation–left-sided infraclavicular and sometime interscapular systolic murmur over back (occasionally continuous in nature).
- **Full-term infant, children and adult**
  - Small PDA usually cause no symptom but may present as endarteritis.
  - On exam—Grade - 1/2 continuous murmur peaking in late systole, best hard in left 2nd and 3rd ICS.
- **Moderate size PDA**
  - Dyspnea and palpitation due to atrial arrhythmia.
  - Louder continuous/mechinary murmur on 1st and 2nd left ICS with LV type of apex and left-sided thrill.
  - When pulmonary HTN develops the diastolic component of murmur disappear.
- **Large PDA**—Presents with short ejection—systolic murmur with cyanosis more over abdomen than in hands (differential cyanosis due to reversal of shunt in PDA).

INVESTIGATIONS OF PDA

ECG

- **In infant**—May be normal/demonstrate LVH/RVH or both.
- **In full-term child and adult**—
  - Small PDA may present with normal ECG
  - Moderate size PDA
    - Notched P-wave
    - Deep Q
    - Tall R
    - Peaked T

    } In V_5,V_6
  - Large size PDA—produce RVH

Chest X-ray

- **In infant**—Cardiomegaly with increased pulmonary vascular marking. (differential diagnosis—hyaline membrane disease of lung).
- **In full-term child and adult**
  - *Small duct*—Normal chest X-ray.
  - *Moderate duct*—Cardiomegaly with LVH
    - With prominent aortic knuckle
    - Increased pulmonary markings
    - Sometimes calcification may be seen.
  - *Large duct*—Present with prominent aortic knuckle characteristic of Eisenmenger syndrome.

ECHO

- **In infants**—PDA can be imaged entirely from high parasternal and suprasternal notch view.
- **In child and adult**—Determine the size, pressure, degreeof shunting with its physiological consequence. It can measure LA and LV size to provide indirect evidence of the magnitude of left to right shunt.

Treatment

1. Transcatheter device closer is the procedure of choice for duct smaller than 8 mm. Complete closer in achieved in >85% within 1 year. Mortality is <1%
2. Surgical treatment : Surgical closer by ligation or division is the method of choice with difficult ductal morphology (calcified or aneurysmal). Complete closer is achieved in 95%. Mortality >25%.

Differential diagnosis of continuous murmur

It includes all the condition capable of producing a contineous murmur over the precordium and also the conditions capable of producing a combination of pansystolic murmur along with a early diastolic murmur

a. Coronary A-V fistula
b. Ruptured sinus Valsalva
c. Aortopulmonary window
d. Pulmonary AV fistula
e. Systemic A-V fistula over the precordium
f. Bronchial collateral
g. Peripheral pulmonary stenosis
h. Small ASD in combination with MS
i. Venous hump arising from TAPVC

Differential diagnosis of combined pansystolic and early diastolic murmur—

a. MR/TR with AR
b. VSD with AR
c. AS and AR—Not as continuous murmur because there is little gap in between the two murmurs

Chapter 8

Cardiomyopathy

DEFINITION

The *cardiomyopathies are group of diseases that affect the heart muscles primarily and the changes in myocardium are not secondary to ischemic, hypertension or congenital or acquired valvular, coronary or pericardial diseases.*

The diffuse myocardial fibrosis that accompanies multiple myocardial scar produced by extensive coronary artery disease can impair LV function and is frequently termed as 'ischemic cardiomyopathies'.

This irrational use of the term should be avoided; the term cardiomyopathy should be restricted to a condition primarily involving the myocardium.

CLINICAL CLASSIFICATION OF CARDIOMYOPATHIES

- **Dilated**—Left ventricular or right ventricular or biventricular enlargement, impaired systolic function, characterized by CCF along with arrhythmias and embolization may be present.
- **Restrictive**—Endomyocardial scarring or infiltration resulting in restriction to ventricular filling.
- **Hypertrophic**—Disproportionate LV hypertrophy, involving IVS more frequently than free wall, with or without intraventricular pressure gradient.

DILATED CARDIOMYOPATHY

About 33% of all cases of CHF is due to dilated cardiomyopathy. Systolic pump function is impaired leading to progressive cardiac enlargement with hypertrophy which is known as 'remodeling'.

Although no cause is apparent in many cases, dilated cardiomyopathy is usually produced by toxic, metabolic or infectious agent (viral).

A reversible form of DCM may be found in **alcoholic, peripartum, thyroid disease, cocaine abuse**. 20–40% have familial form of disease. The disease is genetically heterogenous and most commonly autosomal dominant, but autosomal recessive and mitochondrial or X-linked inheritance is also found.

CLINICAL FEATURES OF DCM

Symptoms

- Symptoms of left or right-sided heart failure develop gradually in most patient.
- Vague chest pain may be present but typical angina does not occure.
- Syncope due to arrhythmia or cerebral embolism from heart is a rare finding.

Signs

- Systolic pressure is low. Diastolic pressure is more or less normal.
- Pulse pressure is narrow (decapitation of blood pressure).
- JVP elevated.
- Apex shifted down and out.
- S_1 and S_2 are soft. S_3 and S_4 are commonly present.
- Murmur of MR or TR may be present.

Investigation

- **Chest X-ray**—Shows enlargement of cardiac silhouette. Lung field shows evidence of pulmonary venous hypertension and interstitial or alveolar edema.
- **ECG**—Shows sinus tachycardia, atrial fibrillation, ventricular arrhythmias, diffuse nonspecific ST-T changes or intraventricular conduction block and low voltage complexes.
- Echo is the *best method for diagnosis. It shows LV dilatation (LVEDD >7 cm) with thinned wall and reduced ejection fraction with hypokinesia of both ventricles.*
- Cardiac catheterization and coronary angio is done to exclude IHD.
- Brain natriuretic peptide (BNP) is elevated due to heart failure.

Prognosis

Majority of patients show rapid down hill course specially over 55 years of ages and die within 3 years.

Spontaneous improvement and stabilization seen in 25% of patients. Death in dilated cardiomyopathy is due to—
- Congestive heart failure (CHF)
- Ventricular arrhythmias
- Embolism.

Treatment

- Standard therapy of heart failure with **diuretic**, **digitalis, ACEI, β-adrenergic blocker and spironolactone**.
- Alcohol—To be avoided.
- About 33% of patients who have conduction defect (RBBB/LBBB) biventricular pacing improves symptoms.
- Immune suppressive therapy—not beneficial.
- Antiarrhythmic agent is best avoided for fear of its proarrhythmic effect. CCB and NSAID are best to be avoided.
- Cardiac transplantation should be considered who are refractory to medical therapy.

HYPERTROPHIC CARDIOMYOPATHY

It is *characterized by left venticular hypertrophy (LVH)* (typically with nondilated chamber) and *not secondary to obvious cause like HTN or aortic stenosis*.
Two characteristic features are—
- Asymmetric LVH with striking regional variation in the extent of hypertrophy in different portions of LV often with *preferential hypertrophy of IVS called asymmetric septal hypertrophy (ASH)*. Other group shows disproportionate hypertrophy.
- Dynamic LV outflow tract obstruction as evidenced by pressure gradient due to *midsystolic apposition of anterior mitral leaflet against the hypertrophied septum [due to systolic anterior motion (SAM) of mitral valve]*.

  Only 33% of patients of HCM demonstrate outflow tract pressure gradient at rest and 66% after provocative test.

GENETIC CONSIDERATION OF HCM

Half of the patients have autosomal dominant transmission.

Clinical Features

Symptoms

- Many patients are asymptomatic.
- Most common symptoms are
  - Dyspnea—Due to increased stiffness of LV wall which impairs LV filling leading to elevated LV diastolic and left atrial pressure.
  - Angina.
  - Fatigue.
  - Syncope: Symptoms are not closely related to outflow pressure gradient and are probably related to diminished ejection fraction and arrhythmia.
- Sudden death can occur during or after physical exercise, probably due to arrhythmia.

Signs

- **Double or tripple apical impulse**.
- Rapidly rising carotid arterial pulse.
- **S_4 is usually present**.
- *Diamond-shaped ejection systolic murmur begins well after S_1 best heard at lower left sternal border, due to dynamic LV outflow tract obstruction and a holosystolic blowing murmur at apex due to MR may be present.*

Investigations

- **ECG findings are the followings**:
  - LVH.
  - *Widespread deep and broad Q simulating old MI but is due to septal hypertrophy*.
  - SVT, atrial fibrillation.
  - VT.

  } Can be demonstrated by holte monitoring
- **Chest X-ray**—
  - May be normal.
  - Mild to moderate cardiomegaly is common.
- **Echocardiography** is the **best method for diagnosis** shows the followings:
  - *LVH.*
  - *IVS is 1.3 times or more thicker than posterior wall and has ground glass appearance due to myocardial fibrosis.*
  - *SAM (systolic anterior motion of mitral valve) is seen with MR and pressure gradient.*
  - *LV cavity size is small with vigorous posterior wall motion and reduced septal excursion.*

Cardiac catheter

It is not essential for diagnosis but two typical features are
- **Elevated LV diastolic pressure**.
- **Systolic pressure gradient between body and sub-aortic region of LV**.

Treatment

- **β-blocker** is used for angina and syncope but does not give protection form sudden cardiac death.
- **Amiodarone** for arrhythmia like SVT and VT.
- **Verapamil** or **diltiazem** may reduce the stiffness of the ventricle and reduce the diastolic pressure and improve disastollic filling.
- Atrial fibrillation must be treated either by **β-blocker or ablation of AV node and insertion of a pacemaker** when sinus rhythm cannot be sustained.
- **Surgical myotomy or myectomy of the hypertro-phied septum**—results in long-lasting improvement in 75% of severely symptomatic patient with large pressure gradient.

- Infarction of the IVS by **intraarterial ethanol injection** reduces obstruction and improves symptoms.
- Digitalis, diuretic, nitrates, vasodilator, β-adrenergic agonist and alcohol are avoided particularly in those with outflow tract pressure gradient.
- **Implantable cardioverter defibrillator (ICD)** should be considered in patients with high-risk profile to prevent sudden cardiac death due to arrhythmia.

RESTRICTIVE CARDIOMYOPATHY

The hallmark of restrictive cardiomyopathies is diastolic dysfunction. The rigid ventricular wall impede ventricular filling. **Myocardial fibrosis, hypertrophy and infiltration** are the causes of restrictive cardiomyopathy.

Infiltrative disease like **amyloid, hemochromatosis, glycogen deposition, endomyocardial fibrosis, sarcoidosis, Fabry's disease, eosinophilia** and **scleroderma, radiation, malignant infiltration** are the common causes of secondary restrictive cardiomyopathy.

CLINICAL FEATURES OF RC

Symptoms

Most prominent symptoms are
1. Exercise intolerance
2. Dyspnea.

Signs

- *Raised JVP does not fall normally or it may actually rise during inspiration (Kussmaul's sign).*
- *Pedal edema.*
- *Enlarged tender liver.*
- *Ascites.*
- *Apex is easily palpable.*
- *Heart sounds are diminished in intensity.*
- *MR usually present.*

Investigation

- **ECG**—Low voltage, nonspecific ST-T changes and various arrhythmias.
- **Echo—Symmetrically thicked LV wall with slightly reduced ventricular volume and systolic function**.
- **Catheter**—Decreased cardiac output with elevated RV and LV end-diastolic pressure and a **dip-and-plateau configuration of the diastolic portion of the ventricular pressure pulse** (resembling constrictive pericarditis).

Differential Diagnosis

- **Constrictive pericarditis**
  - RV transvenous endomyocardial biopsy—reveals myocardial infiltration or fibrosis.
  - CT/MRI —Shows thickened pericardium in constrictive pericarditis.

Treatment (Usually Disappointing Except)

- **Hemochromatosis** by deferoxamine (iron-chelating agent) continuous SC infusion.
- **Fabry's disease**—Infusion of galactose. Stimulate the activity of deficient enzyme with attendant improvement in cardiac function.
- **Chronic anticoagulation**—To reduce the risk of embolization.
- **Endomyocardial fibrosis**—Surgical excision of fibrotic endocardium and replacement of A-V valve.
- **Eosinophilic endomyocardial disease**
  - Diuretic.
  - Afterload reducing agent.
  - Anticoagulation.
  - Glucocorticoid and cytotoxic drug like hydroxy- urea improves survival.
  - Surgical treatment like endomyocardial fibrosis.

Chapter 9

Tachyarrhythmias

Three basic mechanisms responsible for tachyarrhythmia are—

- **Increase automaticity**—It is due to—
  - An increased slope of phase '4' of the action potential.
  - Decrease in the threshold for phase 'O' of the action potential.
- **Triggered activity** (Fig. 9.1)—It is due to—
  - Early after depolarization (EAD) during phase '3' of action potential and is due to alteration of plateau current, responsible for VPC that triggers TDP.
  - Delayed after depolarization (DAD) during phase '4' of action potential due to intracellular accumulation of calcium responsible for atrial, junctional and fascicular tachyarrhythmias due to digoxin toxicity.
- **Reentry**—The basic requirement for reentry is the presence of two pathways that have heterogenous electrophysiologic properties which allow conduction to block in one pathway and to propagate the impulse slowly in the other (due to varied refractory period) allowing sufficient time so that the blocked site gets time to recover and to allow reentry. Reentry is responsible for **VF in AMI**, and polymorphic VT in genetically determined channel abnormality in **Brugada syndrome, LQTS, catecholaminergic polymorphic VT, AVNRT, accessory pathway mediated VT**.

ATRIAL PREMATURE COMPLEXES (APC)

It is the most common arrhythmia and incidence increases with age and presence of structural heart disease and is usually asymptomatic. Patient may complain of palpitation or irregular pulse.

SITE OF ORIGIN OF APC

APC usually arises from orifice of *superior vena cava, pulmonary vein, coronary sinus, crista terminalis, mitral and tricuspid valve annuli, left and right atrial appendages*.

Configuration of P-wave in APC differs from that arising from SA node but APC arising from right atrial appendages, SVC and superior aspect of crista terminalis region may mimic P-wave of sinus origin.

Usually APC has long PR interval as the impulse is conducted through muscle bundle but when the areas of APC is near AV-node it is conducted rapidly through AV node and the partially recovered His-Purkinje system producing RBBB or LBBB pattern. The wide ORS with P-wave overlap looks like VPC.

As APC resets the sinus node the pre and post APC-RR interval is less than twice sinus PP interval.

TREATMENT OF APC

a. APC usually requires **no treatment**.
b. For extremely symptomatic patient **β-blocke**r or when no structural heart disease is present **class IC antiarrhythmic** agent may eliminate APC.
c. **Catheter ablation** may be done in extreme cases.

JUNCTIONAL PREMATURE COMPLEXES

These are extremely rare arrhythmias. It arises from AV node and His bundle region and may cause retrograde atrial conduction. In that condition P-wave distorts the initial or terminal portion of QRS complex producing pseudo Q or S-wave in II, III and AVF.

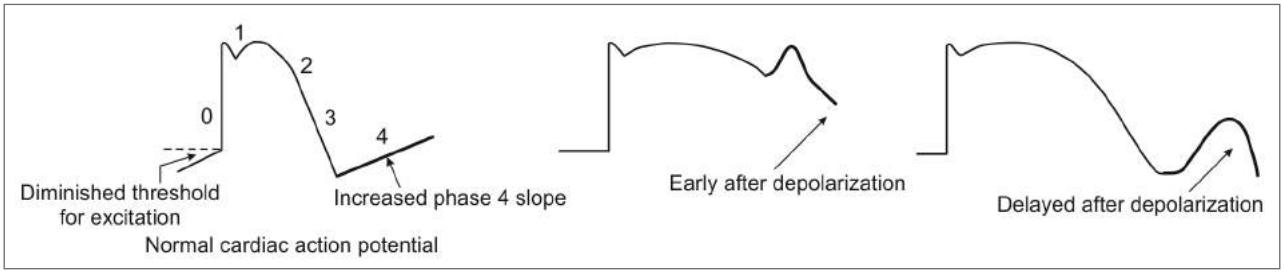


Fig. 9.1: Mechanism of production of ectopic

Junctional ectopic arising from His bundle sometime may not be conducted to ventricle as the lower pathway is in refractory period and also block the oncoming sinus beat producing an unexplained long PR interval that does not follow typical wenckebach periodicity (gradual prolongation of P-R interval with a drop of beat).

Treatment

Symptomatic patient with junctional premature complexes are treated by **β-blocker** or if there is no structural heart disease it can be treated with class **IC antiarrhythmic** agent.

SINUS TACHYCARDIA (ST)

It is recognized by the configuration of P-wave. P-wave is upright in II, III, aVF, negative in aVR and biphasic (positive-negative) in V_1.

Physiological condition producing sinus tachycardia are—exercise, anxiety and fever.

Pathological condition producing sinus tachycardia are—hypotension, thyrotoxicosis and anemia.

Onset of sinus tachycardia is gradual and moderate slowing occurs in response to carotid sinus pressure but there is no abrupt termination.

Inappropriate sinus tachycardia—This form of sinus tachycardia occurs due to dysautonomia after viral fever in which heart rate increases either spontaneously or out of proportion to the degree of physiologic stress or exercise and persist over 3–12 months.

TREATMENT OF ST

Treatment of sinus tachycardia is directed toward the underlying condition, e.g. anemia, thyrotoxicosis and correction of hypotension.

Inappropriate tachycardia usually resolves spontaneously. Rarely **β-blocker** may be needed in the background of IHD and angina.

Those who are intolerant to β-blocker **catheter ablation** and **atrial pacing** may be considered as a second line of therapy.

ATRIAL FIBRILLATION (AFib)

It is the most common sustained arrhythmia.

Initiation of the arrhythmia occurs from atrialized musculature that enters the **pulmonary vein or other vein of the atria** either by focal abnormal automaticity or triggered firing.

The maintenance of arrhythmia is done by **disorganized atrial musculature with microreentry**.

The ventricular rate is usually 120–160/min but may be > 200/min or in patient with heightened vagal tone or intrinsic AV block the rate may be <100/min.

ETIOLOGY OF AFib

- Incidence of AF increases with age and seen in > 5% of adult population over 70 years of age.
- IHD and hypertension.
- Acute thyrotoxicosis.
- Acute vagotonic episode.
- Acute alcohol intoxication.
- Rheumatic mitral stenosis.
- Acute or recovery phase of abdominal vascular or thoracic surgery.
- May be triggered by AVNRT such as paroxysmal SVT in WPW syndrome.

CLINICAL IMPORTANCE OF AFib

- Loss of atrial contractility aggravates heart failure.
- Fast ventricular rate reduces the diastolic period which interferes with ventricular filling and aggravates heart failure.
- Loss of contractility of atrial appendages enhances the chance of clot formation within it and subsequent thromboembolic manifestation.

CLINICAL FEATURES OF AFib

- Occasionally the patient may be asymptomatic or only minor palpitation may be present.
- Occasionally severe dizziness or syncope are associated with long ventricular pause.
- Exercise intolerance and easy fatigability are present when ventricular rate is poorly controlled.
- Hypotension, pulmonary congestion and angina may be present.
- Symptoms may be more severe with fast ventricular rate due to diastolic dysfunction associated with HTN, aortic stenosis and hypertrophic cardiomyopathy.

MANAGEMENT OF AFib

- The following facts are to be considered before starting treatment of atrial fibrillation—
  - Etiology of AF
  - Chronicity of AF
  - Hemodynamic status of the patient and symptom
  - Ventricular rate
  - Level of anticoagulation
  - Presence of risk factor for stroke.
- Correction of etiological factor like anemia, thyrotoxicosis and structural heart disease (like MS) is the first step of management of AF.
- Anticoagulation to be started in patient whose AF is more than 48 hours duration [or TEE (transesophageal echocardiography) shows presence of thrombus in left atria] and to be continued for 1 month after restoration of sinus rhythm.

- Another alternative option of chronic anticoagulation is gradually coming up is in the form of surgical elimination or isolation of left atrial appendages with endovascular insertion of left atrial appendage occluding device.

- Chronic anticoagulation with warfarin targetting INR between 2–3 is recommended in patient with chronic or frequent long paroxysmal AF with risk factors like—(i) TIA, (ii) P/H of stroke, (iii) systemic embolism, (iv) MS, (v) diabetes, (vi) HTN, (vii) LV dysfunction with LA >5 .0 cm, (viii) age >65 year and (ix) history of CCF

- **Termination of AFib**—If hemodynamic compromise is present [as suggested by (i) SBP <90 mm, (ii) presence of angina, (iii) sign of cerebral anoxia, and (iv) dyspnea], emergency termination of AF to be done by—
  - DC transthoracic cardioversion under cover of short-acting anesthesia with 200 J biphasic shock delivered synchronously with QRS complex. It is the most reliable way of termination of AF; success rate > 90%.
  - IV administration of **ibutilide** facilitates termination of AF with DC cardioversion or can be used singly for **pharmacologic termination** of AF.
  - Pharmacological termination of AF is less reliable but can be tried with oral or IV **amiodarone** or **procainamide** with moderate success.
- **Rhythm control**—If hemodynamic compromise is not present (as suggested by SBP >90 mm, absence of angina, no sign of cerebral anoxia and dyspnea), maintenance of sinus rhythm can be tried by:
  - It can be better achieved by class IC agent like **flecainide** or **propafenone** which have no proarrhythmic risk in absence of HTN and LVH.
  - In presence of structural heart disease, like CAD, depressed LV function, HTN, LVH with rapid heart rate and significant symptoms, sinus rhythm can be achieved by **sotalol, amiodarone, dofetilide**. Due to risk of QT prolongation and polymorphic VT, sotalol and dofetilide to be initiated in hospital.

- Over 50% of patients have recurrence of AF within 1 year who are receiving pharmacologic maintenance therapy
- Pharmacologic maintenance of sinus rhythm is not superior to chronic rate control and anticoagulation
- To reduce the risk of tachycardia related cardiomyopathy, heart rate to be kept <80/min during rest or <100/min during moderate exercise

- **Rate control**—
  - **Pharmacotherapy**—This is usually done in asymptomatic patient or symptomatic patient with tachycardia who have persistent form of AF.
    Rate control is done either by **β-blocker, CCB (diltiazem and verapamil)** or **digoxin**. Combination therapy may be done to avoid the side effect of high dose monotherapy.
  - **Ablative therapy**—If rate control could not be achieved by pharmacotherapy; then His bundle/AV junction ablation coupled with implantation of pacemaker to be done.
    Biventricular pacing should be used to minimize the degree of dyssynchronization that occurs with RV apical pacing.
    Rate control treatment (both pharmacologic or ablative) should be coupled with chronic anticoagulation.

Class I agent—Blocks inward sodium current
Class II agent—β-blocker
Class III agent—Prolongs action potential
Class IV agent—Calcium channel blocker

- **Surgical or catheter ablative therapy for prevention of AFib**—Two types of procedure are available. In this new approach isolation of atrial muscle sleeves entering the pulmonary vein are done as these muscle sleeves are thought to be the major trigger for AF. Elimination of AF upto 50–80% can be done with catheter ablation procedure. It can be considered as an alternative to His bundle ablation with pacemaker implantation. Complications are— (i) pulmonary vein stenosis, (ii) atrioesophageal fistula, (iii) systemic embolisms and (iv) perforation of atria with cardiac tamponade.
  - Surgical ablation of AF is usually done at the time of valve surgery or coronary artery surgery. Previously **cox surgical maze procedure** was designed to interrupt all macroreentrant circuit that might potentially develop in atria by giving multiple incision on the atrial wall.
  - Now it is done by linear lines of ablation and pulmonary vein isolation using a variety of energy source.

ATRIAL FLUTTER (AFL) (TABLE 9.1)

Atrial flutter (AFL) and macroreentrant atrial tachycardia are synonymous both denoting a nonfocal source of an atrial arrhythmia.

Table 9.1: Summary of indication of antiarrhythmic in AF

Indication of antiarrhythmic in AF	First line	Second line
Normal heart without CAD	Class IC antiarrhythmic agent	Sotalol/amiodarone
Adrenergic-induced AF without structural heart disease	Standard β-blocker	Sotalol
HF	Amiodarone, defetilide	
CAD with preserved LV function	Sotalol	Amiodarone
HTN with LV wall thickness <1.4 cm	Classic IC antiarrhythmic agent (flecanide, propafenon)	Sotalol/amiodarone
HTN with LV wall thickness >1.4 cm	Amiodarone	

The typical circuit for AFL rotates clockwise or counterclockwise direction around tricuspid valve annulus. The posterior boundary of the right atrial—AFL circuit are crista terminalis, eustachian ridge, the inferior and superior vena cava. 80% AFL circuit in right atrium rotates in an anticlockwise direction with sawtooth-like P-wave in II, III, aVF lead. When the same right atrial circuit rotates in clockwise direction produces upright P-wave in lead II, III, aVF.

The AFL circuit in left atrium is rare but may develop after valve surgery or congenital heart disease or catheter ablation and rotates around mitral valve.

In typical right atrial AFL atrial rate is 250–300/min with 2 : 1 ventricular response.

Sometime coarse AF may look like AFL in V_1 or sometime one atria may show AF and the other may show AFL or may alternate between AF and AFL overtime.

TREATMENT OF AFL

- **Rate control**—Pharmacological ventricular rate control can be tried out but not very effective with CCB (diltiazem, verapamil) β-blocker, and/or digoxin.
- **Rhythm control**—
  - **Pharmacological**—Rhythm control can be tried with procainamide, amiodarone or ibutilide. Antiarrhythmic drug also enhance the efficacy of DC cardioversion and maintenance of sinus rhythm after cardioversion to the range of >80% by 1 year.
  - **DC cardioversion**—Atrial flutter can be termi- nated by low energy external cardioversion using 50–100 J but the risk of thromboembolism to be managed in the line of atrial fibrillation.
  - **Catheter ablation**—An isthmus ablation line from tricuspid annulus to the opening of inferior vena cava can permanently eliminate recurrent atrial flutter. The anticipated success rate is more than 90%.
    Patient who have both flutter in right atrium and fibrillation in left atrium hybrid therapy with antiarrhythmic agent coupled with right atrial isthmus ablation can control both AF and AFL.

MULTIFOCAL ATRIAL TACHYCARDIA (MAT)

It is commonly associated with pulmonary disease like chronic obstructive or restrictive lung disease. There should be at least three distinct type of P-wave morphology and three different P-R interval. Ventricular rate is in between 100–150 beats/min. The presence of isoelectric baseline helps to differentiate MAT from AF.

TREATMENT OF MAT

- Initial therapy to be directed towards COPD and restrictive lung disease.
- Judicious use of **CCB, flecainide** or **propafenone** can resut in decrease in arrhythmia.
- **Low dose amiodarone** can also control the arrhythmia with minimum pulmonary toxicity.

FOCAL ATRIAL TACHYCARDIA

Focal atrial tachycardia are of two types—

- **Focal automatic AT**—Start with a warmup period of 3–10 complexes and a slow in rate for 3–10 complex prior to termination. The first P-wave has the same morphology as the remaining P-waves. This AT can be initiated by isoproterenol infusion and terminated by adenosine with evidence of AV block and slowing of atrial rhythm.
- **Focal microreentrant AT**—This can be initiated by programed atrial stimulation or spontaneous premature beat. The initiating P-waves have different morphology than the P-wave of sustained AT. They usually do not terminate in response to adenosine or carotid massage.

  The focal AT arises by repetitive firing from anatomic location like crista terminalis, valve annulus, limbus of fossa ovalis, atrial muscular sleeves entering SVC, coronary sinus and pulmonary vein.

  P-wave morphology is distinct from P and P-R interval is shorter than sinus (R-P) interval when there is 1:1 conduction.
- **Focal macroreentrant tachycardia incorporating AV node**—The primary difference from focal AT is the

persistence of AT in presence of AV block that may be due to carotid massage or administration of adenosine. The ECG distinction between focal automatic AT, microreentrant AT, macroreentrant AT or atypical AFL is not always possible.

- Sustained focal AT tends to be slower but the ventricular rate may frequently overlap with reentrant tachycardia.
- Focal AT is common in absence of structural heart disease.
- Focal AT tends to demonstrate isoelectric baseline between P-wave.
- Macroreentrant AT represents atrial activation that is continuous.
- In macroreentrant tachycardia, isoelectric base- line is absent.
- History of prior atrial surgery is present in macro-reentrant AT.

Treatment of Focal Atrial Tachycardia

Pharmacological therapy is the first line treatment of choice.

- **Nodal blocking agent** is used for control of rapid ventricular rate.
- Acute IV administration of **procainamide** or **amiodarone** may terminate tachycardia.
- If tachycardia is not responding to pharmacologic therapy **electrical cardioversion** will terminate the tachycardia.
- **Anticoagulation** prior to cardioversion is usually not needed unless there is severe left atrial dilatation >5.0 cm with high-risk AF.
- **Catheter ablative therapy** is highly successful (>90%) in focal AT and should be tried in patients who are resistant to medical therapy and who are reluctant to take chronic drug therapy except when the focal AT arises from para-Hisian location or from left atrium.

AV NODAL REENTRANT TACHYCARDIA (AVNRT) (FIG. 9.2)

- It is the most common regular SVT.
- It is more frequently seen in women and typically manifest in the second to fourth decade of life.
- It is usually well-tolerated except in patient with IHD or HTN.
- AVNRT develops due to the presence of two distinct electrophysiologic pathway within the AV node.

The fast pathway located superiorly with a long refractory period.

The slow pathway located below with a short refractory period.

As a result of inhomogeneous conduction and refractoriness a reentrant circuit can develop within AV node in response to premature stimulation of atria.

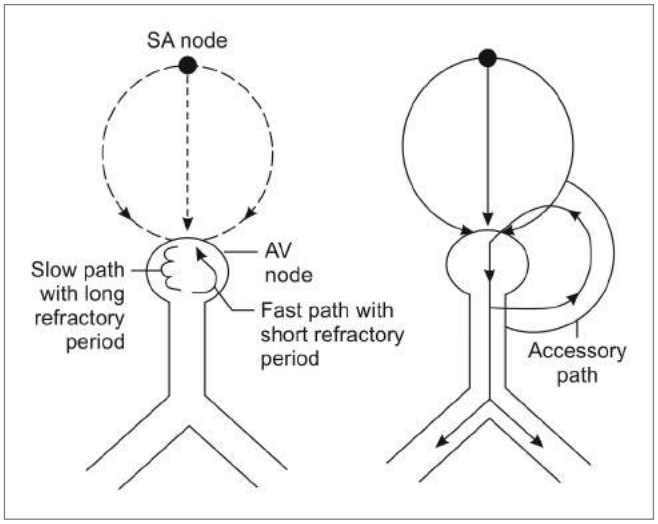


Fig. 9.2: Mechanism of nodal reentry

When an APC occurs after a short pause, it is blocked in the fast pathway due to long refractory period while it is conducted down through the slow pathway due to short refractory period. The blocked fast pathway can recover excitability by this time and the impulse can be conducted retrogradely upwards to activate atria.

The APC initiating AVNRT has a long PR interval as the impulse is conducted via slow pathway. The P-wave in AVNRT is typically buried in the QRS complex either not visible or will distort the QRS complex.

As the atrial activation originates in the region of AV-node a negative P-wave is formed due to retrograde atrial depolarization.

Occasionally AVNRT can occur due to conduction down the fast pathway and returning up via the slow pathway. This type of AVNRT occurs less commonly and produces prolonged RP interval during tachycardia with a negative.

P-wave in lead II, III and AVF.

TREATMENT OF AVNRT

Treatment is directed towards slowing of conduction through AV node. This can be done by

- Physical measure like **Valsalva maneuver or carotid sinus massage**.
- **Adenosine** 6–12 mg IV bolus is the drug of choice.
- **β-blocker or Ca^{++} channel blockers** are 2nd line agent.
- If hemodynamic compromise is present R-wave synchronous **DC cardioversion** using 100–200 J can terminate the tachycardia.

PREVENTION OF AVNRT

- It is done by **digitalis, β-blocker** or **calcium channel blocker** that slows the antegrade conduction through slow pathway. If this drugs fails then class IA or IC agent

directed at alternating conduction through fast pathway can be considered.
- Catheter ablation therapy using cryoablation technique can almost cure AVNRT (> 95%) specially in those who are reluctant to chronic drug therapy. Permanent pacemaker is needed in 1% patient.

AV JUNCTIONAL TACHYCARDIA

This type of arrhythmia can occur in the setting of
- Enhanced normal automaticity
- Abnormal automaticity
- Triggered activity.

This arrhythmias may develop as a manifestation of
- Increased adrenergic tone
- Drug effect in patient with sinus node dysfunction
- Following surgical or catheter ablation
- Digoxin toxicity.

Sinus activity is usually dissociated or there may be intermittent capture with prolonged P-R interval. If the rate is 50–100 beats/min it is termed as accelerated junctional rhythm.

Some AVNRT fails to depolarize the atria when it may mimic AV junctional tachycardia and then the two conditions are differentiated by the presence of triggering premature atrial beat that initiates AVNRT.

Absence of atrial premature beat at the initiation of this type of tachycardia with gradual acceleration suggests automatic AT.

TREATMENT OF AV JUNCTIONAL TACHYCARDIA

- Junctional tachycardia due to abnormal automaticity can be treated by β-blocker.
- A trial of class IA or IC agent may also be given.
- If digoxin toxicity is suspected digoxin therapy to be stopped. Digoxin-specific antibody can be used.
- For incessant automatic junctional tachycardia focal catheter ablation can be done with implantation of pacemaker.

ACCESSORY AV PATHWAY (AP)-MEDIATED TACHYCARDIA

Tachycardia is often encountered in person who have accessory AV pathway bypassing AV node.

Accessory pathway (AP) is typically able to conduct impulse both in antigrade and retrograde direction.

In case of antigrade conduction the sinus impulse quickly activates the ventricle bypassing AV node resulting in ventricular preexcitation. The P-R interval is shorter and the initial portion of QRS is slurred creating characteristic 'delta wave'. The remaining portion of the QRS complex is created by the fusion of faster impulse conducted via AV node His-Purkinje system.

The evidence of AP and ventricular preexcitation includes (a) short P-R interval with (b) slurred delta wave.

In some patient instead of atrioventricular accessory pathway there may be atriofascicular accessory pathway. These atriofascicular accessory pathways have decremental antegrade conduction.

Other accessory pathways connecting AV node with fascicle may exist which are called 'Mahaim fiber'.

a. Most common macroreentrant tachycardia associated with WPW syndrome is 'orthodromic AV conduction' where ventricular activation occurs through AV node and His-Purkinje system and returns to atria via retrograde conduction through accessory pathway (AP) called 'orthodromic AV reentry'.
b. Rarely the impulse activates the ventricle via accessory pathway and returns to atria via AV node His-Purkinje system is called 'antidromic AV reentry or preexcitated macroreentry'.
c. Another most common serious arrhythmia associated with WPW syndrome is rapidly conducting AF (atrial fibrillation).

CONCEALED ACCESSORY PATHWAY (AP)

In half of the AP there is no antegrade conduction over AP but retrograde conduction is preserved and AP is not overt in sinus rhythm and only manifest during sustain tachycardia.

In this situation of retrograde conduction, P-wave will follow ventricular activation with a short R-P interval. As this AP connects left ventricle with left atrium, the atrial activation during the tachycardia frequently produces negative P-wave in lead I and aVL.

Occasionally the AP conducts extremely slowly in a retrograde fashion resulting in 'long R-P tachycardia'.

TREATMENT OF ACCESSORY PATHWAY-MEDIATED TACHYCARDIA

- **Acute treatment**
  - *Vagal stimulation*
    - **Valsalva maneuver**
    - **Carotid sinus pressure**.
  - *Pharmacologic therapy*
    - **Adenosine** 6–12 mg IV bolus.
    - **Calcium channel blocker**—Verapamil and diltiazem IV.
    - β-blocker IV.

  In patient with preexcitation (WPW) and AF.
  - In life-threatening situation—DC cardioversion should be used to terminate AF.
  - In nonlife-threatening situation
    - **Procainamide** at a dose of 15 mg/kg IV over 20–30 min will slow the ventricular rate or can terminate AF.

- **Ibutilide** can also be used to terminate AF.

Digoxin or verapamil should not be used in AP-associated AF, as these two drugs shorten the refractory period of AP thereby can lead to development of VF.

In patient with AP associated with AF and rapid ventricular rate or in patient with recurrent SVT on AV nodal blocking agent, class **IA** or **IC antiarrhythmic drug** such as **quinidine flecainide** or **propafenone** should be considered.

Patient with recurrent symptomatic SVT or incessant SVT or SVT with heart rate > 200 beat/min **catheter ablation** should be considered and is successful in >95% of patients.

Complications of catheter ablation

- ParaHisian AP ablation is associated with complete heart block.
- Ablation of left atrial path is associated with thromboembolic manifestation.

VENTRICULAR TACHYARRHYTHMIAS

VENTRICULAR PREMATURE COMPLEXES (VPC)

Impulse that arises remote from Purkinje network with a QRS duration >140 ms is called VPC.

It increases with age and structural disease of heart.

- **Bigeminy**—In which every sinus beat is followed by a VPC.
- **Trigeminy**—In which two sinus beats is followed by a VPC.
- **Cuplet/Pairs**—Two successive VPC are called cuplets/Pairs.
- **Multiformed VPC**—VPC that have different morphology in ECG are termed as multiformed VPC.
- **Ventricular tachycardia (VT)**—Three or more consecutive VPC with a rate >100 beats/min is called VT.
- **Nonsustained VT**—If the VT terminates spontaneously and is more than three beats in duration is called nonsustained VT.
- **Compensatory pause**—Usually VPC are followed by fully 'compensatory pause', i.e. the gap between the last QRS and the next QRS complex is equal to twice that of sinus rate. The VPC are usually not conducted to the atrium. Occasionally the VPC can occur early and may conduct retrogradely to atrium to reset the sinus node and then pause will be less than compensatory.
- **Interpolated VPC**—When VPC fails to influence outcoming sinus complexes is called interpolated VPC.
- **Parasystolic focus**—VPC which fires repeatedly from a fixed ventricular site at a fixed interval and coupled variably with sinus complex that ventricular site is called parasystolic focus.

Treatment

VPC of sufficient frequency can cause reversible cardiomyopathy but drug therapy that slows myocardial conduction with increase in refractoriness can actually increase the risk of life-threatening arrhythmia (drug-induced, QT prolongation and TDP). For that reason drug therapy is not universally recommended for VPC.

ACCELERATED IDIOVENTRICULAR RHYTHM (AIVR)

Three or more consecutive VPC at a rate of 40–120/min are called AIVR. There is an overlap between AIVR and slow VT that manifests between 90–120 beats/min.

AIVR is a

- Brief self-limiting arrhythmia with a gradual onset and offset.
- AIVR has variable cycle length without any structural heart disease.
- It is usually associated with AMI, acute myocarditis, cocaine intoxication, digoxin and after heart surgery.
- Hemodynamic compromise can occur in AIVR especially in RV infarction due to proximal RCA block. These patients are treated either by atropine (IV) or atrial pacing.

VENTICULAR TACHYCARDIA (VT)

It originates below His bundle at a rate >100 beats/min but usually >120 beats/min. VT at a rate of 100–120/min is confused with AIVR and is usually due to concomitant antiarrhythmic drug. VT usually occurs in chronic infarction or cardiomyopathy and is less likely to be associated with AMI or myocarditis and has a fixed QRS cycle length. Duration of QRS in VT may be uniform (monomorphic VT) or may vary from beat to beat (polymorphic).

Polymorphic VT usually seen in a patient who has long QT interval in basic rhythm and is called 'Torsades de pointes' (TDP).

Polymorphic VT associated with QT prolongation oscillates around the baseline in the ECG mimicking the turning of the points stiching pattern

- Monomorphic VT usually arises from stable tachycardia focus without any structural heart disease or froms a fixed area which forms stable reentrant VT circuit.
- Polymorphic VT is due to dynamic or unstable process like ischemia, myocarditis which causes changes in QT interval (enhanced dispersion of ventricular refractoriness).
  - VT persisting less than 30S is called nonsustained VT.
  - VT persisting for more than 30S or hemodynamically unstable VT that requires termination within 30S is called sustained VT.

  - Ventricular flutter—looks like sine wave on ECG with a rate >250 beat/min.
  - Polymorphic VT, ventricular flutter, or VF produce hemodynamic collapse if allowed to continue.
- The presence of aberrant QRS pattern that matches exactly with wide complex rhythm suggest SVT.

VT usually occurs in the setting of coronary artery disease but there may be other causes like—

- Idiopathic outflow tract VT.
- Idiopathic LV septal/fascicular VT.
- Bundle branch reentrant VT.
- VT associated with LV-DCM.
- VT associated with hypertropic cardiomyopathy.
- VT associated with infiltrative and neuromascular cardiomyopathy.
- Arrhythmogenic RV cardiomyopathy.
- VT after repair of TOF.
- Fascicular tachycardia caused by digoxin.
- Genetically determined VT (LQTS—long QT syndrome).
- Acquired LQTS.
- Short QT syndrome.
- Brugada syndrome.
- Catecholaminergic polymorphic VT.

ECG Criteria for VT

- AV dissociation (atrial capture or fusion beat).
- QRS >140 ms for RBBB type V_1 morphology.
- QRS >160 ms for LBBB type V_1 morphology.
- Frontal plane axis—90°–180°.
- Delayed activation during initial phase of QRS complex—
  - LBBB pattern—R-wave in V_1, V_2 >40 ms.
  - RBBB pattern—Onset of R-wave to nadir of S >100 ms.
- Bizarre QRS pattern that does mimic typical RBBB and LBBB concordance of QRS complex in all precordial lead.

  RS or dominant S is V_6 for RBBB pattern. Q-wave in V_6 with LBBB pattern.

  Monophasic R or biphasic QR or R/S in V_1 with RBBB pattern.

Treatment of VT

- For wide complex tachycardia without hemodynamic compromise—
  - Pharmacologic therapy with **procainamide**, **lidocaine** or **amiodarone** can be tried but with a limited success rate <30%.
  - If unsuccessful R-wave synchronous DC—cardioversion under cover of sedation is appropriate.
- For monomorphic wide complex VT with hemodynamic compromise—A prompt **R-wave synchronous DC shock** is delivered under cover of sedation.
- For sustained polymorphic VT, ventricular flutter and ventricular fibrillation (all leads to hemodynamic collapse)—
  - **Asynchronous defibrillation with 200 J monophasic or 100 J biphasic shock** is the treatment of choice. Asynchronous shock is delivered to avoid delay related to sensing of QRS complex.
  - If arrhythmia still persists **IV lidocaine** or **amiodarone** should be administered **followed by repeated shock** with maximum energy output.
- Focal outflow tract tachycardia who demonstrate triggered or automatic VT may respond to intravenous **β-blocker**.
- Idiopathic LV septal VT—responds to IV **verapamil**.
- VT in a patient with structural heart disease is treated with **ICD** to manage anticipated VT.
- Prevention of VT is an important task.

Prophylactic Pharmacologic Management of VT

More than 50% of patients with ICD require adjunctive antiarrhythmic drug like **sotalol**, **amiodarone** to suppress recurrent VT or atrial arrhythmia. This therapy is specially required in patient with structural heart disease and life-threatening monomorphic or polymorphic VT not due to long QT syndrome. Of these two drugs amiodarone is better tolerated by patient with compromised LV function and low SBP but have high chance of end organ toxicity.

Other antiarrhythmics like **quinidine**, **procainamide** or propafenone are not normally used in patient with structural heart disease but may be considered in patient of recurrent VT with ICD.

Catheter Ablation Therapy for Prevention of VT

Cure rate of *catheter ablation therapy for VT without structural heart disease is > 90%.*

Catheter ablation therapy with epicardial and endocardial mapping in VT patient with structural heart disease can reduce or eliminate the use of adjunctive toxic antiarrhythmic drug therapy.

Catheter ablation therapy is now actively considered even in patient with ICD to reduce the incidence of ICD shock.

Management of VT storms

More than two episodes of VT/24 hour is known as VT storm. Practically repeated episodes of VT requiring external difibrillation or ICD defibrillation is termed as VT storm.

- Recurrent polymorphic VT storm in absence of long QT is due to IHD or myocarditis and is initially managed by **intravenous lidocaine or amiodarone** followed by

search for etiology by coronary angio and endocardial biopsy.
- The amiodarone or procainamide slows the conduction and facilitate recurrent VT. So **early catheter ablation** of the VT focus is the treatment of choice that could eliminate the necessity of defibrillation.
- Patients who have long QT with recurrent pause-dependent polymorphic VT (TDP) is due to drug or electrolyte disturbance. Steps of general management are—
  - **Removal of the offending drug** that prolongs the Q-T interval.
  - **Correction of potassium and magnesium** deficiency.
  - **Emergency pacing** to prevent pause should be considered.
  - **Intravenous β-blocker** should be considered for polymorphic VT storm.

Targeted treatment can be done if the etiology of polymorphic VT is established—
- **For Brugada syndrome**—Quinidine or isoproterenol can be used.
- **For coronary ischemia**—Intraaortic balloon counter pulsation and emergency coronary angioplasty.
- **For repeated VPC** trigger for polymorphic VT storm the VPC focus to be targeted for by catheter ablation.

UNIQUE VT SYNDROME

VT usually occur in the setting of coronary artery disease with prior myocardial infarction. But a significant number of patients develop VT in other setting. These are as follows—

IDIOPATHIC OUTFLOW TRACT VT

VT in absence of structural heart disease is called idiopathic VT.

Approximately 80% of outflow tract VT originates from RV and rest 20% from LV outflow tract.

It appears to rise from an area beginning above the tricuspid valve and extending along the root of the out- flow tract region to include the free wall and septal aspect of right ventricle, just beneath the pulmonic valve, the aortic valve region and the anterior and superior margin of the mitral valve annulus.

This arrhythmia is common in female and manifested as palpitation with exercise, stress and caffeine ingestion.

This VPC and VT can lead to tachycardia-induced cardiomyopathy.

Mechanism of production of these types of VT is probably calcium-dependent triggered activity due to somatic mutation of inhibitory G protein.

Outflow tract VT produce large monomorphic R-wave in II, III aVF. As most VT originates from the RV outflow tract LBBB pattern is seen in V_1 and when originates from LV outflow region it is RBBB in V_1.

Treatment

- No treatment is required as the VT is usually not sustained and hemodynamically tolerable.
- **IV β-blocker** can terminate the tachycardia.
- Oral **β-blocker** or **CCB** can suppress the recurrence.
- **Catheter ablation** therapy to eliminate the tachycardia is successful >90% patient.

IDIOPATHIC LV SEPTAL/FASCICULAR VT

It is the secondmost common idiopathic VT.

It is due to macroreentry involving calcium-dependent slow response fiber of the Purkinje system in LV. In 12 lead ECG there is RBBB with left or right axis deviation, Depending on whether the VT originates from posterior or anterior fascicle.

Treatment

This VT can be effectively suppressed by **verapamil β-blocker** but **catheter ablation** is the method of choice which can eliminate the VT >90% patient.

BUNDLE BRANCH REENTRANT VT

Monomorphic VT with idiopathic nonischemic cardiomyopathy or valvular cardiomyopathy due to large macroentry circuit involving His-Purkinje network.

The VT impulse pass down the right bundle and retrograde up via left posterior or anterior fascicle and left bundle branch producing LBBB and left axis deviation in the ECG during VT.

Rarely the circuit rotates in opposits direction, i.e. antegrade through left bundle and retrograde through right bundle producing RBBB during VT.

Treatment

1. Catheter ablation of the right bundle to block the VT circuit.
2. Implantation of ICD is required as LV function is severly depressed and high-risk of SCD.

VT ASSOCIATED WITH DCM

Monomorphic or polymorphic VT can occur in non-ischemic DCM patient.

Sustained VT can arise from fibrosis around mitral and aortic valve region of DCM patient.

Treatment

- Implantation of **prophylactic ICD** is the best way of treatment. Drug therapy (sotalol and amiodarone) can be tried to reduce the frequency of VT after ICD implantation.

- **Catheter ablation** via endocardial route is not very much effective, as VT originates from epicardium. Catheter ablation through epicardial route via percutaneous pericardial puncture improves the outcome of ablative therapy.

VT ASSOCIATED WITH HYPERTROPIC CARDIOMYOPATHY

VT/VF, unexplained syncope and SCD all are associated with HCM.

HCM with septal wall thickness >30 mm are associated with frequent nonsustained spontaneous VT and SCD. These patients with HCM are associated with PRKAG 2 mutation and WPW syndrome.

- Sustained VT are at high-risk of SCD and ICD implantation is indicated.
- Amiodarone, sotalol and β-blocker are used to control recurrent VT.
- Catheter ablation of the areas of low voltage consistent with fibrosis are promising.

VT WITH INFILTRATIVE CARDIOMYOPATHIES

Sarcoidosis, amyloidosis, hemochromatosis, myotonic muscular dystrophy, Duchenne's and Becker's muscular dystrotrophy and Friedreich's ataxia all infiltrative type of diseases are at increased risk of arrhythmia.

They usually have conduction block and require pacemaker implantation.

When syncope and depressed LV function (EF < 35%) with class 2 or 3 heart failure symptoms are present. ICD implantation is indicated. These conditions may be treated with antiarrhythmic like amiodarone or sotalol before implantation of ICD but not with other antiarrhythmic drugs.

ARRHYTHMOGENIC RV CARDIOMYOPATHY/ DYSPLASIA (ARVCM/D)

It is either a genetically determined process or developed as a sequele of viral myocarditis and associated with VT/VF.

The arrhythmogenic focus is traced to perivalvular fibrosis around tricuspid and pulmonary valve involving mostly free wall.

In sinus rhythm the ECG in $V_1 - V_3$ lead shows terminal notching of QRS complex (epsilon wave) with inverted T. The epsilon wave indicates marked delay in activation of RV free wall near pulmonary and tricuspid valve due to fibrosis. MRI shows fatty infiltration with thinning of RV free wall and apical aneurysm formation.

Treatment

- Medical therapy consist of β-blocker like *sotatol* along with other *antiarrhythmic drug*.
- *ICD* may be implanted in patients who have recurrent VT after drug therapy.
- *Catheter ablation* of endocardial and epicardial scar provides significant amelioration of recurrent VT episodes.

VT AFTER TOF REPAIR

It is due to development of macroreentant circuit around RV scar to valve annuli long after operation. Catheter ablation from pulmonary or tricuspid annuli to the ventriculotomy scar can prevent VT recurrence.

ICD may be required to them who have rapid VT or persistent VT after catheter ablation or with LV dysfunction.

FASCICULAR TACHYCARDIA CAUSED BY DIGOXIN TOXICITY

Digoxin can cause ventricular ectopic with bradycardia which can predispose to sustained polymorphic VT or VF.

This VT is bidirectional and is due to triggered activity as a result of calcium overload from inhibition of Na^+/K^+ ATPase pump by digoxin.

This VT arises either from left anterior or posterior fascicle producing incomplete (narrow) RBBB with rapid alteration from left to right axis from beat to beat in ECG.

Treatment

1. Correction of electrolyte disturbances
2. Infusion of digoxin-specific Fab antibody.

GENETICALLY DETERMINED LQTS (LONG QT SYNDROME)

In LTS the corrected QT interval (by Bazettis formula) lies between 4–460 ms in men and 4–480 ms in women.

- OT interval >500 ms is associated with high-risk of arrhythmia.
- Risk of arrhythmia is also high in those whose QT fails to shorten appropriately with exercise.
- In some individual the syndrome manifests only when they are exposed to drug like sotalol which alter channel function.

Genotype associated with LQTS is very important. The first three genotypes ($LQTS_1$, $LQTS_2$ and $LQTS_3$) account for clinically important LQTS.

- $LQTS_1$ is the most common genotype in whom the QT fails to shorten with exercise or exercise may actually prolong it. The ECG shows broad **T Exercise** and **emotional** stress are the most common trigger for arrhythmia for LQTS.

  Patients respond to **β-blocker** therapy.
- $LQTS_2$ is the 2nd most common genotype and associated with notched or bifid T-wave.

Emotional stress, **auditory stimulus** and **sleep** are the most common trigger for arrhythmia. Patients respond to **β-blocker** therapy.

3. $LQTS_3$ is due to defect in cardiac sodium channel. It has either late onset peaked biphasic T or asymmetric peaked T-wave.

   The arrhythmia is more life-threatening, and prognosis is poorest of all the LQTS. Most **arrhythmia occur during sleep** and β-blocker is not recommended and exercise is not restricted in $LQTS_3$.

Treatment

- **ICD implantation** is strongly recommended to all LQTS patients with arrhythmia.
- Patients with syncope and unequivocal ECG change or positive genetic testing should be strongly considered for ICD.
- Prophylactic ICD implantation is considered in all male with $LQTS_3$ or in all LQTS with QT >500 ms particularly when associated with family history of SCD.
- Drug that prolongs QT must be avoided in all documented or suspected LQTS.

ACQUIRED LQTS

Patients with genetic predisposition can develop marked QT prolongation in response to drug, that alters repolarization current.

QT prolongation and associated polymorphic ventricular tachycardia (TDP) frequently exaggerated in acquired LQTS patient with hypokalemia and bradycardia.

Altered drug metabolism and failure of excretion due to hepatic or renal dysfunction can lead to development of arrhythmia in acquired LQTS.

Treatment

- Elimination of the offending drug.
- **Correction of K^+ and Mg^{++}**.
- **Temporary pacing** in pause-dependent arrhythmia, or cautious infusion of isoproterenol.
- **Lidocaine** (class IB antiarrhythmic agent) which do not cause QT prolongation can be tried but with limited success.
- For anxiety relief by **benzodiazepine** (SQTS).
- **DC shock** therapy for sustained arrhythmia.

SHORT QT SYNDROME

QT interval <320 ms is essential to establish the diagnosis of short LQTS.

Patients with this syndrome are vulnerable to AF and VF. Mutation of HERG, $KVLQT_1$ and $KCNJ_2$ gene are noticed.

Treatment

- **ICD implantation** is recommended.
- **Quinidine** which prolongs QT and reduces the amplitude of T is currently evaluated for long-term medical therapy for this type of arrhythmia.

BRUGADA SYNDROME

The disease is more common in Asian male. Mutation of inward Na^+ current channel in the region of RV outflow tract epicardium appears to be responsible for Brugada syndrome.

Due to lack of inward Na^+ current and the unopposed outward K^+ current results in dramatic shortening of the duration of action potential. This results in a large potential difference between normal endocardiun and a rapidly depolarizing epicardium. This dynamic potential difference predisposes to local reentry and life-threatening VT in absence of any structural heart disease.

Treatment

History of syncope, spontaneous ST elevation in V_1, V_2 provocative drug testing with procainamide and flecainamide (Na^+ channel blocker) may be used to identify the presence of this abnormality in family members.

- Acute arrhythmia responds to **isoproterenol** or **quinidine**.
- **ICD treatment** is recommended to manage the recurrence.

CATECHOLAMINERGIC POLYMORPHIC VT

Mutation of the myocardial ryanodine release channel which creates a leak of Ca^+ from sarcoplasmic reticulum that causes accumulation of intracellular Ca^+ which ultimately results in delayed after depolarization and triggered activity.

ECG manifestations are bidirectional VT, nonsustained polymorphic VT, or reentrant VF. Both autosomal, recessive, dominant and sporadic forms have been identified.

Arrhythmia is precipitated by exercise and emotional stress.

Treatment

Managed by **β-blockers** and **ICD implantation**.

Chapter 10

Ischemic Heart Diseases

DEFINITION

It is a condition that arises due to imbalance between myocardial oxygen demand and supply. The inadequate supply of oxygen and blood is due to atherosclerotic disease of epicardial coronary artery causing regional reduction in myocardial perfusion.

It is composed of two groups of diseases—

- Stable angina
- Acute coronary syndrome.

STABLE ANGINA

It is characterized by chest or arm discomfort (rarely described as pain) but it is reproducibly associated with physical exertion or stress and is relieved by rest or sublingual nitroglycerine within 5–10 minutes.

It is a symptom complex caused by transient myocardial ischemia and constitutes clinical syndrome rather than a disease, occurs whenever there is imbalance be- tween myocardial oxygen demand and supply.

The cause is impaired coronary perfusion and is due to—

- Fixed block of coronary artery by stable atheroma.
- HOCM (hypertrophic obstructive cardiomyopathy).
- Aortic valve disease (aortic stenosis or regurgitation).

ACUTE CORONARY SYNDROME (ACS)

It is characterized by prolong precordial ischemic discomfort (more than 20 minutes duration usually lasting for several hours) at rest and not relieved by sublingual—nitroglycerine.

It comprises of three entities:

- Unstable angina (UA 30–45%).
- Non-ST-elevated myocardial infarction (NSTMI—25–30%).
- ST-elevated myocardial infarction (STEMI—20–25%).

UNSTABLE ANGINA (UA)

It is defined as angina pectoris or anginal equivalent (dyspnea, nausea, fatigue, faintness) ischemic discomfort with at least one of the three following features:

- It occurs at rest or with minimal exertion usually lasting more than 10 minutes.
- It is severe and/or new onset.
- It occurs with crescendo pattern (more severe, more prolonged, more frequent than previously).

NSTEMI

If a patient with clinical and ECG features similar to unstable angina develops the evidence of myocardial necrosis as reflected by the elevated cardiac biomarker (CKMB and cardiac troponin); then the patient is stamped as suffering from NSTEMI.

PATHOPHYSIOLOGY OF UA/NSTEMI

Reduction of oxygen supply can be due to

- Rupture or erosion of atheromatous plaque with superimposed nonocclusive platelet-rich thrombus (most common cause).
- Coronary spasm as in Prinzmetal's variant angina.
- Rapidly advancing coronary atherosclerosis or restenosis following PCI.

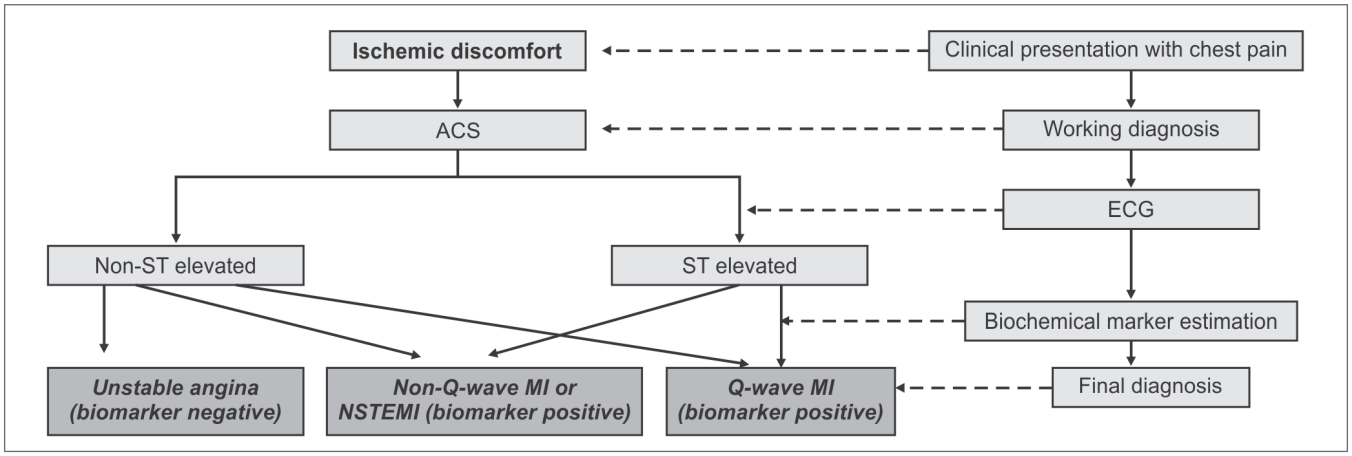
ECG FINDING IN UA/NSTEMI

- **ST depression**
- **Transient ST elevation**
- **T-wave inversion** occur in 30–50% patients.

In patient with clinical features of UA/NSTEMI:

- New ST segment depression even of (0.05 mV) have adverse prognosis.
- Transient ST segment elevation for less than 20 minutes seen in greater than 10% patients.

Flowchart 10.1: Diagnosis of ischemic heart disease



- T-wave changes are sensitive for ischemia but are less specific unless it is—(a) of new onset, (b) deep T-wave inversion greater than 0.3 mV.

CARDIAC BIOMARKER

Elevated level of (Fig. 10.1):

- CKMB rises within 4–8 hours and returns to normal within 2–3 days.
- Troponin (more specific for myocardial necrosis). It is found raised in NSTEMI (for 7–10 days) but normal in UA (unstable angina). However, without a clear history suggestive of angina minor elevation of troponin can occur in **CCF, myocarditis, pulmonary embolism**, **cardiac surgery** and **DC shock**.

  So, without a clear history of angina small elevation of troponin can be considered false-positive.

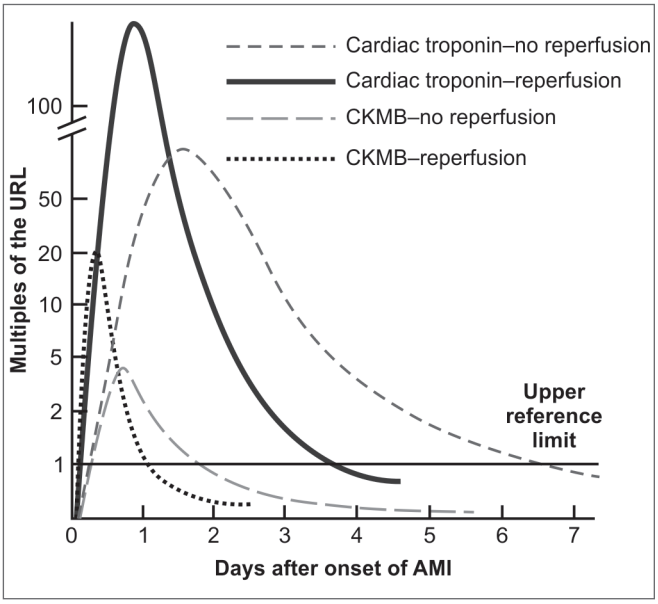


Fig. 10.1: Level of cardiac biomarker after AMI

Apart from these two above-mentioned markers, newer cardiac biomarkers are—

1. C-reactive protein
2. B-type natriuretic peptide
3. CD-40 ligand

These biomarker correlates independently with increased mortality and recurrent cardiac event in patient presenting with clinical features of NSTEMI and STEMI. These multimarkers are now gaining favor to stratify patient's risk

MANAGEMENT OF ISCHEMIC HEART DISEASES

Treatment (Flowchart 10.2)

When a patient with precordial or retrosternal chest pain or discomfort comes to emergency unit, our first task is to differentiate pain of cardiac origin from pain of noncardiac origin. This is done by—

- History
- Physical examination
- ACC/AHA guideline for IHD.

ACC/AHA guidelines for factors associated with high likelihood of ACS (acute coronary syndrome)—

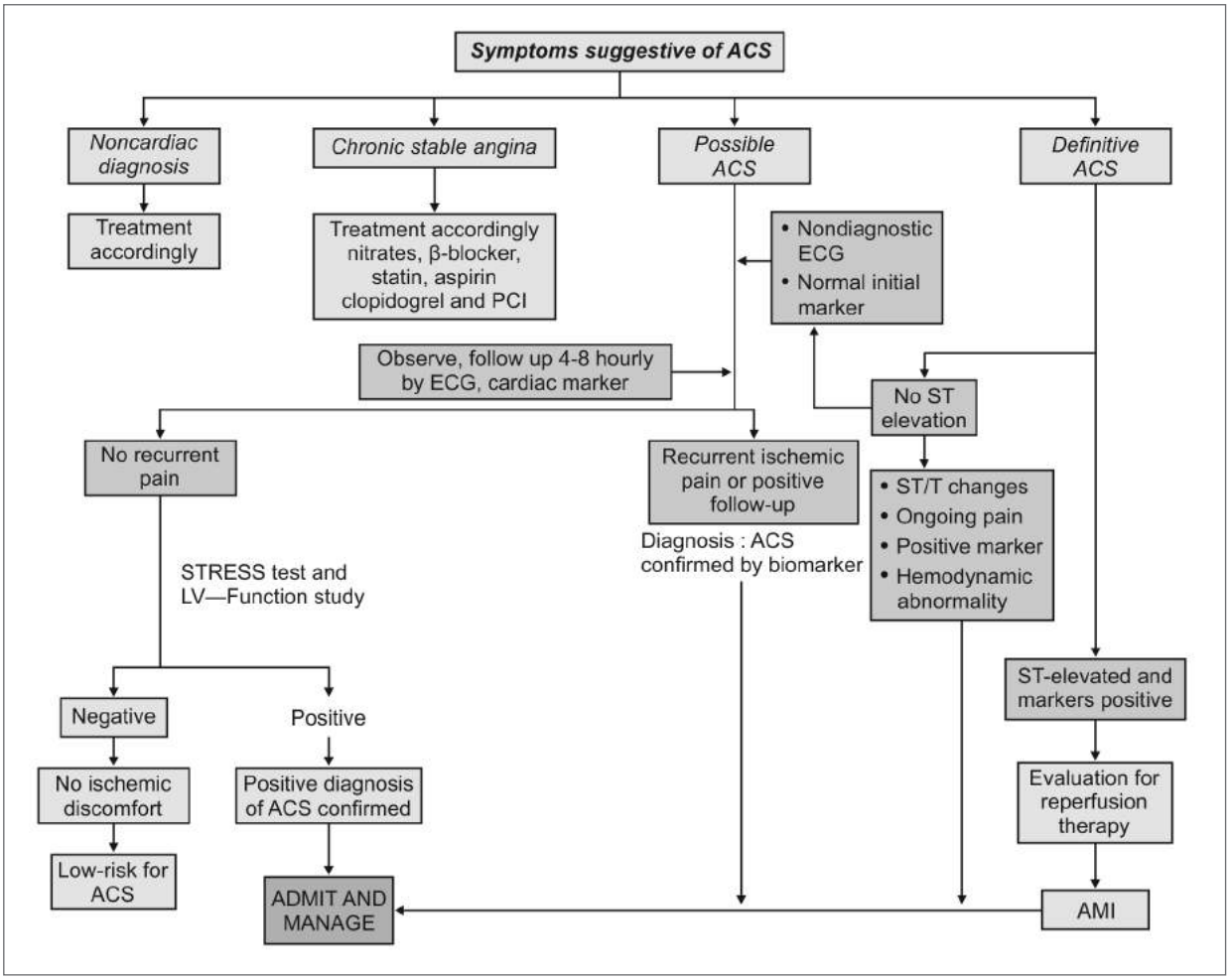
1. History of typical ischemic discomfort
2. History of established CAD by previous angiography
3. Prior myocardial infarction
4. Sign of congestive heart failure
5. New ECG changes
6. Elevated cardiac biomarker

Factors associated with intermediate likelihood disease—

1. Age >70 years
2. Male patient
3. Diabetes mellitus
4. Known peripheral arterial or cerebrovascular disease
5. Old ECG abnormality

Those patients who are diagnosed as pain of noncardiac origin (pulmonary, vascular, gastrointestinal,

Flowchart 10.2: Evaluation and management of ACS



musculoskeletal or infectious diseases) or due to stable angina (relieved by rest and nitroglycerine) are treated accordingly and discussed in the subsequent chapter.

But those patients in whom a noncardiac cause could not be established, they are supposed to be suffering from ACS. In these group of patients next step of management is—

- ECG monitoring (continuous) which differentiates STEMI from UA/NSTEMI.
- Estimation of cardiac biomarker (repeated).

If the ECG shows—typical ST elevation or evolving Q-wave in the precordial or inferior wall lead then the patient is stamped as STEMI and management of these group of patients is discussed in subsequent chapter (75% of STEMI are male).

If instead of typical ST elevation in the ECG we see:

- ST-segment depression >0.05 mV
- Transient ST segment elevation (less than 20 minutes duration).
- New T-wave inversion >0.3 mV.

Then the patient is supposed to be suffering from either **unstable angina or non-ST-elevated MI (UA or NSTEMI)**.

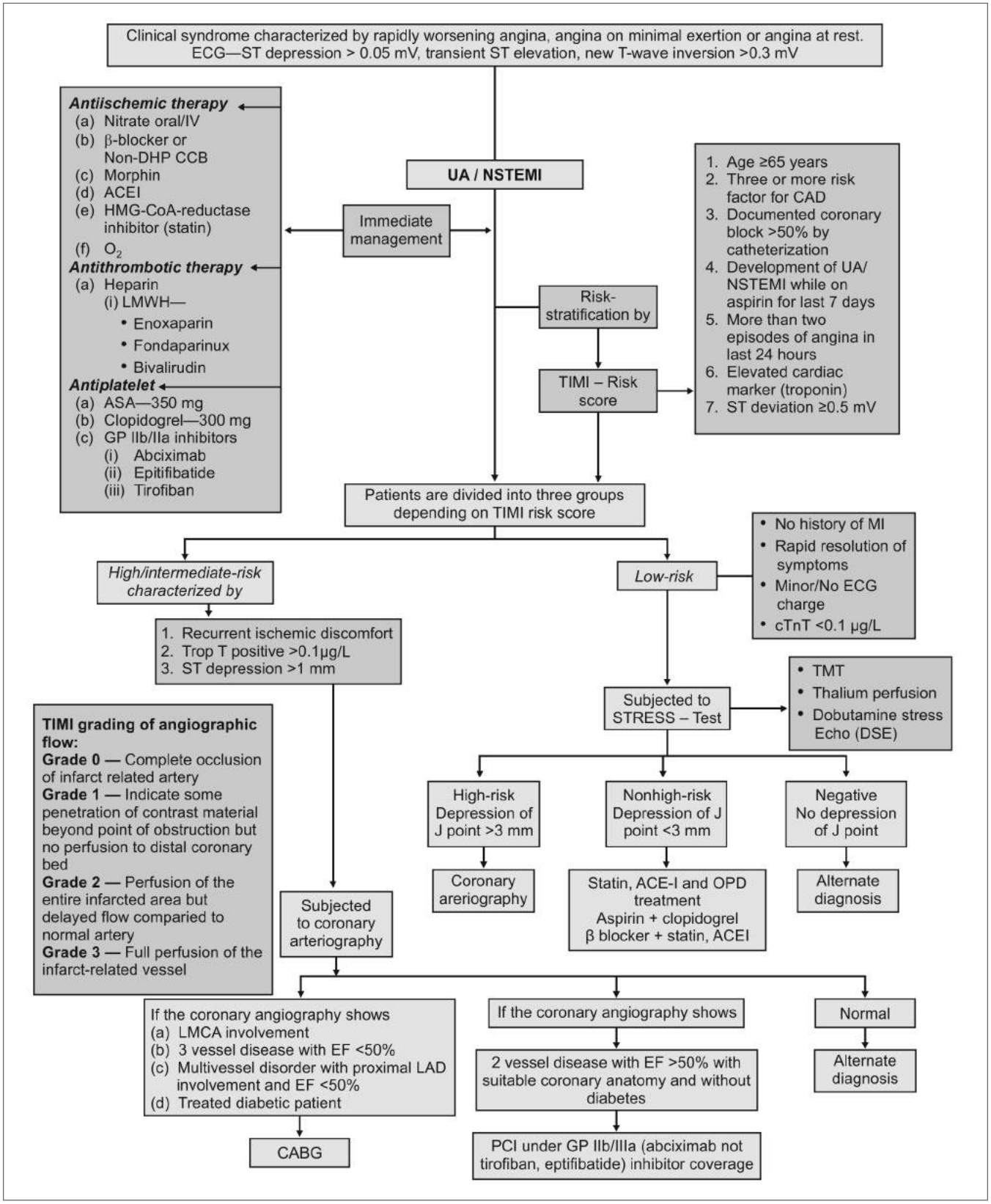
The differentiation between these two groups of patients is done by the presence of elevated cardiac biomarker (troponin, CKMB). Patient with elevated level of troponin and CKMB are stamped as suffering from **NSTEMI** and those who have normal level of cardiac biomarker are stamped as **unstable angina** (50% of UA/NSTEMI are female).

However, both these two groups of patients (UA/NSTEMI) are initially managed by same protocol.

IMMEDIATE MANAGEMENT OF UA/NSTEMI (FLOWCHART 10.3)

- **General management**
  - Continuous ECG monitoring.
  - Bed rest (ambulation is permitted in patient showing no recurrence of ischemic pain or not developing any biomarker for MI within 12–24 hours).
- **Antiischemic management**
  - *Nitrates*—Sublingual or buccal spray 0.3–0.6 mg × 3 dose each at 5 minutes apart—if pain is not controlled by oral agent.

Flowchart 10.3: Management of UA/NSTEMI



Injection NTG—IV infusion 10 μg/min using a non-absorbing tubing—the rate of infusion to be increased by 10 μg/min every 3–5 min until the symptoms are relieved or SBP falls below 100 mm Hg or a ceiling dose of 200 μg/min is reached.

↓

Patient to be transferred to topical/oral NTG when the patient is free from pain 12–24 hours later.

Absolute contraindication of nitroglycerine:

1. Hypophosphatemia
2. Prior sildenafil use wihin 24 hours.

– **β-blocker**—In absence of any absolute contraindication the β-blocker is to be given in the same does as STEMI.

Metoprolol—50 mg 6 hourly.

Targeted heart rate—50–60/min

If pain persists despite IV nitroglycerine and β-blocker.

– Morphin sulfate 4–5 mg IV every 5–30 minutes (maximum 15 mg) as needed to control pain. Side effect of morphine vomiting, shock or respiratory depression may appear which are treated accordingly.

– **CCB**—Non-DHP CCB are used in patients who have persistent/recurrent pain after full dose of β-blocker/nitrate or in a patient with contraindication for β-blocker is present.

– ACEI / ARB.
– HMG-CoA reductase inhibitor.

} These two agents mostly used in long-term management or secondary prophylaxis rather than in emergency management of UA/NSTEMI.

- **Antithrombin therapy**—
  – ACC/AHA guidelines for UA/NSTEMI prefer LMWH to UFH specially for its, (a) anti Xa-IIa activity, (b) SC applicability, (c) twice daily dosing, (d) nonrequirement of APTT monitoring.
  – **LMWH**—Enoxaparin—30 mg IV bolus followed by 1 mg/kg BD.
  – **Fondaparinux** is equivalent to enoxaparin but have less chance of bleeding.
  – **Bivalirudin** (thrombin inhibitor) may be used alternatively.
- **Antiplatelet therapy**
  – *Oral antiplatelet therapy*
    – **Aspirin**
      » It has beneficial effect—at least 21% reduction of mortality from MI in patient presenting with UA/NSTEMI.
      » Dose—325 mg initial chewable tablet followed by 75–162 mg/day (enteric coated).
      » During chronic therapy 5–8% develop aspirin- resistance—they have higher risk of CAD-related death.
    – **Clopidogrel/ticlopidine**
      » It blocks platelet adenosine receptors (P_2Y_{12} AD preceptor).
      » It causes 20% reduction of CAD-related death, MI, stroke compared to ASA alone in both high and low-risk patients with UA/NSTEMI.
      » Moderate (or 1%) increase in bleeding tendency specially in patient undergoing CABG.
      » Continued benefit can be achieved of long-term combination of ASA + clopidogrel for at least 9–12 months in patients treated conservatively/PCI and is recommended for all UA/NSTEMI patient.
      » Loading dose—300 mg initially followed by 75 mg/day.
  – **Intravenous antiplatelet therapy**—Used for upstream management of high-risk patient especially in whom invasive management is intended.
    – **Abciximab** is beneficial for patient undergoing PCI but **epitifibatide** and **tirofiban** are used for patient treated conservatively and bleeding is an important adverse effect.
    – **Abciximab**—0.25 mg/kg bolus followed by 0.125 μg/kg/min (maximum—10 μg/min) for 12–24 hours.
    – **Eptifibatide**—180 μg/kg bolus followed 2.0 μg/kg/minutes for 72–96 hours.
    – **Tirofiban**—0.4 μg/kg/min for 30 minutes followed by 0.1 μg/kg/min for 48–96 hours.

TIMI risk scores

a. Age >65 years
b. Three or more risk factors for CAD
c. Documented coronary block greater than 50% by prior angiography
d. Development of UA/NSTEMI while on aspirin for last 7 days
e. More than two episodes or angina in last 24 hours
f. Elevated cardiac biomarker
g. New ST deviation greater than 0.05 mV

During initial emergency management risk stratification is done by TIMI risk score and the patients are divided into three groups

- High-risk group
- Intermediate-risk group
- Low-risk group.
  – **TIMI high-or intermediate-risk groups are those who have the following risk factor**
    – Recurrent ischemic discomfort
    – Trop T-positive
    – New ST depression.

And they are subjected to **coronary angiography**. The decision for subsequent management (CABG/PCI) depends on angiography finding.

Invasive strategy for UA/NSTEMI (ACC/AHA guideline)
If in the angiography we find—
1. LMCA block—CABG
2. 3 vessel disease with EF <50%—CABG
3. Multivessel disorder with proximal LAD involvement and EF < 50% or diabetic patient —CABG
4. 2–3 vessel disease with EF >50% with suitable coronary anatomy or without diabetes—PCI
5. One or two vessel disease without proximal LAD involvement but large area of myocardial ischemia high-risk patient on noninvasive tasting—CABG/ PCI

Class I recommendation for use of early invasive strategy—
1. Recurrent angina at rest or at low level of activity despite treatment
2. Elevated cTnT or CTnI
3. New ST segment depression
4. Recurrent angina or ischemia with heart failure symptoms and rales or MR
5. Positive stress test
6. Decrease BP
7. Sustain VT
8. PCI <6 months or prior CABG.

Any one of the high-risk factors is indicator for invasive strategy.

B. TIMI low-risk group are those who have—
a. No history of myocardial infarction
b. Rapid resolution of symptoms
c. Minor or no ECG changes
d. cTnT less than 0.1 μg/L

They are subjected to stress testing within 6–72 hours of onset of chest pain by any one of the following tests—
1. Trade mill test (TMT)
2. Dobutamine stress thallium perfusion (DST)
3. Dobutamine stress echo (DSE). Among those patients who have—

a. More than 3 mm depression of J point in the stress testing (TMT/DST/DSE) are subjected to coronary angiography and are managed) according to TIMI high-risk group
b. Those who have less than 3 mm J point depression in the stress testing (TMT/DST/DSE) are managed in the outpatient department with aspirin, clopidogrel, β-blocker, statin and ACEI/ARB
c. The residual group who have no ST depression in the stress testing, are actually have noncardiac chest pain and managed accordingly

ACUTE RETROSTERNAL CHEST PAIN/ CENTRAL CHEST PAIN

DIFFERENTIAL DIAGNOSIS OF CENTRAL CHEST PAIN

- **Cardiac cause**
  - Stable angina.
  - Unstable angina.
  - Acute myocardial infarction (both STEMI and NSTEMI).
  - Pericarditis.
- **Vascular cause**
  - Aortic dissection
  - Pulmonary embolism
  - Pulmonary hypertension.
- **Pulmonary cause**
  - Pleurisy and/or pneumonia
  - Spontaneous pneumothorax
  - Tracheobronchitis.
- **Gastrointestinal cause**
  - Esophageal reflux
  - Peptic ulcer
  - Gallbladder disease
  - Pancreatitis.
- **Musculoskeletal cause**
  - Costochondritis
  - Cervical disk disease
  - Radiculopathy due to collapse of vertebral body (T_2–T_4/T_5).
- **Infectious cause**
  - Herpes zoster.
- **Psychological cause**
  - Panic disorder.

CARDIAC CAUSES FOR CENTRAL CHEST PAIN

- **Stable angina**—Clinical features—Retrosternal chest pain, burning or heaviness, radiating occasionally to neck, jaw, epigastrium and shoulders or left arm.

  Precipitated by exercise, cold weather or emotional stress, duration <2–10 minutes. Diagnosed by positive stress testing defined as flat depression of ST segment >0.1 mV below isoelectric line (i.e. PR segment) and lasting for longer than 0.08 second (2 small square).
- **Unstable angina**—Clinical features—Same as stable angina but may be more severe usually >20 minutes, duration, lower tolerance for exersion. Marker of MI absent.
- **AMI**—Clinical features—Same as angina but usually more severe sudden onset, usually lasting more than 30 minutes, often associated with shortness of breath, weakness, nausea, vomiting. Diagnosed by ECG and cardiac biomarker.
- **Pericarditis**—Clinical features—Sharp pleuritic like pain aggravated by changes in position, highly variable in duration, associated with pericardial friction rub on auscultation.

  ECG—Elevated ST segment with convexity downward but cardiac biomarker are absent.

VASCULAR CAUSES OF CENTRAL CHEST PAIN

- **Aortic dissection**—Clinical features—Excruciating ripping unrelenting pain of sudden onset on anterior chest often radiating to back. Usually associated with HTN and artherosclerosis or connective tissue disorder like Marfan syndrome, ankylosing spondylitis.
  Diagnosed by CT or MRI.

- **Pulmonary embolism**—Sudden onset dyspnea, pleuritic chest pain, tachypnea, tachycardia and signs of right heart failure—diagnosed by pulmonary angiography and confirmed by contrast CT/MRI. Ventilation Perfusion scan V/Q scan.
- **Pulmonary hypertension**—Clinical features—Substernal chest discomfort, accelerated by exercise. Pain associated with dyspnea and sign of pulmonary hypertension like wide split S_2 loud P_2. PCWP (pulmonary capillary wedge pressure) >20 mm Hg.

PULMONARY CAUSES OF CENTRAL CHEST PAIN

- **Pleurisy/Pneumonia**—Clinical featureslo—Pleuritic chest pain, usually brief over involved area, lateral to midline associated with dyspnea-fever and cough—Chest X-ray is diagnostic.
- **Spontaneous pneumothorax**—Clinical features—Sudden onset unilateral pleuritic pain with dyspnea. With past history of tuberculosis or pneumonia or lung abscess–chest X-ray is diagnostic.
- **Tracheobronchitis**—Clinical features—Burning discomfort in midline upper retrosternal location associated with cough and fever.

GASTROINTESTINAL CAUSES OF CENTRAL CHEST PAIN

- **Esophageal reflux**—Clinical features—Burning discomfort substernal and retrosternal in location usually of 10–60 minutes duration after heavy meal or during recumbency—Endoscopy is diagnostic.
- **Peptic ulcer**—Clinical features—Prolong epigastric or substernal pain releived by food, antacid, H_2 blocker and PPI—Endoscopy is diagnostic.
- **Gallbladder disease**—Clinical features—Prolongs epigastric or rightupper quadrant pain, unprovoked or following fatty meal in middle-aged fatty lady radiating to tip of right shoulder or inferior angle of scapula—USG of abdomen is diagnostic.
- **Pancreatitis**—Clinical features—Prolonged intense epigastric and substernal pain with the history of alcohol, hypertriglyceridemia diabetes or gallbladder disease. Diagnosed by high serum amylase, lipase and USG/CT of abdomen also help diagnosis.

MUSCULOSKELETAL CAUSES OF CENTRAL CHEST PAIN

- **Costochondritis**—Clinical features—Sudden onset intense fleeting pain reproduced by pressure over affected joint, occasional patient have swelling and inflammation over costochondral joint—chest X-ray is usually negative. Diagnosed by exclusion.
- **Vertebral disk disease**—Clinical features—Sudden onset of radiating pain may have radiation to back may be reproduced by movement of neck or spine. X-ray cervical spine, CT/MRI of cervical or dorsal spine is diagnostic.
- **Infectious**
  - ***Herpes zoster***— Clinical features—Prolonged burning pain over dermatomal distribution with vesicular rash, never cross the midline—Diagnosed by viral serology.
- **Psychological**
  - ***Panic disorder***—Clinical features—Chest tightness or aching often accompained by dyspnea lasting > 30 minutes, unrelated to exertion or movement. With a background of emotional disorder.

CLINICAL FEATURES OF STEMI

Symptoms

- **Chest pain**—Retrosternal or precordial in location frequently radiates to neck, jaw, left shoulder (but not trapizius), left arm, back, abdomen (epigastric) region (never below umbilicus).

  Nature of pain is usually described as heaviness, squeezing, crushing, stabbing or burning in nature.
- **Angina equivalent—Dyspnea, fatigue, faintness, nausea and epigastric discomfort** may occur.
- But painless infarct can occur in diabetes and elderly.
- It is often associated with weakness, sweating, nausea, vomiting and anxiety.
- Rarely sudden loss of **consciousness, confusional state, profound weakness, unexplained arrhythmia, hypotension or peripheral embolism** are the unusual presenting symptoms.

Signs

- About one-fourth of patients with anterior wall infarction have features of sympathetic overactivity as evidenced by tachycardia and hypertension whereas up to one-half with inferior wall infarction have evidence of parasympathetic overactivity as manifested by bradycardia and hypotension.
- Apical impulse may be difficult to palpate.
- Rarely abnormal systolic pulsation may develop in the periapical area within 1st day of infarction.
- Intensity of S_1 and S_2 decreased with paradoxical splitting of S_2.
- S_3 and S_4 may be audible.
- A transient mid or late systolic apical murmur due to dysfunction of mitral valve apparatus may be audible.
- A pericardial friction rub may be heard in transmural infarct.
- Basal body temperature may be elevated to 38°C in the 1st week.

Investigations

Apart from positive cardiac enzyme, e.g. troponin and CKMB the following investigations can be done in AMI.

- TLC—12000–15000/cmm appear with 1st few hours and persist for 3–7 days.
- ESR—Raised.
- Cardiac imaging.
  - Echocardiography with Doppler flow study is done to see the following—
    - Regional wall motion abnormality
    - Ejection fraction
    - Presence of RV infarct
    - Ventricular aneurysm
    - LV thrombus
    - Pericardial effusion
    - VSD and MR associated with AMI.
  - High resolution cardiac MRI by late enhancement with gadolinium—Images are obtained 10 minutes after gadolinium injection which shows bright signal from area of infarction which appears as a sharp contract to the dark area of normal myocardium.

MANAGEMENT OF STEMI

Treatment of STEMI starts from the time of onset of pain and can be divided into—(a) prehospital care, (b) initial recognition, (c) emergency management, (d) reperfusion, and (e) late hospital management (management of complication and secondary prophylaxis).

MANAGEMENT IN EMERGENCY (OUTLINE)

(According to ACC/AHA class-I recommendation)

1. ECG monitoring (continuous).
2. Aspirin—300 mg chewable tablet.
3. O_2 administration (when hypoxia is present) 2–4 L/min by nasal prong or facemask.
4. Nitroglycerine—0.4 mg (sublingual) × 3 dose at 5 minutes interval.
5. Morphin—2–4 mg IV at 5 minutes interval till the total dose of 15 mg in reached or desired level of analgesia is reached or side effects like hypotension, vomiting or respiratory depression appear.
6. β-blocker—Metoprolol 5 mg IV × 3 dose at 5 minutes interval, wait for 15 minutes after the last dose for appearance of side effect like—(a) heart rate <60 BPM, (b) SBP <100 mm Hg, (c) P-R interval >0.24 sec, (d) Rales >10 cm from the diaphragm. If they are absent, metoprolol—50 mg IV every 6 hourly × 48 hour followed by 100 mg bid.
7. Reperfusion strategy—(a) Thrombolysis and (b) primary PCI.

Details of Emergency Management

- Aspirin
  - Block TxA_2—Receptor of platelet and decrease platelet aggregation
  - Reduce mortality by 21%
  - Useful in primary prevention and also in the whole spectrum of AMI treatment strategy
  - To increase the blood level of aspirin rapidly, patient should chew nonenteric coated ASA tablet (162–325 mg) for better absorption through oral mucosa

Combination treatment strategy for control of chest pain

- Nitrate, morphin, O_2 inhalation and β-blocker is used in combination to reduce the chest pain
- Not to underdose the patient, because pain increases sympathetic response that causes tachycardia which ultimately increases the cardiac demand

Morphin

- It is the analgesic of choice in STEMI patient except in patient with well-documented morphin hypersensitivity
- 4–8 mg IV followed by 2–4 mg repeated at interval of 5–15 minutes until the pain is relieved or evidence of toxicity (hypotension, depression of respiration, vomiting) preclude its use
- Also useful in relieving pulmonary edema associated with CCF in MI
- Hypotension can be managed maintaining the patient in supine posture with leg elevated if SBP <100 mm Hg. If not effective normal saline 500 mL infusion can be given.
- Respiratory depression can be managed by naloxone 0.1–0.2 mg IV repeated every 15 minutes if necessary
- Vomiting can be managed by injection metoclopramide 10 mg IM
- Can cause bradycardia and heart block which is managed by injection atropin 0.5 mg IV

Nitrate

1. It enhance coronary blood flow
2. It decrease preload
   Sublingual nitrate should be given in patient with ACS except—
   a. Inferior wall MI
   b. Right venticular infarction
   c. Marked hypotension SBP <90 mm Hg
   d. Bradycardia
3. In patient with prolonged period of waxing or weaning chest pain IV. NTG is beneficial for controlling pain and ischemia
   - Blood pressure should be regularly checked during nitrate infusion and SBP should be >100 mm Hg

β-blocker

1. Relieve pain
2. Reduce analgesic dose
3. Reduce infarct size
4. It is the only drug that can prolong life expectancy—so should be given in every cases excepting in strongly contraindicated patient

Relative contraindication of β-blocker

1. Heart rate <60 BPM
2. SBP <100 mm Hg
3. P-R interval >0.24 S
4. 2nd or 3rd degree heart block

5. Bilateral rales >10 cm from lung base
6. Signs of peripheral hypoperfusion
7. Severe COPD
8. History of severe asthma
9. Type–I diabetes
10. Severe peripheral vascular disease

Absolute Contraindication of β-Blocker

- Signs
  1. Heart failure
  2. Evidence of low output state
  3. Increased risk for cardiogenic shock

Metoprolol

- Injection metoprolol—5 mg IV × 3 dose at 5 minutes interval → patient is observed for 5 minutes in between the doses for BP/ pulse/rales → if no contraindication appears after three IV bolus

↓

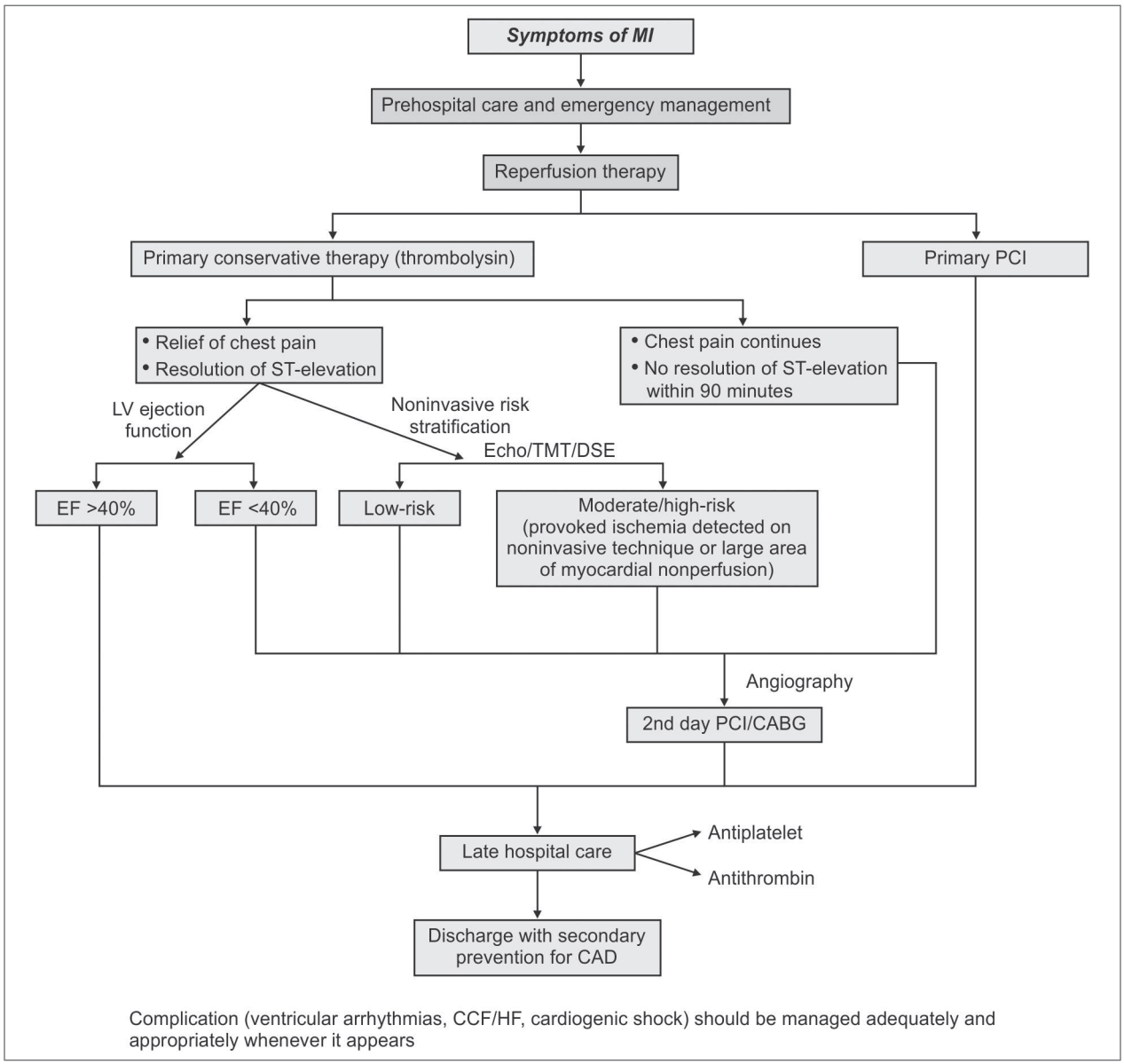
and if hemodynamic stability persist 15 minutes after last IV dose, oral metoprolol is continued in a dose. 50 mg 6 hourly for 1st 48 hours, then 100 mg BD/day

- In patient with relative contraindication to β-blocker. Esmolol 50–250 mg/kg/min given as infusion or non-DHPCCB can be tried

Oxygen

- Augmentation of fraction of O_2 in inspired air does not elevate O_2 delivery significantly in the infarcted area in patient who are not hypoxemic
  Moreover it causes peripheral vasoconstriction so afterload rises which decreases COP
- Patient with STEMI with arterial hypoxia (O_2 saturation <90%). O_2 is delivered at the rate of 2–4 L/min as 100% moist O_2 by nasal prong or mask for 6–12 hours
- For severe hypoxia or in pulmonary edema endotracheal intubation and PEP-ventilation may be required

Flowchart. 10.4: Outline of management of acute myocardial infarction



REPERFUSION THERAPY (FLOWCHART 10.5)

When ST-elevation of at least 2 mm in two contiguous precordeal lead 1 mm in two adjacent limb lead is present, the patient should be considered candidate for reperfusion therapy.

Although late spontaneous reperfusion occurs in some patients, persistent thrombotic occlusion in majority of STEMI patients causes necrosis of the ischemic myocardium. So to limit the infarct size.

- **Two major procedure are available**
  - **Fibrinolysis**
  - **Primary PCI**.
- Extent of myocardial salvage is large when reperfusion is achieved by PCI and is less time- dependent than fibrinolysis. It is due to the fact that—
  - Full restoration of blood flow occurs in PCI (>90%) in comparison to fibrinolysis ~ 70%.
  - Time makes coronary thrombi mature on which fibrinolytic agent cannot act or act very poorly.

Indication for Primary PCI

- Skilled PCI laboratory is available with surgical backup.
- Door to balloon (D-B) time <90 minutes.
- Door to needle (D-N) time >1 hour.
- High-risk STEMI case where cardiogenic shock has developed.
- Contraindication to fibrinolysis in present (past history of bleeding and past history of ICH).
- Late presentation >3 hours from the onset of symptoms.
- Diagnosis of STEMI is in doubt.

Indications for Primary Fibrinolysis

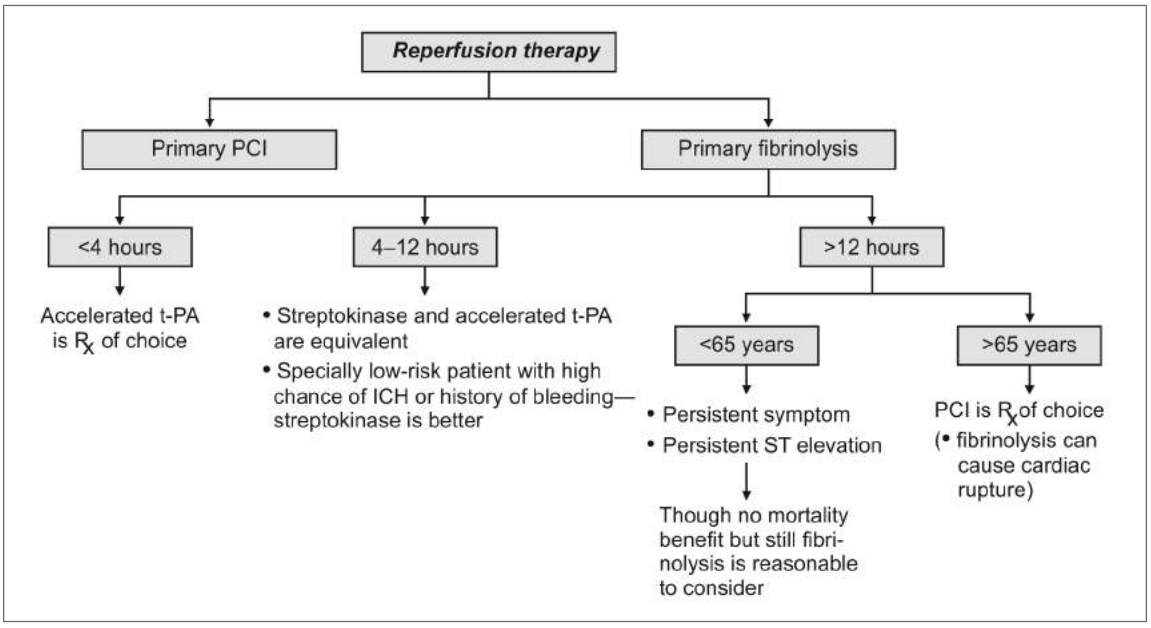
- Early presentation (within 3 hours).
- PCI not favorable as
  - Laboratory is occupied/not available.
  - Vascular access is difficult.
- Delay in invasive strategy
  - Prolonged transport.
  - Door to balloon (D–B)—Door to needle (D–N) time > 1 hour.
  - Door to balloon (D–B) time >90 minutes.

Choices of Agents in Fibrinolytic Therapy

- **Patient presenting within 4 hours of symptom onset**
  - High intensity fibrinolytic regimen (accelerated t-PA) is preferred except in some low-risk individuals.
  - In low-risk individual—streptokinase and accelerated t-PA are equivalent.
- **Patient presenting between 4–12 hours of onset**
  - Speed of reperfusion is of lesser importance. So streptokinase and t-PA are equivalant.
  - In low-risk patient but having a high chance of ICH/bleeding, streptokinase is preferable to t-PA in cost-benefit consideration.

    Candidates appropriate for fibrinolytic therapy with t-PA should better be treated with bolus thrombolytic like reteplase/tenecteplase because
    - Easy administration
    - Low chance of application error
    - Less noncerebral bleeding
    - Potential for prehospital treatment.

Flowchart. 10.5: Reperfusion therapy



- **Late therapy/treatment for patient presenting 12 hours or later**
  - **No mortality benefit** was demonstrated in patient with fibrinolytic therapy when started between 12–24 hours after onset of symptoms.
  - But still fibrinolytic therapy is reasonable to consider in patient with
    - Persistent symptoms
    - Persistent ST-elevation in ECG
    - Persistent chest pain.
  - Patient >65 years treated with fibrinolytic therapy after 12 hours has a higher chance of cardiac rupture hence late fibrinolytic reperfusion therapy is better to restrict in young patient < 65 years of age.
  - So elderly patient with ongoing ischemic symp- toms > 12 hours—PCI is the ideal treatment.
  - All patients with suspected STEMI should receive aspirin regardless of fibrinolytic therapy and should be continued indefinitely.
  - Patient requiring PCWP measurement and trans-venous pacemaker lead (temporary) should be introduced before starting fibrinolytic therapy or it can be given after fibrinolytic therapy, only when it is crucial for patients survival.
  - **Doses**—
    - Streptokinase → 1.5 mU within 30–60 minutes dissolved in 100 mL N saline.
    - Reteplase → 10 U × 2 (each over 2 minutes) each at 10 minutes apart in short push.
    - Tenecteplase → 30–50 mg/kg IV bolus.

LATE HOSPITAL CARE

- **Antithrombin/anticoagulant therapy**
  - Patient undergoing PCI/surgical intervention → UFH.
  - Patient undergoing reperfusion therapy either with t-PA or streptokinase → UFH.

- **Dose**—UFH 60 U/kg (maximum 4000 U). Initially followed by infusion of 12 U/kg/hour (maximum 1000 U/hour) adjusted to maintain INR 1.5–2 times of control.
  - It is not unreasonable to consider intra-venous UFH therapy to all patient receiving streptokinase therapy specially for those who are at high-risk for systemic embolization.
  - LMWH/Fondaparinux—It can be considered as an alternative to UFH for patient <75 years of age receiving fibrinolytic therapy without significant renal dysfunction but still superior to UFH.
- **Enoxaperin**—30 mg IV bolus followed by 1 mg/kg SC BD.
- Patient more than 75 years of age should not receive LMWH.
- Patient with known heparin-induced thrombo- cytopenia → bivalirudin (direct antithrombin) can be given.

- **Antiplatelet agents**
  - Nonenteric coated aspirin should be chewed by patient who have not taken ASA prior to presentation with STEMI—initial dose 162–325 mg followed by 75–162 mg/day.
  - If true ASA allergy is present
    - Clopidogrel (P2Y12 receptor antagonist)→ 300–600 mg followed by 75 mg/day.
    - **Prasugrel** and **ticagrelor** are more effective than clopitogrel in preventing ischemic complication but associated with increased-risk of bleeding.
  - Efficacy and safety of the routine combination of ASA with clopidogrel in patient with STEMI specially those receiving fibrinolytic therapy have been established (prevent death, reinfarction and stroke).
  - In patient <75 years with low-risk of bleeding and anterior wall MI. **Combination reperfusional therapy with *abciximab* and half dose reteplase/ tenecteplase** can be considered to prevent reinfarction/other complications.

- Combination reperfusion regimen facilitate the rate and extent of fibrinolysis by—
  i. Inhibiting platelet aggregation
  ii. Weakening the clot structure
  iii. Allowing fibrinolytic agent to deeper into the clot.
- But this combination should not be used in patient >75 years of age because of chance of ICH and have similar efficacy with bolus fibrinolytics.

  - For patient planned to be treated with PCI should receive GP-IIb/IIIa inhibitors either alone or in combination with reduced dose of fibrinolytic may be considered.
- **β-blocker**—If the 1st dose is given in the emergency then continue and titrate the daily dose according to BP and heart rate.

- **Metoprolol**—50–100 mg twice daily.
  - *Bisoprolol* (10 mg daily) *timolol* and *alprenolol* can also be used *alternatively*.
  - In diabetic patient carvedilol (αβ both blocker) can be considered.
  - In presence of absolute contraindication to β-blocker, it should be avoided and replaced by *non-DHP-CCB*.

  - In presence of relative contraindication, β-blocker should be started at a lower initial dose and titrated weekly to reach the optimal target dose.
- **ACEI/ARB** —It reduce mortality and morbidity after STEMI and the mortality benefits are additive to those achieved with β-blocker and aspirin.
  - It should be started within 24 hours in all patient with STEMI specially to—

- Elderly patient
- Anterior wall infarction
- Prior infarction
- Globally depressed LV function/large RWMA
- Hypertensive.

- **Nitroglycerin**—Injection NTG by IV root should be continued in patient of STEMI with CHF, HTN and persistent chest pain (SBP >90 mm Hg).
- **Statin** (atorvastatin—80 mg PO/day).
- **Absolute bed rest**.
- **Nothing per month** except sips of water—later low salt, low fat, low cholesterol diet should be intro- duced slowly.
- **Stool softener and PPI**—To be added.
- **Continuous monitoring** of vital sign every 1.5 hour till the patient becomes stable.

MANAGEMENT OF COMPLICATION

HEART FAILURE (HF)

The therapy mostly consist on

a. Avoidance of hypoxemia by high flow O_2
b. Diuresis
c. Afterload reduction
d. Inotropic support.

- **Diuretics**—Frusemide (10–40 mg repeated at 3–4 hours interval if necessary). It reduces LV filling pressure and pulmonary congestion resulting in improvement of orthopnea, dyspnea. Reduction of EDV and myocardial wall tension reduces myocardial O_2 requirements.
- **Vasodilator therapy** is recommended in HF when HF is unresponsive to diuretic or when HF in STEMI is associated with HTN/MR/VSD.
  - In those above situation the vasodilators increase the stroke volume and may reduce myocardial O_2 demand. It decrease the preload by vasodilation without decreasing plasma volume.
  - Commonly used vasodilators are **nitroglycerin, nitropruside, ISDN**. All decrease the preload without much lowering of plasma volume and thus advantageous to diuretic. The dose of NTG infusion (commonly used) is adjusted in such a way that—
    - PCWP—to be maintained at 20 mm Hg.
    - BP—to be maintained above 90/60 mm Hg.
- **ACE inhibitors** or **ARB** are used as ideal therapy for long-term management of heart failure but can be started on the first day.
- **Isotropic support**—It is given by

  β-agonist—When heart failure is severe and manifested as marked reduction of **cardiac index** (<2 L/min/m^2) and **PCWP > 20 mmHg** with diuretics then β-agonist dopamine and dobutamine is indicated.
  - **Dopamine**—Started with 1–2 μg/kg/min and should be increased stepwise from 2–10 μg/kg/min with strict monitoring of SBP, PCWP and COP.
  - **Dobutamine**—Though it has the inotropic effect but chronotropic effect is minimal. Starting dose—2.5 μg/kg/min–10 μg/kg/ min.
    Doses must be monitored to maintain it HR >100–110/min.
  - Levosimendan.
  - **Milrinon**—Inotropic agent as well as vasodilator.

  Dose—Starting dose—0.5 μg/kg/min over 10 minutes.
  ↓ Followed by
  Maintenance infusion—0.375–0.75 μg/kg/min.
- **Digitalis**—Digitalis in STEMI patient is unimpressive. Arrhythmias can be increased by digitalis specially if given within first few hours of STEMI. So digitalis is mainly reserved for atrial flutter/atrial fibrillation or in case of refractory HF nonresponsive to diuretics, vesodilator and β-agonist.

ARRHYTHMIAS

- **Ventricular premature beats**—
  - Prophylactic antiarrhythmic agent is contraindicated in absence of clinically important sustained ventricular arrhythmia.
  - *β-blockers* are useful in patient with ventricular ectopic and for prevention of ventricular fibrillation and should be used routinely unless contraindicated.
  - *Hypokalemia* and *hypomagnesemia* should be corrected and to be kept around 4.5 mmol/L and 2.0 mmol/L respectively.
- **VT and VF**—Routine prophylactic antiarrhythmic drug therapy is no longer recommended.
  - Sustained VT if well-tolerated hemodynamically should be treated with—
    - **Injection amiodarone** IV (bolus IV 150 mg over 10 minutes followed by 1 mg/min for first 6 hours and then 0.5 mg/min.)
      - » Alternatively
    - **Injection procainamide** IV (bolus—15 mg/kg over 20–30 min) followed by 1–4 mg/minutes.
  - If VT causes hemodynamic deterioration or develops VF then **unsynchronized DC shock** with 200–300 J (monophasic wave form approximately 50% energy with biphasic wave-form) for prompt cardioversion.
  - VT or VF unresponsive to cardioversion become responsive after treatment with
    - **Injection epinephrine** (1 mg intracardiac) diluted to 10 mL (1 : 10000) via a intracardiac catheter.
    - **Injection amiodarone** 75–150 mg bolus.
  - Patient who developed VF secondary to pump failure face a poorer prognosis—they should be managed with implantation of ICD.
  - Torsades-de-pointes may occurs in patient of STEMI as a consequence of *hypoxia*, *hypokalemia* or following *electrolyte disturbances*, *digoxin* or *quinidine* therapy. A search for the cause to be

undertaken. Withdrawal of such treatment (digoxin and quinidine) and correction of electrolyte disturbance is the treatment of choice in that situation.

- **SVT**
  - Digoxin is the treatment of choice, if SVT is associated with HF.
  - If HF is absent then **β-blocker, verapamil** or *diltiazem* are suitable alternatives.
  - If abnormal rhythm persists > 2 hours with ventricular rate >120 bpm or tachyarrhythmia induces HF, shock, ischemia—**synchronized. DC shock** with (100–200 J) energy (monophasic wave-form) is used.
- **Bradyarrhythmias and heart blocks**—Temporary electrical pacing is the procedure of choice in management of any type of bradyarrhythmias except sinus bradyarrhythmia in which atropin and isoprenaline is of some help. Initial dose of atropin is 0.5 mg, additional dose 0.2 mg up to 2.0 mg may be given.

CARDIOGENIC SHOCK (CS)

Shock usually develops following severe multivessel coronary artery disease.

Goal of therapy—Mean BP >60 mm Hg.

- To maintenance of SBP >90 mm Hg.
- To maintain PCWP 20 mm Hg.
- Correction of hypoxia and acidosis.

Prompt reperfusion to reduce the infant size and treatment of ongoing ischemia have reduced the inci- dence of shock from 20–7% only.

- **Management of cardiogenic shock according to SBP**
  - *SBP <70 mm Hg* with signs and symptoms of shock. **Injection norepinephrine** 0.5–30 μg/min IV infusion.
  - *SBP 70–100 mmHg* with sign and symptoms of shock. **Injection dopamines** 2–20 μg/kg/min IV infusion.
  - *SBP 70–100 mg Hg* without signs and symptoms of shock.
    Injection dobutamine 20 μg/kg/min IV infusion.
  - *SBP >100 mm Hg.*
    Injection nitroglycerine 10–20 μg/min IV infusion.
- **Intraaortic balloon pump (IABP)**—Rapidly stabilizes the patient with cardiogenic shock prior to PCI or prior to surgery for MR or VSD in AMI. It is contraindicated in AR or aortic root dissection.
- **Reperfusion/revascularization**—Patient who deve- lop cardiogenic shock within 36 hours myocardial infarction. **Primary PCI/CABG is class-I recommendation** of ACC/AHA guidelines.

RIGHT-VENTRICULAR INFARCTION

- Patient with inferoposterior wall infarction may demonstrate minor to extensive right ventricular infarction (rarely limited primarily to right ventricle).

Clinical Features

- Signs of severe RV failure—Kussmaul's sign, engorged JVP, hepatomegaly, hypotension, clear lung field, jugular venous distension.
- ST-elevation of the right-sided precordial lead (particularly V_{4R}).
- Positive **cardiac biomarker**.
- 2-D echo shows RV dysfunction with RWMA.
- Catheterization of right-side of heart show distinctive hemodynamic pattern resembling cardiac tamponade/ constrictive pericarditis.

Therapy

- Volume expansion by normal saline infusion to maintain RV preload.
- Measure taken to decrease pulmonary arterial pressure and PCWP by improving LV function.
- Avoidence of β-blocker – (heart block may be there).
- Cautious consideration of streptokinase (to avoid risk of hypotension).

OTHER COMPLICATIONS OF AMI

- **Recurrent chest discomfort**—It develops in 25% of STEMI patient. It is due to extension of original infarct or reinfarction. It should be evaluated thoroughly by coronary angio and managed accordingly.
- **Pericarditis**—Pericardial friction rub or pains are frequently encountered in STEMI patient. It is important to differentiate pain of pericarditis from pain of extension of original infart/reinfarct which does not radiates to trapezius. Pain of pericarditis are usually managed by aspirin 650 mg 6 hourly.
- **Thromboembolism**—Thromboembolism is clinically detected in 10% of STEMI cases and 20% by autopsy. It occurs in association with large anterior wall infarct, LV thrombus is usually detected by echocardiography but rare with inferior or posterior wall infarction.

  When thrombus is detected by echocardiography or large area of RWMA is present, systemic anticoagulation with warferin should be started prophylactically and to be continued for 3–6 months.
- **Left ventricular aneurysm**—This term is usually used to describe **ventricular dyskinesia or local expansile paradoxical wall motion**. Clinically it is detected by double or diffuse or displaced apical impulse. It is readily diagnosed by echocardiography and may usually contain mural thrombus. When it is associated with localized myocardial rupture it should be treated surgically.

Postinfarction Risk Stratification and Management

High-risk patient are identified by the following points

- Age >75

- Presence of diabetes mellitus
- Prolong sinus tachycardia
- Symptomatic ventricular arrhythmia
- Hypotension
- ST-segment changes at rest without angina
- Complete heart block
- New interventricular conduction disturbances
- Rales above the lung bases
- EF <40%
- Persistent ischemia.

And due attention must be paid in the management of the above-mentioned condition.

ADVISE AT DISCHARGE (FOR SECONDARY PREVENTION)

These are given for improvement of long-term mortality and morbidity.

- **Antiplatelet**—Aspirin 75–150 mg daily or clopidogrel 75 mg/day who are intolerant to aspirin.
- **ACE inhibitors**—To be continued indefinitely who have the following features:
  - Heart failure.
  - Moderate decrease in global ejection fraction (<40%).
  - Large RWMA.
- **β-blocker**—Chronic routinue use of β-blocker after STEMI for at least 2 years **reduces total mortality, sudden death** and **reinfarction**.
- **Warferin**—It lower the risk of late mortality and reinfarction after STEMI. Warferin with aspirin 75 mg for 3–6 months is more effective than aspirin along for prevention of recurrent MI and cerebrovascular embolism below the age of 75.
- **Lifestyle modification**—To control the risk factor for atherosclerosis the recommendations are as follows—
  - Cessation of smoking.
  - Moderation of alcohol use.
  - Reduction of body weight with attainment of optimum BMI (18.5–25).
  - DASH diet.
  - Control of hypertension (if not properly con- trolled by β-blocker or ACEI).
  - Control of hyperlipidemia (target LDL <100 mg/dL with help of HMG CoA reductase inhibitor (atorvastatin).
  - Regular aerobic physical exercise.

EXERCISE

1. Draw and label a schematic diagram of the conducting system of heart.
2. Draw and describe physiological and clinical cardiac cycle.
3. Write on updated Jone's criteria for diagnosis of acute rheumatic fever (ARF).
4. Write on treatment and prophylaxis of ARF.
5. Write on clinical features of bacterial endocarditis.
6. Write on diagnosis of bacterial endocarditis by Duke's criteria.
7. Write on prophylaxis against bacterial endocarditis.
8. Write on clinical features of mitral stenosis.
9. Write on management of mitral stenosis.
10. Write on peripheral signs of aortic regurgitation (AR).
11. Write on auscultatory finding of AR.
12. Write on types of aortic stenosis (AS).
13. Write on clinical features of AS.
14. Write on clinical features of mitral regurgitation
15. Define heart failure.
16. Write on etiology of heart failure.
17. Write on types of heart failure.
18. Write on clinical features of heart failure.
19. Write on Framingham's criteria for diagnosis of heart failure.
20. Write on stages of heart failure and therapeutic measures at different stages.
21. Write on refractory heart failure and its management.
22. Write on diastolic heart failure.
23. Write on management of acute left ventricular failure.
24. Define hypertension, labile hypertension, malignant hypertension and isolated systolic hypertension.
25. Classify hypertension (by JNC and European society)
26. Write on types of hypertension.
27. Write on investigation for hypertension.
28. Write on treatment of essential hypertension.
29. Write on drug therapy of accelerated hypertension.
30. Write on causes of secondary hypertension and its investigation.
31. Write on types of atrial septal defect (ASD).
32. Write on hemodynamic alteration and clinical features of ASD.
33. Write on types of VSD.
34. Write on pathophysiology, complication and clinical features of VSD.
35. Write on clinical features of tetralogy of Fallot's (TOF).
36. Management of TOF.
37. Clinical features of patent ductus arteriosus (PDA).
38. Define and write on diagnosis of acute coronary syndrome.
39. Write on differential diagnosis of central or precordial chest pain.
40. Write on management of STEMI in the first half an hour.
41. Write on thrombolysis in STEMI.
42. Write on late hospital care and management of complications of STEMI.
43. Write on management of UA or NSTEMI in early hours.

SECTION II

CENTRAL NERVOUS SYSTEM

- Coma and Related Disorders
- Meningitis
- Epilepsy
- Hemiplegia
- Cerebrovascular Accident
- Spinal Cord Disease (Paraparesis and Quadriparesis)
- Guillain-Barré Syndrome
- Peripheral Neuropathy
- Myasthenia Gravis
- Myopathy and Myotonia
- Parkinsonism
- Motor Neuron Diseases
- Multiple Sclerosis
- Polymyositis–Dermatomyositis–Inclusion Body Myositis

Chapter 11

Coma and Related Disorders

COMA

It is a deep sleep like state from which arousal is not possible (whatever may be the intensity of stimulus).

STUPOR

It is a lighter from of coma from which arousal is possible transiently and accompanied by motor activity that leads to avoidance of uncomfortable stimulus.

DROWSINESS

It simulates light sleep and is characterized by easy arousal and the persistence of alertness is for a brief period.

Drowsiness and stupor is accompanied by some degree of confusion.

VEGETATIVE STATE (AWAKE COMA)

It is an awake but unresponsive state where the patient have emerged from coma, he is wakeful but unresponsive.

Eyelids are open, yawning, coughing, swallowing and limb and head movement persist but there is no response to external or internal stimulus. This is accompanied by decerebrate or decorticate limb posturing and is due to extensive damage to both cerebral hemisphere as a result of—

- *Cardiac arrest with cerebral hypoperfusion*.
- *Head injury*.

AKINETIC MUTISM

It signify partially or fully awake state in which the patient is able to from impression and think as demonstrate by later recalling of events but remain virtually immobile and mute.

This condition results from *lesion of the medial nucleus of thalamus or deeper orbitofrontal surface of frontal lobe* from extreme hydrocephalus.

ABULIA

It is a milder form of akinetic mutism characterized by mental and physical slowness and diminished ability to initiate activity and is due to lesion of frontal lobe and its connection.

CATATONIA

It is characterized by hypomobility and mute syndrome that occurs in schizophrenia and major depression. They make few voluntary or responsive movement although they blink and swallow. Eyelid elevation is actively resisted, blinking occurs in response to visual threat and conjugate eye movement to opposite direction occurs on head rotation (Doll's eye).

It is also characterized by **cataplexy** or **waxy flexi- bility** in which the limbs retain the postures in which they are placed.

LOCKED-IN-STATE

It is a type of pseudocoma in which an awake patient cannot produce any speech or voluntary movement but retain vertical eye movement and lid elevation. The pupil are of normal size and reactive. The usual cause is infarction or hemorrhage in the *ventral pons that transect all corticospinal or corticobulbar pathway*.

A similar state can result from total neuromuscular paralysis in **Guillain-Barré syndrome, critical illness neuropathy and pharmacological neuromuscular blockade**.

STRUCTURE RELATED TO COMA

The pathogenesis of diminished alertness in coma is either due to —

- Widespread abnormality of cerebral hemisphere
- Reduced activity of reticular activating system (RAS).

The causes of coma are—

- Lesion that *damage the RAS* in upper midbrain or its projection.
- *Suppression of reticulocerebral function* by drugs, toxin, metabolic derangement like hypoglycemia, anoxia, uremia and hepatic encephalopathy.
- *Destruction of a large portion of cerebral hemisphere*.

As the RAS ascends through midbrain which control pupillary light reaction, its size with vertical and adduction movement of eye, *preservation of pupillary light reflex and eye movement suggest that the lesion is not in the midbrain but due to widespread structural lesion of cerebral cortex or metabolic suppression of the cerebral hemisphere*. Whereas loss of pupillary light reflex and eyeball movement suggest lesion is in the midbrain.

ETIOLOGY OF COMA

- **Group of diseases that have no focal or lateralizing neurological sign with normal CT scan, CSF and brainstem function**.
  - Intoxication by alcohol, sedative and opiates.
  - Metabolic disturbances like anoxia, hypo or hypernatremia, hypercalcemia, diabetic ketoacidosis or HONK, hypoglycemia, uremia, hepatic coma, hypercarbia, hypo and hyperthyroid coma, addisonian crisis hyper and hypothermia.
  - Severe systemic infection like septicemia, pneumonia and malaria.
  - Postseizure and subclinical status epilepticus.
  - Hypertensive encephalopathy and eclampsia.
  - Acute hydrocephalus.
  - Concussion of brain.
- **Group of diseases with CSF abnormality with or without fever but no focal or lateralizing neurological sign and normal CT/MRI**.
  - Acute meningitis
  - Viral encephalitis
  - Subarachnoid hemorrhage.
- **Group of disease that cause focal or lateralizing neurological sign with abnormal CT/MRI with or without changes in CSF**.
  - Cerebral, pontine or cerebellar hemorrhage with secondary brainstem compression.
  - Cerebral or brainstem infarct.
  - Brain abscess.
  - Brain tumor.
  - Epidural or subdural hemorrhage and brain contusion.

MECHANISM OF DAMAGE TO COMA PRODUCING STRUCTURE

- Structural compression of midbrain by herniation.
  - **Transtentorial herniation**—Uncal herniation (anterior medial temporal gyrus) cause coma due to compression of midbrain against opposite tentorial edge by the displaced parahippocampal gyrus with ipsilateral pupillary dilatation. Lateral displacement of midbrain may compress opposite (cerebral peduncle) producing extensor plantar and hemiparesis contralateral to original hemiparesis known as *Kernohan-Woltman sign*.

    This herniation can cause compression of ventricular system causing acute hydrocephalus.
  - **Central transtentorial herniation** cause downward displacement of thalamus through tentorial opening with compression of upper midbrain cause miotic pupil and drowsiness due to progressive compression of brainstem (midbrain, pons and medulla).

A direct relationship between transtentorial herniation and coma is not always established.

Other herniation that usually does not produce coma:
a. Transfalcine herniation—Displacement of cingulate gyrus under falx, across the midline.
b. Foraminal herniation—Downward displacement of cerebellar tonsil into the foramen magnum which cause compression of medulla with respiratory arrest and death.

Acute horizontal displacement of pineal calcification of 3–5 mm is associated with **drowsiness.**

6–8 mm displacement of pineal calcification is associated with **stupor.**

>9 mm displacement of pineal calcification is associated with **coma.**

COMA DUE TO WIDESPREAD DAMAGE TO HEMISPHERE

- **Hypoxic ischemia**—Cause coma due to reduced supply of energy substrate which initially cause diffuse slowing of EEG similiar to metabolic coma ultimately brain metabolic activity ceases.
- **The mechanism of coma in metabolic diseases** like *hypoglycemia, hyponatremia, hyperosmolarity, hypercapnia, hypercalcemia, hepatic and renal failure* is ill understood and the reversible effect of this condition on the brain may be due to impaired *energy supply, changes in ion fluxes across neuronal membranes*, neurotransmitter abnormalities and *decrease blood brain barrier (BBB)*.
- **Epileptic coma** is probably due to *exhaustion of energy reserve* or due to *accumulation toxic molecule or large transcellular shift of sodium and water in brain* which produces generalized slowing of background EEG activity.
- **Coma in systemic metabolic disorder** like diabetic ketoacidosis, nonketotic hyperosmolarity, hyponatremia is due to large shift of water and sodium balance in the brain.
  Na level <125 mmol/L induce confusion.
  Na level <115 mmol/L induce coma and convulsion.
  Serum osmolarity >350 mosmol/L induces coma.
- **Toxic drug-induced coma**—They produce coma by depressing both brainstem nuclei including RAS and cerebral cortex.

Combination of brainstem sign and cortical sign which occurs in certain drug overdose may lead to incorrect diagnosis, i.e. drug that have atropin-like action produce dilated pupil, tachycardia, dry skin whereas opiates analog produce bilateral pinpoint pupil < 1 mm in diameter.

- **TTP, malaria and hyperviscosity**—Cause coma by diffuse occlusion of small blood vessel.
- **Cranial trauma and inflammatory demyclinating disease**—Cause coma by diffuse white matter damage.

APPROACH TO DIAGNOSIS IN A PATIENT OF COMA

History of *trauma*, cardiac arrest, use of *illicit drug, alcohol, fever, seizure, double vision, vomiting, chronic liver disease, chronic kidney disease, heart disease* or *COPD* or any HTN and *diabetes* should be searched for as cause of coma.

GENERAL SURVEY

In general survey the following points helps in diagnosis of coma are

- **Fever**—Suggest meningitis, encephalitis, heatstroke, malignant hyperthermia, neuroleptic malignant syndrome, anticholinergic drug overdose or central fever and vigorous convulsion as a cause for coma.
- **Hypothermia** in comatosed patient suggest alcohol, barbiturate, sedative, phenothiazine, hypoglycemia, peripheral circulatory failure and extreme hypothyroid state as etiology of coma. Core temperature below < 31°C itself can cause coma.
- **Tachypnea**—Indicate acidosis (DKA), pneumonia or infiltration of brain by lymphoma as a cause of coma.
- **Hypertension**—Suggest hypertensive encephalopathy but it may be secondary to raised ICP (Cushing response) in cerebral hemorrhage or head injury.
- **Hypotension** in comatosed patient suggest alcohol, barbiturate, AMI, sepsis, internal hemorrhage, hypothyroid and Addisonian crisis as an etiology of coma.
- **Fundoscopy**—Can detect subhyaloid hemorrhage in subarachnoid hemorrhage, hypertensive and diabetic changes in comatosed patient and helps in diagnosis.
- **Cutaneous petechiae**—Suggest TTP and meningococcemia or bleeding disorder as a cause of coma.
- **Cyanosis and pallor**—Suggest other systemic disease as the etiogoly of coma.

NEUROLOGIC SIGN

Tossing in the bed, crossing of leg, yawning, coughing and swallowing suggest **drowsiness**.

- **Lack of movement on one side** suggest **hemiplegia**. **Multifocal myoclonus** indicate metabolic disorder like uremia, anoxia or prion disease, lithium or haloperidol toxicity.
- **Bilateral asterixis** is a sign of metabolic encephalopathy and drug intoxication.
- **Decorticate rigidity (posturing)**—It is indicated by flexion of elbow and wrist and supination of arm suggested bilateral damage rostal to midbrain.
- **Decrebrate posturing** is indicated by extension of elbow and wrist with pronation of forearm. Suggest bilateral damage to motor tract in midbrain or caudal diencephalon.
- **Extension of arm with leg flexion or flaccid leg** is associated with pontine lesion.
- **Acute widespread disorder** of any type regardless of location cause **limb extension** and all extensor posturing become predominantly flexor in course of time.
- **Flexor posturing** in response to noxious stimulus **indicate severe damage to corticospinal tract**.
- **Abduction avoidance** movement of limb indicate intact corticospinal system.
- **Brainstem reflexes** are— (a) Pupillary size, (b) light reflex, (c) spontaneous or elicited eye movement, (d) cor- neal reflex, (e) oculovestibular response and (f) respiratory pattern.

It helps to localize the site of damage in coma.

- **Pupil size**—Normal size pupil 2.5–5 mm with normal light reflex exclude primary midbrain damage or secondary compression.
  - **Unilateral dilated pupil > 6 mm** with poor light reflex signify *compression or stretching of ipsilateral 3rd nerve* due to mass lesion above.
  - **Oval or eccentric pupil** is a early sign of 3rd nerve compression.
  - **Bilateral dilated and unreactive pupil**—Indicate severe *damage to midbrain due to compression from supratentorial mass, mydriatic eyedrop, direct ocular trauma, anticholinergic drug.*
  - **Unilateral miosis** is occasionally seen in *large cerebral hemorrhage* that compress the thalamus.
  - **Bilateral small (1–2.5 mm) but reactive pupil** seen in *metabolic encephalopathy or deep bihemispheral lesion* such as hydrocephalus or thalamic hemorrhage.
  - **Smaller reactive pupil (<1 mm) is characteristic of narcotic overdose,** e.g. (barbiturates and opiates) and **extensive pontine hemorrhage**. In case of opiates it will dilate with naloxone. Presence of reflex eye movement also helps to differenciate sedative from pontine hemorrhage as a cause of coma. *Reflex eye movement is absent in pontine hemorrhage where it will be present in sedative overdose.*
- **Ocular movement**—Eyes are observed after elevating the eyelid and note the resting position and spontaneous movement.
  - **Horizontal divergence** of the eye at rest is normal in **drowsiness**.

- Ocular axes become **parallel in deep coma**.
- *Conjugate horizontal roving of eyeball in comatosed patient exclude damage to the pons and midbrain.*
- *Conjugate ocular deviation to one side indicate damage to pons on the opposite side or frontal lobe lesion on the same side. "The eye looks towards the hemispheral lesion and moves away from brainstem lesion."*
- **Eye turn down and inward in thalamic and upper midbrain lesion** (hemorrhage).
- **"Ocular bobbing"** means brisk downward and slow upward movement along with loss of horizontal movement in diagnostic of bilateral pontine damage usually due to thrombosis of basilar artery (**also known as down beating nystagmus**).
- **"Ocular dipping"** slower arrhythmic downward movement and faster upward movement along with normal light reflex and horizontal gaze indicate diffuse anoxic cortical damage (**also known as upbeating nystagmus**).
- **Oculocephalic reflex or Doll's eye** movement is the conjugate movement of the eyes opposite to the movement of the neck (both vertical and horizontal) depends on the intregity of the midbrain, pons and medulla and oculomo- tor nuclei which is **absent in awake patient**.
- **Presence of Doll's eye** indicate lesion or **dysfunction of cerebral hemisphere with intact brainstem pathway**.
- **Absent oculocephalic reflex (Doll's eye)** indicate **either brainstem damage or overdose of certain drug**. Pupillary size and light reaction differentiate drug-induced coma from structural brainstem damage.

- **Normal caloric response or oculovestibular reflex** to thermal stimulus indicate **normal function of frontal lobe and brainstem and their interconnection** and indicate hysterical coma.
- **Normal corneal reflex** along with reflex eye move- ment **indicate normal pontine function**.
- **CNS-depressant drug**—(a) First, paralyses reflex eye movement, (b) then loss of corneal reflex and (c) pupil become unreactive at last.
- **Respiration**
  - **Shallow, slow but regular breathing** suggest metabolic cause or drug as a cause of coma.
  - **Cheyne-Stokes respiration** suggest bihemispheral damage or metabolic suppression associated with light coma.
  - **Kussmaul breathing** (rapid and deep breathing) indicate metabolic acidosis or pontomesencephalic lesion.
  - **Tachypnea** suggest CNS lymphoma.
  - **Agonal gasp** or terminal respiratory pattern seen in severe brain damage.

Laboratory Investigation in a comatosed patient

- Toxicological screeming of blood and urine.
- CT/MRI of brain.
- ECG.
- CSF study.
- Blood glucose, Na^+, K^+, calcium osmolarity, urea, creatinine NH_3 pH, PCO_2 HCO_3.

ECG: High voltage slow (δ or triphasic) have over frontal lobe is lypical of metabolic coma (hepatic coma).

Wide-spread fast (B) activity indicate sedative drug.

Alpha coma (wide spread) 8–12 H_2 activity not altered by environmental stimuli results from pontine or diffuse cortical damage associated with poor prognosis.

EEG is also diagnostic of subclinical status epilepticus.

Brain death: Criteria for brain death are:

- Widespread cortical damage as suggested by deep coma unresponsive to all form of stimulus.
- Global brain stem damage as suggested by
  - Absent pupillary light reflex
  - Absent corneal reflex
  - Absent oculovestibular reflex.
- Destruction of medulla as suggested by complete apnea.

An Isoelectric EEG is confirmasy for total cerebral damage.

Chapter 12

Meningitis

DEFINITION

Inflammation of meninges is called meningitis.

Bacterial meningitis is an acute purulent infection within subarachnoid space.

It is associated with CNS inflammatory reaction that results in complications like—

- Impaired consciousness, even loss of consciousness
- Seizure
- Stroke
- Raised ICT
- Death.
- Meninges, subarachnoid space, brain parenchyma all are involved in this inflammatory reaction that is why it is sometime called meningoencephalitis by some authors.

ETIOLOGY

In community-acquired bacterial meningitis the common pathogen are discribed in Table 12.1.

Table 12.1: Common pathogen in meningitis

Age of onset	Common	Less common
Neonates	Gram-negative bacili (*E. coli*, Proteus) Gr B Streptococci	*L. monocytogenes*
Preschool children	*H. influenzae* *N. meningitidis* *S. pneumoniae*	*M. tuberculosis*
Older children and adults	*S. pneumoniae* *N. meningitidis*	*L. monocytogenes* *M. tuberculosis*

Streptococcus pneumoniae—50%
Meningococcus—25%
Gr B *Streptococcus*—15%
Listeria monocytogenes—10%
H. influenzae~ <10%. (incidence drastically. Fall after introduction of Hib vaccine).

- Streptopneumonia is the causative agent in the adult in the age group 20–55 years.
- *N. meningitis* accounts for 60% of case in between 2–20 years.
- Group B *Streptococcus* (*Streptococcus agalactiae*) was previously responsible for meningitis in neonates but now it is seen with increased frequency >60 years age group.
- Listeria monocytogenes is an important causative agent in neonates <1 month, pregnant woman, >60 years age group and in immunocompromised individuals of all ages. The infection is acquired by consumption of contaminated food (specially milk products).
- *Staphylococcus* and coagulase negative streptococcus are important causes of meningitis that follow neurosurgical procedure and head injury.

PATHOPHYSIOLOGY

S. pneumoniae and *N. meningitidis* colonize in the nasopharynx.

↓

Invade blood vessel by membrane-bound vesicle through nasopharyngeal epithelial cell or by creating separation in the apical tight junction of columnar nasopharyngeal epithelial cells.

↓

Avoid phagocytosis by neutrophil and complement-mediated bactericidal activity due to presence of LPS capsule.

↓

Bloodborne bacteria reach the intraventricular choroid plexus and penetrates its capillary endothelial cell and enter the CSF space.

↓

They multiply very rapidly because of almost absence of WBC, complement and immunoglobulin in CSF.

↓

Lysis of bacteria liberates cell wall components composed of *LPS, teichoic acid and peptidoglycan*.

↓

Stimulate immune competent cell in the vicinity (microglia, astrocyte, endothelium and monocyte) to produce cytokines like TNF and ILs which subsequently induces a massive inflammatory response liberating various cytokine and chemotactic factors, excitatory amino acids,

Table 12.2: Typical CSF changes in different forms of meningitis

	Bacterial meningitis	Viral meningitis	Tubercular meningitis
• Appearance	→ Turbid/purulent	Clear/turbid	Turbid/viscus with cobweb coagulation on standing
• Cell	→ Total cell 500–10000 cmm Lymphocyte— <50 cmm PMN → >500 cmm	 10–100 cmm Nil	 100–500 cmm 0–200
• Protein	→ 0.5–2 g/L	0.05–0.1 g/L	0.1–0.4 g/L
• Glucose	→ <50% of blood glucose	>50% of blood glucose	<50% of blood glucose

reactive oxygen and nitrogen species. The results of which are—

- Brain cell death.
- Obliterative endarteritis of leptomeningeal arteries causing secondary cerebral infarction.

CLINICAL FEATURES

- The course of the disease may be acute fulminant rapidly progressive or subacute slowly progressive.
- **Classical triad**—*Fever, occipitocervical headache, nuchal rigidity* present in 90% of patients. *Patient lies on side, curled up attitude* and *resistive if disturbed*.
- **Mental obtundation** starting from lethargy to coma present in >75% of patients (due to raised ICT).
- **Nausea, vomiting, photophobia** are other accompanying symptoms.
- **Seizure** present in 20–40% of patients, may be focal or generalized, may be an early or a late presentation.
- Other features of raised ICP are **papilledema, dialated and poorly reacting pupil, VIth nerve palsy, decerebrate posturing and Cushing's reflex** (*bradycardia, hypertension, irregular respiration due to cerebral herniation*) may be present.
- **Diffuse erythematous maculopapular rash**, spreading over trunk, lower extremity, mucous membrane, conjunctiva, palm and sole, resembling viral exanthem but **rapidly turns into petechiae** is specific clinical features of meningococcal meningitis.
- **Kernig's sign**—Inability to extend the knee when the thigh is flexed to a right angle over the abdomen.
- **Brudzinski's sign.**
- **Brudzinski's neck sign**—When the head is passively flexed over the chest there will be active flexion of the hips and the knees even there may be flexon of upper limb.
- **Brudzinski's leg sign**—Passive flexon of one hip with extension of knee of one side, cause active flexon of hip and knee on the other side.

DIFFERENTIAL DIAGNOSIS

Common differentials are:

1. Viral meningoencephalitis (HSV)
2. Rickettsial disease (RCMF)
3. Subdural and epidural empyema
4. Brain abscess
5. Subarachnoid hemorrhage (SAH).

Less common differentials

1. Chemical meningitis.
2. Drug-induced hypersensitivity.
3. Carcinomatous or lymphomatous meningitis (sarcoid).
4. SLE.
5. Behçet's disease.
6. Meningism caused by apical pneumonia, enteric fever, empyema thoracis, diphtheria, acute pyogenic tonsillitis, viral encephalitis, leukemia, lymphoma and Weil's disease.
7. Neck rigidity/retraction is also present in tetanus/strichnine poisoning.

DIAGNOSIS

- **Routine blood examination** and blood sugar estimation—Before starting antimicrobials.
- **Blood culture**.
- **LP with CSF study (Table 12.2)**—To confirm the bacterial meningitis.
  PCR for *N. meningitidis*, *E.coli*, *L. monocytogenes*, *N. influenzae*, *S. agalactae*, *S. pneumoniae to confirm etiological diagnosis*.
- CT of brain shows diffuse meningeal enhancement.
- MRI (superior to CT is differentiating meningitis from encephalitis) shows *meningeal enhancement with gadolinium and FLAIR and DNI from orbitofrontal, anterior and medial-temporal lobe and insular cortex in 90% patient*.
- **EEG**—Important in differentiating bacterial meningitis from viral encephalitis by periodic sharp and slow wave complexes originating in one/ both temporal lobe repeating at regular interval of 2–3 seconds in between 2nd–15th day of HSV meningoencephalitis.

TREATMENT (TABLES 12.3 AND 12.4)

- Bacterial meningitis is a medical emergency.
- Start antibiotic therapy within 60 minutes of patient's arrival in emergency.

Table 12.3: Empirical antibiotic in case of meningitis according to age

Indications	Drug and dose
• Infant <1 month →	Injection ampicillin IV (200 mg/kg/day) → dose to be divided and given 4 hourly. + Injection cefotaxime IV (200 mg/kg/day) → dose to be divided and given 4 hourly. Same (in place of cefotaxime, ceftriaxone may be added)
• Infant 1–3 months →	
• Infant 3 months to 55 years	Injection cefotaxime/ceftriaxone (100 mg/kg/day → dose to be divided (55 years →) and given 12 hourly. Adult → 2 g BD) + Injection vancomycin → 2 g/day → dose to be given 12 hourly and infused over 1 hour + rifampicin
• Adult >55 years → (alcoholics or other debilitating illness)	Ampicillin + Cefotaxime / Ceftriaxone + Vancomycin + Rifampicin (3 g 4 hourly) (2 g 6 hourly) (2 g 12 hourly) (1 g 12 hourly)
• Nesocomial/posttraumatic/ postsurgery →	Ampicillin + Ceftazidime + Vancomycin (3 g 4 hourly) (2 g TDS) (1 g 12 hourly)

Table 12.4: Antibiotic therapy for meningitis—based on culture sensitivity

Pathogen		Regimen of choice	Alternative agents
• *N. meningitidis*	→		
Penicillin-sensitive		Benzylpenicillin	Ampicillin
Penicillin-resistant		Ceftriaxone/cefotaxime	Ampicillin
• *S. pneumoniae*	→		
Penicillin-sensitive		Penicillin G	Chloramphenicol
Penicillin-intermediate		Cefotaxime/ceftriaxone	Chloramphenicol
Penicillin-resistant		Cefotaxime/ceftriaxone + vancomycin	Vancomycin + Rifampicin
• *Pseudomonas aeruginosa*	→	Ceftazidime/cefepime/Meropenem	
• *H. influenzae*	→	Cefotaxime/ceftriaxone	Chloramphenicol
• *Streptococcus agalactiae*	→	Penicillin/ampicillin	
• *L. monocytogenes*	→	Ampicillin + Gentamicin	Ampicillin + Cotrimoxazole (25 mg/kg BD)
• *Staphylococcus*	→		
Methicillin-sensitive		Nafcillin	
Methicillin-resistant		Vancomycin	
• Bacteroides/Furobacterium	→	Metronidazole	

- Empirical antibiotic therapy is to be initiated in bacterial meningitis after sending the blood and CSF for examination and culture.

General and Symptomatic Management

- **Nursing care**
- **Maintenance of nutrition and bladder-bowel care**
- **Management of raised ICT**—Injection mannitol (20%)—250 mL 4–6 hourly IV for 3 days. Alternatively oral glycerine—20–30 mL 6 hourly.
- **Convulsion**—Lorazepum (0.1 mg/kg IV maximum 5 mg. If not controlled phenytoin 10–20 mg/kg IV subsequently 5 mg/kg orally.
- **Fluid and electrolyte**—Restricted (two-third of maintenance dose) fluid intake as there is chance of SIADH.
- **Hypotension**—Fall of BP should be corrected with IV fluid and vasopressor (dopamine/dobutamine/noradrenaline).
- **Treatment of complication**—
  - **Hydrocephalus**—May occur in acute phase. If not regress after conservative treatment, ventriculoperitoneal or ventriculoatrial shunt (VP/VA) shunt is required.
  - **Subdural empyema**—Drainage with appropriate antibiotic therapy.
  - Patient with typical meningococcal rash → Benzylpenicillin (2.4 g IV 6 hourly).
  - Patient with history of anaphylaxis to β-lactam → Chloramphenicol (25 mg/kg IV 6 hourly) + Vancomycin (1 g IV BD).
    - A 7-day course of IV antibiotic is adequate for meningococcal meningitis whereas for

pneumococcal meningitis it requires 2 a week antibiotic therapy.
  - When reports of culture and sensitivity of CSF are available, the antibiotic regimen can be modified accordingly.
- **Adjunctive dexamethasone therapy**
  - **Dexamethasone** → 10 mg IV 6 hourly for 4 days.

The available evidence on adjunctive dexamethasone therapy confirms benefit for *H. influenzae* and *S. pneumoniae* in reducing sensory neural deafness and death. Dexamethasone therapy should commence 20 minutes before or at least with the parenteral antibiotic but it is useless to start dexamethasone 6 hours after commencing antibiotic therapy

Dexamethasone exerts its beneficial effects

1. Inhibiting the synthesis of 1L–1 and TNF at the level of mRNA.
2. By decreasing the CSF outflow resistance
3. By stabilizing the bloodbrain barrier

- Dexamethasone should not be used with vancomycin as it decreases the penetration of vancomycin into the CSF and delays sterilization, in that condition vancomycin can be administered by intraventricular route

Management of raised intracranial pressure

To maintain ICP <20 mm Hg.

a. **Drain CSF** via ventriculostomy.
b. **Elevation of patient's head** to 30–45° in midline position
c. **Intubation and hyperventilation** ($PaCO_2$→ 25–30 mm Hg)
d. **IV Mannitol** (20%) —25–100 g every 4 hourly
e. **Hypertonic saline** 3.4%—30 mL bolus
f. **Dexamethasone** 4 mg every 6 hourly for vasogenic edema from tumor, abscess avoid glucocorticoid in head trauma, ischemic and hemorrhagic stroke

Contd...

Contd...

g. **Sedation** by (Morphine, propofol or midazolam) add neuromuscluar paralytic agent if necessary (patient may require endotracheal intubation and mechanical ventilation
h. **Pressor therapy** to raise SBP and CPP (cerebral perfusion pressor) >60 mm Hg by phenylephrine, dopamine and norepinephrine
i. Consider second line therapy for refractory ICP
   i. High dose barbiturate therapy or pentobarbital coma
   ii. Aggressive hyperventilation $PaCO_2$ < 30 mmHg
   iii. Craniotomy
j. Ventriculoatrial/ventriculoperitoneal shunt
k. Carbonic anhydrase inhibitor in communicating hydrocephalus.

PROGNOSIS

- Mortality is in the range of 3–7% for *H. influenzae*, Gr. B *Streptococcus*, *N. meningitidis.*
- *L. monocytogenes* mortality is 15%.
- *S. pneumoniae* mortality is 20%.

CHEMOPROPHYLAXIS OF CLOSE CONTACTS MENINGOCOCCAL MENINGITIS

Rifampicin (600 mg BD) for 2 days in adults or in child (10 mg/kg BD for 2 days).

Rifampicin → Not given in pregnant women.

Alternative → One dose of ciprofloxacin (750 mg) or azithromycin (500 mg) or ceftriaxone (250 mg) IM stat.

Chapter 13

Epilepsy

Seizure—***It is due to paroxysmal (abnormal*, excessive) *hypersynchronous electrical discharge from a group of neuron in CNS, resulting in clinical*** *manifestation ranging from* ***dramatic convulsion to features not readily detected by the observer***.

Epilepsy: It is a condition in which the person has **recurrent seizure due to chronic noncorrectable cause**.

- When a person has single seizure or recurrent seizure due to correctable or avoidable circumstances that does not necessarily called epilepsy.
- **Two or more unprovoked seizure is called epilepsy**.

CLASSIFICATION OF SEIZURE

- **Partial seizure**:
  - Simple partial seizure (without unconsciousness)—(i) sensory, (ii) motor, (iii) autonomic and (iv) psychic.
  - Complex partial seizure (with loss of consciousness).
  - Partial seizure with secondary generalization.
- **Primary generalized seizure**
  - Absence (petit mal) seizure
  - Tonic clonic (grand mal) seizure
  - Tonic seizure
  - Atonic seizure
  - Myoclonic seizure.
- **Unclassified seizure**
  - Neonatal seizure
  - Infantile spasm
  - Febrile convulsion.

CAUSES OF GENERALIZED SEIZURE

- **Genetic**
  - Inborn error of metabolism
  - Storage disease.
- **Birth injury**
- **Cerebral anoxia**
- **Hydrocephalus**
- **Drugs**
  - Antibiotic—Penicillin, INH and metronidazole
  - Antimicrobial—Chloroquine and mefloquine
  - Antiarrhythmic—Lignocaine
  - Psychotropic—TCAD, phenothiazine and lithium.
- **Alcohol withdrawal**
- **Metabolic disease**
  - Liver failure
  - Renal failure
  - Hypoglycemia
  - Hypocalcemia
  - Hyponatremia
  - Hypomagnesemia.
- **Infection**
  - Meningitis
  - Encephalitis
  - Abscess
  - Toxoplasma
  - Tuberculoma.
- **Inflammatory**
  - Multiple sclerosis
  - SLE
  - Vasculitis.
- **Degenerative**
  - Alzheimer's disease
  - Creutzfeldt-Jakob disease.

CLINICAL FEATURES OF DIFFERENT TYPES OF EPILEPSY

SIMPLE PARTIAL SEIZURE

May present with the following symptomatology:

- **Motor symptom**—Typically clonic movement (2–3 Hz), but may be of pure tonic variety.
- **Sensory symptoms**:
  - Paresthesia
  - Formed hallucination
  - Flashing of light
  - Disturbance of equilibrium.
- **Autonomic symptoms**
  - Flushing
  - Sweating
  - Piloerection.
- **Psychic symptoms**
  - Higher cortical function disturbances
  - Hearing hallucination
  - Olfaction hallucination

- Epigastric sensation
- Feeling of Déjá Vu's phenomenon
- Micropsia/macropsia.

EEG

Ictal EEG shows abnormal discharge over a very limited and appropriate area of cerebral cortex (If the epileptic foci is located on the medial temporal zygus or under aspect of frontal lobe then sphenoidal or intracranial electrode may have to be applied to detect EEG abnormality).

Three additional features of simple partial seizure—

1. *Jacksonian march*—Spread of seizure impulse over a progressively larger area of motor cortex.
2. *Postepileptic Todd's paralysis*—Temporary weakness or paralysis of muscle due to exhaustion of neurotransmitter.
3. *Epilepsy partialis continua*—Seizure may continue hours to days and may be refractory to medical therapy.

FEATURES OF COMPLEX PARTIAL SEIZURE

- Seizure activity is restricted to discrete areas of motor cortex usually associated with structural abnormalities of brain.
- Transient impairment of patient's ability to maintain normal contact with the environment.
- Seizure is preceded by an aura.
- Sudden behavioral arrest accompanied by automatism (i.e. involuntary autonomic varied behaviors).
- Antegrade amnesia.
- Postictal aphasia.
- Confused state after the seizure persists for seconds to hours.

EEG Findings

- May be normal or brief discharge of epileptiform spikes.
- If the epileptic focus located on medial temporal lobe—then use of sphenoidal/intracranial electrode is essential for detection of EEG changes.

FEATURES OF PETIT MAL (ABSENCE) SEIZURE

- Sudden loss of consciousness without loss of postural control is the cardinal sign.
- The seizure activity lasts for a few seconds.
- Consciousness returns as suddenly as it is lost without any postictal confusion.
- May be associated with subtle motor sign (rapid blinking, chewing and clonic movement of hand).
- May occur hundred times per day and begins in school life.
- Evidenced by unexplained daydreaming and decline in school performance.
- Often associated with GTCS and responds well to specific therapy.
- EEG findings— 3 Hz spikes and wave pattern discharge begin and end suddenly in a background of normal EEG.

FEATURES OF GTCS

This is the most common type of seizure

Clinical stages of grand mal seizure (tonic/clonic seizure) are as follows :

a. Stage of aura.
b. Stage of cry and fall with loss of consciousness.
c. Tonic phase.
d. Tonic/clonic phase.
e. Stage of recovery and postepileptic automatism or Todd's paralysis.
f. Postepileptic sleep.

1. **Stage of aura**—Some patient complain a vague premonitory symptom called aura which may be like higher cortical disturbances, hearing or visual hallucination and flashes of light.
2. **Stage of cry and fall**—Patient become unconscious with loss postural control and fall occurs. Tonic contraction of respiratory muscle starts in this stage cause prolong expiration and produce the epileptic cry.
3. **Ictal phase**—
   - Tonic phase—This phase persists for only 10–20 seconds.
     - Ictal cry (due to simultaneous tonic contraction of laryngeal and respiratory muscles).
     - Impaired respiration.
     - Biting of tongue.
     - Hypertension.
     - Tachycardia.
     - Dilated pupil are seen in this phase.
   - Clonic phase—In this phase there is—
     - Superimposition of muscle relaxation period in between tonic muscle contraction. Period of relaxation progressively increases until the end of ictal phase, usually not more than 1 minute.
4. **4th phase is the postictal period**—This phase is characterized by:
   - Unresponsiveness with muscle flaccidity
   - Excessive salivation
   - Stridorous breathing
   - Bladder and bowel incontinence.
5. **Postictal confusion** may persists for minute to hours. Patient complains of headache, fatigue and muscleache with impaired consciousness.
   - Duration of this phase may increase in:
     - Prolonged seizure
     - Underlying CNS disease
     - Alcoholic cerebral atrophy.

EEG Findings

- **Tonic phase**—Progressive increase in generalized low voltage fast activity followed by generalized high amplitude polyspike discharge.

- **Clonic phase**—High amplitude activity typically interrupted by slow waves to create spikes and waves pattern.
- **Postictal**—Diffuse slowing of curve that gradually recovers as the patient awakens.

VARIENTS OF GTCS

- Pure tonic seizure
- Pure clonic seizure
- Atonic seizure
- Lennox-Gastaut syndrome.

DIAGNOSIS

- The first goal is to determine whether the event is truly a seizure and in depth history is essential as because in many cases diagnosis of seizure is based solely on clinical ground. Examination and laboratory study are often normal.
- Laboratory study—It includes—
  - Estimation of blood glucose and urea creatinine.
  - Estimation of Na^+, K^+, Ca^{+2} and Mg^{+2}.
  - Toxicological screening of blood and urine (in appropriate cases).
  - LP and CSF study if encephalitis or meningitis is suspected.
- EEG—

All patients who have a possible seizure disorder should be evaluated with EEG. EEG measures the electrical activity of brain by recording from (electrode) monteg placed on scalp. The potential difference between the pair of electrodes (monitoring) is amplified and displayed on computer monitor or recorded on paper

In normal awake adults lying quietly with eyes closed a α-rhythm 8–13 Hz is seen over occipital cortex intermixed with a variable amount of generalized faster β-rhythm (> 13 Hz) and it is attenuated when the eyes are open

During drowsiness α-activity is also attenuated. With light sleep, slower activity in the range of θ rhythm (4–7 Hz) and δ rhythm (< 4 Hz) appear

Abnormal repititive rhythmic activity having an abrupt onset and termination establish the diagnosis of seizure. Absence of EEG seizure activity does not exclude seizure disorder because partial seizure originating from the inferior frontal gyrus and medial temporal gyrus is beyond the range of superficial electrodes placed on scalp. So surgically placed intracranial electrode and sphenoidal electrodes are necessary for recording such seizure activity

EEG are always abnormal during GTCS but routine interictal EEG may be normal in 60% cases. Thus EEG cannot establish the diagnosis in many cases.

Interictal EEG showing bursts of abnormal discharge containing spikes and slow wave (Delta wave) is highly supportive but not specific.

In general normal interictal EEG implies a better prognosis whereas an abnormal background of profuse epileptiform activity suggest a poorer outlook.

EEG is not helpful in predicting or forecasting which patient is epileptic and when an epilepsy will develop.

If routine EEG is normal provocative measures like—
- Hyperventilation (3–4 minutes).
- Photic stimulation.
- Sleep induction or sleep deprivation is performed in an attempt to provoke abnormalities.

- Imaging—
  - CT is routinely performed to detect any structural abnormality.
  - MRI is superior to CT in localizing the cerebral lesion associated with epilepsy [e.g. tumor, neurocysticercosis (NCC), tuberculoma, arterio-venous malformation, arterial aneurysm, cerebral diplegia, abnormality of cortical architecture, hippocampal atrophy associated with mesial temporal sclerosis apart from intracerebral hemorrhage, infarction, abscess and encephalitis].
  - Functional imaging procedure (e.g. PET → Positron emission tomography) and single pho- ton emission computed tomography (SPECT) and MR-spectroscopy are helpful to evaluate medically refractory seizure.

DIFFERENTIAL DIAGNOSIS OF SEIZURE

- **Syncope**
  - Vasovagal attack
  - Orthostatic hypotension
  - Cardiac arrhythmia
  - Valvular heart disease
  - Heart failure.
- **Psychological disorders**
  - Psychogenic seizure
  - Panic attack
  - Hyperventilation.
- **Metabolic disturbances**
  - Alcohol
  - Delirium tremens
  - Hypoglycemia
  - Hypoxia
  - Hallucinogenic drugs.
- **Migraine**
- **Basilar artery TIA**
- **Sleep disorder**
  - Nercolepsy
  - Cataplexy
  - Benign sleep disorder
  - Sleep walking
  - Night tremor.
- **Movement disorders**
  - Tics
  - Myoclonus
  - Chorea
  - Athetosis.

- **In children**
  - Breadth holding spell
  - Hemiplegic migraine
  - Abdominal pain and cyclic vomiting
  - BPV (benign positional vertigo).

TREATMENT (TABLE 13.1)

- All patients with recurrent seizure should be put under antiepileptic drugs.
- Single seizure with definite CNS abnormality like tumor, trauma, infarction, infection, hemorrhage must be given antiepileptic drugs.
- Patient having single seizure without any clinical or investigational abnormality whether to be treated with anticonvulsant is controversial.
- Risk factors for recurrent seizure
  - Abnormal CNS examination
  - Abnormal EEG
  - Patient presenting with status epilepticus
  - Postictal Todd's paralysis
  - Strong family history.
- Patient having one or more than one of the risk factors should be treated.
- The goal of antiepileptic therapy is to prevent seizure and to minimize the side effects which is done by starting with a single antiepileptic drug with low dose and gradually building up the dose while monitoring the side effects and ideally the free drug levels in blood.
- **Add-on therapy**—Monotherapy should be the goal whenever possible but if the seizure cannot be controlled by one drug it is better to add a second drug without increasing the dose of 1st drug to the toxic range. Approximately 1/3rd patients require a combination of two or more drugs to control the seizure.

Table 13.1: Drugs in the management seizure

		First line	Second line/ Alternative
GTCS	→	1. Valproic acid 2. Lamotrigine 3. Topiramate	1. Phenytoin 2. Carbamazepine 3. Zonisamide 4. Oxcarbazepine 5. Phenobarbital
Partial seizure	→	1. Carbamazepine 2. Phenytoin 3. Valproic acid 4. Lamotrigine 5. Oxcarbazepine	1. Levetiracetam 2. Topiramate 3. Tiagabine 4. Primidone 5. Phenobarbital
Absence seizure	→	1. Valproic acid 2. Ethosuximide	1. Lamotrigine 2. Clonazepum

- **Withdrawal of antiepileptic therapy**—It seems reasonable to attempt the withdrawal of the antiepileptic therapy, if —
  - The patient remains seizure free for at least 2 years.
  - Patient have single seizure type (either partial/ generalized).
  - Normal CNS examination (including investi- gation).
- In most cases it is wise to gradually reduce the dose over 3–6 months—most recurrences occur within first 3 months.
- **Surgery**—
  - Approximately 20% patients are resistant to medical therapy and some surgery is extremely effective in substantially reducing the seizure frequency and seizure control.
  - Surgery is extremely valuable in focal seizure arising from temporal lobe or from other parts of brain or hemimegaloencephalopathy or other dysplastic abnormality.
  - The surgical method of choices
    - Temporal lobectomy.
    - Amygdalohippocampectomy.
    - Subpial resection to disrupt the intracortical connections.
    - Hemispherectomy or multilobular resection or corpus calosotomy.
      - » 70% patients will become seizure-free.
      - » 90% patient will have reduction in seizure frequency after surgical therapy.

STATUS EPILEPTICUS

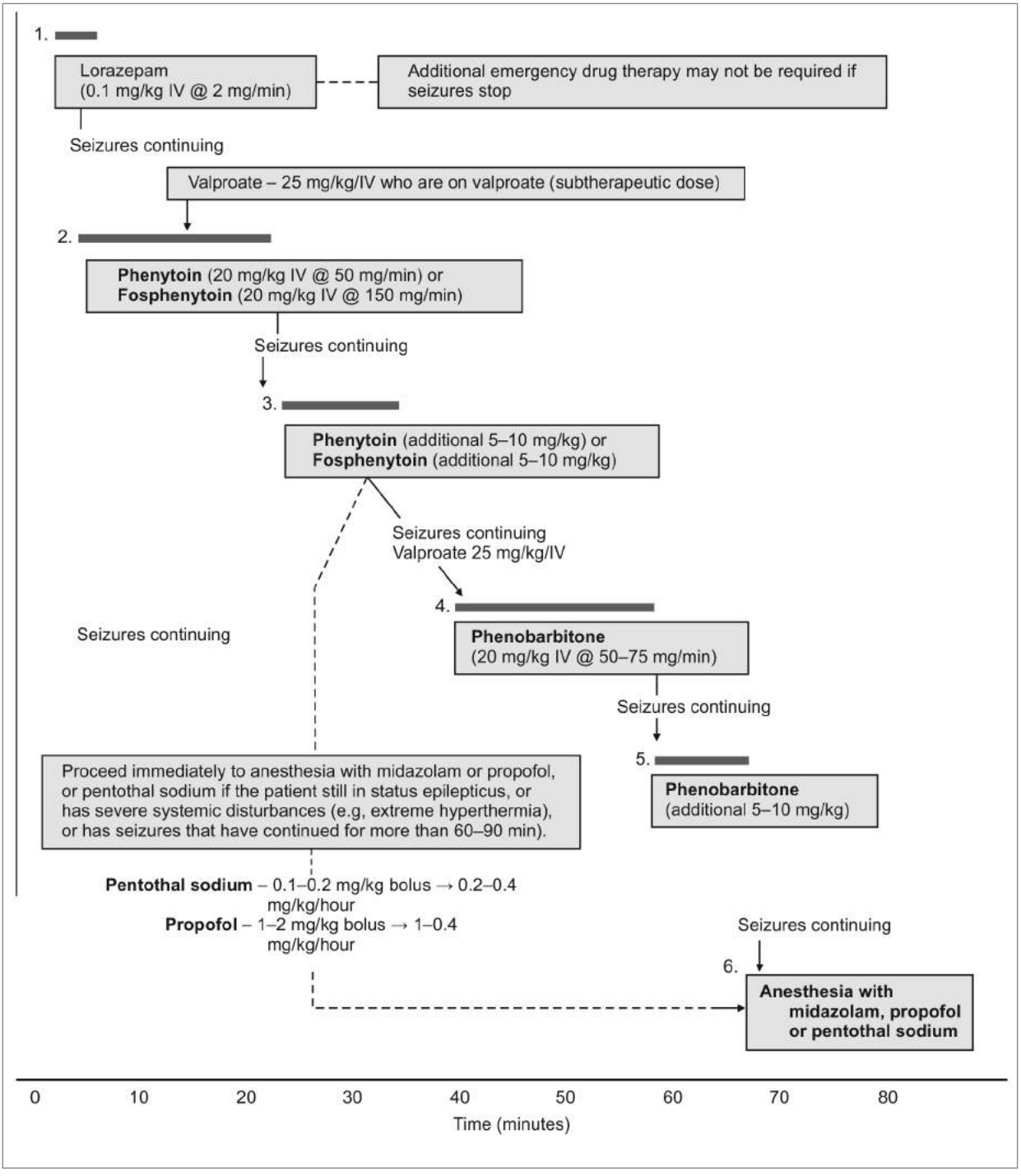
- It is defined as continuous seizure or repetitive discrete seizure with impaired consciousness in the interictal period for more than 15–30 minutes.
- But practical definition of status epilepticus is a serious condition where the duration of seizure prompts emergency use of anticonvulsant therapy or when the seizure last for more than 5 minutes.
- It is an emergency as cardiorespiratory dysfunction, hyperthermia and metabolic derangement prompts immediate therapy before irreversible neuronal injury occurs.

Management of status epilepticus is described in Flowchart 13.1

CAUSES

- Common causes
  - Anticonvulsant withdrawal.
  - Noncompliance to drugs.
  - Metabolic disturbance.
  - Drug toxicity.
  - CNS—Infection.

Flowchart 13.1: Management of status epilepticus



  - CNS—Tumor.
  - CNS—Trauma.
  - Refractory epilepsy.
- Typical features of status epilepticus is usually seen in initial period but after 30–45 minutes of uncontrolled, uninterrupted seizure the feature become less prominent except mild clonic movements of the fingers, fine rapid movement of the eyes, associated with tachycardia, hypertension and pupillary dialation. At that time EEG is the only method of diagnosis.

Chapter 14

Hemiplegia

DEFINITION

Weakness of one-half of the body is called hemiplegia.

Paralysis and **plegia** indicates weakness that is complete or near complete and is usually due to LMN lesion whereas **paresis** refers to weakness that is mild to moderate and is usually due to UMN lesion

Prefix 'hemi' refers to one-half of the body. Prefix 'para' means weakness of both the legs. Prefix 'tetra'/'quadri' means weakness of all four limbs

COMPLETE HEMIPLEGIA (CAPSULAR HEMIPLEGIA)

Refers to paralysis/paresis of lower half of face along with hand and leg on one side (contralateral to the side of lesion).

It is due to involvement of corticospinal tract on the opposite side at the posterior limb of internal capsule as a result of occlusion or hemorrhage of **deep perforating branch of middle cerebral artery** (lenticulostriate branch of middle cerebral artery).

Capsular hemiplegia is contralateral to the side of lesion as because pyramidal tract has contralateral supply.

Pyramidal track crosses the midline at lower level of medulla called great decussation of pyramid and supply the opposite half of body.

Motor cranial nerves (3rd, 4th, 5th, 6th, upper half of 7th and 9th, 10th, 11th and 12th) are not involved in complete hemiplegia as because these nucleus have dual supply from corticonuclear tract (pyramidal tract) of both sides except the lower half of facial nerve nucleus which has unilateral supply from corticonuclear tract of the opposite side. That is why all the motor cranial nerves are speared except lower half of the face which is involved in complete hemiplegia/capsular hemiplegia

INCOMPLETE HEMIPLEGIA

It means weakness of upper and lower limb but there is no involvement of cranial nerves. It is a very rare condition and occurs due to hemisection of spinal cord between C_{1-4} (ipsilateral to the side of paralysis).

CROSSED HEMIPLEGIA (NUCLEAR HEMIPLEGIA)

This rare type of clinical syndrome is seen in brainstem lesion due to vertebrobasilar territory involvement. Here, the clinical feature is **ipsilateral LMN motor cranial nerve weakness with contralateral UMN type of weakness** of upper and lower limbs.

- Motor cranial nerve involvement depends on the level of brainstem lesion (midbrain, pons or medulla).
- *In midbrain lesion—3rd and 4th cranial nerves are involved on the side of lesion with contralateral hemiplegia.*
- *In pontine lesion—5th, 6th and 7th cranial nerve are involved on the side of lesion with contralateral hemiplegia.*
- *In medullary lesion—Two types of syndrome are encountered.*
- *In medial medullary syndrome—12th cranial nerve is involved with contralateral UMN hemiplegia.*
- *In lateral medullary syndrome—9th, 10th and 11th cranial nerves are involved with paresthesia over face on the same side of lesion with contralateral hemisensory loss.*

CAUSES OF HEMIPLEGIA

- **Acute onset** (evolves over hours to days) hemiplegia
  - Cerebral embolism.
  - Cerebral thrombosis.
  - Cerebral hemorrhage (atherosclerotic, head injury, hemophilia, anticoagulation and hemorrhage within ICSOL); Substance abuse (cocaine).
  - Subarachnoid hemorrhage.
  - Multiple sclerosis.
- **Subacute onset** (evolves over days to weeks) hemiplegia
  - Cerebral abscess
  - Subdural hematoma
  - Fungal granuloma
  - Meningitis
  - Parasitic infestation
  - Primary/secondary neoplasm
  - Toxoplasmosis in AIDS
  - Multiple sclerosis
  - Sarcoidosis.

- **Chronic onset** (evolves over weeks to months) hemiplegia:
  - Chronic subdural hematoma.
  - Primary/secondary neoplasm.
  - Unruptured arteriovenous malformation.
  - Degenerative disease (primary spastic paraplegia, pseudobulbar palsy).
  - Foramen magnum lesion.
  - High cervical cord lesion.

CLINICAL FEATURES OF HEMIPLEGIA

Clinical features of hemiplegia can be divided into three stages:

1. Stage of neurological shock
2. Stage of recovery
3. Stage of residual paralysis.

Stage of Neurological Shock

The patient is usually drowsy/comatosed in this stage:

- All the muscles are flaccid.
- Muscle power grossly diminished.
- All deep jerks are depressed.
- Plantar could not be elicited/equivocal.
- Retention of urine and spontaneous defecation can occur.

Stage of Recovery

Recovery is usually in the following order:

1. Face—earliest.
2. Extensors of lower limb.
3. Flexors of upper limb.
4. Plantar flexon of ankle joint.
5. Distal limb muscles and movement of the finger usually do not recover or recover very late.

Stage of Residual Paralysis

Features are seen on the affected side only and that is opposite to the side of pyramidal tract lesion.

- **Nutrition**—There is disuse atrophy of muscle more on the distal part of the limb. No gross wasting and fasciculation is seen.
- **Tone**—Clasp knife type of spasticity is present on the affected side. Specially in antigravity group of muscle, i.e. flexor and adductor in upper limb, extensor and abductor in lower limb.
- **Power**—Loss of power is more in the distal limb muscle, i.e. fingers and toes. Power is comperatively preserved in proximal group of limb muscle.
- **Superficial reflex**—Lost on the affected side (abdominal and cremasteric).
- **Deep tendon jerk** are exaggerated (e.g. biceps, triceps, supinator, finger flexon jerk, Hoffman, knee and ankle jerk) on the affected side.
- **Plantar**—Babinski's sign positive (extensor plantar response).
- **Gait**—Classical hemiplegic gait (or circumduction gait), i.e. flexion and adduction of upper limb, with mid pronation of forearm and extension and abduction of hip with extension of knee and plantar flexion of ankle joint is seen at the stage of residual paralysis.

CLINICAL FEATURES OF CROSSED HEMIPLEGIA

In Midbrain Lesion (Fig. 14.1)

- **Dorsal midbrain lesion—Parinaud's syndrome**
  - Cause—Pinealoma/germinoma of pineal gland.
  - Involvement
    - Superior colliculus and pretectal area of midbrain—Lesion causes bilateral
      - » Paralysis of vertical gaze
      - » Pupillary disturbances
      - » Absence of convergence.
- **Paramedian midbrain lesion—Benedict's syndrome**
  - Oculomotor nerve, red nucleus, dentatothalamo rubrocortical path and medial lemniscus are involved.
    - *Oculomotor nerve roots* (ipsilateral intraaxial fiber).
      Lesion results in **ipsilateral paralysis of all extraocular muscle, except**
      - » *Superior oblique* (IVth cranial nerve) and *lateral rectus* (VIth cranial nerve).
      - » *Ptosis* (paralysis of levator palpabrae superioris).
      - » *Dilated and fixed ipsilateral pupil* (complete internal ophthalmoplegia).
    - *Dentatothalamic fibers and red nucleus lesion results in* contralateral cerebellar dystaxia with intension tremor.
    - *Medial lemniscus*—Lesion results is contralateral loss of tactile sensation over trunk and extremities.
- **Medial midbrain lesion—Weber's syndrome**
  - Intraaxial fibers of IIIrd nerve and cerebral peduncle are involved. Results are as follows:
    - Ipsilateral IIIrd nerve palsy
    - Contralateral UMN type of facial weakness
    - Contralateral hemiparesis (UMN type).

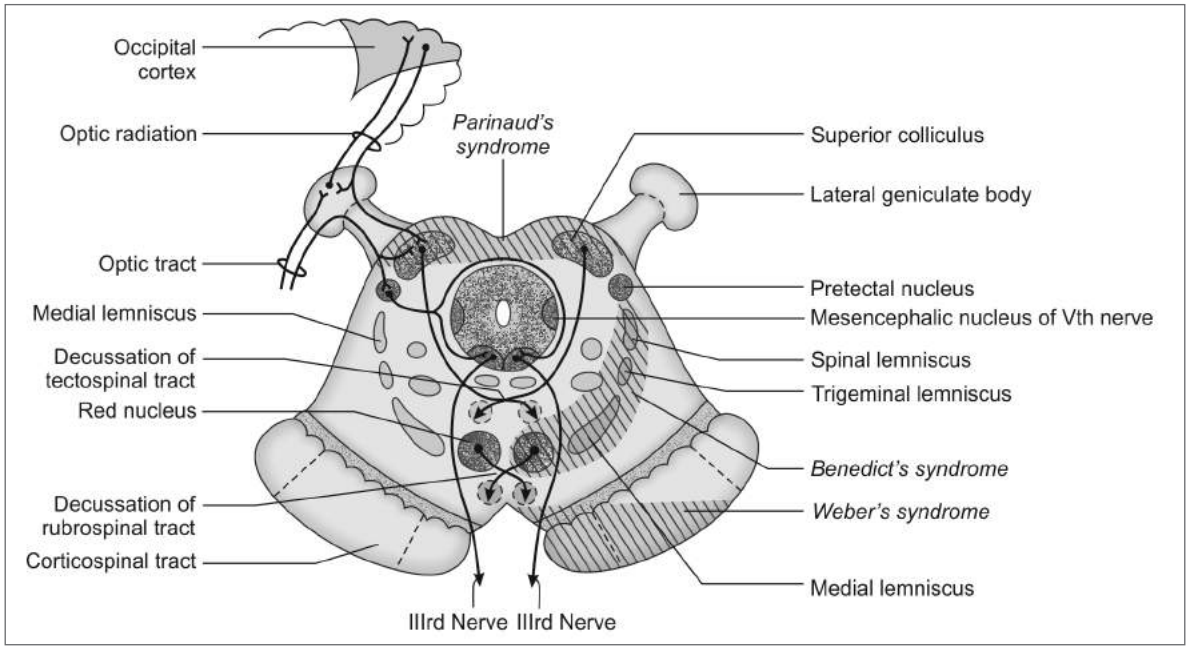


Fig. 14.1: Lesions in the midbrain (at the superior colliculus)

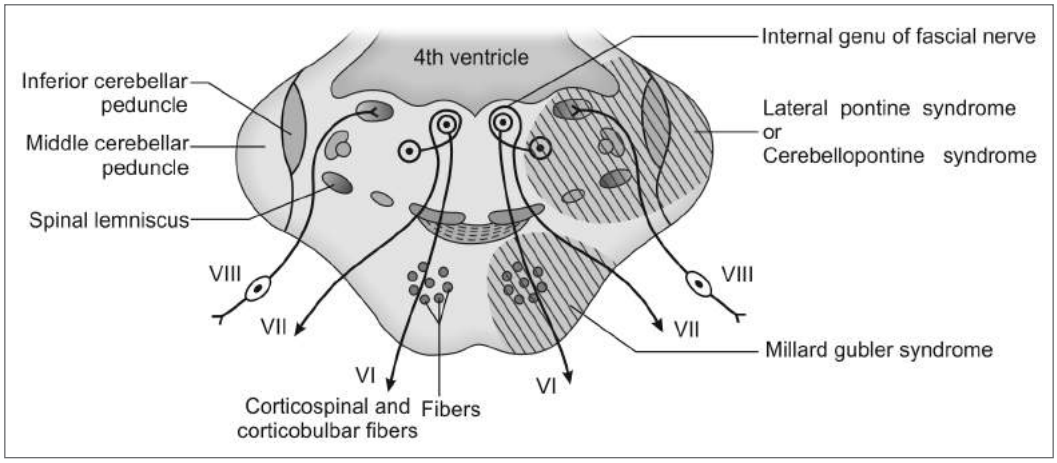


Fig. 14.2: Lesions in the caudal pons

Lesion of Pons (Fig. 14.2)

Table 14.1 Medial superior pontine syndrome (paramedian branches of upper basilar artery)

On the side of lesion	Opposite to the side of lesion
1. Cerebellar ataxia—due to superior and middle cer- ebellar peduncle lesion	1. Paralysis of face, arms and leg due to pyramidal tract lesion
2. Internuclear ophthalmoplegia due to lesion of—MLF	2. Loss of touch, vibration and position sense due to medial lemniscus involvement
3. Myoclonus of palate, pharynx, vocal cord face, respiratory or facial muscle—central tegmental bundle, dentate projection and inferior olivary nucleus	

Table 14.2 Lateral superior pontine syndrome (superior cerebellar artery)

On the side of lesion	Opposite to the side of lesion
1. Ataxia of limb and gait falling to the side of lesion due to involvment of superior and middle cerebellar peduncle, superior surface of cerebellum and dentate nucleus	1. Impairment pain and thermal sense on face, limb and trunk—spinothalamic tract involvement
2. Dizziness, nausea, vomiting, horizontal nystagmus due to vestibular involvement nucleus	2. Impaired touch, vibration, position sense more in leg than in the arm due to medial lemniscus involvement
3. Paralysis of conjugate gaze due to pontine contralateral gaze nucleus involvement	
4. Horner's syndrome due to descending sympathetic fiber involvement	

Table 14.3 Medial midpontine syndrome (paramedian branch of midbasilar artery)

On the side of lesion	Opposite to the side of lesion
1. Ataxia of limb and gait due to bilateral pontine nuclei involvement	1. Paralysis of face, arms and leg—corticobulbar and corticospinal tract
	2. Variable loss of touch and proprioceptions— medial lemniscus

Table 14.4 Lateral midpontine syndrome (short circumferential artery)

On the side of lesion	Opposite to the side of lesion
1. Paralysis of muscle of mastication—due to Vth cranial nerve and its fiber involvement	1. Impaired pain and temperature sensation over limb and trunk—spinothalamic tract involvement
2. Impaired sensation over face—due to Vth cranial nerve and its sensory fiber involvement	

Table 14.5 Medial inferior pontine syndrome (paramedian branch of basilar artery)

On the side of lesion	Opposite to the side of lesion
1. Paralysis of conjugate gaze center for conjugate lateral gaze	1. Paralysis of face, arms and leg—pyramidal tract
2. Nystagmus due to vestibular nucleus lesion	2. Loss of touch and proprioception over the half of body—medial lemniscus
3. Ataxia of limb—middle cerebellar peduncle involvement	
4. Diplopia on lateral gaze VIth cranial nerve lesion	

Table 14.6 Lateral inferior pontine syndrome (anterior inferior cerebellar artery)

On the side of lesion	Opposite to the side of lesion
1. Horizontal and vertical nystagmus, vertigo nausea, vomiting, oscillopsia due to vestibular nerve and nucleus lesion	1. Impaired pain and temperature sensation over body and limb including face due to spinothalamic tract involvement
2. Facial paralysis due to VIIIth cranial nerve, nucleus and nerve lesion	
3. Paralysis of conjugate gaze center for conjugate gaze lesion	
4. Deafness and tinnitus due to VIIIth cranial nerve and its nucleus involvement	
5. Ataxia due to—Middle cerebellar peduncle and cerebellar hemisphere lesion	
6. Impaired sensation over face due to Vth cranial nerve and its descending tract lesion	

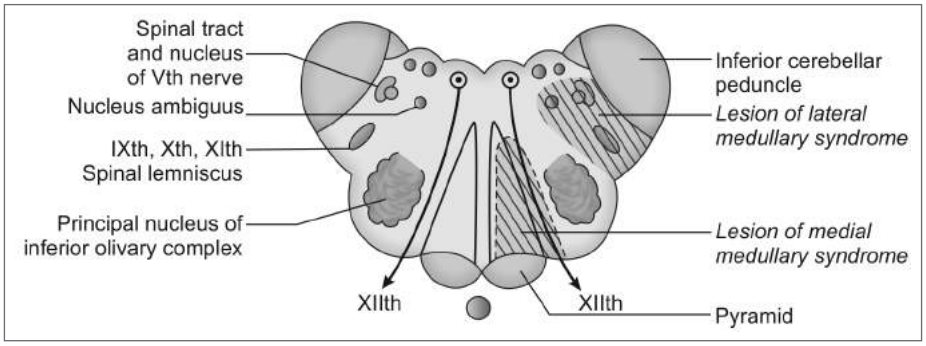


Fig. 14.3: Lesions in the medulla oblongata

Lesion of Medulla (Fig. 14.3)

Table 14.7 Medial medullary syndrome (due to occlusion of vertebral or basilar artery or its paramedian branch)

Ipsilateral features	Contralateral features
1. XIIth nerve lesion causes → paralysis and atrophy of same half of the tongue	1. Paralysis of arm and leg except face due to pyramidal tract lesion
	2. Medial lemniscus involvement causes → numbness and loss of proprioceptive sense over the opposite half of the body

Crossed pattern of sensory disturbances in which one side of the face and opposite half of the body are affected due to lesion localized to the lateral medulla as a result of involvement of ipsilateral descending trigeminal tract and ascending spinothalamic tract subserving opposite half of body.

Table 14.8 Lateral medullary syndrome (wallenberg syndrome) due to occlusion of vertebral pica, (posterior inferior cerebellar artery) superior, middle, inferior lateral medullary artery

Ipsilateral features	Contralateral features
1. Vth nerve involvement (descending tract and sensory nucleus) causes loss of sensation over same side of the face.	1. Anterior spinothalamic tract involvement causes • Loss of pain and thermal sense over the opposite half of the body (contralateral to the side of lesion)
2. IX, X, XI, nerve involvement – • Dysphagia with nasal intonation and nasal regurgitation due to IX and cranial root of XI th cranial nerve involvement causing paralysis of palate and pharyngeal muscle	

Contd...

Ipsilateral features	Contralateral features
• Hoarseness of voice due to Xth CrN involvement – paralysis of vocal cord	
3. VIIIth nerve (vestibular div) nystagmus, diplopia, oscillopsia, vertigo, nausea and vomiting	
4. Horner's syndrome—due to descending sympathetic tract involvement—(a) Ptosis, (b) miosis, (c) hemianhydrosis, (d) enophthalmos and (e) loss of ciliospinal reflex are the features of Horner syndrome	
5. Loss of taste sensation → Due to nucleus of tractus solitareous (NTS) lesion	
6. Numbness of arm and trunk due to nucleus cuneate and graciles involvement	

- **Foville's syndrome**—Dorsal pontine injury causes lesion of VIth and VIIth nerve nucleus and involvement of corticospinal fiber which results in ipsilateral lateral gaze palsy with LMN type of facial weakness and contralateral hemiparesis.
- **Millard-Gubler syndrome**—Ventral pontine injury resulting in almost same feature of Foville's syndrome except lateral gaze palsy which is replaced by lateral rectus weakness (because abducent fascicle is injured rather than abducent nuclei).

Chapter 15

Cerebrovascular Accident

STROKE MEANS STRUCK BY HAND OF GOD

It is the most common cause of hemiplegia and is defined as abrupt onset neurodeficit [most commonly hemiplegia with/without higher cerebral dysfunction (aphasia, hemisensory loss, visual field defect or brainstem defect) which lasts for >24 hours] and is due to focal vascular cause.

CEREBROVASCULAR DISEASE (CVD) RESPONSIBLE FOR STROKE

- Thromboembolic infarct (80%)
- Cerebral and cerebellar hemorrhage (10%)
- Subarachnoid hemorrhage (5%)
- Dissecting carotid/vertebral aneurysm (3%)
- Cranial venous sinus thrombosis (<1%)
- Subdural/extradural hemorrhage/hematoma (1–2%).

TYPES

- **Completed stroke**—Persistent neurodeficit which has become maximum usually within 6 hours.
- **Stroke in evolution**—Progression (progressive increase) of neurodeficit during the first 24 hours.
  On other words neurodeficit is coming in step ladder fashion.
- **Minor stroke**—When the patient recovers without any significant residual neurodeficit within a week.
- **Transient ischemic attack (TIA)**—Focal neurodeficit (e.g. → monoparesis, aphasia and hemianopia) lasts from few seconds to 24 hours and leaving no residual neurodeficit after 24 hours regardless of whether there is imaging evidence of new permanent brain injury.

CAUSES OF CEREBRAL EMBOLISM OR TIA

- Artery to brain embolization—
  - Intracerebral—Anterior communicating and posterior communicating, basilar and vertebral.
  - Extracerebral—Arch of aorta, common carotid, bifurcation of common carotid and internal carotid.
- Heart to brain embolization—Left atrium, mitral valve and left ventricle.
- Arteritis—SLE and PAN.
- Hypercoagulable state—Sickle-cell diseases, polycythemia, myeloma, APLA syndrome and myeloproliferative disorder.

MECHANISM OF STROKE

- The common mechanisms of stroke are as follows—
  - Arterial embolism fromed at a distant site [carotid bifurcation (most common), aortic arch, common carotid, internal carotid, vertebral, basilar artery and heart] dislodges from its primary site of formation and ultimately caught in the cerebral artery in the dominant cause of CVA.
  - Atheromatous occlusion of carotid or vertebral artery or their branches (anterior, middle or pos- terior cerebral and basilar artery) and subsequent brain infarction.
  - Primary hemorrhage into the brain parenchyma.
  - The other uncommon mechanisms of stroke are as follows—
    - Venous sinus thrombosis.
    - Multiple sclerosis (MS).
    - Mass effect from the tumor, abscess and subdural hematoma.
    - Arteritis in SLE and PAN.
    - Hypercoagulable state → e.g. thrombophilia, APLA syndrome and hyperhomocysteinemia.

PATHOPHYSIOLOGY

There are some compensatory changes that can prevent stroke even in case of occlusion of a carotid artery from having any apparent clinical effects. These compensatory mechanisms are as follows—

- After occlusion of a cerebral artery, the opening of anastomotic channels from other arterial territories may restore perfusion of its territory.
- Furthermore, a reduction in perfusion pressure leads to other homeostatic changes to maintain oxygenation to the brain.

When this compensatory mechanism fails, the clinically apparent effects appear.

Normal brain requires 70–100 mL blood/100 g of brain tissues/min.

- Blood flow <16–18 mL/100 g of brain tissue/min causes infarction within 1 hour.
- Blood flow <20 mL/100 g of brain tissue/min may causes ischemia without infarction unless prolonged for several hours to days. The area is called **ischemic penumbra**.
- But a fall in cerebral blood flow to zero causes brain death within 4–10 minutes.
- If blood flow is restored prior to significant brain cell death and patient goes to TIA.
- Tissue surrounding the core region of infarction is ischemic but reversibly dysfunctional is called **ischemic penumbra** and can be easily detected by perfussion-diffusion MRI.

Ischemic penumbra will eventually develop infarct if no improvement in blood flow occurs within few hours.

- Neuronal death occurs via the following two distinct pathways—
  - Necrotic pathway
  - Apoptotic pathway.

CAUSES OF ISCHEMIC STROKE

Common Cause

- Thrombosis
  - Large vessel thrombosis.
  - Lacunar stroke (small vessel thrombosis— Usually associated with dehydration or hypotension/ hypercoagulable state).
- Embolism
  - Artery to brain embolism
    - Aortic arch.
    - Carotid bifurcation.
    - Arterial dissection of aorta, carotid and vertebral artery.
  - Heart to brain embolism (cardioembolic)
    - Left atrium—Mitral stenosis and atrial fibrillation.
    - Mural thrombus— Myocardial infarction and dilated cardiomyopathy.

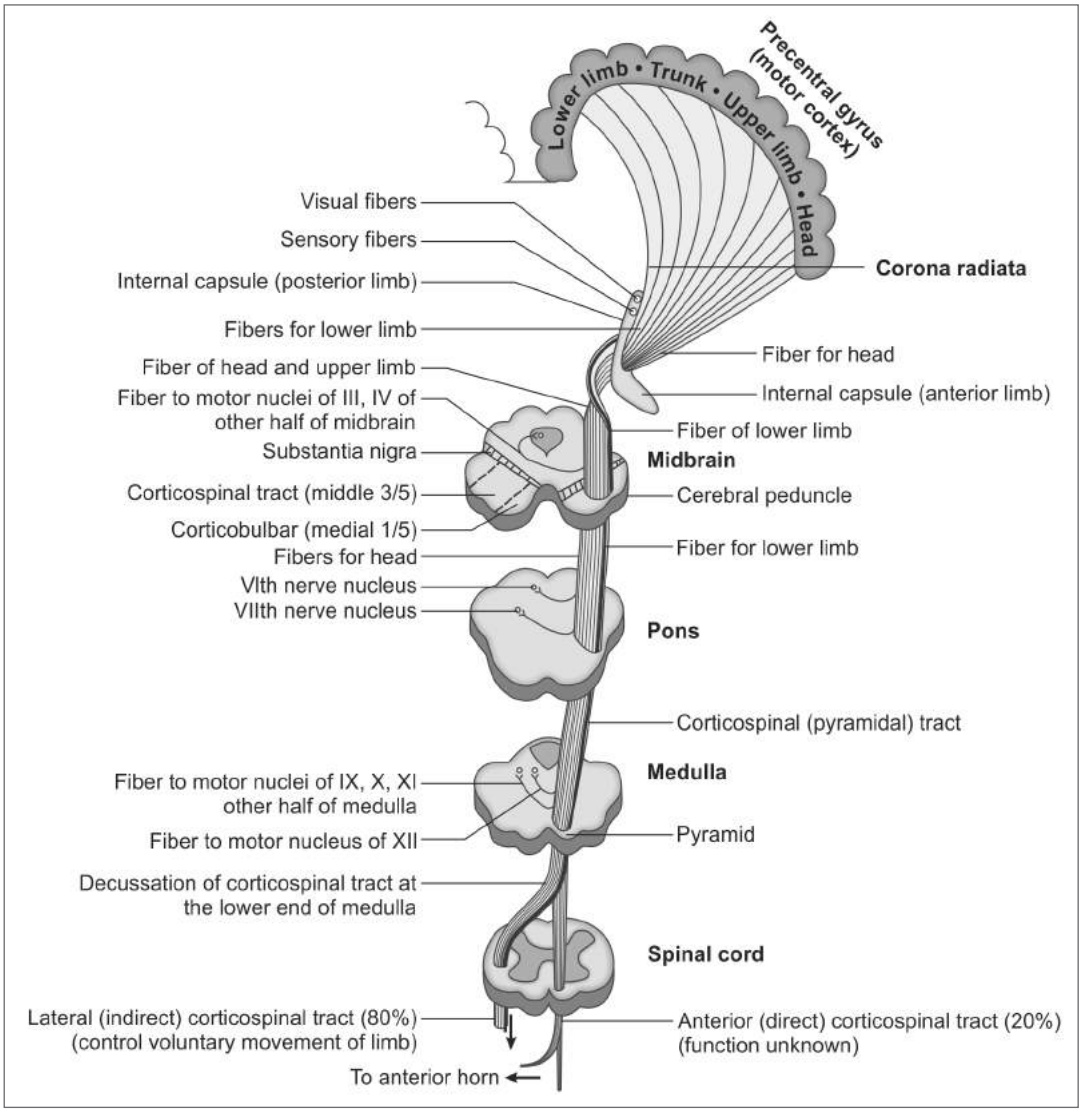


Fig. 15.1: Schematic diagram of pyramidal tract

  - Valvular lesion—Mitral stenosis, prosthetic valve and bacterial endocarditis.
  - Paradoxical embolus—Fallot's tetralogy and atrial septal defect.

Rare causes

- Hypercoagulable disorder
  - Protein C, S, or antithrombin–III deficiency and dysproteinemia.
  - Antiphospholipid antibody (APLA) syndrome and SLE.
  - Factor V leiden and prothrombin G 20210 mutation.
  - Sickle cell, β-thalassemia and polycythemia vera.
  - TTP and DIC.
  - Nephrotic syndrome, inflammatory bowel disease.
  - Oral contraceptive.
- Vasculitis—PAN, Wegener's, Takayasu's and Giant cell arteritis.
- Meningitis—Syphilis, tuberculosis, fungal and bacterial.
- Cardiogenic—Mitral valve calcification, atrial myxoma, marantic endocarditis and Libman-Sacks endocarditis in (SLE).
- Subarachnoid hemorrhage—Vasospasm.
- Drugs—Cocaine and amphetamine.
- Eclampsia.
- Moyamoya disease.

RISK FACTORS FOR STROKE

- Systemic hypertension
- Diabetes
- Dyslipidemia
- Hyperhomocysteinemia
- Smoking;
- Obesity
- OCP
- Hyperviscosity syndrome
- Bleeding diathesis
- Trauma
- Valvular heart disease with or without atrial fibrillation
- Vasculitis
- Bacterial endocarditis.

HISTORY IN SOME FORM OF CVA

Special features according to different etiology—

- **Cerebral embolism**—In the younger individual with history of valvular heart disease/SABE neurodeficit coming in lightening fashion over few seconds usually in the form of monoparesis/aphasia.

  In the elderly individual the neurodeficit coming in same lightening fashion with the background of hypertension, diabetes, accentuated atherosclerosis, smoking and obesity.
- **Cerebral hemorrhage**—In these patient with positive history of hypertension, diabetes and accentuated atherosclerosis at the height of excitement suddenly develops headache, vomiting, unconsciousness, convulsion and neurodeficit—everything coming within half to one hour time.
- **Cerebral thrombosis**—In the background of hypertension, diabetes, accentuated atherosclerosis neuro- deficit coming in step-ladder fashion over few hours specially in situation of sluggish circulation/ hemo- concentration due to diarrhea, hypotension, cardiac arrhythmia, myocardial infarction and anesthesia.
- **Subarachnoid hemorrhage**—Sudden onset headache, vomiting persisting for few hours with meningeal signs (neck rigidity) followed by slowly evolving neuro- deficit (usually hemiparesis).

CLINICAL FEATURES OF CVA

- **Common abnormality due to occlusion of anterior circulation (carotid territory—80%)**.
  - **Hemiparesis**—Due to pyramidal tract infarction at posterior limb of internal capsule.
  - **Hemisensory loss**—Due to thalamocortical fiber infarction or ventral thalamic infarction.
  - **Aphasia**—Due to infarction of Broca's area, or central speech area infarction.
  - **Hemianopic visual loss**—Due to visual pathway infarction (optic tract).
  - **Amaurosis fugax**—Due to embolism of central artery to the retina.
- **Common abnormality due to occlusion of posterior circulation (vertebrobasilar territory—20%)**.
  - **Diplopia**—Due to IIIrd, IVth and VIth cranial nerve nucleus or MLF infarction.
  - **Vertigo**, **Vomiting** } Due to VIIIth cranial nerve infarction
  - **Chocking**—Due to infarction of respiratory center.
  - **Dysarthria**—Due to IXth, Xth, XIth and XIIth cranial nerve infarction.
  - **Ataxia**—Due to infarction of cerebellum and its connection.
  - **Syncope**—Due to pons and ascending reticular system infarction.
  - **Hemisensory loss**—Due to spinothalamic tract infarction.
  - **Hemianopic visual loss**—Due to visual path or occipital cortex infarction.
  - **Transient global amnesia**—Due to parieto-temporal cortex infarction.
  - **Tetraparesis**—Due to infarction of great decussation of pyramid.

CLINICAL FEATURES DUE TO RISK FACTOR

- Hypertension.
- Difference of BP in two hands (subclavian stenosis) → Coarction of aorta/Takayasu's disease.
- Carotid bruit.
- Atrial fibrillation/other arrhythmia.
- Valvular heart disease/endocarditis.
- Recent MI.
- Features of diabetes mellitus.
- Rarely features of arteritis, polycythemia, APLA syndrome, SLE and PAN.

CLINICAL FEATURES ACCORDING TO VASCULAR TERRITORY

Stroke syndrome can be subdivided into following three entities:

1. Large vessel stroke in anterior circulation
2. Large vessel stroke in posterior circulation
3. Small vessel stroke.

Large vessel disease can be predominantly due to following three causes:

1. Embolism of artery
2. Atherothrombotic occlusion
3. Dissection of artery.

STROKE IN ANTERIOR CIRCULATION

Clinical features according to arterial distribution:

Middle Cerebral Artery (MCA) Occlusion

- **Proximal MCA (M_1 segment—extend from origin to bifurcation in Sylvian fissure)**—Gives rise to penetrating branches (lenticulostriate arteries) supply—outer globus pallidus, putamen, posterior limb of internal capsule, corona radiata, and most of the caudate nucleus. Occlusion of lenticulostriate branches produce lacunar stroke in the internal capsule which results in—
  - **Pure motor stroke.**
  - **Sensorimotor stroke** contralateral to the side of lesion, alternatively.
  - **Contralateral hand may be ataxic**.
  - **Dysarthria** will be prominent.
  - **Lacunar stroke in globus pallidus and putamen** may be asymptomatic but sometime **Parkinsonism** and **hemiballismus** may be seen.
- **Distal MCA (M_2 segment)**—MCA in Sylvian fissure is divided into superior and inferior divisions.
  - **Branches of superior division of M_2** supply frontal and superior parietal cortex—occlusion of which results in—
    - **Arm and hand weakness** (brachial syndrome).
    - **Facial weakness with nonfluent aphasia (Broca)** with or without arm weakness (**frontal opercular syndrome**). A combination of **sensory disturbance, motor weakness and nonfluent aphasia suggest occlusion of proximal part of superior division of M_2.**
  - **Branches of inferior division of M_2** supply the inferior parietal and temporal cortex—occlusion of which in the dominant hemisphere results in—
    - **Flucent aphasia, called Wernicke's aphasia** (jargon speech with inability to comprehend written and spoken language).
    - Without any weakness but with.
    - Contralateral homonymous superior quadrantanopia.

Combination of *acalculia, alexia, finger agnosia, right left confusion* called **Gerstmann syndrome** can develop due to lesion of *central and suprasylvian speech area* as a result of occlusion of inferior division of middle cerebral artery.

If the inferior division of M_2 in the nondominant hemisphere is occluded **hemineglect or spatial agnosia** without weakness results.

Complete MCA syndrome can occur when an embolus occludes the steam of the artery. But cortical collateral flow and differing arterial configurations are responsible for development of many partial syndromes which are described above.

Anterior Cerebral Artery Occlusion

It has following two divisions :

A_1 segment—Extends from its origin from internal carotid to anterior intercommunicating artery.

A_2 segment—Extends distal to anterior communicating artery.

A_1 segment gives rise to several deep penetrating branch which supply anterior limb of internal capsule anterior perforate substance, amygdala, anterior hypothalamus and inferior part of the head of the caudate nucleus.

Occlusion of proximal ACA is compensated by collateral flow through MCA and PCA and anterior communicating artery.

If A_2 segment of both sides arise from single anterior cerebral artery (contralateral A_1 segment atresia) occlusion of the patent A_2 segment results in—

a. Paraparesis with bilateral pyramidal sign
b. Profound abulia (a delay in verbal and motor response).

Occlusion of A_2 segment results in contralateral symptoms like—

- **Paralysis of opposite foot and leg** due to motor leg area and corona radiata involvement.
- **Cortical sensory loss over toes, foot and leg** due to lesion of sensory area for foot and leg.
- **Urinary incontinence due to involvement** of sensory and motor area in paracentral lobule.
- **Contralateral grasp reflex, sucking reflex, gegenhalten (paratonic rigidity)** due to medial surface of posterior frontal lobe involvement.

- **Abulia (akinetic mutism) slowness, delay, intermittent interruption lack of spontaneity, whispering speech, reflex distraction to sound and sight** due to cingulate gyrus and inferior portion of medial frontal, temporal and parietal lobe involvement.
- **Impairment of gait and stance (gait apraxia)** due to frontal cortex adjacent to motor leg area involvement.
- **Dyspraxia and *tactila* aphasia of left limb** due to corpus callosum lesion.

Anterior Choroidal Artery Occlusion

The artery arises from internal carotid artery and supplies posterior limb of internal capsule and some geniculocalcarine fibers (visual path).

Anterior choroidal stroke occurs due to thrombosis of the vessel or during surgical clipping of aneurysm arising from internal carotid artery.

Complete occlusion results in

- Hemiplegia
- Hemianesthesia (hypesthesia)
- Homonymous hemianopia.

Because this area is also supplied by M_1 segment, posterior communicating and posterior choroidal artery—minimal neuro deficit develop due to occlusion of anterior choroidal artery and the patient recovers substantially.

Internal Carotid Artery Occlusion

It may be occluded by in situ thrombosis, embolism or low-flow state.

Occlusion of internal carotid may be asymptomatic if circle of Willis is competent but usually it produces features of proximal MCA occlusion.

Sometime there is **massive infarction of entire deep white matter** and **cortical surface**. When origin of both MCA and ACA are occluded:

- Abulia
- Stupor
- Hemiplegia
- Hemianesthesia
- Aphasia
- Anosognosia may occurs.

In about 25% of patients of internal carotid occlusion transient recurrent monoocular blindness (amaurosis fugax) may be seen due to propagation of thrombus through ophthalmic artery which is a branch of internal carotid. Patient complains of horizontal shades that sweeps down or up across the visual field or transient blurring of lower or upper half of the field

STROKE IN POSTERIOR CIRCULATION

Posterior circulation consist of—(a) two vertebral artery, (b) one basilar artery and (c) a pair of posterior cerebral artery.

This arteries gives rise to—(a) deep penetrating branches and (b) small or long circumferential branches which supply cerebellum, medulla, pons, midbrain, hypothalamus, thalamus, hippocampus, medial temporal and occipital lobes.

Posterior Cerebral Artery Occlusion

In 75% patients both posterior cerebral artery arises from basilar artery.

In 20% patients one arise from internal carotid.

In 5% patients both posterior cerebral arteries arise from internal carotid (fetal posterior cerebral artery).

P_1 segment of posterior cerebral artery extends from bifurcation of basilar artery to the union with posterior communicating artery. It supplies midbrain, thalamus, hypothalamus from its trunk or penetrating branches like thalamogeniculate, Percheron branch and posterior choroidal artery.

Two clinical syndromes are observed with occlusion of PCA, P_1 and P_2 segments.

1. **P_1 syndrome**—It is due to infarction of medial thalamus, subthalamus, midbrain and cerebral peduncle.
   Clinical features are the following:
   - **Weber's syndrome**—IIIrd nerve palsy with contralateral hemiplegia.
   - **Claude syndrome**—IIIrd nerve palsy with contralateral ataxia (due to involvement of red nucleus or dentatorubrothalamic tract), contraindicated hemiplegia is due to involvement of cerebral peduncle.
   - **Hemiballismus**—It is due to involvement of subthalamic nucleus.
   - **Paresis of upward gaze with drowsiness and abulia**—It is due to occlusion of artery of Percheron.
   - **Coma with unreactive pupil, bilateral pyramidal sign and decerebrate rigidity**—It is due to bilateral proximal PCA occlusion causing extensive damage to midbrain and subthalamus.

   Occlusion of penetrating branches to thalamic and thalamogeniculate region causes less extensive thalamic and thalamocapsular lacunar syndrome.
   - **Thalamic Dejerine—Roussy syndrome**—consist of contralateral hemisensory loss followed by agonizing burning pain (treatment by carbamazepine, gabapentin or TCAD).
2. **P_2 segment of posterior cerebral artery**—extends distal to union with posterior communicating artery and supply medial, temporal and occipital lobes.
   Occlusion of P_2 segment produces the followings:
   - Contralateral homonymous hemianopia with macular sparing.
   - Sometimes homonymous quadrantanopia can occur, or
   - Visual hallucination of brightly colored scenes and object (peduncular hallucination).
   - If the dominant hemisphere is affected and the infarct extends to involve the splenium of corpus callosum, the patient complains of

  - Ataxia without agraphia.
  - Visual agnosia for faces, objects, mathematical symbol and colors.
  - Anemia with paraphasic error (amnestic aphasia).
- Medial temporal and hippocampal involvement may cause temporary acute disturbances of memory but it passes away as memory has bilateral representation.
- Bilateral distal PCA occlusion produces cortical blindness (blindness with preserved pupillary light reaction), patient may not aware of it or even deny it (**Auton's syndrome**) or only peripheral vision is lost and sparing central vision (**gun barrel vision**).
- **Balint's syndrome**—A disorder of orderly visual scanning of surrounding due to low flow in the watershed area between PCA and MCA territories. Persistence of visual image for minutes despite shifting to another object (**palinopia**).
- **Asimultanagnosia**—Inability to synthesize whole image.
- **Embolic** occlusion on the top of basilar artery produces bilateral pupillary asymmetry with loss of light reflex and somnolence.

Vertebral and Posterior Inferior Cerebellar Artery Occlusion

Vertebral artery has the following four segments—

- V_1—Extends from origin to the entrance to C_6 transverse vertebral foramen.
- V_2—Extends from C_6-C_2 vertebra.
- V_3—Extends from C_2 to the point where the artery pierces the dura at formen magnum.
- V_4—Extends from entry into the dura to join with other vertebral artery.

V_1 occlusion at origin is usually asymptomatic due to collateral from other vertebral, thyrocervical trunk, ascending cervical or occipital artery.

When one V_1 is atretic and the other V_1 segment is occluded, a low-flow TIA can occur like vertigo, alternating hemiplegia and syncope.

If subclavian artery is occluded proximal to origin of vertebral artery, there is reversal in the direction of blood flow. At that time exercise of ipsilateral arm can produce **subclavian steal syndrome**.

V_4 or PICA (posterior inferior cerebellar artery) occlusion causes ischemia of **lateral medulla produce lateral medullary syndrome (Wallenburg syndrome)** which consist of vertigo, numbness of ipsilateral face and contralateral limb, diplopia, hoarseness, dysarthria, dysphagia and ipsilateral Horner's syndrome.

Occlusion of medullary penetrating branch of V_4 or PICA results in partial syndrome.

Quadriparesis may results from occlusion of the anterior spinal artery but hemiparesis is not a feature of vertebral artery occlusion.

Medial medullary syndrome results from infarction of pyramid of medulla causes contralateral hemiparesis of arm and leg sparing face with loss of joint and position sense (medial lemniscus) and ipsilateral LMN tongue palsy due to involvement of XIIth nerve.

Cerebellar infarction initially leads to gait, unsteadiness, headache, dizziness, nausea, vomiting, drowsiness, dysarthria, positive Babinski with bifacial weakness but may suddenly develop respiratory arrest.

Initial symptom mimic viral labrynthitis but the main differentiating points are headache, neck stiffness and unilateral dysmetria which favors stroke.

Basilar Artery Occlusion

It has the following three groups of branches—

1. **Paramedian**—7–10 in number supply anterior one-third of pons on each side of midline. **Short paramedian branch of basilar artery** occlusion causes infarction of a wedge-shaped area on one side of midline of pons called **medial pontine syndrome**.
2. **Short circumferential**—5–7 in number supply lateral two-third of pons with middle and superior cerebellar peduncle.
3. **Long circumferential**—Anterior inferior cerebellar artery (AICA) and superior cerebellar artery (SCA) which encircle pons and supply cerebellar hemisphere.

In general basilar artery occlusion causes bilateral sign and carries high mortality whereas occlusion of branch of basilar artery causes unilateral sign.

Complete basilar occlusion causes pontine and lower midbrain infarction produces '*Locked in state' characterized by preserved consciousness with quadriplegia and cranial nerve sign and cerebellar dysfunction sparing IIIrd and sometime IVth cranial nerve* (internuclear ophthalmoplegia).

Proximal basilar TIA produces vertigo or **sensation of swimming, swaying, moving, unsteadiness** and **lightheadedness**. Other symptoms that herald basilar occlusion include **diplopia**, **dysarthria, facial or circumoral numbness** and **hemisensory loss**. TIA involving basilar artery or its branches are short-lived (5–30 min) and repetitive and are treated by intravenous heparin.

Superior cerebellar artery occlusion causes severe ipsilateral cerebellar ataxia, nausea, vomiting, dysarthria, contralateral loss of pain and temperature sensation over body and face (spinothalamic and trigeminothalamic tract), **partial deafness, ataxic tremor of ipsilateral upper extremity. Horner's syndrome and palatal myoclonus** may occur.

Anterior inferior cerebellar artery occlusion usually causes—

- *Ipsilateral deafness, facial weakness, vertigo, nausea, vomiting, nystagmus, tinnitus, cerebellar ataxia, Horner's syndrome, paresis of conjugate lateral gaze.*

- *Contralateral loss of pain and temperature sensation (due to spinothalamic tract).*

Short circumferential branch of basilar artery occlusion causes infarction of lateral two-third of pons and middle and superior cerebellar peduncle called lateral pontine syndrome.

INVESTIGATION OF CVA

Routine Examination

- Routine blood count—for polycythemia and thrombophilia.
- Lipid profile.
- Sugar, urea, creatinine or diabetes and uremia.
- Na^{+}, K^{+}, Ca^{+2} and Mg^{+2}—Serum level estimation.
- Serologic test for syphilis.
- Noncontrast CT—Diagnostic of intracerebral hemorrhage.

- CT is important in excluding cerebral hemorrhage. But may not allow detection of small cerebral infarct in the early hours and also cerebral tumor. After completed ischemic stroke it may take at least 12 hours or so before an area of low density appears (if at all) and by the end of 2 weeks an unenhanced CT may appear normal even with substantial infarction due to invasion by macrophage and blood vessel which renders it isodense. But contrast enhanced CT (CECT) reveals at least a thin rim of lesion. → CT is preferable to MRI in acute stage because intracranial hemorrhage may not be detected by MRI in first 48 hours.

  MR angio is necessary for detection of vascular abnormality and perfusion diffusion weighted. MRI have to be done for detection of cerebral ischemia.

- Lumbar puncture (LP) mainly indicated for subarachnoid hemorrhage.
- Chest X-ray may reveal cardiomegaly, valvular calcification and bronchogenic carcinoma.
- ECG—Myocardial infarction and cardiac arrhythmias.

SPECIAL EXAMINATIONS/INVESTIGATIONS IN CVA

Investigations for identification of risk factors are as follows:

- **Cerebral embolism**—Echocardiography (transesophageal) and carotid-Doppler for identification of source of emboli.
- **Arterial dissection**—MR angiography.
- **Premature atherosclerosis**—Serum lipid profile and measurement of carotid intimal thickening.
- **Thrombophilia**—Protein C, S and antithrombin III estimation.
- **Homocystinuria**—Urinary amino acid estimation and methionine loading test.
- **Anticardiolipin syndrome**—APLA antibody.
- **SLE**—ANA and anti-ds-DNA detection.
- **Vasculitis**—ESR, C-reactive protein and ANCA estimation.
- **Mitochondrial cytopathy**—Serum lactate estima- tion and muscle biopsy.
- **Primary intracranial hemorrhage**—Arteriovenous malformation—MR angiography/CT angio.
- **Drug misuse**—Drug screening for amphetamine and cocaine.
- **Coagulopathy**—PT, APTT and platelet count.
- **Subarachnoid hemorrhage**:
  - Berry aneurysm
  - Arteriovenous malformation
  - Carotid-dissection/vertebral artery dissection.

  } MR angio and LP

DIFFERENTIAL DIAGNOSIS OF CVA

- Primary cerebral tumor.
- Metastatic cerebral tumor.
- Cerebral abscess.
- Postepileptic Todd's paralysis.
- Multiple sclerosis.
- Metabolic encephalopathy, e.g. hepatic encephalopathy, hyperglycemic encephalopathy hypercal- cemic encephalopathy.
- Hemiplegic migraine.

TREATMENT

Immediate General Management

- **Hospital admission.**
- **General medical measures**
  - **Care of unconscious patient**.
  - **Prevention of infection** (pneumonia, UTI and skin infection).
  - **Prevention of deep vein thrombosis** and pulmonary embolism by pneumatic compression stocking and subcutaneous low molecular weight heparin.
  - **BP check-up**—Blood pressure should be lowered if there is
    - Malignant hypertension.
    - Concomitant myocardial ischemia.
    - If BP>185/110 and thrombolytic therapy is anticipated. Lowering of BP and heart rate is done by β-adrenergic blocker (esmolol).
  - **Fever** is detrimental and should be lower by paracetamol or surface cooling.
  - **Anticonvulsive measures**—Valproate/phenytoin (if convulsion present).
  - **Blood glucose** to be monitored and to be kept < 110 mg/dL by insulin infusion.
  - **Brain edema**—Approximately 10% of the patients develop enough brain edema to cause brain herniation that peaks on 2–10 days for which following measures are taken—
    - *Water restriction*—Also reduces the chance of SIADH.
    - *IV Mannitol*—20% Mannitol 300–400 mL IV. 4–6 hourly.
    - *Temporary craniotomy*.

Table 15.1: Eligibility/exclusion criteria for thrombolysis

Eligibility criteria	Exclusion criteria
1. Clinical diagnosis of ischemic stroke	1. BP >185/100 despite proper treatment
2. Age >18 years	2. Platelet count <1 lakh
3. Onset of symptom <3 hours	3. Hematocrit <25%
4. Noncontrast CT excludes cerebral hemorrhage	4. Glucose → <50 mg/dL >400 mg/dL
	5. Use of heparin within last 48 hours
	6. Increased APTT/ INR
	7. Rapidly improving symptoms
	8. Major surgery/trauma in last 14 days
	9. Myocardial infarction or pericarditis in the recent past
	10. Neurosurgery/head trauma in last 3 months, coma and stupor
	11. GI bleeding in last 3 weeks

- **Emergency plain CT**—To differentiate between ischemic stroke/hemorrhagic stroke/other causes.

Special Measure

- **Treatment for Cerebral Infarction (ischemic stroke)**
  - If CT shows infarction—aspirin (300 mg/day) initially.
  - **Thrombolysis (Table 15.1)**—In ischemic stroke or thromboembolic stroke consider r-TPA thrombolysis. [Dose → 0.9 mg/kg (max—90 mg) 10% of total dose by IV bolus over 1 minute, remainder by slow IV infusion in 60 minutes] within 3 hours of onset of symptom.
  - **Endovascular mechanical thrombectomy**—It is the recent alternative method of treatment of acute stroke patient who are ineligible or have contraindications to thrombolytic therapy or have failed to vascular recanalization with IV thrombolytics.
- **Treatment of cerebral hemorrhage (hemorrhagic stroke)**
  - If CT shows intracranial hemorrhage—Do not give any therapy that interferes with clotting. Neurosurgery is preferred for cerebellar hemorrhage >3 cm size.
  - For cerebral hemorrhage—Surgical decompression can be done when a superficial hematoma in the putamen or cerebral white matter exerting mass effect.
- **Treatment for subarachnoid hemorrhage (SAH)—Immediate treatment**
  - Bed rest
  - Supportive measure
  - Control of BP
  - Nimodipine—60 mg 4 times daily
  - Paracetamol—for headache.

All SAH patients should be urgently investigated by MR angio for taking decision about surgery or other measures like

- *Microembolization.*
- *Focal radiotherapy by γ-knife.*
- *Insertion of stent at the site of aneurysm or arteriovenous malformation.*

- **Treatment of subdural hematoma and epidural or extradural hemorrhage**—Surgical evacuation.
- **Long-term management**—All risk factors should be identified and if possible treated—
  - *Antihypertensive therapy*—DBP should be kept >100 mmHg at the onset. Later pressure should be lowered slowly to avoid sudden fall of cerebral perfusion pressure.
  - *Antiplatelet agents*—Long-term aspirin—150 mg/day, reduces infarction and thromboembolic stroke tendency. Combination of aspirin 75 mg and clopidogrel 75 mg is probably the best.
  - *Anticoagulant agents*—Heparin and warfarin to be given with the background of atrial fibrillation/paroxysmal dysrrhythmia or vegetation in cardiac valve or cardiomyopathy and APLA syndrome. (but intracranial hemorrhage, must be excluded before starting anticoagulant therapy).
  - HMG-CoA reductase inhibitor for dyslipidemia.
- **Other Measures**
  - Hyperhomocysteinemia → treated by folic acid.
  - SLE, APLA syndrome → treated by prednisolone, mycophenolate motifil and cyclophosphonide and LMWH.
  - Internal carotid endarteriotomy to be considered in TIA/ischemic stroke, who have narrowing of lumen of internal carotid artery by 70% or more.
  - Rehabilitation, physiotherapy and speech therapy.
  - Cessation of smoking.
  - Moderation of alcohol consumption.
  - Reduction of body weight.
  - Adoption of active lifestyle.

TRANSIENT ISCHEMIC ATTACK

DEFINITION OF TIA

It is a condition where transient focal neurological signs and symptoms persist (typically for 5–15 min) but must be <24 hours due to embolic stroke.

CAUSES OF TIA

1. Artery to brain embolism.
2. Heart to brain embolism.
3. Rarely sickle-cell anemia, polycythemia, SLE, APLA, myeloma and PAN.

CLINICAL FEATURES OF TIA

It can affect both anterior or posterior circulation. Clinical feature depends on which artery has been involved.

FEATURES OF INVOLVEMENT OF ANTERIOR CIRCULATION (CAROTID SYSTEM)

Symptoms

- **Weakness of contralateral lower half of face, arm and leg** due to involvement of precentral gyrus or posterior limb of internal capsule on the opposite side.
- **Paresthesia or impaired sensation** of the opposite half of body due to involvement of postcentral gyrus or posterior limb of internal capsule on the opposite side.
- **Transient homonymous hemianopic loss of vision** due to involvement of optic tract and radiation on the opposite side.
- **Dysphasia or aphasia** due to involvement of Broca's area or its connection (arcuate fasciculus).

Signs

- **UMN type of weakness** on opposite half of body.
- **Plantar** extensor.
- **Deep tendon reflex (DTR)**—depressed in acute stage but brisk in the stage of recovery.
- **Ophthalmoscopy**—Retinal artery occlusion or embolism (confirmatory diagnosis) may be present.
- **Amaurosis fugax**—Sudden transient loss of vision in one eye due to passage of emboli through retinal artery which is sometime visible by ophthalmoscope.

FEATURES DUE TO POSTERIOR TERRITORY (VERTEBROBASILAR SYSTEM) INVOLVEMENT

- **Vertigo**—Due to vestibular nucleus involvement.
- **Chocking**—Due to respiratory center involvement.
- **Difficulty in speech**—Due to central speech area (parietotemporal gyrus) or its connection involvement.
- **Weakness of all 4 limbs**—Due to involvement of pyramidal tract of both sides.
- **Transient loss of consciousness**—Due to involvement of pons or asending reticular system involvement.
- **Transient loss of memory**—Parietotemporal gyrus involvement.
- **Double vision**—Due to IIIrd, IVth, VIth cranial nerve involvement.

Signs

- **Quadriparesis**—Due to involvement of pyramidal tract of both side at the lower end of medulla (great decussation of pyramid).
- **Syncope**—Due to involvement of pons or ascending reticular formation.
- **Ataxia**—Due to cerebellar involvement.
- **Dysarthria**—Due to IXth, Xth, XIth and XIIth cranial nerve involvement.
- **Hemisensory loss**—Due to spinal lemniscus involvement.
- **Hemianopic visual loss**—Due to optic tract and lateral geniculate body involvement.
- **Transient global amnesia** (loss of memory lasting for several hours occurring commonly in aged person >65 years followed by complete recovery presumed to be due to vertebrobasilar insufficiency).

CLINICAL FEATURES IN OTHER SYSTEM

- Clinical evidence of source of embolism
  - Carotid artery bruit
  - Atrial fibrillation or other arrhythmia
  - Valvular heart disease
  - Endocarditis
  - Recent AMI
  - Difference in pressure in between right and left brachial artery.
- Underlying condition that may be evident
  - Atheroma
  - Hypertension
  - Postural hypotension
  - Bradycardia or low cardiac output state
  - Diabetes mellitus
  - Rarely arteritis, polycythemia and APLA syndrome.

DIAGNOSIS

Investigation is done to establish the followings:

- Clinical diagnosis.
- Differentiate between hemorrhage or thromboembolic infarct from TIA.
- Look for the underlying cause of TIA and to direct therapy either medical and surgical accordingly.
  - Blood—CBC to exclude polycythemia, thrombophilic disorder, syphilitic serology, clotting study, autoantibodies (ANA, ds-DNA, APLA) and lipid profile.
  - Chest X-ray.
  - ECG.
  - Echo with Doppler and transesophageal echo for presence of thrombus or SABE in the left side of heart.
  - Carotid Doppler—For carotid atheroma.
  - CT/MRI—To exclude hemorrhage or thromboembolic infarct.
  - MR angio of cerebral vessel.

MANAGEMENT

- Admit in multidisciplinary hospital.
- General medical measure.
- Care of unconscious patient
  - Airway and breathing support.

  - If bradycardia, decrease COP and absent pulse—cardiopulmonary resuscitation.
- O_2 by mask
- BP—Check-up.
- Thorough clinical examination to find any source of emboli.
- Aspirin (300 mg/day—initially by chewing) should be given as antiplatelet treatment, provided no other contraindication present.
- Appropriate drug for HTN, DM, heart disease or other medical conditions like dyslipidemia.
- Carotid end arteriotomy if the condition requires.
- Indication for anticoagulation therapy—
  - Valvular heart disease (especially MS)—Initially LMWH and followed by warfarin.
  - Recent AMI (with intracardiac thrombus or atrial fibrillation)—LMWH followed by warfarin sodium.
  - Acute thrombosis of internal carotid or basilar artery.
  - Acute internal carotid/basilar artery dissection—heparin followed by warfarin.
  - Prothrombotic state—Thrombophilia and APLA syndrome—Anticoagulation.
  - Recurrent TIA on full antiplatelet therapy (Aspirin + clopidogrel)—Anticoagulant is justified.

Chapter 16

Spinal Cord Disease (Paraparesis and Quadriparesis)

UMN—Upper moter neuron, LMN— Lower motor neuron, ALS—Amyotrophic latral sclerosis, MND—Motor neuron disease.

Paraparesis—Weakness of both the lower limbs with or without sensory loss and sphincteric disturbances is called paraparesis.

Quadriparesis (tetraparesis)—Weakness of all four limbs is called quadriparesis.

TYPES OF PARAPLEGIA OR PARAPARESIS

- **Spastic paraplegia**—It is due to involvement of upper motor neuron, or pyramidal tract which arises from large pyramidal cell of layer five of Brodmann's area four in the precentral gyrus and extend up to motor cranial nerve nucleus in brainstem or anterior horn cell in spinal cord (from cervical to coccygeal segment).
- **Flaccid paraplegia**—It is due to involvement of lower motor neuron which consists of—
  - Motor cranial nerve nucleus in brainstem and anterior horn cell in spinal cord.
  - Motor cranial nerve or motor fiber of mixed spinal nerve.
  - Myoneural junction.
  - Muscle.

  All are included in lower motor neuron.
- **Mixed paraplegia**—It is due to involvement of both upper and lower motor neuron (e.g. ALS) (amyotrophic lateral sclerosis).

CAUSES OF PARAPLEGIA OR PARAPARESIS

Causes of paraplegia: It lies in the spinal cord below T_1 spinal segment and is due to involvement of—

- **Upper motor neuron (UMN)** (i.e. lateral corticospinal tract lesion) causes spastic paraplegia.
- **Lower motor neuron (LMN)** lesion cause flaccid paraplegia. The following structure of LMN are involved.
  - **Anterior horn cell** below L_1 spinal segment supplying lower limb muscle.
  - **Ventral nerve root** arising from those anterior horn cell of (L_1 to coccygeal) segment.
  - **Nerve plexus** (lumbar and sacral plexus).
  - **Mixed peripheral nerve**, e.g. femoral or sciatic nerve or its branches.
  - **Myoneural junction and muscle** are also included in LMN and lesion of which may cause paraplegia.

CRANIAL CAUSES OF PARAPLEGIA

Rarely some expanding mass in the interhemispheric fissure causes compression of the paracentral lobule of motor cortex of the frontal lobe on both the sides (which control the lower limb muscle) causing paraplegia. These are—

- *Parasagittal meningioma*
- *Superior sagittal sinus thrombosis*
- *Thrombosis of the unpaired anterior cerebral artery*
- *Hydrocephalus*.

Spastic paraplegia in extension—In the initial stage of spinal cord compression (compressive myelopathy) causing spastic paraparesis, the compression cause impairment of *pyramidal tract* function only which leads to extension of hip, knee and plantar flexion of ankle—called *spastic paraplegia in extension*. In pure spastic paraplegia the lesion involve pyramidal tract between D_1–D_9 vertebra containing T_2– T_{12} spinal segment.

Spastic paraplegia in flexion—In the late stage of compressive myelopathy, there is compression of *both pyramidal and extrapyramidal tract* which leads to unmasking of local spinal flexion reflexes from the higher control and result in flexion attitude of lower limb (flexion of hip, flexion of knee and dorsiflexion of ankle) called **paraplegia in flexion**.

Flaccid paraplegia—In flaccid paraplegia, the lesion is usually from D_{10} vertebral body downward involved structurs may be any one of the following—

- **Anterior horn cell** from L_1 spinal segment downward tocoxygealsegment.
- **Ventral nerve root** arising from those anterior horn cell including cauda equina.
- **Nerve plexus** of both sides (lumbar and sacral plexus)
- **Mixed peripheral nerve**
- **Myoneural junction**
- **Muscle of lower limb**.

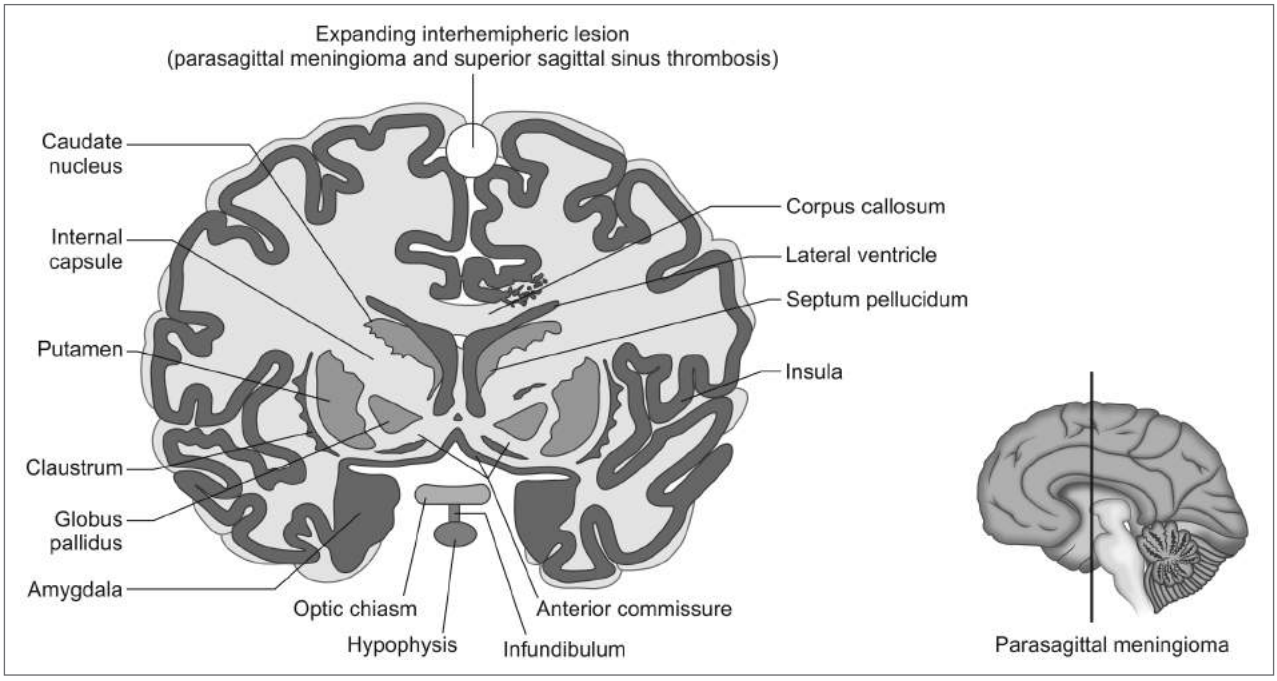


Fig. 16.1: Location of lesion in cranial causes of paraplegia

Mixed paraplegia—The muscles of the lower limb are supplied by lumbar and sacral spinal segment and these spinal segments are situated within D_{10}–L_1 vertebra, when a lesion involve the spinal cord in between D_{10}–L_1 vertebral bodies a mixed picture of UMN and LMN involvement is seen.

Table 16.1: In adults relationship of vertebral bodies with spinal segment

Vertebral body		Spinal segment
Upper cervical vertebra	contain	Same spinal segment
Lower cervical vertebra	contain	One spinal segment below
D_1 to D_5 vertebra	contain	Two spinal segment below
D_6 to D_9 vertebra	contain	Three spinal segment below
D_6 vertebra	contain	T_9 spinal segment
D_7 vertebra	contain	T_{10} spinal segment
D_8 vertebra	contain	T_{11} spinal segment
D_9 vertebra	contain	T_{12} spinal segment
D_{10} vertebra	contain	L_1 + L_2 spinal segment
D_{11} vertebra	contain	L_3 and L_4 spinal segment
D_{12} vertebra	contain	L_5 + few upper sacral segments (S_1 + S_2)
L_1 vertebra	contain	Rest of the lower sacral and coccygeal segments (S_3 + S_4 + S_5 + C) (known as conus medullaris)

Table 16.2: Clinical differences between LMN and UMN palsy

Features of UMN palsy	Features of LMN palsy
a. Nutrition: Wasting is minimal called disuse atrophy	a. Nutrition: Wasting and atropy is profound called LMN atrophy
b. Tone: Hypertonia— Clasp knife spasticity seen in antigravity group of muscle, i.e. flexor plus adductor of upper limb and extensor plus abductor in lower limb	b. Tone: Gross hypotonia— flaccidity

Contd...

Contd...

Features of UMN palsy	Features of LMN palsy
c. Power: Diminished (grade 1/5–4/5)	c. Power: Absent (grade– 0/5)
d. Involuntary movement: Absent	d. Involuntary movement: Fasiculation may be present [In slow degeneration of anterior horn cell, e.g. MND]
e. Reflex → Superficial reflex—lost deep tendon reflex → Hyperreflexia in recovery stage.	e. Both superficial and deep tendon reflex are lost
f. Plantar → Extensor	f. Plantar: No response

CAUSES OF ACUTE ONSET SPASTIC PARAPARESIS

Lesion located in between T_1–T_{10} vertebra.

- **Spinal cord compression**
  - Intervertebral disk prolapse.
  - Subdural/epidural hematoma and abscess.
  - Vertebral fracture with dislocation due to trauma, TB and tumor.
- **Inflammatory and demyelinating lesion**
  - Multiple sclerosis
  - Devic's neuromyelitis optica
  - Acute transverse myelitis (ATM)
  - Acute necrotic myelopathy.
- **Ischemic causes**
  - Anterior spinal artery thrombosis
  - Disecting aneurysm.
- **Infective**
  - Viral myelitis (acute transverse myelitis).

CAUSES OF ACUTE ONSET FLACCID PARAPARESIS

- **Lesion involving anterior horn cell**—Poliomyelitis and traumatic injury to vertebral column below T_{10} vertebra.
- **Lesion involving the anterior root of the spinal nerve or peripheral nerves**—
  - Lumbar disk prolapse
  - Lumbar plexus injury (psoas abscess or hematoma)
  - Guillain-Barré syndrome
  - Traumatic injury of peripheral nerve.

CAUSES OF CHRONIC ONSET SPASTIC PARAPLEGIA

Compressive

- Metastatic deposit.
- Cervical spondylosis.
- Disk protrusion (chronic).
- Primary vertebral benign neoplasm—Sarcoma, myeloma, osteoma, chordoma and hemangioma.
- Vertebral infection—TB
- Craniovertebral anomalies
- Atlantoaxial subluxation
- Thalassemia (by extramedullary erythropoiesis).

Other causes

- Epidural abscess
- Chronic arachnoiditis—TB, syphilis and sarcoidosis
- Meningeal infiltration—Lymphoma and leukemia
- Extramedullary tumor
- Intramedullary tumor.

Noncompressive

- Inflammatory
  - Multiple sclerosis
  - Devic's disease.
- Vascular
  - AV malformation
  - APLA syndrome.
- Infective
  - HTLV–1, HIV–1
  - Progressive encephalomyelitis with rigidity.
- Developmental
  - Syringomyelia
  - Meningomyelocele.
- Others
  - MND (motor neuron diseases)
  - Lathyrism
  - Paraneoplastic myelitis.
- Metabolic
  - Subacute combine degeneration of spinal cord
  - Adrenomyeloneuropathy.

CAUSES OF CHRONIC FLACCID PARAPLEGIA

- Chronic disk prolapse of lower lumbar region.
- Cauda equina syndrome and spinal canal stenosis.
- Myasthenia gravis and Lambert-Ealon syndrome.
- Peripheral neuropathy including CMT (Charcot-Marie-Tooth disease).
- Myopathies.

CAUSES OF CAUDA EQUINA SYNDROME

- Compressive—Ependymoma, neurofibroma, chordoma, lipoma, meningioma and spinal canal stenosis.
- Noncompressive—Arachnoiditis involving lumbosacral region.
- Degenerative—Intervertebral disk protrusion.

CLINICAL FEATURES OF SPINAL CORD INJURY (AT A PARTICULAR LEVEL)

When a lesion involves a segment of spinal cord, it destroys both—

- **Peripheral white matter contain**
  - Descending motor tract (both pyramidal and extrapyramidal).
  - Ascending sensory tract.
- **Central gray matter** contains motor and sensory neuron.

Outlines of clinical features of cord compression (Paraplegia)

- **Features at the level of lesion**
  - Motor function—LMN type of motor weakness (wasting, hypotonia, loss of muscle power grade (0/5).
  - Sensory function—All modalities of sensation are lost. But sometimes a girdle constricting pain due to nerve root irritation in extradural lesion or a burning pain in intramedullary lesion may be present at the level of lesion.
  - Reflexes
    - DTR is lost at the level of lesion.
    - Superficial reflex is also lost at the level of lesion.
    - Plantar—Not elicitable if the lesion involve S_1 segment but extensor when the lesion in above SI dermatome.
- **Features below the level of lesion**
  - Motor function—UMN type of motor weakness (disuse atrophy, spasticity, loss of muscle power grade 1/5–4/5).
  - Sensory function—Loss of all modalities of sensation (both large fiber and small fiber).
  - Reflexes
    - DTR—Brisk below the level of lesion.
    - Superficial reflexes—Lost below the level of lesion.
    - Plantar—Extensor.
- **Features above the level of lesion**
  - Motor function—Normal.
  - Sensory function—A zone of hyperasthesia at the junction of normal with the diseased segments due to loss of inhibitory impulse from the injured segment below.
  - Reflexes—Both superficial and deep sensation are normal.

BLADDER AND BOWEL CONTROL IN PARAPLEGIA

Bladder and bowel is controlled by sympathetic and parasympathetic nurve which is coming from lumbar (L_2- L_4) segment and sacral S_3-S_4 segment respectively. Sympathetic supply internal urethral sphincter and function as a nerve of retention. Parasympathetic supply detrusor muscle and act as nerve of evacuation. There is also a higher control which is coming from cerebral cortex.

In Higher Cord Lesion

In case of paraplegia due to lesion of cervical or thoracic cord there is loss of higher control over lower spinal center. In that condition sympathetic fiber takes the upper hand, internal urethral sphincter remain contracted and there is retention of urine. But when the intravasical pressure rises above the physiological limit of urethral sphincter, the sphincter partially open and there is dribbling of urine but bladder remain full. This condition is called *Retention overflow* or *overflow incontinence*.

In Lumbar Cord Lesion

When lumbar sympathetic nerve (L_2–L_4) is damaged in lumbar cord lesion and there will be loss of both cortical (or higher) and sympathetic control on bladder. In this condition parasympathetic nerve takes the upper hand. As a result detrusor muscle remain contracted and the urethral sphincter remain open so there will be constant dribbling of urine but the bladder remain empty. This is called *true incontinence*.

In Sacral Cord Lesion

When sacral parasympathetic nerve in damaged in sacral cord lesion, sympathetic will take the upper hand and there will retention of urine with loss of voluntary contraction of detrusor but the detrusor muscle can be reflexly contracted by stimulation of perinium which results in *partial evacuation of bladder*.

CLINICAL FEATURES OF MYELOPATHIES

Upper Cervical Cord (C_1–C_4)

- Sensory involvement of all four limbs and trunk.
- Features of UMN lesion in all four limbs and trunk (quadriparesis).
- Compromised diaphragmatic function.
- Lesion in the region of foramen magnum (Arnold-Chiari malformation) produces up beating nystagmus with cerebellar ataxia.

Lesion at the Level of C_5–C_6 Spinal Segment

- LMN atrophy and weakness of deltoid, biceps, brachioradialis, supra-and infraspinatus and rhomboids.
- UMN paralysis of remaining muscle of upper limb, trunk and lower limbs.
- Biceps and triceps jerks are lost with inversion of supinator jerk.
- Sensory loss of almost whole of the upper limb excluding some area over deltoid with loss of sensation over trunk and leg.

Lesion at the Level of C_8–T_1 Spinal Segments

- LMN atropy with weakness of flexors of wrist, fingers and small muscles of hands.
- Horner's syndrome.

- UMN paralysis of trunk muscle and lower limb muscle.
- Sensory involvement of medial part of arm, forearm and little finger with loss of sensation over trunk and legs.

Lesion at the Midthoracic Level

- LMN type paralysis with atrophy of the muscle confined to that intercostal space.
- Diaphragmatic movement normal (root value—C_3, C_4 and C_5).
- UMN type palsy of muscles of abdomen and lower limb below the level of lesion.
- Loss of sensory function found at the corresponding segment of lesion but some time.
  - *Root pain may be present*—If the lesion compresses the posterior root (extramedullary lesion).
  - *Dull aching pain may be present*—Over the segment in case of intramedullary lesions.
  - A zone of hyperesthesia with sense of girdle constricting pain just above the level of lesion.
  - Loss of all modalities of sensation below the level lesion.

Lesions of the Level of T_9, T_{10} and T_{11} Neural Segments

- UMN palsy of lower limb and lower abdominal muscle.
- Sensory loss below the umbilicus.
- Beevor's sign—Upward pulling of umbilicus when the patient raises his head against resistance due to contraction of unaffected upper abdominal muscles.
- Upper abdominal reflexes are preserved while those of lower abdomen is lost.

Special feature of T_{11} segment involvment. There will be inguinal hernia due to involvment of lower oblique muscle of abdomen.

Lesion at the level of T_{12}–L_1 Spinal Segments

- Rectus abdominis are normal.
- LMN lesion of lower fibers of internal oblique and transverse abdominis causes—increased tendency of herniation due to weakness of posterior wall of inguinal canal.
- UMN palsy of lower limb.
- Loss of all modalities of sensation over lower limb.
- Abdominal reflex is preserved while cremasteric reflexes are lost.
- Lesion at any level above L_1 segment will cause retention overflow or overflow incontinence.

Lesion at the Level of L_3–L_4 Spinal Segments

- Mixed LMN, UMN lesion found in lower limb.
- Flexion of hip is preserved through psoas and iliacus (L_1 and L_2).
- LMN wasting and weakness of lower part of quadriceps and hip adductors.
- UMN palsy of calf muscles and hamstrings.
- Sensory loss starting from just above the knee whole of the leg back of thigh and perineum.
- Knee jerk depressed with exaggerated ankle jerk and extensor plantar response.
- True incontinence of bladder.

Lesion at the Level of S_1–S_2 Spinal Segments

- LMN palsy of small muscle of the foot, calf, hamstring and gluteus.
- Sensory impairment over buttock, perineum, posterior aspect of lower limb including sole.
- Knee jerk—preserved but ankle and plantar is lost.
- Flexion of the hip, adduction of thigh, extension of knee and dorsiflexion of foot are preserved.

Lesion Involving S_3–S_4 Spinal Segments

- Large bowel, bladder is paralyzed with retension of urine and feces due to uninhibited action of sympathetic supply.
- External sphincter are paralyzed.
- Anal and bulbocavernosus reflexes are lost.
- Sensory loss over perineum and buttock over a saddleback distribution.
- Lower limb is normal.

SOME SPECIAL PATTERNS OF SPINAL CORD DISEASE

Brown-Séquard Hemicord Syndrome (Fig. 16.2)

- Classic forms of Brown-Séquard syndrome is rare—partial forms commonly encountered.

Hemisection of the spinal cord produce Brown- Séquard syndrome with absent pain and temperature Sénsation contralaterally and loss of proprioception with motor power ipsilaterally below the level of lesion. In simplified form we can say.

- Maximum motor loss on same side.
- Maximum sensory loss on the opposite side.
  - **Ipsilateral**—UMN weakness (pyramidal sign) with loss of joint, position and vibration sense (posterior column).
  - **Contralateral** loss of pain and temperature (lateral spinothalamic tract)—below the level of lesion.

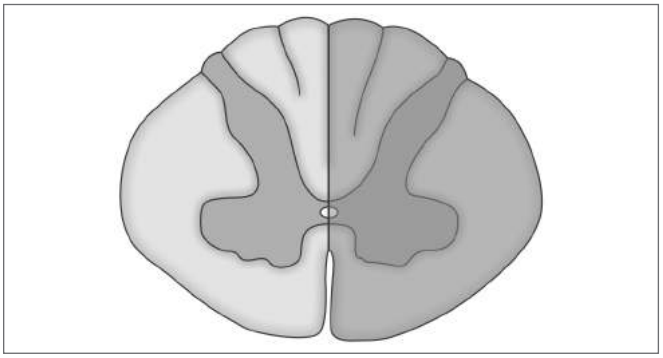


Fig. 16.2: Brown-Séquard hemicord syndrome

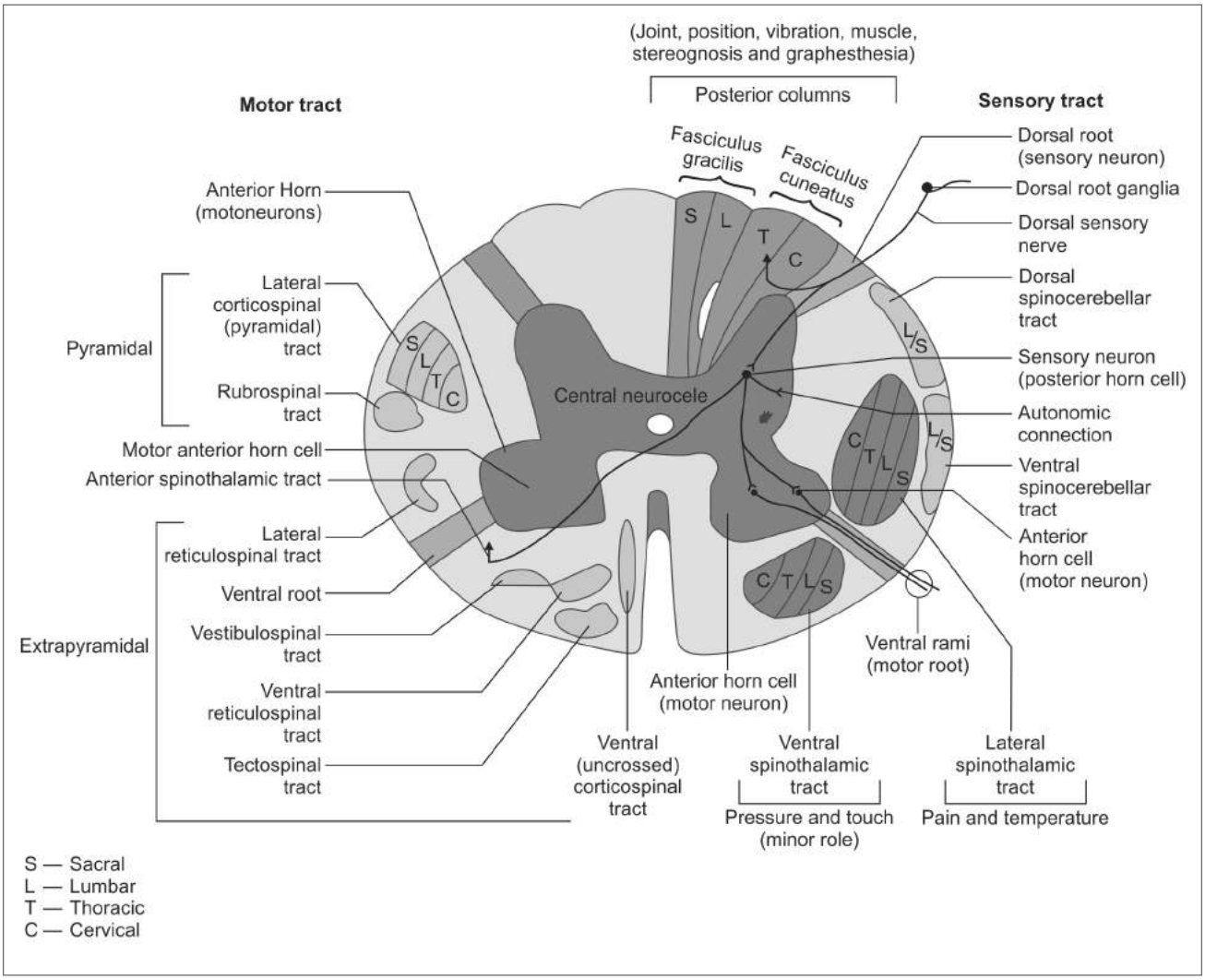


Fig. 16.3: Schemic diagram of cross section of spinal cord at upper cervical level

– Segmental signs, such as radicular pain, muscle atropy, areflexia are unilateral at the level of lesion.

Difference between Intramedullary and Extrame- dullary Lesions

- **Extramedullary lesion**—
  1. There is radicular pain at the level of lesion.
  2. Saddle back anesthesia with early sacral sensory loss due to involvement of lateral spinothalamic tract.
  3. Spastic weakness of leg due to involvement of corticospinal tract with early involvement of hamstring due to superficial location of sacral fiber in (hamstring) corticospinal tract (Fig. 16.3).
- **Intramedullary lesion**—Poorly localizing. Burning pain rather than radicular pain with sparing of sensation over perineal and sacral area (sacral sparing) reflecting the laminated configuration of spinothalamic tract. Corticospinal tract sign appear later (Fig. 16.3).

Differentiation between Intradural and Extradural Lesion

- Extradural lesions due to malignant condition— gives a comparatively short history.
- Intradural lesion due to benign tumor (neurofibroma)—have a long duration of symptom.

Tetraparesis or Quadriparesis

- In case of compressive neuropathy involving upper cervical cord (C_1–C_5). The march of neuro deficit starts in the ipsilateral lower limb and then subsequently ipsilateral upper limb, contralateral upper limb and contralateral lower limb are involved sequentially. So the march of neuro deficit runs in an inverted U-shaped manner due to the laminated disposition of the pyramidal and spinothalamic tract in the lateral column of the cervical spinal cord (Fig. 16.3).

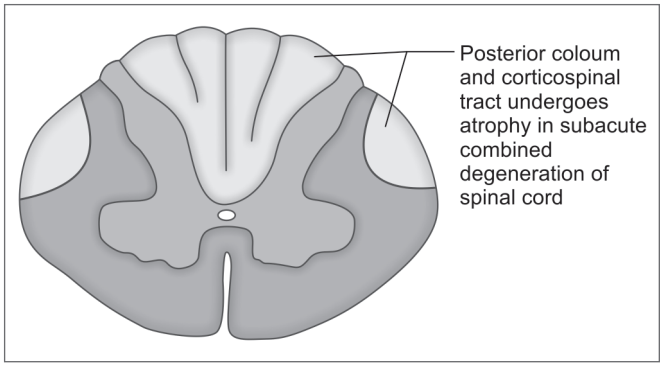


Fig. 16.4: Subacute combined degeneration of spinal cord (B_{12} neuropathy)

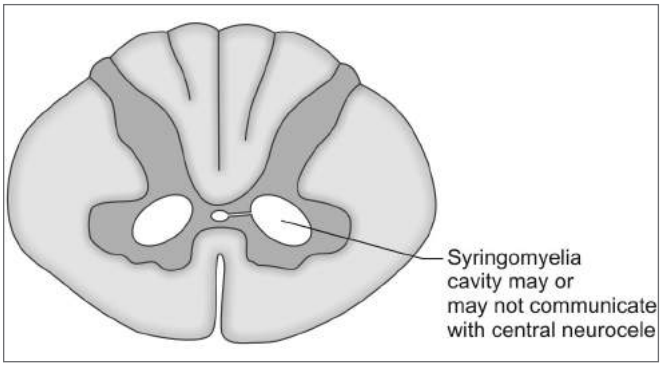


Fig. 16.5: Syringomyelia

Subacute Combined Degeneration of Spinal Cord (B_{12} neuropathy) (Fig. 16.4)

- Associated with pernicious anemia.
- Dorsal column is involved—bilateral loss of tactile discrimination position sense, muscle sense and vibration sense.
- Lateral corticospinal tract is involved—causing bilateral spastic paraparesis with positive Babinski's sign.
- Spinocerebellar tract involvement—bilateral arm and leg dystaxia.

Friedreich's Ataxia

- Spinal cord pathology is same as subacute combined degeneration (due to B_{12} deficiency).

Syringomyelia (Usually Involve Cervical Cord) (Fig. 16.5)

Formation of central cavitation or extension of the neurocele of the cervical cord of unknown pathology? It is a degenerative disorder.

- Ventral white commissural fiber destruction causes bilateral loss of pain and temperature sense. Dissociated sensory loss with impairment of pinprick and temperature sensation but relative preservation of light touch, position sense and vibration sense.
- Ventral horn involvement causes flaccid paralysis—Specially of the intrinsic muscle of hand.

DIFFERENCE BETWEEN CAUDA EQUINA SYNDROME AND CONUS MEDULLARIS SYNDROME (TABLE 16.3)

Cauda Equina (Horsetail)

- Bunch of 40 nerve fiber (20 nerve on each side) with a dural process (phyllum terminale) is called cauda equina which emerge from the terminal end of spinal cord below L_1 vertebrae. It contains segmental nerve from L_2 to coccygeal segment. Four nerve for lumbar segment five nerve for sacral segment and one nerve for coccygeal segment. Total ten segmental nerve on each side so altogether 20 nerve. As the ventral and dorsal root arises from the spinal cord separately so there will 40 nerve fiber.

Conus Medullaris

- Triangular cone-shaped lower end of spinal cord is called conus medullaris located within L_1 vertebrae.

Table 16.3: Comparison between cauda equina and conus medullaris lesion

Points	Cauda equina syndrome	Conus medullaris syndrome
1. Involvement	Spinal root from L_2 to coccygeal spinal nerve	Spinal cord segment (S_3+ S_4 + S_5 coccygeal segment)
2. Onset	Gradual and unilateral	Sudden and bilateral.
3. Cause	PID and nerve root tumor	Intramedullary tumor
4. Pain	Severe, unilateral and radicular pain	Bilateral burning pain but not severe and spontaneous sweating over sacral segment
5. Sensory loss	Unilateral area around anus on the side of lesion	Bilateral dissociated sensory loss (symmetrical and saddle-shaped area around anus)
6. Muscle involvement	Unilateral muscle atrophy	Muscle changes are not marked
7. Reflexes	Knee and ankle jerk are lost	Ankle jerk is absent and usually knee jerk is also lost
8. Plantar response	Lost	Extensor plantar response
9. Bladder control and sexual function	Involvement not marked	Loss of bladder bowel control

Chapter 17

Guillain-Barré Syndrome

IMMUNE-MEDIATED NEUROPATHY

DEFINITION

It is an acute fulminant polyradiculoneuropathy of autoimmune nature associated with the clinical picture of rapidly developing ascending areflexic motor paralysis with/without sensory loss and sphincteric disturbances.

INCIDENCE

Male and female are equally involved.
Adult >child.

SUBTYPES

- **Acute inflammatory demyelinating polyneuropathy** (AIDP)—90%.
- **Acute motor axonal neuropathy** (AMAN).
- **Acute motor sensory axonal neuropathy** (AMSAN).
- **Regional Gullain-Barré (GB) syndromes**
  - Miller-Fisher syndrome.
  - Pure sensory form.
  - Ophthalmoplegia with anti-GQ–1b antibody.
  - GBS with severe bulbar or facial paralysis (antecedent CMV infection and anti-GM–2 antibody).
  - Acute pandysautonomia (disordered autonomic nervous system).

ETIOLOGY

Immune responses to nonself antigen (infectious agent and vaccines) *misdirected to host nerve tissue* due to molecular mimicry.

75% cases of GB is preceded by an antecedent infec- tion 1–3 weeks.

- Respiratory infection by EBV, mycoplasma and CMV.
- GI infection by *Campylobacter jejuni* (most common).
- Apart from infection—
  - Nerve tissue derived vaccine (NDV) in rabies.
  - Swine-influenza vaccine.
  - HIV seropositivity.
  - Lymphoma—Both Hodgkin and non-Hodgkin lymphoma.
  - SLE.

All are increminated in the development of AIDP.

IMMUNE PATHOGENESIS

1. Misdirected antibody targeted against nonself antigen (vaccines and infectious agents) cross react with glycoconjugates (specially gangliosides of the myelin sheath) due to molecular mimicry which plays the central key pathogenic role in the development of GBS.
2. Both humeral and cellular immune mechanism contribute to tissue damage.

   T-cell activation is suggested by the presence of IL-2, IL-2R, INF-γ, TNF-α, IL-6 (Table 17.1).

Table 17.1: Antibody in different, subtype of GB syndrome

Clinical presentation	Target antibody	Antibody type
AIDP	GM_1	IgG
AMAN	GM_{1b}, GM_1, GD_{1a}	IgG
Miller-Fisher	GQ_{1b}	IgG

CLINICAL FEATURES

- Usual clinical pattern is an ascending paralysis accompanied by tingling disasthesia evolved over hours to days.
- Legs are more frequently affected than arms.
- Facial diaparesis occurs in 50% cases.
- Lower cranial nerves are frequently involved resulting in weakness of bulbar muscle, dysphagia, difficulty in handling saliva and palatine palsy.
- 30% requires ventilatory support due to respiratoy muscle involvement.
- Muscle bulk is not grossly diminished.
- Gross hypotonia of the muscle—present.
- Power may be grossly diminished (grade—0–II).
- Deep tendon reflex are absent.

- Loss of pain and temperature are relatively insignificant.
- Posterior column senses (proprioceptions, vibration sense, position, fine touch and other cortical senses) are severely affected.
- Patient may complain of—
  - Dull aching pain from weakened muscle
  - Low back pain from spinal cord and vertebral body
  - Dysesthetic pain due to posterior column involvement.
- Bladder dysfunction may be present but transient. Early bladder dysfunction raises the question about diagnosis and is possibly due to spinal cord disease.
- Autonomic involvement in the form of cardiac arrythmia and postural hypotension may be found in severe cases.

Once the clinical worsening stops and the patient reaches a **plateau within 4 weeks** of onset, further progression is unlikely.

DIAGNOSIS

- *Diagnosis is mostly clinical—Rapidly developing ascending, areflexic motor weakness usually starting from lower limb with minimal sphincteric disturbances and some amount of dysesthesia with/ without involvement of bulbar muscle is the hallmark of clinical diagnosis of GBS.*
- **CSF study**—Changes are evident at the end of 1st week.
  - Classical picture—**Cytoalbuminic dissociation**.
  - Protein—100–1000 mg/dL
  - Cell count—10–100/mL.

  Pleocytosis suggests CSF, Viral/HIV myelitis.
- **Electrodiagnostic study (EDX)**—Electrodiagnostic features are mild or absent in early case of GBS and lags behind clinical evolution.

EDX features of AIDP (demyelinating neuropathy)

- Slowing of conduction velocity.
- Evidence of conduction block.
- Prolonged distal latency.
- Temporal or lateral dispersion of compound action potential.

EDX features of axonal neuropathy (AMAN and AMSAN)

- Reduced amplitude of compound action potential without conduction slowing or prolongation of distal latencies.

PROGNOSIS

- About 80–85% patient shows spontaneous usually complete recovery both in AIDP and axonal neuropathy group.
- About 5% patient die of respiratory involvement and lung infection.
- About 15% patient recover partially and survive with residual neurodeficit.
- Patient with axonal neuropathy have a very good and rapid recovery as the lesion is thought to be localized in the preterminal neuron.

DIFFERENTIAL DIAGNOSIS

- Acute transeverse myelitis (ATM) with prolong back pain and sphincter disturbances.
- Botulinism (pupillary reaction lost early).
- Diphtheria (Oropharyngeal paralysis).
- Porphyria (abdominal pain, seizure and psychosis).
- Vascular neuropathy (raised ESR).
- Polio (child with fever and diarrhea) asymmetrical, involvement of legs are more frequent.
- CMV polyradiculitis in immune-compromised patient.
- Myasthenia gravis (cranial nerve and shoulder girdle and respiratory muscle are predominently involved).
- Toxic peripheral neuropathy (thallium, arsenic and organophosphorus).
- Lyme polyradiculitis.
- Tick-borne polyradiculopathy.
- Critical illness neuropathy.

TREATMENT

Treatment should be initiated as soon as the clinical diagnosis is made and the motor symptoms respond maximally if treatment started within 2 weeks of onset of symptoms.

- **High dose intravenous immunoglobulin** (IV Ig) → 0.4 g/kg/day for 5 days (total dose 2 g/kg) or 1 g IV on D_1 and D_3.
- **Plasmapheresis** of 40–50 mL plasma/kg. 4 times a week is equally effective as IV Ig therapy. But combination therapy has no additional benefit.
- **Ventilatory support** required in 30% patient → If respiration is compromised.
- General care of paralyzed patient.
  - IV methylprednisolone has no role.

Chapter 18

Peripheral Neuropathy

- **DM**— Diabetes mellitus
- **TOCP**—Triorthocresyl phosphate
- **CIDP**—Chronic inflammatory demyelinating polyneuropathy
- **AIDP**—Acute inflammatory demeylinating polyneuropathy
- **GBS**—Guillain Barré syndrome
- **CMT**—Charcot marie tooth disease
- **HMSN**—Hereditary motor sensory neuropathy
- MMN—Multifocal motor neuropathy with conduction block.

- *Peripheral neuropathy is a general term indicating disorder of peripheral nerve.*
- The disorder may be due to affection of the anterior root (radicle), nerve plexus, peripheral nerves, posterior root ganglia and trigeminal ganglion.

  Involvement of anterior horn cell gives the picture similar to peripheral neuropathy but should be ideally termed as *neuronopathy*.

Peripheral neuropathy can be classified in various ways:

- *According to number of nerve involved*
  - Mononeuropathy
  - Mononeuropathy multiplex
  - Polyneuropathy
  - Plexopathy.
- *According to the type of nerve involved*
  - Pure motor neuropathy
  - Pure sensory neuropathy
  - Autonomic neuropathy
  - Mixed neuropathy.
- *According to clinical profile*
  - Acute onset neuropathy
  - Subacute onset neuropathy
  - Chronic onset neuropathy.
- *According to pathological type of involvement*
  - Axonopathy
  - Demyelinating polyneuropathy.
- *According to region involvement*
  - Proximal neuropathy
  - Distal neuropathy.

ETIOLOGY OF NEUROPATHY

- **Metabolic**—Diabetes mellitus, renal failure, porphyria and amyloidosis.
- **Infectious**—Leprosy, diphtheria, HIV, cytomega-lovirus and lyme disease.
- **Immune-mediated**—GBS, CIDP, MMCB and antibody to myelin-associated glycoprotein.
- **Hereditary**—CMT.
- **Drug**—Anticancer drug, anti-HIV drug, metronidazole, ethambutol, dapsone, thalidomide and isoniazid.
- **Toxic**—Alcohol and heavy metal, tick bite.
- **Vasculitis**—PAN, Churg-Strauss syndrome and Cryoglobulinemia.
- **Paraneoplastic**—Bronchogenic carcinoma.
- **Nutritional**—Vitamin B_1, B_6 and B_{12} deficiency.
- **Miscellaneous cause**—Celiac disease and hypothyroid Fabry disease.

MODE OF ONSET OF MAJOR TYPES OF POLYNEUROPATHY

Axonal

- Acute (days to week)
  - Porphyria
  - Massive intoxication with arsenics
  - Guillain-Barré syndrome.
- Subacute (weeks to months)
  - Mostly toxic and metabolic.
- Chronic (months to years)
  - <5 years—Toxic and metabolic
  - >5 years—Hereditary, diabetes and dysproteinemias.

Demyelinating

- Acute (days to week)
  - Guillain-Barré all forms
  - Diphtheria.

- Subacute (weeks to months)
  - Relapsing form of CIDP.
- Chronic (months to years)
  - Hereditary and inflammation
  - Autoimmune
  - Dysproteinemia
  - Metabolic and toxic.

ETIOLOGY ACCORDING TO MODE OF ONSET OF NEUROPATHY

- **Acute**—GBS, porphyria, diphtheria, toxin like— TOCP, thallium and brachial neuritis.
- **Subacute**—Alcoholic, nutritional, angiopathic and toxichexacarbon acrylamide.
- **Chronic**—Diabetic, CIDP, paraneoplastic and paraprotein.
- **Hereditary**—CMT and Friedreich's ataxia.
- **Recurrent**—CIDP, porphyria, refsum disease and HNPP.

FEATURES OF DEMYELINATING NEUROPATHY

- **Etiology**—GBS, CIDP, diphtheria, MMN (multifocal motor neuropathy) with conduction block).
- **Onset**—Acute or subacute.
- **Symptom**—Paresthesia and weakness.
- **Sensory sign**—Loss of posterior column sensation (loss of vibration and proprioception is greater that loss of pain and temperature).
- **Motor loss**—Weakness is equal on proximal and distal group of muscle.
- **Reflex**—Areflexia in both proximal and distal group of muscle.
- **Nerve conduction study**—Nerve conduction velocity is affected more than amplitude of motor unit action potential.
- **Nerve biopsy**—Both demyelination and remyelina- tion is seen in HP examination.
- **Prognosis**—Rapid recovery.

FEATURES OF AXONAL NEUROPATHY

- **Etiology**—Toxic, metabolic (DM), HIV and CMT-2.
- **Onset**—Slow evolution.
- **Pattern**—Distal involvement more than proximal involvement and length-dependent.
- **Symptoms**—Dysesthesia and distal weakness.
- **Signs**—
  - *Sensory*—Pain and temperature sensation affected more that vibration and proprioception. Anterior column or small fiber are affected more than posterior column or large fiber.
  - *Motor*—Weakness of distal group of muscle is more than proximal group.
- **Reflexes**—Areflexia of the distal group. Loss of ankle and supinator jerk more than knee, biceps and triceps jerk.
- **Nerve conduction study**—Amplitude of motor unit potential is more affected than nerve conduction velocity.
- **Histopathology**—Axonal degeneration and regeneration can be demonstrated.
- **Prognosis**—Very slow recovery.

FEATURES OF NEURONAL DISEASE

- **Etiology**—Pyridoxin defficiency, cisplatin toxicity and Sjögren's syndrome.
- **Onset**—Rapid onset.
- **Pattern of involvement**—Nonlength-dependent, upper limb, lower limb and face.
- **Symptoms**—Gait ataxia and paresthesia.
- **Signs**—
  - *Sensory*—Loss of vibration and proprioception greater than pain and temperature, large fiber (postcolumn) involvement > small fiber (anterior column).
  - *Motor*—Proprioceptive weakness.
- **Reflexes**—Areflexia.
- **Nerve conduction study**—Sensory amplitude affected. Affection of radial nerve greater than sural nerve. Axonal degeneration but no regeneration.
- **Prognosis**—Poor recovery.

CLINICAL FEATURES OF PERIPHERAL NEUROPATHY

Demyelination affects motor and sensory fiber equally, whereas axonal process involves sensory fiber > motor fiber.

Large Fiber (Postcolumn) Neuropathy (Ataxic Neuropathy)

Large fiber polyneuropathy is characterized by loss of vibration and position sense with absent tendon reflex, variable motor deficit and ataxia but preservation of most cutaneous sensation. Band-like sensation with tingling dyserthesia may be present.

- **Etiology**—Sjögren's, cisplatin, pyridoxin deficiency and Friedreich's ataxia.
- **Symptoms**—Numbness, pins and needle sensation.
- **Signs**—Decreased vibration sense, poor balancing, decrease muscle, ligament and joint sense.
- **Investigations**—
  - Nerve conduction study
  - Nerve biopsy and electromyography (EMG)
  - Lumbar puncture.

Small Fiber (Anterior Column) Neuropathy (Painful Neuropathy with Dissociated Sensory Loss)

Small fiber neuropathy are characterized by burning, painful dysesthesia, reduced pinprick and thermal sensation but

sparing proprioception, motor function and deep tendon reflexes. Touch sensation is variably involved when spared called dissociated sensory loss which can also occur in spinal cord lesion.

- **Etiology**—
  - Hereditary sensory neuropathy
  - Leprosy
  - Diabetes
  - Amyloidosis
  - HIV and antiretroviral therapy
  - Dysautonomia
  - Fabry's disease.
- **Symptoms**—Pain-like-burning, shock-like shooting, lancinating, stabbing and prickling.
- **Sign**—Decreased pinprick and temperature sensation.
- **Investigations**—Skin biopsy, nerve biopsy and quantitative sensory testing.

Motor Neuropathy

- **Etiology**—Guillain–Barré syndrome, HMSN, diphtheria, diabetes, lead and acute intermittent porphyria.
- **Symptoms**—Wrist drop, foot drop, weak grip, muscle cramp and twitching of muscle.
- **Sign**—Diminution of muscle power grade 1/5–4/5 with decreased DTR.
- **Investigations**—Nerve conduction study and electromyography.

Autonomic Neuropathy

- **Etiology**—
  - *Acute*—Pandysautonomia, botulism, porphyria, GBS, amiodarone and vincristine.
  - *Chronic*—Amyloid, diabetes, Sjögren, HSAN-I and III and paraneoplastic disorder.
- **Symptoms**—
  - Disturbances in sweating (decreased or increased).
  - Dryness of eye and mouth and erectile dysfunction.
  - Gastroparesis and diarrhea.
  - Faintness and lightheadedness.
- **Sign**—Orthostatic hypotension, unequal pupil size.
- **Investigations**—Valsalva, tilt table, R-R interval, quantitative sudomotor axon reflex testing.

MONONEUROPATHY

- Focal involvement of a single nerve trunk.
- Ulnar neuropathy and carpal tunnel syndrome are the two most common varieties of mononeuropathy.
- Other mononeuropathies are—tarsal tunnel syndrome and cranial mononeuropathy.

ULNAR NEUROPATHY

Causes

- At the elbow—by pressure palsy.
- Entrapment distal to elbow in cubital tunnel.
- Prolonged pressure over base of palm at wrist due to the use of hand tools and bicycling.

Clinical Features

- Clawhand deformity owing to waisting and weakness of small muscle of hand which results in hyperextension of finger at MP joint and flexion at IP joint.
- Flexion deformity is most pronounced in 4th and 5th finger.
- Sensory loss occur over 5th and half of the 4th finger with ulnar border of the plam.
- Tinel's sign at elbow.
- Forment sign.

Management

Surgical release, at cubital tunnel or anterior trans- position of the nerve at the elbow.

CARPAL TUNNEL SYNDROME

Causes

Median nerve at the carpal tunnel lies in a close space with nine tendons. So it can easily be compressed at that site.

- Inflammatory—Osteoarthritis, rheumatoid arthritis and tenosynovitis.
- Post-traumatic—Colles' fracture.
- Endocrine—Myxedema, diabetes and acromegaly.
- Metabolic—Amyloid and mucopolysaccharidosis.
- Idiopathic (most common).

Clinical Features

- Nocturnal paresthesia of thumb, index and middle finger.
- Weakness and atrophy of abductor policis brevis (thenar eminence).

Management

Surgical section of carpal ligaments.

MONONEUROPATHY MULTIPLEX

- Simultaneons or sequential involvement of individual noncontiguous nerve trunk, either partially or completely evolving over days to years.
- Since the disease process underlying mononeuritis multiplex affects peripheral nerve in multifocal and random fashion, progression of the disease gives the picture of distal symmetric neuropathy.

- So for diagnosis, attention to be paid on the early symptom and the examination findings at the early stage of the disease.

Cause

- Leprosy
- DM
- Vasculitis—PAN, SLE and Sjögren's
- Sarcoidosis
- HIV
- RA
- Amyloidosis.

POLYNEUROPATHY

The typical picture of polyneuropathy is seen in acquired toxic and metabolic disorders.

In polyneuropathies sensory deficit are generally graded, distal and symmetric in distribution. The process is usually nerve length-dependent and the neuro deficit is often described as glove and stocking type.

CLINICAL FEATURES

- First symptom usually is sensory, consists of tingling, prickling, burning or band-like dysesthesia at the ball of the feet or tips of toes or over the sole. Symptom is usually symmetric, graded distally and preceeds objective sensory and motor sign.
- As the disease progresses sensory loss moves centripetally and when it reaches the upper shin the dysesthesia usually involves the tips of fingers in the hand.
- When the sensory loss reaches elbow and midthigh a tent-shaped area of hypoesthesia can be demonstrated on lower abdomen with its apex directed rostally towards xiphisternum.
- Motor
  - Usually weakness of the dorsiflexor of toe specially great toe.
  - Weakness of dorsiflexors of ankle.

Differential diagnosis of polyneuropathy/ plexopathy/ mononeuropathy multiplex

A. Polyneuropathy—
- Symmetric distribution of symptoms (tingling dysesthesia)
- Initial symptoms over gloves and stocking area
- May or may not be painful
- Symmetric diminution of muscle power over both sides
- Symmetric diminution of DTR over both side

B. Plexopathy—
- Asymmetric distribution of symptoms
- Usually painful onset
- Multiple nerve involvement in a single limb
- Rapid asymmetric onset of muscle weakness and atrophy
- Asymmetric loss of DTR over limb

Contd...

Contd...

C. Mononeuropathy multiplex—
- Initial involvement like mononeuropathy
- Gradual involvement of different nerves of different limb
- In late stage clinical feature stimulate polyneuropathy
- May or may not be painful
- Isolated loss of DTR
- Etiology—Diabetes, vasculitis and pressure palsy

  - Later weakness appears on dorsiflexor of wrist. Extensors are more commonly affected than flexors. There will be associated muscle atrophy and areflexia.
- Overall the nerve fibers are affected according to axon length irrespective of route or nerve trunk distribution, that is why sensory loss appears in stocking and gloves pattern.

PURE MOTOR PERIPHERAL NEUROPATHY

It is due to the disease affecting anterior root and peripheral nerve.

Clinically it is very difficult to distinguish this entity from disorder of anterior horn cell (neuronopathy).

Causes

- Lead poisoning.
- Dapsone.
- Porphyria.
- MMCB (multifocal motor neuropathy with conduc- tion block).
- GBS (Guillain-Barré syndrome).
- CIDP (chronic inflammatory demyelinating polyneuropathy).
- Hereditary motor neruopathy (Charcot-Marie-Tooth disease).

Clinical Features

- Weakness
- LMN atrophy sign
- Fasciculation
- Areflexia.

Electrodiagnostic Study (EMG and NCV)

It also fails to localize the primary site of lesion (neuropathic vs neuronopathic) unless the lesion is of demyelinating pattern.

So the diagnosis is mainly done based on history and clinical examination.

PURE SENSORY NEUROPATHY

- It is the most common form of peripheral neuropathy.

- It may be of three types involving primary sensations only—
  - **Large affarent fiber neuropathy** (postcolumn involvement) with deficit of vibratory and proprioceptive sense (muscle sense and joint sense) with areflexia and sensory ataxia with/ without tingling dysesthesia.
  - **Small fiber neuropathy**—Lateral and anterior spinothalamic tract are involved resulting in numbness and cutaneous hypoesthesia to pin- prick and temperature stimuli often with painful and burning dysesthesia.
  - **Both large and small fiber** (pain sensory) involvement—The pattern of distribution although variable but distal symmetrical involvement is particularly seen for large fiber neuropathy.
- Severe and pure, widespread peripheral sensory neuropathy with poor or no recovery suggest degeneration of dorsal root ganglia or trigeminal ganglia.
- Mild to moderate form of peripheral sensory neuropathy are potentially reversible.

AUTONOMIC NEUROPATHY

It is usually a manifestation of more generalized polyneuropathy.

Causes

- Diabetes mellitus (DM)
- Guillain-Barré syndrome (GBS)
- Alcoholic polyneuropathy.

Symptoms of dysautonomia are mainly of two types—

1. **Negative symptoms (loss of function)**
   - Postural hypotension with faintness or syncope.
   - Anhidrosis.
   - Hypothermia.
   - Bladder atony—Neurogenic bladder.
   - Absolute constipation.
   - Dry mouth and dry eyes—Failure of lacrimal and salivary glands.
   - Blurring of vision (due to pupillary and ciliary regulation loss).
   - Sex impotence in male.
2. **Positive symptoms (hyperfunction)**
   - Episodic hypertension
   - Diarrhea
   - Hyperhidrosis
   - Tachycardia/bradycardia.

Management

It is mostly symptomatic and also directed at underlying cause if it can be identified.

PLEXOPATHY

- The term reffers to either brachial/lumbosacral plexus involvement.
- Brachial plexus involvement is more common—
  - Upward jerk causes lower cord injury
  - Downward jerk causes upper cord injury.

Etiology

- Direct trauma or downward jerk occure during lifting of heavy object—Upper cord injury.
- Idiopathic brachial neuritis (neuralgia amyotrophy).
- Cervical rib or band.
- Infiltration by malignant tumor (Pancoast tumor).
- Radiation therapy >60 Gy.
- Lower cord injury occurs in upward arm jerk during catching running bus or train.

Clinical Features

- Both motor and sensory signs are seen and which are different from mono/polyneuropathies.
- Involvement of upper part of brachial plexus C_5–C_7. Leads to—
  - Weakness and atrophy of shoulder girdle.
  - Weakness and atrophy of upper arm muscle.
  - Focal sensory deficit over shoulder girdle and lateral aspect of arm.
- Involvement of lower part of brachial plexus C_8–T_1. Leads to—
  - Distal arm weakness and atrophy.
  - Focal sensory deficit of forearm and hand—Medial aspect.
- Lumbosacral plexopathy—Less common.

Causes of lumbosacral plexus involvement

- Trauma
- Intraoperative injury
- Retroperitoneal hemorrhage
- Malignant tumor
- Infiltration and TB of lumbar spine
- DM.

DIAGNOSIS OF PERIPHERAL NEUROPATHY

Electrodiagnosis

Electromyography (EMG)

1. Myopathic disorders are marked by small, short duration, polyphasic muscle action potential recruited in excessive number for a given degree of voluntary muscle contraction.
2. Neuropathy shows features of denervation with positive sharp wave and complex repetitive discharges—followed by long duration, enlarged, polyphasic waves

in chronic phase indicating collateral innervation of denervated muscle fiber by axonal sprouts form surviving motor axons.
- When disorder of neuromuscular junction is suspected more specialized technique is used—muscle response to repetitive nerve stimulation (2–3 Hz) and single fiber EMG study shows blocking and Jitter with normal fiber density is confirmatory of MG.

Nerve conduction velocity (NCV)

The axonopathy and demyelinating variety can be distinguished by nerve conduction study.
- **Features of demyelination**—
  - Slowing of nerve conduction velocity.
  - Temporal (lateral) dispersion of evoked action potential.
  - Conduction block of nerve impulse.
  - Marked prolongation of distal latencies.
- **Features of axonal injury**—
  - Reduction of amplitude of evoked compound action potential.
  - Relative preservation of NCV (nerve conduction velocity).

Nerve Biopsy

- **Sural nerve at the ankle**—Preferred site.
- **Indications**—
  - Asymmetrical and multifocal neuropathic disorder.
  - One or more cutaneons nerve is thickened.
  - Determination of genetically determined childhood diseases.
- In distal symmetrical polyneuropathy of acute/subacute variety. Nerve biopsy should not be done as—
  - No additional inference or information can be gathered.
  - Yield is low, not worth of the risk as wound infection, poor healing, persistent pain are the common complication.

TREATMENT OF PERIPHERAL NEUROPATHY

- Pain management.
- Supportive care to protect and rehabilitate damage tissue.
- Treatment of underlying disorder—
  - Diabetic neuropathy—Glycemic control.
  - Vitamin deficiency neuropathy—By vitamin B_1, B_6 and B_{12}.
  - Immune suppression for vasculitis.
  - Surgery for entrapment neuropathy.
  - Liver or bone marrow transplant for amyloid neuropathies.
  - Enzyme replacement for Fabry disease.

  Treatment of immune-mediated neuropathies.

PAIN MANAGEMENT OF PAINFUL SENSORY NEUROPATHY

Burning, aching, sharp, throbbing pain—Managed by TCAD— amitriptyline, imipramine and desiparamine.

Neuropathic pain of diabetes—Managed by duloxetine and tramadol.

Lancinating pain—Managed by anticonvulsant like phenytoin, carbamazepine, clonazepam, gabapentin, topiramate, venlafaxine and pregabalin.

Focal neuropathic pain—Managed by lidocaine, mexiletine and capsaicin isosorbide dinintrate spray.

Severe refractory neuropathic pain—Managed by narcotic analgesic.

HEREDITARY POLYNEUROPATHY (CHARCOT-MARIE-TOOTH DISEASE AND OTHER RELATED DISORDERS) (CMT)

DEFINITION

Charcot-Marie-Tooth (CMT) neuropathy comprises a heterogeneous group of inherited peripheral nerve disease.

CLINICAL FEATURES

- Onset is often during the 1st/2nd decade of life although presentation in mid-adult life is not unusual.
- Clinical presentation is exceptionally wide ranging from minimal or no distal muscle weakness with pes cavus to severe distal atrophy most marked in hand and foot.
- Common signs and symptoms are related to muscle weakness initially involving feet and leg—later progressing to hand and forearm.
- Pes cavas or high arched foot results from atrophy of intrinsic muscle of feet.
- History of abnormal high stepped gait with frequent tripping and falling, due to foot drop.
- Sensory—Subjective symptoms are unusual although few objective signs may be present.
- Deep tendon jerk (DTR)—Depressed or absent.
- Transmission is most frequently autosomal dominant but may be autosomal recessive or X-linked.

TYPES OF HEREDITARY MOTOR SENSORY NEUROPATHY (HMSN)

It can be classified as—

- CMT–1 (demyelinating form) (HMSN–1)
- CMT–2 (axonal degeneration) (HMSN–2)
- CMT–3 (dejerine-Sottas disease) (HMSN–3)
- CMT–4 (autosomal recessive form) (HMSN–4)
- CMT–X (X-linked variety).

[HMSN = Hereditary motorsensory neuropathy].

DEJERINE SOTTAS DISEASE (DSD)

- Patient never ambulate or loose ambulation in early infancy—also known as congenital hypomyelinating neuropathy.
- Clinical feature of DSD and congenital hereditary neuropathy overlap with CMT.
- Laboratory diagnosis—
  - CSF protein is eleveted.
  - NCV—Substantially slow 10 m/sec.

Chapter 19

Myasthenia Gravis

It is a disorder of neuromuscular junction charecterized by progressive inability to repeated conduction of impulse to sustain a maintained or repeated contraction of striated muscle.

ETIOLOGY AND PATHOLOGY (FIG. 19.1)

- The underlying defect is the decrease in the number of acetylcholine (ACh) receptor in the postsynaptic membrane of motor end plate.
- The neuromuscular abnormality in this disease is brought about by a T-cell-dependent autoantibody of IgG class against acetylcholine receptor (AChR).
- Reduction in number of the AChR at the neuromuscular junction is brought about by three distinct mechanism—
  - Accelerated turnover of AChR by a mechanism involving crosslinking and rapid endocytosis of the receptor.
  - Blockade of active site of AChR (acetylcholine receptor), i.e. the normal binding site of acetylcholine.
  - Damage to the postsynaptic muscle membrane by antibody in collaboration with complement.
- Thymus appears to play a major role in this process. Thymus is abnormal in 75% of patient out of which 65% has hyperplastic thymus with the presence of active germinal center detected histologically. 10% of patients

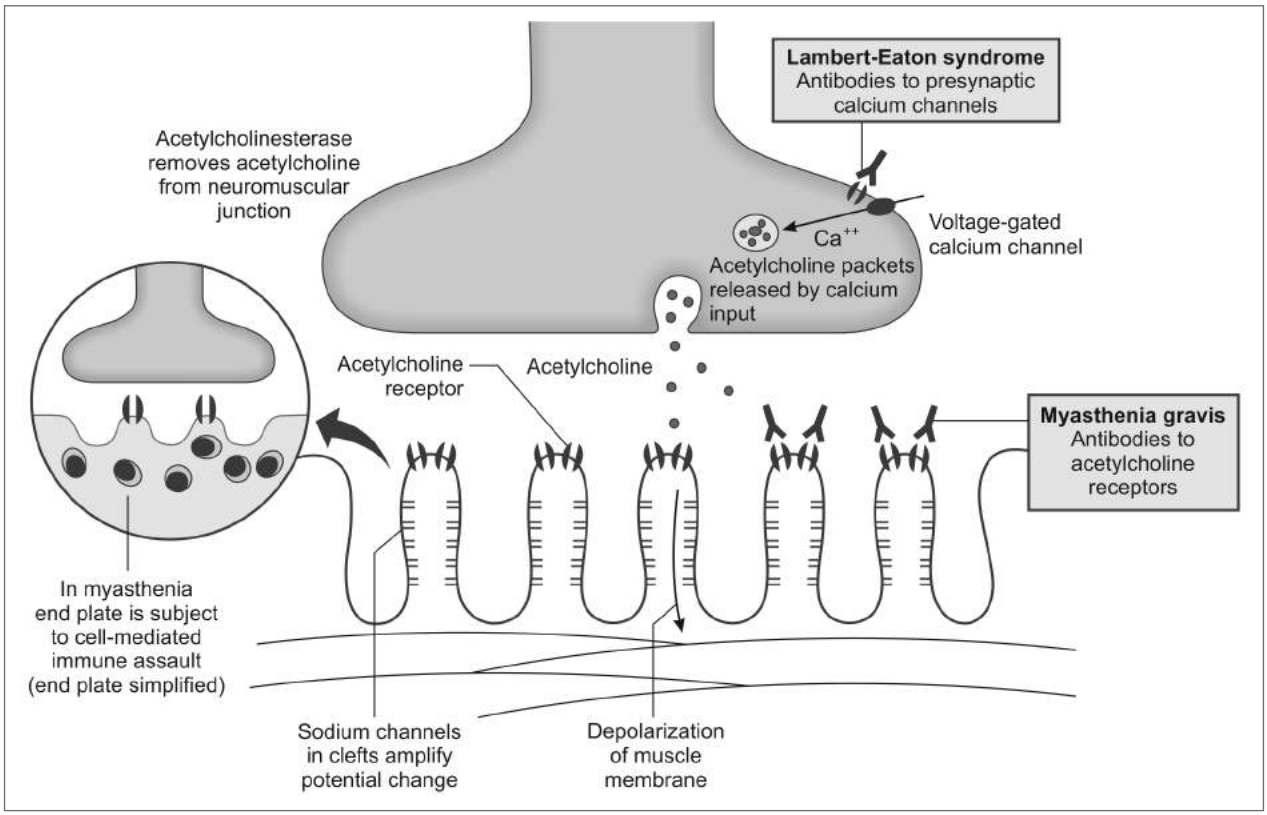


Fig. 19.1: Schematic diagram of motor and plate with the pathophysiology of myasthenia and Lambert-Eaton syndrome

have thymoma composed of muscle-like cell (myoid cell) within the thymus which bears AChR (acetylcholine receptor) on their surface which serve as a source of autoantigen and triger an antoimmune reaction.

CLINICAL FEATURES

- It can affect people of all age group.
- Women are more frequently involved than men (M: F—2 : 3). Women are affected in the 2nd and 3rd decade while man are affected in 5th and 6th decade of their life.
- **Cardinal features** are progressive weakness and easy fatiguability of muscle.
  History—
  - Diplopia, ptosis and weakness.
  - Weakness increases during repetitive use (fatigue) and may improve following rest, sleep or treatment.
  - Weakness may be generalized (85%) but cranial nerve muscle, shoulder girdle and respiratory muscle are specially involved.
- Mode of presentation:
  - **Ocular myasthenia gravis**—Extraocular muscle involvement resulting in intermittent ptosis and diplopia specially in the evening is the most common mode of presentation.
  - Other cranial nerve involvement—
    - **Facial diaparesis** due to bilateral LMN weakness of facial muscle.
    - **Weakness during chewing, swallowing, speaking** *leading to nasal intonation, nasal regurgitation, aspiration and facial snarling due to Vth, IXth, Xth and XIth cranial nerve involvement.*
  - Weakness of limb movement specially those of shoulder girdle as evident by fatigue during repetitive combing of hairs and diminution of forward arm abduction time.
- The course of myasthenia gravis is often variable—exacerbation and remission occur particularly during first few years of the disease. Remission is rarely complete or permanent—*unrelated infection or systemic disorder usually leads to increased myasthenic weakness and may precipitate myasthenic crisis.*
- **The distribution of muscle weakness has a characteristic pattern**
  - The cranial muscle particularly eyelid and extra-ocular muscle (EOM) are involved early in the course, leading to diplopia and ptosis as a common initial symptoms. If the weakness remain restricted to extraocular muscle for 3 year, it is unlikely to become generalized and the patient said to have **ocular myasthenia**.
  - Facial weakness produce a snarling expression with an attempt to smile (due to facial muscle involvement).
  - Patient may complain weakness during prolonged chewing (due to weakness of muscle of mastication).
  - Speech have a nasal intonation due to weakness of muscle of tongue, palate and pharynx with difficulty in swallowing giving rise to nasal regurgitation (due to weakness of muscle supplied by IXth, Xth, XIth and XIIth cranial nerve).
  - Weakness of respiratory muscle may require ventilatory support and then the patient is said to be in **myasthenic crisis**.
  - In 85% patient, the weakness become generalized affecting limb muscle as well. The limb weakness in MG is often proximal and asymmetric in nature. Despite limb weakness the deep tendon reflexes are preserved.

PHYSICAL EXAMINATION

- Presence of ptosis and diplopia.
- Motor power survey—quantitative testing of muscle strength.
- Forward arm abduction time (< 5 min).
- Vital capacity measurement. Respiratory muscle weakness and respiratory failure is not an uncommon cause of death—that should be checked by **single breath count test**.
- Laryngeal and other muscle related to voice production may be examined by continuous counting of number and noting the slurring of speech.
- Absence of other neurological signs.

DIAGNOSIS

- **Clinical**—Diagnosis is made on the basis of weekness and easy fatigability with typical distribution without any loss of DTR and sensory impairment.
- **Laboratory testing**—
  - Anti-AChR antibody assay—
    - *Definitive diagnosis of myasthenia is done by the presence of anti-AChR antibody but absence cannot exclude myasthenia gravis.*
    - Anti-AChR antibody is positive in 85% generalized myasthenia gravis.
    - Anti-AChR antibody is positive in 50% of ocular myasthemia gravis.
    - 40% of anti-AChR negative patient with generalized MG have **anti-MUSK antibody**.
    - Anti-**MUSK antibody** is rarely present in anti-AChR positive patient and myasthenia gravis limited to ocular muscle.
    - There is evidence that myasthenia gravis patient without anti-AChR or MUSK antibody have other unidentified antibody.
  - **Repetitive nerve stimulation**—Anti-AChE medication is stopped 6–24 hours before testing. Test is performed on proximal group of muscle. Muscle is stimulated at 2–3 Hz. Rapid decrement of response >15% is highly probable of myasthenia gravis.

As a further test a single dose of edrophonium may be given to prevent/diminish the decremental response.

- **Edrophonium (tensilon) stimulation test**—Intravenous injection of 2 mg edrophonium initially given if no improvement occur a further 8 mg is given in two divided dose just to reduce the unplasent cholinergic side effects (diarrhea, abdominal pain, excessive salivation, lacrimation, fasciculation, bradycardia and syncope). If there is significant objective improvement in muscle power seen within 30 seconds following IV edrophonium and which last for 3–5 minutes, it is highly probable of myasthenia gravis.
- **Single fiber EMG**—Blocking and Jitter with normal fiber density is confirmatory but not specific of MG.
- For ocular myasthenia gravis/cranial myasthenia gravis—Exclude intracranial lesion by CT/MRI.

DIFFERENTIAL DIAGNOSIS

- Congenital myasthenia syndrome (nonautoimmune).
- Drug-induced myasthenia (aminoglycoside, procainamide, penicillamine).
- Lambart-Eaton myasthenic syndrome (commonly in paraneoplastic disorder usually involve lower limb muscle, muscle power improve with repetitive use.
- Hyperthyroidism.
- Botulism.
- Intracranial mass lesion.
- Progressive external ophthalmoplegia.
- Neurasthenia.

TREATMENT

Principles of treatment are as follows:

- **To maximize the activity of acetylcholine at the remaining receptor of the neuromuscular junction**—Commonly used anticholinesterase drug is *pyridostigmine* (30–120 mg orally divided 6 hourly). Muscarinic side effect include diarrhea, abdominal colic, salivation, sweating and small pupil which can be reversed by propantheline (15 mg).
- **Immunological treatment of myasthenia**
  - *Thymectomy*—It should be done as soon as possible in patient between puberty to 55 years of age and in antibody positive patient with symptoms not confined to extraocular muscle, unless the disease has been established >7 years.

    85% patient experience improvement in symptoms and of those 35% achieve drug-free remission which requires a latent period of 9 months to 1 year. The patient with MUSK antibody positive may not improve from thymectomy.
  - *Plasmapheresis*—For removal of antibody from blood a course of 5 exchange (3–5 L/exchange) is generally administered over a period of 2 weeks. It is useful as a temporary measure in myasthenic crisis condition or in preoperative preparation for thymectomy.
  - *Immunoglobulin (IV–Ig)*—An alternative to plasma exchange in the treatment of myasthenic crisis.

    Dose—400 mg/kg/day for 5 days. Improvement occurs in 70% of patient.

    IV–Ig and plasmapheresis are reserved for immediate relief in myasthenic crisis and bridge up therapy before surgery.
  - *Corticosteroid*—Improvement is commonly preceded by marked exacerbation of myasthenic symptoms—treatment should be initiated in the hospital.
    - Initial dose is 15–25 mg/day and increase stepwise 5 mg/day at 2–3 days interval until there is marked clinical improvement or a dose of 50–60 mg/day is reached.
    - Dose should be given as a single morning dose to reduce the side effects.
    - Dose is maintained for 1–3 months then slowly switch over to alternative day regimen over 1–3 months patient.
    - Patient on long-term glucocorticoid therapy should be followed carefully for early detection of adverse side effects.
    - The most common side effect of glucocorticoid treatment is—
      - » Insufficient persistence—Improvement will be delayed and gradual.
      - » Too early, too rapid and excessive tappering of dose.
      - » Lack of attention to prevent the adverse effect of glucocorticoid.
  - **Immunosuppressive drugs**
    - *Mycophenolate mofetil*
    - *Azathioprine*
    - *Cyclosporine*
    - *Tacrolimus*
    - *Cyclophosphamide*.
- **Mycophenolate mofetil—(Now the most preferred agent)**

  1–1.5 g bid inhibit the proliferation of lymphocyte but not other cells. Therefore clinical improvement may be delayed from months to years. The drug may be used alone or with glucocorticoid.
- **Azathioprine**

  Initially 50 mg/day gradually increased to 2.5 mg/kg/day is of value in reducing the dose of steroid or allow the steroid to be withdrawn.

  Effect of treatment on the clinical course of the disease may be delayed for several months, associated with fewer treatment failure, longer remission and lower side effects. However it is probably not useful as an initial immunosuppresant.

Side effects—Idiosyncratic reaction like fever, malaise bone marrow suppression and abnormal LFT.

- **Cyclosporine**
  4–5 mg/kg/day in two equally divided dose either alone or in combination with glucocorticoids.
  The beneficial effects appear to be more rapid than azathioprine.
- **Tacrolimus**
  0.1 mg/kg given in two equal divided dose.
  Side effects—Hypertension and nephrotoxicity.
- **Cyclophosphamide**
  It is reserved for patient refractory to other drugs. High dose cyclophosphamide may induce long lasting (possibly permanent) improvement by rebooting the immune system.
  Causes of death
  – Respiratory failure—Due to myasthenic or cholinergic crisis.
  – Aspiration—Due to weakness of pharyageal and laryngeal muscle.

Chapter 20

Myopathy and Myotonia

MYOPATHY

It is a genetically determined disease of the muscle characterized by *degeneration of a group of muscle without involvement of nervous system.* (Muscular dystrophy can be defined as a *group of hereditary progressive diseases of muscle each with unique phenotypic and genotypic feature).*

CLASSIFICATIONS

Myopathesis can be classified initially into two subgroups:

- **Muscular dystrophies**
- **Mytonic disorder** (autosomal dominant).
  - **Progressive muscular dystrophies** can be again subclassified according to their mode of inheritance.
    - Sex-linked recessive disorders
      - » **Duchenne's** *muscular dystrophy*
      - » **Becker's** *muscular dystrophy*.
    - Autosomal disorders—
      - » **Limb girdle type** (autosomal dominant/autosomal recessive) **dystrophy**.
      - » **Facioscapulohumeral** (autosomal dominant) **dystrophy**.
      - » **Oculopharyngeal** (autosomal dominant) **dystrophy**.
      - » **Congenital** (autosomal recessive) **dystrophy**.
  - **Myotonia**—This condition is composed of two clinical disorder with overlapping phenotype and distinct genetic defect.
    - **Myotonic dystrophy type–I** (classical disease—originally described by *Steinert*)—DM1.
    - **Myotonic dystrophy type–II** proximal myotonic myopathy (PROMM).
    - **Myotonia also seen in myotonia congenita-A** chloride channel disorder but muscle weakness is not so prominent.
    - **Myotonia** are also seen with **sodium channel mutation, hyperkalemic** periodic paralysis or **potassium-sensitive** myotonia.
    - **Paramyotonia** is associated with muscle stiffness is also due to sodium channelopathy and is so named as myotonia worsen with repetitive activity is contrast to other myotonia which is eased with repetitive activity.
    - **Drug-induced myotonia**—Statin, fibrates, cyclosporine and chloroquine.
    - **Myotubular/center nuclear myopathy**.
    - **Chondrodystrophic myotonia**.
    - Glycogen storage disorder (Pompe disease, braching enzyme deficiency).
    - Myofibrillar myopathies.

DUCHENNE'S MUSCULAR DYSTROPHY

- It also known as pseudohypertrophy muscular dystrophy. Pseudohypertrophy is as a result of deposition of fibrofatty tissue within calf muscle, glutei, quadriceps and deltoid.
- Duchenne dystrophy is caused by a *mutation of the gene that encodes dystrophin a 427 KDa protein located on the inner surface of the sarcolemma* of the muscle fiber. Dystrophin gene is one of the largest human gene *located on the short arm of 'X' chromosome*. Duchenne is caused by gene duplication or point mutation or deletion. Diagnosis of Duchenne dystrophy is done by western blot analysis of muscle biopsy for quantity and molecular weight of dystrophin protein.

  Immunocytochemical staining of muscle with dystrophin antibodies can be used to demonstrate the absence or deficiency of dystrophin to the inner surface of sarcolemma.
- Disease is present at birth usually become apparent by the age of 3–5 with history of frequent fall.
- On getting up from floor the patient needs his hands to climb up his own leg (Gower's sign positive).
- Contracture of heal with tendo Achilles and iliotibial tract is apparent by the age of 6 when toe walking is associated with a lordotic posture.
- Initially there is weakness of proximal limb muscle and neck flexors. Leg involvement is greater than arm involvement.
- By the age of 8–10 walking requires use of braces.
- By the age of 12 the patient is wheelchair-dependent.

- Chest deformity with scoliosis impairs pulmonary function which is already compromised by muscle weakness.
- Patient usually die in between 16–18 years due to fatal pulmonary infection as a result of aspiration of food, or acute gastric dialation or pulmonary infection.
- Cardiomyopathy is seen in almost all patients but it is not a cause of death.
- Intellectual impairment is common but non- progressive and affects verbal ability.
- ECG changes are :
  - Increase RS in V_1.
  - Tall R in V_1.
  - Deep narrow Q in the precordial lead.

TREATMENT

- The disease cannot be cured at present. It may be cured by gene therapy in future.
- Prednisolone (0.75 mg/kg/day)—Significally slows the progression of Duchenne up to 3 years but cannot cure the disease or halt the progress of the disease.

BECKER'S MUSCULAR DYSTROPHY

- Pattern of muscle wasting is Becker's type closely resemble Duchenne's myopathy.

  Proximal group involvement > Distal group involvement.

  Lower extremity involvement > upper extremity involvement.
- Facial weakness is not a feature.
- Hypertrophy in calves is a early prominent finding.
- Onset of symptoms is between 5–15 years. Although it may be delayed up to 3–4 decade or even later.
- By definition the patient of Becker type can walk, beyond the age of 15 while Duchenne is typically wheelchair-dependent by the age of 12.
- Cardiac involvement is in the form of CCF may be present.
- Patient usually survive upto 4–5th decade.
- Mental retardation may occurs but less common than Duchenne.

FACIOSCAPULOHUMORAL MYOPATHY

- Onset in childhood/early adulthood.
- Facial weakness is a early manifestation in the form of inability to smile, whistle or fully close the eye.
- Weakness of shoulder gridle usually draws medical attention.
- Biceps and triceps are severely affected with relative sparing of deltoid.
- There is wrist drop and foot drop.
- Weakness is restricted to facial, upper extremity and distal lower extremity.
- 20% patient have progressive weakness of pelvic gridle muscle.
- No other organ is involved.

TREATMENT

1. Physiotherapy
2. Ankle foot orthosis
3. Scapular stabilization to prevent winging of scapula.

LIMB-GIRDLE TYPE

Prominent contracture of elbow and neck is the earliest manifestation appear in the childhood or early teenage. It precedes muscle weakness. Initial muscle weakness involve humeral or peroneal muscle later spread to limb-gridle distribution. *Dilated cardiomyopathy (DCM) is the cause of sudden death, apart from atrial fibrillation and AV block.*

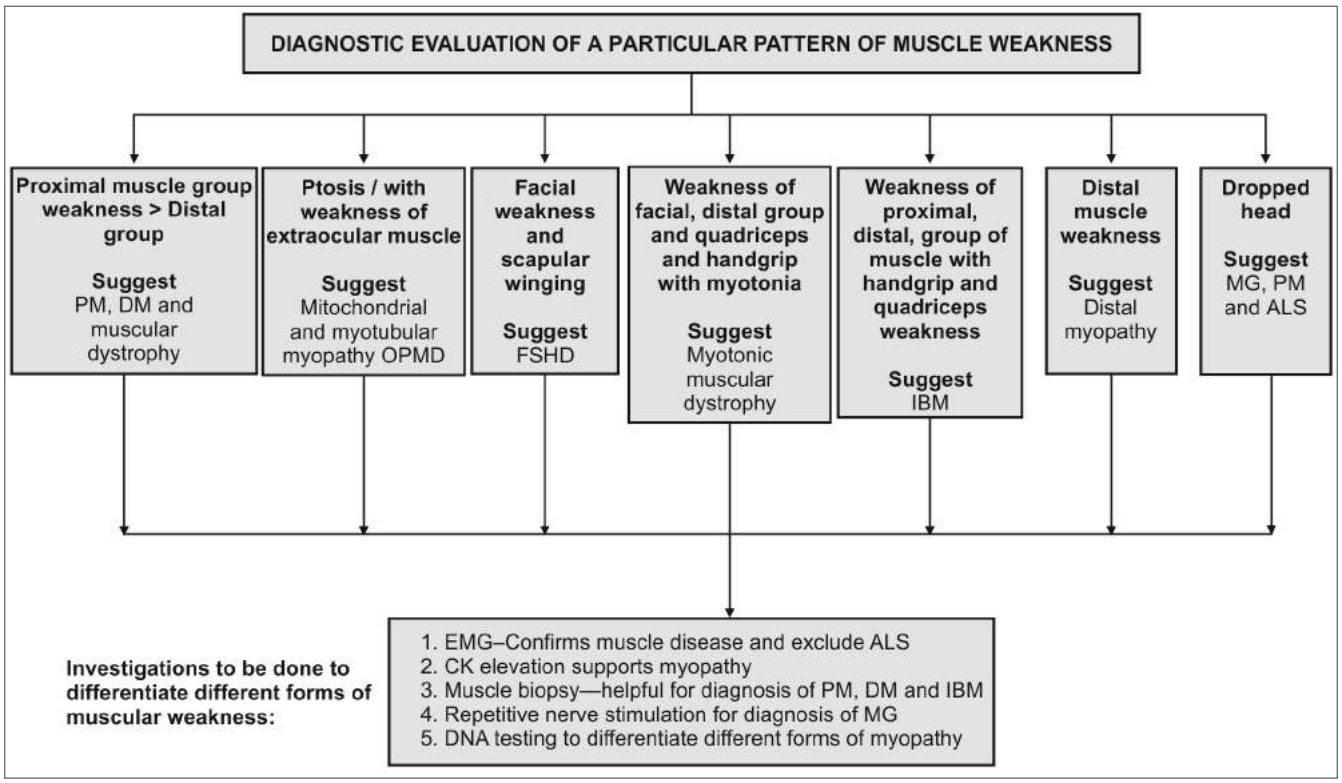
TREATMENT

- Supportive care
- Management of cardiomyopathy and arrhythmia
- Surgery for contracture.

MYOTONIA AND OPHTHALMOPLEGIA

- It involves many system other than muscle.
- Affected person have 'hatchet' facies due to atrophy and weakness of temporalis, masseter along with frontal baldness.
- Weakness and atrophy of neck muscles including flexors, sternomastoid with distal limb muscles which are involve early.
- Weakness of wrist extensors, finger extensors and intrinsic hand muscle along with ankle dorsiflexor—causing foot drop and wrist drop.
- Proximal muscle remains stronger throughout the course, except preferential atrophy of quadriceps muscle.
- Palatal, pharyngeal and tongue muscle involvement produce a dysarthric speech, nasal voice and swallowing problem.
- In some patient, involvement of diaphragm and intercostal muscles results in respiratory insufficiency.
- Myotonia which appears by the age of 5 is demonstrated by—
  - Slow relaxation of hand grip after hand shaking.
  - Percussion on thenar eminence, tongue and wrist extensor produces a dimple which disappear slowly. Precussion over thenar prominence produce dimpling along with peculiar movement of thumb (opponence movement).
- In advance state muscle wasting makes myotonia more difficult to detect.

Flowchart 20.1: Differential diagnosis of different group of muscle



Abbreviations: PM, Polymyositis; DM, Dermatomyositis; OPDM, Oculopharyngeal muscular dystrophy; FSHD, Facioscapulohumeral muscular dystrophy; IBM, Inclusions body myositis; MG, Myasthenia gravis; ALS, Amyotrophic lateral sclerosis.

- Cardiac involvement is common with DM–1 and ranges from 1st degree heart block to complete AV block and sudden death, congestive heart failure, mitral valve prolapse and cor pulmonale can develop.
- Other associated features are—
  - Intellectual impairment
  - Hypersomnia
  - Posterior subcapsular cataract
  - Insulin resistance
  - Gonadal atrophy
  - Decreased esophageal and colonic motility.

DM–2/ PROMM (PROXIMAL MYOTONIC MYOPATHY)

- Patient usually have severe facial and bulbar weakness.
- Transient neonatal respiratory insufficiency may develop.
- Other distinctive features is involvement of proximal group of muscle.

TREATMENT

- Phenytoin is the preferred agent.
- Other agents are quinine and procainamide but may produce cardiac conduction defect.
- Pacemaker can be applied.

CAUSES OF PTOSIS AND OPHTHALMOPLEGIA

- Peripheral nerve (neuropathy)
  - Guillain-Barré syndrome
  - Miller-Fisher syndrome.
- Neuromuscular junction
  - Botulism
  - Eaton-Lambert syndrome
  - Myasthenia gravis
  - Congenital myasthenia.
- Myopathy—
  - Mitochondrial myopathies.
  - Oculopharyngeal/oculopharyngodistal muscular dystrophy.
  - Myotonic dystrophy.
  - Congenital myopathy.
  - Graves disease.

Chapter 21

Parkinsonism

DEFINITION

Parkinson's disease (PD) is most common neuro- degenerative disorder characterized (biochemically by accumulation of presynaptic protein α-syneuclein) and clinically by paucity and slowness of movement (bradykinesia), tremor at rest, rigidity, shuffling gait, flexed posture with loss of postural reflexes.

PATHOLOGY

- Loss of normal dark melanin pigment due to *degeneration of dopaminergic cell in the pars compacta of substantia nigra and mild frontal lobe atrophy*.
- Microscopically there is presence of **Lewy body** (LB) which has **high concentration of α-syneuclein**, the pathological hallmark of the disease.
- Other areas of brain involvement are *anterior olfac- tory nuclei, IXth and Xth cranial nerve nuclei, locus ceruleus, gigantocellularis, raphe magnus. These are reponsible for nonmotor symptoms (autonomic, sleep, emotional disturbances, cognitive disturbances) and refractory motor symptoms (postural instability, gait and bulbar disturbances)*.

PATHOGENESIS

Dopaminergic and other cells die due to combination of many factors like

- Genetic vulnerability
- Oxidative stress
- Proteosomal dysfunction
- Environmental factor.

Endogenous oxidative stress comes from free radical generated by metabolism of dopamine and melanin and defect in the mitochondrial complex–1 of oxidative phosphorylation chain. This oxidative stress and proteosomal dysfunction leads to aggregation of α-syneuclein.

TYPES

Primary Parkinsonism

- Familial PD (5%)
- Idiopathic PD (sporadic) [75%]
- Other neurodegenerative disease
  - Striatonigral degeneration Olivopontocerebellar atrophy.
  - Shy-Drager syndrome
  - Motor neuron disease (MND) with Parkinson's feature.
  - Progressive supranuclear palsy.
- Genetically-mediated disorders
  - Wilson's diseases
  - Spinocerebellar atrophy (SCA–3)
  - Huntington's disease.

Secondary Parkinsonism

- Repeated head trauma.
- Postencephalitic Parkinsonism.
- Neurosyphilitic Parkinsonism.
- Metabolic—Hypothyroidism.
- Drugs—Neuroleptics, antiepileptic, antiemetics, methyldopa, reserpine and lithium.
- Toxins—MTTP, manganese, cyanide, methanol and carbon monoxide.

CLINICAL FEATURES

- **Resting tremor (4–6 Hz)**—Typically appears unilaterally, initially distally (involving digits and wrists—giving the **pill rolling character**), some- time drum beating movement of finger are also seen. It usually spreads ipsilaterally and proximally rarely to the leg before crossing to other side which takes about 1 year or more. At this stage it is called **hemiparkinsonism**. It may involve leap, jaw and tongue but sparing the head.

- **Bradykinesia**—Interferes with both gross movement of big joints and fine motor activity (e.g. handwriting—micrographia).
- **Rigidity—Lead-pipe rigidity** is usually more marked on one side of the body and also present in the neck and axial muscles. Rigidity increases in the examined arm when the opposite arm is moved actively. When stiffness is combined with tremor, lead-pipe rigidity is broken up into jerky resistance to passive movement—known as **cogwheel rigidity**. It is more prominent in wrist joint where the other wrist inactively moved.
- **Postural changes and gait**—A stoop is characteristic. The posture is sometimes called '**simian** posture' to describe the ape-like forward flexion of knee, hip and spine with lack of facial expression.

  Gait disturbances with shuffling short steps and tendency to run enblock known as *festinating gait*—a classic Parkinsonian sign results from flexed posture and loss of postural reflexes.

  Glabellar Tap sign—Tap over of middle of forehead cause blinking which persists for 2–3 taps in normal man, but in case of Parkinsonism blinking will continues as long the tap over Glabella is continued.
- **Nonmotor features** of parkinsonism
  - Depression
  - Anxiety
  - Cognitive impairment
  - Sleep disturbances
  - Sensory abnormality
  - Loss of pain and smell sensation
  - Autonomic dysfunction.

TREATMENT (FLOWCHART 21.1)

Aim of treatment is to improve the motor symptom and neuroprotection.

Motor symptoms (bradykinesia, rigidity and tremor) and abnormal posture respond well to medical therapy whereas cognitive symptoms, hypophonia, autonomic disfunction and balance difficulty respond poorly to medical therapy.

- *Neuroprotective therapy*

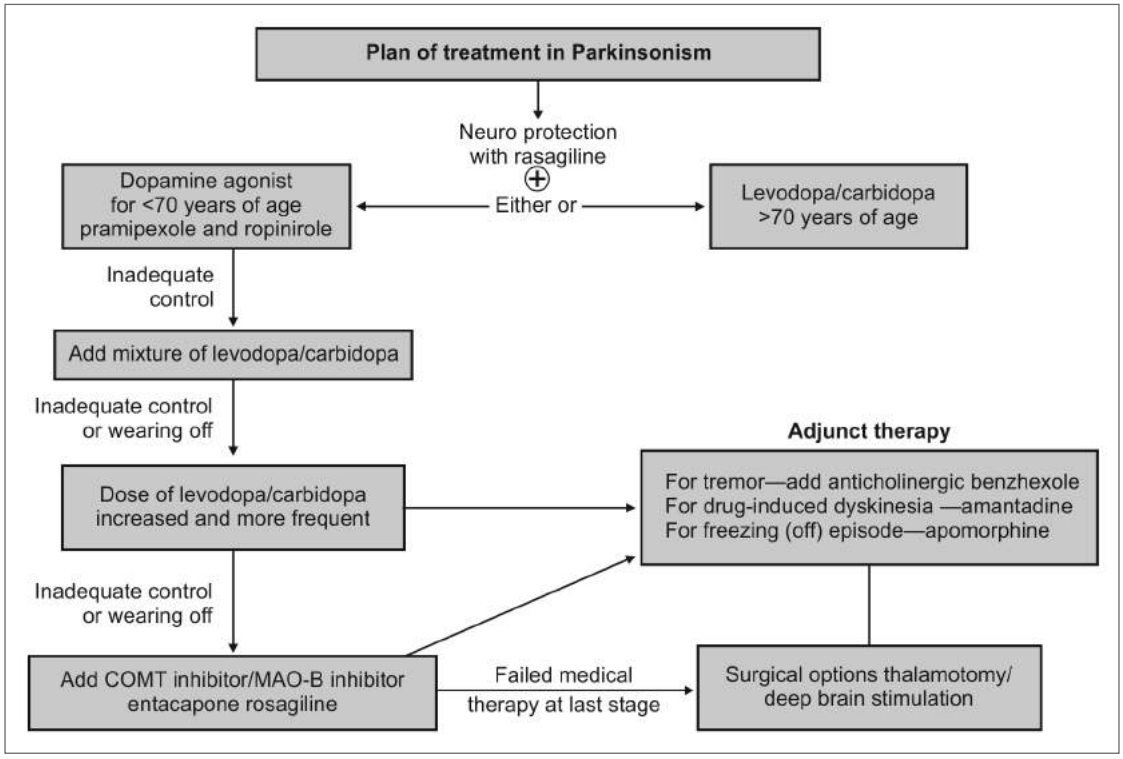
  Dopamine breakdown product creates major free radicle which cause degeneration of dopaminergic neuron. MAO-B inhibitor (selegiline and rosagiline) and COMT inhibitor (tolcapon and entacapon) prevent dopamine breakdown and cause neuroprotection.
  - Selegiline (MAO-B inhibitor)—2.5 mg/day to 5 mg BD (breakfast and lunch).
  - Rosagiline.
  - Entacapone—COMT inhibitor 200 mg with each dose of levodopa.
  - Coenzyme—Q^{10} (high dose) as free radical scavenger.
  - Intrastriatal infusion of neurotrophic factors are investigational agents.
- *For motor symptoms*—Treatment of choice is either **levodopa** or **dopamine agonist**. But the present trend is to start with **dopamine agonist for the younger age group** while that in case of aged people > 70 years of age with levodopa.

  Early initiation and prolonged use of L-dopa-Carbidopa mixture cause various side effects—
  - Weaning off phenomenon.
  - On-off phenomenon.
  - Increased chance of dyskinesia.
  - Enhanced degeneration of nigrostriatal pathway. This side effects can be avoided by using dopamine agonist (D_2A agonists). Moreover in case of complete degeneration of nigrostriatal pathway where L-dopa cannot produce any action then dopaminergic agonists act on postsynaptic dopaminergic receptors and improves motor symptoms.
- **Modalities of treatment of Parkinsonism are as follows**:
  - *Dopamine agonists*
    - Nonalkaloid
      - » Pramipexole (1.5–4.5 mg/day in 3 divided doses).
      - » Ropinirole (1.2–2.4 mg/day in 3 divided doses).
    - Alkaloid
      - » Bromocriptine (7.5–15 mg/day in 3 divided doses).
      - » Pergolide (1.6 mg/day in 2–3 divided doses) (withdrawn from market).
      - » Cobergoline—(Used in Europe).
  - *L-dopa/carbidopa mixture*
    - 100 : 25 mg—bid/tid
    - 200 : 50 mg—continuous release (CR).
  - *L-dopa augmentation*
    - By MAO-B inhibitor—Selegiline and rasagiline (they have additional neuroprotective role and weak symptomatic improvement).
    - COMT inhibitor—Tolcapone (50–200 mg tid) Tolcapone is notorious for hepatotoxicity and hematological disorders and withdrawn from market.

      Entacapone (200 mg with each dose of L-dopa and carbidopa mixture).

      When they are coadministered with L-dopa they increase the effect of L-dopa by 30%.
  - Anticholinergic drugs—Benzhexol (1–4 mg tid)—Useful for controlling resting tremor and dyskinesia.
  - Amantadine—It can reduce drug-induced dyskinesia up to 70%. Dose : 100 mg bid/tid.

Flowchart 21.1: Flowchart of treatment Parkinsonism disease



- For nonmotor symptoms
  - Night-time awakening → L-dopa/carbidopa at night
  - Depression—SSRI
  - Psychological symptoms—Quiteapine/clozapine.

MANAGEMENT OF 'ON-OFF' PHENOMENON

- Increased frequency of dosing.
- Occasional drug holiday.
- Drug to be taken 1 hour before or 2 hours after food for maximum absorption.
- Protein restriction—Amino acid from high protein meal—compete with L-dopa for transport and decrease level of L-dopa at the site of action.
- Addition of other drugs specially D_2A agonist.
- Administration of L-dopa or carbidopa in liquid form.
- Substitution of L-dopa or carbidopa with other drugs like dopamine agonist/amantadine.

SURGICAL TREATMENT

Resurgence of surgery in the treatment of Parkinsonism is motivated by the development of significant drug-induced side effects after 5 years of treatment.

- The **ablation of subthalamic nucleus (STN)** results in dramatic reduction of all clinical features of parkinsonism.
  Indications—
  - Idiopathic Parkinsonism
  - Poor response to L-dopa and carbidopa mixture
  - Significant intractable symptoms
  - Weaning off phenomenon.
- **Bilateral deep brain stimulation of STN** (subthalamic nucleus) is more preferred now than thalamotomy. Stimulation is better than subthalamotomy as—
  - Less invasive and more reversible than ablation
  - Adjustable effect.

Both procedures improve patient's quality of life and more effectively than medical therapy in target population in patient with advanced Parkinson's disease particularly improve troublesome dyskinesias, dystonia and motor fluctuation. But as a rule *benefit from surgery unlikely to exceed the best result obtain from dopaminergic therapy in early Parkinson's disease*.

Signs and symptoms not responding to levodopa, e.g. postural instability and falling, hypophonia, drooling of saliva and autonomic dysfunction are unlikely to improve from surgery.

Chapter 22

Motor Neuron Diseases

DEFINITION

Motor neuron disease (MND) is a neurodegenerative disorder and include all those diseases that involve selective structural or functional loss of upper motor neuron and/or lower motor neurons innervating the voluntary musculature of limbs and bulbar regions.

CLASSIFICATIONS

- **Both upper motor neuron (UMN) and lower motor neuron (LMN) involvement**
  - Amyotrophic lateral sclerosis (ALS).
- **Pure LMN involvement**
  - Proximal hereditary motor neuropathy (PHMN).
  - Multifocal motor neuropathy with conduction block (MMCB).
  - Motor predominant peripheral neuropathy (MPPN).
  - Motor neuropathy associated with paraproteinemia (MNAP).
  - Spinal muscular atrophy (SMA).
    - Type–I—Infantile variety/Werdnig-Hoffman type.
    - Type–II—Chronic childhood variety.
    - Type–III—Juvenile variety/Kugelberg-Welander type.
  - Hereditary bulbar palsy
    - With deafness (Brown-Vialetto-van-Laere)
    - Without deafness (Fazio-Londe).
  - Tay-Sachs disease—Hereditary β-hexosaminidase deficiency (X-linked recessive).
  - Kennedy's syndrome—Bulbospinal atrophy with androgen insensitivity (X-linked recessive)—characterized by gynecomastia and reduced fertility.
  - Postpolio syndrome.
  - Postirradiation syndrome.
  - Monomelic and focal or segmental SMA.
- **Pure UMN involvement**
  - *Primary lateral sclerosis*
    Clinical features
    - Sporadic.
    - Adult onset.
    - Spinal and bulbar involvement.
    - Absent fasciculation.
    - Amyotrophy.
    - No sensory changes.
    - Loss of large pyramidal cells of layer five of precentral cortex.
    - Survival 3 years.
  - *Familial spastic paraplegia (ad)*
    - Adult onset.
    - Long survival due to late involvement of respiratory muscle.
    - Weakness starts from lower limbs.
    - Bladder—Bowel involvement present.
    - Sometimes associated with posterior column involvement and Friedreich's ataxia.
  - Pseudobulbar palsy
    - Bilateral lesion in the corticobulbar connections.
    - Bilateral UMN tongue paralysis—nut in shell tongue (small contracted and slowly moving tongue)
    - Brisk jaw jerk with risus sardonicus (exaggerated emotional facial expressions).
  - Lathyrism.
  - Konzo.

AMYOTROPHIC LATERAL SCLEROSIS ALS

- It is the most devastating neurodegenerative disorder with progressive loss of both categories of motor neuron (UMN and LMN).
- In the absence of clear involvement of both UMN and LMN—the diagnosis of ALS is questionable.
- LMN involvement is recognized clinically by gross muscle atrophy and on muscle biopsy there is **amyotrophy**.
- UMN involvement is recognized by loss of fibers of lateral column of spinal cord with fibrillary gliosis—hence known as lateral sclerosis.

PATHOLOGY

- Early accumulation of pigmented lipid—Lipo- fuschin with shrinkage of affected motor neuron.
- Focal enlargement of proximal motor neuron due to early involvement of motor neuron cytoskeleton— due to accumulation of neurofilament forming spheroid-like structure.

- Compensatory gliosis, i.e. hypertrophy of astrocyte and microglia.

PATHOGENESIS

It is not well-defined—Several theory are proposed:

- Glutamate excitotoxicity
  - Due to diminished reuptake of synaptic glutamate via astrocyte glutamate transporter, called EAAT-2 (excitatory amino acid transporter-2).
- **Superoxide dysmutate (SOD-1) gene mutation**—Leading to—
  - Aggregation of SOD protein.
  - Superoxide accumulation.
  - Decreased ATP production and depressed mitochondrial function.
  - Impaired axonal transport.
  - Activation of cyclooxygenase pathway.
    - All these effects ultimately leads to neuronal death via caspases pathway.
- **Diminished VEGF (vascular endothelial growth factor) expression**—
  - Increased risk of ALS mostly due to—Spinal cord hypoxia which is secondary to diminished neurotropic influence of VEGF.

CLINICAL FEATURES

Depends whether UMN or LMN is predominantly involved.

- **Features due to LMN involvement**—
  - *Features due to spinal anterior horn cell involvement*:
    - Asymmetric distal limb muscle involvement leading to progressive, wasting, weakness and fasciculation of limb muscle.
    - Predominance of extensor weakness over flexor weakness.
    - Early involvement of respiratory muscle responsible for early death before florid features of MND develops.
  - Features due to bulbar motor cranial nerve nucleus involvement
    - Weakness of muscle of mastication, facial muscle, difficulty in deglutition and tongue movement.
- *Features due to UMN involvement*
  - Corticospinal tract involvement
    - Tone—Spasticity.
    - DTR—Hyperreflexia.
    - Nutrition (Without gross atrophy)—Disuse atrophy.
    - Extensor plantar response.
    - Hyperreflexia and spasticity predominates over weakness.
  - Corticobulbar fiber involvement
    - Dysarthria
    - Exaggeration of motor facial expressions of emotions (risus sardonicus) due to bilateral UMN involvement of facial nerve nucleus.
- *Whatever be the initial involvement UMN or LMN, at a later stage of the disease, there will be symmetric involvement in all regions, with eventual implication of both upper and lower motor neuron.*
- *In absence of clear involvement of both upper and lower motor neuron the diagnosis of ALS is questionable.*
- *Until very late stage of the disease*
  - *Sensory*
  - *Cognitive*
  - *Ocular motility*
  - *Bladder* (*function is preserved).*

DIAGNOSIS

- Diagnosis of ALS mostly based on clinical findings and the region of CNS involvement.
- Diagnostic guidelines of ALS by WFN (World Federation of Neurologists).
  - *Presence of simultaneous UMN-LMN involvement.*
  - *Progressive increasing weakness.*
  - *Exclusion of all other possibilities, e.g. compressive myelopathy, syringomyelia, benign fasciculation.*
- *Four regions of CNS are commonly involved in ALS—*
  - *Bulbar*
  - *Cervical*
  - *Thoracic*
  - *Lumbosacral.*

1. *When 3 out of 4 regions are involved—Definitive of ALS*
2. *When 2 out of 4 regions are involved—Probable of ALS*
3. *When 1 out of 4 regions is involved—Possible of ALS.*

Differential Diagnosis

- Compressive myelopathy involving cervical cord/cervicomedullary junction.
- Syringomyelia.
- Benign fasciculation of viral infection.
- Lymphoma/multiple myeloma.
- Chronic lead poisoning.
- Thyrotoxicosis.
- Multifocal motor neuropathy with conduction block.

TREATMENT

ALS is currently untreatable. No satisfactory treatment has yet come out. The commonly used drugs in ALS are as follows:

- Riluzole—100 mg/day.
  (But prolongation of survival time using Riluzole is questionable/doubtful).
- Insulin-like growth factor (1 GF – 1) } Undergoing
- Ceftriaxone } clinical trial
- Physiotherapy and other rehabilitative measures.

DIFFERENTIAL DIAGNOSIS OF MOTOR NEURON DISEASES (MND)

LOWER MOTOR NEURON DISORDER

Kennedy's Disease (X-Linked Spinobulbar Atrophy)

It is an X-linked lower motor neuron disease characterized by

- A disease of the middle-aged male.
- There is progressive weakness and wasting of limb and bulbar muscle.
- Gynecomastia with reduced fertility is due to androgen receptor insensitivity.
- There is absence of pyramidal sign.
- Presence of subtle sensory neuropathy.
- Molecular defect is in expanded trinucleotide repeat (– CAG –) is the first exon of androgen receptor.
- Age of onset inversely correlates with the number of – CAG – repeat.

Adult Tay-Sachs Disease

- Adult onset lower motor neuropathy due to deficiency of enzyme β-hexosaminidase.
- Slowly progressive dysarthria develops.
- Rarely spasticity may be seen.
- Cerebellar atrophy—Seen in CT/MRI.

Spinal Muscular Atrophy (SMA)

Group characteristic of SMA

- There is selected lower motor involvement.
- Age of onset is very early.
- There is extensive loss of large motor neuron cell.
- Biopsy shows denervation atrophy.
- Genetic defect is in the locus on chromosome-5 encoding putative motor neuron survival protein.
  - **Infantile SMA (Werdnig-Hoffman disease – SMA-1)**.
  - Age of onset—early even before birth indicated by decreased fetal movement.
  - If born alive, baby is floppy (hypotonic) although alert and die within 1 year.
  - **Chronic childhood SMA**
    - Slowly progressive course begins late childhood.
  - **Juvenile SMA (Kugelberg-Welander disease)**
    - Begins at late childhood.
    - Runs an indolent course.
    - Weakness present in proximal muscle.
    - EDX study and muscle biopsy show denervation which helps to differential the disease from myopathic disorder.

Multifocal Motor Neuropathy With Conduction Block (MMCB)

- High titer of mono and polyclonal antibody to ganglioside (GMI).
- Antibody cause selective focal paranodal demyelination of motor neuron.
- No pyramidal sign present.
- May respond dramatically with IV immunoglobulin or chemotherapy.

UPPER MOTOR NEURON DISORDER

Primary Lateral Sclerosis (PLS)

- It is a disease of mid or late life and sporadic disorder.
- Progressive spastic weakness of limbs.
- Preceded or followed by spastic dysarthria or dysphagia suggesting involvement of corticospinal and corticobulbar track.
- Fasciculation and LMN atrophy absent.
- No sensory change.
- EDX study does not show denervation.
- Long-term survival is possible.
- Multiple sclerosis, adrenoleukodystrophy and HTLV–1 comes in close differential separated by clinical and laboratory examinations.

Familial Spastic Paraplegia (FPS)

Autosomal dominant form shows the following characteristics:

- Usually starts in the 3rd or 4th decade but may start in early life.
- Progressive spastic weakness involve distal part of lower limb.
- Long survival is possible as respiratory function is affected late.
- Urinary urgency and urinary and fecal incontinence are seen in the late stage.
- Sexual function is preserved.
- Often associated with loss of posteriar column sensation.

Autosomal Recessive form of FSP Shows

- Altered pyramidal and dorsal column function.
- Amyotrophy.
- Mental retardation.
- Optic atrophy.
- Sensory neuropathy.
- Degeneration of corticospinal tract at the caudal part of spinal chord.
- Culprit gene of autosomal dominant form of FSP is spastin which encode microtubule interacting protein.

Chapter 23

Multiple Sclerosis

It is a demyelinating disorder of CNS characterized by inflammation, selective demyelination and gliosis (scarring) of CNS. There is no associated systemic illness and the peripheral nervous system remains unaffected.

Genetic susceptibility with a subsequent triggering viral infection (probably EBV) stimulates a autoimmune reaction that plays key role in the development of multiple sclerosis.

- Genetic susceptibility is proved by familial aggregation.
- Susceptibility to MS is polygenic in nature.
- Each gene have little contribution in overall risk for MS.
- Genetic heterogenisity is present in MS which means that different gene is responsible for MS in different person.
- MHC (major histocompatibility complex gene) on chromosome 6 is the strongest MS susceptibility region.
- Fine mapping shows class II region on MHC specially DR_2 alle is the culprit in most of the MS patient.
- In others, the abnormality in the gene that encode receptor for two proinflammatory cytokine, IL-7 receptor—α chain (CD 127) and IL-2 receptor—α chain (CD 25) makes the person vulnerable to MS.
- Axonal damage is mediated by resident and migrated inflammatory cell, i.e. microglia, macrophage CD_8 and their toxic cytokine, NO and oxygen radical.
- Autoimmune reaction: Autoimmunity is supported by the study of immune system in MS patient.

CELLULAR RESPONSE

Myelin basic protein (MBP) is the T-cell antigen in MS MBP reactive T-cell found in blood and CSF.

ABNORMALITY

Abnormality in DR_2 region causes high affinity binding of DR_2 region with the fragment of MBP stimulating T-cell response to self-protein.

HUMORAL RESPONSE

Activated B-cell with antibody against myelin oligodendrocyte glycoprotein (MOG) have been detected in MS plaque. *In CSF elevated levels of immunoglobulin and oligoclonal antibodies are found*. The pattern of oligoclonal band is different in each individual patient. *Some band of oligoclonal antibody are directed against EBV virus*.

CYTOKINES

Proinflammatory cytokine TH_1 including IL_2, TNFα and INFγ injure oligodendrocyte or myelin membrane and plays a key roles in inactivating and maintaining autoimmune response.

Activated microglia causes axonal injury through release of NO, oxygen radical and via glutamet which is toxic to oligodendrocyte and neuron.

CLINICAL FEATURES

Onset of MS may be *abrupt or insidious*. Symptom may vary from *severe to trivial*.

Autopsy or MRI may show MS lesion in otherwise healthy individual.

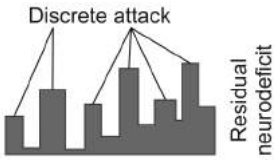
Symptom of MS depends on the location and severity of lesion within CNS.

SYMPTOMS OF MS

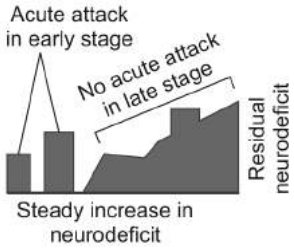
- Sensory symtoms present in 37% of patients
- Lhermitte's sign present in 3% of patients
- Optic neuritis present in 36% of patients
- Pain present in symptoms 3% of patients
- Motor symptoms present in 35% of patients
- Dementia present in 2% of patients
- Paresthesia present in 25% of patients
- Visual loss present in 2% of patients
- Diplopia present in 15% of patients
- Facial palsy present in 1% of patients
- Ataxia present in 10% of patients
- Epilepsy present in 1% of patients
- Vertigo present in 5% of patients
- Impotence present in 1% of patients
- Bladder disturbances present in 5% of patients
- Onset and progression of the symptom vary from patient to patient.

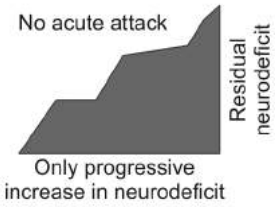
Four clinical pattern of onset of MS have been described.

1. **Relapsing and remitting MS (RRMS—85%)**—This type constitute 85% of MS patient at the beginning they have discrete attack that evolve over days to weeks but usually complete recovery takes place over months in the initial stage. When ambulation is severely impaired during acute attack in the later stage of the disease approximately half the patient fails to improve completely leaving some residual neurodeficit after each attack which are addictive.

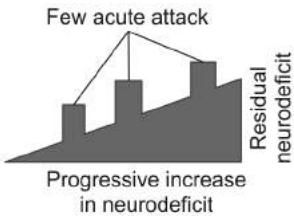


2. **Secondary progressive MS (SPMS)**—It appears to be in the late stage RRMS. In the initial stage of the disease the patients have the clinical course like that of RRMS but at some point of time the patient have steady deterioration of clinical status unassociated with acute attack. Approximately 2.5% of RRMS develop SPMS each year.





3. **Primary progressive MS (PPMS—15%)**—These patients do not have acute attack but have steady deterioration of the clinical state from the beginning. This type of clinical course is usually seen among elderly age >40 year with Male : Female ratio (1 : 1) and accounts for 15% of the patients.



4. **Progressive/Relapsing MS (PRMS—5%)**—These patient experienced occasional acute attack superimposed on the progressive course of the disease. It accounts for 5% or the patient.

Sensory symptoms are paresthesia, numbness, tingling, prickling formication, burning and pins and needle sensation, hyperesthesia and reduced sensation.

Unpleasant sensation like that the body parts are swollen, wet, raw or tightly rapped may be present. *Sensory impairment of trunk and leg below a horizontal line indicate spinal cord disease.*

Pain is present in > 50% of patient and can occurs anywhere and can change location from time to time.

Motor symptom—Weakness of limb, i.e. loss of strength, increased fatigue, disturbance of gait are usually associated with pyramidal sign like brisk DTR, Babinski positive, spasticity. Occasionally DTR may be depressed indicating that the lesions interrupt the afferent path of the reflex are in the spinal cord.

Exercise-induced weakness is characteristic of MS.

Spasticity—More than 30% of patients have moderate to severe spasticity which may be present at rest or during work. Muscle spasm may interfere with ambulation, work or self-care and sometime may be painful.

Ataxia—Manifest as cerebellar tremor or ataxia of trunks, head and voice producing scanning speech (cerebellar dysarthria).

Optic neuritis (ON)—Symptom may be mild or may progress to visual loss. Diminished visual acuity and decreased color vision is the common symptom.

- Usually the symptoms are monocular but may be bilateral. Periorbital pain may proceed or accompany visual loss.
- Defect in the affarent pathway of pupillary reflex may be present.
- Fundus may be normal or shows papillitis (swelling of optic disk) with pallor of optic disk which follows ON due to optic atrophy.
- Visual blurring may result from diplopia or ON.
- If blurring of vision disappears after covering one eye, then the symptom is due to diplopia.
- Diplopia is due either to internuclear ophthalmoplegia (INO) or from palsy of 6th cranial nerve and rarely from IIIrd and IVth cranial nerves.
- **INO (internuclear ophthalmoplegia)** consists of impaired adduction of one eye with prominent nystagmus in the abducting eye along with small skew deviation is due to the lesion of MLF (medial longitudinal fasciculus) of the side of adducting eye.
- Bilateral INO is strongly suggestive of MS.
  Other gaze disturbances are—
  - Horizontal gaze palsy.
  - One and a half syndrome (horizontal gaze palsy plus INO.
  - Acquired pendular nystagmus.

  Bladder dysfunction like *frequency, urgency, nocturia incontinence, hesitancy, difficulty in initiation, retension, overflow incontinence and UTI present in > 90% of MS patients.*

  Constipation—Present in > 30% of patients.
- Fecal urgency and bowel incontinence present in > 15% of patients.

Cognitive dysfunction in the form of memory loss impaired attention, euphoria. Difficulties is problem- solving, slowed information processing is present in < 20% patient.

Depression may be endogenous or reactive and contribute to fatigue and suicide.

Fatigue is present in > 90% can be exacerbated by elevated temperature and depression.

Sexual dysfunction—Decreased libido, impotence-impaired genital sensation in men and diminished vaginal secretion and adductor spasm in women.

Facial weakness like Bell's palsy but not associated with loss of taste sensation and retroauricular pain may be present.

Vertigo—Due to brainstem lesion resembling acute labyrinthitis may present in minor percentage.

Hearing loss—Uncommon.

Heat sensitivity and Uhthoff's symptom—Neurologic symptom develop after elevation of 'core' body temperature or during exercise or hot shower or after fever like unilateral visual blurring is called '**Uhthoff's symptom**' is due to transient conduction block.

Lhermitte's sign—Electric shock like sensation down the spine towards the leg rarely towards the arm on flexion or movement of neck. This symptom can also occur in cervical spondylosis.

Paroxysmal symptoms—This syndrome include Lhermitte's symptom, tonic contraction of limb, face, trunk, paroxysmal dysarthria, ataxia, sensory disturbances. This is due to spontaneous discharge arising at the edge of the demyelinated plague and spreading to adjacent white matter. They are of brief duration (10s–2 min) high frequency 5–40 episode/day without alteration of consciousness or EEG change.

Trigeminal neuralgia, hemifacial spasm, glossopharyngeal neuralgia—It can occur due to involvement of entry or exit of Vth, VIIth or IXth nerve.

DIAGNOSTIC CRITERIA FOR MS

- Two or more clinical attack or objective clinical evidence of two or more lesion or objective clinical evidence of one lesion with history of one prior attack.
- Two or more clinical attack with objective clinical evidence one lesion and T_2 lesion of MRI in at least one out of four MS typical site in CNS (paraventricular, juxtacortical, infratentorial or spinal cord).
- One clinical attack with objective clinical evidence of two or more lesion or MRI evidence of two or more lesion or appearance of new lesion on T_2-MRI or wait for a second clinical attack.
- One clinical attack with objective clinical evidence of one lesion with one T_2-MRI lesion in at least two out of four MS typical site or wait for second clinical attack at different CNS site and presence of asymptomatic gadolinium enhancing on nonenhancing lesion or a new T_2/gadolinium enhance lesion on follow up MRI or wait for second clinical attack.
- Insidious progressive neurological lesion suggestive of MS with two out of three following criteria—
  T_2-MRI lesion in the MS-specific area (paraventricular juxtacortical, infratentorial). Two T_2-MRI lesion is spinal cord. Positive CSF (oligoclonal band and elevated IgG index).

DIAGNOSTIC

- **Definite MS**—All five criteria are present.
- **Probable MS**—All five criteria is present except—
  - Only one objective abnormality despite two symptomatic episode.
  - Only one symptomatic episode despite two or more objective abnormality.
- **At risk for MS**—criteria (1) + (2) + (3) + (5) fulfilled but the patient have either only one symptomatic episode or one objective abnormality.

DIFFERENTIAL DIAGNOSIS

- Acute disseminated encephalomyelitis (ADEM).
- APLA.
- SLE and related collagen vascular disease and vasculitis.
- Behçet's disease.
- Sjögren' syndrome.
- Congenital leukodystrophy (adrenoleukodystrophy and metachromatic leukodystrophy).
- HIV.
- Tropical spastic paraplegia (HTLV I and II).
- Lyme disease.
- Sarcoid.
- CVA and vascular malformation.
- Neoplasm (lymphoma, glioma and meningioma).
- Vitamin B_{12} deficiency.

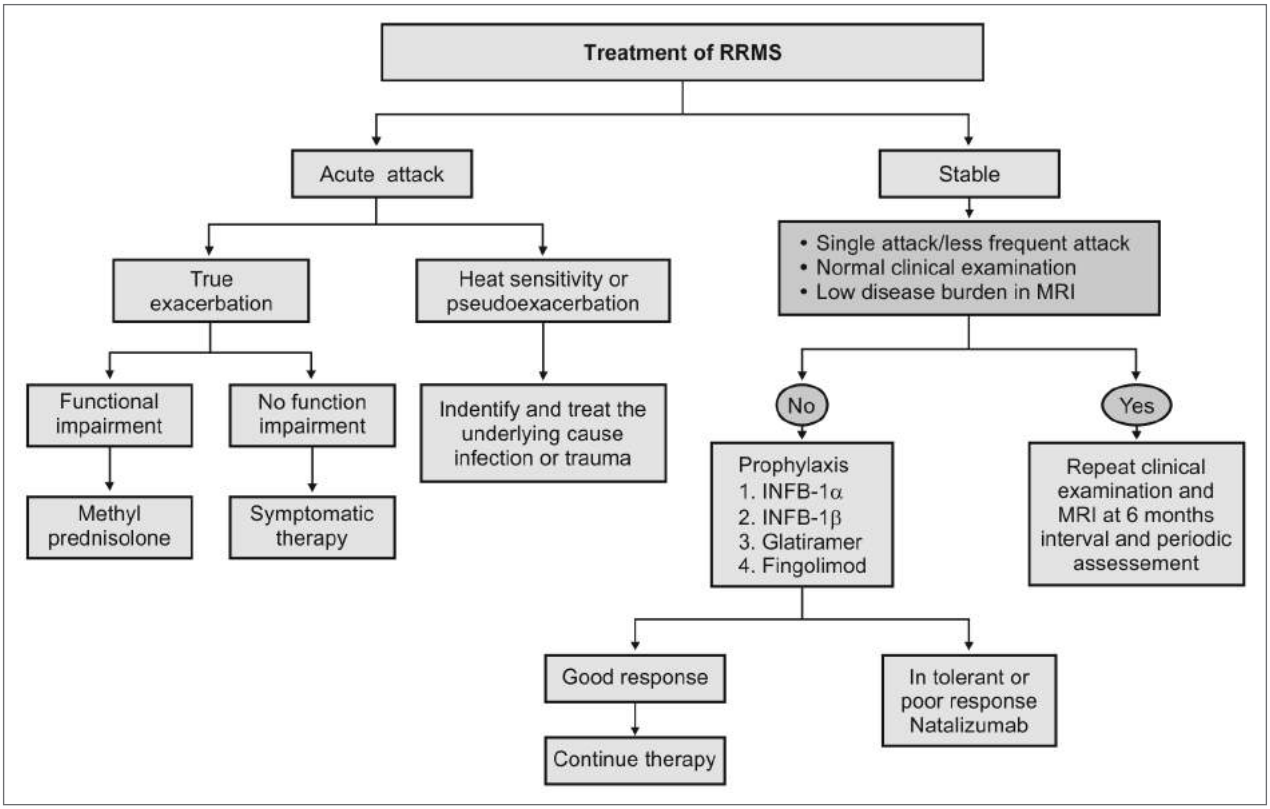
TREATMENT OF MULTIPLE SCLEROSIS (FLOWCHARTS 23.1 AND 23.2)

- Treatment of acute attack
- Treatment with disease-modifying agent
- Symptomatic therapy.

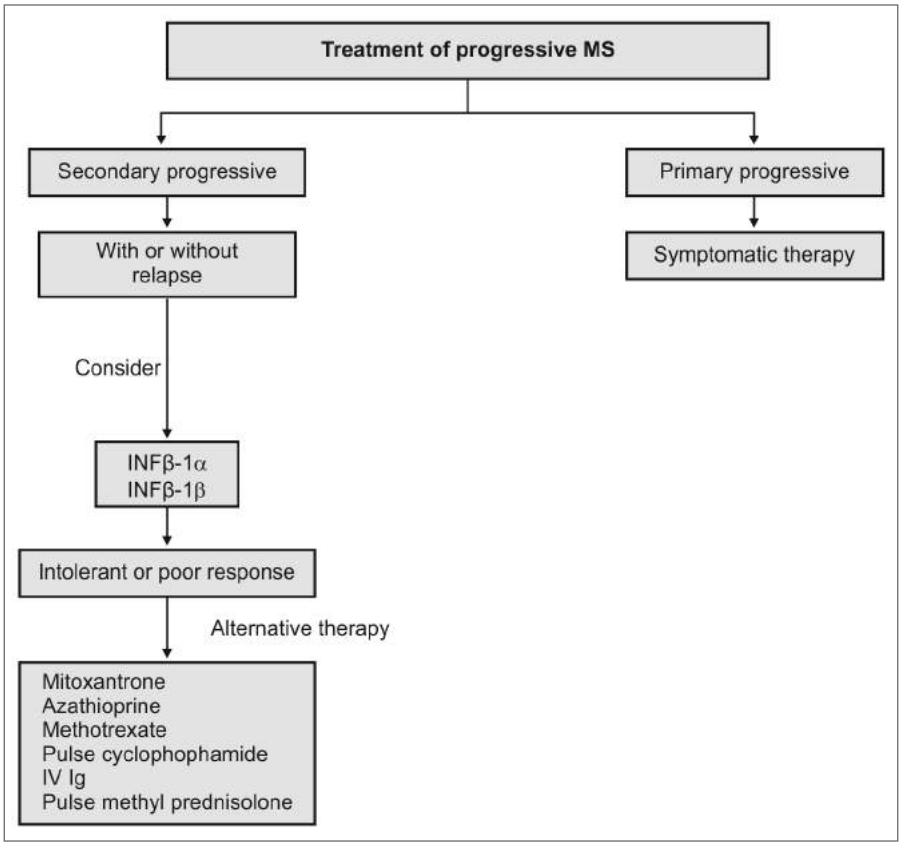
Treatment of Acute Attack

- **Methyl prednisolon—500–1000 mg/day IV × 3–5 day** without a tappering dose of prednisolone or with 60–80 mg oral/day for 2 week.
- **Alternatively plasma exchange 40–60 mL/kg per** exchange on every alternate day × 2 weeks (total 5–7 or change) may benefit patient with fulminant attack who are unresponsive to glucocorticoid. **Glucocorticoid are used to manage either first attack or acute exacerbation**.
  - **They provide short-term benefit** but regarding long-term benefit is uncertain.
  - That is why mild attack or pseudoexacerbation due to fever, infection or rise in environmental temperature are not treated with glucocorticoid.
  - Side effects of glucocorticoid therapy are treated accordingly.
  - Emotional lability and insomnia—Treated by lithium carbonate— 300 mg bid

Flowchart 23.1: Treatment of RRMS



Flowchart 23.2: Treatment of progressive MS



– Peptic ulcer—Ranitidine — 150 mg bid and pantoprazole—40 mg bid.

Treatment with Disease-modifying Agent

Disease-modifying therapy for relapsing from of MS—**Seven agents** are approved by FDA.

- *INFB 1a*
- *INFB 1b*
- *Glatiramer*
- *Natalizumab*
- *Fingolimod*
- *Mitoxantrone*
- *Cladribine.*

These agents are used for treatment SPMS/RRMS and have fewer clinical exacerbation and fewer new MRI lesion compaired to placebo.

- **Interferon** acts through its immune modulatory action—
  – Down regulation of MHC molecule on APC cell.
  – Inhibition of proinflammatory and stimulation of regulatory cytokines.
  – Inhibition of 'T' cell proliferation.
  – Limiting the entry of inflammatory cells in CNS.
- **Glatiramer acetate**—A polypeptide composed of L-glutamic acid, L-lysine, L-alanine and tyrosine acts by—
  – Induction of antigen-specific suppressor 'T' cell.
  – Binding to MHC molecule—thereby replacing bound MBP.
  – Altering the balance between proinflammatory and regulatory cytokines.
- **Natalizumab**—A humanized monoclonal antibody against a cell adhesion molecule $\alpha_4\beta_1$ integrin expressed on the surface of lymphocyte which helps to penetrate BBB. Thereby prevent the lymphocyte from penetrating BBB to enter CNS. Complication in PML with prolong therapy.
- **Fingolimod**—Prevents the movement of lymphocyte from spleen and lymph node to brain. It reduces the attack rate and significantly improves all measures of disease severity in MS. It can be administered orally and well-tolerated and superior to low dose weekly INF-B. So, it is recommended for firstline therapy for MS by FDA. Complications are first degree heart block, bradycardia, elevated liver enzyme and lymphopenia.
- **Cladribine**—It is a purine analog inhibit DNA synthesis. Easy oral dosing only 2 weeks/year makes it convenient.
- **Mitoxantrone**—12 mg/m^2 every 3 months for 2–3 years for SPMS, PPMS and RRMS.
  Side effects—Permanent amenorrhea, cardiomyopathy and leukemia.

Second line (disease-modifying) agent—

- **Azathioprine**—2–3 mg/kg/day for SPMS.
- **Methotrexate**—(7.5–20 mg/week for upper extremity dysfunction in SPMS.
- **Cyclophosphamide**—700 mg/m^2 on alternate month.
- **IVIG**—1 g/kg monthly pulse for 2 years.
- **Methyl prednisolone**—500 mg–1 gm monthly pulse.

Symptomatic Therapy

- **Heat-sensitive symptom**—Potassium channel blocker—4 aminopyridine 3–4 diaminopyridine—40–80 mg/day.
  Side effect—Seizure.
- **Ataxia and tremor**
  Clonazepam—1.5–20 mg/day
  Mysoline—60–200 mg/day
  Propanolol—40–200 mg/day
  Ondansetron—8–16 mg/day.
  Physical measure—Wrist weight, thalamotomy, deep brain stimulation, may be tried.
- **Spasticity**
  Lioresol—100–120 mg/day by a pump to deliver the drug into CSF.
  Diazepam—20–40 mg/day.
  Tizanidine—8–32 mg/day.
  Dantrolene—25–400 mg/day.
  Cyclobezapirine—10–60 mg/day.
  Physical therapy—Exercise, stretching and avoidence of constipation and infection.
- **Pain**
  Carbamazepine 100–1000 mg/day
  Phenytoin—300–600 mg/day
  Gabapentine—300–3600 mg/day
  Pregabalin—50–300 mg/day
  Amitriptyline—25–150 mg/day
  Desipramine—100–300 mg/day
  Venlafaxine—75–225 mg/day.
- **Bladder dysfunction**—
  – **Detrusor hyperreflexia**
    Propantheline bromide—10–15 mg/day
    Oxybutyrin—5–15 mg/day.
    Hyoscyamine—0.5–0.75 mg/day.
    Tolterodin—2–4 mg/day.
    Solifenacin—5–10 mg/day.
    Coadministration of pseudoephedrine 30–60 mg/day may be beneficial.
  – **Detrusor/sphincter dyssynergia**—
    Phenoxybenzamine—10–20 mg/day
    Terazosin—1–20 mg/day Loss of reflex bladder contraction—**Bethanicol** 15–150 mg/day.
- **Depression**—Fluoxetin—20–80 mg/day sertaline—50–200 mg/day
  Amitryptaline.
- **Fatigue** is treated by—
  Amantadine—200 mg/day
  Methylphenidate—5–25 mg/day
  Modafinil—100–400 mg/day.
- **Cognitive problem**—Donepezil—10 mg/day.

Chapter 24

Polymyositis, Dermatomyositis, Inclusion Body Myositis

INTRODUCTION

- These are inflammatory muscle disorder, consist of three major disease:
  1. **Polymyositis (PM)**—It is a rare disease affecting adult.
  2. **Dermatomyositis (DM)**—Affects both child and adult. Women are more often affected than men.
  3. **Inclusion body myositis (IBM)**—It is 3 times common in men than women and whites are more commonly affected than black.

GROUP CHARACTERISTICS OF POLYMYOSITIS

- **PM** and **DM** are **subacutely progressive** (over weeks to months).
  They are **symmetric** inflammatory myopathy involving **proximal group of muscle**. Distal group of muscle which are required for fine motor movement are affected late in the course of the disease of PM and DM.
- **IBM** is a very **slowly progressive muscle disorder** involving **distal group of muscle but quadriceps** develop early in the course of the disease.
- *Ocular muscles are not involved in inflammatory myositis.*
  - *Facial muscles are unaffected in* **PM** *and* **DM**.
  - *Mild degree of facial involvement seen in IBM.*
  - *Pharyngeal and neck flexors are involved in all forms of inflammatory myopathies* causing dysphagia and head drop.
  - *Respiratory muscles are involved in late stage* and rarely in acute stage.
  - *Muscle wasting in associated with severe weakness.*
  - *DTR are preserved* until very late stage but may be absent in severly atrophied muscle specially in IBM where atrophy of quadriceps and distal group of muscle predominate.
  - *Sensation remains normal* in inflammatory myopathies.
  - *Myalgias and muscle tenderness seen in a small percentage of patient usually with DM* which are associated with connective tissue disorder like scleroderma, MCTD and overlap syndrome.
  - Myalgia and tenderness are not seen in IBM and polymyositis (PM).

SPECIAL FEATURES OF POLYMYOSITIS

- Rare subacutely progressive inflammatory myopa- thies affecting adults rarely children.
- No cutaneous rash seen.
- No involvement of extraocular or facial muscle.
- No family history of neuromuscular disease.
- Associated with systemic autoimmune or connective tissue disease or viral or bacterial infection.
- D-penicillamine or zidovudine may produce PM-like syndrome.

SPECIAL FEATURES OF DERMATOMYOSITIS

- Skin rash may accompany or precede the onset of muscle weakness.
- Blue purple discoloration on the upper eyelid with edema—called **heliotrope rash** diagnostic of DM.
- Flat red rash on the face and upper trunk and erythema of the knuckles with raised violaceous scally eruption—called **Gottron's sign** seen in DM.
- Erythematous rash can also occur on knee elbow malleoli, neck, anterior chest ('V' sign), back and shoulders—worsen with sun exposer—called **'Shawl' sign**. Seen in DM.
- In some patients pruritic rash may be present on scalp, chest and back.
- Dilated capillary loop at the base of finger's nail.
- Cuticles are irregular, thicker, distorted on lateral and palmar aspect of the fingers which are rough and thickened, cracked with dirty horizontal line simulating **mechanic's hand**.
- Sometime muscle power may be normal in this disease and is termed as **dermatomyositis sine myositis**.
- Perivascular and perimysial inflammation seen on muscle biopsy.
- Dermatomyositis may overlap with scleroderma and MCTD.

- Chronic DM-like features are seen in eosinophilic myalgic syndrome associated with ingestion of contaminated L–tryptophan.
- Incidence of malignancy appear to increase with DM.
- Common tumors associated with DM are ovarian cancer, breast cancer, melanoma, colon cancer and non-Hodgkin's lymphoma. Nasopharyngeal cancer are common association in Asian population.
- Overlap syndrome in a patient of DM is characterized by features of systemic sclerosis or mixed connective tissue disease, e.g. sclerotic thickening of the dermis, contracture, esophageal hypomotility microangiopathy and calcium deposit. They have specific antinuclear antibody, Anti-PM/Scl 70 nuclear protein complex.
- It is associated with rheumatoid arthritis, SLE and Sjögren's is rare.

SPECIAL FEATURES OF INCLUSION BODY—MYOSITIS

- It is the most common inflammatory myositis.
- Age on onset is ≥ 50 years.
- It is a slow but steady progressive disorder require walking assistance or wheelchair within several year.
- Initial features are similiar to PM.
- Weakness and atrophy of distal group of muscle specially long flexor of fingers and foot extensor which develop very early and gives a clue to early diagnosis.
- Inability to perform fine movement like turning key or knotting, holding object and stiching.
- Some patients present with history of repeated fall due to weakness of quadriceps.
- Weakness and atrophy may be asymmetric and selectively involve quadriceps, iliopsoas, triceps, biceps, finger flexor mimic lower motor neuron disease.
- Dysphagia with chocking may be present in 60% patients.
- Sensory function is almost normal except mild diminution of vibration sense at lower limb in some patient.
- The pattern of distal weakness makes it a close differential diagnosis of MND or peripheral neuropathy, systemic autoimmune or connective tissue disorder.
- There is a subgroup called hereditary inclusion body myopathy (h-IBM) which has familial aggregation.

EXTRAMUSCULAR MANIFESTATION OF PM AND DM

- Systemic manifestation like, fever myalgia, arthralgia, weight loss, Raynaud's phenomenon are present when inflammatory myositis is associated with connective tissue disorder.
- Arthralgia, synovitis or joint deformity or contracture with subluxation of interphalangeal joint can occur in some patients of DM and PM who have JO-1 antibody positive.
- Subcutaneous calcification in DM patient sometime project on skin and cause ulceration and infection.
- Dysphagia with GI symptoms due to involvement of oropharyngeal and esophageal muscle occurs specially in DM and IBM.
- Cardiac symptoms like AV conduction disturbances, tachyarrhythmias, DCM, low ejection fraction with CCF is due to involvement of heart. HTN can develop from glucocorticoid therapy.
- Pulmonary dysfunction is due to weakness of tho- racic muscle, ILD, or drug-induced pneumonitis (from methotrexate). Symptoms of pulmonary dysfunction are dyspnea, nonproductive cough and aspiration pneumonia. ILD may precede or accompany PM or DM who have antibodies to tRNA synthetase.

PATHOGENESIS

An autoimmune reaction is the reason behind inflammatory myopathies and is supported by the following reasons—

- Overlap with scleroderma and MCTD.
- Associated with specific MHC gene like—DR3 and DRW52. DR3 haplotype occurs in 75% of PM and IBM whereas in Juvenile DM there is increase frequency DQA1.
- Presence of various antinuclear antibody-like anti-Jo-1.
- Demonstrable 'T' cell-mediated myocytotoxicity and complement-mediated microangiopathy.
- Response to immunotherapy.

DIFFERENTIAL DIAGNOSIS

Typical skin rash with proximal or diffuse skin rash is almost diagnostic of DM.

Proximal muscle weakness without any skin rash which is seen in PM and IBM have many differentials such as—

Chronic progressive muscle weakness develop in the following condition—

- Spinal muscular atrophy.
- Amyotrophic lateral sclerosis.
- Muscle dystrophy.
- Collagen storage disease.
- Lipid storage disease.
- Endocrine myopathies—Cushing, hypo and hyperthyroidism and hypoparathyroidism.
- Myoneural junction disorder—Myasthenia and Lambert-Eaton myopathy.

Acute muscle weakness develop in the following condition—

- GB syndrome.
- Transverse myelitis.

- Neurotoxin.
- Neurotropic virus—Polio and West Nile virus.
- Parasitic infestation—Toxoplasma, trypanosoma and cysticerci.
- Bacterial infection—Staphylococcus, *Streptococcus yersinia*, anaerobic bacteria, *Legionella*, pneu- mophilia, *Borrelia burgdorferi*.
- Periodic paralysis—Hypokalemia, hypophosphatemia, hypomagnesemia, chronic alcoholic and parenteral hyperalimentation.

Myofascitis

Parasitic infection, vasculitis, MCTD, hypereosinophilic syndrome and toxic exposure.

Drug-induced Myopathies

D-penicillamine, procainamide, AZT, contaminated L-tryptophan, cholesterol lowering agent, amphotericin, heroin, growth hormone and glucocorticoids with pan-curonium.

DIAGNOSIS OF MYOPATHY IS CONFIRMED BY

1. **Serum muscle enzyme—CK which is always elevated (up to fifty fold)** in PM but may be **normal in IBM** and **DM** when associated with connective tissue disease.
   SGOT, SGPT, LDH and aldolase may also be elevated.
2. **Needle EMG** shows myopathic potential characterized by **short duration**, **low amplitude, polyphasic** unit on voluntary contraction and increased **spontaneous activity** with **fibrillation, complex repetitive discharge** and **positive sharp wave**.
   EMG finding is not diagnostic but helps to differentiate it from neurogenic disorder.
3. **Muscle biopsy is the gold standard for diagnosis Myositis** inflammation is the histological hallmark for diagnosis.
   In PM—Inflammation is primarily located within the muscle fascicles (endomysial) characterized by CD8 + T cell and MHC–I molecule expressed on sarcolema is fundamental for confirming the diagnosis.
   In DM—Inflammation occurs around the muscle fascicles instead of within the muscle fascicles predominantly perivascular or in interfascicular septa.
   In IBM—There is endomysial inflammation with T-cell infiltration with MHC-I expressing nonvacuolated muscle fiber, basophilic granular deposit around the edge of slit-like vacuoles, loss of fiber, hypertropic fiber, angulated or round fiber, eosinophilic cytoplasmic inclusion, abnormal mitochondria, ragged red fiber, cytochrome oxidase negative fiber, amyloid deposit, filamentous inclusion are detected by congo red or crystal violet staining using fluorescent microscope.

In summery—

- **In polymyositis**—There is endomysial inflammation with CD8/MHC-I complex without vacuoles but minimal inflammation.
- **In dermatomyositis**—Perifascicular, perimysial or perivascular infiltrate and perifascicular atrophy.
- **Inclusion body myositis**—Primary inflammation with CD8/MHC-I complex with vacuolated fibers and β-amyloid deposit, cytochrome oxygenase-negative fibers, sign of chronic myopathy.

TREATMENT

1. **Glucocorticoids**—Prednisolone—1 mg/kg/day for 4 weeks— reduced slowly over a period of 10 weeks to 1 mg/kg on alternate day—if the patient improves and no serious side effects are seen then the dose is further reduced by 5–10 mg every 3/4 weeks until the lowest possible dose that controls the disease is reached.
   If no objective benefit is noted after 3 months of high dose therapy, prednisolone is rapidly withdrawn and switched over to immunosuppressive drug.
- **Immunosuppressive drug**—75% patient requires this type of drug when prednisolone fails to improve the patient within 3 months.
  - Azathioprine—2–3 mg/kg/day.
  - Methotrexate—7.5 mg/weekly for 3 weeks gradu- ally increase the dose to 25 mg/week.
  - Mycophenolate—Mofetil 2.5 mg/kg/day.
  - Rituximab (anti-CD–20).
  - Cyclosporine.
  - Cyclophosphamide 0.5–1 mg/IV for 6 months.
  - Tacrolimus.
- **Immunomodulation**—IV immunoglobulin (IV Ig)—2 gm/kg divided over 2/5 days can be repeated every 6– 8 weeks for sustained improvement for refractory DM.
  Plasmapheresis or leukopheresis have no roll in PM or DM.

Treatment protocol

- Step 1—High dose *prednisone*.
- Step 2—*Azathioprine, myeophenolate mofetil and methotrexate* are used as steroid sparing agent.
- Step 3—IV *immunoglobulin*.
- Those who do not have optimal response with the above agents for those patients.
- Step 4—*Rituximab, cyclosporin, cyclophosphamide* or tacrolimus can be tried.

EXERCISE

Write short notes on

1. Draw schematic diagram of visual pathway and effect of lesion at different levels.

2. Draw schematic diagram of pyramidal tract from cortex to anterior horn cell/motor cranial nerve nucleus.
3. Write the clinical features of nuclear hemiplegia at the level of—(a) midbrain, (b) pons and (c) medulla.
4. Compare medial pontine syndrome with lateral pontine syndrome and medial medullary syndrome with lateral medullary syndrome.
5. Write on thrombolysis in ischemic stroke.
6. Compare the clinical features of LMN with the UMN type of lesion.
7. Compare between the extramedullary with the intramedullary lesion.
8. Write the clinical features of quadriparesis due to lesion at upper cervical cord.
9. Write short notes on spastic paraplegia and flaccid paraplegia.
10. Write the clinical features of compressive myelopathy at the level of D_8 vertebra.
11. Write short notes on subacute combined degeneration of spinal cord.
12. Write the comparison between the clinical features of conus medullaris lesion with the cauda equina lesion.
13. Write the bacteriological profile of pyogenic meningitis.
14. Write the clinical features of pyogenic meningitis.
15. Write on management of pyogenic meningitis.
16. Define seizure and epilepsy.
17. Classify seizure.
18. Write on management of status epilepticus.
19. Write in detail clinical features of generalized tonic-clonic seizure (GTCS).
20. Differentiate between complex partial seizure and Petit mal (absence) seizure.
21. Write a short note on EEG.
22. Classify peripheral neuropathy.
23. Write the etiology of peripheral neuropathy.
24. Write short notes on carpal tunnel syndrome.
25. Write on etiology and clinical features of Guillain-Barré syndrome.
26. Write on electrodiagnostic test and treatment of Guillain-Barré syndrome.
27. Write on diagnosis of myasthenia gravis (both clinical and laboratory).
28. Write on drug therapy of myasthenia gravis.
29. Write a short note on Duchenne myopathy.
30. Write on clinical features of Parkinsonism.
31. Write on treatment of Parkinsonism.
32. Classify motor neuron sclerosis.
33. Write on diagnosis of amyotropic lateral sclerosis (ALS).
34. Write on polymyositis, dermatomyositis and inclusion body myositis.
35. Write in short about the different clinical profile of multiple sclerosis.
36. Write about diagnosis and treatment of multiple sclerosis.

SECTION III

NEPHROLOGY

- Acute Glomerulonephritis
- Nephrotic Syndrome
- Acute Renal Failure Acute Kidney Injury
- Chronic Renal Failure
- Urinary Tract Infection
- Interstitial Nephritis

Chapter 25

Acute Glomerulonephritis

INTRODUCTION

Acute Glomerulonephritis (AGN) is clinically characterized by abrupt onset of oliguria, hematuria, edema and hypertension.

The clinical spectrum may range from very mild disease which may go undetected, to severe anuria, hematuria, hypertensive encephalopathy and heart failure.

CAUSES

- **Postinfections**:
  - **Bacterial**:
    - Group A streptococci (most common)
      - » 4a, 12, 25 associated with pharyngitis
      - » 49 associated with pyoderma
    - Staphylococci
    - Pneumococci
    - *Salmonella*
    - Subacute bacterial endocarditis.
  - **Viral**:
    - Hepatitis—B and C
    - Infectious mononucleosis (EBV)
    - Human immunodeficiency virus (HIV).
- **Glomerulonephritis of undetermined etiology**:
  - Rapidly progressive glomerulonephritis (RPGN).
  - Membranoproliferative glomerulonephritis (MPGN).
- **Systemic vasculitis**:
  - Systemic lupus erythematosus (SLE)
  - Henoch-Schonlein purpura (HSP)
  - Hemolytic-uremic syndrome (HUS)
  - Polyarteritis nodosa (PAN)
  - Wegener's granulomatosis.
- **IgA nephropathy**.
- **Familial glomerulonephritis**: Alport syndrome.

POSTSTREPTOCOCCAL GLOMERULONEPHRITIS

- Poststreptococcal glomerulonephritis (PSGN) is common among the school going children >3 years.
- AGN commonly develops following group-A-β-hemolytic streptococcus infection.

- **Causes of microscopic hematuria**
  1. Benign prostatic hypertrophy
  2. Interstitial nephritis
  3. Papillary necrosis
  4. Hypercalciuria
  5. Renal stone
  6. Cystic kidney disease
  7. Vascular injury
  8. Malignancy of urinary tract
- **Causes of gross hematuria**
  1. IgA nephropathy
  2. Sickle cell disease
- **RBC cast, or dysmorphic RBC** are found in glomerulonephritis
- **Types of proteinuria**:
  1. *Glomerular proteinuria* >1 g/day
     a. Selective (MCD)
     b. Nonselective (nephrotic syndrome)
  2. *Tubular proteinuria* is due to failure of reabsorption of low molecular weight plasma protein that are normally reabsorbed and metabolized by tubular epithelium < 1 g/day. They consist of:
     a. Tamm-Horsfall protein
     b. β_2-microglobulin
  3. *Overflow proteinuria* results from filtration of low molecular weight protein usuallyimmunoglobulin-light chain (lambda) but that are present in low amount in normal plasma usually seen in massive amount in plasma cell dyscrasia.

     In overflow proteinuria, Dip stick test is negative but sulfosalicylate precipitation test is positive
  4. *Sustained proteinuria* (1–2 g/24 hour) are associated with glomerular disease
  5. *Benign proteinuria* (functional or transient proteinuria) found in:
     a. Fever
     b. Exercise
     c. Obesity
     d. Sleep apnea
     e. Emotional stress
     f. Congestive cardiac failure (CCF)
     g. Orthostatic proteinuria
  6. *Massive proteinuria* found in:
     a. MCD
     b. FSGS
     c. Mesangioproliferative glomerulonephritis

Contd...

Contd...

   d. Diabetic nephropathy. It is nonselective proteinuria and composed of albumin with mixture of other protein
7. *Selective proteinuria* (mostly albumin) seen in minimal change disease

- **Pyuria** is associated with:
  a. Acute PSGN
  b. MPGN
  c. Urinary tract infection
- **Causes of acute nephritic syndrome**
  a. PSGN
  b. SABE
  c. Lupus nephritis
  d. Antibasement membrane disease
  e. IgA nephropathy
  f. ANCA vasculitis, e.g. Wegener's vasculitis
  g. Microscopic polyangiitis, Churg-Strauss syndrome
  h. HSP
  i. Membranoproliferative glomerulonephritis
  j. Mesangioproliferative glomerulonephritis
  k. Cryoglobulineuria
- **Causes of pulmonary renal syndrome**
  a. Good pasture
  b. ANCA vasculitis
  c. HSP
  d. Cryoglobulinemia
- **Causes of basement membrane syndrome**
  a. Anti-GBM disease
  b. Alport syndrome
  c. Thin basement membrane disease
  d. Nail- patella syndrome
- **Causes of glomerular vascular syndrome**
  a. Atherosclerotic
  b. Hypertensive
  c. Cholesterol embolic
  d. Sickel cell disease
  e. Thrombotic microangiopathies
  f. APLA syndrome
  g. ANCA associated vasculitis
  h. HSP
  i. Amyloidosis
  j. Cryoglobulinemia
- **Infections causing glomerulonephritis**
  a. PSGN
  b. SABE
  c. HIV
  d. HBV
  e. HCV
  f. Syphilis
  g. Leprosy
  h. Malaria
- **Causes of nephrotic syndrome**
  a. MCD
  b. FSGS
  c. Membranous glomerulonephritis
  d. MPGN
  e. Diabetes
  f. Amyloidosis

- Boys are more commonly affected.
- Usually associated with streptococcus throat and skin infection which precedes AGN by 1–4 weeks.
- It is a typical example of immune complex disease.
- Streptococcal antigen-antibody complex is trapped in glomerular capillary where it activates complement and initiates inflammatory response.

PATHOLOGY

The disease is actually termed as **acute diffuse proliferative glomerulonephritis**. Hence, it is characterized by:

- Diffuse (> 50% glomeruli involvement) proliferation and marked hypercellularity of the glomeruli with occlusion of capillary loop.
- Initial hypercellularity is due to neutrophil infiltration.
  - Proliferation involves mesangial and endothelial cell with infiltration of neutrophil in capillary lumen.
  - Occasional epithelial cell proliferation which may be extensive, forming crescents, could be seen.
- Immunofluorescent study shows granular deposit of IgG, IgM and C_3.
- EM study shows subepithelial electron dense 'lumpy' deposit.

CLINICAL FEATURES

- **Age**: Commonly children between **3–12 years**.
- The disease usually starts with **periorbital puffiness** with **oliguria** and **hematuria**. As the disease progresses **edema** and **hypertension** appear.
- Pleural effusion and ascites are uncommon.
- Degree of oliguria, correlates with the severity of the disease and may progress to acute renal failure (ARF).
- Urine is usually **reddish-brown (smoky)**.
- May present as **hypertensive encephalopathy or acute congestive cardiac failure (CCF)**.

DIFFERENTIAL DIAGNOSIS

Many primary and secondary glomerular diseases may present for first time as AGN—however history, clinical findings and course will help in differentiating PSGN from other progressive diseases like **RPGN** and **MPGN**.

Persistence of **microscopic hematuria, hypertension, nephrotic range proteinuria for > 4 weeks with progressive renal failure** suggests the later situations.

LABORATORY INVESTIGATIONS

- **Urine**:
  - Proteinuria 1^+ to 2^+
  - RBC/RBC cast and granular cast
  - WBC—indicative of glomerular inflammation.
- **Blood**—
  - Normocytic anemia—due to hemodilution.
  - Raised ESR.

- **Elevated urea, creatinine**—depends on the degree of renal impairment and oliguria.
- **Hyponatremia and hyperkalemia**—due to continued oliguria and hemodilution.
- **Complement level**—Level of serum C_3 and total hemolytic complement (CH–50) is low in 1st week.

In 90% of cases C_3 level returns to normal within 5–6 weeks. Persistent low level of C_3 indicate other form of GN (glomerulonephritis). Normal C_4 level.

- **Throat swab**—Culture may rarely show β-hemolytic streptococcus (40%).
- **Serology**—The following antibodies are present in PSGN.
  - ASO (30%)
  - Anti-DNAase (40%)
  - Antihyaluronidase (40%)
  - Rheumatoid factor (35%)

  } Rising titer is more convincing evidence of recent streptococcus infection
  - Cryoglobulin and circulating immunocomplex (65%).
  - ANCA against myeloperoxidase (10%).
- **X-ray chest**—Increased vascular marking suggestive of hypervolemia.
- **Renal biopsy**—Rarely indicated in PSGN.

  Indications are but
  - Severely impaired renal function for 2 weeks
  - Decrease of serum C_3 level for > 6–7 weeks
  - Persistence of hypertension and hematuria for > 3 weeks
  - Features of systemic illness—rash, petechiae and hepatomegaly
  - Absence of elevated (anti-streptolysin O).
  - Age < 2 years.

MANAGEMENT

- Treatment of mild oliguria with normal BP can be done at home but anuria, hypertension, CCF and hypertensive encepha- lopathy hematuria is best managed at hospital settings.

A. General Management

- **Rest**—Absolute bed rest is not essential.
- **Penicillin** (for 10 days)—To eradicate skin/throat infection and to prevent community spread.
- **Diet**
  - Protein restricted to 0.6 g/kg/day.
  - Water restriction (500 mL + urine volume of previous 24 hours).
  - Salt (if severe hypertension and volume overload is present) should be restricted to <2 g/day.
- **Body weight**—Should be weighed daily.
  - Patient should loose 0.5% of body weight per day. A gain in weight suggests more severe fluid restriction is required

B. Specific Management

- **Diuretic**
  - Not indicated if edema is not massive which gradually disappears with return of renal function. [If diuretic has to be given—loop diuretic should be used but never spironolactone—for fear of hyperkalemia due to ARF in AGN].
  - In presence of severe volume overload and pulmonary edema IV frusemide (2–4 mg/kg/day) and if not controlled then dialysis.
- **Hypertension**
  - To be treated with antihypertensive like **calcium channel blocker/β-blockers** —If there is severe hypertension presenting as hypertensive encephalopathy or acute congestive cardiac failure.
  - Malignant hypertension should be managed by IV labetalol or nitroprusside.
- **Left ventricular failure**
  - **Frusemide IV** (2–4 mg/kg/day).
  - Venesection with removal of 100–200 mL of blood or rotating trourniquet to reduce venous return.
  - Respiratory support with positive end-expiratory pressure.
- **Prolonged oliguria**
  - **Dialysis** is often required in children with severe renal failure and prolong oliguria with fluid overload and electrolyte disturbances.

PROGNOSIS

- **PSGN patient usually have**:
  - Excellent prognosis.
  - Subsidence of edema and fall of BP with return of urine voloume within 7–14 days occurs in 95% patients.
- Microscopic hematuria, slight proteinuria may persist for several months and is of no significance.
- AGN with nonstreptococcal etiology have a variable and unpredictable outcome should be closely followed with regular checkup of BP, blood, urine. Kidney biopsy is usually necessary. It is to be managed according to etiology.

COMPLICATIONS

1. Acute renal failure (ARF)
2. Congestive cardiac failure (CCF)

3. Hypertensive encephalopathy
4. Pulmonary edema.

EXERCISE

Write short notes on

1. Causes of hematuria
2. Causes of proteinuria
3. Causes of pyuria
4. Causes of nephritic syndrome
5. Causes of nephrotic syndrome
6. Causes of pulmonary renal syndrome
7. Causes of basement membrane syndrome
8. Causes of glomerular vascular syndrome
9. Clinical features of PSGN
10. Management of PSGN.

Chapter 26

Nephrotic Syndrome

INTRODUCTION

Nephrotic syndrome (NS) is a clinical syndrome complex characterized by **massive proteinuria** [greater than 3.5 g/1.73 m^2/24 hours (3–3.5 g/day)] with **hypoalbuminemia, edema, hyperlipidemia, lipiduria** and **hypercoagulability**.

ETIOLOGY

- **Primary/idiopathic (90%)**
  - Minimal change disease (MCD)
  - Focal segmental glomerulosclerosis (FSGS)
  - Membranous glomerulopathy (MGN)
  - Membranoproliferative GN (MPGN).
- **Secondary**—
  - Infection—Endocarditis, malaria, syphilis, Hep-B, leprosy and HIV.
  - Connective tissue dissease—SLE and RA.
  - Neoplasm—Hodgkin's lymphoma, NHL, leukemia, carcinoma of lung, breast and ovary.
  - Drugs—Penicillamine, captopril, gold and mercury.
  - Metabolic—DM and amyloidosis.
- **Congenital**—
  - Alport syndrome.

Table 26.1: Urine assay for albumin/protein

	24 hour albumin	24 hour protein	Albumin: Creatinine ratio
Normal	8–10 mg	<150 mg	<30
Micro albuminuria	50–150 mg	150–300 mg	30–300
Proteinuria	>150 mg	>300 mg	>300

PATHOGENESIS

Proteinuria results from increased permeability of glomerular filtration barrier for protein (namely GBM, podocyte and their slit diaphragm).

Other components of the nephrotic syndrome and the ensuing metabolic complications are all secondary to urinary protein loss and may or may not occur in spite of proteinuria.

MAJOR METABOLIC COMPLICATIONS

- Hypoalbuminemia *is due to*:
  - Proteinuria
  - Increased renal catabolism of protein.
- **Edema**—It is due to hypoalbuminemia, which results in decreased intravascular oncotic pressure, leading to leakage of intravascular fluid into interstitium. As a result intravascular fluid volume falls which causes:
  - Activation of RAAS
  - Activation of sympathetic nervous system
  - Release of vasopressin
  - Suppression of ANP.

  This neural and hormonal response, promote renal salt water retention restoring intravascular volume triggering further leakage of fluid into interstitium.
- Hyperlipidemia *is multifactorial in origin and is due to*:
  - Increased hepatic lipoprotein synthesis triggered by decreased oncotic pressure.
  - Increased urinary loss a protein which regulates lipid homeostasis.
  - Sympathetic overactivity leads to defective lipid catabolism (TC and LDL will increase in majority of cases whereas TG and VLDL will rise in severe disease) hyperlipidemia leads to accentuated atherosclerosis which causes progression of renal disease.
- **Hypercoagulability** is multifactorial in origin. It is due to:
  - Increased urinary loss of antithrombin-III.
  - Altered level/activity of protein-c and protein-s.
  - Hyperfibrinogenemia is due to increased hepatic synthesis of fibrinogen.

- Impaired fibrinolysis.
- Increased platelet aggregation.

All these above-mentioned factors are responsible for hypercoagulability.

- **Thromboembolic complication**—It leads to peripheral arterial and (superficial and deep) venous thrombosis usually presents with—
  - Pulmonary embolism.
  - Renal vein thrombosis.
  - **Particularly seen (~ 40%) in membranous** glomerulonephritis, membranoproliferative glomerulonephritis and amyloidosis.

Clinical features of acute renal vein thrombosis seen in nephrotic syndrome.
- Sudden onset flank pain
- Gross hematuria
- Acute increase in proteinuria
- Acute decrease in GFR
- Left-sided vericocele in case of left testicular vein thrombosis

MINOR METABOLIC COMPLICATIONS

- Iron-resistant microcytic hypochromic anemia is due to urinary transferrin loss.
- Hypocalcemia and secondary hyperparathyroidism is due to vitamin D deficiency which results from urinary loss of cholecalciferol binding protein.
- Low thyroxine level is due to loss of thyroxine binding globulin.
- Increased susceptibility to infection is due to urinary loss of IgG and their increased catabolism.

CLINICAL FEATURES

It is common in child of 1–10 years of age.

- **Pedal edema**—Usually with ascites and hydrothorax (anasarca) and facial puffiness.
- **BP**—Usually normal but may be elevated.
- **Signs of infection**—Especially spontaneous bacterial peritonitis may be present.

Features of Complication

- **Infection** due to urinary loss and increased catabolism of IgG.
- **Thromboembolic** complication—Renal vein thrombosis, pulmonary embolism and leg vein thrombosis.
- **Oliguria** and ARF.

Rarely

- **Anemia**.
- Features of **hypocalcemia** like tetany may be present.
- Features of **hypothyroidism**.
- Features of **steroid overdose** (iatrogenic): Cushingoid features, osteoporosis, subcapsular cataract, short stretcher and hypertension occasionally present.

INVESTIGATION

- **Urine**
  - Routine examination of urine for quantification of proteinuria and demonstration of fatty cast, hyaline cast and granular cast.
  - Urine culture sensitivity in case of concomittent UTI.
  - 24-hour urinary protein estimation (Table 26.1).
  - Test for selectivity of protein loss (IgG:transferrin ratio).
- **Blood**
  - Routine examination of blood
  - Total protein with albumin-globulin ratio
  - Serum lipid profile
  - Serum urea and creatinine
  - Serum, Na^+, K^+, Ca^{++} and Po_4^{--}.
- **Serum immune electrophoresis** for IgG, IgM and compliment estimation.
- **Kidney biopsy**—Usually not indicated in uncomplicated nephrotic syndrome (NS) but to be done when nephrotic syndrome is associated with the following conditions—
  - Age of onset of nephrotic syndrome <1 year >10 years.
  - Kidney biopsy is also indicated when nephrotic syndrome is associated with hematuria, hypertension, impaired renal function, low compliment C_3 level, not responding to usual therapy, with frequent relapse and steroid dependance, before starting cyclosporine therapy.

MANAGEMENT

- **General Management**
  - High protein diet.
  - Infection in nephrotic syndrome to be treated with appropriate antimicrobial.
  - Diuretic in nephrotic syndrome is indicated only when ascites impede diaphragmatic movement. Frusemide 40–80 mg/day with aldosterone antagonist (spironolactone, triamterine and amiloride) rapid loss of fluid should not be attempted.
  - Statin therapy—For hypercholesterolemia.
  - No role of prophylactic anticoagulation in NS.
- **Specific Treatment**
- Before starting specific treatment of tuberculosis and UTI to be excluded by proper investigation.
  - Classical nephrotic syndrome to be treated by:
    - 1st episode—**Prednisolone** 2 mg/kg/day × 6 weeks, then 1.5 mg/kg on alternate day × 6 weeks.

– For 2nd and 3rd relapse—**Prednisolone** 2 mg/ kg/ day × 2 weeks followed by 1.5 mg/kg/on alternate day × 6 weeks.

Before stopping steroid urine should be protein-free on three occasion.

For frequent relapse and steroid dependance.

- **Prednisolone**—0.3–0.7 mg/kg × 9–12 months.
- **Levamisole**—2–2.5 mg/kg + prednisolone 1.5 mg/kg on alternate day × 1–2 years. Prednisolone may be tapered or discontinue.
- **Cyclophosphamide**—2 mg/kg/day + prednisolone 1.5 mg/kg on alternate day × 12 weeks.
- **Ciclosporin**—5 mg/kg/day + prednisolone 1–1.5 mg/kg on alternate day for 1–3 years.

Alkylating agents are reserved for patient

- Who failed to achieve remission.
- Relapse during/shortly after withdrawal of steroid (steriod-dependent).
- Relapse > 3 times/year.

Side effects of cyclophosphamide and chlorambucil

1. Infertility
2. Hemorrhagic cystitis
3. Alopecia
4. Infection
5. Secondary malignancy

Frequent relapse—Four or more relapse per year.

Infrequent relapse—Three or less relapse per year.

Steroid-dependent—Remission phase lasts only when steroid is continued and relapse occurs whenever steroid dose is reduced or withdrawn.

Steroid-resistant—Either does not respond to initial treatment or do so transiently.

COMPLICATIONS OF NEPHROTIC SYNDROME

1. Spontaneous bacterial peritonitis
2. Pneumococcal septicemia
3. Renal vein thrombosis
4. Deep vein thrombosis of leg
5. Thromboembolism of mesenteric artery.

MINIMAL CHANGE DISEASE

Silent features of minimal change disease (MCD)

- MCD is responsible for 80% of NS patients in children < 16 years.
- MCD is responsible for 20% of adult (nephrotic syndrome).
- Peak incidence at 6–8 years of age.
- Patients usually present with edema with benign urinary sediment but 20–30% patients have microscopic hematuria.
- Hypertension and renal insufficiency are very rare.
- Light microscopy shows no change (so-called minimal change disease).
- Immunofluorescence shows no immunoglobulin deposit/C_3. Occasional messengial hypercellularity.
- EM stydy shows **diffuse effacement of foot process of visceral epithelial cell (foot process fusion)**.

ETIOLOGY

Exact etiology not known. Common association are:

- URTI
- Immunization
- Atopic subject (HLA B_{12})
- Rarely NSAID and α-interferon.
- Hodgkin's disease.

Selective proteinuria which is usually seen in children composed of albumin and minimal HMW IgG. In conjunction with foot process effacement and loss of fixed negative charge in glomerular filtration barrier are responsible for increased permeability of basement membrane which is probably due to cytokine related to T-cell response.

Proteinuria is nonselective in adult suggesting more extensive damage of membrane permeability in adult.

COURSE AND PROGNOSIS

- Spontaneous remission occurs in 30–40% child which is less common in adult.
- About 90% of child and 50% of adult enter remission following 8 weeks of high dose glucocorticoids.
- Up to 90% of adult enters remission if therapy is extended to 20–24 weeks.
- In 50% of cases—relapse occurs following withdrawal of glucocorticoids.

MANAGEMENT

- **General management**
  Same as management of nephrotic syndrome.
- **Specific management**
  Same as management of nephrotic syndrome.

Complications of long-term steroid therapy

1. Stunted growth
2. GI hemorrhage and gastritis
3. Osteoporosis and pathological fracture
4. Posterior subcapsular opacity of lens
5. Glaucoma
6. Cushingoid feature
7. Diabetes
8. Hypertension and encephalopathy
9. Flairing of infection—TB, chickenpox and pneumococcal septicemia
10. Steroid psychosis
11. Steroid myopathy
12. HP axis suppression

FOCAL SEGMENTAL GLOMERULOSCLEROSIS

Sclerosis with hyalinosis involving a segment of the glomerulas (segmental) and fewer than 50% (focal) of glomeruli in a tissue section is called focal segmental glomerulosclerosis (FSGS).

The pathological changes are predominantly located at corticomedullary junction.

- FSGS accounts for 33% of nephrotic syndrome in adult and 50% of nephrotic syndrome in black.
- FSGS can complicate a number of systemic disease and sustained glomerular capillary hypertension due to nephron loss from any cause.

PATHOGENESIS

- T-cell-mediated circulating permeability factor.
- TGF β-mediated cellular proliferation and matrix systhesis.
- Genetic mutation-mediated podocyte abnormality is probably responsible for pathogenesis.

ETIOLOGY

- Idiopathic FSGS (66%).
- Secondary FSGS due to
  - HIV, HBV and parvovirus
  - Hypertensive nephropathy
  - Drugs—Heroin, pamidronate and analgesic
  - Sickle cell nephropathy
  - Lymphoma
  - Radiation nephritis
  - Charcot-Marie-Tooth disease.
- FSGS can also develop as a consequence of sustain glomerular hypertension in
  - Congenital oligonephropathy
  - Unilateral renal agenesis
  - Oligomeganephronemia
  - Surgical resection
  - Reflux nephropathy
  - Alport syndrome
  - Tubulointerstitial nephritis.

CLINICAL FEATURES

- **Idiopathic FSGS (66%)**
  Initially presents with:
  - Nonselective proteinuria (any level of proteinuria).
  - Hypertension.
  - Renal insufficiency.
  - Hematuria with abnormal urinary sediment— RBC and pus cell.

TREATMENT

- Spontaneous remission is rare.
- Renal prognosis is poor.
- Primary FSGS should be treated with renin angiotension system (RAAS) blocker.
- Uncontrolled study suggests remission of nephrotic range of proteinuria up to 35% may be achieved by glucocorticoid therapy for 24–36 weeks.
- Cyclosporine induce partial/complete remission can be achieved in 50–60% of steroid responsive patient but relapse frequently occurs after withdrawal of cyclosporine.
- **Renal transplantation** is complicated with recurrence in 35% cases and graft loss in10% cases.
- **Poor prognostic marker are**:
  - Renal insufficiency at the onset
  - Black race
  - Persistence of heavy proteinuria.
- 50% develop renal failure within 6–8 years.
- **Chance of recurrence is high in patient**:
  - With short time interval between development of NS and ESRD.
  - Young age.
  - Mesengial hypercellularity.

MEMBRANOUS GLOMERULONEPHRITIS

Membranous glomerulonephritis (MGN) accounts for 30% nephrotic syndrome in adult.

It is characterize morphologically by subepithelial immunoglobulin containing deposit along the GBM.

ETIOLOGY

- Idiopathic MGN (66%)
- Secondary MGN (33%)
  - Peak incidence at 30–50 years of age
  - Male—Female ratio = 2:1.

ETIOLOGY OF SECONDARY MGN

- **Infection**—Hepatitis B, syphilis, schistosomiasis, leprosy, malaria and filaria.
- **Malignant tumors**—(25–30%) carcinoma of lung, breast, colon, stomach, kidney and lymphoma.
- **SLE and other autoimmune diseases**.
- **Drugs**—Penicillamine, gold, Hg and NSAID probenecid.

PATHOGENESIS

- **Idiopathic MGN:** Antibodies against M-type phosphate A_2 receptor (PLA_2R) circulate and bind to receptor on human podocyte is responsible for idiopathic MGN.
- **Secondary MGN:** Due to in situ formation of immune complex against neutral endopeptidase expressed by podocyte, HBV/HCV, *H. pylori* and tumor antigen.
- **Light microscope shows** diffuse thickening of GBM along the peripheral capillary loop.
- **Electron microscope shows** subepithelial electron dense deposit against GBM and they are separated from

each other by small spike-like protrusion of GBM matrix which later on close over the deposit incorporating them into GBM.
- **Immunofluorescence** shows typical granular deposit of IgG and complement (C_3) along GBM.

CLINICAL FEATURES OF MGN

- Principal mode presentation is nephrotic syndrome (80%).
- Microscopic hematuria seen in 50%.
- It may present, with acute nephritic syndrome.
- Rarely it may begin with mild proteinuria.
  - Onset is insiduous in idiopathic variety without antecedent illness and the proteinuria initially may not be in nephrotic range and nonselective in nature. Features of oliguria and uremia develop later.
  - It is necessary in all patients to rule out the secondary cause first.

COURSE AND PROGNOSIS

- Spontaneous remission occurs in 33%.
- In 33% patients, relapse and remission are seen without decline in renal function.
- Another 1/3rd die either due to renal failure or from complications of nephrotic syndrome.
- **Bad prognostic marker**:
  - Male gender
  - Elderly age group
  - Hypertension
  - Severe proteinuria.

TREATMENT

- Treatment of edema—Diuretics.
- Treatment of dyslipidemia—Statin.
- Treatment of hypertension—CCB, ACEI and β- blocker.
- Inhibitor of RAAS blocker.
- Glucocorticoids fails to show consistent improvement in proteinuria and renal protection.
- **Cyclophosphamide, chlorambucil, cyclosporine and mycophenolate mofetil** each has shown to reduce the proteinuria and/or slow the decline in GFR in patients with progressive disease.
- Nonresponders to above drug are treated with **Rituximab (an anti-CD 20 antibody) with glucocorticoid**.
- Renal transplant is a successful treatment option.

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

- **Silent features in MPGN**
  - Membranoproliferative (MPGN) accounts for 5–10% of idiopathic nephrotic syndrome in children and adults.
  - Some patients present with hematuria and proteinuria in subnephrotic range and other have combined nephrotic-nephritic picture.
  - They are manifested histologically by alteration in basement membrane and mesangium and proliferation of glomerular cells.

Etiology

- Type–I (most common)
  - Idiopathic
  - (a) SABE, (b) HCV, (c) SLE, (d) cryoglobulinemia, (e) HBV and (f) carcinoma of lung, breast and ovary.
- Type–II (dense deposit)
  - Idiopathic
  - C_3-nephritic factor associated partial lipodystrophy.
- Type–III
  - Idiopathic
  - Complement receptor deficiency.

PATHOLOGY

- **Type–I**—Proliferation and interposition of mesangium in between endothelium and basement membrane producing trams-track appearance. It is due to circulating or in situ formation of immune complex.
- **Type–II**—Low serum complement (C_3) with dense thickening of GBM containing ribbon of dense deposit and C_3 is characteristic of Type–II disease.
- **Type–III**—Subepithelial laminated and dispersed deposit with rare mesangial proliferation.

Type–II and III are due to nephritic factor which are antibodies that stabilizes C_3 convertase and allowes it to activate serum C_3.

CLINICAL FEATURES

- Fatigue and malaise more common in children.
- Proteinuria, hematuria and pyuria seen in 30% patient.
- Acute nephritic picture with RPGN and rapid deterioration of renal function seen in 25% patient.
- Serum complement is low.

PROGNOSIS

- About 50% develop ESRD by 10 years.
- About 90% have renal insufficiency by 20 years.
- Nephrotic syndrome, hypertension and renal insufficiency are poor prognostic parameter.

TREATMENT

- Inhibitors of renin-angiotensin-aldosterone axis.
- For primary or idiopathic MPGN in children— Steroid, plasma exchange and immunosuppressive drugs are effective.

- In secondary MPGN—Treatment of primary disease, e.g. peginterferon and ribavirin for HCV and appropriate treatment of carcinoma, e.g. SABE, SLE.
- Warfarin and dipyredamol—not very effective.
- Renal transplant—recurrence of disease is very common.

IMMUNOGLOBULIN A NEPHROPATHY (BERGER'S DISEASES)

Immunoglobulin A nephropathy (IgAN) is the most common glomerulopathy worldwide and accounts for 10–40% glomerulonephritis in most cases.

Common in southern Europe and Asia, more common in Black than White. Male > Female.

The renal and serological abnormality in IgA nephropathy and Henoch-Schönlein purpura are indistinguishable. Most authorities consider these two as a spectrum of same disease.

Less commonly IgA nephropathy is found in association with systemic disease like chronic liver disease, Crohn's disease, gastrointestinal adenocarcinoma, chronic obstructive bronchiolitis and idiopathic interstitial pneumonia, dermatitis herpitiformis, mycosis fungoides, leprosy, ankylosing spondylitis and Sjögren's syndrome.

In many of these conditions IgA is deposited in the glomeruli without inducing inflammation.

CLINICAL FEATURES

- **Gross hematuria**—Often 24–48 hours after:
  - Pharyngeal and gastrointestinal infection
  - Vaccination
  - *Strenuous* exercise.
- **Hypertension** present in 20–30% of patients.
- **Nephrotic syndrome** present in 10% of patient.

RENAL BIOPSY

- Mesangial expansion by increased matrix and cell.
- Diffuse epithelial proliferation leading to cellular crescent, interstitial inflammation and areas of glomerular sclerosis.
- Mesangial deposit is composed of IgA, C_3 and occasionally IgG.
- electron microscopy study shows electron-dense deposit in mesangium, paramesangium and subendothelial space.

PATHOGENESIS

- Incompletely understood but probably due to:
  - Increase production of IgA.
  - Abnormal glycosylation of IgA.
  - Impaired clearance of IgA is responsible for IGA nephropathy.

Although, IgA nephropathy is associated with altered mucosal defence, most IgA deposit in kidney are derived from bone marrow cell.

TREATMENT

- Wait and watch policy till GFR is not compromised and proteinuria <1 g/day.
- **ACE inhibitors**—For renoprotection with more severe disease.
- **Glucocorticoid** (high dose)—For 6 months when GFR is impaired and proteinuria >1 g/day.
- **Cyclophosphamide and mycophenolate mofetil** are reserved for patients presenting with nephritic syndrome, RPGN, aggressive crescent formation and marked glomerular inflammation on kidney biopsy.

COURSE AND PROGNOSIS

In patient presenting with nephritic syndrome, RPGN, aggressive crescent formation and marked glomerular inflammation on kidney biopsy, the disease typically smolder for decades with often exacerbation of hematuria and renal impairment during intercurrent infection.

20–50% patients develop ESRD within 20 years.

- **Poor prognostic parameters are**:
  - Older age.
  - Male sex.
  - Hypertension.
  - Nephrotic range proteinuria.
  - Renal insufficiency at presentation.
  - Crescent, immune attack into subendothelial space, glomerulosclerosis, interstitial fibrosis and arteriolar hyalinosis.

EXERCISE

Write short notes on

1. Definition and etiology of nephrotic syndrome (NS).
2. Major and minor metabolic complication of NS.
3. Management of NS.
4. Complications of NS.
5. FSGS, MGN, MPGN and IGA nephropathy.

Chapter 27

Acute Renal Failure/Acute Kidney Injury

INTRODUCTION

Acute renal failure (ARF) is a syndrome characterized by rapid decline in GFR (within hours to days) with retension of nitrogenous waste product in the body.

TYPES OF ACUTE RENAL FAILURE

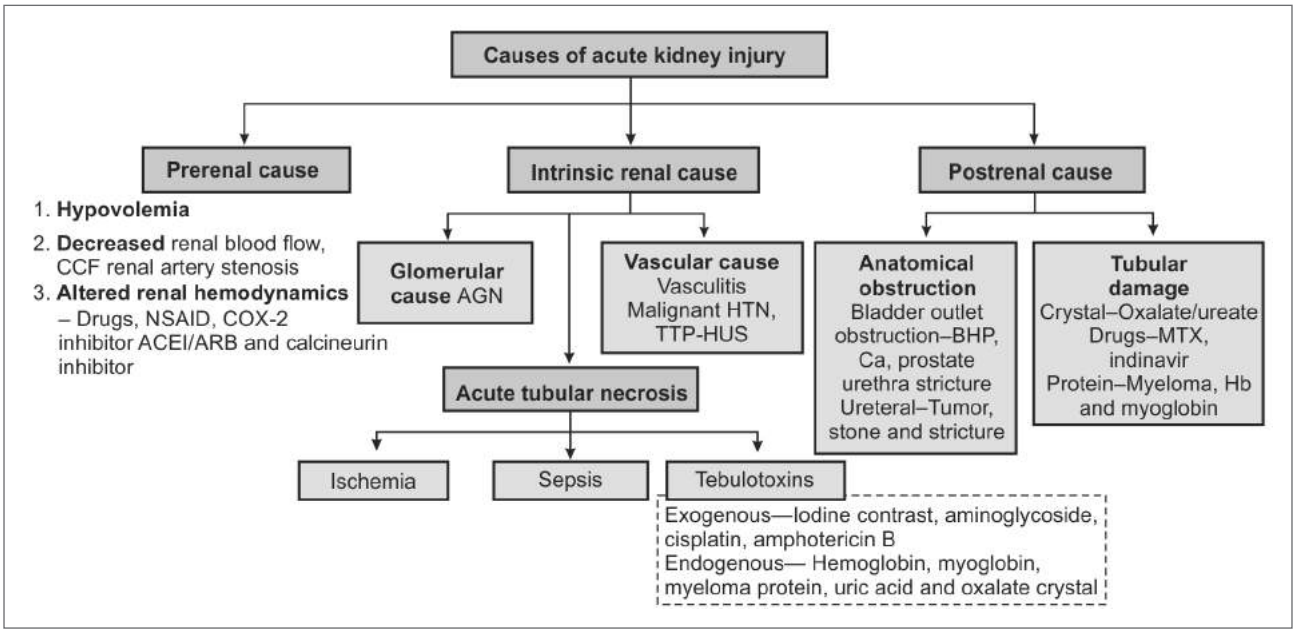
- Prerenal ARF
- Intrinsic renal ARF
- Postrenal ARF.

CAUSES OF ACUTE RENAL FAILURE (TABLE 27.1 AND FLOWCHART 27.1)

- **Causes of prerenal ARF**
  - **Hypovolemia**
    - Hemorrhage
    - Burn
    - Dehydration
    - Gastrointestinal (GI) fluid loss
    - Renal fluid loss
    - Sequestration (acute pancreatitis).
  - **Low cardiac output**
    - Acute myocardial infarction (AMI)
    - Arrhythmia
    - Pulmonary embolism.
  - **Impaired renal autoregulation**
    - Systemic vasodilation caused by:
      - » Anesthesia
      - » Anaphylaxis
      - » Sepsis
      - » ACE–I.
    - Renal vasoconstriction by:
      - » Hypocalcemia
      - » Epinephrine, norepinephrine
      - » Amphotericin–B
      - » Cyclosporine
      - » Hepatorenal syndrome
      - » NSAID
      - » ACE–I.
- **Causes of intrinsic renal ARF**
  - **Renal artery obstruction** by atherosclerotic, plaque, thrombosis, embolism, vasculitis.
  - **Renal vein obstruction** by thrombosis/compression.
  - **Disease of the glomeruli and renal microvasculature**:
    - Glomerulonephritis and vasculitis.
    - Secondary diseases—Hemolytic uremic syndrome
    - (HUS), Thrombotic thrombocytopenic purpura (TTP), Disseminated intravascular coagulation (DIC), Systemic lupus erythematosus (SLE), Progressive systemic sclerosis (PSS), toxemia of pregnancy and malignant HTN.
  - **Causes of acute tubular necrosis (ATN)**
    - **Ischemic causes of ATN**—Causes are same as prerenal ARF.

      Due to vasoconstriction of efferent arteriole in severe hypovolemia leads to severe decrease in blood supply to tubular cells.
    - **Nephrotoxic substance causing ATN**
      - » *Exogenous*—Radiocontrast dye, aminoglycoside, paracetamol, solvent like ethylene glycol, cyclosporine and cisplatin.
      - » *Endogenous*—Myoglobin, hemoglobin, uric acid, oxalate and myeloma protein.
  - **Interstitial nephritis**—Responsible for ATN
    - *Allergic causes*:
      - » β-lactam and sulfonamide
      - » Trimethoprim and rifampicin
      - » NSAID and captopril.
    - *Infections*:
      - » Pyelonephritis
      - » Leptospirosis
      - » CMV
      - » Candida.
    - *Idiopathic*
    - *Infiltration*:
      - » Lymphoma
      - » Leukemia
      - » Sarcoidosis.
  - **Renal allograft rejection**.

Flowchart 27.1: Etiology of acute kidney injury



Flowchart 27.2: Pathogenesis of ischemic acute renal failure

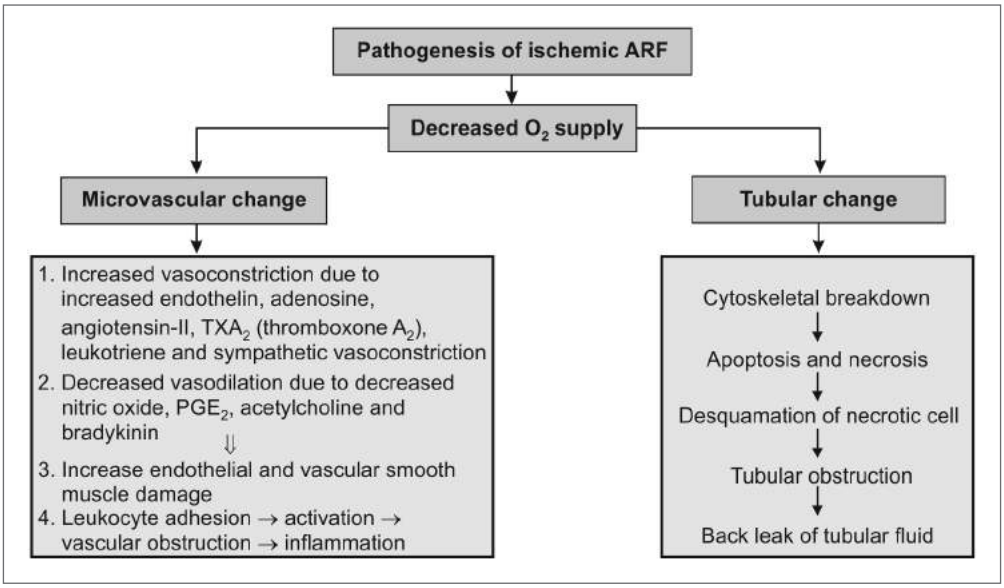


Table 27.1: Causes of postrenal acute renal failure/acute kidney injury

Ureteric obstruction	Bladder neck obstruction	Urethra obstruction
• Calculi	• Neurogenic bladder	• Stricture
• Clot	• BHP	• Valve
• Sloughed papilla	• Calculi	• Phymosis
• Cancer	• CA prostate	
• External compression	• Clot	
• Retroperitoneal fibrosis		

STAGES OF ARF

- Initiation phase of ischemic ARF
- Maintenance phase of ischemic ARF
- Recovery phase of ischemic ARF.

CLINICAL FEATURES OF ARF

History

Suggestive of the following condition to be searched for:

- Past history of treatment with NSAID, ACEI, radio contrast material, trimethoprim, aminoglycoside and cyclosporin.

- Stigma of chronic liver disease and portal hypertension.
- History of advance cardiac failure and acelerated HTN.
- History of sepsis, pancreatitis, diarrhea and anesthesia.
- History of crush injury.
- History of hemorrhage, burn and hemolysis.
- Hyperuricemia and use of uricosuric agent.
- History suggestive of multiple myeloma.
- Elevated serum Ca^{+2}.

Symptoms

- Oliguria (urine output < 500 mL/day). But oliguria may not be always present.
  - Increase thirst
  - Orthostatic dizziness and hypotension
  - Tachycardia
  - Decreased skin turgor
  - Dry mucous membrane
  - Reduced sweating in axilla
  - Reduced jugular venous pressure.

Signs

- Flank pain is due to:
  - Renal artery/vein occlusion.
  - AGN produce pain by distending the renal capsule.
  - Pyelonephritis and obstructive uropathy can produce pain.
- Subcutaneous nodule, Livido reticularis } Suggest SLE
- Bright orange retinal artereolar plague
- Digital ischemia—Indicates atheroembolism as a cause for ARF.
  - ARF with oliguria, hypertension, edema and active urinary sediment indicate AGN or vasculitis.
  - Very high BP in malignant HTN can cause ARF which is associated with LVH/LVF/papilledema/neurologic dysfunction.
  - Fever, arthralgia and pruritus following some drugs may cause allergic interstitial nephritis.

SPECIAL POINTS OF POSTRENAL ARF

- Suprapubic and flank pain is a feature of distention of bladder or renal pelvis and capsule.
- Colicky pain radiating to groin suggests ureteric cotic due to obstruction.
- Prostatic disease is suggested by nocturia, frequency, hesitancy, difficulty in initiation, narrow stream and confirmed by rectal examination of prostate or USG of kidney ureter bladder prostate (KUBP).
- Neurogenic bladder is caused by anticholinergic drugs, autonomic dysfunction and paraplegia due to spinal cord injury.

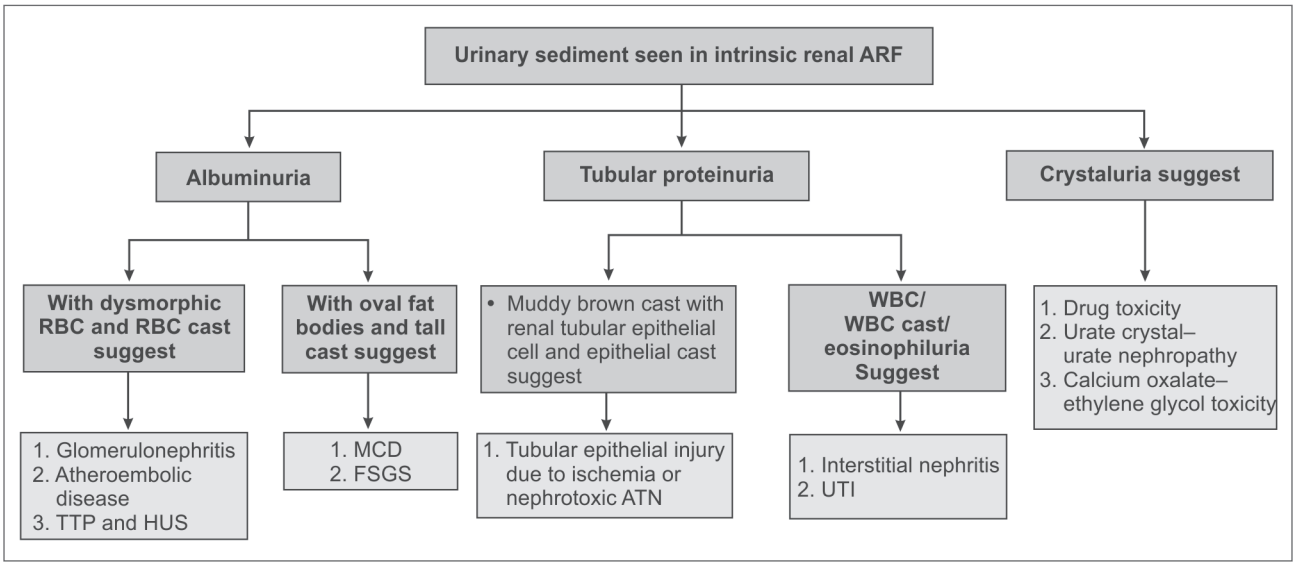
LABORATORY DIAGNOSIS

- **Urine (Flowchart 27.3)**—

Cliical features of uriene
- Oliguria—< 400 mL urine/day (Anuria—Complete suppresion of urine)
- Polyuria or wide fluctuation in urine volume suggest intermittent obstruction
- Reduction of urine output <0.5 mL/kg/hour for 24–48 hours is diagnostic of ARF

  - **In prerenal ARF**
    - Bland or benign or inactive urinary sediment.
    - Acellular or hyaline cast may be seen.
  - **In postrenal ARF**
    - May be associated with inactive urinary sediment.
    - Active urinary sediment or hematuria or pyuria may be seen which suggests intraluminal obstruction or prostatic disease.
  - **In intrinsic renal ARF**
    - **In ischemic ATN:** Pigmented muddy brown urine with granular cast containing tubular epithelial cells usually with microscopic hematuria and mild proteinuria (<1 g/day).
    - **Cast may be absent** in 20–30% of ischemic or nephrotoxic ATN.
    - **In interstitial fibrosis** and **CRF** broad cast may be seen.
    - **In microvasculature** affection and acute tubulointerstitial nephritis—RBC cast may be seen.
    - **In interstitial nephritis**—WBC cast may be seen.
    - Lymphocyturia indicates allergic interstitial nephritis induced by NSAID.
    - **Eosinophiluria** (>5% of urinary WBC) indicates antibiotic-induced allergic interstitial nephritis and atheroembolic ARF.
    - **Uric acid crystal** indicates acute urate nephropathy.
    - **Hippurate** (needle-shaped crystal), **oxalate** (envelope-shaped crystal) suggest ethylene glycol toxicity.
    - **In hemoglobinuria and myoglobinuria** supernatant of centrifused urine becomes strongly positive for free heme.
    - No set of test can rule out ARF superimposed on CRF. Serial blood test showing continued substantial rise of serum creatinine is a clear evidence of ARF.
- **Serum creatinine**—Elevation of serum creatinine at least 0.3 mg/dL or 50% higher than baseline within 24–48 hours is suggestive ARF.
  - In prerenal azotemia—There is moderate rise in serum creatinine which returns to baseline with improvement in hemodynamic status.

Flowchart. 27.3: Etiological diagnosis of ARF from uninary sediment



  - Contrast nephropathy causes rise in serum creatinine which peaks within 3–5 days and returns to baseline within 5–7 days
  - Aminoglycoside and cisplatin cause rise in serum creatinine after 4–5 days to 2 weeks after exposure
- AGN and vasculitis are associated with low complement, high titer of ANA, ANCA, Anti-GBM antibody and cryoglobulin.
- In USG following features are suggestive of postrenal ARF:
  - Hydronephrosis
  - Hydroureter
  - Prostatomegaly
  - Increase in postvoid RUV (residual urine volume).

COMPLICATIONS

- **Expansion of ECF** volume leads to:
  - Edema
  - CCF
  - Seizure
  - Neurological symptom.

  } due to cerebral edema
- **Hyperkalemia**: Causes of massive increase in potassium level are rhabdomyolysis, hemolysis and tumor lysis syndrome.

ECG features of hyperkalemia
- Tall peaked T-wave (earliest change)
- Prolonged PR interval due to AV conduction delay
- Absence of P
- Prolonged QRS duration
- Progressive widening of QRS merging with T-wave producing SINE-WAVE pattern

- **Acidosis**—Metabolism of dietary protein creates 50–100 mmole of nonvolatile acid (hippurate, phosphate, sulphate and urate) which produce increase in anion gap acidosis. Normal anion gap acidosis suggests multiple myeloma due to cationic protein.
- **Hyperphosphatemia**—Mild degree of hyperphosphatemia is always present. But it may be severe in rhabdomyolysis, hemolysis and tumor lysis syndrome.
- **Hypocalcemia**—It occurs when the product of serum Ca^{+2} (mg%) and PO^{-3} (mg/dL) exceeds 60. It is the main cause of hypocalcemia which also occur due to increased resistance to PTH and decreased DHCC (dihydroxycholecalciferol).

Clinical features of hypocalcemia
- Perioral paresthesia
- Muscle cramp, carpopedal spasm
- Seizure
- Prolongation of QT and nonspecific T-wave changes in ECG

- **Anemia** is due to:
  - Decreased EPO
  - Bleeding
  - Diminished RBC survival in TTP and HUS
  - Multiple myeloma.
- **Bleeding** is due:
  - Thrombocytopenia
  - Platelet dysfunction
  - Clotting factor abnormality.

DIFFERENTIAL DIAGNOSIS OF ACUTE RENAL FAILURE (PRERENAL VS INTRINSIC RENAL)

ARF may be develop (Table 27.2):

- In response to decreased renal perfusion (prerenal)
- Intrinsic renal parenchymal injury (intrarenal ARF)
- Obstruction (postrenal ARF).

Diagnosis is made from history with particular focus on nephrotoxic and hemodynamic insult. The history, physical examination and other laboratory and hemodynamic parameter accurately define the status of extracellular fluid volume. Analysis of fractional excretion of Na (FE_{Na}) defined as the percent of the filtered load of Na excreted in the urine is used in assessing oliguric renal failure.

$$FE_{Na} = \frac{Urine_{Na+} \times Plasma\ creatinine}{Plasma_{Na+} \times Urine\ creatinine} \times 100\%$$

FE_{Na} < 1% suggest prerenal cause of ARF whereas

FE_{Na} > 2% suggest tubular epithelial injury (intrarenal cause of ARF).

FE_{Na} must be interpreted carefully in the context of history, examination analysis of urine sediment because more than one process may occurs simultaneously.

FE_{Na} may be low early in the coarse of ischemic tubular injury, urinary tract obstruction and radiocontrast tubular injury conversely diuretic can increase FE_{Na} in patient of prerenal azotemic Fe_{Na} may be low in nephrotic syndrome and glomerulonephritis.

TREATMENT OF ARF

Outline of Management of ARF

- Judicious fluid resuscitation and correction of hemodynamic abnormality.
- Avoidance of further ischemic and nephrotoxic insult.
- Modifying drug-dosing according to GFR.
- Frequent monitoring of drug level.
  - **Prerenal ARF** is rapidly reversible if hemodynamic abnormality (hypotension, hypovolemia) is corrected quickly.
  - **Management of ARF due to intrinsic renal disease**—
    - AGN, vasculitis and allergic interstitial nephritis is managed by—
      - » Glucocorticoid
      - » Alkylating agent
      - » Plasmapheresis.
    - ARF due to malignant hypertension, toxemia of pregnancy and other vascular diseases response to **aggressive control of BP**.
    - ARF and HTN due to **scleroderma** is very much sensitive to **ACEI**.
  - **Postrenal ARF** can be reversed if obstruction to the urinary tract is removed quickly.
  - **Intrinsic renal failure**—There is no specific therapy for ARF due to ischemia and nephrotoxic agent.
  - **Correction of hemodynamic abnormality is to be done**—
    - Hypovolemia due to severe hemorrhage is corrected by packed cell transfusion.
    - Mild to moderate hemorrhage and plasma loss is corrected by isotonic saline.
    - Urinary or GI fluid loss is corrected by isotonic saline.
  - **Elimination of nephrotoxins** by forced alkaline diuresis.
  - Avoidence of **initial insult**.
  - Prevention and **treatment of complication**.

Table 27.2: Differentiation of prerenal from intrinsic renal ARF

	Diagnostic test	Prerenal	Intrinsic renal
•	Urinary specific gravity	>1020	1010–1012
•	Urinary osmolality	>500	~ 300
•	Plasma BUN: Creatinine ratio	>20	10–15
•	Fractional excretion of Na^+ (%) $\frac{U_{Na} \times P_{Cr}}{P_{Na} \times U_{Cr}} \times 100$ (Most specific index)	<1 (may be < .1)	>1 / = 1
•	Urinary Na^+ concentration → (m mol/L)	<10	>20
•	Urinary creatinine/plasma creatinine	>40	<20
•	Plasma BUN/Urine UN	>8	<3
•	Renal failure index $\frac{\text{U-sodium} \times \text{P-creatinine}}{\text{U-creatinine}}$	<1	>1
•	Urinary sediment	Hyaline cast	Muddy brown granular cast

TREATMENT OF COMPLICATIONS OF ACUTE RENAL FAILURE

- **Volume overload is managed by**:
  - Salt restricted to 1–2 gm/day.
  - Water intake <500 mL + previous 24 hours urine output.
  - Diuretic—Frusemide and thiazide (metolazone).
  - Ultrafiltration and dialysis.
- **Hyponatremia is managed by**:
  - Restriction of water <1 L/day.
  - Avoid IV hypotonic solution like dextrose In severe hyponatremia.
  - V_2 receptor antagonist—Tolvaptan.
  - 3% hypertonic saline infusion.
- **Hyperkalemia is managed by**:
  - **Restrict dietary potassium** <40 mmol/day.
  - **Eliminate potassium supplement** and **potassium spareing diuretic**, fruit and fruit juice, ACEI/ARB.
  - **Calcium gluconate or calcium chloride** (10%) 10 mL over 10 minutes (emergency treatment).
  - Slow IV infusion of **50 mL 50% dextrose with 12 U regular insuline**.
  - **Sodium bicarbonate**—50–100 mmol IV infusion if ARF is associated with acidosis.
  - **Potassium binding resins**—Na-polysterine sulfonate by month every 8 hourly.
  - *Nebulization with* **β_2 agonist**.
  - **Dialysis or hemofiltration**.
- **Metabolic acidosis is managed by**:
  - Restrict dietary protein to 0.5 gm/kg/day.
  - Inj. *Na bicarbonate* (50–100 mmol IV) to maintain pH >7.2 and bicarbonate >15 mmol/L. Na-bicarbonate 500 mg tds orally.
  - Dialysis.
- **Hyperphosphatemia is managed by**:
  - Restrict dietary phosphate <800 mg/day.
  - Phosphate binding agent–*Ca acetate* (667 mg bid or tid).
  - *Sevelamer.*
- **Hypocalcemia is managed by**:
  - **$CaCO_3$**—1000–1500 mg/day orally.
  - *1α-hydroxycholecalciferol* (0.25 μg/day) may be used.
- **Hypermagnesemia is managed by**:
  - Discontinue Mg containing antacids.
- **Hyperuricemia is managed**:
  - Usually no treatment is necessary if serum uric acid <7.0 mg/dL.
  - *Allopurinal of*— 200 mg/day
  - *Febuxostat* 40 to 80 mg/day.
- **Nutrition is managed by**:
  - Restrict dietary protein <0.5 g/kg/day.
  - Carbohydrate 100 g/day.
  - Enteral/parenteral nutrition—If the recovery is prolonged.
- **Anemia is treated by**:
  - Packed cell transfusion and injection *erythropoietin* by subcutaneous route. 4000 K on alternate day.
- **Renal replacement therapy**.

INDICATIONS OF DIALYSIS

- **Diuretic resistance**—Severe hypervolemia causing CCF and pulmonary edema.
- **Acidosis**—pH <7.2.
- **Hyperkalemia**—K^+ level >7 mcg/L.
- **Blood urea** >200 mg/dL.
- **Plasma creatinine** >10 mg/dL.
- **Pericardial rub**.
- **Uremic encephalopathy**.
  - Dialysis in ARF is initiated earlier particularly in oliguric and critically ill patient.
  - Stable patient with ARF is expected to recover renal functions within several days and may benefit from fluid restriction, restriction of protein, Na^+, K^+ and PO_4^-.

Inspite of best treatment, mortality rate is approximately 60%. Bad prognostic indicators are:

- Older age group
- Multiorgan failure
- Severe oliguria/anuria at presentation
- High plasma creatinine at presentation
- Cachexia.

Most patients who survive ARF recover renal function sufficiently.

EXERCISE

Write short notes on

1. Etiology of prerenal, renal and postrenal ARF.
2. Etiology of ATN.
3. Differential diagnosis of prerenal from intrinsic renal ARF.
4. Management of ARF.
5. Indication of dialysis.

Chapter 28

Chronic Renal Failure

DEFINITION

Chronic renal failure (CRF) is a syndrome characterized by gradual suppression of Glomerular filtration rate (GFR) over weeks to months leading to accumulation of nitrogenous waste product in the body.

Chronic Renal Disease

It is a pathophysiologic process of multiple etiology resulting in irreversible loss of number and function of nephrons frequently leading to end-stage renal disease (ESRD).

End-stage Renal Disease

It is a clinical stage of chronic renal disease due to irreversible loss of renal function to a degree sufficient to render the patient dependent on renal replacement therapy (dialysis or transplant).

Azotemia

Retension of nitrogenous waste products when renal insufficiency develops.

Uremia

This is a clinical and laboratory syndrome that reflects dysfuction of all organs due to accumulation of nitrogenous waste product as a result of untreated or undertreated acute or chronic renal failure.

- About 90% of ARF is reversible and do not reach the level of uremia.
- 90% of ESRD is due to CRF.

CAUSES OF CHRONIC RENAL FAILURE

- **Primary glomerular disease**
  - Focal segmental glomerulosclerosis
  - Membranoproliferative glomerulonephritis
  - IGA nephropathy (commonest)
  - Membranous glomerulonephritis.
- **Secondary glomerular disease**
  - Diabetes
  - Amyloidosis
  - Postinfective glomerulonephritis
  - HIV-associated nephropathy
  - Vasculitidis. } 5%
- **Tubulointerstitial nephritis**—(5–15%)
  - Drug hypersensitivity
  - Analgesic nephropathy
  - Heavy metal poisoning
  - Chronic pyelonephritis
  - Reflux pyelonephritis.
- **Obstructive uropathy**
- **Vascular**
  - Hypertensive (5–25%)
  - Renal artery stenosis.
- **Congenital**
  - Polycystic kidney disease (autosomal dominant)
  - Medullary cystic kidney
  - Alport syndrome.

IMPORTANT CAUSES OF CHRONIC RENAL FAILURE

- Diabetes (35–40%)
- Hypertension (35–40%)
- Glomerulonephritis
- Autosomal dominant polycystic kidney disease (ADPKD)
- Interstitial nephritis.

BASIC MECHANISM

Loss of functioning nephron (irrespective of etiology)

↓

Hyperfiltration of the surviving nephron due to increased glomerular flow and filtration pressure (mediated by RAAS)

↓

↓

Hypertrophy of surviving nephron is mediated by cytokine and growth factor

↓

This initial short-term adaptation later proved to be maladaptive process and predispose to sclerosis of remaining viable nephron. (Increased RAAS activity appears to be responsible for initial adaptive hyperfiltration and to subsequent maladaptive hypertrophy and sclerosis through TGF-β as downstream growth factor).

Table 28.1: Stages of chronic renal failure

Stage of CKD	GFR mL/min/1.73 meter^2
Stage 0: CKD	GFR > 90 with presence of risk factor for CKD, e.g. 1. Hypertension 2. DM 3. Autoimmune diseases 4. Old age 5. Past history of ARF 6. Family history of renal disease
Stage 1: Kidney damage with normal GFR	GFR ≥ 90 → Diagnose and treat comorbid condition
Stage 2: Kidney damage with slight decrease in GFR	GFR 60–89 → Estimate progression of CKD
Stage 3: Kidney damage with moderate decrease GFR	GFR 30–59 → Evaluate and treat complication
Stage 4: Severely decrease GRF	GFR 15–29 → Prepare for RRT
Stage 5: Kidney failures	GFR <15 → Start RRT

Estimated creatinine clearance =

$$\frac{(140 - \text{Age}) \times \text{body weight (kg)}}{72 \times \text{plasma creatinine (mg/dL)}}$$

- **Stage 0**—GFR > 90 with the presence of risk factor for CKD.
- **Stage 1 (Table 28.1)**—Demonstrable kidney damage but with normal/increased GFR ≥ 90.
  Stage 1 is clinically silent but diagnosed by—
  - Proteinuria.
  - Abnormal urinary sediment.
  - Urinary tract structural abnormality (vesico- ureteric reflux).
  - Renal reserve is lost, proved by protein challenge. High protein diet cause rise in GFR by 20% in CKD-stage I this renal reserve to protein challange is lost.
  - Abnormal blood and urine chemistry.
- **Stage 2**—GFR = 60–89
  - Kidney damage with mildly decreased GFR
  - Clinically silent.
- **Stage 3**—GFR = 30–59.
  - Kidney damage with moderate decrease GFR.
  - Clinically evident.
- **Stage 4**—GFR = 15–29.
  - Severely decreased GFR.
  - Clinically evident. Prepare for renal replacement therapy (RRT).
- **Stage 5**—GFR = <15
  - End-stage renal disease. Renal replacement therapy is necessary for survival of the patient at this stage.

Clinical and biochemical features of CKD
That become evident from stage 3 onwards are—
- Anemia
- Lack of energy, easy fatigability
- Decreased appetite/nausea/vomiting
- Disturbance in nutrional status
- Abnormality of calcium and phosphate metabolism with metabolic bone disease and abnormalities of Na, K, H_2O and acid-base balance are the major metabolic abnormality seen in CRF

MAJOR METABOLIC COMPLICATIONS IN CRF

Acid-base Disorder

Reduced ability of production of ammonia due to limited utilization of ATP resulting in diminished Na absorption in PCT. In advanced CRF cases kidney can excrete 30–40 mmole of H^+ ion/day and the remaining 20–40 mmole of H^+ ion (urate, hippurate, sulfate and phosphate) is buffered by bone salts and the accompanying organic anion are excreted in the urine resulting in metabolic acidosis of nonanion gap variety but in the late stage fairly large anion gap of 20 mmol/L may develop with a fall in plasma bicarbonate level.

Potassium Homeostasis

Decrease in GFR is not necessarily accompanied by proportionate decrease in urinary potassium excretion. Clinically significant hyperkalemia develops due to any of the following reason:
- When GFR goes below 10 mL/min/1.73 m^2.
- Due to endogenous potassium load like hemolysis, trauma, infection acidosis.
- Due to exogenous potassium load like transfusion of stored blood, potassium-sparing diuretic and ACEI and ARB, potassium containing salt—all contribute to hyperkalemia.

Fluid-Electrolyte Disorder

- Progressive glomerular injury results in retension of Na and H_2O producing edema and hypertension.
- Progressive tubular injury causes saltwater wasting.

Renal Osteodystrophy (Fig. 28.1)

About 10% of ESRD patients present with clinical symptom of bone disease.

Radiological evidence of bone disease is present in 35% patients of CKD. Histological evidence present in 90% patients of CKD.

The three types of principal renal osteodystrophy seen in CRF are discussed below:

High Turnover Osteodystrophy (Fig. 28.1)

Initially, it is due to secondary hyperparathyroidism as a result of low serum Ca^{+} due to low 1–25 dihydroxy cholecalciferol and increased plasma phosphate due to diminished excretion but later due to constant stimulation by hypocalcemia, parathyroid gland becomes autonomous causing tertiary hyperparathyroidism causing osteitis fibrosa cystica.

X-ray findings of high turnover osteodystrophy

1. Subperiosteal bone erosion along the radial border of digital bone
2. Terminal resorption of distal phalanges
3. Demineralization of bone—Pepper-pot appearance of the skull (seen in lateral view of skull)
4. Chondrocalcinosis and nephrocalcinosis
5. Soft tissue calcification in arterial wall, hand, cornea, lungs and myocardium
6. Rugger-Jersey appearance of vertebra—due to osteosclerosis and osteoporosis in alternate fashion involving the vertebral body

Low Turnover Osteodystrophy

- **Osteomalacia**—Initially, it was thought to be solely from vitamin–D deficiency. But it is now seen more closely associated with aluminium toxicity, which is coming from the:
  - *Dialysate fluid*
  - *Aluminium salt*—It is used as phosphate-binder. This aluminium-induced osteomalacia leads to pathological fracture neck femur.
- **Adynamic bone disease**—Adynamic bone disease is often as a consequence of over gillous treatment of hyperparathyroidism mostly due to supraphysiologic Ca^{+2} concentration in dialysate and the excessive use of vitamin D and Ca^{+2} preparation in these patients. This leads to high serum calcium level that results in suppression of PTH to such a level, which is inadequate for normal bone turnover.

  So, suppression of PTH level <120 μg/mL is not desirable.

Amyloid Deposition

Amyloid deposits in the bone occur as a result of chronic hemodialysis.

Clinical features of amyloid deposition

- Carpal tunnel syndrome
- Tenosynovitis of the hand
- Bone cyst
- Shoulder arthropathy
- Cervical spondyloarthropathy
- Cervical pseudotumor

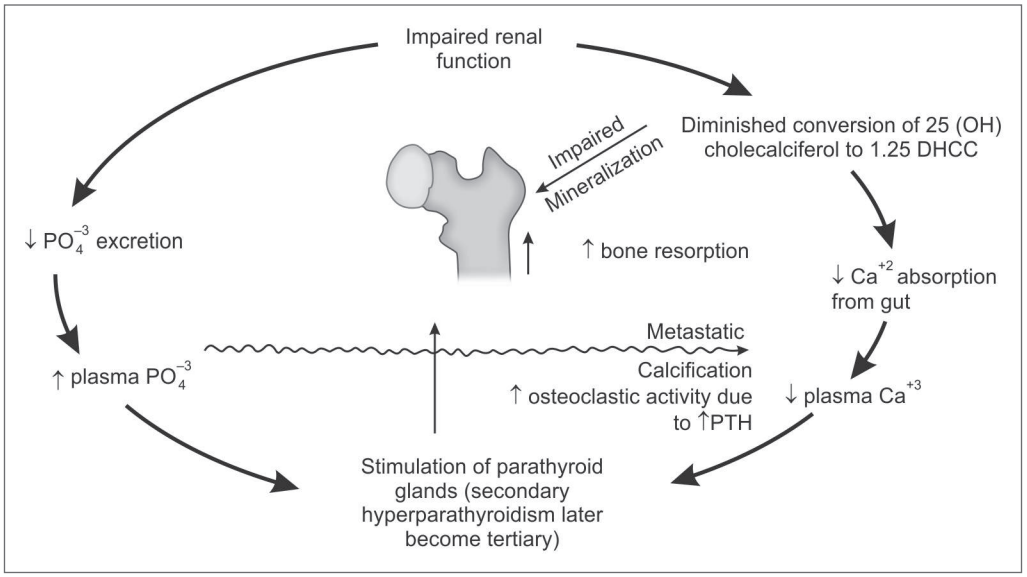


Fig. 28.1: Mechanism of high turnover renal osteodystrophy

Diagnosis

- X-ray shows cyst in femoral neck and carpal bone
- Ultrasonography.

Clinical features of RBD

- Fractured rib commonly seen in osteitis fibrosa cystica.
- Pathological fracture of femoral neck is related to aluminium-induced osteomalacia.
- Dialysis related to amyloidosis.
- Proximal myopathy giving rise to gait abnormality, seen with osteitis fibrosa cystica.
- Metastatic calcification occurs when $Ca^{+2} \times PO^{-3}$ product crosses 60 (mg/dL). The metastatic calcification occurs at places like:
  - Subcutaneous, articular and periarticular tissue
  - Myocardium

Calciphylaxis—Devastating necrotic extremity and soft tissue lesion related to metastatic calcification, secondary to vascular occlusion

  - Eyes
  - Lungs
  - Medium-sized blood vessel.

GI Manifestation

- Anorexia.
- Nausea.
- Vomiting.

} due to uremia (℞ → Protein restriction)

- Uremic fetor (due to breakdown of urea into ammonia in saliva. It also gives rise to unpleasant metallic taste—dysgeusia).
- Peptic ulcer (enhanced colonization of *H. pylori*) and GI blood loss.
- Hepatitis-B and C infection due to blood transfusion and dialysis.
- Constipation.

CVS Manifestation

- **Hypertension** is due to:
  - Volume overload
  - Hyperreninemia
  - External erythropoietin.
    - **Treatment**
      - » Restriction of salt and water intake.
      - » Diuretics.
      - » Classical antihypertensive agents—β-blocker, CCB, α-blocker.
      - » ACEI/ARB—Have a renoprotective role and may be considered so long creatinine < 3 mg/dL.
      - » It is also indicated in diabetic patient.
- **CCF** is due to salt and water retention.
  - **Treatment**
    - Restriction of water intake (500 mL + previous 24 hour urine volume).
    - Usual measure.
    - Hemodialysis.
- **Pulmonary edema** is due to:
  - CCF.
  - Increased capillary permeability in perialveolar region.
- **Left ventricular hypertrophy** is due to:
  - Hypertension
  - Volume overload
  - Anemia
  - Arteriovenous fistula.
- **Increased atherosclerosis and peripheral vascular disease**—is due to:
  - Dyslipidemia
  - Hypertension
  - Hyperhomocysteinemia
  - Mönckeberg's calcific medial sclerosis
- **Uremic pericarditis** (indication for dialysis).

Endocrine Abnormality

- **Alteration of glucose metabolism**
  - *Hypoglycemia*—is due to:
    - Diminished metabolism of insulin.
    - Diminished excretion of insulin through kidney.
  - *Hyperglycemia* is due to increased insulin resistance.
- **Secondary or tertiary hyperparathyroidism**.
- **Galactorrhea** is due to hyperprolactinemia.
- **Oligomenorrhea and infertility in female**—is due to increased and abnormal pulsatility of LH.
- **Impotence and decreased spermatogenesis in male** is due to decreased testosterone.
- **Stunted growth** is due to abnormality of GH release.
- Spontaneous abortion when GFR < 40 mL.

Hematologic

- Anemia is due to:
  - Anorexia resulting in diminished intake.
  - Volume overload leading to engorgement of GI vasculature resulting in diminished absorption.
  - Hypoproteinemia leading to decreased transferrin level.
  - Bone marrow depression is due to uremia.
  - Diminished EPO.
  - Hemolysis.
  - Aluminium toxicity.
  - Dialysis related blood loss.
  - Anemia of acute and chronic infection.

  - **Treatment**
    - » Erythropoietin (80–120 U/kg SC/week) divided and given on alternate day.

    Darbepoetin α—A long-acting analogue of erythropoietin can be used SC at monthly interval for pure red cell aplasia.
- **Altered immune response** is due to—
  - Functional abnormality of leukocyte.
  - Lymphocytopenia.
- **Abnormal homeostasis** is due to prolongation of bleeding time which results from
  - Decreased activity of platelet factor 3.
  - Abnormal platelet adhesion and aggregation.

  These two are the indirect effect of chronic renal disease via guanidinosuccinic acid which is a metabolite of creatinine.
  - **Treatment**
    - Desmopressin (DDAVP)
    - Blood transfusion
    - Cryoprecipitate
    - Intravenous conjugated estrogen
    - Dialysis
    - Erythropoietin therapy (EPO).

Neuromuscular

Central nervous system, peripheral and autonomic nervous systems are commonly involved in CKD.

- Inability to concentrate.
- Drowsiness.
- Insomnia.
- Mild behavioral changes.
- Loss of memory.
- Hiccup.
- Muscle cramp.
- Fasciculation/twitching.
- Asterixis/metabolic encephalopathy.
- Chorea.
- Stupor, seizure and coma.
- Restless leg syndrome.
- Peripheral neuropathy—It is a indication of renal replacement therapy.

  Both sensory and motor neuropathy are seen:
  - Sensory involvement predominates over motor involvement.
  - Lower limb involvement predominates over upper limb involvement.
  - Distal limb muscle involvement predominates over proximal limb muscle involvement.
    - **Sensory neuropathy**
      - » Restless leg syndrome.
      - » Carpal tunnel syndrome due to β_2-microglobulinemia.

    Treatment—
      - » Iron and EPO supplementation
      - » Clonazepum
      - » Codeine phosphate
      - » Renal replacement therapy.
    - **Motor neuropathy**
      - » Weakness
      - » Peroneal nerve palsy leads to foot drop
      - » Rarely flaccid quadriplegia
      - » Depression of deep tendon reflexes (DTR).
    - **Autonomic neuropathy**
      - » Increased catecholamine level
      - » Downregulation of adrenergic receptor
      - » Increased baroreceptor sensitivity
      - » Impaired vagal function.
- **Dialysis dementia**—Due to aluminium toxicity.
- **Dialysis disequilibrium syndrome**—Due to retained solute in the neuron of brain after vigorous dialysis.

  Treatment—Slow regular dialysis.

Skin Manifestations

- **Pruritus** is due to:
  - Retension of nitrogenous waste product
  - Hyperphosphatemia
  - Hypercalcemia
  - Hyperparathyroidism
  - Fe-deficiency
  - Elevated Ca^{+2} and PO^{-3} product.

  Treatment—Renal replacement therapy.
- **Dry skin**

  Treatment—Aqueous (moisturising) cream.
- Eczematous lesion over arteriovenous fistula.
- **Pseudoporphyria cutanea tarda**—Blistering photosensitive skin lesion/rash due to diminished hepatouroporphyrinogen decarboxylase combined with decreased clearance of porphyrin in urine.

  Treatment—Dialysis.
- Pallor.
- Loss of skin turgor and dehydration.
- Hematoma/ecchymosis.
- Calcinosis cutis.

INVESTIGATIONS

- Urine for RE and ME with C/S.
- Blood
  - BUN, creatinine, sugar and Hb.
  - Na^+, K^+, Ca^{++}, HCO_3^- and PO_4^{-3}
  - Parathyraid hormone.
- X-ray of skeleton—Renal osteodystrophy.
- ECG and echocardiography.
- Insulin and other hormone assay (parathormone).
- USG of KUBP.

- Kidney biopsy.
  To differentiate between ARF and CRF
  - History
  - Presence of anemia
  - Presence of complication
  - Increased echogenicity and small kidney in USG.

  Contraindications of renal biopsy
  - Bilateral small kidney <8.5 cm
  - ADPKD
  - Perinephric abscess
  - Obesity
  - Bleeding disorder.

GENERAL TREATMENT OF CHRONIC RENAL DISEASE (TABLE 28.2)

- **Removal of superimposed acute process that leads to acute decline in the GFR in CKD**
  - Correction of volume depletion.
  - Management of hypertension/hypotension.
  - Management of urinary tract infection/sepsis.
  - Removal of obstruction in the urinary flow in obstructive uropathy.
  - Withdrawal of nephrotoxic drug.
  - Prevention of reactivation of the underlying disease process, i.e. glomerulonephritis and SLE.
- **Slowing of the progression of chronic renal disease**
  - **Protein restriction** <0.6–0.7 g/kg/day with high biologic value. Usually 30–35 g/day.
  - **Control of BP** (<130/85 if diabetic 125/75) with the help of ACEI/ARB/non DHP-CCB, α-blocker.
    - Cessation of smoking and weight control
    - Antiplatelet therapy
    - Void nephrotoxic drug
    - Reduce Ca^{++} and PO_4^{--} product <70.
  - **Glycemic control** in both type-I and type-II, diabetics. PPBS should be within 100–140 mg/dL, HBA1C < 7 either by insulin or OHA (sulfonyl-urea/α glucosidase inhibitors, DPP_4 inhibitors).

Table 28.2: Ideal goal for chronic renal failure therapy

Treatment	Goal
ACEI/ARB	Proteinuria <0.5 g/day decrease of GFR <2 mL/min/year
Additional anti-hypertensive	Target-BP 130/80 if proteinuria <1 g/day Target-BP 125/75 if proteinuria >1 g/day
Target glycemic control	HbA1C <6.5
Dietary protein	0.8–1.0 g/kg/day
Cholesterol	LDL <100 mg
Erythropoietin therapy	Hb >10 g/dL
Salt	3–5 g/day

- **Management of complications**
  - **Volume overload and hypernatremia is managed by**:
    - Salt intake (NaCl) < 2 g/day.
    - Water intake < 500 mL + urine volume.
    - Loop diuretic (frusemide) + thiazide (metolazone).
    - Renal replacement therapy—Ultrafiltration, hemodialysis and renal transplant.
  - **Hyponatremia is managed by**:
    - Fluid intake < 1 L/day
    - Avoid dextrose infusion.
  - **Hyperkalemia is managed by**:
    - Restriction of dietary potassium <40 mmol/day.
    - Eliminate potassium supplement and potassium sparing diuretic and ACEI ARB.
    - Calcium gluconate 10 mL (10%) intervenous infusion over 10 minutes.
    - Glucose insulin infusion 50 mL (50%) with 12 units of insulin.
    - Sodium bicarbonate infusion 50–100 mmol over 30 minutes.
    - Nebulization with β_2 agonist.
    - Oral potassium exchange resin 8 hourly.
    - Renal replacement therapy.
  - **Metabolic acidosis is managed by**
    - Restriction of dietary protein < 0.6 g/kg of high biologic value.
    - Sodium bicarbonate infusion to maintain bicarbonate >20–23 mmol/L and arterial pH >7.2
    - Oral sodium bicarbonate 500 mg tds
    - Renal replacement therapy.
  - **Hyperphosphatemia is managed by**:
    - Restriction of dietary phosphate < 800 mg/day.
    - Calcium carbonate 1500 mg/day.
    - Calcium acetate 667 g/day.
    - *Sevelamer*—Nonabsorbable noncalcium containing polymer, for chelation of phosphate.
    - It slows protein catabolism and progression of CKD.
  - **Hypocalcemia**—*Calcat*–CaSR agonist
    - *Calcium carbonate* 1500 mg/day.
    - *Activated vitamin D_3 (calcitrol)* 25 μg/day.

      The dose of calcium and vitamin D_3 should be adjusted to maintain parathormone level above 120 μg/dL to avoid adynamic bone disease.
  - **Aluminium bone diseases is avoided** by avoiding aluminium-containing antacid and aluminium in dialysate fluid.
  - **Hypermagnesemia**—Discontinue magnesium-containing antacid.
  - **Heart failure**
    - Management of volume overload by fluid restriction, loop diuretic and metolazone.

  - Antihypertensive by β-blocker, α-blocker, non-DHP-CCB.
  - Renal replacement therapy (RRT).
- **Dyslipidemia**
  - Dietary modification
  - Statin.
- **Hypertension**
  - Fluid restriction.
  - Diuretic.
  - Antihypertensive—*CCB, β-blocker, α- blocker* and *ACEI/ARB* (if creatinine < 3 mg/dL.
- **Pericarditis**
  - Dialysis.
- **Hematologic complications**
  - Anemia—blood transfusion, recombinant *erythropoietin (darbepoetin).*
  - Target hemoglobin 12 g%.
  - Abnormal hemostasis—*Cryoprecipitate, desmopressin, conjugated estrogen, blood transfusion* and *renal replacement therapy*.
  - Thromboembolic disorder—LMWH.
- **Infection**—Early diagnosis and treatment with appropriate antimicrobial.
- **Neuromuscular complications** — Renal replacement therapy.
- **Gastrointestinal complications**
  - Nausea, vomiting, anorexia—Protein restriction.
  - Peptic ulcer—*Anti-H. pylori regimen*.
  - Uremic fetor—RRT.
  - *HEP-B prophylaxis* by Engerix B 40 μg on 0, 1, 6 month.
- **Endocrine complications**
  - Glucose metabolism—Strict glycemic control to keep PPBS 100–140, HBA1C <7 g, many diabetic patients require dose reduction of insulin in CRF when GFR is < 50 mL/min.
  - Pregnancy—Hasten progression of CRD so pregnancy should be avoided. Impotence oligospermia, germinal cell dysplasia, growth and sexual maturation all are improved with successful renal transplant.
- **Dermatologic complications**—Deposition of urochrome/urea improves with dialysis.
  - Uremic pruritus is managed by suppression of calcium and phosphate product.
  - Application of nonspecific systemic and topical therapies.

RENAL REPLACEMENT THERAPY

Renal replacement therapy (RRT) has now become a routine procedure in the treatment of all patients of acute and chronic renal failure when conservative management fails. This treatment does not replace the endocrine and metabolic functions of the kidney but achieves the biochemical control of the body and gives a route to eliminate excess water from body.

Indications of renal replacement therapy
- Acidosis pH <7.3
- Hyperkalemia >7 mEq/L
- Extracellular volume overload as evidence by pulmonary edema
- Uremic pericarditis
- Uremic encephalopathy
- In ARF: Blood urea > 200 mg/dL
  Blood creatinine > 10 mg/dL

There are various modalities of renal replacement therapy.
- Hemodialysis/Hemofiltration
- Peritoneal dialysis
- Renal transplant.

HEMODIALYSIS

It is a standard blood purification therapy for all end-stage renal failure patients when despite adequate conservative medical management complication develops.

PRINCIPLES OF HEMODIALYSIS

- Blood is usually taken out of the body through the arterial end of a double lumen catheter placed in the internal jugular vein or subclavian vein or femoral vein (in case of ARF) or through an A-V fistula or Scribner shunt in case of CRF.
  Vascular access is usually made from—
  - Arteriovenous fistula.
  - Double lumen catheter placed in a major veins (jugular/subclavian/femoral).
- The extracorporeal circuit is made of synthetic polymar with a very high ultrafiltration capacity and bathed in a dialysate fluid where the ion and electrolyte diffuse out of blood through the synthetic polymar membrane down a concentration gradient to the dialysate fluid.
- Blood is driven through the extracorporeal circuit by means of a pump.
- Anticoagulation is required to prevent clotting of the extracorporeal circuit and is done by means of continuous low dose heparin infusion.
- The returning blood is infused via the venous end of the catheter.

Hemodialysis is usually carried out for 3–5 hours a day, three times a week. Most patients show a clinical improvement.

It is possible to maintain normal active life with this form of treatment and possible to survive > 20 years with this mode of treatment.

PERITONEAL DIALYSIS

It is less efficient than hemodialysis and seldom possible to achieve good biochemical control.

It is useful in patients with unstable cardiovascular status and with diabetes but not possible after recent abdominal surgery.

A trocar and cannula system is used for peritoneal access in ARF patient but usually a permanent silastic catheter is placed in peritoneum in case of CRF patient.

1.5–2.5 liters of sterile isotonic dialysis fluid is introduced and left in peritoneal cavity for approximately 6 hours. During this period metabolic waste product diffuses from peritoneal capillary into dialysis fluid down a concentration gradient and the water comes out due to osmotic gradient. The fluid is then drained and fresh dialysis fluid is introduced either manually or by a mechanical device.

Long-term use of this method is limited by bacterial peritonitis. Cloudy effluent indicates the development peritonitis and such condition is managed by removal of the catheter and appropriate antibiotic like vancomycin/gentamicin.

This method extends the life expentancy by approximately 10 years.

RENAL TRANSPLANTATION

It is possible to restore almost normal kidney function and correction of all metabolic abnormalities of CRF by this method of treatment.

The kidney is taken either from:

- Cadaver.
- From ABO compatible donor usually a close relative (sibling or parents).

HLA matching is essential as this improves the survival of graft as immune-mediated graft rejection is the major cause of graft failure.

Three-year graft survival is about 80–90%.

Long-term immunosuppressive therapy is always done in renal transplant recipient patient by:

- Methylprednisolone
- Antithymocyte globulin
- Cyclosporin
- Azathioprine.

To avoid nephrotoxicity cyclosporin is now replaced by **either tacrolimus/mycophenolate mofetil or gapamycin**.

The immune suppression is associated with a increased incidence of:

- Opportunistic infection.
- Malignant neoplasm particularly of skin.
- Lymphoma (rare but may occur early with EBV). In spite of all these drawbacks, it is the best mode of treatment for CRF.

TRANSPLANT-RELATED DISORDER

TRANSPLANT REJECTION

- **Hyperacute rejection**—Occlusion of blood supply to the transplant organ is the cause of this type of rejection and is also called 'white graft reaction' and is due to mismatch of A, B, O blood groups between donor and recipient.

  This type of rejection occurs within minutes to hours of transplant.

  Presence of preformed antidonor antibody (specially anti-A, B, O blood group antibody) in the transplant recipient causes this type of hyperacute rejection. This antibody cross react with A, B, O blood group specific antigen present on the surface endothelium of the donor.
- **Acute rejection**—This is the most important and commonest mode of rejection.

  This type of rejection occurs due to MHC mismatch between donor and recipient.

  This type of rejection is mediated via cytotoxic T-lymphocyte (CD_8 T-Cell). This type of rejection is usually seen weeks after transplantation.

  Treatment—This type of rejection is reversible with immune-suppressive drugs like **cyclosporine and antithymocyte globulin (ATG)**.
- **Chronic rejection**—Antibody-mediated vascular damage causing atherosclerosis and fibrinoid necrosis of the blood vessel is the main mechanism behind this type of chronic rejection.
  - This type of rejection is seen months to year after the transplantation.
  - This type of rejection is due to minor MHC mismatch and is a side effect of long-continued immune-suppressive therapy used for prevention of acute rejection.

  Treatment: It is an irreversible phenomenon and does not respond to any treatment.

GRAFT VERSUS HOST DISEASE

In this type of rejection immune-competent T-cell within the graft proliferates in the irradiated immune-compromised host and causes this type of rejection.

The three main criteria for development of GVHD

- Graft must contain immune-competent T-cell.
- Host must be immune-compromised.
- Recipient must express antigen (MHC) foreign to the donor.

Clinical Features

Maculopapular rash, hepatosplenomegaly, jaundice, diarrhea.

Treatment

This reaction is reduced by:

- Pretreatment of donor tissue with monoclonal antibody antithymocyte globulin (ATG).
- Cyclosporin treatment of the host after engraftment.

EXERCISE

Write short notes on

1. CRF, ESRD, uremia and azotemia.
2. The causes of CRF.
3. The stages of CRF.
4. The renal bone disease.
5. CVS and endocrine and neuromuscular complications of CRF.
6. The treatment of CRF.
7. The treatment of hyperkalemia, anemia, hyperphosphatemia, hypocalcemia.
8. Renal replacement therapy.
9. The complication of transplant.
10. Differential diagnosis of prerenal from intrinsic renal ARF.
11. The management of ARF.
12. The indication of dialysis.

Chapter 29

Urinary Tract Infection

DEFINITION

Urinary tract infection (UTI) is defined by multiplication of organism anywhere in urinary tract, associated with ≥ 10^5 organism/mL in MSU (midstream clean catch urine).

- UTI is more common in women due to:
  - Small urethra (4 cm)
  - Close proximity of urethra with anus
  - Absence of bacteriocidal prostatic secretion.
- In male, it is more common at the first decade or after 60 years of age (due to BHP) and is due to absence of prostatic secretion (which is bactericidal).

CAUSATIVE ORGANISMS

- In hospital-acquired UTI common organism are
  - *Klebsiella*
  - *Streptococcus*
  - *Escherichia coli*
- Community acquired UTI common organism are
  - *E. coli* (75%).
  - Proteus.
  - Pseudomonas.
  - *Strepto/staphylococcus epidermidis.*

PATHOGENESIS

- **In uncomplicated patient who have**
  - Normal urinary tract.
  - Normal renal function.
  - Immune competent host, in these patients UTI is caused by ascending virulent organism from urethral orifice.
- **In complicated patient who have**
  - **Abnormal urinary tract**—Obstruction, calculus, reflux, indwelling catheter, prostatitis and neurogenic bladder and postinstrumentation.
  - **Immunocompromised patient**—Diabetes, HIV, iatrogenic and extremes of age either by ascending infection from utethra and also by hematogenous spread chemotherapy in this group of patients. UTI can be caused by less virulent organism.

CLINICAL PRESENTATION

Clinical presentation depends on which anatomical part of the urinary tract is predominantly involved.

Patient may be completely asymptomatic or may have the following features:

- **In involvement of kidney and pelvis**—Patient usually presents with high rise of temperature with chill and rigor, nausea and vomiting, pain and tenderness over renal angle and flank and features of septicemia.
- **In involvement of bladder**—Patient usually presents with fever, polyuria and hypogastric discomfort.
- **In involvement of urethra and lower urinary tract**—Patient presents with *dysuria*, *frequency* and *urgency*. Even patient may present with combination of the above feature.

DIAGNOSIS

- Clinical diagnosis is made from above-mentioned signs and symptoms.
- **Laboratory**
  - **Urine**—Routine examination and culture.
  - **Microscopical examination of** midstream clean catch urine **(MSU)** shows the followings:
    - White blood cells (WBC) >8/HPF.
    - Red blood cells (RBC) >2/HPF.
    - Cast—WBC and RBC. Cast usually present.
    - Blood ±.
    - Protein + + +.
    - Glucose—Usually absent unless associated with diabetes.
    - Culture shows ≥ 10^5 organism/mL.
  - **Blood**
    - TC, DC and ESR
    - Sugar, urea and creatinine
    - Blood culture to detect septicemia if associated with UTI.
  - **Pelvic examination**
    - Per rectal examination in case of male for prostate and per vaginal in female.

- **Radiology**
  - USG of KUBP in male and pelvic organ in case of female for information about kidney, ureter, bladder, pelvic organ and prostate.
  - Intravenous urography (IVU) is usually done if suggested by clinical examination and investigation for detection of any structural abnormality in the urinary tract, stone and obstruction.
  - Micturating cystourethrogram (MCU) for detection of urethral valve and stricture.
- **Instrumentation**—Cystoscopy for direct **visualization** of the condition of bladder and bladder mucosa and prostate.

MANAGEMENT

- **General/prophylactic measure** (For an women facing repeated attack of UTI in her reproductive age group).
  - Plenty of water—2–3 L/day.
  - High calorie diet.
  - Regular emptying of bladder every 3 hourly, double micturation at bedtime, micturation before and after intercourse.
  - Search for underlying complicating factor—DM, BHP (in case of male), calculus and catheter.
  - Urinary analgesic is given if dysuria is present.
- **Specific measure**—
  - **Emperical antibiotic**—Co-amoxiclav—625 mg 3 times/day for 6 days.
    Or
    Fluoroquinolones for 6–8 days.
    Treatment to be continued for 7–10 days.
  - In case of resolution—Prophylactic management.
  - If resolution does not occurs search for complicating factor and if any of such detected take appropriate measure to remove the cause. If not detected, another course of antibiotic for 7 days.
    - If there is any failure of treatment then suppressive antibiotic therapy according to the culture sensitivity report.
  - **Specific antibiotic regimen**—
    - Co–trimoxazole—800/160 mg twice daily orally.
    - Co-amoxiyclav—(1 g/200 mg) thrice daily (1.2 g) oral/IV tds × 7 days.
    - Gentamicin—80 mg IV tds × 6 days.
    - Amikacin—500 mg IV bd × 6 days.
    - Cefuroxime/cephalaxine—250 mg bd orally/750 mg IV bd × 10 days.
    - Quinolones—Ciprofloxacin—500 mg bd orally × 10 days of ofloxacin (200 mg) BD × 10 days.
  - Penicillin and cephalosporin can safely be used in pregnancy.

EXERCISE

Write short notes on

1. Define urinary tract infection.
2. Name the causative agent of UTI and the clinical feature of pyelonephritis, cystitis and urethritis.
3. Write short notes on management of UTI.

Chapter 30

Interstitial Nephritis

ACUTE INTERSTITIAL NEPHRITIS

Acute interstitial nephritis (AIN) is also called as acute inflammation within the tubulo- interstitium of kidney.

ETIOLOGY

- **Allergic drugs—**if β-lactam, sulfonamide, quinolones, vancomycin, rifampin, ethambutol, acyclovir, NSAID diuretics, anticonvulsant, PPI, H_2-blocker, mesalazine, indinavir and allopurinol.
- *Immunological*—Autoimmune diseases with or without uveitis, SLE and Sjögren's syndrome.
- *Infection (recurrent or chronic infection)*
  - Acute bacterial pyelonephritis.
  - Leptospirosis (Weil's disease), rickettsia and mycoplasma infection.
  - Tuberculous pyelonephritis.
  - Cytomegalovirus, EBV, CMV and HIV hantavirus.
- *Obstructive*
  - Myeloma light chain protein, urate and phosphate
  - Mushroom.

CLINICAL FEATURES

About 30% patients with drug-induced acute interstitial nephritis have additional features of drug hypersensitivity reaction like fever, rash, eosinophilia, oliguric renal failure after 7–10 days of treatment with methicillin or β-lactam antibiotics.

- **Urine shows**: Pyuria, WBC and RBC by uteroscopic examination.
  - Eosinophil are found in 70% patients.
- **Renal biopsy shows**:
  - Intense inflammation of tubules with PMN leukocytosis.
  - Lymphocyte, surrounding and invading tubule and blood vessels.
  - Eosinophil is seen in drug-induced acute inters- titial nephritis.

Degree of chronic inflammation in biopsy is a useful predictor of outcomes of the disease. Rapid deterioration in renal function like RPGN is seen in drugs induced acute interstitial nephritis.

Many patients are not oliguric despite moderately severe ARF and acute interstitial nephritis should always be considered in all causes of nonoliguric ARF.

- **Indication of corticosteroid and immunosuppressive in interstitial nephritis**:
  - **Absolute indications**—Sjögren, sarcoidosis, SLE and TIN with cavities.
  - **Relative indications—**if drug-induced or idiopathic AIN, children with TINU and postinfectious AIN with delayed recovery.

MANAGEMENT

- Withdrawal of offending drug.
- ARF in managed conservatively.
- Dialysis in required for symptomatic patient.
- Corticosteroid 1 mg/kg/day accelerates recovery.
- Especially in drug-induced acute interstitial nephritis.
- Other specific etiology should be treated whenever possible.

CHRONIC INTERSTITIAL NEPHRITIS

Chronic interstitial nephritis (CIN) is caused by a heterogeneous group of disease but it is very difficult to find out the etiology at late stage when the disease is usually diagnosed.

ETIOLOGY

- Acute interstitial nephritis.
- Inflammatory glomerulonephritis.
- **Immunological**—SLE, Sjögren's syndrome and sarcoidosis chronic transplant rejection.
- **Toxic**—Mushroom, Balkan nephropathy, Chinese herb and lead.
- **Drug**—Drugs causing ATN, lithium, analgesic ciclosporin and tacrolimus.
- **Infection**—Severe pyelonephritis.
- **Congenital**—
  - Vesicoureteric reflux
  - Medullary sponge kidney
  - Sickle cell nephropathy.
- **Metabolic and systemic disease**—Hypokalemia, hypercalciuria and hyperoxaluria.

CLINICAL FEATURES

Symptoms

- Hypertension
- Features of hyperkalemia
- Features of acidosis.

Age of Onset

- Usually adult.
  - Many patients are symptomatic and detected during routine examination.
  - Most of the patients present with HTN (60%) and CRF with features of oliguria, hyperkalemia, acidosis.
  - A minor percentage (10%) present with polyuria hypotension and features of salt water depletion due to damage to collecting duct. Impairment of urinary concentrating prower and Na conservation makes the patient prone to develop ARF in the face of moderate salt water depletion.
  - Renal tubular acidosis is seen with all CIN but most severely with myeloma, sarcoidosis, amyloidosis.
  - Hyperkalemia is disproportionate to CIN with diabetic nephropathy because of hyporeninemic hypoaldosteronism.

SPECIAL CONDITIONS

BALKAN NEPHROPATHY

Combination of CIN with tumor of collecting duct develops due to chronic ingestion of a fungal toxin ochratoxin A which is present in stored food grain in the Balkan state.

Another toxin aristolochic acid present in Chinese herb is responsible for rapidly developing CIN.

ANALGESIC NEPHROPATHY

All NSAIDs specially combination of aspirin and phenacetin cause renal papillary necrosis and CIN, chronic low water intake causing diminished tubular flow and increase concentration of the drug within tubule is probably importnat contributory factor.

SICKLE CELL NEPHROPATHY

Patients surviving with sickle cell disease usually develop CIN due to occlusion of microvasculature of vasa recta by sickled RBC as there is hypoxia and hypertonicity (two important factors responsible for sickling).

MANAGEMENT

1. Full diagnostic workup may help to identify specific drugs and toxin.
2. Salt water wasting group—Requires 2–3 L water/day.
3. Treatment of HTN and UTI as necessary.
4. Acidosis—Requires sodium bicarbonate by month.
5. Hyperkalemia—Managed accordingly.
6. CRF—Initially managed conservatively; if cannot be controlled RRT is required.

EXERCISE

Write short notes on

1. AIN and CIN.

SECTION IV

RESPIRATORY SYSTEM

- Approach to a Patient of Hemoptysis
- Approach to a Patient of Dyspnea
- Bronchial Asthma
- Chronic Obstructive Pulmonary Disease
- Pneumonia
- Pleural Effusion
- Respiratory Failure
- Cor Pulmonale
- Acute Respiratory Distress Syndrome
- Bronchogenic Carcinoma
- Pneumothorax

Chapter 31

Approach to a Patient of Hemoptysis

INTRODUCTION

Coughing out blood irrespective of an amount is an alarming symptom. Hemoptysis must always be assumed to have a serious cause until proved otherwise by appropriate investigations.

CAUSES OF HEMOPTYSIS

- **Bronchial causes**
  - Bronchogenic carcinoma or adenoma
  - Bronchiectasis
  - Acute bronchitis.
- **Parenchymal diseases**
  - Pulmonary tuberculosis
  - Pneumonia (usually bacterial)
  - Lung abscess
  - Parasite—Hydatid cyst and lung flukes.
- **Diseases of the pulmonary vasculature**
  - Pulmonary infarction
  - Polyarteritis nodosa
  - Goodpasture syndrome } Vasculitis
  - Wegener's granulomatosis.
- **Cardiovascular diseases**
  - Acute left ventricular failure
  - Mitral stenosis.
- **Hematological disorders**
  - Leukemia
  - Hemophilia and thrombocytopenia
  - Anticoagulant overdose.

But many episodes of hemoptysis are unexplained even after full investigation and are likely to be caused by bronchial infection.

HISTORY

- A history of repeated small hemoptysis or blood streaking of sputum in a middle-aged heavy smoker is suggestive of carcinoma of lung.
- A history of low-grade long continued fever with loss of appetite and chronic cough in a malnourished patient with history of close contact with tuberculosis patient suggest pulmonary tuberculosis.
- History of blood disorder or history of repeated blood transfusion or with history of taking antiplatelet/anticoagulant suggest hematological disorder.
- History of rusty sputum or frank hemoptysis in a patient with sudden high rise of temperature and heaviness of chest and cough suggest pneumonia.
- Severe hemoptysis in a patient with previous history of tuberculosis or pneumonia in early life suggest bronchiectasis or aspergilloma.
- History of sudden onset dyspnea, chest pain and hemoptysis in a patient with prolonged immobilization heart failure, pregnancy suggest pulmonary thromboembolism.
- History of hemoptysis with profuse fetid expectoration suggest lung abscess/bronchiectasis.

PHYSICAL EXAMINATION

- **Fever**: Present in tuberculosis, pneumonia, lung abscess.
- **Clubbing**—seen in bronchial carcinoma, bronchiectasis, lung abscess.
- **Cervical or supraclavicular lymphadenopathy**: Present in tuberculosis, carcinoma.
- **Purpura and hematuria**—seen in platelet disorder and anti- coagulant overdose.
- **Cachexia, hepatosplenomegaly and lymphadenopathy**: Present in carcinoma.
- **Signs of leg vein thrombosis**: Present in pulmonary thromboembolism.

MANAGEMENT

Investigation

- **Blood count**: Helpful in diagnosis of pneumonia, TB, lung abscess, thrombocytopenia, leukemia.
- **Coagulation study**: To be done in suspected cases of hemophilia and anticoagulant overdose.
- **Chest X-ray (PA and lateral)**: It is helpful in diagnosis of tuberculosis, pneumonia, carcinoma and lung abscess.

- **Bronchoscopy** (rigid and fiberoptic): To diagnose early centrally located bronchial carcinoma specially endobronchial growth and bronchoscopic biopsy/ brushing helps to provide tissue diagnosis.
- **Ventilation perfusion**: Lungs scan (V/Q) which is helpful in establishing a diagnosis of thrombo-embolism.
- **CT scan of thorax**: A very helpful mode of investigation for peripherally located lesion and facilitates accurate percutaneous biopsy where indicated. Thereby helps in diagnosis of TB, pneumonia, bronchiectasis, carcinoma, lung abscess and aspergilloma.

TREATMENT

A rapid history and thorough clinical examination specially pulse, BP and respiratory system gives information about the diagnosis and amount of blood loss.

- Patient to be nursed on the side of suspected source of bleeding.
- Patient should be sedated with diazepam 10 mg to alay anxiety.
- Hemodynamic resuscitation where necessary to be done with normal saline/Ringer lactate or blood transfusion according to the severity of blood loss.
- Urgent bronchoscopy with a rigid bronchoscope allows optimal bronchial suction and can be used to maintain ventilation during anesthesia.
- Angiography and bronchial arterial embolization or even emergency pulmonary surgery can be life-saving in appropriate situation.

In vast majority of patients, hemoptysis itself is not life-threatening and it is possible to follow a logical sequence of investigations and treatment of the etiology.

EXERCISE

Write short notes on

1. Approach to a patient of hemoptysis.
2. Investigations and management of hemoptysis.

Chapter 32

Approach to a Patient of Dyspnea

COMMON ETIOLOGY OF ACUTE ONSET SEVERE DYSPNEA

- Acute left ventricular failure (LVF)
- Acute severe asthma
- Acute exacerbation of chronic obstructive pulmonary disease (COPD)
- Massive pulmonary embolism
- Metabolic acidosis
- Pneumothorax
- Pneumonia.

It is one of the most common medical emergency.

Detailed history and a rapid but thorough clinical examination holds the key to arrive at a correct diagnosis and it should be supplemented by investigation like chest X-ray, ECG and arterial blood gas examination.

HISTORY

- Acute onset dyspnea with retrosternal chest pain, palpitation, orthopnea with past history of hypertension and atherosclerotic heart disease— suggest acute LVF.
- Acute onset dyspnea with wheeze—usually following exposer to external allergen or exercise or cold air or with history of late night or early morning exacerbation or previous history recurrent episode and seasonal variation suggest acute severe asthma.
- Acute onset dyspnea with mucoid or mucopurulent expectoration specially in winter months with history of smoking suggest acute exacerbation of COPD.
- Acute onset dyspnea along with chest pain with history of surgery or prolonged recumbancy/immobilization or childbirth suggest massive pulmonary embolism.
- Acute dyspnea—in a uncontrolled diabetic or renal failure patient or patient with history of intake of large amount of aspirin/ethylene glycol suggest metabolic acidosis.
- Acute dyspnea—with fever, chill, rigor, malaise, cough and pleuritic chest pain suggest pneumonia.
- Sudden onset unilateral chest pain and breathlessness which do not resolve spontaneously suggest pneumothorax.

CLINICAL FEATURES

- **Signs of acute LVF**
  - Sweating and cold extremity
  - Central cyanosis
  - Jugular venous pressure (JVP)—Normal or raised
  - Hypertension in case of hypertensive LVF
  - Crepitation over lung base
  - Left ventricular S_3 and S_4
  - ECG and Trop (T) is diagnostic of post MI LVF.
- **Signs of acute severe asthma**
  - Tachycardia
  - Pulsus paradoxus present in severe cases
  - Accessory muscle of respiration are working
  - JVP—usually not raised in acute severe asthma
  - Polyphonic ronchi all over both lung
  - Crepitation—a few may be present
  - Diminished peak expiratory flow rate (PEFR).
- **Signs of acute exacerbation of COPD**
  - Cyanosis and edema.
  - With signs of CO_2 retension, e.g. warm extremity flapping tremor and bounding pulse.
  - Barrel-shaped chest
  - Intercostal suction
  - Pursed lip breathing
  - Tracheal tug.
- **Signs of massive pulmonary embolism**
  - Severe central cyanosis
  - Elevated JVP
  - Feature of shock with tachycardia
  - Reduced BP
  - Absence of signs over lung.
- **Signs of pneumonia**
  - Fever, confusion and cyanosis
  - Pleural rub

  - Features of consolidation or pleural effusion (bronchial breath sound with dullness on percussion).
- **Signs of metabolic acidosis**
  - Ammonia or acetone smell in breath
  - Dehydration
  - Hyperventilation (Kussmaul's respiration)
  - No physical sign in heart or lungs
  - Presence of ketone bodies in blood or urine
  - Elevated urea and creatinine in blood.
- **Sign of pneumothorax**
  - Shifting of mediastinum with trachea to the opposite side.
  - Intercostal fullness with depressed movement of chest wall.
  - Hyper-resonant percussion note over affected side
  - Decreased or absent breath sound.

CHEST X-RAY

- Cardiomegaly and pulmonary edema with prominence of upper zone vessel with or without pleural effusion suggest LVF.
- Hyperinflation of lung only suggest asthma.
- Increased radiolucency of lung with tubular heart, RVH, terracing of diaphragm with obtuse costophrenic and cardiophrenic angle suggest COPD.
- Oligemic lung field with prominent hilar vessel suggest embolism.
- Lobar consolidation suggest pneumonia.
- Normal lung field indicate metabolic acidosis.
- Pneumothorax is indicated by increased radiolucency with absent lung marking and sharply defined edges of lung. Care to be taken to differentiate it from large emphysematous bullae.

ELECTROCARDIOGRAPHY

1. Features of AMI or LBBB or LVH suggests acute LVF
2. Sinus tachycardia or rarely bradycardia (due to severe hypoxemia) seen in acute severe asthma
3. Sign of RVH with slow progression of R-wave in precordial lead with P pulmonale indicate COPD
4. Sinues tachycardia, S1Q3T3 pattern, inverted T in V_1–V_4 RBBB—Pulmonary embolism
5. Tachycardia—Pneumonia.

ARTERIAL BLOOD GAS

1. PaO_2—Depressed in COPD, pulmonary embolism, bronchial asthma and LVH and pneumonia. severely depressed in embolism and COPD.
   Normal in metabolic acidosis.
2. PCO_2—Depressed in metabolic acidosis, LVF, embolism, asthma and pneumonia.
   Severely depressed in metabolic acidosis—Increased in COPD.

EXERCISE

Write short note on

1. Approach to a patient of acute severe dyspnea.

Chapter 33

Bronchial Asthma

INTRODUCTION

Bronchial asthma is defined as reversible obstruction of small airway of lung due to hyperresponsiveness of the respiratory tract to external or internal allergen or nonspecific stimulus like exercise, cold and is characterized pathologically by chronic airway inflammation and clinically by cough, wheeze, chest tightness and dyspnea.

It is not a uniform disease and have normal lung function in well-controlled asymptomatic patient, in between the two acute attacks.

PATHOPHYSIOLOGY

Asthma is multifactorial in origin and interaction of genetic and environmental factor leads to its development.

Airway inflammation characteristic of bronchial asthma occurs where a genetically susceptible person is exposed to environmental factor like allergen, or exercise, and cold air.

GENETIC FACTOR

The genetic contribution in asthma is poorly understood and is polygenic in nature.

Acute asthma usually begins in childhood in atopic subject who produces significant amount of IgE on exposure to common antigen.

Whereas nonatopic, intrinsic or late onset asthma develop in adult life.

TRIGGERING AGENT

There are several factors that can trigger asthma in an apparently healthy subject.

- **Environmental agent**—House dust mite, cockroach antigen, pet (dog/cat) driven antigen are usual indoor antigen.

  Nitrogen dioxide, ozone, sulfer dioxide, air-borne particulate, fungal spore and flower pollen are the **common external allergen**.
- **Drugs**—β-blocker, aspirin and NSAID can induce bronchoconstriction.
- **Infection**—Bacterial and specially viral infections of respiratory tract are the important causes of asthma exacerbation as these transiently increase the responsiveness of airway.
- **Smoking**—Smoking during pregnancy is supposed to increase the risk of atopic disease in infancy. Passive smoking has adverse effect on asthma and respiratory disease.
- **Anxiety and stress**—These can aggravate asthma and acute emotional upset can precipitate an acute attack.

CLINICAL FEATURES

The symptoms and signs are usually **episodic in acute asthma and persistent in chronic asthma**.

Episode of acute asthma is usually precipitated either by—(a) viral infection, (b) exposure to external and internal allergen, (c) anxiety and stress, (d) drugs.

Patients with episodic acute asthma have clinical signs and symptoms during the attack and are asymptomatic in between the attack.

Patients of chronic asthma have persistent symptom.

Typical symptoms of asthma are:

- Wheeze
- Cough
- Chest tightness
- Breathlessness.

Whereas typical signs of acute asthma are:

- Central cyanosis (rare) diminished vesicular breath sound with prolonged expiration.
- Polyphonic expiratory ronchi all over both lung.
- Few fine crepitation.

It is sometime difficult to distinguish wheeze of chronic asthma from wheeze due to COPD or acute LVF. These three diseases are differentiated by:

1. Variable nature of symptoms.
2. Diurnal fluctuation in symptom.
3. Diurnal fluctuation of PEFR help to differentiate asthma from COPD.

Early morning dip in peak expiratory flow rate (PEFR) and early morning exacerbation of symptom is characteristic of chronic bronchial asthma (that is why sometimes it is called as '**Nocturnal asthma**) (Fig. 33.1).

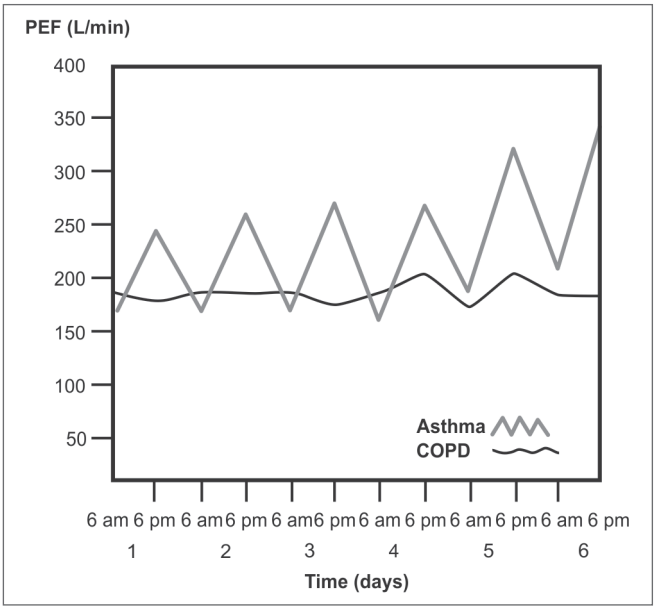


Fig. 33.1: Morning dip in PEF in asthma

Cough may dominate over wheeze particularly after exposure to cold air and exercise and is called **cough variant asthma**.

Asthma is classified as mild, moderate and severe depending on the PEF converted to percentage of the best or percentage predicted.

1. **Mild asthma**—PEF 76–100% of the best or predicted.
2. **Moderate asthma**—PEF 51–75% of the best or predicted.
3. **Severe asthma**—PEF 0–50% of the best or predicted.

LABORATORY INVESTIGATION FOR BRONCHIAL ASTHMA

- Increase blood eosinophil.
- Increase sputum eosinophil (>2%).
- Increase in total or allergen-specific IgE in serum (may be done) to differentiate asthma from COPD.
- Morning dip in PEF (in difficult situation, exercise, histamine and methacholine provocative test can be done to demonstrate dip in FEV_1 by 20%).
- Sometime postprednisolone (30 mg daily for 2 weeks orally) improvement may be demonstrated in PEFR.
- Pulmonary function test— FEV_1—Reduced.
  FEV_1/FVC ratio less than 80%.

  Reversibility of FEV_1 is demonstrated by >12% or 200 mL increase in FEV_1 after 15 minutes of inhaled short-acting β_2 agonist or after 30–40 mg prednisolone for 2–4 weeks.

  Early morning or postprovocative dip in PFR is diagnostic of bronchial asthma.
- Chest X-ray—Usually normal. Sometimes hyperinflatted during acute attack (differential diagnosis are pneumothorax, rarely mediastinal, pericardial, subcutaneous emphysema).

DIAGNOSIS OF ASTHMA

- Clinical history.
- I**ncrease in FEV_1 ≥12%** (200 mL) following administration of bronchodilator or corticosteroid.
- **Greater than 20% diurnal variation of FEV_1** on >3 days a week for 2 weeks.
- **PEF >15% decrease after 6 minutes of exercise**.

MANAGEMENT PROTOCOL OF CHRONIC PERSISTENT ASTHMA

Management of chronic asthma is divided into five steps.

1. **Step 1**—Occasional short acting β_2-adrenoceptor agonist inhalation [**occasional short acting β_2 agonist (SABA)**].
2. **Step 2**—Regular low dose steroid inhalation plus step 1 (**low dose inhaled corticosteroid + occasional SABA**).
3. **Step 3**—Regular high dose steroid inhalation or (regular low dose steroid inhalation plus regular long acting β_2-adrenoceptor agonist inhalation).
   [**LICS + occasional long acting β_2 agonist (LABA)**].
4. **Step 4**—Regular high dose steroid inhalation plus step 1 plus sequential trial of any one of the following six. [**high-dose inhaled corticosteroid (HICA) + occasional LABA** + (a) to (g)].
   a. Inhaled long-acting β_2-adrenoceptor agonist (salmetarol—50 μg/12 hourly or formoterol 12 μg/12 hourly).
   b. Leukotriene receptor antagonist (**montelukast** 10 mg/day) and zafirlukast modest clinical benefit.
   c. Inhaled ipratropium bromide (0.5 mg) or oxitopium bromide.
      Side effect—Dry mouth, urinary retension and glaucoma.
   d. Long-acting oral β_2-adrenoceptor agonist (sustain release salbutamol or terbutaline).
   e. High dose inhaled β_2-adrenoceptor agonist.
   f. Sodium cromoglycate or nedocromil sodium.
   g. Oral slow release theophylline.
      (Side effect—arrhythmia and epilepsy)

Drugs

- *Inhaled adrenoceptor agonist*
  - Short-acting inhaled β_2-adrenoceptor agonists are:
    - **Salbutamol** 50 μg
    - **Terbutaline** 50 μg
  - Long-acting inhaled β_2-adrenoceptor agonists are:
    - **Salmeterol** 50 μg 12 hourly (onset of action longer and persist for 12 hours)
    - **Formoterol** 6 μg 12 hourly (quick onset of action but persist for 12 hours)
- *Inhaled steroid*
  - **Beclomethasone and budesonide**:
    - High dose—800–2000 μg/day
    - Low dose—800 μg/day
  - **Fluticasone**:
    - High dose—More than 660 μg/day
    - Low dose—90–260 μg/day

Side effects—Oral candidiasis and hoarseness of voice

5. **Step 5**—Addition of regular oral corticosteroid therapy at lowest possible single morning dose to step 4 therapy.

If symptoms of asthma are not controlled by lower step regime then move up to next higher step regime but it is better to start with a higher step and after control of symptom achieved move down to lower step.

Rescue Steroid Treatment

Oral prednisolone 30–60 mg in the early morning (8 am) and continue for two days after control in achieved.

- **Indications of rescue steroid**
  - Symptoms or PEF progressively worsening.
  - Fall of PEF below 60%.
  - Sleep disturbance by asthma.
  - Persistence of morning symptom until midday.
  - Diminishing response to inhaled bronchodilator.
  - Symptoms are severe enough requiring treatment with nebulized or injectable bronchodilator.
- **Steroid sparing therapy**—*Anti-IgE—Omalizumab*—A neutralizing antibody that neutralize circulation IgE—S/C injection every 2 weeks for 3–4 months reduce number of exacerbation and improve asthma control.

ACUTE SEVERE ASTHMA

INTRODUCTION

Acute severe asthma has replaced status asthmaticus as description. Patient is usually extremely distressed with tachypnea and hyperinflated lung and accessory muscle of respiration are working.

Symptoms of Respiratory

- **Tachycardia**.
- **Central cyanosis**.
- **Pulsus paradoxus** (decapitation of SBP during inspiration due to diminished cardiac preload as a result of severe hyperinflation of lung).
- **Sweating**.

Criteria of Acute Severe Asthma

- Pulse >110/min
- Pulsus paradoxus or pulsus normalis exaggeratus
- Unable to speak a complete sentence in one breath
- PEF < 50% of the predicted (200 L/min)
- Respiratory rate is > 25/min.

Clinical Criteria of Life-threatening Asthma

- Cannot speak
- Central cyanosis
- Exhaustion, confusion and drowsy
- PEF < 33% of predicted (<100 L/min)
- Bradycardia (heart rate <60/min)/arrhythmia
- Silent chest (air entry is minimum)
- Unrecordable PEFR.
- **Silent chest and bradycardia** are ominous sign.

ABG in Life-threatening Asthma

- Normal or high PCO_2 >6 kPa.
- Severe hypoxemia PO_2 <8 KPa/SPO_2 < 92% (60 mm Hg) when treated with O_2.
- Low pH <7.2 a high $[H^+]$ concentration.

MANAGEMENT OF ACUTE SEVERE ASTHMA

If a single criterion is taken then **PEF <200 L/min** is indicative of **severe asthma and PEF <100 L/min** must be taken as evidence of **life-threatening asthma**.

Immediate Treatment (Fig. 33.2)

- **Oxygen—High concentration** (60%), high-flow oxygen by facemask till PaO_2 > 8.5–9 kPa is reached or PO_2 > 90%.
- **High-dose inhaled β_2-adrenoceptor agonist**—Salbutamol 5 mg or terbutaline 2.5 mg should be given by nebulization when possible with O_2. If O_2 is not available compressed air can be used to drive the nebulizer and can be repeated within 30 minutes if necessary.
- **Systemic corticosteroid**—Intravenous hydrocortisone —200 mg or methylprednisolone 40–80 mg should be given initially.
- **IVβ_2-agonist** may be given.
- A slow infusion of **aminophylline** may be effective. 5 mg/kg loading dose followed by 1 mg/kg/hour.

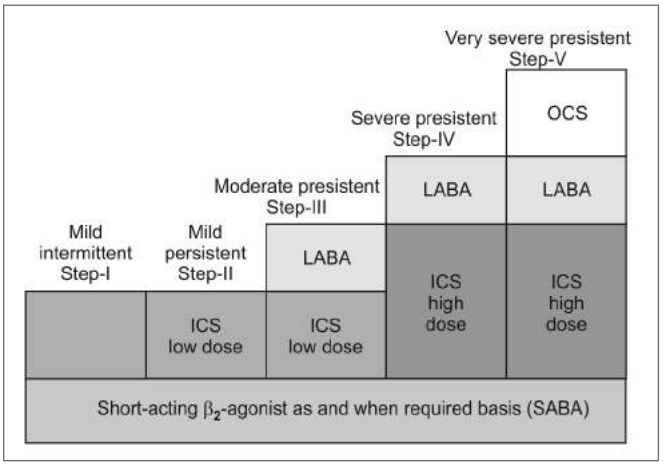


Fig. 33.2: Concept of step-up and step-down drug treatment in asthma

Abbreviations: OCS—Oral corticosteroids; ICS—Inhaled carticosteroids; LABA—Long-acting β_2 agonist

- **Magnesium sulfate** 1.2–2 g IV or by nebulization over 20 minutes has shown to be effective, where added with inhaled β_2 agonist.
  Prophylactic intubation may be indicated for impending respiratory failure.
- **Ipratropium bromide**—500 μg by nebulization.
- **Halothane (anesthetic)** after intubation and ventilation.

Subsequent Treatment

- Intravenous hydrocortisone 200 mg or methylprednisolone 40–80 mg 6 hourly to be continued in seriously ill patient. As the patient improves switch over to oral prednisolone 30–60 mg/day.
- Systemic antibiotic in case of associated bacterial infection of lower airway.
- Mechanical ventilation after intratracheal intubation may be required. Indication of mechanical ventilation are:
  - Coma, exhaustion, confusion and drowsiness
  - Respiratory arrest
  - PaO_2 < 8 kPa and falling (60 mm Hg)
  - $PaCO_2$ > 6 kPa and rising (45 mm Hg)
  - pH—low < 7.3 and falling.

EXERCISE

Write short notes on

1 Criteria for acute severe asthma.
2. Step care approach for treatment of chronic bronchial asthma.
3. Treatment of acute severe asthma.
4. Indication of mechanical ventilation in acute severe asthma.

Chapter 34

Chronic Obstructive Pulmonary Disease

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is defined as a chronic slowly progressive airflow obstruction (FEV_1 <80% of predicted and FEV_1/VC ratio <70%) which does not change markedly over several months.

The impairment of lung function is largely fixed but partially reversible by bronchodilator therapy.

Chronic Bronchitis

It is defined clinically by **excessive expectoration for at least 3 consecutive months in a year for more than 2 successive years**.

Emphysema

It is defined pathologically by **permanent destructive enlargement of the airspaces distal to terminal bronchioles**.

Pathology

Chronic bronchitis is characterized by:

- Airway wall inflammation
- Hypertrophy and hyperplasia of the mucus secreting goblet glands
- Increase in number of goblet cell in bronchi and bronchioles
- Decrease in number and function of ciliated columnar epithelial cell

Airflow limitation is due to both mechanical obstruction by mucus and inflammatory edema of mucous membrane of small airway

Emphysema is characterized by—Loss of alveolar attachment with surrounding small airway makes these small airway more liable to collapse during expiration. Pathologically emphysema may be classified into:

- Centrilobular (common variety)—Where respiratory bronchioles, alveolar duct and centrally located alveoli are involved
- Paraseptal—Superficial alveolai of the lobule are involved and responsible for blebs or giant bullae on the surface of the lung
- Panacinar—Rare variety

Associated pulmonary vascular remodeling causes persistent hypoxemia which results is pulmonary hypertension, right ventricular hypertrophy and dilatation.

Although pure form of chronic bronchitis and emphysema can exist usually there is a considerable overlap in majority of the patient.

ETIOLOGY

Two important factors are:

1. Genetic predisposition—Which is polygenic in nature.
2. Smoking or exposer to smoke, dust and polluted air which increase the risk of development of COPD by inducing persistent airway inflammation causing a direct imbalance in oxidant/antioxidant capacity or proteinase/antiproteinase load in the lung.

There is also a correlation between low birth weight and airway hyperresponsiveness with the development of COPD.

α_1-antitrypsin deficiency can cause emphysema in nonsmoker but the risk increases significantly when an enzyme-deficient patient smokes.

CLINICAL FEATURES

Symptoms

- Productive cough—Specially during winter months which shows steady increase during successive year.
- Regular morning cough.
- Wheeze.
- Breathlessness which is aggravated by infection, smoking and atmospheric pollution.
- Streaky hemoptysis or frank hemoptysis is usually associated with bacterial coinfection.

Signs

- General survey:
  - Loss of weight.
  - Central cyanosis.
  - Raised jugular venous pressure (JVP) due to right ventricular failure (RVF).
  - Pedal edema (due to right ventricular failure).
  - Flapping tremor and bounding pulse (due to hypercapnia).

  - Pursed lip breathing.
  - Paradoxical inward movement of rib cage with inspiration (Hoover's sign).
  - Clubbing usually absent—If present suggests presence of bronchogenic carcinoma.
  - Pink-puffers—Emphysematous patient, thin and noncyanotic.
  - Blue bloaters are chronic bronchitic patient cyanotic with edema which is due to pulmonary hypertension (PHTN) and RVF.
- Systemic examination:
  - Barrel-shaped chest (increase in anteroposterior diameter relative to transverse diameter of thoracic cage).
  - Wide subcostal angle.
  - Tracheal tug.
  - Accessory muscle of respiration are working.
  - Intercostal suction and indrawing of suprasternal and supraclavicular fossa.
  - Loss of cardiac dullness on percussion.
  - Right ventricular heave (due to PHTN).
  - Ronchi-during forced expiration due to small airway obstruction.
  - Splitting of S_2 with loud P_2 due to PHTN.
  - Murmur of tricuspid regurgitation (due to PHTN).

COMPLICATIONS

- Large pulmonary bullae
- Pneumothorax—due to rupture of bullae
- Respiratory tract infection and pneumonia
- Pulmonary hypertension and cor pulmonale.

CLINICAL FEATURES OF ACUTE EXACERBATION OF COPD

- Sudden increase in sputum volume
- Sputum becomes purulent
- Increased breathlessness
- Chest tightness
- Wheeze
- Pedal edema.

DIFFERENTIAL DIAGNOSIS OF ACUTE EXACERBATION OF COPD

- Pneumonia
- Pneumothorax
- Left ventricular failure (LVF)
- Pulmonary embolism
- Upper airway obstruction
- Acute severe asthma.

INVESTIGATION

- **Complete blood count**
  - Polycythemia
  - Leukocytosis with neutrophilia if LRTI is present.
- **Lung function test**—COPD is classified into three grades by measuring FEV_1 (Table 34.1).

Table 34.1: Classifications of COPD

COPD stage	Stage	Breathlessness/ Symptoms
0.	**At risk—**Spirometry normal	Chromic cough and sputum production
1.	**Mild**—FEV_1 ≥80% of predicted FEV_1 / FVC < 0.7	None/mild
2.	**Moderate**—50% ≤ FEV_1 < 80% FEV_1 / FVC <0.7	Symptom appear on exertion
3.	**Severe**—30% ≤ FEV_1 < 50% FEV_1 / FVC < 0.7	Symptomatic on minimal exertion, e.g. dressing at rest
4.	**Very severe**—FEV_1 <30% FEV_1 / FVC < 0.7 with chronic respiratory failure and sign of right heart failure	Symptomatic at rest

  Abnormal FEV_1 <80% of predicted with FEV_1/ VC ratio <70% with little variation of PEF after bronchodilator strongly suggest COPD. A normal FEV_1 exclude the diagnosis of COPD.
  - *Differential diagnosis of COPD from chronic asthma*—
    - Reversibility of FEV_1 testing using salbutamol, ipratropium or oral prednisolone (30 mg OD × 2 weeks) should be performed in all patients of COPD to differentiate from chronic asthma. Those who have substantial reversibility in FEV_1 (more than 15% increase in FEV_1 or 200 mL increase in FEV_1) have asthma. This reversibility test helps to differentiate chronic asthma from COPD patient.
    - Total lung capacity (TLC), residual volume (RV) and carbon monoxide transfer factor and coefficient are markedly reduced in emphysematous patient.
- **PaO_2 and $PaCO_2$**—Should be measured in cases of severe COPD with EEV_1 <40% of predicted.

  There is a fall in PaO_2 and a permanent increase in $PaCO_2$ in severe cases.
- **X-ray**—Chest X-ray cannot diagnose chronic bronchiti but is done to exclude other pathology.

  Emphysematous patient presents with the following chest X-ray (features)
  - Hypertranslucent lung field.
  - Terracing of the hemidiaphragm (low flat diaphragm).

- Obtuse cardiophrenic and costophrenic angle.
- Prominent pulmonary artery with RVH.
- Rarely bullae or pneumothorax.
- Tubular heart shadow.

- **CT scan of chest is done**—To quantify the extent and distribution of emphysema and before lung volume reduction surgery or lung transplant.
  - α_1-antitrypsin deficient patient typically have basal disease.
  - Smoker with normal α_1-antitrypsin level typically have apical disease.

MANAGEMENT

- **Cessation of smoking:** If necessary nicotin replacement therapy with bupropion 150 mg od/bd × 8 weeks to be started 1–2 weeks prior to stopping of smoking. (Contraindications are seizure and ICSOL).
- **Treatment of respiratory infection** to be done as soon as possible when the sputum becomes purulent because it aggravates breathlessness and may precipitate type–II respiratory failure.
  (Causative agents are *Streptococcus pneumoniae* or *Hemophilus influenzae*).
  - Amoxicillin—500 mg 8 hourly × 5–10 days.
  - Clarithromycin—250–500 mg 12 hourly × 5–10 days.
  - Co-amoxiclav—375–625 mg 8 hourly × 5–10 days.

  Influenza immunization and pneumococcal vaccine should be offered to all patients each year. Continuous antibiotic therapy is not recommended as it causes emergence of resistant starin.
- **Bronchodilator and antiinflammatory therapy**
  - *Mild COPD*—Patient usually treated with inhaled bronchodilator (anticholinergic and short-acting β_2 agonist incombination as and when require basis).
  - *Moderate COPD*—Usually requires combination of long-acting β_2 agonist (LABA) and tiotropium bromide are more appropriate.
  - *Severe COPD*—Usually require the above mentioned regimen with low dose inhaled steroid.
  - *Oral bronchodilator*—Can be used who cannot use inhaled devices.
  - *Theophylline*—Improve breathlessness and quality of life but their use is limited by their side effect.
  - *Corticosteroid*—Inhaled corticosteroid (ICS) reduces frequency and severity of exacerbation and recommended in severe disease (FEV_1 < 50%) who require two courses of antibodies and steroid per year. Oral steroid is required during exacerbation but not for daily use.
- **Other measures**
  - Exercise should be encouraged.
  - Expectorant, mucolytic, cough suppressant are of no proven benefit.
  - Sedative and opiates-based analgesic are contra-indicated.
  - Obesity, undernutrition and depression to be corrected.
- **Long-term treatment**: Long-term low-concentration oxygen therapy (2–4 L/min for minimum 15–20 hours/day) to achieve a PaO_2 >8 kPa 60 mm Hg or SaO_2 90% without unacceptible rise in $PaCO_2$ by nasal catheter. This helps in:
  - Prevention of the development of pulmonary hypertension.
  - Prevention of the development of secondary polycythemia.
  - Improve neuropsychological health.
  - Prolongation of life in COPD who are complicated by severe hypoxemia.
    - Criteria for long-term O_2 therapy
      - » PaO_2 < 7.3 kPa irrespective of $PaCO_2$
      - » FEV_1 < 1.5 L
      - » PaO_2 7.3–8 kPa (60 mm Hg SaO_2 90%) plus pulmonary hypertension, pedal edema and nocturnal hypoxemia.
      - » Patient stopped smoking.
- **Surgical treatment**:
  - Lung transplantation (usually single lung) Indication—Young patient with α_1-antitrypsin deficiency severe disease.
  - Surgical removal of expanding or very large bullae may be indicated in young patients with minimal airflow resistance without generalized emphysema.
  - Lung volume reduction—By removal of severely affected areas of emphysematous lung in order to improve pulmonary mechanics particularly enhancing diaphragmatic function who have upper lobe emphysema with preserved gas transfer without pulmonary hypertension.

Air travel—Hypercarbia and gross hypoxemia (PaO_2 <9 kPa) is a relative contraindication to air travel. Patients with resting PaO_2 on room air <9 kPa will require supplemental oxygen because inflight cabin pressure is equivalent to an altitude of 5,000–8,000 ft. With this air pressure PaO_2 of such patient's will fall below 7 kPa.

MANAGEMENT OF ACUTE EXACERBATION OF COPD

- **Add or increase bronchodilator therapy**—As mentioned above.
- **Antibiotic—**As mentioned above.
- **Oral corticosteroid**—Prednisolone 30 mg/day × 7–10 days.
- **Check ABG, chest X-ray, ECG, blood count, urea, electrolyte, FEV and sputum for culture**.

Table 34.2: BODE index for prognosis

BODE index for prognosis	0	1	2	3
FEV_1	> 65	50–64	36–49	> 35
Distance walked in 6 min (meter)	> 350	250–349	150–249	< 149
NMRC dyspnea scale	0–1	2	3	4
Body mass index (BMI)	> 21	< 21	< 21	< 21

Note: BODE index 0–2 has a mortality around 10% in 52 month; BODE index 7–10 has a mortality around 80% in 52 month

- **Supplemental O_2:** 24–28% O_2 via mask or nasal catheter 2 L/min by nasal prong to keep PaO_2 > 8 kPa (60 mm Hg) or SaO_2 > 90% without acidosis.
- **Bronchodilator:** Nebulized with β_2 + Ipratropium bromide 4–6 hourly.

  In unresponsive patient consider infusion of aminophylline—250–500 mg slowly over 8–12 hours (although not advocated by RCT at present) can be given in refractory cases.
- **Diuretic:** If JVP is raised and edema is present.
- **Intermittent positive pressure ventilation:** In spite of all the above measure if pH <7.35, $PaCO_2$ > 6 kPa consider ventilatory support. (Invasive or noninvasive IPPV intermittent positive pressure ventilation).
- **Doxapran** can be considered 1.5–4.0 mg/min by slow IV infusion.
- **Low molecular weight heparin** therapy to prevent leg vein thrombosis.

Prognosis (Table 34.2)

- Patient with atopy have a significant better survival.
- Best guide to progression of COPD is the decline in FEV_1 over time (normally 30 mL/year)
- Prognosis is inversely related to age and directly related to bronchodilator therapy.
- Pulmonary hypertension is a poor prognostic parameter.
- **No treatment apart from long-term oxygen therapy has shown to affect the disease outcome**.

EXERCISE

Write short notes on

1. The stages of COPD and clinical features.
2. Management of COPD.
3. Investigation of COPD.

Chapter 35

Pneumonia

Pneumonia is an acute lower respiratory infection associated with recently developed radiological shadow affecting one lobe or segment.

Lobar pneumonia refers to homogenous consolidation (red hepatization) of one or more lung lobes usually often associated with pleural inflammation.

Bronchopneumonia refers to alveolar consolidation associated with bronchial or bronchiolar inflammation often affecting both lower lobe (Fig. 35.1).

COMMON PATHOGEN IN COMMUNITY-ACQUIRED PNEUMONIA (CAP)

- Streptococcus pneumoniae
- Mycoplasma pneumoniae
- Haemophilus influenzae
- Chlamydia pneumoniae
- Respiratory viruses (influenza A and B, parainfluenza, adenovirus respiratory syncytial virus).

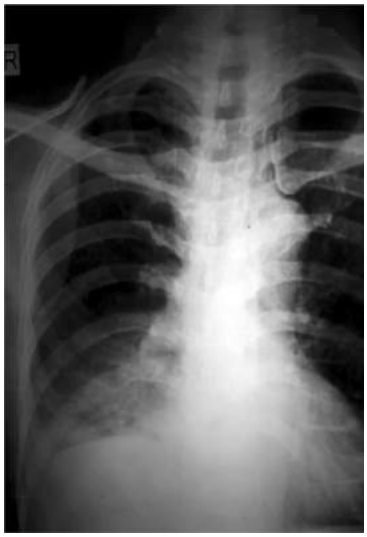


Fig. 35.1: Right lower lobe pneumonia

COMMON PATHOGEN FOR VENTILATOR-ASSOCIATED PNEUMONIAL AND HOSPITAL-ACQUIRED PNEUMONIA (VAP AND HAP)

- Methicillin-resistant *Staphylococcus aureus*
- *Pseudomonas aeruginosa*
- *Acinetobacter*
- *Enterobacteriaceae* (multidrug-resistant).

Predisposing Factors for CAP

- Alcohol
- Chronic obstructive pulmonary disease (COPD)
- Smoking
- Structural lung disease (bronchiectasis)
- Cerebrovascular accident (CVA), parkinsonism
- Lung abscess
- Travel
- Exposure to bats, bird, rabbit, sheep and goat.

CLINICAL FEATURES

Symptoms

- **Cough** at first dry and later becomes productive and rusty or frank hemoptysis may be present.
- **Fever** with chill and rigor usually present. Recurrence of fever suggests associated empyema.
- Malaise and headache, fatigue, myalgia and arthralgia.
- **Pleuritic chest pain**.
- **Nausea, vomiting, diarrhea (up to 20%) and convulsion**—Rarely present in children.
- Herpes labialis—Specially in *Streptococcus pneumoniae*.
- Mental confusion can be early in severe pneumoniae.

Physical Signs

- Pyrexia.
- Tachypnea.

- Tachycardia.
- Evidence of hypoxemia.
- Hypotension.
- Diminished chest movement.
- Impaired note on percussion (Woody dull on percussion over pneumonia).
- High pitch bronchial breathing.
- *Coarse crepitation* specially during resolution phase. In case of associated pleurisy and pleural effusion.
- *Pleural rub* may be heard during early phase, over the consolidated area.
- If synpneumonic effusion develops— then features of pleural effusion—like diminished movement of chest wall, stony dull note on precussion and diminished breathsound are usually found.
- Upper abdominal tenderness is present in lower lobe pneumonia or with associated hepatitis.
- May have features of septic shock and organ failure in severe cases.

CLINICAL FEATURES SUGGESTIVE OF SUPPURATIVE PNEUMONIA

- Acute onset.
- High remittent pyrexia.
- Profound systemic symptom and rapid deterioration of general health.
- Digital clubbing—Quickly develops (within 10–14 days).
- Features of consolidation early develops.
- Pleural rub in early stage.
- Signs of cavitations—Rarely found.

INVESTIGATION

- **Chest X-ray**—Homogeneous opacity localized to affected lobe or segment detected usually 12–18 hours after the onset of illness. Also helps in diagnosis of associated pleural effusion, empyema and lung abscess. Lobar consolidation takes 4–12 weeks to clear.

  If a relapse or recurrence occurs in the same lung or segment, possibility of an underlying neoplasm must be considered.
  - Hilar lymphadenopathy usually seen with *Mycoplasma pneumoniae*.
  - Lung abscess cavity are more frequently observed in staphylococcal (thin-walled) or pneumococcal (serotype-3) pneumonia.
  - Failure of resolution of pneumonia with appropriate therapy indicates underlying bronchial obstruction by foreign body or carcinoma.
- **Blood count** shows leukocytosis with neutrophilia.
- **Blood culture** is positive in pneumococcal pneumonia in 50% cases.
- **Serology** is done to diagnose, *Mycoplasma*, *chlamydia*, *Legionella*, viral and pneumococcal pneumonia.
- **Sputum** examination is done by:
  - Gram staining
  - Acid fast staining (AFB) staining
  - Culture and sensitivity testing.

  In case of severe pneumonia where patient cannot expectorate:
  - Tracheal aspirate.
  - Induced sputum.
  - Bronchoalveolar lavage.
  - A percutaneous needle aspirate can be examined.
  - Throat or nasopharyngeal swab-in children and during an epidemic is examined.
- Aspiration of pleural fluid if present (under ultrasound guidance) for Gram stain, AFB stain and culture.

MANAGEMENT

Culture specimen should be sent prior to starting antibiotic.

Emperical antibiotic regimen in uncomplicated community-acquired pneumonia:

- *Amoxicillin*—500 mg 8 orally
  If allergic to penicillin
  Clarithromycin—500 mg 12 hourly orally/IV
  Azithromycin—500 mg bd for 5 days.
- **In severe CAP**—
  - *Clarithromycin*—500 mg 12 hourly IV alternatively *Azithromycin*—500 mg bd for 5 days plus *Co-amoxiclav* 1.2 g 8 hourly IV or *Ceftriaxone*—1–2 g daily IV or Cefuroxime—1.5 g 8 hourly IV.
  - *Amoxicillin* —1 g 6 hourly IV plus *Flucloxacillin*—2 g 6 hourly IV.
- **If *Staphylococcus* is cultured or suspected**
  Flucloxacillin —1–2 g 6 hourly IV
  Clarithromycin— 500 mg 12 hourly IV
  Linezolid—600 mg IV bd
  Vancomycin—1 g IV bd.
- **If *Mycoplasma* or *Legionella* is suspected**
  Clarithromycin—500 mg 12 hourly orally or IV
  Azithromycin—500 mg bd for 5 days plus
  Rifampicin—600 12 hourly IV in severe cases.
- **Psittacosis is treated with**
  Tetracycline—500 mg 6 hourly, orally or 500 mg IV bd alternatively *Erythromycin*—500 mg 6 hourly IV.
- *Chlamydia pneumoniae*
  Erythromycin or *tetracyclinae* (dose same as psittacosis).

- *Klebsiella pneumoniae*
  Gentamicin (dose according to body weight and creatinine clearance) plus ceftazidime—1 g 8 hourly IV or
  Ciprofloxacin—200 mg IV 12 hourly.
- *Actinomycosis pneumonia*—Benzyl penicillin—2–4 g 6 hourly.
- **Chickenpox pneumonia**—Oral acyclovir 800 mg 5 times daily for 5 days.
  Duration of treatment
  - Pneumococcal pneumonia requires—7–10 days treatment.
  - *Legionella* and *Klebsiella* and *Staphylococcus* require 14 days or longer duration of therapy.
    For pleural pain—Paracetamol or pethidine.
    Morphin—Should not be used in depressed respiratory function.

COMPLICATIONS

- Parapneumonic effusion.
- Empyema.
- Suppurative pneumonia and lung abscess (Figs 35.2 and 35.3).
- Thromboembolic disease.
- ARDS, renal failure and multiorgan failure.
- Hepatitis, pericarditis, myocarditis and meningoencephalitis.
- Ectopic abscess.
- Pneumothorax.

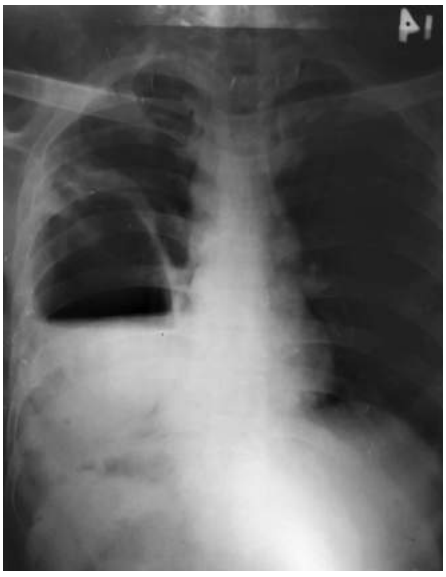


Fig. 35.2: Lung abscess (Posteroanterior view)

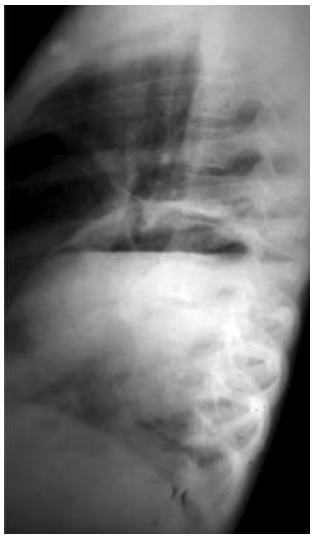


Fig. 35.3: Lung abscess (lateral view)

FACTORS PREDISPOSING NOSOCOMIAL (HOSPITAL-ACQUIRED) PNEUMONIA

- Suppressed host defence—Due to steroid, diabetes, malignancy, HIV and immune suppression therapy.
- Suppressed cough reflex—Due to sedative cough mixture and postoperative condition.
- Suppressed mucociliary clearance—General anesthesia.
- Bulbar or vocal cord palsy.
- Aspiration of nasopharyngeal or gastric secretion—Reduced consciousness, vomiting, reflux, achalasia and nasogastric intubation.
- Bacteria introduced in LRT—By endotracheal intubation, tracheostomy, ventilation, nebulizer and bronchoscope.
- Septicemia—Abdominal sepsis, IV cannula, embolism and urosepsis.

PREVENTION

- Vaccination with influenza and pneumococcal vaccine (7 valent pneumococcal conjugate vaccine).
- Oseltamivir/zanamivir for 2 weeks (alternatively for influenza vaccine).

EXERCISE

Write short notes on

1. Common pathogen for CAP.
2. Clinical features of suppurative pneumonia.
3. Complication of CAP.
4. Drug therapy for CAP.
5. Factor responsible for HAP.

Chapter 36

Pleural Effusion

DEFINITION

Accumulation of excess fluid in pleural space is called pleural effusion. Normally 25–30 mL of fluid is present in pleural space which is in a dynamic equilibrium.

Pleural effusion occurs when pleural fluid formation exceeds pleural fluid reabsorption. Fluid enters the pleural space from the capillary in the parietal pleura and is removed via lymphatic in the parietal pleura. Fluid can also enter the pleural space from interstitial space of lung via visceral pleura or from peritoneal cavity via small hole in diaphragm. The lymphatic can absorb 20 times of normal fluid formed.

Pleural effusion develops when excess fluid is formed from:

- Interstitial spaces of lung.
- Parietal pleura.
- Peritoneal cavity.
- Alternatively, where there is diminished pleural fluid removal by lymphatic due to blockage of lymphatics in malignancy and lymphoma.
  - **Empyema**—Accumulation of frank pus in pleural space is called empyema.
  - **Hemothorax**—Accumulation of blood in pleural space is called hemothorax.
  - **Exudative effusion**—When pleural fluid accumulates due to increased microvascular permeability from diseases of pleura or lung is called exudative effusion as seen in tuberculosis, pneumonia, malignancy.
  - **Transudative effusion**—When pleural fluid accumulate either due to increase hydrostatic pressure or decreased osmotic pressure of blood is called transudative effusion, which is seen in cardiac, liver or renal failure and nephrotic syndrome.

CAUSES OF PLEURAL EFFUSION

Causes of Exudative Effusion

- **Tuberculosis**
- **Pneumonia**—Bacterial, viral and fungal
- **Bronchogenic carcinoma** and pleural mesothelioma

} Most common causes

- Pulmonary infarction
- Collagen vascular diseases—systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) Wegener's granulomatosis and Sjögren's syndrome
- Lymphoma and leukemia
- Pancreatitis, liver abscess, subphrenic abscess and esophageal rupture
- Radiation injury
- Hemothorax
- Chylothorax
- Pericarditis
- Drug-induced—Neurofibrillary tangles (NFT), dantrolene, methysergide procarbazine and amiodarone.

Causes of Transudative Effusion

- **Cirrhosis of liver**
- **Nephrotic syndrome**
- **Congestive cardiac failure**

} Most common causes

- Malnutrition
- Constrictive pericarditis and pericardial effusion
- Hypothyroid
- Superior vena caval obstruction
- Peritoneal dialysis
- Pulmonary embolism.

Causes of Hemorrhagic Effusion

- Lung cancer—Primary and secondary
- Pleural mesothelioma
- Chest trauma
- Bleeding disorders
- Anticoagulant overdose
- Tuberculosis
- Pulmonary embolism
- Hemorrhagic pancreatitis.

Causes of Chylous Effusion

- Filariasis
- Lymphoma
- Hypothyroid
- Lung cancer
- Tuberculosis
- Trauma.

Causes of Bilateral Pleural Effusion

- All causes of transudative effusion.
- Pulmonary tuberculosis (bilateral).
- Lymphoma and leukemia.
- Connective tissue diseases—SLE, RA, Wegener's, Sjögren and Churg-Strauss.
- Pulmonary embolism (bilateral).
- Trauma.

Causes of Right-sided Pleural Effusion

- Portal hypertension
- Amebic liver abscess
- Congestive cardiac failure (CCF)
- Meigs' syndrome.

Causes of Left-sided Pleural Effusion

- Esophageal rupture.
- Acute pancreatitis.
- Postmyocardial infarction syndrome (Dressler syndrome).
- After coronary artery bypass grafting (CABG).

Causes of Recurrent Pleural Effusion

- Lung cancer and pleural mesothelioma.
- All causes of transudative effusion.
- Tuberculosis.
- Collagen vascular diseases—SLE and rheumatoid arthritis.

Common Causes of Pleural Effusion

- Pulmonary tuberculosis.
- Bronchial carcinoma.
- Parapneumonic/synpneumonic effusion.
- Heart failure, nephrotic syndrome, liver failure and malnutrition.
- Constrictive pericarditis.

CLINICAL FEATURES

- Frequently insidious in onset and breathlessness is the only symptom.
- Sometimes symptoms and signs of pleurisy often precede the development of pleural effusion specially in tuberculosis, pneumonia, infarction and connective tissue diseases.

Signs

- **Inspection**—Intercostal fullness and reduced chest wall movement.
- **Palpation**—Shifting of trachea and cardiac apex with mediastinum to opposite side.
  Reduced chest wall movement.
  Diminished vocal fremitus.
- **Percussion**—Stony dull.
- **Auscultation**—Reduced or absent breath sound and vocal resonance.

INVESTIGATION (FLOWCHART 36.1)

- **Chest X-ray**—Shows **dense, uniform homogenous opacity occupying lower and lateral part of the hemithorax obliterating the costophrenic angle with a concave upper border** is diagnostic of pleural effusion.
  - *Subpulmonary effusion*—Occasionally the fluid is localized below the lower lobe simulating elevated hemidiaphragm.
  - *Encysted effusion*—A localized opacity may be seen as in interlober effusion where the periphery of the effusion is sealed by proteinaceous exudate.
- **Ultrasonography**—It is a very important tool in detecting small effusion and differentiating localized or encysted effusion from lung tumor, subdiaphragmatic collection and subpulmonary effusion.

  It is also helpful in guiding pleural aspiration and pleural biopsy.
- **Pleural aspiration**—Diagnostic aspiration should be done in all patients with radiological evidence of pleural effusion to differentiate between exudative and transudative type. It some cases it may give clues for a partienal etiology. It is better to do the aspiration under USG or CT guidance in case of small effusion.

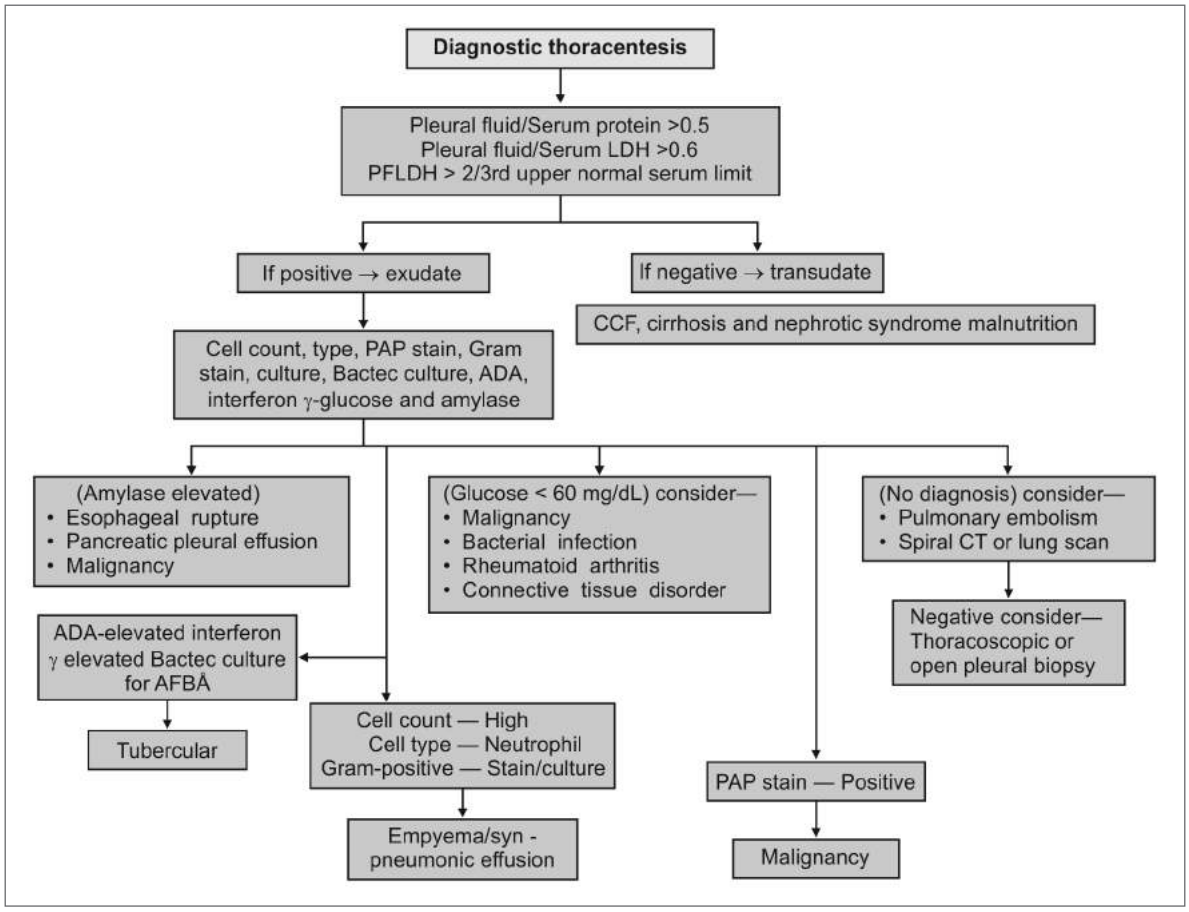
  At least 50 mL of fluid should be withdrawn and sent for:
  - Cytological examination.
  - Biochemical examination.
  - Microbiological examination and culture (both ordinary bacterial culture and for TB).

Pleural biopsy should be taken after initial pleural fluid sample has been aspirated for diagnostic purposes and before further drainage is undertaken.

Characteristic features of pleural fluid

- **Physical appearance**
  - *Watery*—Transudative effusion
  - *Straw colored*—Tubercular and infarction
  - *Blood stained*—Tubercular, malignancy and infarction
  - *Purulent*—Parapneumonic effusion or empyema
  - *Chylous/milky*—Obstruction to lymphatic by malignancy, filaria and hypothyroid or trauma
- **Cell type**:
  - *RBC*— Malignancy, tubercular, infarction and trauma
  - *Neutrophil*—Parapneumonic/empyema
  - *Lymphocytic*—Tubercular and viral.
- **Biochemical**—
  - *Pleural protein with serum protein ratio* > 0.5 seen in exudative effusion found in *TB, rheumatoid arthritis, malignancy, pancreatitis, esophageal rupture, SLE* pleural protein *and* serum protein ratio <0.5 suggest transudative effusion found in *heart failure, liver failure, renal failure, hypothyroid, malnutrition and pulmonary infarction*
  - *LDH increased >200 IU/L or pleural LDH and* serum LDH ratio >0.6 in exudative effusion.
  - *Glucose* diminished in malignancy and rheumatoid arthritis, bacterial infection
  - *pH* diminished (7.2) in empyema and esophageal rupture
- **Microbiological**
  - Smear for Gram stain and Ziel-Neelsen stain
  - Culture for ordinary bacteria and *Mycobacterium tuberculosis*

Flowchart. 36.1: Diagnosis of pleural effusion



MANAGEMENT

- Therapeutic aspiration can be done to relieve breathlessness. But should not be done more than 1 liter in one sitting due to the danger of
  - Re-expansion pulmonary edema (ARDS).
  - Pneumothorax.

  A chest X-ray to be repeated after all therapeutic aspirations.
- Specific treatment is done according to etiology.
  Tubercular—ATD for 6 months + Prednisolone 20 mg/day for initial 4–6 weeks.
  Empyema—Intercostal drain to be given till the hemithorax becomes dry along with antibiotic according to culture and sensitivity report for 2–4 weeks.
  Malignant effusion—Attempt to be made to drain all fluid by intercostal tube and obliterate the pleural space (pleurodesis) by injection of talc or bleomycin, doxycycline 500 mg plus cancer chemotherapy.
  Cardiac failure—Diuretic, ACEI, β-blocker and digitalis.

FEATURES OF SPECIAL TYPE OF EFFUSION

- **Pleural effusion due to heart failure**—It is the most common cause of transudative pleural effusion. The effusion is due to increased amount of fluid in the interstitial spaces of lung that comes out through visceral pleura which exceeds the absorption capacity of lymphatic of the parietal pleura.
  Diagnostic thoracentesis should be performed if—
  - Effusion is not bilateral.
  - Patient is febrile.
  - There is pleuritic chest pain.
  - Effusion persists despite diuretic therapy.
  - N terminal ProBNP >1500 pg/mL is diagnostic of effusion due to CCF.
- **Hepatic hydrothorax**—Pleural effusion occurs in approximately 5% of patients of cirrhosis with ascites. It is caused by movement of fluid through the small hole in the diaphragm from peritoneal cavity to pleural space. The effusion is usually right-sided and may be large enough to produce dyspnea.
  - *Treatment*—Medical management to control ascites and pleural effusion. If not successful—
    - Insertion of transjugular intrahepatic portal systemic shunt (TIPSS).
    - Liver transplant can be performed.
- **Parapneumonic/synpneumonic effusion**—It develops along with pneumonia, lung abscess, bronchiectasis.

- *Clinical features*:
  - Pneumonia with aerobic organism causes effusion with fever, chest pain, sputum production, leukocytosis.
  - Pneumonia with anaerobic organism frequently presents with subacute illness without fever but with weight loss, brisk leukocytosis, mild ane-mia and a history of a condition that predisposes to aspiration.
- *Diagnosis*:
  - Presence of pleural fluid by lateral decubitus radiograph.
  - USG of the thorax.
  - CT of thorax.
- *Treatment*:
  - If the chest wall is separated from lung by 10 mm then therapeutic thoracentesis is done.
  - Loculated effusion, complicated effusion as defined by pH<72, fluid glucose (60 mg/dL, positive Gram stain or culture empyema) or in recurrent effusion tube thoracostomy is warrented in addition to thoracentesis.
  - Insertion of an intercostal chest drain with instilling streptokinase 25,000 units to breakdown adhesion.
  - Thoracoscopy with breakdown of adhesion in case of loculated effusion.
  - Decortication of lung may sometime necessary if effusion cannot be controlled by medical management.
  - Appropriate antibiotics according to culture and sensitivity report.

- **Pleural mesothelioma**—It is a primary malignant tumor arising from pleural mesothelial cell and most commonly related to asbestos exposer.
  - *Clinical features*— Chest pain and shortness of breath.
  - *Chest X-ray*
    - Pleural effusion
    - Generalized pleural thickening
    - Shrunken hemithorax.
  - *Diagnosis*—It is established by thoracoscopic or open pleural biopsy with histopathological examination.
  - *Treatment*—No curative treatment is available for pleural mesothelioma. Symptomatic treatment with
    - Opiates analgesic
    - Oxygen
    - Radical surgery
    - Chemotherapy.

  Radiotherapy is not effective in prolonging life.
- **Hemothorax**—If thoracentesis reveals bloody fluid, a hematocrit should be done on pleural fluid. **If hematocrit of pleural fluid exceeds 50% that of the peripheral blood, it is called hemothorax**.
  - Most patients with hemothorax require tube thoracostomy which allow measurement of bleeding.
  - If bleeding comes from pleura, usually spontaneous apposition of two pleural surfaces occur.
  - If pleural hemorrhage exceeds 200 mL per hour open thoracotomy should be done.
- **Chylothorax**—Chyle accumulate in pleural space when thoracic duct ruptured into pleural space.
  - *Causes of chylothorax*:
    - Lymphoma
    - Tuberculosis (TB)
    - Filariasis
    - Trauma.

  Thoracentesis reveal milky fluid and on biochemical analysis triglyceride level exceeds 110 mg per dL. Patients with chylothorax who have no history of trauma, CT of thorax and lymphangiogram to be done to assess the mediastinal lymph node.
  - *Treatment:*
    - Insertion of a chest tube plus the administration of octreotide.
    - Implantation of pleuroperitoneal shunt.
    - Prolong tube thoracostomy with drainage leads to malnutrition and immunologic failure.
- **Tuberculous pleural effusion**—It is the most common cause of pleural effusion in India. Tuberculous pleural effusion occurs primarily due to hypersensitivity reaction to tuberculous protein in the pleural space.
  - *Clinical features*—Additional features are irregular low grade fever, chest pain, cough, weight loss and dyspnea.
  - *Diagnosis*—Pleural fluid is exudative in type with small lymphocyte.

  Diagnosis is established by the examination of pleural fluid:
  - Elevated adenosine deaminase more than 45 IU per liter.
  - Interferon gamma more than 140 picogram per mL.
  - PCR positive for tuberculous DNA.
  - Culture in bactec media positive for *Mycobacterium tuberculosis*.
  - Needle biopsy of pleura for HP examination.
  - *Treatment*—Same as pulmonary tuberculosis. Adjunctive glucocorticoid (prednisolone 20–30 mg/day for 4 weeks) helps in prevention of pleural fibrosis.
- **Malignant effusion**—It is the second most common cause of pleural effusion. Carcinoma of lung, breast carcinoma and lymphoma is responsible for 75% of all malignant pleural effusion.
  - *Clinical features*—Dyspnea is out of proportion to the amount of effusion, apart from other features of malignancy.
  - *Diagnosis*—Pleural fluid is exudative in nature and glucose level is reduced if tumor burden is high.

Diagnosis is confirmed by cytology of pleural fluid—if negative, biopsy of pleura is done through needle or thoracoscopy.

- *Treatment*—If dyspnea is severe but is relieved by thoracentesis:
  - Tube thoracotomy with instillation of sclerosing agent, e.g. doxycycline (500 mg) or bleomycin in the pleural space.
  - Insertion of a small indwelling catheter with one way (Heimlich) valve.

EXERCISE

Write short notes on

1. Approach to a patient of pleural effusion.
2. Hemothorax and chylothorax.
3. Cause of exudative and transudative pleural effusion.
4. Management of synpneumonic/parapneumonic effusion/malignant pleural effusion/pleural mesothelioma.
5. Cause of right-sided, left-sided and bilateral pleural effusion.

Chapter 37

Respiratory Failure

INTRODUCTION

Respiratory failure in a condition (results from variety of disease or disorder) in which lung function is inadequate for metabolic requirement of body.

- **Type–I respiratory failure**—Patients only have hypoxia but no hypercapnia.
- **Type–II respiratory failure**—Patients have hypercapnia along with hypoxia.
- **Type–III respiratory failure**—Postoperative respiratory failure.
- **Type–IV respiratory failure**—Respiratory failure seen in shock.

TYPE–I RESPIRATORY FAILURE OR ACUTE HYPOXEMIC RESPIRATORY FAILURE

This form of respiratory failure occurs as a result of alveolar flooding and subsequent development of shunt physiology.

Alveolar flooding develops in:

- Pulmonary edema
- Pneumonia
- Alveolar hemorrhage.

Pulmonary edema may again be due to:

- Elevated pulmonary intravascular pressure as seen in—LVF and mitral stenosis.
- Intravascular volume overload.
- Low pressure pulmonary edema, seen in ARDS characterized by diffuse bilateral air space edema in absence of left atrial hypertension.

Pulmonary capillary occlusion pressure is less than 18 mm Hg.

COMMON CAUSES OF TYPE–I RESPIRATORY FAILURE

- Acute left ventricular failure
- Mitral stenosis
- Acute respiratory distress syndrome
- Pneumothorax
- Pneumonia
- Pulmonary embolism
- Initial stage of acute severe asthma.

DIAGNOSIS

- Chest X-ray
- Arterial blood gas
  PaO_2 <8.0 kPa
  $PaCO_2$ <6.6 kPa
- pH—Normal or low
- Bicarbonate—Normal.

MANAGEMENT OF TYPE–I RESPIRATORY FAILURE

- Prompt diagnosis and management of underlying precipitating disease.
- All patient should be treated with high concentration (greater than 35%) of oxygen by oronasal mask. Young children are managed by oxygen tent.
- Close monitoring is very essential, blood gas analysis is repeated after 20 minutes to look for PaO_2 which should be greater than 8 kPa, if not achieved.
- Tracheal intubation and mechanical ventilation with low tidal volume 7 mL per kg of ideal body weight will cause dramatic reduction in mortality.
- In case of acute LVF, massive pulmonary embolism and pleural pain due to pneumonia treatment with opiates analgesic are appropriate but should never be used in Type–I respiratory failure due to asthma or COPD.

TYPE–II RESPIRATORY FAILURE (ASPHYXIA)

This form of respiratory failure occurs due to alveolar hypoventilation and results in inability to eliminate CO_2 effectively.

The mechanism of type–II respiratory failure are:

- Impaired CNS drive to breath—Narcotic overdose, brainstem injury, sleep apnea and hypothyroidism.
- Impaired strength of respiratory muscle:
  - Amyotrophic lateral sclerosis
  - Phrenic nerve injury
  - Guillain-Barré syndrome
  - Myasthenia gravis.
- Increased load on the respiratory system:
  - Resistive load due to bronchospasm— COPD, chronic asthma.

  - Load due to reduced lung compliance—Alveolar edema and atelectasis.
  - Load due to reduced chest wall compliance—Pneumothorax, pleural effusion and abdominal distension.
- Load due to increased minute volume—Pulmonary embolism and sepsis.

COMMON CAUSES OF TYPE–II RESPIRATORY FAILURE

- COPD
- Retension of secretion.
- Acute severe asthma.
- Pulmonary embolism.
- Pneumothorax.
- Rib fracture.
- CNS depression due to drug (morphine and pethidine), head injury and encephalitis.
- Impaired neuromuscular transmission—Guillain-Barré syndrome, myasthenia, phrenic nerve palsy and myopathy.

INITIAL ASSESSMENT

Patient may not appear distressed despite being critically ill :

- Conscious level, e.g. ability to cough out or respond to vocal command to be looked for.
- Feature of CO_2 retension is usually present—High volume pulse, warm extremity and flapping tremor.
- Features of airway obstruction—Wheeze, intercostal indrawing, pursed lip breathing and tracheal tug.
- Features of right ventricular failure—Edema, raised JVP, hepatomegaly and ascites.
- Search for other sign of precipitating factor or disease.

INVESTIGATION

- Chest X-ray.
- ABG for hypoxemia (PaO_2 <8.0 kPa), hypercapnia ($PaCO_2$ >6.6 kPa_2), acidosis (pH—low). Bicarbonate —Raised.
- CT/MRI of brain—Brainstem injury.
- NCV and EMG—Amyotrophic lateral sclerosis, myopathy and phrenic nerve injury.
- CSF study for cytoalbuminic dissociation (Guillain-Barré syndrome).

MANAGEMENT OF TYPE–II RESPIRATORY FAILURE

- Reversing the underlined cause of respiratory failure.
- Maintenence of airway.
  - Treatment of specific precipitating event.
  - Frequent physiotherapy and pharyngeal suction in COPD patient.
  - Nebulized bronchodilator for asthma and COPD patient.
  - Controlled oxygen therapy start with 24% O_2 flow mask to keep PaO_2 >7 kPa, PaO_2 <5 kPa is very dangerous.
  - Antibiotic.
  - Diuretic to manage RVF.
    If the $PaCO_2$ continue to rise > 6.6 kPa or P_aO_2 < 5.5–6 KPa or acidemia developes—Doxapram.
- Noninvasive positive pressure ventilation by mechanical ventilator with tight-fitting face or nasal mask without endotracheal intubation.

TYPE–III RESPIRATORY FAILURE

This form of respiratory failure occurs as a result of basal lung atelectasis commonly seen in the postoperative period. After general anesthesis there is decrease in functional residual capacity which leads to collapse of the dependent lung unit. That is why this type of respiratory failure is called perioperative respiratory failure.

TREATMENT

- Frequent change of posture.
- Chest physiotherapy.
- Upright positioning.
- Aggressive control of incisional abdominal pain.
- Noninvasive positive pressure ventilation may be used to reverse the regional atelectasis with the help of tight-fitting face or nasal mask without endotracheal intubation.

TYPE–IV RESPIRATORY FAILURE

This form of respiratory failure occurs due to hypo-perfusion of respiratory muscle in patients with shock. Normally respiratory muscle consume less than 5% of total cardiac output and oxygen delivery. Patient in shock often suffers respiratory distress due to superimposed:

- Pulmonary edema
- Lactic acidosis
- Anemia.

In this setting up to 40% of cardiac output may be distributed to respiratory muscle. To divert cardiac output from respiratory muscle to vital organ mechanical ventilatory support is required.

TREATMENT

Intubation and mechanical ventilation allow redistribution of cardiac output away from respiratory muscle back to vital organ while the shock is being treated.

EXERCISE

Write short note on

1. Type-I, Type-II, Type-III and Type-IV respiratory failure.

Chapter 38

Cor Pulmonale

INTRODUCTION

Cor pulmonale is also called pulmonary heart disease. It is defined as dilation and hypertrophy of right ventricle in response to disease of lung parenchyma or lung vasculature but not due to congenital heart disease or RHD that may also cause RVH or RVF.

ETIOLOGY

- **Causes of hypoxemic vasoconstriction**:
  - Chronic bronchitis
  - COPD
  - Cystic fibrosis
  - Chronic hypoventilation
    - Obesity
    - Neuromuscular disease
    - Chest wall dysfunction
    - Living at high altitude.
- **Occlusion of pulmonary vascular bed**:
  - Acute or chronic thromboembolic disease
  - Pulmonary arterial hypertension (HTN)
  - Pulmonary veno-occlusive disease.
- **Lung parenchymal disease**:
  - Chronic bronchitis
  - COPD
  - Bronchiectasis
  - Interstitial lung disease (ILD)
  - Pneumoconiosis
  - Sarcoidosis.

PATHOPHYSIOLOGY

The common mechanism of cor pulmonale is pulmonary hypertension that leads to RV hypertrophy and dilation.

In acute cor pulmonale (that occurs following massive pulmonary embolus) there is RV dilatation and failure but no RV hypertrophy, but in chronic cor pulmonale there is progressive pulmonary hypertension that results in initial modest RV hypertrophy followed by RV dilatation.

Decompensation of chronic cor pulmonale can be aggravated by intercurrent infection that induces pulmonary vasoconstriction and increases RV afterload by—

- Hypoxemia and hypercarbia-induced respiratory acidosis.
- Acute pulmonary emboli.
- Positive pressure mechanical ventilation.

RV failure can also be precipitated by:

- Atrial arrhythmia
- Polycythemia
- Sepsis
- Large left to right extracardiac shunt.

The most common mechanism that leads to pulmonary hypertension including vasoconstriction is activation of coagulation cascade and obliteration of pulmonary arteries.

CLINICAL FEATURES

Symptoms of chronic cor pulmonale that are due to underlying pulmonary disorder.

The most common symptoms are:

- **Dyspnea**:
  - It is due to increased work of breathing secondary to increase elastic recoil of the lung (fibrosing lung disease).
  - Altered respiratory mechanics (overinflation in emphysema).
  - Inefficient ventilation (pulmonary vascular disease causing ventilation perfusion mismatch).
- **Orthopnea and PND**—It is a rare symptom of isolated RVF usually points towards LVF.
- **Post-tussive or effort-related syncope**—Because of the inability of the RV to deliver adequate amount of blood to left side of the heart.
- **Pedal edema**—It is secondary to neurohormonal activation, elevated RV filling pressure, or increased level of CO_2 and hypoxemia that lead to peripheral vasodilation and edema formation.

SIGNS

- **Tachypnea**
- **Elevated jugular venous pressure**
- **Prominent CV-waves** in jugular venous pulse as a result of tricuspid regurgitation.
- **Pedal edema**.
- **Cyanosis**—It is a late finding in cor pulmonale, is secondary to low cardiac output with systemic vasoconstriction and ventilation perfusion mismatch.

- **RV heave** palpable along left sternal border or epigastrium is due to RVH.
- Increase intensity of holosystolic murmur of tricuspid regurgitation with inspiration (**Carvallo's sign**), may be lost when RVF worses.
- **Hepatomegaly and ascites**—Mechanism is same as chronic heart failure.

DIAGNOSIS

- **ECG**—Shows P-pulmonale, right axis deviation and RV hypertrophy.
- **Chest X-ray**—Enlargement of main pulmonary artery, hilar vessels, and descending right pulmonary artery.
- **Spirometry and lung volume study**—Identify obstructive or restrictive defects indicative of lung parenchymal disease.
- **Arterial blood gas analysis** demonstrate hypoxemia and/or hypercapnia.
- **Spiral CT**—For acute thromboembolic disease.
- **Ventilation/perfusion lung scan** for chronic thromboembolic diseases.
- High-resolution computed tomography (**HRCT)**—For identification of ILD.
- **2D echocardiography** for measuring RV wall thickness and chamber dimensions and anatomy of pulmonary and tricuspid valve. Interventricular septum may move paradoxically during systole in presence of pulmonary hypertension.

  Calculated measurement of RV function (tricuspid annular plane systolic excursion) replaces more subjective study of right ventricular function.
- **MRI**—It is useful when 2D-echocardiography is difficult due to poor echo window.
- **Right heart catheterization** is useful for confirming pulmonary hypertension and for excluding elevated left atrial pressure (by PCWP) as a cause for right heart failure.
- **B-type natriuretic peptide (BNP) and N-terminal ProBNP** are elevated in cor pulmonale secondary to RV stretch and may be dramatically elevated in acute pulmonary embolism.

TREATMENT

Most pulmonary diseases that lead to chronic cor pulmonale are in advanced stage and less amenable to treatment.
General principles of treatment are:

- Decreasing the work of breathing by noninvasive mechanical ventilation.
- Bronchodilation.
- Treatment of underlying respiratory infections.
- Adequate oxygenation to keep O_2 saturation >90–92%.
- Correction of respiratory acidosis for decreasing pulmonary vascular resistance.
- Correction of anemia.
- Phlebotomy may be considered in extreme case of polycythemia.
- Diuretic are necessary in RVF but contraction alkalosis and hypercapnia can develop following prolong diuretic use.
- Digitalis—It's role is uncertain; and it can lead to arrhythmia.

Treatment of Pulmonary Artery Hypertension

Treatment of pulmonary artery hypertension (PAH) is initiated with either oral or inhalation therapy. Patient who fails to improve within 2–3 month should be switched to different form of therapy. Greatest benefit is obtained from combination of **sildenafil and epoprostenol**.

Common Drugs for PAH

- Calcium channel blocker (**CCB)**—Nifedipine 240 mg/day or amlodipim 20 mg/day.
- **Phosphodiesterase 5 inhibitors**—Sildenafil 20–80 mg tid, tadalafil 40 mg once daily.
- **Prostacycline**
  - *Ilioprost*—2.5–5 μg 2 hourly inhalation.
  - *Epoprostenol*— 25–40 μg/kg/min by continuous IV infusion.
  - *Treprostinil*—75–150 μg/kg/min by SC or IV or inhalation.

Intravenous prostacyclin has the greatest efficacy in the treatment of PAH.

Treatment of Pulmonary Thromboembolism

- Unfractionated heparin (**UFH)**—Bolus and continuous infusion to achieve INR 2–3.
- **LMWH**
  - Enoxaparin 1 mg/kg BID
  - Dalteparin 150–200 U/kg once daily
  - Fondaparinux.
- **Warfarin**—Starting dose 5 mg/day target INR 2–3.
- Alternative to warfarin is coming up.
  Rivaroxaban—factor Xa inhibitor.
  Dabigatran—direct thrombin inhibitor.

EXERCISE

Write short notes on

1. Definition of cor pulmonale.
2. Clinical features of cor pulmonale.
3. Diagnosis of cor pulmonale.
4. Treatment of pulmonary hypertension and pulmonary thromboembolism.

Chapter 39

Acute Respiratory Distress Syndrome

INTRODUCTION

A clinical syndrome of severe dyspnea of rapid onset with hypoxemia and diffuse pulmonary infiltrate leading to type–I respiratory failure caused by diffuse lung injury from many medical/surgical disorder results in diffuse bilateral air-space edema in the absence of left atrial hypertension with pulmonary arteriovenous shunt.

The acute respiratory distress syndrome (ARDS) is caused by diffuse lung injury from many underlying medical or surgical disorder. Acute lung injury (ALI) is a less severe disorder but has the potential to evolve into ARDS.

PaO_2 in mm Hg/FiO_2 (inspiratory oxygen fraction <200 mm Hg is characteristic of ARDS).

PaO_2/FiO_2 between 200–300 mm Hg identify patient with acute lung injury who are likely to be benefited from aggressive therapy.

ETIOLOGY

- *Direct lung injury:*
  - Pneumonia
  - Aspiration of gastric contents
  - Pulmonary contusion
  - Near drowing
  - Toxic inhalational injury.
    - Smoke, wargas, N_2O and metal fumes.
- *Indirect lung injury:*
  - Sepsis
  - Severe trauma
    - Multiple rib fracture
    - Flail chest
    - Head trauma
    - Burn
  - Multiple transfusion
  - Drug overdose—Narcotic, salicylate
  - Pancreatitis
  - Postcardiopulmonary bypass.

PATHOGENESIS (FLOWCHART 39.1)

Clinical Course and Pathophysiology

The natural history of ARDS is marked by three phases

- Exudative phase
- Proliferative phase
- Fibrotic phase.

Exudative phase

In this phase, alveolar Type I pneumocyte and capillary endothelial cells are damaged by IL-1, 8, TNF-α and leukotriene B_4, leading to loss of tight alveolar barrier to fluid and macromolecule. As a result edema fluid rich in protein accumulate in lung interstitium and alveoli. In response to this proinflammatory cytokines neutrophil traffic into the interstitium and alveoli which also mediate this damage.

Condensed plasma proteins aggregate with cellular debris in the air space forming hyaline membrane whorls.

Pulmonary vascular injury is caused by obliterative microthrombi, and fibrocellular proliferation also occur in this phase.

This alveolar edema occurs predominantly in the dependent portion of the lung leading to diminished aeration and atelectasis. Consequently, intrapulmonary shunting of blood and hypoxemia occur in addition to hypercapnia and increase in dead space. Chest X-ray shows alveolar and interstitial opacity involving at least 3/4th lung (lower and mid zone).

Differential diagnosis of exudative phase of ARDS

- Cardiogenic pulmonary edema
- Diffuse pneumonia
- Alveolar hemorrhage
- Acute interstitial pneumonia
- Hypersensitivity pneumonitis
- Radiation pneumonitis
- Neurogenic pulmonary edema.

Differential diagnosis from cardiogenic pulmonary edema

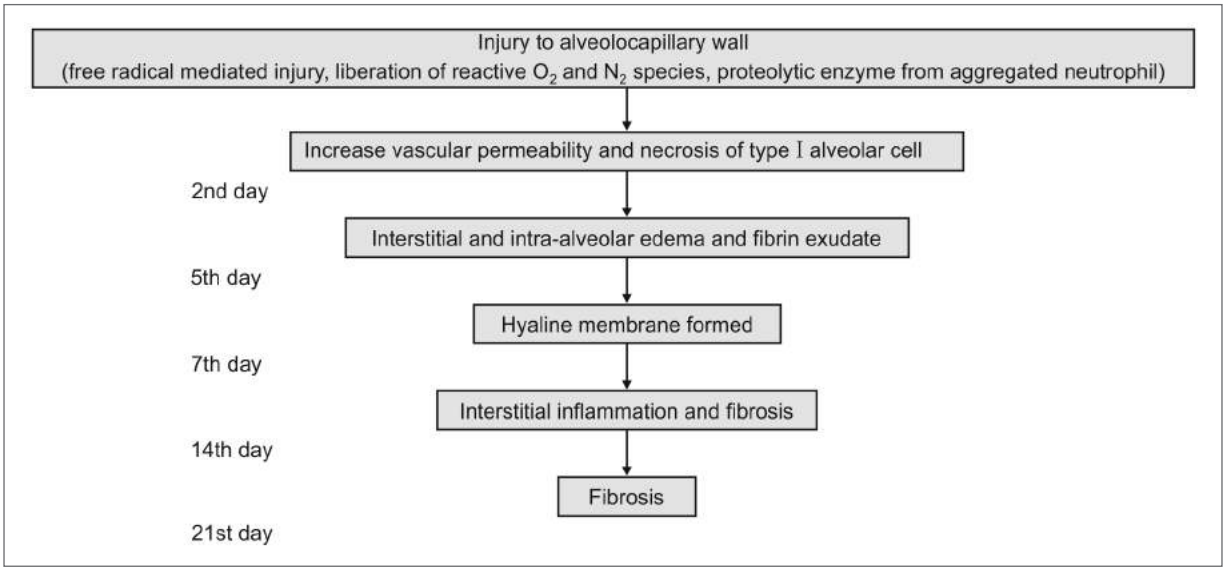
- No cardiomegaly
- No pleural effusion
- No pulmonary vascular redistribution.

Proliferative Phase

This phase last for 7–21 days.

Most patients recover rapidly and liberated from ventilator in this phase.

Flowchart. 39.1: Pathogenesis of ARDS



Those who experience tachypnea, dyspnea and hypoxemia they have progressive lung injury and develop pulmonary fibrosis early.

Histologically this phase is marked by:

- Organization of alveolar exudate.
- Shifting from neutrophilic infiltrate to lymphocytic infiltrate.
- Proliferation of type II pneumocyte which synthesize surfactant and differentiate to type I pneumocyte to line the alveolar wall.

Fibrotic phase

Those who do not recover lung function in 2–3 week's time have usually enter into fibrotic phase and require long-term support on mechanical ventilation with supplemental oxygen. Histologically, alveolar edema and inflammatory exudate now converted to ductal and interstitial fibrosis with formation of emphysema like large bullae and intimal fibrosis leading to pulmonary vascular occlusion and pulmonary hypertension.

TREATMENT

It constitutes six important points:

- Recognition and treatment of underlying medical and surgical disorder like sepsis, aspiration, trauma, pneumonia, etc.
- Minimizing procedure and their complication.
- Prophylaxis against venous thrombosis and GI hemorrhage, central venous line infection.
- Prompt recognition and treatment of nosocomial infection.
- Maintenance of adequate nutrition.
- Ventilatory support—This intervention represents the most important modalities of treatment in lowering the mortality.

  In most clinical setting positive-end expiratory pressure (PEEP) mode with empirical set point at usually <10 cm of H_2O and low tidal volume <6 mL/kg of ideal predicted body weight) to minimize FiO_2 <0.6 and maximize PaO_2 (88–95%). pH >7.3 mean arterial pressure 65 mm Hg RR <35 bpm is ideal for managing ARDS.

  The mortality in ARDS is largely attributable to nonpulmonary cause like sepsis and nonpulmonary organ failure (>80%). The improvement in survival is likely secondary to advances in the care of sepsis and with multiorgan failure.

EXERCISE

Write short notes on:

1. Causes of ARDS
2. Stages of ARDS
3. Treatment of ARDS.

Chapter 40

Bronchogenic Carcinoma

INTRODUCTION

Bronchial carcinoma is the most common (>90%) of lung tumor. Apart from that metastatic carcinoma from breast, kidney, uterus, ovary, testis, thyroid and osteogenic sarcoma may give rise to metastatic lung cancer up to 5–10%.

The incidence of bronchial carcinoma has increased dramatically during the 20th century and accounts for >50% of all deaths due to malignancy.

ETIOLOGY

- Cigarette smoking is by far the most important cause of lung cancer.
- Passive smoking is believed to be related to 5% of lung cancer.
- Exposure to naturally occurring radon is possibly related to 5% of the lung cancer.
- Asbestos, beryllium, cadmium and chromium are also associated with lung cancer.

PATHOLOGY

Bronchial carcinoma arises from bronchial epithelium and mucous gland.

Primarily lung cancer are of two types.

- Nonsmall cell lung cancer (NSCLC) (85–90%)
- Small cell lung cancer (10–15%)

NSCLC accounts for 85–90% of lung cancer and histologically have three subtypes

- **Adenocarcinoma (60%)** are most common among non-smoker and present as peripheral lesion. A subtype of adenocarcinoma termed as *bronchoalveolar carcinoma* which is less strongly associated with tobacco and commonly have intrapulmonary metastasis and have indolent course.
- **Squamous cell cancer** (25–30%) are located centrally with endobronchial growth.
- **Large cell carcinoma** are differentiated carcinoma accounts for 10% of NSCLC.

When tumors arise from a large bronchus symptoms usually appear early but tumor originating in peripheral location can attain a very big size without producing any symptom. Such tumors are usually squamous cell type and may undergo central necrosis and cavitation and which may have similar radiological picture to that of lung abscess.

Bronchial carcinoma may involve pleura either directly or via lymphatic and may extend to the chest wall involving intercostal nerve and brachial plexus which causes severe pain.

The primary tumor or metastatic growth may spread to mediastinum and compress pericardium, esophagus, superior vena cava, trachea, phrenic nerve and recurrent laryngeal nerve. Lymphatic spread to supraclavicular and mediastinal groups of gland are also seen. Blood-borne metastasis occurs in liver, bone, brain, adrenal and skin.

CLINICAL FEATURES

Presenting signs and symptoms of lung cancer are:
(a) Cough, (b) weight loss, (c) dyspnea, (d) chest pain, (e) hemoptysis, (f) bone pain, (g) clubbing, (h) fever, (i) weakness, (j) dysphagia, (k) wheeze or stridor and (l) features of superior caval obstruction.

- **Clinical features**:
  - Local tumor growth
  - Obstruction and invasion of adjacent structure
  - Regional lymph node involvement
  - Distant metastasis
  - Paraneoplastic syndrome.

Features due to local tumor growth

Clinical features due to obstruction and invasion of adjuscent structure—Collapse of lung due to bronchial obstruction by endobronchial growth or hilar gland.

Regional lymph node involvement causes

- Tracheal obstruction causing dyspnea, stridor
- Esophageal obstruction causing dysphagia
- Recurrent laryngeal nerve compression producing hoarseness of voice
- Phrenic nerve compression causing elevation of hemidiaphragm with dyspnea
- Horner's syndrome—Ptosis, miosis, hemi-anhidrosis, enophthalmos and loss of celiospinal reflex due to involvement of cervical sympathetic ganglion
- Superior vena cava syndrome.

Table 40.1: Comparison between central and peripheral growth

	Central/endobronchial growth		Peripheral growth
1.	Cough with excess expectoration	1.	Pain due to parietal pleural/chest wall involvement
2.	Wheeze	2.	Cough and dyspnea
3.	Stridor	3.	Symptoms due to lung abscess cavity
4.	Hemoptysis	4.	Pleural effusion
5.	Dyspnea		
6.	Postobstructive pneumonia		

Distant metastasis 50% of **squamous cell carcinoma**, 95% of **small cell carcinoma**, 80% of **adenocarcinoma** usually metastasize distally in the following organs which produces the following clinical features:

- *Liver*—Jaundice and liver dysfunction.
- *Bone*—Pain, pathological fracture, marrow and spinal involvement.
- *Brain*—CVA, ICSOL and seizure.
- *Adrenal*—Adrenal failure.
- Sclene and supraclavicular group of gland enlargement.

Features due to paraneoplastic syndrome

- **Endrocrine manifestation** (12%)
  - Syndrome of impppropriate antidiuretic hormone secretion (SIADH)
  - Hypercalcemia
  - Cushing disease
  - Carcinoid syndrome
  - Gynecomastia.
- **Neurological manifestation**
  - Cerebellar dysfunction
  - Myelopathy
  - Eaton-Lambert myasthenia isyndrome gravis
  - Polymyositis/dermatomyositis.
- **Coagulation/thrombotic/hematological manifestation** (1–8%)
  - Trousseau's sign
  - Marantic endocarditis
  - Disseminated intravascular coagulation (DIC)
  - Anemia
  - Granulocytosis
  - Eosinophilia
  - Suppressed immunity.
- **Cutaneous manifestation** (1%)
  - Acanthosis nigricans
  - Dermatomyositis.
- **Renal manifestation** (1%)
  - Nephrotic syndrome
  - Acute glomerulonephritis (AGN).
- **General manifestation**
  - Clubbing and hypertrophic osteoarthropathy (10%)
  - Weight loss (30%)
  - Cachexia
  - Anorexia
  - Fever.

INVESTIGATIONS

Apart from routine examination of blood and sputum for malignant cell the following examination is very much essential:

- **Chest X-ray**—Radiological changes in chest X-ray that may be seen in bronchogenic carcinoma patients are (Fig. 40.1):
  - **Peripheral pulmonary opacity**—Irregular well-circumscribed mass lesion/coin lesion.
  - **Mass lesion with cavity (cavitary lesion)**.
  - **Unilateral hilar glandular enlargement**.
  - **Collapse** of whole lung or lobe or segment due to obstruction of airway by endobronchial growth or compression of airway by enlarged hilar gland.
  - **Pleural effusion**.
  - **Broadening of the mediastinum**—Due to paratracheal lymphadenopathy.
  - **Enlarged cardiac shadow** due to malignant pericardial effusion.
  - **Elevation of the hemidiaphragm** due to phrenic nerve palsy.
  - **Rib destruction/erosion**.
- **CT of thorax** with CT-guided fine needle aspiration cytology (FNAC) for definitive cellular diagnosis in case of peripheral growth.

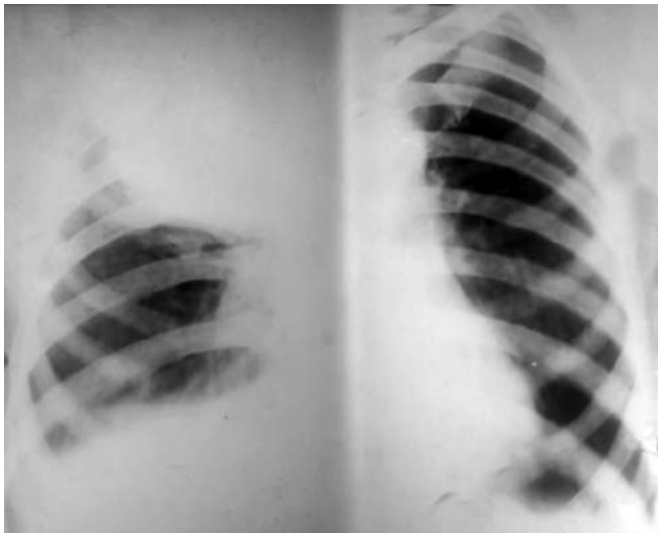


Fig. 40.1: Bronchogenic carcinoma at upper zone of right lung

- **Bronchoscopy** with bronchoalveolar lavage from suspected site for definitive cellular diagnosis in case of growth within large airway near helium.
- **Examination of pleural fluid** for malignant cell in case of suspected pleural effusion.

MANAGEMENT

- Supportive management
- Specific therapy.

Specific Management of Stage I and II Non-small Cell Lung Cancer

- Surgical lobectomy is the treatment of choice for stage I and II NSCLC.
- Adjuvant chemotherapy with **cisplatin**-based regimen for patient of stage II and III disease 6–8 weeks after surgery is currently recommended (Carboplatin is recommended in patient with CKD, neuropathy, hearing impairment instead of cisplatin).
- Radiotherapy—There is no role of adjuvant radiation therapy in patient of stage I and II following surgical resection.

  There is no data supporting neoadjuvant chemotherapy (chemotherapy before surgery).

Management of Stage III NSCLC

Surgery followed by adjuvant chemotherapy is the treatment of choice for stage IIIA disease. Chemotherapy with radiotherapy is superior to chemotherapy with radiotherapy and surgery in stage IIIB disease.

Specific Management of Small Cell Lung Cancer

- SCLC accounts for 15% of all lung cancer.
- More than 95% is due to smoking.
- It is usually centrally located with hilar mass and mediastinal lymphadenopathy.
- The disease is again subclassified into:
  - *Limited stage disease*—Where the disease is confined to one hemithorax with hilar and mediastinal lymphadenopathy that can be encompressed within one radiotherapy portal.
  - *Extensive stage disease*—The disease that exceed the above mentioned boundaries.

Management of Limited Small Cell Cancer

- **Surgery**—SCLC is highly aggressive disease characterized by rapid doubling time. So, surgery is not recommended even for limited disease SCLC as they have micrometastasis.
- *Chemotherapy*—Combination chemotherapy with cisplatin or carboplatin with etoposide for 4–6 cycle is the mainstay of treatment.
- *Radiation*—Chemotherapy when given concurrently with radiation is more effective than sequential chemoradiation. Complete response rate is 80–85%. With median survival of 18 months and cancer-free survival for 15 years in 15–25% can be achieved.
- Monthly IV bisphosphonate with zolidronate decrease skeletal events with bony metastasis.
- Prophylactic cranial irradiation after initial chemotherapy in patient with limited or extensive stage disease of SCLC improves survival.
- Patient with extensive stage of SCLC is treated with chemotherapy to improve symptoms and increase survival.

EXERCISE

Write short notes on

1. Clinical features of bronchogenic carcinoma.
2. Paraneoplastic features of bronchogenic carcinoma.
3. Radiological changes in bronchogenic carcinoma.
4. Management of bronchogenic carcinoma.

Chapter 41

Pneumothorax

INTRODUCTION

Presence of air in the pleural space is called pneumo- thorax. It can occur spontaneously due to rupture of subpleural bleb/alveolus/bulla or secondary to trauma to chest wall or lung which can again be accidental or iatrogenic (Fig. 41.1).

ETIOLOGICAL CLASSIFICATION OF PNEUMOTHORAX

- **Spontaneous**
  - **Primary**—Spontaneous pneumothorax develops in patients without any evidence of overt lung disease. Air usually enter into the pleural space through rupture of apical subpleural emphysematous bulla or pleural bleb (occur exclusively in smoker).
  - **Secondary**—Spontaneous pneumothorax develops in patients with some underlying lung disease like tuberculosis, COPD, asthma, lung abscess, pulmonary infarct, all forms of fibrotic and cystic lung diseases, bronchogenic carcinoma.
- **Traumatic**
  - **Iatrogenic**—Following pleural aspiration or pleural biopsy, thoracic surgery.
  - **Traumatic**—Following stab injury or accident.

CLINICAL CLASSIFICATION OF PNEUMOTHORAX

- Closed type
- Open type
- Tension type.

PATHOPHYSIOLOGY

- **Closed type**—Where the communication between the lung and pleura seals spontaneously (as the lung deflate). This pneumothorax referred to as closed variety. In such circumstances, the mean intrapleural pressure remains negative. Spontaneous resorption of intrapleural air and re-expansion of the lungs occur within a few weeks and the infection of the pleural space is uncommon.
- **Open type**—Where the communication between the pleura and the lung fails to seal spontaneously and the atmospheric air enters freely into the pleural space *(called bronchopleural fistula)* and it facilitates entry of infection from lower respiratory tract to pleural space and empyema is a very common equally.

  Open pneumothorax is most common following rupture of emphysematous bulla, tuberculous or lung abscess cavity.
- **Tension type**—It develops when the communication between the lung and the pleural space is guarded by a one-way valve which allows atmospheric air to enter into the pleural space during inspiration and coughing but does not permit escaping from pleural space during expiration. In this way with each respiration some amount of air is trapped in the pleural space and the intrapleural pressure may rise well above the atmospheric level.

  This results in—
  - Compression collapse of the underlying deflated lung.

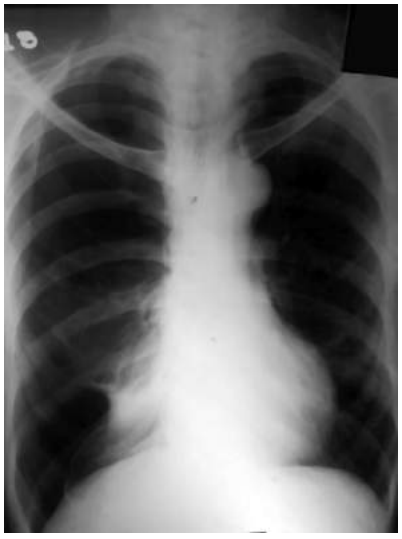


Fig. 41.1: Pneumothorax

- Mediastinal shifting to opposite side (due to positive intrapleural pressure) causing compression of opposite lung.
- Cardiovascular function is also compromised due to decreased venous return and reduced cardiac output.

CLINICAL FEATURES

It depends mainly on the clinical subtype.

Symptoms

- Almost all patients with pneumothorax experience sudden onset **unilateral chest pain and breathlessness** which in case of secondary pneumothorax do not resolve spontaneously.
- Dyspnea.
- Shortness of breath.
- Cough:
  - Most of the primary spontaneous pneumothorax occurs while the patient is at rest.
  - In very small pneumothorax, there will be no abnormality except tachycardia.
  - A large pneumothorax (>5% of the hemithorax) results in unilateral chest pain breathlesness dyspnea. Shortness of breath and coughs.

Signs

- **Inspection**
  - Hyperinflation of involve hemithorax with intercostal fullness.
  - Decreased movement of the chest wall on the affected side.
- **Palpation**
  - Shifting of mediastinum with trachea and apex beat to the opposite side.
- **Percussion**—Hyper-resonant percussion note on the affected side.
- **Auscultation**—Absent or decreased vesicular breath sound but amphoric type of bronchial breath sound present in open pneumothorax over bronchopleural fistula.

Special Features of Tension Pneumothorax

- Rapidly progressive breathlessness
- Trachycardia
- Hypotension
- Cyanosis.

INVESTIGATIONS

- **Chest X-ray**—Shows sharply defined edges of deflated lung with increased radiolucency and loss of lung marking between the lung border and chest wall.

  Care must be taken to differentiate it from large emphysematous bulla.
- **CT scan of thorax**—This also gives information about the—
  - Presence of pleural fluid.
  - Degree of mediastinal shifting.
  - Presence of underlying pulmonary pathology, e.g. TB, pneumonia, bronchogenic carcinoma.
- **Routine blood examination**.
- **Sputum for smear and culture**.

MANAGEMENT

- Small closed pneumothorax *absorbs spontaneously and requires only follow-up*.
- *Percutaneous needle aspiration of air is a simple well-tolerated and effective procedure in case of moderate-sized closed pneumothorax (15%)*. Aspiration is done in 2nd intercostal space (ICS) on micdavicular line (MCL) using 16 F cannula. In stopped aspiration when
  - Resistance is felt
  - When more than 2.5 liter of air has been aspirated
  - Patient coughs excessively.
- **Tension pneumothorax to be considered as medical emergency**. If the tension in the pleural space is not relieved the patient will develop decreased COP or hypoxemia. A large wide bore needle to be inserted through the 2nd ICS on MCL. Usually, a large amount of air escape through the needle after insertion.
- Intracostal tube drainage should be inserted in all tension pneumothorax through 4th or 5th or 6th intercostal space in the midaxillary line and the tube is advanced to apical direction and is connected to:
  - An underwater seal drain or one-way Heimlich valve.
  - Entry point of the catheter into the hemithorax is secured firmly to the chest wall by a purse string suture so that atmospheric air cannot leak in by the side of the tube.

  The drain should be removed 24 hours after the lung has fully reinflated, checked by X-ray and the bubbling in the water seal has stopped.

  If the bubbling in the underwater bottle stops prior to the full re-expansion of lung, the tube is either blocked or kinked or displaced.

The patient should not fly or dive for 3 months following full re-expansion of the lung.

- Recurrent spontaneous pneumothorax (the risk of recurrence is 30–50% following first spontaneous pneumothorax), secondary pneumothorax, open pneumothorax or who continue to fly or dive following open pneumothorax or had persistent air leak for more than 7 days require **surgical or chemical pleurodesis**. Chemical pleurodesis is done by introducing betadine, bleomycin or doxycyclin (500 mg) in the pleural space. Surgical pleurodesis is done by pleural abrasion or stapling of bleb by thoracotomy or thoracoscopy which is successful in almost 100% patients presenting with recurrence.
- Open pneumothorax who have bronchopleural fistula usually require appropriate antibiotic coverage with chemical or surgical pleurodesis.

EXERCISE

Write short notes on

1. Classification of pneumothorax.
2. Management of pneumothorax.
3. Clinical features of pneumothorax.

SECTION V

GASTROINTESTINAL SYSTEM

- Viral Hepatitis
- Chronic Hepatitis
- Alcoholic Liver Disease
- Nonalcoholic Steatohepatitis
- Cirrhosis and its Complications
- Approach to a Patient of Upper Gastrointestinal Bleeding
- Budd-Chiari Syndrome
- Acute Pancreatitis
- Approach to a Patient with Malabsorption
- Inflammatory Bowel Diseases

Chapter 42

Viral Hepatitis

DEFINITION

Infection with inflammation of hepatocyte by virus is called viral hepatitis. Almost all cases of viral hepatitis is caused by one of the five viral agents.

Hepatitis A, B, C, D and E virus.

Clinical Features

1. **Prodromal phase**—Usually precedes 1–2 weeks before development of jaundice. Symptoms and sign are variable.

Low-grade fever 100°–102°F may be with hepatitis A virus (HAV) and hepatitis E virus (HEV) infection whereas 102°–104°F is seen in HBV infection. Associated serum sickness like syndrome with dark urine, clay-colored stool may be noticed 1–5 days before the onset of jaundice in HBV infection.

Common symptoms are fever, chills, headache, malaise, anorexia, nausea, vomiting, distaste for smoking, fatigue, photophobia, cough. During prodromal phase of acute hepatitis–B a serum sickness-like syndrome characterized by arthralgias or arthritis,

Table 42.1: Main features of viral hepatitis

Points	HAV	HBV	HCV	HDV	HEV
Nucleic acid	RNA	DNA	RNA	RNA	RNA
Morphology	Icosahedral Nonenveloped, contain four capsid inactivated by boil up to 1 min, formaldehyde, chlorine, UV ray	Double shelled (surface and core) spherical and filamentous represent excess viral coat material	Enveloped	Enveloped hybrid particle with HBsAG coat and HDV core	Icosahedral Nonenveloped
Incubation period	2–6 weeks	2–24 weeks	2–20 weeks	6–9 weeks	3–8 weeks
Mode of spread	Fecal-oral	Hematogenous sexual, vertical	Hematogenous sexual, vertical	Hematogenous sexual, vertical	Fecal-oral
Chronic infection	No	Yes	Yes	Yes	No
Chronic–phage	Ig G-anti-HAV	Chronic phase–IgM anti-HBC HBsAg Marker of replication: HBe Ag, HBV DNA $>10^3$ IU/mL	Chronic phase—anti-HCV RAN	Anti-HDV Super infection IgG anti-HBC and anti- HDV	Anti-HEV
Vaccine and immunization	Present both active and passive immunization	Present both active and passive immunization	No	Vaccine for HBV protect from HDV infection	At present no but under trial
Diagnosis	Acute phage-IgM, anti-HAV	Acute phase: HBsAg and anti-HBc (IgM)	Acute phase: anti-HCV (IgM)	Anti-HDV HDV RNA Coinfection IgM anti-HBC	IgM/IgG anti-HEV

Abbreviations: HAV, Hepatitis A virus; HBV, Hepatitis B virus; HCV, Hepatitis C virus; RNA, Ribunucleic acid; HDV, Hepatitis D virus; DNA, Deoxyribonucleic acid; HTV, Hepatitis E virus

rash, angioedema, rarely hematuria and proteinuria may develop in 5–10% of patients. Mild cases may run an anicteric course recognized only from history of contact with a definite case and vague GI complain and biochemical evidence of hepatic dysfunction (elevated serum transaminase and HBs Ag).

Physical signs are:

- Enlarged tender liver with steady dull aching pain over right upper quadrant (RUQ) due to stretching of hepatic capsule.
- Splenomegaly may present particularly in children.
- Cervical glands are palpable in (10–20%) patient.

- **Acute icteric phase**—Usually persist for 10–15 days. Constitutional symptoms usually diminish but weight loss usually continues through icteric phase and slight pain over RUQ may persist.

  Physical signs are:

  - Dark color urine.
  - Yellowish tint of sclera. Jaundice becomes deeper as obstruction to biliary canaliculi develops.
  - Stool gradually turns paler.
  - Liver is easily palpable.
  - Splenomegaly, Cervical lymphadenopathy } Present in 10–20% patient.
  - Rarely spider angioma.

  Diagnosis of anicteric hepatitis is based on clinical features and elevated serum transaminase level.
- **Recovery phase**—Usually starts 1–2 weeks after the onset of icteric phase but may be delayed from 6 weeks to 6 months and persists usually for 2–12 weeks. Constitutional symptoms usually disappear but liver enlargement and biochemical abnormalities may persist. Complete clinical and biochemical recovery is expected in 1–2 months in all cases of HAV, and HEV without any comorbid medical disorder and 3–4 months after onset of jaundice in about 75% of uncomplicated HBV and HCV infection.

  Acute hepatitis-like clinical events in chronic hepatitis B may be seen in:

  - Superinfection with hepatitis HDV.
  - Spontaneous seroconversion from HBeAg to anti-HBe.
  - Therapeutically immune-suppressed patient with chronic HBV infection when immunosuppressive drugs are withdrawn or with immune reconstitution syndrome in HIV.
- Emergence of precore mutant.

LABORATORY INVESTIGATIONS (FIG. 42.1 AND (TABLE 42.2)

Liver function tests to be done first.

- Rise of ALT (SGPT) and AST (SGOT) starts during early prodromal phase of acute viral hepatitis and preceed the rise of serum bilirubin. Peak level vary from 400–6000 IU but the level of these enzyme donot coerelate well with the severity of liver cell damage. The diagnosis of anicteric hepatitis is based on clinical feature and on aminotransferase elevation.
- Rise in bilirubin level is an early finding and starts in the late prodromal phase and continue up to convalescent period. Bilirubin level is usually between 2.5–20 mg/dL but the level >30 mg% is usually seen in hemoglobinopathies, or G–6–P D deficiency or other severe disease when associated with it but it is not associated with poor prognosis.
- P-time gradually rise and unusual prolongation of P–time is an indicator of severe liver damage.
- Serum-albumin level usually below normal but may fall to a very low level in severe hepatitis.
- Serum-alkaline phosphatase rarely exceeds 200 U/L unless marked cholestasis develops.
- Neutropenia and lymphopenia are transient and are followed by relative lymphocytosis. Atypical lymphocyte (2–20%) are common during acute phase. Total WBC count is low and helps to differentiate it from Weil's disease.
- Hypoglycemia is noted in some patient associated with nausea, vomiting and inadequate carbohydrate intake and poor hepatic glycogen store.
- Mild hematuria and proteinuria may be present.
- Serological test can identify HAV HBV, HCV, HDV and HEV infection.

Serological Diagnosis of Viral Hepatitis

- **Diagnosis of HAV**: Depends on the detection of IgM anti-HAV (rheumatoid factor can give rise to false positive result in this test).
- **Diagnosis of HBV**—In acute phase, diagnosis of HBV is made by detection of HBsAg in the serum. Sometime level of HBsAg are too low to be detected but if the clinical setting suggest acute viral hepatitis the diagnosis can be established by the presence of IgM-anti-HBc.
- **Marker of replication** of HBV—Presence of HBeAg is an indicator of viral replication and suggest infection is in active phase. In case precore-mutant or core promoter mutation (YMDD– mutation) HBeAg will be absent. In this condition marker of viral replication is the absolute number of HBV DNA in liver and in serum ($>10^3$ IU/mL). They are more sensitive and quantitative and better marker of viral replication and infectivity.

  In recent infection IgM anti-HBc is positive.

  In remote infection IgG anti-HBc is positive.

  A false-positive test for IgM anti-HBc may be seen with high titer of rheumatoid factor.

HBsAg and anti-HBsAg may be simultaneously present in very rare situation (10–20% patient). The

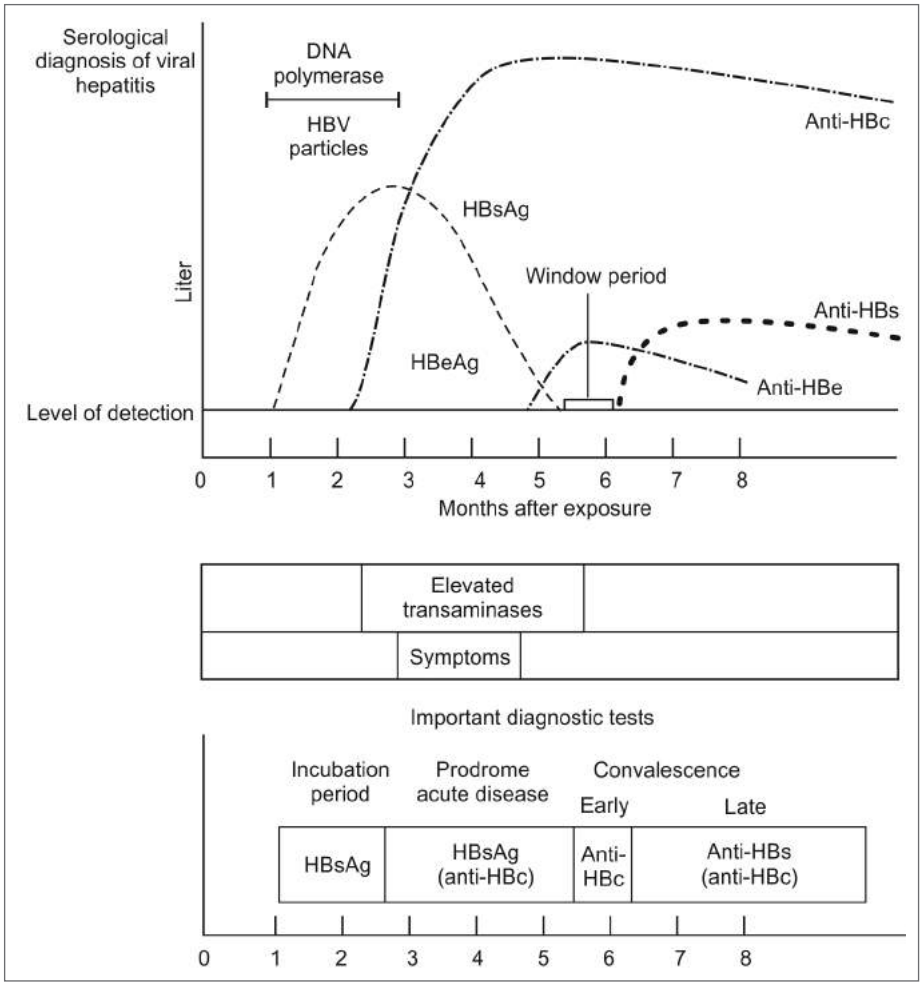


Fig. 42.1: Antibody titer in HBV infection

Table 42.2: Serological diagnosis of acute hepatitis

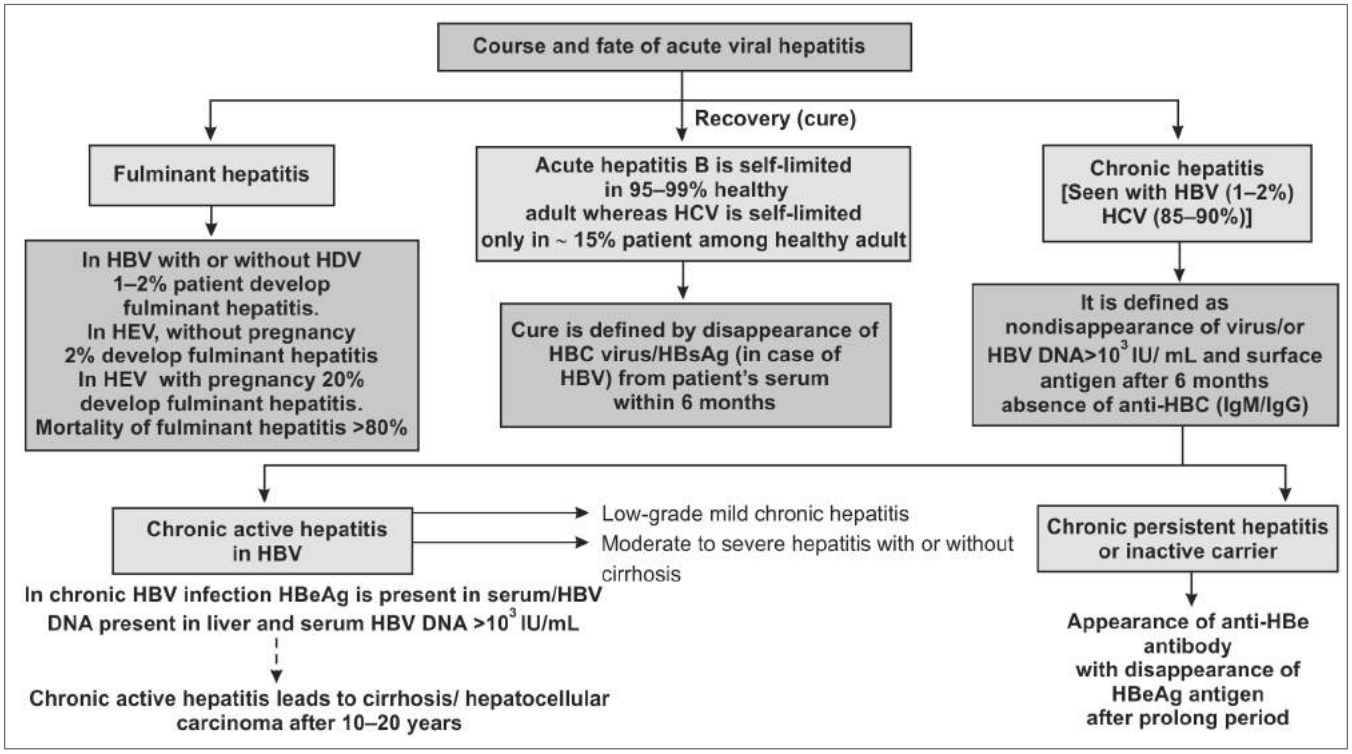
HBsAG	Anti-HAV (IgM)	Anti-HBC (IgM)	Anti-HBC (IgG)	Anti- HCV	Interpretation
+	–	+	–	–	Acute HBV infection
+	–	–	+	–	Chronic HBV infection
+	+	–	+	–	Acute HAV superimposed on chronic HBV infection
+	+	+		–	Acute HAV and HBV infection
–	+	–		–	Acute HAV infection
–	+	+		–	Acute HAV and HBV infection (HBsAG below detection threshold)
–	–	+		–	Acute HBV infection (HBsAG below detection threshold)
–	–	–		+	Acute HCV infection

antibody is directed not against common group determinant 'a'. HBsAg of subtype 'ad' with anti-HBsAg of subtype 'ay'.

After immunization with hepatitis B vaccine anti-HBs is the only serological marker detected in the serum.

- **Diagnosis of HCV**— Diagnosis of HCV is suggested by the presence of anti-HCV in the serum but detection of HCV RNA is more confirmatory.
- **Diagnosis of HDV**—In patient who are HBsAg positive presence of anti-HDV confirm the diagnosis and to be

Flowchart. 42.1: Prognosis of acute viral hepatitis HBV, HCV and HEV



done in fulminant disease or chronic hepatitis with acute exaggeration. During acute viral hepatitis many other antibody may be present in the serum they are—(a) *antibodies to smooth muscle*, (b) *antinuclear antibody*, (c) *heterophile antibody*, (d) *rheumatoid factor* and (e) *anti LKM antibody*.

In HCV and HDV antibody against LKM may be present but the species of LKM antibody are different in two types of hepatitis and also differ from autoimmune hepatitis type–II.

COMPLICATIONS AND SEQUALE OF VIRAL HEPATITIS (FLOWCHART 42.1)

- **HAV** : *Relapsing hepatitis* and *cholestatic hepatitis.*
- **HBV**: *Fulminant hepatitis*, *cirrhosis*, *hepatocellular carcinoma*, *Gianotti-Crosti syndrome* in children and essential mixed cryoglobulinemia (EMC).
- **HCV**: *Cirrhosis, hepatocellular carcinoma*, *EMC* which is a part of the spectrum of B–cell lymphoproliferative disorder and may rarely lead to B-cell lymphoma, *porphyria cutanea tarda*, *lichen planus, hepatic steatosis, hypercholesterolemia, insulin resistance, metabolic syndrome and T2DM*.
- **HDV**: *Fulminant hepatitis*.
- **HEV**: *Fulminant hepatitis* (especially in pregnancy 20%).

COMPLICATIONS OF ACUTE VIRAL HEPATITIS

Hepatic Complications

- **Fulminant hepatitis (massive hepatic necrosis)**—Primarily seen in hepatitis B and D as well as E (1– 2%).
- **Relapsing hepatitis**—Biochemical or clinical, especially in HAV infection.
- **Cholestatic hepatitis** (HAV).
- **Post-hepatitis syndrome**.
- **Hyperbilirubinemia (Gilbert syndrome)**.
- **Chronic persistent hepatitis—***In HBV (1–2%) and in HCV (85–90%)* infection develop chronic hepatitis. HAV and HEV have no chronic phase.
- **Cirrhosis** develops in chronic HBV and HCV infection after 10–15 years.
- **Hepatocellular carcinoma develops** in chronic HBV and HCV infection after 15–20 years.

Extrahepatic complications of HBV infection:

Connective tissue disease:

- *Polyarteritis nodosa*
- *Glomerulonephritis* (membranoproliferative)
- *Henoch-Schönlein purpura*
- *Papular acrodermatitis of childhood (Gianotti-Crosti syndrome*—Nonpruritic papular rash on face, buttock and limb with lymphadenopathy).

- **Rare complications of HBV infection**—*Pancreatitis myocarditis*, *atypical pneumonia*, *transverse myelitis, peripheral neuropathy* and *aplastic anemia.*

- Autoimmune hepatitis may be triggered by a bout of self-limited acute hepatitis A, B and C infection.
- **Complications of HCV infection**
  - **Essential mixed cryoglobulinemia** (EMC) is a immune complex disorder and is a part of B-cell lymphoproliferative disorder which can rarely evolve into β-cell lymphoma.
  - **Lichen planus**.
  - **Porphyria cutanea tarda**.

FULMINANT HEPATITIS (MASSIVE HEPATIC NECROSIS)

Primarily seen in hepatitis B and D. It is seen rarely in hepatitis C but hepatitis E can be complicated by fatal fulminant hepatitis in 1–2% of all cases but up to 20% with pregnancy. *Patient usually presents with hepatic encephalopathy and usually hepatic coma with combination of shrinking liver size, rapidly rising bilirubin level, marked prolongation of p-time and fall in SGPT and albumin level which indicate massive hepatic necrosis.*

Clinical features are *ascites, edema confusion, disorientation* and *somnolence*.

Causes of death:
- *Hepatic encephalopathy*
- *Renal failure (hepatorenal syndrome)*
- *Cerebral edema with brainstem compression*
- *Gastrointestinal bleeding*
- *Sepsis*
- *Respiratory failure*
- *Cardiovascular collapse*.

Mortality is >80% with deep coma but survivor had a complete biochemical and histological recovery.

Treatment
- Conservative
- Liver transplant (may be life-saving).

HbsAg carrier is high among:
- *Neonates*
- *Down's syndrome*
- *Chronic hemodialysis patient*
- *Immunosuppressed patient and HIV*.

Relapsing hepatitis (in hepatitis A)—return of jaundice with symptoms and signs of acute hepatitis during recovery phase is characteristic of relapsing hepatitis and occurs in 5–15% patient.

Biochemical relapse with increase of aminotransferase activity and fecal excretion of virus are more common, usually resolves spontaneously and does not carry worse prognosis.

Cholestatic hepatitis (usually in hepatitis A):
- It can develop at any stage of illness
- Biochemically, it is of obstructive type
- On liver biopsy, there is no evidence of liver damage
- It can continue for many months
- Prognosis is good.

Post-hepatitic syndrome is characterized by:
- Prolonged malaise.
- Anorexia and nausea.
- Discomfort in right upper quadrant of abdomen.
- It persists for 2–3 months after clinical and biochemical recovery.
- No clinical and biochemical evidence of liver disease is present.
- It is particularly seen in anxious patient.

Prognosis of Acute Viral Hepatitis

Hepatitis A—Virtually, all healthy patients recover completely with no clinical sequelae.

HBV—*95–99% of healthy people recover completely. Poor prognostic parameters are*
- Advance age.
- Serious underlying medical disorder.
- Symptoms of hepatic encephalopathy.
- Ascites.
- Peripheral edema.
- Low serum albumin.
- Hypoglycemia.
- Prolonged P-time.
- Very high serum bilirubin suggests severe hepatocellular disease and prompt hospital admission.
- Chronic hepatitis specially develops after neonatal infection and coinfection with HIV.

Clinical and laboratory features suggesting progression of acute HBV to chronic HBV

- Lack of complete resolution of clinical symptom of anorexia, weight loss, fatigue and persistence of hepatomegaly.
- Failure of the SGOT, SGPT, bilirubin and globulin level to return to normal within 6–12 months.
- Persistence of HBeAg >3 months and HBsAg >6 months after acute hepatitis.
- Presence of bridging or multilobular hepatic necrosis on biopsy.

HCV—It is less severe in acute phase than HBV and is more likely to be anicteric. The likelihood of developing chronic hepatitis is 85–90% with HCV infection, only 15% patient recover spontaneously.

Fatalities due to fulminant hepatitis is rare in HCV infection.

HBV and HDV—Simultaneous infection do not necessarily experience a higher mortality (5%) than with acute hepatitis B alone.

However, HDV superi nfection on hepatitis B carrier state has a high mortality of 20%.

HEV—Case fatality is 1–2% in normal subject but may be up to 20% in pregnant women.

Differential diagnosis of viral hepatitis

- Infectious mononucleosis, *Cytomegalovirus, Herpes simplex virus, Coxsackievirus* and toxoplasmosis may share certain climical features of acute viral hepatitis.
- *Leptospira, Candida, Brucella, Mycobacteria, Pneumocystis* infections can be confused with acute viral hepatitis.
- Certain anesthetics agent can produce picture of acute hepatitis or cholestasis.
- Past history of repeated episode of acute hepatitis suggest underlying chronic hepatitis with flare.
- In alcoholic hepatitis serum aminotransferase activity is not so high and liver biopsy shows fatty infiltration, neutrophilic reaction and alcoholic hyaline.
- Acute cholecystitis, stone in CBD and ascending cholangitis may mimic acute viral hepatitis.
- Right heart failure, right atrial myxedema and Budd-Chiari-syndrome sometime confuse with acute viral hepatitis.
- *HELLP syndrome* (hemolysis, elevated liver enzyme, low platelet count) *acute fatty liver of pregnancy* and *cholestasis of pregnancy* can be confused with viral hepatitis during pregnancy.

GENERAL MANAGEMENT OF HEPATITIS

The treatment of acute viral hepatitis is mainly supportive. Only severely affected patients require hospital care.

- **Nutritious diet**—Containing 2,000–3,000 kcal. This is often not tolerated due to anorexia and nausea. As vomiting in more severe in the late hours of the day maximum calorie intake best tolerated in the early hours of the day.
- **If vomiting is severe**
  - Intravenous glucose may be given.
  - Antiemetic like—*Domperidone, metoclopramide ondansetron* can be used.
- Forced and prolonged bed rest is not essential for full recovery but many patients will feel better with restricted physical activity.
- **If severe pruritus is present**—Bile salt sequestering agent **cholestyramine** can be used.
- Glucocorticoid therapy has no value and hazardous.
- **Drugs**—All *hepatotoxic, cholestatic, sedative, hypnotic, alcohol and oral contraceptive* are strictly contraindicated.
- Surgery carries significant risk of postoperative hepatic failure.

All HAV and 99% of HEV require no specific antiviral therapy as they undergo spontaneous remission.

MANAGEMENT OF FULMINANT HEPATITIS

Hepatitis B and E account for fulminant hepatitis.

The treatment is mainly supportive but hospitalization is required. Steps for management are:

- Maintenance of fluid balance.
- Support of circulation and respiration.
- Control of bleeding with **vitamin K, fresh blood transfusion and factor concentrate of factor VII**.
- Correction of **hypoglycemia** with intravenous glucose.
- Treatment of other complication of comatosed patient in anticipation of liver regeneration.
- Protein administration should be restricted.
  Oral **lactulose/lactitol**—15–30 mL 6 hourly till diarrhea starts then adjust the dose so that the patient have 2–3 semisolid stool per day.
- **Rifaximin (550 mg bid)**.
- Bowel wash with **neomycin** twice daily to prevent development of hepatic encephalopathy.
- Glucocorticoid therapy is ineffective.
- **Orthotopic liver transplantation is resorted to with increasing frequency with excellent result** in patient with fulminant hepatitis.

Meticulous intensive care is the one factor that does appear to improve survival.

Specific Therapy in Severe HBV and HCV Hepatitis

- For HBV in acute viral hepatitis **entecavir and tenofovir** (most potent and least resistant prone) oral therapy to be continued for 3 months after HBsAg seroconversion and 6 month after HBeAg seroconversion.
- Many authority recommend **pegylated interferon** plus **ribavirin** for 24 weeks for treatment of acute hepatitis-C to decrease the number of patient that become chronic carrier following acute HCV infection. After 2014 oral brief duration, low resistance antiviral regimen **telaprevir** and **boceprevir** replace the current standard care (pending outcome of clinical trial).

PROPHYLAXIS OF VIRAL HEPATITIS

- **HAV**—Both active and passive immunization is available. **Active immunization** is done with *formaldehyde inactivated killed virus* containing vaccine which gives life-long immunity after two doses of vaccination 6–12 months apart.
  Passive immunization is done with immunoglobulin containing *anti-HAV* **0.02 mL/kg** given prior to exposure or at least 14 days within exposure (within the incubation period).
  Combined active and passive immunization can be given to an appropriate patient simultaneously at two different sites.
- **HBV—Active immunization** is done with three intramuscular (deltoid not gluteal) injection of HBV vaccine at 0, 1 and 6th months. Pregnancy is not a contraindication for vaccination. Currently, booster

Table 42.3: Pre-exposure HBV active immunization schedule

Doses	Recombivax	No. dose	Engerix	No. dose
Child <20 years	5 microgram	3/4	10 microgram	3/4
Adult >20 years	10 microgram	3	20 microgram	3/4
Hemodialysis	40 microgram	3	40 microgram	4

immunization is not recommended routinely except in immune-compromised patient. In case of hemodialysis patient double dose of vaccine is given.

Passive immunization is done with a single intramuscular injection of HBIG 0.06 mL/kg administered as soon as possible after exposure and is to be followed by a complete course of hepatitis B vaccine to be started within 1 week.

Combined vaccine for HAV and HBV for active immunization is also available in the market.

- **Infection with HDV** can be prevented by vaccinating with HBV vaccine. No product is available for immune prophylaxis to prevent HDV superinfection.
- No prophylactic measures (active and passive immunization) is available for HCV infection.
- Recombinant vaccine for HEV has been developed and is under trial.

EXERCISE

Write short notes on

1. Clinical features of viral hepatitis.
2. Prognosis of viral hepatitis.
3. Complications of viral hepatitis.
4. Management of viral hepatitis/fulminant hepatitis.
5. Prophylaxis of viral hepatitis.

Chapter 43

Chronic Hepatitis

INTRODUCTION

Chronic hepatitis is a liver disorder of varying etiology in which hepatic inflammation and necrosis continue for more than 6 months.

The clinical and pathological spectrum of disease varies from mild asymptomatic chronic hepatitis with mild or nonprogressive form of chronic hepatitis to more severe form of hepatitis leading to cirrhosis associated with scarring and architectural reorganization.

ETIOLOGICAL CLASSIFICATION OF CHRONIC HEPATITIS

- Chronic viral hepatitis is caused by:
  - HBV infection
  - HBV+ HDV coinfection
  - HCV infection.
- Autoimmune hepatitis—Type I, II and III.
- Drug-associated chronic hepatitis.
- Cryptogenic chronic hepatitis.

CHRONIC VIRAL HEPATITIS

Chronic hepatitis occurs as a sequela of acute viral hepatitis B alone or superimposed with hepatitis D and acute viral hepatitis C. Enterically transmitted form of viral hepatitis HAV and HEV are self-limited and do not develop chronic hepatitis (except rare report in which acute hepatitis A serves as a trigger for onset of autoimmune hepatitis in genetically susceptible patient).

CHRONIC HEPATITIS B

Overall 1–2% of patients infected with acute HBV develop chronic viral hepatitis. The likelihood of chronicity after acute hepatitis B varies with age. Infection at birth is associated with clinically silent acute infection but 90% patient develop chronic viral hepatitis whereas in young immunocompetent persons, the risk of developing chronic hepatitis following acute HBV is approximately 1%.

Table 43.1: Clinical, diagnostic and therapeutic outline of chronic hepatitis

Type of hepatitis	Diagnostic test	Autoantibody	Therapy
1. Chronic HBV	HBsAG, HBeAG, HBV-DNA	–	INF, **pegylated INFα, entecavir**, telbivudine, adefovir, **tenofovir** and lamivudine
2. Chronic HCV	• HCV RNA • Anti-HCV	Anti-LKM–1	• Pegylated INFα + Ribavirin • **Telaprevir** • **Boceprevir**
3. Chronic HDV	• HDV RNA and HBsAG • Anti-HDV	Anti-LKM–3	INF and PEGINF+ Ribavirin
4. Autoimmune hepatitis	• ANA (homogenous) • Anti-LKM-1 ± globulinemia	• ANA • Hyper-ANA LKM–1 • Anti-SLA (soluble liver antigen)	• Prednisolone • Azathioprine
5. Drug-induced chronic hepatitis	–	Unknown	Withdraw the offending agent
6. Cryptogenic hepatitis	All-negative	Nil	• Prednisolone • Azathioprine } with unknown efficacy

Most of the cases of chronic hepatitis B among adult however occur in patient who never had a recognized episode of clinical apparent acute viral hepatitis.

Those in the replicative phase of viral hepatitis B (HBeAg positive) tend to have more severe chronic hepatitis while those in the nonreplicative phase (HBeAg negative), HBV DNA $<10^3$ virion/mL and absence of intrahepatocyte HBcAg tend to have minimal or mild chronic hepatitis or to be *inactive hepatitis carrier*.

Inactive carrier are those patient that have circulating HBsAg with normal aminotransferase activity, undetectable HBeAg with HBV DNA $<10^3$ IU/mL. This serological profile can occur in both inactive carrier and HBeAg negative chronic hepatitis 'B' infection with relative inactivity. Distinction between these two conditions requires sequential serological and virological monitoring.

The marker of viral replications are:

- Hepatitis E antigen (HBeAg) present.
- HBV DNA in serum $>10^5$–10^6 virion/mL.
- Presence of intrahepatocyte nucleocapsid antigen (core antigen) [HBcAg].
- High infectivity.
- Evidence of liver injury (elevated SGPT).
- However, HBV replication does not always have correlation with histiologic category of chronic viral hepatitis.

There may be spontaneous conversion from replicative to nonreplicative phase at the rate of 10%/year associated with transient elevation of SGPT resembling acute hepatitis. Occasionally, there may be spontaneous resumption of replicative activity from nonreplicative infection.

There is a genetic variant of HBV virus in which serological marker of viral replication (HBeAg) are absent in blood, despite presence of active replicative infection. In HBeAg negative chronic hepatitis B active viral replication is detectable by the presence of HBV DNA (10^6 IU/mL). Most such cases represent *precore or core promoter or YMDD mutation* acquired late in the natural history of the disease.

Although, the level of HBV DNA tend to be lower among patients with HBeAg negative chronic hepatitis B but they tend to have progressive liver injury (complicated frequently with cirrhosis and hepatocellular carcinoma) and are more refractory to antiviral therapy and have an episodic reactivation of the disease activity (flare).

Clinical Features

Usually, they are asymptomatic but may be associated with *fatigue, recurrence of malaise and anorexia*.

- Persistent jaundice with intermittent deepening or intermittent jaundice often coinciding with evidence of viral reactivation.
- Features of cirrhosis, e.g. ascites, edema, bleeding gastroesophageal varices, coagulopathy, hypersplenism and hepatic encephalopathy develop at the end stage of chronic hepatitis.

Extrahepatic complications of chronic hepatitis-B are similiar to those seen in prodromal phase of acute HBV infection. These are associated with deposition of circulating HBV antigen-antibody complex and include:

- Arthritis and arthralgias
- Purpura (due to leukocytoclastic vasculitis)
- Generalized vasculitis (polyarteritis nodosa)
- Immune complex glomerulonephritis.

Investigation

Laboratory data do not distinguish between mild and severe hepatitis:

- SGPT—Usually modestly elevated (> 3 times of normal) but may be as high as 1000 U in fulminant hepatitis.
- SGPT > SGOT but when cirrhosis is established SGOT > SGPT.
- Alkaline phosphate marginally elevated.
- Serum bilirubin—Usually ranges between 3–10 mg/dL.
- Hypoalbuminemia.
- Prolonged P-time occurs in severe end stage cases.
- Hyperglobulinemia and circulating antibody against LKM antigen are absent in chronic hepatitis B in contrast to autoimmune hepatitis.
- Liver biopsy and HP examination is most helpful for staging and presence of virus.

Treatment

Although, progression to cirrhosis is more likely in severe than in mild to moderate chronic HBV, all forms of chronic HBV can be progressive and progression occurs primarily in those with active viral replication. Apart from that patient with chronic HBV are at increased risk of developing hepatocellular carcinoma specially those with continued high level of viral replication. So, management of chronic HBV infection is directed at suppression of viral replication.

No treatment is recommended for nonreplicative HBV carrier (i.e. undetectable HBe Ag, normal ALT, HBV DNA $\leq 10^3$ IU/mL.

Suppression of viral replication is done with:

- Injectable **interferon** α (**INF** α)/**pegylated interferon**
- Oral agent—**Lamivudine, adefovir dipivoxil,** *entecavir*, **telbivudine and** *tenofovir*.

Recent data support the use of:

Pegylated interferon (PEG-IFN), entecavir or *tenofovir as first line therapy*. Oral agents suppress HBV more profoundly than PEG-IFN and are effective in patient who fail to respond to INF-based therapy.

Telbivudine and *tenofovir* can be used safely during pregnancy. *Tenofovir* and *emtricitabine* in one pill is *best for HBV-HIV coinfected patient*. Optimal duration of antiviral therapy is not known but 6 months for inactive hepatitis-B carrier and long duration of therapy for patient with base line HBV DNA level $>2 \times 10^3$ IU/mL until standard clinical end point is reached which are as follow.

- Suppression of HBV DNA to undetectable level $<1 \times 10^3$ IU/mL.
- Normalization of alanine aminotransferase (ALT).

Entecavir—Oral 0.5 mg/day is the most potent of anti-HBV antiviral. Its high barrier to resistance coupled with its high potency renders entecavir a first line drug for chronic HBV infection.

Lamivudine—100 mg daily for 1 year.

Tenofovir—Oral 300 mg/day × 48 weeks. It has negligible renal toxicity and mild reduction in bone density and high potency make tenofovir a first line agent in the treatment of chronic HBV infection.

For patient with end-stage chronic hepatitis B liver transplant is the only potential life-saving measure.

CHRONIC HEPATITIS D

Although, HDV coinfection increases the severity of acute hepatitis B, it does not increase the likelihood of progression to chronic hepatitis B. Except for severity HBV + HDV has similar clinical and laboratory features to those seen in chronic hepatitis B alone.

Relatively severe chronic hepatitis with or without cirrhosis is the rule with chronic HDV infection and mild hepatitis is rare with chronic patient.

Treatment

INF or PEG-INF is recommended at present for chronic HDV infection for 48 weeks and extend the therapy until HDV RNA or HBeAg clear. None of the neucleoside analog antiviral for HBV is effective in HDV infection.

No antiviral is satisfactory. Liver transplant is effective and superior to antiviral in chronic hepatitis D.

CHRONIC HEPATITIS C

- Chronic hepatitis C develops in 85–90% patients regardless the mode of acquisition of virus (85–90%).
- Chronic hepatitis C tends to be very slowly and insidiously progressive in vast majority of patients.
- Those who have mild necrosis, inflammation and limited fibrosis on histology have excellent prognosis and limited progression to cirrhosis.
- Progression of chronic hepatitis C is influenced by the following factors:
  - Older age group
  - Longer duration of disease
  - Advanced histologic stage and grade
  - Steatohepatitis and obesity
  - Complex quasispecies diversity
  - Increased hepatic iron/hemochromatosis
  - Alcohol and liver disease
  - α_1 antitrypsin deficiency
  - Coinfection with HBV and HIV.
- Prognosis—Among patients with compensated cirrhosis associated with chronic hepatitis C.
  - 10 years survival is 80%.
  - Mortality is 2–6%/year.
  - Decompensation takes place at the rate of 4–5%/year.
  - Development of hepatocellular carcinoma occurs at the rate of 1–4%/year.

Clinical Features

- Fatigue—Most commonly present.
- Jaundice is rare.
- Features of essential mixed cryoglobulinemia—Immune complex-mediated extrahepatic complication of chronic hepatitis C are less common than HBV but can evolve into B-cell lymphoma.
- Other—Late complications of chronic HCV are:
  - Sjögren's syndrome
  - Lichen planus
  - Porphyria cutanea tarda.

  Overall in chronic hepatitis C (78%) patient progression of the disease is very slow whereas in 25% patient of chronic hepatitis C the HCV infection progress eventually to end stage liver disease.

Laboratory Features

- Fluctuating level of SGPT.
- Anti-LKM1 antibody is present (as seen in autoimmune hepatitis-II). The presence of this autoantibody with chronic HCV suggests that autoimmunity may have a role in the pathogenesis of chronic HCV infection.

Treatment

Patient with chronic hepatitis C
- Elevated SGPT level
- Detectable HCV-RNA
- Chronic hepatitis of moderate grade and stage (portal and bridging fibrosis) are treated with following:

Interferon + Ribavirin
- *For HCV genotype I and IV*
  - Peg INFα 2b—180 μg/SC weekly + ribavirin 1000–1200 mg/day orally for 48 weeks.
- *For HCV genotype II and III*
  - Peg INFα 2a—180 μg/SC weekly + ribavirin 800 mg/day for 24 weeks.

    Or
  - Peg INFα 2b—1.5 μg/kg SC weekly + ribavirin 800–1400 mg/day for 48 weeks.
- *Newer combination regimen*
  - **HCV RNA undetectable at 8 and 24 weeks**

    Dual therapy for 4 weeks then triple therapy for 36 = total 40 weeks
  - **HCV RNA detectable at 8 weeks but undetectable—24 weeks.**

    Dual therapy × 4 weeks + triple therapy × 32 weeks + dual therapy for 12 weeks = 48 weeks.

– **Patient with cirrhosis and undetectable HCV RNA at 8 weeks and 24 weeks**
Dual therapy × 4 weeks + triple therapy × 44 weeks = total 48 weeks, or
Telaprevir 750 mg TDs with fatty food without PEG-INF and ribavirin × 48 weeks or
– **For partial responder/Nonresponder:**
PEGINF with ribavirin and telaprevir × 12 weeks + PEGINF and ribavirin × 36 weeks = total 48 weeks.

Dual therapy = PEG-INF + ribavirin.
Triple therapy = PEG-INF + ribavirin + boceprevir.

NOVEL ANTIVIRUS

An oral combination of 2nd generation antiviral
- *Asunaprevir + daclatasvir*
- *Sofosbuvir + ribavirin*
- *Sofosbuvir + daclatasvir + ribavirin*
- *Ritonavir* + ABT 450 + ABT 333 + ABT 267 + *Daclatasvir* ± *ribavirin* have been studied in clinical trial. Several of these drug combination have achieved SVR rate >90% even approaching 100% with a treatment duration of 8–24 weeks even at 8 weeks. Such combination of antiviral agent will replace INF based regimen in future.

AUTOIMMUNE HEPATITIS

It is a group of chronic heterogenous liver disorder of unknown etiology, a portion of which have autoimmune features characterized by continuing hepatocellular necrosis and inflammation usually with fibrosis which tends to progress to cirrhosis and liver failure.

Presence of serologic abnormality supports autoimmune pathogenesis and extrahepatic features of autoimmunity is usually present in a group of patients but autoantibody and typical features of autoimmunity is not present in all cases of autoimmune hepatitis.

Types

- **Type I autoimmune hepatitis**—Occurs in young women associated with marked hyperglobulinemia, lupoid feature and circulating ANA.
- **Type II autoimmune hepatitis**—Often seen in children more common in Mediterranean population (not associated with ANA) but with anti-LKM-1 antibody. (This is same as anti-LKM seen in some patients of chronic HCV infection).
  Another antibody known as anti-liver-cytosol-1 is found in type II autoimmune hepatitis.

Anti-LKM-2 is seen in drug-induced hepatitis
Anti-LKM-3 is seen in chronic hepatitis D

Type II autoimmune hepatitis is further subdivided into two categories
– *Type IIa autoimmune hepatitis* is seen in young women associated with hyperglobulinemia, *high titer of anti LKM-1* and respond to glucocorticoid seen in Western Europe.
– *Type IIb autoimmune hepatitis* is associated with normal globulin level and *low titer of anti LKM-1* seen commonly in Mediterranean countries. They have anti-liver-cytosol-1 antibody.
- **Type III autoimmune hepatitis (controversial)**—They lack anti LKM-1 and ANA but have *antibodies to soluble liver antigen* or liver pancreas antigen and have clinical features similar to perhaps more severe than those of type-I autoimmune hepatitis. Most of these patient are women. Type–III autoimmune hepatitis does not represent a separate category but it is a part of the spectrum of type–I autoimmune hepatitis.

Pathogenesis

Progressive liver injury in idiopathic/autoimmune hepatitis is due to cell-mediated cytotoxicity in a person with autoimmune predisposition, is supported by the fact that:
- Liver is massively infiltrated with plasma cell and cytotoxic 'T'cell and shows interface hepatitis and plasma cell rosettes.
- Strong association with DR3-DR4.
- Presence of circulating antibody like ANA, anti-SM, anti-TPO, RF and anti-LKM–I.
- Hyperglobulinemia.
- Associated with other autoimmune disorders like *thyroiditis, RA, autoimmune hemolytic anemia, ulcerative colitis, acute glomerulonephritis, type-I DM and Sjögren's syndrome*.

Extrahepatic manifestation of autoimmune/idiopathic hepatitis are:
- Arthralgia and arthritis
- Cutaneous vasculitis
- Glomerulonephritis that are mediated by deposition of circulating immune complex in the affected tissue followed by complement activation, inflammation and tissue injury.

Autoantibody found in idiopathic/autoimmune hepatitis are:
- ANA (homogeneous pattern).
- Anti-Sm antibody (directed against actin).
- Anti-LKM antibody (liver kidney mitochondria).
- Antibody to soluble liver antigen/soluble liver pancreas antigen.

Clinical Features

Onset may be insidious or abrupt—when abrupt it may be confused with acute viral hepatitis. Common features are:
- Fatigue
- Malaise
- Anorexia
- Amenorrhea

- Acne
- Arthralgia and arthritis
- Jaundice is common
- Occasionally, maculopapular rash including cutaneous vasculitis, erythema nodosum, colitis, pleurisy, pericarditis, anemia, azotemia, and sicca syndrome can occur.

A subset of patient with autoimmune hepatitis has distinct features. They are middle-aged lady with marked hyperglobulinemia and high titer of circulating ANA. These are called lupoid hepatitis with positive LE cell preparation.

Prognosis

1. Natural history of milder diseases is a fluctuating course of spontaneous remission and exacerbation
2. Those with mild disease (piecemeal necrosis without bridging) progression to cirrhosis is limited
3. Those with severe symptomatic autoimmune hepatitis (SGPT >10 times of normal) with marked hyperglobulinemia, bridging necrosis with multilobular collapse and cirrhosis. Mortality is as high as 40% within 6 months. Such severe diseases account for 20% of cases

Poor prognostic features are:

1. Multilobular collapse
2. Failure of the bilirubin to come down within 2 weeks of therapy
3. Death may be due to complication of cirrhosis.

Laboratory Investigation

- Similar to those of chronic viral hepatitis. Liver biochemistry is abnormal but does not correlate with clinical severity or histopathologic features.
- AST and ALT are increased and fluctuate in between 100–1000 unit/L.
- Serum bilirubin ranges from 3–10 mg/dL.
- Hypoalbuminemia occurs in active and advanced disease.
- Alkaline phosphate is mild to moderately elevated, those with very high level of alkaline phosphate have overlap features of **primary biliary cirrhosis**.
- Prothrombin time is often prolong.
- Hypergammaglobulinemia >2.5 g/dL.
- Rheumatoid factor is positive.
- ANA present (homogeneous pattern)
- Anti-Sm antibody is positive.
- There may be false-positive reaction to HCV.

Liver histology shows expanding portal tract inflammation which extends beyond the plate of periportal hepatocyte into the parenchyma designated as interface hepatitis or piecemeal necrosis with mononuclear cell infiltrate including plasma cell in autoimmune hepatitis. Necroinflammatory activity and hepatocellular regeneration as reflected by rosette formation, thicken liver cell plate, regenerative pseudolobule, septal fibrosis, bridging fibrosis and cirrhosis.

Diagnostic criteria—Female, predominant SGPT elevation, high serum globulin, positive ANA, anti-Sm, Anti LKM-1 concurrent other autoimmune disease, characteristic histologic features of interface hepatitis, plasma cell, rosette formation, HLADR-3 and 4 marker and response to treatment, support the diagnosis of autoimmune hepatitis.

Simplified diagnostic criterion of autoimmune hepatitis:

- Presence of auto antibody.
- Raised serum IgG level.
- Histology—Interface hepatitis and plasma cell rosette formation.
- Absence of marker of viral hepatitis.

Treatment

- **Prednisolone/prednisone**—60 mg/day tapered over a month to 20 mg/day.
- **Prednisolone**—30 mg/day with **azathioprine** 50 mg/day.

The dose of prednisolone tapered to 10 mg/day over a month keeping the dose of azathioprine at 50 mg/day. The therapy to be continued for 12–18 months. This combination reduces the side effect of steroid therapy from 66–20% over a period of 18 months therapy.

Improvement in symptoms (fatigue, anorexia, malaise and jaundice) occur in days to weeks and improvement in biochemical parameter in weeks to month and improvement in histologic picture from 6–24 months are seen in 80% patients. After cessation of therapy relapse occurs in 50% case. Azathioprine 2 mg/kg after stopping prednisolone reduces the frequency of relapse or prednisolone <10 mg/day keeps autoimmune hepatitis under control.

In refractory cases treatment with:

a. High dose of glucocorticoid 60 mg/day
b. Combination of glucocorticoid 30 mg/day + high dose of azathioprine 150 mg/day for 1 month, thereafter reducing the dose of prednisolone 10 mg/day × 1 month and azathioprine 50 mg/day × 1 month for the maintenance therapy.

If medical therapy fails liver transplant is the only option but recurrence of autoimmune hepatitis occurs in one third of such cases.

EXERCISE

Write short notes on

1. Etiology of chronic hepatitis.
2. Clinical features, investigations and treatment of chronic HBV and HCV infection.
3. Classify autoimmune hepatitis.
4. Clinical features, diagnosis and treatment of autoimmune hepatitis.

Chapter 44

Alcoholic Liver Disease

INTRODUCTION

Alcoholic liver disease comprises of:

- **Fatty liver** (present in 90% chronic alcoholic)
- **Alcoholic hepatitis** (present in 10–20% of alcoholic)
- **Cirrhosis**.

Fatty liver is present in 90% of chronic drinker, but a much smaller percentage (10–20%) of alcoholic will develop alcoholic hepatitis. Alcoholic hepatitis is thought to be a precursor to cirrhosis. Mortality of alcoholic hepatitis with cirrhosis is 60% in 4 years.

PREDISPOSING FACTOR

- **Quantity**—In men, Ethanol 60–80 g/day for 10 years produces severe alcoholic liver disease.
- Ladies are more susceptible to alcoholic liver diseases (> 20 g/day to 40 g/day produces hepatitis).
  It is possibly due to gender difference in the gastric and hepatic metabolism of alcohol and hormonal factor which make women more susceptible to alcohol-induced liver injury.
- Chronic HCV coinfection with alcoholic liver disease is associated with more severity, advanced histology and decreased survival.
- Gene polymorphism may induce alcohol dehydrogenase and P_{450} 2 E1 responsible for alcoholic liver disease.
- **Malnutrition**—Once considered to be the key factor in production of alcoholic liver disease is not true. Alcohol initiates a pathogenic process in the hepatocyte by production of a protein— **Aldehyde adducts, and lipid peroxidation, immunologic** activity and cytokine (TNF-α, TGF-β, IL-1, IL-6) release. The complex *interaction between hepatocyte stellate cell* and *Kupffer cell leads to stellate cell activation* and *collagen production which is crucial for fibrogenesis* and cause of *architectural derangement of liver following alcohol ingestion*.

PATHOLOGY

- Fatty liver is the initial change in response to hepatotoxic stimuli of alcohol. The early accumulation of fat within the perivenular hepatocyte coincides with the location of alcohol dehydrogenase (major enzyme responsible for alcohol metabolism), later fat accumulate in the entire hepatic lobule. Despite extensive distortion of hepatocyte by the macrovesicular fat accumulation, cessation of drinking at this stage results in normalization of hepatic architecture and fat content. Certain pathologic changes **steatohepatitis, giant mitochondria, perivenular fibrosis and macrovesicular fat** may be associated with progressive liver injury. But the transition between fatty liver and alcoholic hepatitis is blurred.
- The hallmark of alcoholic hepatitis are ballooning degeneration, spotty necrosis, polymorphonuclear infiltrate and fibrosis of perivenular and perisinusoidal space of Disse with or without Mallory hepatitis.
- Alcoholic hepatitis is thought to be a precursor to the development of cirrhosis; however, it is potentially reversible with cessation of drinking and 50% of alcoholic hepatitis at diagnosis have cirrhosis.

CLINICAL FEATURES

- It may be asymptomatic.
- There may be RUQ discomfort with silent or tender hepatomegaly.
- Nausea and jaundice are usually present.
- Differential diagnosis of alcoholic hepatitis from nonalcoholic fatty liver is difficult unless history is available.
- Fever, spider nevi, jaundice and abdominal pain stimulating an acute abdomen represent the worst end of the spectrum.
- In may patient, it is associated with edema and ascites.

LABORATORY FEATURES

- **Modest elevation of SGOT <400 U/L**.
- **Rise in SGPT** (2–7 fold) <400 U/L.
- **SGOT**: **SGPT** ratio >1.
- **GGPT** is not specific for alcoholic liver disease may be elevated with all forms of fatty liver.
- **Bilirubin**—May be markedly increased in alcoholic hepatitis despite modest elevation in alkaline phosphatase.
- **Neutrophil** >5500/μL predict severe hepatitis when discriminant function score >32.

Prognosis

Critically ill patient with alcoholic hepatitis have short-term mortality approaching 70%.
Ominius signs are:

- Prothrombin time increased by 5 seconds
- Anemia
- Serum albumin <2.5 g/dL
- Serum bilirubin >8 mg/dL
- Renal failure
- Ascites
- A discriminant function as calculated by:
  4.6 × P-time – control (in second) + serum Bilirubin (mg) dL > 32, suggest poor prognosis.

Poor Prognostic Parameter

- Presence of ascites.
- Discriminant function score >32 [4.6 × prolongation of P-time above control (in second) + serum bilirubin (mL/DL)].
- Model for end-stage liver disease score (MELD) >21.
  Discriminant function >32 or MELD score >21 are criteria for starting treatment with either pentoxifylline or prednisolone.
- Variceal hemorrhage.
- Hepatorenal syndrome.
- Hepatic encephalopathy, suggests dismal prognosis.

TREATMENT

- Complete abstinence from alcohol is the cornerstone of treatment.
- Correction of malnutrition.
- Psychological support.
  Patient with discriminant function (DF) >32 or MELD >20 should be treated with:
  - **Prednisolone** 32 mg/day × 4 weeks followed by a steroid taper over another 4 weeks.
    (exclusion criteria—GI hemorrhage, sepsis, renal failure and pancreatitis), alternatively
  - **Pentoxifylline (TNF inhibitors)** as an alternative to steroid in severe alcoholic hepatitis—400 mg tid × 4 weeks.
- Hepatic transplant—Associated with high mortality.
- Infliximab and etanercept have been tried as a suppressor of TNF α but without clear-cut benefit.
  - Anabolic steroid antioxidant, propylthiouracil, colchicine and penicillamine all have been tried but there is no clear-cut improvement.

  Acamprosate calcium reduces the craving for alcohol.

EXERCISE

Write short notes on

- Clinical features of alcoholic liver disease.
- Treatment of alcoholic liver disease.

Chapter 45

Nonalcoholic Steatohepatitis

INTRODUCTION

Mild to moderate enlargement of liver due to diffuse accumulation of neutral fat (triglyceride) in hepatocytes is a clinical and pathological finding in hepatic steatohepatitis. When the fatty infiltration is accompanied by necroinflammatory activity **in absence of history of chronic alcohol abuse**, then it is turned as nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH). Fatty liver can be divided into 2 types depending on the deposition of the fat in the hepatocyte:

- Macrovesicular
- Microvesicular.

ETIOLOGY OF HEPATIC STEATOSIS

Causes of Macrovesicular Steatohepatitis (Large Fat Droplet in Hepatocyte)

- Alcohol.
- Syndrome X, triglyceride (obesity, diabetes mellitus, increased triglycerides, hypertension).
- Rapid weight reduction.
- Starvation, malnutrition, malabsorption.
- Total parenteral nutrition.
- Intestinal bypass.
- Drugs—Methotrexate, calcium channel blocker (CCB), glucocorticoid, conjugated estrogen, minocycline, iron.
- Inflammatory bowel disease (IBD).
- Lipodystrophy.

Causes of Microvesicular Steatohepatitis (Small Fat Droplet in Hepatocyte)

- Reye's syndrome.
- Acute fatty liver of pregnancy (AFLP).
- Drugs—Valproate, tetracycline, didanocin.
- Inheritate metabolic disorder—Urea cycle defect, beta oxidation of fatty acid defect.
- Toxin—Phosphorus and petrochemical.

Pathogenesis

Pathogenesis is not clear. All the above etiology causes imbalance in hepatic triglyceride synthesis and export.

This steatosis cannot itself produce necroinflammatory activity. When an oxidative stress is superimposed on steatosis it results in abnormal lipid peroxidation and subsequent cytokine release (specially TNF) resulting in hepatic fibrosis.

Fatty liver → Steatohepatitis (NASH) → NASH + Fibrosis → Cirrhosis.

Most of the cases are associated with obesity and one-third cases are characterized by type-II diabetes and hyperlipidemia.

Microvesicular steatosis occurs in more serious condition and may be associated with mitochondrial damage which causes impaired fatty acid β-peroxidative metabolism.

- **Syndrome X** is strongly associated with NAFLD. Age > 45, obesity BMI > 30, AST : ALT > 1 and diabetes are all associated with increased risk of development of significant fibrosis.
- **Protein malnutrition**—In infancy and childhood accounts for most of the severe fatty liver in tropical countries.
- **Jejunoileal bypass**—Done for morbid obesity or for other condition associated with severe fatty liver.
- **Parenteral hyperalimentation**—It is also associated with development of fatty liver.
- **In many other chronic illness**—Ulcerative colitis, chronic pancreatitis, prolonged congestive cardiac failure (CCF), Cushing syndrome are associated with the development of fatty liver.
- **Acute fatty liver** may be caused by dichlorodiphenyltrichloroethane (DDT) and yellow phosphorus poisoning.

In some cases, fatty infiltration and steatohepatitis may occur in the absence of an identifiable cause.

MICROVASCULAR NASH

- **Acute fatty liver of pregnancy (AFLP)**—A syndrome of late pregnancy associated with jaundice and hepatic failure. It is most common with male fetus with deficiency of long chain 3 hydroxyacyl-CoA dehydrogenase. Treatment is termination of pregnancy because of the risk of fatal deterioration.
- **HELLP**—Hemolysis, elevated liver enzyme (SGPT < 500 U/L), low platelet count (which complicate eclampsia

in similar fashion of AFLP). Treatment is termination of pregnancy as the disease resolves with termination of pregnancy.

- **Reye's syndrome (fatty liver with encephalopathy)**—The causes are unknown, viral agent and drug (high dose aspirin) have been implicated. However, the illness may occur in the absence of exposure to salicylate. In fatal cases liver is enlarged, yellow in color with diffuse fatty microvacuolation of cell. Peripheral zone hepatic necrosis may also be present. Fatty changes in the renal tubule, cerebral edema, neuronal degeneration are the extrahepatic changes. The onset usually follows viral episode of chickenpox or measles. It is associated with vomiting, stupor which rapidly deteriorate to coma associated with convulsion. Liver is enlarged. Jaundice is usually absent or minimal, elevation of SGPT and prothrombin time with hypoglycemia, acidosis elevated serum amonia. Mortality is 50%.

Treatment

- 20% glucose intravenous.
- Fresh frozen plasma.
- Intravenous mannitol (20%)—for cerebral edema. Chronic liver disease is not a sequela.

Clinical Features

Symptoms and signs of hepatic steatosis is related to:

- Degree of fatty infiltration
- Rate of fatty infiltration
- Underline cause.

In obese diabetic patient with chronic liver disease patient is asymptomatic and mild tenderness over the enlarged liver.

Liver function test (LFT) is normal with mild elevation of alkaline phosphatase and serum glutamate-pyruvate transaminase (SGPT).

But in rapid accumulation of fat in the setting of parenteral hyperalimentation may lead to marked tenderness due to stretching of the Glisson's capsule.

Although steatohepatitis has a benign course with improvement following elimination of associated precipitant factor in some individual it may lead to significant fibrosis or even cirrhosis.

Microvesicular steatosis may be associated with fatigue, vomiting, and progressive CNS injury—encephalopathy and coma. Jaundice is typically absent in Reye's syndrome with history of salicylate intake. This is the less common form of fatty liver.

On microscopic examination fat is present within the hepatocyte in many small vesicles and the deposited fat is triglyceride in both micro and macrovesicular form of the disease. The reason for the difference in size of the droplet is not clear.

Diagnosis

- Firm nontender generally enlarged liver with minimal hepatic dysfunction.
- History of malnutrition or poorly control diabetes, obesity. Total parenteral hyperalimentation/ pregnancy, chickenpox and measles suggest hepatic steatosis.
- Modest elevation of serum aminotransferase.
- USG/CT/MRI to evaluate the size of the liver.

Disproportionate elevation of serum SGOT leading to SGOT: SGPT ratio > 2 is generally associated with alcoholic hepatitis

- Needle biopsy is confirmatory and shows typical histologic pattern with increased fibrosis.

TREATMENT

- Adequate nutritional intake.
- Withdrawals of offending toxin.
- Potentially, a reversible process in total parenteral hyperalimentation. The condition reverse back within 2 weeks of discontinuing therapy.
- Ursodeoxycholic acid—300 mg bid.
- Betaine (precursor of S adenosylmethionine).
- Vitamin E.
- Troglitazone—Some benefit in insulin resistance cases.
- Phlebotomy.
- Acute steatohepatitis due to microvesicular steatosis require intensive care and management.
- Careful control of diabetes by insulin or oral hypoglycemic agent.
- Attainment of optimal weight.
- Correction of intestinal malabsorption.

EXERCISE

Write short note on

- NASH.

Chapter 46

Cirrhosis and its Complications

Cirrhosis is pathologically defined as:

- Irreversible chronic injury of hepatic parenchyma, associated with extensive fibrosis with formation of regenerative nodules.

Features

- Hepatocyte necrosis.
- Collapse of supporting reticulin network with subsequent connective tissue deposition.
- Distorsion of liver vascular bed.
- Nodular regeneration of remaining liver parenchyma.

Classifications (Depending on Etiology)

- Central event leading to hepatic fibrosis, is the activation of hepatic stellate cells (Ito cells) upon activation by factors released from hepatocyte and Kupffer's cells, the stellate cells assume myofibroblast like confirmation and under influence of cytokines TGF-β produces fibril forming type-I collagen which is basic step in the development of cirrhosis

- Alcoholic cirrhosis
- Chronic viral hepatitis (HBV and HCV infection)
- Biliary cirrhosis:
  - Primary
  - Autoimmune cholangiopathy
  - Primary sclerosing cholangitis
- Cardiac cirrhosis
- Autoimmune hepatitis
- Nonalcoholic steatohepatitis
- Metabolic cirrhosis:
  - Wilson's disease
  - Hemochromatosis
  - Glycogen storage disease
  - Galactosemia
  - α_1-antitrypsin deficiency
  - Fanconi's syndrome.
- Drugs and toxins:
  - MXT
  - Methyldopa
  - INH
  - Sulfonamide
  - Amiodarone
  - Arsenicals
  - Cryptogenic cirrhosis.

These are the common drug that causes liver injury and ultimately leads to cirrhosis.

- **Miscellaneous**
  - Nonalcoholic steatohepatitis (NASH)
  - Cystic fibrosis
  - Jejunoileal bypass
  - Sarcoidosis

  Can be complicated with cirrhosis.

Pathologically cirrhosis can be classified as:

- Micronodular (nodule < 3 mm in size) → Postalcoholic/lanec cirrhosis.
- Macronodular (large nodules may be 10 cm/more) → Postviral/postnecrotic cirrhosis.
  - Biliary cirrhosis may produce both macro and micronodular cirrhosis.

Clinical Features

- Cirrhosis clinically may be silent in 10–40% cases and discovered accidentally at laparotomy/autopsy.
- Clinical features may be divided into two groups—
  - Features related to etiology of cirrhosis.
  - Features related to disease itself and its complications.
- **Special features due to etiology**
  - **Features of alcoholic cirrhosis**
    - From history try to assess amount and duration of alcohol consumption.
    - Hollow temporal fossa.
    - Jaundice with muddy appearance of conjunctiva.
    - Malar flush (Cushingoid facies).
    - Bilateral enlarged parotid.
    - Spider nevi.
    - Gynecomastia.
    - Palmar erythema.
    - Clubbing.
    - Dupuytren's contracture.
    - Testicular atrophy and diminished libido with infertility in male and amenorrhea in female due to hormonal abnormality or direct effect of alcohol on gonad.

- Features of malnutrition.
- Neuropsychiatric manifestations—Loss of memory and concentration, insomnia, irritability, hallucination, convulsion, tremor and delirium tremens.
- Hepatorenal syndrome is common in alcoholics.

Treatment of alcoholic liver disease—See Chapter 44.

- **Biliary cirrhosis**
  - Earliest symptom—Pruritus over palm and sole and may be present before the appearance of jaundice.
  - Jaundice with gradual darkening of exposed skin—Melanosis.
  - Steatorrhea.
  - Xanthelasmas around eyes, joint and tendon.
  - Features of autoimmune diseases like RA, scleroderma, CREST, sicca syndrome, pernicious anemia and type-1 diabetes may be associated with primary biliary cirrhosis.
- **Cardiac cirrhosis**
  - Features of long-standing right heart failure and its etiological cause.

Treatment of primary biliary cirrhosis
- UDCA 13–15 mg/kg/day
- For pruritus—Antihistaminic, narcotic receptor antagonist (naltrexone), rifampin and cholestyramine
- Osteopenia and osteoporosis—bisphosphonate
- Liver transplant

- **Posthepatitic cirrhosis**
  - History of blood transfusion, multiple sexual exposure or infected needle prick followed by prodromal features of hepatitis like fever, malaise, bodyache, anorexia, nausea, vomiting, joint pain, jaundice, weakness, sometimes lymphadenopathy.
- For other metabolic disorders—history will depend on etiology.

- **Clinical features due to cirrhosis itself and its complication**
  - Features due to portal hypertension.
  - Features due to hepatocellular failure.
  - Features due to combination of hepatocellular failure and portal hypertension.
    - These features are *exclusively due to cirrhosis* and are *independent of the etiology* of underlying liver disease.
  - **Features due to portal hypertension (portal venous pressure >10 mmHg)**
    - *Prominent abdominal vein with/without caput medusae.*
      A number of prominent collateral vein radiating from umbilicus giving the picture of spider leg. It is a very rare condition and is due to collateral anastomosis between paraumbilical vein (tributary of portal vein) with superior epigastric, lateral thoracic, superficial epigastric, inferior epigastric, posterior intercostal and lumbar vein (tributary of vena cava).
    - *Cruveilhier-Baumgarten syndrome*—Very rarely a venous hump may be audible over the umbilicus over the caput due to extensive collateral connections known as *Cruveilhier-Baumgarten syndrome*.
    - *Splenomegaly*—When massive it leads to heaviness of LUQ of abdomen, early satiety, which may contribute to anemia and/or thrombocytopenia.
    - *Hematemesis and melena or hematochezia* may result from rupture of dilated esophageal varices or from rectal hemorrhoids.
  - **Features due to hepatocellular failure**
    - **Features due to hyperestrogenism**
      - » Spider nevi/arterial spider/spider telangiectasia/spider angiomas.
      - » Palmar erythema.
      - » Gynecomastia.
      - » Loss of body hair, axillary hair, pubic hair.
      - » Loss of libido.
      - » Testicular atrophy and infertility.
      - » Menstural irregularity in female.
        - This is mostly due to decreased metabolism of estrogen precursor (androstenedione) in the liver giving the feature of hyperestrogenism.
    - **Features due to nondetoxification of NH_3** and related compound
      - » Fetor hepaticus
      - » Hepatic flap (asterixis)
      - » Hepatic encephalopathy.
    - **Features due to nonconjugation of bilirubin** Jaundice (unconjugated hyperbilirubinemia). It may also be due to:
      - » Intrahepatic cholestasis.
      - » Increased hemolysis due to membrane damage owing to hypercholesterolemia.
    - **Features due to nonsynthesis of albumin**
      - » Alteration of A : G ratio.
      - » White nails (leukonychia)—Nails become white and brittle due to hypoalbuminemia.
    - **Features due to nonsynthesis of clotting factors and thrombocytopenia**
      - » Increased bleeding
      - » Increased clotting time and P-time/INR.
  - **Combined features of hepatocellular failure and portal hypertension**
    - Ascites
    - Fetor hepaticus
    - Hepatic encephalopathy
    - Hepatorenal syndrome.

Fetor hepaticus
- Sweetish, slightly fecal smell obtained from the mouth of advanced cirrhotic patient is due to presence of *methyl mercaptans derived from methionine* produced in intestine. It is found in severe hepatocellular disease due to failure of demethylation of methyl mercaptan in liver and through extensive collateral circulation it reaches systemic circulation

Coagulopathy
- Diminished protein synthesis leads to reduced production of fibrinogen (factor-I), prothrombin (factor-II) and factors VII, IX, X
- This is also due to coincidental malabsorption of fat-soluble vitamin K due to cholestasis
- Of this factors, factor–VII appears to play the pivotal role, as selective replacement of factor–VII can correct the PT in cirrhotic patient

Complications of Cirrhosis

- Ascites.
- Spontaneous bacterial peritonitis.
- Hepatic hydrothorax.
- Upper GI hemorrhage (gastroesophageal varices and portal gastropathy).
- Hepatic encephalopathy.
- Hepatorenal syndrome (type I and type II).
- Hepatopulmonary syndrome.
- Hepatocellular malignancy.
- Splenomegaly and hypersplenism.
- Hematological abnormalities—Anemia, hemolysis, thrombocytopenia and neutropenia.

Treatment of Cirrhosis

- **Alcoholic cirrhosis**:
  - Corner stone of therapy is cessation of alcohol.
  - Acamprosate calcium reduce the craving for alcohol.
  - When discriminant function (DF) value >32, pentoxifylline 400 mg TDS alternatively and prednisolone 30 mg daily × 28 days gives improved survival.
    [Discriminant function (DF) = (Patient P time–control P time) + serum albumin mg/dL × 4.6].
  - Specific management for *ascites, edema, variceal hemorrhage and hepatic encephalopathy*.
- Cirrhosis due to chronic HBV and HCV infection: Specific antiviral therapy for HBV: *Lamivudine, adefovir, telbivudine, entecavir* and *tenofovir* shows beneficial effect as evidenced by reduction of aminotransferase level, suppression of HBV–DNA level and improving histology of liver by reducing inflammation.
  Specific antiviral for HCV infection (discussed under Chapter 43).

HEPATIC ENCEPHALOPATHY

It is defined as alteration of mental status and cognitive function occurring in the presence of liver failure.

Encephalopathy is much more commonly seen in patient with chronic liver disease. Gut-derived neurotoxin that are normally removed by liver, reach brain due to vascular shunting and are responsible for hepatic encephalopathy.

Ammonia is elevated in patient of hepatic encephalopathy but that does not correlate well with the clinical picture. That is why it is assumed that false neurotransmitter and mercaptan may play a role in the development of hepatic encephalopathy.

PATHOGENESIS

- Specific cause is unknown.
- Most important factors in pathogenesis are severe hepatocellular failure with intra/extrahepatic portosystemic shunt.
- The noxious agents responsible for hepatic encephalopathy are:
  - Ammonia

- It is the most widely investigated toxic substance
- It is derived from nitrogenous contents of intestine by bacterial action on protein and present in high concentration in portal blood. Due to hepatocellular failure, there is nondetoxification of NH_3 and via increased collateral circulation it reaches the brain
  a. NH_3 interfere with cerebral metabolism by:
     - Increased glutamine synthesis

  - Other possible mechanism for hepatic encephalopathy

- False neurotransmitter (**octapamine**)—act as competitive antagonist for neurotransmitter
- Other compound (**mercaptan, short chain fatty acid and phenol**).
- Increased sensitivity of **neurotransmitter** receptor
- Change is carbohydrate metabolism in brain is due to hypoglycemia
- Reductive amination of ketoglutarate and subsequent stoppage of TCA cycle
- Excess manganese deposition in basal ganglia
- Alteration of blood brain barrier (**BBB**)
- It also damages the **neural membrane**
  - Upper limit of blood NH_3 0.8–1 µg/mL

  - Altered permeability of BBB and increased sensitivity of CNS due to electrolyte and metabolic imbalance, towards these noxious agents is the basic pathogenic mechanism for production of hepatic encephalopathy.

FACTORS PRECIPITATING HEPATIC COMA

- **Increased nitrogen load**
  - GI bleeding
  - Excess diatery protein
  - Azotemia
  - Constipation.
- **Electrolyte and metabolic imbalance**
  - Hypokalemia
  - Alkalosis
  - Hypoxia
  - Hyponatremia
  - Hypovolemia.
- **Drugs**
  - Narcotic/sedative/tranquilizer
  - Diuretic.
- **Miscellaneous**
  - Infection
  - Portacaval shunt surgery
  - Superimposed acute liver disease
  - Progressive liver disease.

Clinical Features (Table 46.1)

DIFFERENTIAL DIAGNOSIS

- Subdural hematoma
- Drug and alcohol intoxication
- Delirium tremens
- Wernicke's encephalopathy
- Hypoglycemic encephalopathy
- Wilson's disease
- Primary psychiatric disorder.

MANAGEMENT

- **Acute encephalopathy**
  - *General measures*:
    - Endotracheal intubation of patient in deep encephalopathy.
    - Introduction of nasogastric tube (for feeding 80 mL/hour total 18 feed/day).
    - Correction of fluid and electrolyte imbalance.
    - Identification and avoidance of precipitating factors and drugs.
  - *Specific measures*:
    - Empty the bowel of N_2-containing material
      - » By stopping the upper GI bleeding with Sengstaken tube and injection terlipressin.
      - » By phosphate enema, neomycin enema.
    - Diet:
      - » When patient in deep coma oral feeding is suspended and glucose (IV) is provided until improvement occurs. If improvement does not occur within 48 hours parenteral nutrition can be started with protein restriction (20 g/day).
      - » Caloric intake should be maintained ≥2,000 cal/day either orally/parenterally.
    - Lactulose—(10–30 mL tid) via nasogastric tube/ enema in deep encephalopathy.
      Dose is adjusted to such a level that 2–3 semisolid evacuation per day occurs.
      Lactitol—(0.3–0.5 g/kg/day) can also be used specially for those who are intolerant to lactulose.
    - Antibiotic—
      - » Metronidazole (200 mg qid)—as effective as neomycin.
      - » Rifaximin—1100 mg/day is effective for grade 2–3 of hepatic encephalopathy.
    - Maintenance of fluid electrolyte balance:
      - Check serum electrolyte level.
- **Chronic encephalopathy**
  - Avoidance and prevention of precipitating factors and institution of prophylactic measures.
  - Nutrition—Improved protein intake by dairy product and vegetables-based diet.
  - Avoidance of N_2-containing drugs.
  - Oral branched chain amino acid—To those intolerant to all proteins.

Table 46.1: Clinical features of hepatic encephalopathy

Stage	Neutral	Asterixis	EEG
I	• Euphoria/depression • Altered sleep rhythm • Mild confusion • Slurred speech	• +/– • Sudden extension of wrist when the arm is held at extended position with wrist in extended position	Triphasic wave
II	• Lethargy • Mental confusion	+ +	Triphasic wave
III	• Marked confusion • Incoherent speech • Arousable	+ +	Triphasic wave
IV	• Coma—Initially responsive to noxious stimulus	–	Delta wave

- Lactulose—Dosing aims at 2–3 soft bowel movements/day.
- Antibiotics (rifaximin)—Reserved for patients who respond poorly to lactulose/who do not exhibit diarrhea or acidification of stool.
- Neomycin/metronidazole—It can be used chronically but require careful renal, neurological and otological monitoring.
- Reference for hepatic transplant for appropriate candidates. If that is not feasible, consider imaging of large vessel to identify *large portosystemic shunt* which *should be radiologically occluded*.
  In addition *TIPSS/prior surgical shunts* are *also to be occluded*.
- Additional experimental agents—Oral zinc supplementation.

PORTAL HYPERTENSION

It is a condition characterized by prolonged elevation of *portal venous pressure >10 mm Hg*.

CLASSIFICATIONS

- **Extrahepatic cause—Extrahepatic portal venous obstruction (EHPVO)**.
  Causes:
  - Portal vein thrombosis
  - Splenic vein thrombosis
  - Massive splenomegaly
    - *Infections*:
      - Umbilical cord sepsis
      - Acute appendicitis
      - Peritonitis
      - Inflammatory bowel disease
      - Primary sclerosing cholangitis
      - Gallstone infection.
    - *Postoperative*:
      - Splenectomy
      - Repair of stricture of CBD
      - Removal of choledochal cyst.
    - *Trauma*:
      - Blunt trauma over abdomen
      - Surgery.
    - *Hypercoagulable state*:
      - Myeloproliferative disorder
      - Protein C/S deficiency
      - Antithrombin 3 deficiency
      - Pregnancy
      - Oral contraceptive pill consumption.
    - *Invasions and compression*:
      - Hepatocellular carcinoma
      - Pancreatic carcinoma.
    - *Congenital:*
    - *Miscellaneous*:
      - Thrombophlebitis migrans
      - Retroperitoneal fibrosis
      - Behçet's disease and pancreatitis.
    - Unknown:
      - Diabetes
      - Rheumatoid arthritis
      - Dermatomyositis
      - Pernicious anemia
      - Hypothyroidism.
- **Intrahepatic cause**
  - *Presinusoidal obstruction*
    - Schistosomiasis.
    - Congenital hepatic fibrosis
      - Myeloproliferative disorder
      - Systemic mastocytosis
      - Primary biliary cirrhosis
      - Sarcoidosis.
    - Toxic
      - Inorganic arsenic.
      - Copper.
      - Vinyl chloride vapor.
      - Vitamin-A intoxication.
      - Cytotoxic drugs—Methotrexate, 6-mercaptopurin and azathioprim.
  - *Sinusoidal obstruction*
    - Cirrhosis
    - Alcoholic hepatitis.
  - *Postsinusoidal obstruction*
    - Veno-occlusive disease affecting central hepatic venule.
- **Posthepatic causes**
  - Budd-Chiari syndrome.
  - IVC web.
  - CCF, constrictive pericarditis and restrictive cardiomyopathy.

CHARACTERISTIC FEATURES OF PORTAL HYPERTENSION

- Prominent abdominal vein and caput medusae.
- Venous hump and Cruveilhier-Baumgarten sign.
- Hemorrhoids and esophageal varices.
- Hematemesis and melena.
- Splenomegaly with features of hypersplenism in some patient.
- Stigma of liver cell failure—in case of cirrhosis.
- Fetor hepaticus—in case of cirrhosis.
- Hepatomegaly in case of postsinusoidal obstruction.
- Ascites.

INVESTIGATIONS

- **Barium swallow**—Feeling defect in lower 1/3 rd of esophagus, producing bag-of-worms appearance.

- **USG shows**—
  - Diameter of portal vein >12 mm.
  - Presence of thrombus—in portal, splenic, hepatic vein and inferior vena cava.
  - Increase size and echogenicity of liver.
  - Presence of portacaval shunt.
  - Presence ascites.
  - Hepatofugal flow in portal vein.
- Splenoportal venography—Obsolete nowadays.
- Upper GI endoscopy—It is the most reliable method for demonstration of varices and also grading of varices can be done.
  - Grades of varices
    - Grade I—Bluish discoloration of veins on inspiration.
    - Grade II—Bluish discoloration of veins during both phases of respiration.
    - Grade III—Bluish discoloration with elevation from surface of esophagus but endoscope can be smoothly introduced through it.
    - Grade IV—Grade III + occlusion of lumen.
- Proctoscopy.
- Liver function test.

COMPLICATIONS

- Variceal bleeding
- Hepatic encephalopathy
- Ascites
- Congestive gastropathy
- Hypersplenism.

MANAGEMENT

- Acute reduction of pressure can be done with—
  - Somatostatin.
  - Octerotide—50 μg IV bolus dose followed by 50 μg/hour for 2–5 days.
  - Vasopressin—0.4 mg/min until bleeding stops and them 0.2 mg/min for a further 24 hours (obsolate).
  - Terlipressin.
- **To stop variceal bleeding**
  - Balloon-tamponade (Sengstaken-Blakemore tube or Minnesota tube).
- **Chronic management**
  - Endoscopic variceal banding/ligation (EVL)—*Now method of choice*.
  - Sclerotherapy—To stop bleeding from esophageal varices.
  - Transjugular intrahepatic portosystemic stent shunt (TIPSS) when esophageal varices extend into proximal stomach.
  - Drugs—(a) β-blocker (propranolol—80–160 mg/day). (b) isosorbide mononitrate.
  - Portal venous thrombosis or Budd-Chiari syndrome can be managed with heparin (UFH/LMWH).
  - Shunt operation—(*not done nowadays*)
    - Nonselective—End to side anastomosis of portal vein with inferior vena cava.
    - Partial selective—Side to side anastomosis of portal vein with inferior vena cava.
    - Selective—Distal splenorenal anastomosis or shunt (Warren shunt).
- **Management of complications**.

ASCITES

It is defined as accumulation of excess free fluid within the peritoneal cavity.

ETIOLOGY OF ASCITES

- **Transudative ascites**
  - Cirrhosis with portal hypertension.
  - Congestive cardiac failure.
  - Constrictive pericarditis.
  - Inferior vena caval obstruction, Budd-Chiari syndrome.
  - Nephrotic syndrome.
  - Hypoproteinemia of any cause (malabsorption, malnutrition, protein-losing enteropathy).
- **Exudative ascites**
  - Tubercular peritonitis
  - Bacterial peritonitis
  - Malignant peritonitis
  - Pancreatic ascites
  - Chylous ascites.
- **Miscellaneous**
  - Meigs syndrome.

MECHANISM

- *Hypoproteinemia* (hypoalbuminemia) causing decreased osmotic pressure is a main factor in the production of ascites in case of nephrotic syndrome and hypoproteinemia (due to any cause).
- *Increased hydrostatic pressure* is the main factor in production of ascites in CCF, constrictive pericarditis, inferior vena caval obstruction, Budd-Chiari syndrome.
- In case of *exudative ascites inflammatory cytokine* causing increased vascular and peritoneal permeability plays the key role.
- Mechanism of production of ascites in cirrhosis is more complex. The abnormality associated with cirrhosis in the formation of ascites are:
  - Portal hypertension (increased hydrostatic pressure)
  - Hypoalbuminemia—Reduced osmotic pressure
  - Renal factors—Also plays important role.
    - Increased plasma renin
    - Secondary hyperaldosteronism
    - Renal vasoconstriction from increased prostaglandin and increased catecholamine level.

  - Insensitivity to atrial natriuretic peptide.
  - Endothelin.
- Increased hepatic lymph outflow from surface (hepatic sweating).

Accumulation of ascitic fluid represent excess total body Na^+ and water. But the event which initiates the imbalance is unclear. Three theories have been proposed:

- Underfilling theory
- Overflow theory
- Peripheral arterial vasodilatation hypothesis.

- In **underfilling theory**, primary event is inappropriate sequestration of fluid in splanchnic vascular bed and consequent decrease in effective circulatory volume which is sensed by baroreceptors of arch of aorta activating RAAS that stimulate kidney to retain salt and water.
- In **overflow theory**, primary event is inappropriate renal retension of salt and water in the absence of volume depletion in response to a hepatic signal in the form of:
  - Reduced synthesis of hepatic natriuretic agent.
  - Reduced hepatic clearance of Na-retaining hormones.
  - A hepatorenal reflex of unknown etiology.

  The combination of portal hypertension and circulatory hypervolemia leads to ascites.
- The third theory, the peripheral arteriolar vasodilatation hypothesis, is probably a recent modification of underfilling theory in which splanchnic vasodilatation in response to *'NO' and 'adrenomodulin'* which is secreted in response to portal hypertension probably from intestine, play the central key role.

  In response to the apparent circulatory hypovolemia baroreceptor-mediated stimulation of RAAS, increased sympathetic output and increased ADH release cause Na^+ and water retention, thus contributing to the formation of ascites.

DIAGNOSIS OF ASCITES

It is mainly clinical.

By demonstrating shifting dullness and fluid thrill.

Little ascites is diagnosed by ultrasound or CT scan. Hepatic hydrothorax is more common on the right side of chest.

Diagnostic paracentesis to be done to obtain a sample of fluid for *cell count, type, presence of RBC, protein, SAAG estimation, culture, ADA and PAP stain CA-125 and α-fetoprotein*.

PMN > 250/mL suggest infection. Usually ascitic protein is <1 g/dL in portal hypertension but now **serum ascites albumin gradiet (SAAG) is found superior and > 1.1 g/dL suggest portal hypertension**. Amylase in ascitic fluid is high in pancreatitis. When SAAG < 1.1 g/dL infection and malignant cause of ascites is suspected.

When ascitic fluid protein is very low there is increased chance of SBP.

A high level of RBC suggests traumatic tap, hepatocellular carcinoma or ruptured omental varix.

CA–125 suggests ovarian carcinoma, α-fetoprotein suggests hepatocellular carcinoma.

TREATMENT

- Dietary sodium restriction < 3 g/day.
- Diuretic—Spironolactone 100–200 mg/day, furosemide 40–80 mg. The dose may be increased in case of spironolactone to 400–600 mg/day and furosemide to 120–160 mg/day in case of huge ascites when diaphragmatic movement in compromised.
- *Refractory ascites are treated* with:
  - Large volume paracentesis
  - TIPS—mortality < 50% by 2 years
  - Liver transplant.

SPONTANEOUS BACTERIAL PERITONITIS (FLOWCHART 46.1)

Patient with ascites and cirrhosis may develop acute bacterial peritonitis without any primary source of infection. It is termed as **spontaneous or primary bacterial peritonitis**.

- Infection of ascitic fluid may be spontaneous or following paracentesis.
- Spontaneous type develops in 8% of cirrhotic patients particularly when it is severely and rapidly decompensated.
- The infection is 90% **monomicrobial**.
- Causative organisms are mostly gram-negative bacilli *Escherichia coli* and gram-postive cocci.
  Streptococcus viridans, *Staphylococcus aureus* and *Enterococcus* species can also be found.

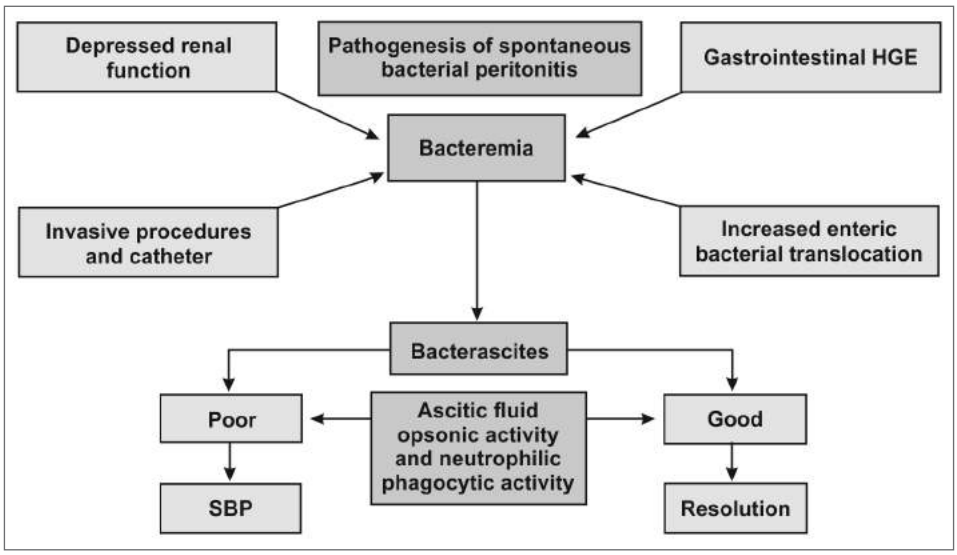
PATHOGENESIS

- There is increased rate of **translocation of bacteria across the intestinal wall to mesenteric lymph node**. Host defence is abnormal as RE function is impaired and neutrophil is abnormal in alcoholic with low opsonic activity of ascites fluid.
- Ascitic fluid favors bacterial growth as they are deficient in opsonins leads to defective coating of bacteria which are indigestible by the abnormal polymorphs.

CLINICAL FEATURES

- The most common manifestation *is fever* (present in 80% patients), *with altered mental status.*
- *Acute onset abdominal pain* or an peritoneal irritation sensation during physical examination is helpful for diagnosis. But absence of any of these findings does not exclude the diagnosis.

Flowchart 46.1: Pathogenesis of spontaneous bacterial peritonitis



- *PMN count > 250/μL of ascitic fluid is diagnostic of SBP.*
- Ascites is present virtually in all patient.
- Many patients may present without any clinical symptom.

DIAGNOSIS

- It is difficult to recover organism from peritoneal fluid as bacterial load is very low. Yield can be improved by culturing 10 mL of fluid in blood culture bottle.
- Blood culture should also be done simultaneously.
- Free gas under the diaphragm on abdominal X-ray suggests gut perforation.

TREATMENT

- Cefotaxime (2 g BD/TDS IV for 5 days) is the drug of choice.

Prophylaxis

As upper GI bleeding is a risk for SBP all patients of upper GI bleeding and those who have recovered from SBP should receive a weekly prophylactic antibiotic.

Prognosis

- Deterioration is shown by marked increase in serum bilirubin and creatinine with a very high WBC count in blood.
- Mortality is about 50%.
- In 70% patients it recurs within 1 year of which 50% will die.
- Outcome is poor if associated with:
  - GI bleeding
  - Renal impairment
  - Hepatic impairment
  - Severe infection
  - Presence of hepatocellular carcinoma.

HEPATORENAL SYNDROME

Hepatorenal syndrome (HRS) is a form of functional renal failure without renal pathology that occurs in about 10% patients of advanced cirrhosis or acute liver failure.

DEFINITION

It is a serious complication of cirrhosis with ascites characterized by *worsening azotemia, oliguria* and *avid Na retention in the absence of identifiable specific cause of renal dysfunction*. There is inappropriate renal vasoconstriction in response to splanchnic vasodilation accompanying cirrhosis. Kidney of hepatorenal syndrome patient can be successfully transplanted to other person even the same kidney function satisfactorily in the same person after liver transplantation.

TYPES

- **Type-I**—Patients have a rapidly progressive (< 2 weeks) reduction of renal function with doubling of initial serum creatinine (> 2.5 mg/dL) or a 50% reduction of initial 24 hours creatinine clearance (< 20 mL/min).
  - 80% mortality in 2 weeks
  - 10% survive >3 months.
- **Type-II**—Patient satisfy the criteria of renal failure but the renal failure does not progress rapidly. These

patients usually have residual hepatic function with refractory ascites.

CLINICAL FEATURES

Hepatorenal syndrome (HRS) is often seen with refractory ascites and requires exclusion of other cause of acute renal failure.

This syndrome is precipitated by:

- Severe GI hemorrhage.
- Sepsis.
- Vigorous attempt for diuresis.
- Vigorous attempt at paracentesis.
- The syndrome may develop without any known precipitating factor.
- Marked *decrease in urine volume/progressive oliguria, hypotension* are the two most important clinical findings.

DIAGNOSIS

- Major criteria and additional criteria (not necessary for diagnosis).

Major Criteria

- Low GFR—
  - Creatinine > 1.5 mg/dL
    - Urine volume < 500 mL/day.
  - Creatinine clearance—
    - Urine Na^+ < 10 mmol/day
      < 40 mL/min.
    - Urine osmolarity > plasma osmolarity.
    - Urine red cell < 50/HPF.
    - Absence of shock and sepsis.
    - Serum Na^+ <130 mmol/L in absences of fluid loss, nephrotoxic drug.

Additional Criteria

- No sustained improvement in renal function (serum creatinine <1.5 mg/dL, creatinine clearance >40 mL/min) after diuretic therapy stopped and expansion of plasma volume with 1.5 L of plasma expanders.
- Proteinuria, < 500 mg/day. No USG evidence of urinary tract obstruction or renal disease.

DIFFERENTIAL DIAGNOSIS

- Prerenal azotemia/acute tubular necrosis—Secondary to hypovolemia due to:
  - GI hemorrhage
  - Diuretic therapy.
- Increased N_2 load due to GI hemorrhage.
- Iatrogenic—Aminoglycoside, iodine contrast dye.

TREATMENT

- **IV fluid challenge** with 1.5 L of saline or colloid such as human albumin solution.
- **Nephrotoxic drug** to be stopped immediately.
- A search for sepsis should be done.
- **Broad spectrum antibiotic** started empirically.
- **Tense ascites may be drained** to improve renal hemodynamics by decreasing pressure over inferior venae cava and renal vein.
- Hemodialysis is not effective.
- **Liver transplantation** (treatment of choice) very much effective in type-I hepatorenal syndrome. New pharmacological approaches reversing/stabilizing renal dysfunction may allow elective transplantation.
- In type II hepatorenal syndrome liver transplantation results in return of renal function >90% of patients.
- **Pharmacological therapy (not satisfactory)**
  - Vasodilators (dopamine and prostaglandins) show no improvement in renal function (not used).
  - Combination therapy with long-term midodrine (α-adrenergic agonists) with octotides and IV albumin improves renal function with no side effects.

HEPATOPULMONARY SYNDROME

Hepatopulmonary syndrome is defined as a clinical disorder (associated with advanced liver disease) due to disturbed pulmonary gas exchange leading to hypoxemia and widespread intrapulmonary vasodilation and shunting of blood in the absence of detectable primary cardiopulmonary disease.

In chronic liver disease, pulmonary affection is common and may result in hypoxia and cyanosis. The pulmonary changes that may complicate chronic liver diseases are:

- Hypoxia.
- **Intrapulmonary shunting of blood** via microscopic AV fistula (from pulmonary arteriole to vein).
- Reduce transfer factor—due to deposition of collagen in the vessel wall causing thickening of vessel wall resulted in reduced gas exchange.
- Pleural effusion.
- Raised diaphragm.
- Basal atelectasis.
- Primary pulmonary hypertension.

The syndrome is characterized by:

- Platypnea (dyspnea in sitting posture).
- Orthodeoxia (reduced O_2 saturation in sitting and standing posture than supine posture).
- Cyanosis.
- Spider nevi and clubbing (inconstant finding).

The disease is mostly found with autoimmune hepatitis or long-standing cirrhosis.

PATHOLOGY/PATHOPHYSIOLOGY

The Aa-PaO_2 gradient exceeds 15 mm Hg.

The intrapulmonary shunting is via microscopic arteriovenous (AV) fistula.

The vasoactive substances that could involve in pulmonary vasodilatation are unknown probably NO, endothelin and other arachidonic acid metabolites are responsible for pulmonary vasodilation and shunting.

DIAGNOSIS

- **Increase Aa-Pa gradient O_2 > 15 mm Hg**.
- Transthoracic contrast enhanced echocardiography.
- **^{99mm}Tc macroaggregated albumin lung scan**.
- **Pulmonary angiography—***Spongy appearance of basal pulmonary vessels correspond to the infiltrate* in lung field.

MANAGEMENT

- No pharmacological treatment is effective.
- Hepatic transplantation is the best mode of therapy.
- Reversal is not always guaranteed where AV shunts are large. Then they require coil embolic therapy which should precede transplant.
- TIPS—It can be useful for palliation in a patient awaiting for hepatic transplantation.

EXERCISE

Write short notes on

1. Hepatopulmonary shunts and hepatorenal syndrome.
2. Predisposing factor for hepatic encephalopathy.
3. Spontaneous bacterial peritonitis.

Chapter 47

Approach to a Patient of Upper Gastrointestinal Bleeding

APPROACH

- First assess hemodynamic status of the patient quickly.
- Resuscitation
  - Make IV channel.
  - Draw blood for sampling and start intravenous infusion of crystalloid to restore blood pressure.
  - Plasma expanders like low molecular weight dextran may be infused to maintain blood volume till blood is not available.
  - Blood transfusion is required when the patient is in shock (pulse rate >SBP) or when Hb concentration is less than 100 g/L. [Normal saline should not be given in patients with liver disease because it can cause ascites].
  - Moist O_2 inhalation to all patients in shock by face-mask.
  - Central venous pressure (CVP) monitoring is required particularly in cardiac patient to assist in defining the volume of fluid replacement and identify rebleeding.
- When the patient becomes hemodynamically stable, a quick clinical survey is done by history and examination of the patient for the etiological diagnosis of upper GI hemorrhage.

HISTORY (TABLE 47.2)

- Whether history of peptic ulcer disease present.
- Any history of drug intake like aspirin, NSAID and steroid.
- Any history of alcoholism favor (cirrhosis and esophageal variceal bleeding).
- Any history of previous bleeding.
- History of severe anorexia, cachexia in recent past (gastric carcinoma).
- History of repeated forceful vomiting preceding the episode of bleeding (Mallory-Weiss tear).

EXAMINATION

- Patient may be cold, sweating and irritable.
- **General skin**—Pale.

Table 47.1: Causes of upper gastrointestinal bleeding

Common causes	Less common causes	Rare causes
• Gastric ulcer	• Gastric varices	• Gastric erosion
• Duodenal ulcer	• Portal hypertensive gastropathy	• Esophageal laceration
• Esophageal varices	• Vascular ectasia	• Gastroduodenitis
• Mallory-Weiss tear	• Gastric antral vascular ectasia (watermelon stomach)	• IBD
• Coagulation disorder	• Esophagitis	• Acute/chronic pancreatitis
	• Gastric carcinoma	• Idiopathic
	• Dieulafoy's lesion	

Table 47.2: First assess hemodynamic status of the patient quickly

Check pulse, BP and urine output		Blood loss
Tachycardia + Resting hypotension (pulse > SBP)	→ severe bleeding	→ > 20–25% of IV volume loss
Tachycardia + Orthostatic hypotension	→ moderate bleeding	→ 10–20% of IV volume loss
No clinical feature	→ mild bleeding	→ < 10% of IV volume loss

- In Peutz-Jeghers syndrome—Pigmentation in oral cavity may be present.
- **Acanthosis nigricans** seen in esophageal carcinoma.
- Purpuric spot seen in **HUS, PAN** and **bleeding diathesis**.
- In **chronic liver disease**—Spider nevi and palmar erythema may be present.
- **Pulse** shows tachycardia—If pulse rate > SBP suggests massive blood loss and an indication of blood transfusion.
- **Blood pressure**—In hypotension it's present suggest severe bleeding.
- **Jaundice**—Suggests cirrhosis.
- **Palpable lymph nodes**—If present, suggest malignancy (Virchow's gland present in—gastric carcinoma).
- **Palpate abdomen**—For the followings
  - Rigidity suggest associated perforation
  - Lump in abdomen suggest gastric carcinoma
  - Hepatosplenomegaly suggest portal hypertension
  - Ascites suggest portal cirrhosis.

Biochemical

- **Full blood count**—Hb concentration may remain normal after sudden major bleeding until hemodilution occurs (usually after 48 hours).
- **Serum urea, creatinine** if raised—Evidence of renal failure.
- Blood electrolytes. Na^+ K^+
- LFT [bilirubin, SGOT, SGPT, alkaline phosphatase. Total protein (Alb : Glob ratio)].
- **Prothrombin time**—Increased in liver disease.

Other Tests

- **Endoscopy**—As soon as the patient is resuscitated, an endoscopy is done to ascertain the cause of bleeding, site of bleeding and nature of bleeding, e.g. esophageal varices, bleeding peptic ulcer, bleeding gastric carcinoma, hemorrhagic vascular ectasia, gastric varices and portal hypertensive gastropathy.
- **Barium meal X-ray**—Obsolete now (Moth-eaten appearances in case of esophageal varices).
- When endoscopy is normal but the patient is actively bleeding.
  - Visceral angiography (although not usually performed).
  - Radionucleotide scan (with ^{99m}Tc may show bleeding from Meckel's diverticulum in young patients).

How would you diagnose at bedside that the patient is having active bleeding ?

- Tachycardia, pallor and hypotension. Pulse rate > SBP.
- Peristaltic sound—Hurried peristalsis due to irritation by fresh bleeding.
- Introduce Ryle's tube and 1/2 hourly suction is done—fresh/altered blood is gastric suction is a definite sign of continued bleeding.

MANAGEMENT

- Pharmacotherapy
- Endoscopic therapy
- Angiography
- Surgery.

MANAGEMENT OF PEPTIC ULCER BLEEDING

HISTORY AND EXAMINATION

- History of pain abdomen with hematemesis/melena.
- History of alcohol/NSAID intake.
- On examination tenderness is found to be present in epigastrium.
- Endoscopy found peptic ulcer.

TREATMENT

- **Proton pump inhibitor**—Omeprazole and pantoprazole or lansoprazole 80 mg/IV 8 hourly by continuous infusion.
- **Endoscopy**
  - If on endoscopy, it is found that patient is still suffering from active bleeding—then management is done in the form of endoscopic cryotherapy.
  - Ulcer with adherent clot (there is maximum chance of rebleeding)–watch the patient (do not dislodge the clot proceed for endoscopic cryotherapy).
  - Clean-cut ulceration with hemorrhagic spots (intermediate risk)—give the patient IV proton-pump inhibitors 80 mg/8 hourly by continuous IV infusion and watch for 3 days.
  - Clean-cut ulcer with no bleeding spot—(no risk of bleeding)—Give the patient proton-pump inhibitor. PPI (omeprazole/rabeprazole/pantoprazole) 80 mg IV 8 hourly by continuous IV infusion on first day followed by 20 mg/8 hourly.
- **Injection therapy** (via endoscope)—
  - With sclerotherapy agent like absolute alcohol, normal saline, etc.
  - With dilute adrenaline (vasoconstrictor).
- **Angiotherapy**—When endoscopic therapy is contraindicated, push dye into celiac artery—identify the bleeding site, then with the help of multipurpose catheter push adhesive (foam/artefact) into the branch of gastric artery.
- **Follow up**—Continue proton-pump inhibition for 6–8 weeks.

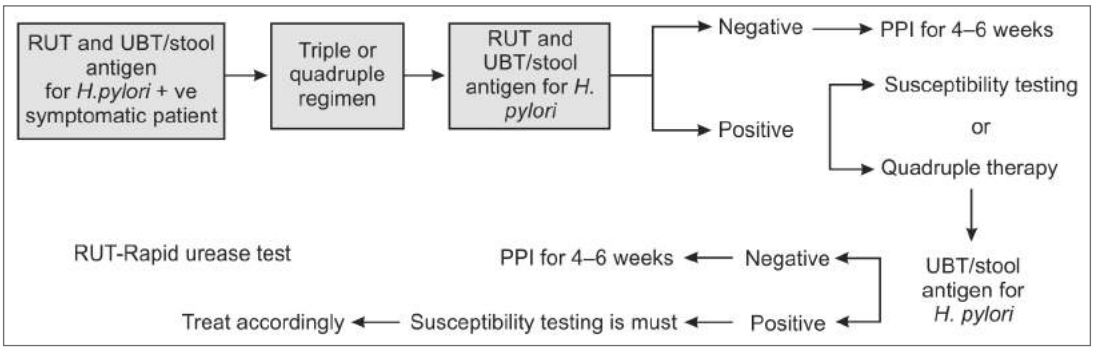
Treatment of *Helicobacter pylori* Infection

Helicobacter pylori is diagnosed by urea breath taste (UBT) or stool antigen for *H. pylori*.

Indication for *H. pylori* eradication

- *H. pylori* related gastric/duodenal ulceration.
- Low-grade gastric β-cell lymphoma.

Flowchart 47.1: Algorithm of *H. pylori* eradication



Whether *H. pylori* eradication reduces the chance of gastric carcinoma is still unclear except in some high-risk individual.

Cure rate with triple/quadruple therapy >75% in clinical practice (Flowchart 47.1)

- **1st line**:
  - Regimen 1—OCA for 14 days—**Omeprazole** (40 mg bid) + **clarithromycin** (500 mg bid) + **amoxicillin** (1 g bid).
  - Regimen 2—OCM for 14 days—**Omeprazole** (40 mg bid) + **clarithromycin** (500 mg bid) + **metronidazole** (500 mg bid).
- **2nd line**:
  - OBTM for 14 days—**Omeprazole** (40 mg bid) + **bismuth subcitrate** (2 tab qid) + **tetracycline** (500 qid) + **metronidazole** (500 mg tid).
  - Omeprazole can be replaced by any other PPI.
  - Metronidazole resistant strains of *H. pylori* are more common but still they respond to metronidazole containing regimen.

VARICEAL BLEEDING

Presence of spider nevi, jaundice, ascites, splenomegaly, caput medusae and other features of portal hypertension suggest variceal bleeding.

- Variceal bleeding occurs from esophageal varices within 3–5 cm of esophageal gastric junction or from gastric varices.
- Sources of bleeding should be always confirmed by endoscopy.

GRADES OF VARICES

- Grades I—Bluish discoloration of veins of esophagus on inspiration.
- Grade II—Bluish discoloration of veins of esophagus during both phases of respiration.
- Grade III—Bluish discoloration with elevation of vein of esophagus from mucosal surface.
- Grade IV—Grade-III + occlusion of lumen of esophagus.

PHARMACOTHERAPY FOR VARICEAL BLEEDING (TABLE 47.3)

- **Terlipressin**
  It is the drug of choice for treatment of esophageal varices. Vasopressin is slowly released from it over several hours in sufficient amounts and causes reduction of portal pressure without producing systemic side effects.
- **Octreotide**—
  Dose—Octreotide 50 μg IV bolus dose followed by 50 μg/hour for 2–5 days.
- **Somatostatin**—
  Dose—Somatostatin—250 μg IV bolus followed by 250 μg/ hour for 2–5 days.

BALLOON TEMPONADE (FOR ACUTE MANAGEMENT OF VARICEAL BLEEDING)

It is the best step to stop esophageal and gastric fundal variceal bleeding by pressure hemostasis.

- *Sengstaken-Blakemore tube*—With two balloons which exert pressure in the fundus of stomach and lower part of esophagus respectively and occlude the varices.

Table 47.3: Treatment of variceal bleeding

Acute therapy	Chronic therapy
1. **Pharmacotherapy**—Terlipressin and octerotide, Somatostatin	1. **Pharmacotherapy**—Propranolol, isosorbide mononitrate
2. **Balloon tamponade**	2. **Surgical therapy—Portacaval shunt esophageal transection (obsolete)**
3. **Sclerotherapy**	3. Transjugular intrahepatic portosystemic shunt (TIPSS) (rarely done)

- *Minnesota tube*—Incorporate sufficient lumen to allow pharyngeal secretions and saliva to be aspirated from esophagus above esophageal balloon. Gastric and esophageal balloon should be deflated for 10 minutes after every 3 hours to avoid esophageal mucosal ischemic damage.

ENDOSCOPIC THERAPY FOR VARICEAL BLEEDING

- Sclerotherapy
- Banding (for chronic management).
  - *Sclerotherapy (for chronic management):* Varices are injected with sclerosing agents. Injection is repeated every 1–2 weeks until varices are obliterated.
    Disadvantages:
    - Transient chest/abdominal pain
    - Transient dysphagia
    - Esophageal stricture.
  - *Banding (for chronic management):* Can be done for only grade II, III and IV varices. Varices are sucked into an (endoscopic accessory allowing them to be occluded with a tight rubber band.
    Disadvantage—Slipping of band)—The occluded varix subsequently sloughs with variceal obliteration.

TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC STENT SHUNT

A stent is placed between the portal vein and hepatic vein in the liver which provide a portosystemic shunt to reduce portal pressure.

Procedure—Under radiological guidance a catheter is introduce via right internal jugular vein → Superior vena cava → Right atrium → Inferior vena cava → Hepatic vein → Stent is placed in between hepatic vein and portal vein.

Disadvantage—Increase chance of hepatic encephalopathy.

SURGICAL THERAPY (FOR CHRONIC MANAGEMENT OF VARICEAL BLEEDING) (TABLE 47.4)

- Esophageal transection
- Portosystemic shunt surgery.
  - *Esophageal transection*—Transection of varices with a stappling gun. Disadvantages of the procedure is → Risk of subsequent esophageal stenosis and rupture.
  - *Nonselective*—End to side anastomosis of portal vein with inferior vena cava.
  - *Partial selective*—Side to side anastomosis between portal vein and IVC.
  - *Selective*—Distal splenorenal shunt (Warren shunt).

Table 47.4: Portosystemic shunt surgery (nowadays obsolete)

Nonselective	Selective
1. Direct majority of portal blood away from liver	1. Distal splenorenal Warren shunt
2. Chance of hepatic encephalopathy and postoperative liver failure	2. Decompress esophageal varices and preserves portal blood flow to liver with decrease chance of postoperative encephalopathy

MAINTENANCE THERAPY (FOR CHRONIC MANAGEMENT OF VARICEAL BLEEDING)

Pharmacotherapy

- **Propranolol**—80–160 mg/day reduces portal venous pressure in portal hypertension.
- **Isosorbide mononitrate**—60 mg/day who are intolerant to propranolol.

Management of Mallory-Weiss tear

It develops at gastroesophageal junction, following repeated vomiting/retching; more common in alcoholics; generally resolves spontaneously.

- **Treatment**—Observe—If bleeding continue endoscopic therapy.

Dieulafoy's lesion (In India Lafoy's lesion)

Arteriole present in submucosal layer in Dieulafoy's lesion (normally only capillary is present). It may occur in any part of GIT but more common in stomach. Hence, mucosal erosion leads to bleeding from arteriole.

- **Treatment**—Endoscopic cryotherapy.

EXERCISE

Write short notes on:

1. Causes of upper GI bleeding.
2. Management of peptic ulcer bleeding.

Chapter 48

Budd-Chiari Syndrome

INTRODUCTION

In Budd-Chiari syndrome there is obstruction to hepatic vein at any site from the efferent vein of the acinus in liver up to the entry of the inferior vena cava into the right atrium. A close differential diagnosis is either—

- Constrictive pericarditis
- Right heart failure.

Clinical feature of the syndrome comprises **hepatomegaly**. **Abdominal pain and ascites**. Hepatic histology shows zone 3 sinusoidal distension and pooling.

ETIOLOGY

- **Myeloproliferative disorder**—Polycythemia, rubra vera (60%).
- SLE with lupus anticoagulant and antiphospholipid antibody (APLA).
- Disseminated intravascular coagulation (DIC).
- Idiopathic granulomatous venulitis.
- Paroxysmal nocturnal hemoglobinuria (PNH)
- Deficiency of anticoagulant like protein C, protein S and antithrombin III.
- Behçet's disease complicated with extension of caval thrombosis to the ostium of hepatic vein.
- Oral contraceptive pill and pregnancy.
- Secondary to malignancy—Adrenal or renal carcinoma, hepatocellular carcinoma, or testicular carcinoma.
- Alcoholic and veno-occlusive disease.
- Following hepatic transplant associated with azathioprine.

CLINICAL FEATURES

Clinical features are of three types—(1) It may be asymptomatic (2) chronic form and (3) acute form.

- **Asymptomatic form**—No ascites, no hepatomegaly, no abdominal pain. It is diagnosed by imaging or liver biopsy (accidentally), CT or MRI.
- **Chronic form**—Patient presents with pain over an enlarged tender liver and ascites developing over 1–6 months.

  Jaundice is mild or absent unless zone-3 necrosis is marked.

  Negative hepatojugular reflux.

  Prominent vein over back (lumbar region) and abdomen—If inferior vena cava is blocked.

  Splenomegaly—It may be present when there is portal hypertension.

  Enlarged caudate lobe may be palpable in the epigastrium may simulate a tumor.
- **Acute form**—Usually present in patient suffering from some other disease like polycythemia, renal cell carcinoma or hepatocellular carcinoma and suddenly presents with:
  - Abdominal pain.
  - Vomiting.
  - Ascites.
  - Liver enlargement.
  - Mild icterus.
  - Prominent vein over abdomen and back.
  - Watery diarrhea following mesenteric venous obstruction is an inconstant feature.
  - Delirium, coma, death due to hepatocellular failure occur within few days.

If the inferior vena cava is blocked—edema of legs is gross and vein distended over abdomen flank and back.

DIAGNOSIS

- **Bilirubin** rarely exceeds 2 mg/dL.
- **Alkaline phosphatase**—Raised.
- **Albumin**—Reduced.
- **Transaminase**—Raised if very high suggest concomitant block of portal vein.
- **P-time**—Increased in acute type.
- **Needle biopsy of liver shows**—Congestion of zone 3 and pale portal areas.
- **Hepatic venography**—May or may not show occluded hepatic vein. Adjacent vein show a tortuous lace like spider web pattern representing venous collaterals.
- **Inferior vena cava venography**—Establishes patency of the inferior vena cava. Hepatic segment shows side-

to-side narrowing due to distortion from the enlarged caudate lobe.

- **Celiac arteriography**—Branches appear stretched and displaced producing the appearance of multiple space occupying lesion simulating metastasis.
- USG shows:
  - Hepatic vein abnormality
  - Caudate lobe hypertrophy
  - Compression of inferior vena cava.

  Liver is hypoechoic in the early stage.

  Liver is hyperechogenic due to fibrosis in late stage.
- **Doppler ultrasound**—Abnormal direction of flow in the hepatic vein, retrohepatic inferior vena cava. Blood flow in the inferior vena cava and hepatic vein may be absent, reversed and turbulent or continuous.
- **CT specially MRI**—This is helpful in early diagnosis. Absence of normal hepatic drainage into inferior vena cava. Caudate lobe can be seen deforming the inferior vena cava. Signal density alteration in hepatic parenchyma.

MANAGEMENT

- Anticoagulant—Helpful in anticoagulant deficiency state and APLA.
- Vene section—In myeloproliferative disorder.
- Cytotoxic drug in thrombocytosis and polycythemia.
- Ascites is treated with:
  - Low sodium diet
  - Diuretic
  - Paracentesis.
- Surgical:
  - Portacaval shunt.
  - TIPS.
  - Orthotropic liver transplant.
  - Percutaneous transluminal angioplasty for suprahepatic portion of inferior vena cava obstruction.

EXERCISE

Write short notes on

1. Etiology and clinical features of Budd-Chiari syndrome.
2. Treatment/management of Budd-Chiari syndrome.

Chapter 49

Acute Pancreatitis

INTRODUCTION

Acute pancreatitis is an acute inflammatory disease of the pancreas with variable involvement of surrounding tissue.

It occurs as a consequence of premature activation of zymogen granule releasing *trypsin, chymotrypsin, proelastase and phospholipase* A which digest the pancreas and surrounding tissue. The severity of the inflammation (pancreatitis) is dependent upon the balance between the activity of released proteolytic enzyme and antiproteolytic factor which are intracellular *trypsin inhibitor proteins, mesotrypsin, chymotrypsin and enzyme Y circulating* α_1 *globin and* α_2 *globulin*.

Pancreatic inflammatory disease may be classified according to the mode of onset into:

1. Acute pancreatitis
2. Chronic pancreatitis.

AUTOPROTECTION OF PANCREAS

Autodigestion of pancreas is prevented by:

- The packaging of pancreatic enzyme in precursor form.
- The synthesis of protease inhibitor, e.g. *pancreatic secretory trypsin inhibitor* (PSTI) which can inactivate 20% of trypsin activity.
- Apart from that, *mesotrypsin, chymotrypsin and enzyme 'y' can inactivate trypsin*. These protease inhibitors are found in acinar cell, pancreatic secretion and α_1 and α_2 globulin fraction of plasma.
- In addition to that *low calcium concentration* in the acinar cell causes destruction of spontaneously activated trypsin.

  Loss of any of these protective mechanism leads to zymogen activation, autodigestion of pancreas and acute pancreatitis.

CAUSES OF ACUTE PANCREATITIS

Common Causes

- Gallstone including microlithiasis (30–60%).
- Alcohol (15–30%).
- Hypertriglyceridemia (1.5–4%).
- After ERCP and manometry (5–20%).
- Blunt abdominal trauma.
- Postoperative (abdominal and nonabdominal operation).
- Drugs (azathioprine, 6-mercaptopurine, sulfonamide (2–5%) estrogen, tetracycline, valproic acid and anti-HIV medication).
- Sphincter of Oddi dysfunction.

Uncommon Causes

- Vascular cause and vasculitis (hypoperfusion)
- Connective tissue disorder and thrombotic thrombocytopenic purpura (TTP)
- Cancer of pancreas
- Hypercalcemia
- Cystic fibrosis
- Periampullary diverticulum.

Rare Causes

- Infections—Mumps, cytomegalovirus, coxsackievirus and echovirus.
- Autoimmune—Sjögren's syndrome.

CAUSES OF RECURRENT ACUTE PANCREATITIS

Approximately 25% patients who have had an attack of pancreatitis have a recurrence. The common cause of recurrent pancreatitis are

- Alcohol
- Cholelithiasis
- Microlithiasis
- Hypertriglyceridemia
- Drug
- Pancreatic cancer
- Sphincter of Oddi dysfunction
- Pancreas divisum
- Cystic fibrosis.

Bacterial exotoxin, **viral infection**, **ischemia**, **anoxia** and **direct trauma** are believed to activate these proenzyme.

Phases of acute pancreatitis

1. Initial phase—In this phase, xymogen activation appears to be mediated by **lysosomal hydrolase** such as cathepsin 'B' which is stored with digestive enzyme in the same intracellular organelles.
2. Second phase—In this phase, chemoattraction, sequestration and activation of neutrophil and macrophage in the pancreas. Which also activate trypsinogen to trypsin. So activation of trypsinogen to trypsin is done both by *cathepsin 'B'* and *neutrophil*.

   So intrapancreatic activation of trypsinogen has two steps—
   - Initial step—By hydrolase—(*Cathepsin B)*
   - Second step—By *activated neutrophil*.
3. Third phase: Activated trypsin not only digest pancreas but also activate **elastase** and **phospholipase**. This phase is due to effects of activated proteolytic enzyme and mediators released by the inflamed pancreas and distant organ.

   The active enzyme then digests cellular membrane and causes proteolysis, edema, interstitial hemorrhage, vascular damage, coagulation necrosis, fat necrosis, parenchymal cell necrosis and cell death. Death of cell results in the liberation of *bradykinin, peptides, vasoactive substance* and histaminase which produce increases vascular permeability and edema and profound effect on many other organs including lung producing (a) *Acute respiratory distress syndrome (ARDS)*, (b) *Systemic inflammatory response syndrome (SIRS)* and (c) *Multiorgan failure.*

Activated proenzyme specially trypsin not only digest pancreatic and peripancreatic tissues but also can activate other enzymes such as elastase and phospholipase.

CLINICAL FEATURES

Symptoms

- **Abdominal pain**—It is the major symptom of acute pancreatitis. Pain is steady and boaring in character located in the epigastrium and periumbilical region and often radiates to the back as well as to chest, flank and lower abdomen. Pain is frequently more intense when the patient is in supine posture and get some relief on sitting up with trunk flexed and knees drawn up.
- **Nausea, vomiting and abdominal distension**—It is due to gastric and intestinal hypomotility and chemical peritonitis.

Signs

- Patient is distressed and anxious
- **Low-grade fever**
- **Tachycardia**
- **Hypotension and shock is due to:**
  - Hypovolemia secondary to exudation of blood and plasma protein into retroperitoneal space (retroperitoneal burn).
  - Increase formation and release of kinin which causes vasodilation and increase in vascular permeability.
  - Systemic effect of proteolytic and lipolytic enzyme.
- **Jaundice** develops infrequently due to compression of the intrapancreatic portion of CBD by edematous pancreatic head or due to biliary stone and sludge.
- **Erythematous skin nodules** due to subcutaneous fat necrosis.
- **Cullen sign**—Faint blue discoloration around umbilicus as a result of hemoperitoneum.
- **Grey Turner's sign**—Red-blue-purple or greenish-brown discoloration of the flank reflect tissue catabolism of hemoglobin.

  The later two findings are uncommon and indicate severe necrotizing pancreatitis and difficult to detect is black.
- **Abdominal tenderness** and muscle rigidity is less impressive compared to pains.
- **Pancreatic ascites**.
- **Pancreatic pseudocyst** may be palpable in the upper abdomen (4–6 weeks later).
- **Bowel sound**—Sluggish or absent
- **Pulmonary findings**—Present in 10–20% patient and consist of:
  - Basilar rales
  - Atelectasis
  - Pleural effusion (usually left-sided).

LABORATORY INVESTIGATIONS

- **Serum amylase** > 3 times of the upper limit of normal is diagnostic of pancreatitis provided salivary gland disease, gut infection, perforation and ischemia are excluded (elevated within 24 hours).

Falacy

a. In chronic pancreatitis, amylase may be low
b. Amylase level comes down to normal after 3–7 days even with continuing evidence of pancreatitis
c. However, pancreatic isoamylase and lipase remain elevated for 7–14 days
d. In acidemia pH <7.3 (diabetic ketoacidosis) patient may have elevation of serum amylase, which is predominantly salivary type isoamylase
e. Hypertriglyceridemia cause spurious low level of amylase in pancreatitis

- **Serum lipase** activity increase >3 times (more specific than amylase) is parallel with amylase activity and measurement of both these enzyme increases the diagnostic yield.
- **Leukocytosis**—15000–20000/mL
- **Hematocrit** >44% due to hemoconcentration as a result of loss of plasma into retroperitoneal space.

- **Hyperglycemia** is due to:
  - Decreased insulin release
  - Increased glucagon release
  - Increased glucocorticoid and catecholamine output.
- **Hypocalcemia**—Present in 25% patients due to intraperitoneal saponification of calcium by fatty acid in areas of fat necrosis and dissolved or suspended in ascitic fluid.
- **Hyperbilirubinemia**—>4 mg/dL occurs in 10% patient transiently and return to normal within 4–7 days.
- **Alkaline phosphatase and SGPT**—Also transiently elevated is due to gallbladder pathology or edema of pancreatic head.
- **Marked elevation of LDH**— > 500 U/dL suggests poor prognosis.
- **Hypertriglyceridemia** found in 5–10% patient. In these patients serum amylase is spuriously normal.
- **PO_2** ≤60 mm Hg which herald onset of ARDS.
- **Blood urea nitrogen (BUN)** >22 mg% and a risk factor for mortality.

X-ray

X-ray is important in exclusion of other diagnosis specially peptic perforation.

USG and CT: Confirm the Clinical Diagnosis

Provide information about edema, inflammation, calcification, pseudocyst, mass lesion of pancreas and simultaneous scanning about gallbladder, liver and bile duct, for information about gallstone and microlithiasis.

DIAGNOSIS OF PANCREATITIS

Require any two of the followings
- Typical abdominal pain
- > 3 fold rise of lipase and/or amylase
- Confirmatory finding in CT/USG (most diagnostic).

DIFFERENTIAL DIAGNOSIS OF PANCREATITIS

- Peptic perforation (X-ray shows free gas under diaphragm).
- Acute cholecystitis (pain never radiate to LUQ and Ileus usually does not occur).
- Biliary colic (by USG).
- Acute intestinal obstruction (by X-ray).
- Mesenteric vascular occlusion (causes bloody diarrhea).
- Acute myocardial infarction (AMI) by ECG.
- Diabetic ketoacidosis (serum lipase not elevated and ketone body present).
- Pneumonia (by CXR).
- Vasculitis with connective tissue disorder.
- Renal colic (by USG).

RISK FACTOR THAT ADVERSELY AFFECT SURVIVAL IN ACUTE PANCREATITIS

Risk Factor for Severity

- Age >60
- Body mass index (BMI) >30
- Comorbid illness (Charlson comorbidity index).

Marker of Severity on 1st Day of Illness

- Systemic inflammatory response syndrome (SIRS)
  - 36°C > core temperature >38°C
  - Pulse > 90/min
  - Tachypnea >24/min PCO_2 <32 mm Hg
  - 4,000/ mL > WBC count > 12,000/mL or 10% band cell
  - Hematocrit > 44%
  - APACHE stage II
  - BUN >22 mg/dL.

  SIRS is considered positive by the presence of two or more criteria out of these seven criteria.
- **BISAP**:
  B—Blood urea nitrogen > 25 mg/dL
  I—Impaired mental status
  S—SIRS positive 2 out of 7 criteria
  A—Age >60 years
  P—Pleural effusion on CXR.
  Presence of 3 out of 5 criteria is associated with increased mortality.
- **Signs of organ failure**:
  - Cardiovascular system (CVS)—SBP < 90 mm Hg, Pulse >130/min
  - Lungs—PaO_2 < 60 mm Hg
  - Kidney—Creatinine > 2.0 mg%.

Severity of Acute Pancreatitis is Graded into Mild, Moderate and Severe

- **Mild acute pancreatitis**: There is no local complication or organ failure. Most patient have interstitial acute pancreatitis. The disease is self-limited, subside spontaneously within 3–7 days oral feeding can be started with clear liquid diet in a patient who is hungry and has normal bowel function.
- **Moderately severe acute pancreatitis**: It is characterized by transient organ failure that subside within 48 hour or have local or systemic complication is absence persistent organ failure. These patient may or may not have tissue necrosis but develop local complication, i.e. fluid collection and required hospitalization > 7 days.
- **Severe acute pancreatitis**: It is characterized by persistent organ failure (may be single or multiple). A CT scan or MRI to be done to assess tissue necrosis and complication. If a local complication is seen it in managed symptomatically and conservatively.

COMPLICATIONS OF PANCREATITIS

Local Complications

- Pancreatic necrosis.
- Pancreatic abscess.
- Pancreatic pseudocyst.
- Pancreatic ascites.
- Massive intraperitoneal hemorrhage.
- Thrombosis of blood vessels (splenic vein and portal vein).
- Obstructive jaundice.
- Gut infarction.

Pulmonary Complications

- Left-sided pleural effusion
- Atelectasis
- Acute respiratory distress syndrome (ARDS)
- Pneumonia.

Hematologic Complications

- Disseminated intravascular coagulation (DIC).

Gastrointestinal Complications

- GI hemorrhage
- Peptic ulcer disease
- Erosive gastritis
- Portal vein thrombosis.

Metabolic Complications

- Hyperglycemia
- Hypertriglyceridemia
- Hypocalcemia.

Cardiovascular Complications

- Hypotension
- Nonspecific ST-T changes
- Pericardial effusion.

Renal Complications

- Acute renal failure
- Renal artery/vein thrombosis
- Oliguria
- Azotemia.
  - CNS complication
  - Fat embolism.

MANAGEMENT

- Establishing the diagnosis and stratifying disease severity.
- Early treatment according to the severity.
- Diagnosis and treatment of complication.
- Treatment of underlying cause.

It is important to note that 85–90% cases are self-limited and subside spontaneously within 3–7 days of initiation of treatment and do not have organ failure.

Initial Management

- **Stop-oral feeding** for 2–4 days.
- **Analgesic**—Using pethidine and tramadol
- **A central venous line** to monitor and manage shock.
- **Correction of hypovolemia** with infusion of normal saline/or lactated Ringer 15–20 mL/kg/hour followed by 200–250 mL/hour to maintain urine output >0.5 mL/kg/hour. A fall in hematocrit and BUN is a strong evidence that sufficient fluid is administered. On the contrary a rising hematocrit and BUN suggest a repeat volume challenge with 2L lactated Ringer followed by 1.5 mL/kg/hour.
- **Hypoxic** patient need O_2 (2L/min) via nasal catheter.
- **ARDS** patients require ventilatory support.
- **Hyperglycemia** is corrected by using insulin.
- **Hypocalcemia**—Requires IV calcium if tetany is present.
- **Nasogastric suction** for 2–4 days if paralytic ileus develops.
- Several drugs have been evaluated in the management of acute pancreatitis of which two drugs are important:
  - **Octreotid**—Reduces mortality but no change in complication rate.
  - **Gabexate (antiprotease)**—Reduces complication but no effect on mortality.
- **Diet**—A clear liquid diet is given on the 3rd–6th day and regular (with low fat) diet on 5th–7th day. The decision to reintroduce oral intake is based on:
  - Decrease or resolution of abdominal pain.
  - Patient is hungry.
  - Organ dysfunction has improved (bowel function resumed).

  When oral feeding restarted consider addition of pancreatic enzyme supplementation and proton pump inhibitors to assist fat digestion and reduce gastric acid.
- Prophylaxis of thromboembolism with low molecular weight heparin (LMWH).
- No role of prophylactic broad spectrum antibiotic like piperacillin + tazobactam or imipenem + cilastatin. *Broad spectrum antibiotics only to be started with appearance of sepsis.*
- **Emergency ERCP** with biliary sphincterotomy and stone extraction where a stone is identified in the CBD or stenting of pancreatic duct where it is disrupted improves outcome in severe acute pancreatitis. Greatest benefit occurs in those patients who have ascending cholangitis.

MANAGEMENT OF COMPLICATION

- Necrotizing pancreatitis or pancreatic abscess require urgent surgical debridement and drainage of pancreatic abscess.
- Pancreatic pseudocyst is treated by drainage into stomach or duodenum. Which is done after at least 6 weeks when a pseudocapsule has matured either by open surgery or endoscopic method.

Prognosis

Despite recent advancement in management overall mortality is 3%. In severe cases mortality is 20% of all acute pancreatitis. 98% of death occurs in severe cases.

Death occurs in 1st week due to multiorgan failure. Late mortality is from sepsis.

Long-term Management of Hypertriglyceridemia Associated with Pancreatitis

- Weight reduction
- Fat restricted diet
- Exercise
- Control of diabetes
- Avoid alcohol
- Stop drugs like estrogen, vitamin A, thiazide and propranolol.

EXERCISE

Write short notes on

1. Etiology of pancreatitis.
2. Management of acute pancreatitis.
3. Clinical features of acute pancreatitis.

Chapter 50

Approach to a Patient with Malabsorption

INTRODUCTION

Malabsorption syndrome results from suboptimal absorption of essential nutrients from gut, (carbohydrate, protein, fat, vitamins, minerals) which is not compensated by adequate intake resulting in deficiency symptoms and signs.

Basic pathophysiology behind malabsorption are:

- Defective intraluminal digestion
- Defective absorption
- Defective transepithelial transport
- Endocrine disorder.

ETIOLOGY OF MALABSORPTION

Defective Digestion

- Postgastrectomy.
- (Z-E syndrome) Zollinger-Ellison syndrome/gastrinoma.
- Pancreatic insufficiency.
- Impaired micelle formation due to reduced bile acid
  - Liver disease.
  - Bacterial overgrowth due to anatomic stasis (gastrojejunostomy) and functional stasis (PSS).
  - Interrupted enterohepatic circulation—Ileal resection and Crohn's disease.
  - Drugs—Cholestyramine and neomycin.
- Disaccharidase deficiency.
- Drug—Orlistat.

Defective Absorption

- Crohn's disease
- Whipple's disease
- Celiac disease
- Tropical sprue
- Dermatitis herpetiformis
- Protein-losing enteropathy
- Amyloidosis
- Intestinal resection or bypass
- Folate and B_{12} deficiency
- Infection
- Scleroderma
- Eosinophilic enteritis.

Postabsorptive Transport Defect due to Lymphatic and Venous Obstructions

- Lymphoma
- Tuberculosis of intestine
- A-β lipoproteinemia
- Intestinal lymphangiectasia
- CCF/constrictive pericarditis.

Endocrine disorder associated with malabsorption

- Diabetes
- Hyperthyroid
- Carcinoid
- Adrenal insufficiency
- Hypoparathyroid.

HISTORY

- **Age**
  - Younger age group support diagnosis of:
    - Cystic fibrosis
    - Intestinal lymphangiectasia
    - Celiac diseases
    - A-β-lipoproteinemia
    - Milroy's disease (congenital lymphedema).
  - Elderly age group favors diagnosis of:
    - Blind loop syndrome
    - Amyloidosis
    - Lymphoma
    - Mesenteric artery atherosclerosis.
- **Sex**
  - Male predominance support diagnosis of:
    - Celiac disease
    - Whipple's disease
    - Systemic mastocytosis.
  - Female predominance common in progressive systemic sclerosis (PSS).
- **Race**
  - Caucasian may have Whipple's diseases.
- **Residence**
  - Celiac disease—More common in North Europe.
  - Tropical sprue—More common in South India, Philippines and West Indies.
  - Lactase insufficiency—More common in Asia.

- **Diet**
  - Gluten (gliadin): Present in flower causes celiac disease.
  - Lactose (milk): Intolerance in lactase deficiency.
- **Past history of**
  - Radiation—Causes radiation enteritis and proctocolitis.
  - Small bowel resection—Causes short bowel syndrome.
  - Chronic celiac sprue, become refractory—in intestinal T-cell lymphoma.
  - Gastrojejunal bypass for acid peptic disorder can cause malabsorption.
  - Dermatitis herpetiformis is associated with chronic celiac sprue.
- **Drug history**
  Chronic use of sorbitol, neomycin, lactulose and laxative may cause malabsorption.
- **Family history**
  - Positive in celiac disease.

CLINICAL FEATURES

Symptoms

- Weakness if present is due to
  - Anemia.
  - Electrolyte depletion.
- **Weight loss** is due to malabsorption and associated anorexia.
- **Diarrhea** is the most common feature of malabsorption syndrome. It may be of three types
  - **Osmotic diarrhea** as a results of increased osmotic pressure in the lumen is due to malabsorption of dietary nutrients and drugs (sorbitol and lactulose).
  - **Secretory diarrhea** is due to enterotoxin from bacteria.
  - **Fatty diarrhea**—May be due to:
    - Defective digestion of fat causes fatty diarrhea, e.g.
      - » Fibrocalcific pancreatic disease (FCPD).
      - » Zollinger-Ellison syndrome.
    - May be due to decrease absorption of fat causing fatty diarrhea in blind loop syndrome (due to decrease michele formation).
    - May be due to decrease transport of fat causing fatty diarrhea in
      - » A-β lipoproteinemia.
      - » Intestinal lymphangiectasia.
      - » Tuberculosis of intestine.
      - » Lymphoma of mesenteric lymph node.
- **Abdominal pain may be present in**
  - Inflammatory bowel disease—Ulcerative colitis and Crohn's disase.
  - Chronic pancreatitis.
- **Flatus**—Increase flatus is due to bacterial fermentation of carbohydrate in disaccharidase deficiency.
- **Bone pain** present in calcium and vitamin D deficiency.
- **Night blindness** present in vitamin A deficiency.
- **Bleeding** present in vitamin C and K deficiency.
- **Muscle cramp** present in Ca and vitamin E deficiency.

Signs

- **Growth retardation**—Seen in protein-losing enteropathy.
- **Nutrition**—Poor nutrition is due to severe malabsorption syndrome from any cause.
- **Pallor** is due to in Fe, vitamin B_{12} and folate deficiency.
- **Edema** is associated with hypoproteinemia.
- **Clubbing (mild degree)** seen in celiac disease and Whipple's disease.
- **Neck gland** may be enlarged in lymphoma and tuberculosis of intestine.
- **Neck vein**—Prominent in CCF (extreme late case of hypoproteinemia).
- **Hypotension** is due to fluid and electrolyte deficiency seen in severe malnutrition.
- **Temperature raised**—In lymphoma, tuberculosis of intestine.
- **Skin changes**—Petechiae may be present in vitamin K deficiency.
- **Deficiency features**
  - *Xerophthalmia*, *toad skin*, *increased incidence of URTI* and increased incidence of *renal stone* seen in vitamin A deficiency.
  - *Ricket, osteomalacia, tetany, bone pain, paresthesia* seen in vitamin D and calcium deficiency.
  - *Infertility* associated with vitamin E deficiency.
  - *Bleeding* associated with vitamin C and K deficiency.
  - *Angular stomatitis, cheliosis* and *glossitis* is associated with vitamin B complex deficiency.
  - Polyneuropathy, subacute combined degeneration of spinal cord seen in vitamin B complex and vitamin B_{12} deficiency.
- *Dementia* is associated with Whipple's disease.
- *Neuropsychiatric symptoms* seen in systemic mastocytosis and Hartnup syndrome.
- *Ataxia* and *arrhythmia* present in A-β lipoproteinemia.
- Features of *diabetes mellitus*, *hyperthyroid* and *Addison's* may be associated with:
  - Celiac disease
  - PGA-II
  - Fibrocalcific pancreatic diseases (FCPD).

INVESTIGATION

- **Blood**
  - Hemoglobin—reduced in Fe deficiency.
  - Mean corpuscular volume (MCV)
    - Reduced in Fe deficiency.
    - Increased in B_{12} and folate deficiency.
  - *Lymphocytopenia* seen in eosinophilic enteritis. *Abnormal cell* found in lymphoma.

- **LFT**—abnormal in:
  - Chronic liver disease.
  - Protein-losing enteropathy.
  - Increase P-time seen in vitamin K deficiency and chronic liver disease.
- **Abnormal lipid profile**—Present in Abetalipoproteinemia.
- **Autoantibody**—
  - **Antiendomysial antibody** is associated with celiac disease.
  - **Antisaccharomyces cerevisiae antibody** seen in Crohn's disease.
  - **Antitropoisomerase 1 antibody** seen in scleroderma.
- **Serum B_{12} and folate level estimation**—Deficiency seen in bacterial overgrowth syndrome and pernicious anemia which can be determined by **Schilling test** for B_{12} deficiency and for folic acid **stool formiminoglutamic acid (FIGLU) estimation**.
- Serum iron study (serum iron, ferritin and transferin saturation) abnormal in iron deficiency.

- **Stool examination**—Routine examination and microscopical examination for *ova protozoa* and *cyst*. *Stool fat* estimation in case of suspected fatty diarrhea.
- **Pancreatic exocrine function study**—HCO_3 and enzyme level assay.

  Test for pancreatic exocrine function
  - *Direct stimulation of pancreas by secretin*—(0.2 μg/kg IV bolus) Volume output > 2 mL/kg/hour. Concentration of bicarbonate > 80 mmol/L or >10 mmol/hour.
  - Test of intraluminal digestion—Undigested meat fiber, stool fat, fecal nitrogen estimation.
  - Measurement of fecal pancreatic enzyme, e.g. elastase.
- **Serum tryptase level**—Increase in systemic mastocytosis.
- **Special test**
  - *Urinary D-xylose test*—To assess proximal small intestinal mucosal function.
  - *C_{14} tagged glycolic acid and hydrogen breath test*—For intestinal bacterial overgrowth syndrome.
- **Radiology**
  - Straight X-ray abdomen—Calcification seen in fibrocalculous pancreatic diabetes (FCPD).
  - Barium-meal follow through
    - Stricture and fistula seen in Crohn's disease and TB of intestine.
    - Fistula seen in Crohn's disease.
    - Feeling defect seen in lymphoma.
    - Enteroclysis for small bowel mucosal detail.
    - ERCP, MRCP for hepatopancreatic disorder.
- **Endoscopy and colonoscopy** and **capsule enteroscopy**
  - **Small white spot**—Intestinal lymphangiectasia.
  - **Smooth mucosa, reduced fold** and **scalloped valvulae conniventes**—Villous atrophy (Celiac disease/Tropical sprue/Whipple's disease).
  - **Ulceration in terminal ilium**—Celiac disease, tuberculosis of intestine and Crohn's disease.
- **Small intestine biopsy:**
  - *Diffuse specific lesion*—Whipple's, Abetalipoproteinemia and agammaglobulinemia.
  - *Patchy specific lesion*—Lymphoma, lymphangiectasia, eosinophilic enteritis, mastocytosis, Crohn's disease and amyloidosis.
  - *Diffuse nonspecific lesion*—Celiac disease, tropical sprue, bacterial overgrowth and B_{12} deficiency. Radiation enteritis, Z-E syndrome, PCM and drug-induced enteritis.

HISTOPATHOLOGICAL DESCRIPTION OF SMALL INTESTINAL MUCOSAL LESION

- **Diffuse specific lesion:**
  - Whipple's disease—Presence of PAS positive macrophage in lamina propria detected by electron microscope.
  - Abetalipoproteinemia—Normal mucosa with lipid containing cell postprandially—disappear during fasting.
  - Immunoglobulin deficiency—Absent or reduced number of plasma cell in lamina propria with villous atrophy.
- **Patchy specific lesion:**
  - *Lymphoma*—Identification of malignant lymphocyte in lamina propria.
  - *Lymphangiectasia*—Dilated lymphatics in lamina propria and submucosa.
  - *Eosinophilic gastroenteritis*—Eosinophilic infiltrate of lamina propria of mucosa and submucosa with or without peripheral eosinophilia.
  - *Amyloid deposition*—Identified by Congo-red stain in amyloidosis.
  - *Crohn's disease*—Specific histology.
- **Diffuse nonspecific lesion:**
  - *Celiac disease and tropical sprue*—These are associated with characteristic mucosal lesion in duodenal and jejunal mucosa but are not diagnostic. *Celiac disease* is diagnosed by clinical, histologic and immunologic response to gluten-free diet.

    Tropical sprue—Histological appearance is similar to celiac disease but improvement occurs with antibiotics and folate.
- Several microorganisms responsible for malabsorption can be identified in small intestinal biopsy—Whipple's disease, giardia, cryptosporidium, isospora belli, microsporidia, cyclospora, cytomegalovirus, adenovirus and monkey-adapting component (MAC). In immune compromised host—candida, aspergillus, *Cryptococcus* or histoplasma can also be identified.

EXERCISE

Write short note on

1. Approach to a patient of malabsorption syndrome.

Chapter 51

Inflammatory Bowel Diseases

INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease (CD) are two inflammatory disease of gut with a relapsing and remitting course extending over years. Comparison of macroscopic and microscopic features of CD and UC is classified in Table 51.1.

Both disease have bimodal peak incidence, first one is between 2nd–3rd decade and the second one in the 7th decade.

Table 51. 1: Comparison of macroscopic and microscopic features of Crohn's disease and ulceratic colitis

Feature	Crohn's disease	Ulcerative colitis
Macroscopic features:		
• Distribution of lesion	• Segmental with skip areas	• Continuous without skip areas
• Location of lesion	• Commonly terminal ileum and/or ascending colon	• Commonly rectum, sigmoid colon and extending upwards
• Extent of involvement	• Usually involves the entire thickness of the affected segment of bowel wall	• Usually superficial, confined to mucosal layers
• Description of ulcers	• Serpiginous ulcers may develop fissures	• Superficial mucosal ulcers without fissures
• Pseudopolyps formation	• Rarely seen	• Commonly present
• Fibrosis	• Common	• Rare
• Shortening of bowel	• Due to fibrosis	• Due to contraction of muscularis
Microscopic features:		
• Depth of inflammation	• Typically transmural	• Mucosal and submucosal
• Type of inflammation	• Noncaseating granulomas and infiltration of mononuclear cells (lymphocytes plasma cells and macrophages)	• Crypt abscess and nonspecific acute and chronic inflammatory cells (lymphocytes, plasma cells, neutrophils, eosinophils, mast cells)
• Involvement of mucosa	• Patchy ulceration	• Hemorrhagic mucosa with ulceration.
• Involvement of submucosa	• Widened due to edema and lymphoid aggregates	• Normal or reduced in width
• Involvement of muscularis	• Infiltrated by inflammatory cells	• Usually spared except in cases of toxic megacolon
• Fibrosis of intestinal wall	• Presents	• Usually absent
Complications:		
• Fistula formation	• Internal and external fistulae in 10% cases	• Extremely rare
• Malignant changes	• Rare	• May occur in disease of more than 10 years duration
• Fibrous strictures	• Common	• Never

Table 51.2: Epidemiology of Inflammatory bowel disease (IBD)

	Ulcerative colitis	Crohn's disease
1. Age of onset	15–30 and 60–80	15–30 and 60–80
2. Male : Female	1 : 1	1.5 : 1
3. Smoking	Protective	Aggrevate
4. Oral contraceptive	No increase risk	Increased risk
5. Appendectomy	Protective	Nonprotective

CLINICAL FEATURES

Predisposing Factor

- Emotional stress.
- Intercurrent infection with *Salmonella, Shigella, Campylobacter, Clostridium, Escherichia, Bacteroides* and gastroenteritis.
- Antibiotic and NSAID.

Mode of Onset

Three types of clinical pattern noticed:
- Acute onset type
- Relapse and remission pattern
- Chronic unremitting form.

CLINICAL FEATURES OF ULCERATIVE COLITIS

Clinical features of ulcerative colitis depends on the parts of the gut involved (Figs 51.51A to C)

General Symptom

- Anorexia, nausea, vomiting, fever and weight loss.

Intestinal features

Symptoms

- Diarrhea (may be nocturnal or postprandial)
- Rectal bleeding
- Tenesmus, urgency, sense of incomplete evacuation
- Passage of mucus
- Crampy abdominal pain.

When disease extend beyond rectum—gross bloody diarrhea usually noted.

Rarely, patients with proctitis and proctosigmoiditis have slow proximal transit which accounts for constipation.

Intestinal physical sign

- Tender anal canal.
- Blood on rectal examination.
- Tenderness of colon on abdominal palpation.
- Patients with toxic colitis have severe pain, bleeding and signs of peritonitis if perforation occur.
- Toxic megacolon have tympanic note over liver.

CLINICAL FEATURES OF CROHN'S DISEASE

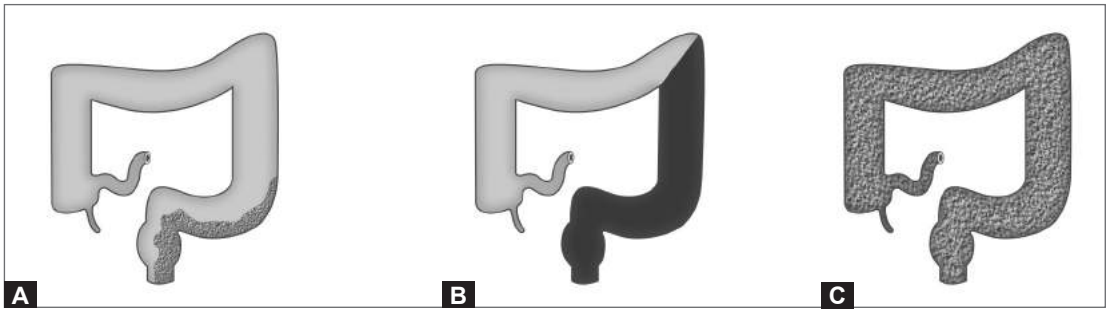
Clinical features of Crohn's disease depends on the part of the gut involved (Figs 51.2A to D).

- **Iliocolitis**—It is the most common type and present with *pain* and *palpable mass* in the right lower quadrant (RLQ) of abdomen with the *fever, anorexia, diarrhea, weightloss (10–20%), dysuria* and *leukocytosis mimicking acute appendicitis.*

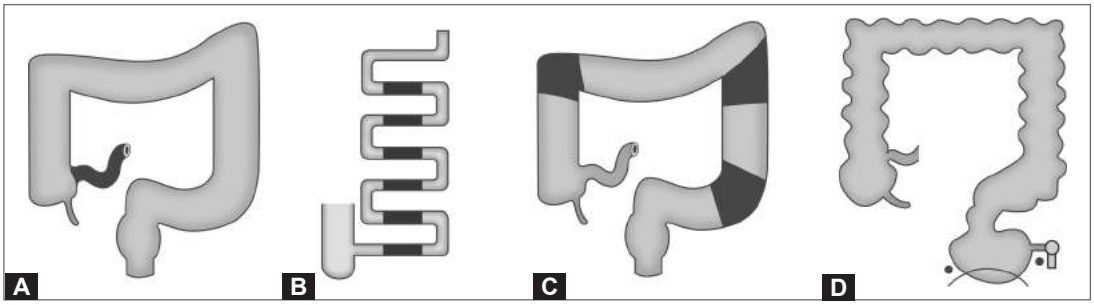
  Two common patterns are seen:
  - *Fibrostenotic obstruction*—In the early stage, the obstruction is due to bowel wall edema and spasm produce intermittent intestinal obstruction, but after several years of persistent inflammation fibrostenotic narrowing and stricture appear.
  - *Penetrating fistula* occur due to:
    - Microperforation of intestine and fistula formation with:
      - » Bladder leads to pneumaturia and fecaluria.
      - » With vagina leads to foul smelling vaginal discharge.
      - » With skin leads to discharging sinus.

    High fever suggest intra-abdominal abscess.
- **Crohn's colitis and perianal disease—**
  - *Crohn's colitis*: Presents with low-grade fever, malaise, diarrhea, crampy abdominal pain. Sometime hematochezia. Massive bleeding is rare.
    - Toxic mega colon like ulcerative colitis is also rare.
    - Stricture can occur in colon is about 10% patient.
    - Gastrocolic or duodenocolic fistula can cause feculent vomiting.
    - Small gut colonic fistula can cause malabsorption. 10% of women with Crohn's colitis develop rectovaginal fistula.
  - *Crohn's perianal disease*: Occur in one-third of Crohn's colitis and present with fecal incontinence, *large hemorrhoidal tags, anal stricture, anorectal fistulae* and *perirectal abscesses*.
- **Jejunoileitis** manifest as *steatorrhea* and *malabsorption which leads to anemia, hypoalbuminemia, hypocalcemia, coagulopathy, hyperoxaluria* and *nephrolithiasis*.

  Low levels of vitamin A, D, E, K, niacin copper, zinc, selenium and magnesium are noted during investigations in Crohn's jejunoileitis.



Figs 51.1A to C: Regions of gut involved in ulcerative colitis: (A) Proctitis or proctosigonoiditis (40–50%); (B) Left-sided extensive colitis (40–50%); (C) Pancolitis (20%)



Figs 51.2A to D: Regions of gut involved in Crohn's disease: (A) Ileal or ileocolonic disease (40%); (B) small intestinal disease (30–40%); (C) Crohn's colitis (20%); (D) Crohn's anorectal disease

- *Gastroduodenal disease* presents with *nausea, vomiting and epigastric pain*. If 2nd part of duodenum is involved, it leads to *chronic gastric outlet obstruction or fistula formation with small or large gut* leads to diarrhea and malabsorption.

EXTRAINTESTINAL MANIFESTATIONS IN IBD (TABLE 51.3)

- **Cutaneous manifestation**
  - Pyostomatitis vegetans—Involve mucous membrane
  - Pyoderma vegetans—Involve intertriginous area
  - Sweet syndrome—Neutrophilic dermititis
  - Metastatic CD— Cutaneous granualoma (rare disorder)
  - Psoriasis (5–10%) of IBD
  - Pyoderma gangrenosum common over dorsum of foot and leg but may occur on arm, chest and face (Fig. 51.3).
- **Rheumatologic—Ankylosing spondylitis** (10% in CD) (two-third are HLA B27 positive), asymmetric migratory peripheral polyarthritis and affecting large joints of upper and lower extremity.
- **Ocular (10%)**—*Conjunctivitis, anterior uveitis/iritis* and *episcleritis* (both UC and CD).
- **Hepatobiliary**—*Hepatic steatosis, cholelithiasis, primary sclerosing cholangitis* leading to biliary cirrhosis and hepatic failure less often with CD.
- **Urologic—Calculi** (10% in CD), *ureteral obstruction* and **fistula** (ileal bladder fistula).
- **Metabolic bone disease**—Loss of bone mass due to glucocorticoids, cyclosporine, methotrexate, total parenteral nutrition, gut inflammation and malabsorption.
- **Others—Thromboembolic disease** due to platelet endothelial interaction, hypohomocysteinemia impaired fibrinolysis and vasculitis.

  Endocarditis, myocarditis, pleuropericarditis and interstitial lung disesase may be present (rare complication).

LABORATORY FEATURES

- Active disease is associated with a *rise in acute phase reactant*. These are:
  - **High ESR**.
  - **Elevated level of C-reactive protein** (rarely occurs in proctitis or proctosigmoiditis).
  - **High platelet count** associated with fulminant disease.
  - **Raised orosomucoid level**.
  - **Fecal calpronectin** is a very good marker of gut inflammation and predict relapse.
  - **Fecal lactoferrin** highly sensitive marker of intestinal inflammation.

Fig. 51.3: Pyoderma gangrenosum in ulcerative colitis

Table 51.3: Extraintestinal manifestation of inflammatory bowel disease (IBD)

Rheumatologic	Crohn's disease	Ulcerative colitis
• Peripheral arthritis	15%	10%
• Axial or sacroiliac arthritis	15–20%	10–15%
• Septic arthritis	Rare	Not reported
Skin		
• Erythema nodosum	15%	<15%
• Erythema multiforme	Rare	?
• Pyoderma gangrenosum	0.5–2%	< 0.5%
• Aphthous ulcer	Rare	1–8%
Miscellaneous		
• Nephrolithiasis (oxalate)	<15%	?
• Amyloidosis	Very rare	Not reported
• Liver disease	3–5%	7%
• Uveitis	13%	4%
• Vasculitis	Takayasu	<5%
• Clubbing of finger	Yes	1–5%
• Increase prevalence of asthma	Yes	Yes
• Increase prevalence of MS	No	Yes

- **Hypoalbuminemia** due to malabsorption and protein-losing enteropathy.
- **Hemoglobin is low** due to bleeding, malabsoption of Fe, B_{12}, folic acid and protein-losing enteropathy.
- **Leukocytosis**—Usually present but not a specific indicator of disease activity.
- **Stool examination**—is negative for bacteria, ova, parasites or *Clostridium difficile* toxin.
- **Blood culture** is indicated in those who develop fever with IBD.
- **Lower GI endoscopic appearance:**
  In ulcerative colitis the macroscopic appearance is confluent ulcer which is most severe in rectum and distal colon whereas rectal sparing, perianal disease and discrete ulcer suggest Crohn's disease. Endoscopic biopsy are taken to define the extent of the disease and search for dysplastic changes.
  - In ulcerative colitis:
    - **Mild disease**—Characterized by moderate erythema, decreased vascular pattern and mild friability.
    - **Moderate disease**—Characterized by marked erythema, absent vascular pattern, increased friability and erosion.
    - **Severe disease**—Characterized by spontaneous bleeding and ulceration.
  - In Crohn's disease—The endoscopic abnormalities are
    - Patchy ulcer with normal mucosa in between the ulcer (skip lesion).
    - **Aphthous or deep ulcer, fistulas and stricture** are common.

Severity of ulcerative colitis can be graded by the following features (*BBFTASE*) (Table 51.4)

Table 51.4: Grading of severity of ulcerative colitis (BBFTASE)

		Mild disease	Moderate disease	Severe disease
1.	Bowel movement	< 4/day	4–6/day	> 6/day
2.	Blood in stool	Small	Moderate	Severe
3.	Fever	Absent	<37.5°C	>37.5°C
4.	Tachycardia	Absent	< 90/m	> 90/m
5.	Anemia	Mild	Moderate	Severe
6.	Hematocrit		>75%	< 75%
7.	ESR	< 30 mm		> 30 mm
8.	Endoscopy	Erythema decreased vascular pattern	Marked erythema coarse granularity absent vascular pattern, contact bleeding no ulceration	Spontaneous bleeding and ulceration

- **St X-ray**—X-ray of abdomen is done for:
  - Evidence of perforation.
  - Toxic dilatation of the colon—in ulcerative colitis.
  - Evidence of intestinal obstruction or displacement of bowel by a mass—in Crohn's disease.
- **Barium studies**—Less sensitive than endoscopy.

  In ulcerative colitis:
  - Colon is short and narrowed with fine mucosal granularity deep collar button ulcer.
  - Loss of haustration with tubular appearance.
  - Presence of pseudopolyp or adenomatous polyp. **In Crohn's disease**—The appearance may be identical to those of ulcerative colitis but—
    - Skip lesion
    - Stricture
    - Deep ulcer
    - Reflux into terminal ileum are characteristic.

  Barium contrast studies of small bowel are normal in ulcerative colitis but in Crohn's disease the affected areas are **narrowed,** *ulcerated* and *multiple* **strictures** are common with *string sign*.

Radiologically string sign is due to narrowed intestinal lumen, within the mass which is composed of inflamed bowel, mesentery, enlarged abdominal lymph node.

- **MRI**—Accurately delineate the pelvic and perineal involvement in Crohn's disease.
- **CT scan in UC**—Mild mural thickening (< 1.5 cm) and inhomogenous wall density, absence of small bowel, thickening with **increase perirectal and presacral fat with target appearance of rectum** and **lymphadenopathy**.
- Antineutrophil cytoplasmic antibody (ANCA)—positive in 60–70% of ulcerative colitis.
- Anti-saccharomyces cerevisiae antibody (ASCA)—Positive in 60–70% of Crohn's disease.

COMPLICATIONS OF ULCERATIVE COLITIS

- **Massive bleeding**.
- **Toxic megacolon** usually confined to transverse or right colon with diameter >6 cm and loss of haustration (in X-ray).
- Colonic malignancy or dysplasia.
- **Stricture** due to neoplasia (5–10%).
- Rarely **perforation**, anal fissures, perianal abscesses and hemorrhoids.

COMPLICATIONS OF CROHN'S DISEASE

- **Stricture formation** with **intestinal obstruction** (40%)
- **Serosal adhesion causing intestinal obstruction**
- **Perforation**
- **Fistula formation**
- **Intra-abdominal** and **pelvic abscess** (10–30%)
- **Severe perianal disease**
- **Malabsorption**.

MANAGEMENT

Treatment can be divided into four part
- Treatment of acute attack
- Prevention of relapse
- Selection of patient for surgery
- Detection of carcinoma at an early stage.

The principles of drug treatment are similar for UC and CD.

For Active Colitis

- **Corticosteroid**—It is the mainstay of therapy.
  - **IV methylprednisolone** 60 mg/day
    Hydrocortisone —100 mg 8 hourly × 3–5 days for **life-threatening severe active colitis**.
  - **Oral prednisolone**—40–60 mg/day
    Hydrocortisone 300 mg/day orally × 8 weeks for those who have *extensive active colitis* and *unable to retain enema*. Tapered to 20 mg/day over 4–6 weeks.
  - **Steroid foam a liquid retention enema** for active proctosigmoiditis to avoid systemic effect of corticosteroid.
- **Immunosuppressant therapy**—It required in those Patients who relapse frequently after a course of steroid or who require maintenance steroid therapy.
  - **Azathioprine**—2–3 mg/kg/day.
  - **6-mercaptopurine**—1–1.5 mg/day.

Immunosuppressant drug exert its maximal effect after 12 weeks and corticosteroid therapy may be required to bridge up this gap (complication—bone marrow

suppression, nausea, vomiting, myalgias and acute pancreatitis).

Antidiarrheal agents like—*codeine phosphate, loperamide, diphenoxylate, sometime* useful but should be avoided in severe active disease.

Maintenance of Remission

- **5-ASA** (newer sulfa-free aminosalicylate preparation) which acts by modulating intestinal inflammatory activity (acute disease—3–6 g, in chronic disease—2–4 g).
- **Mesalamine**—It is an enteric coated preparation, from which 5-ASA is slowly released from a cellulose base or pH-dependent coating (acute disease—2.4–4.8 g, chronic disease—1.6–4.8 g).
- **Olsalazine**—Two molecule of 5-ASA bound by AZO bond to optimize delivery to the colon. Dose 1–3 g.
- *Topical 5-ASA liquid or foam retension enema* **are also available and are more effective than steroid enema for treatment of active proctitis**.

DRUG TREATMENT OF CROHN'S DISEASE

Combination of ciprofloxacin with metronidazole can be used as first line drug for short period in active fistulating and perianal Crohn's disease.

- **Prednisone**—30–40 mg daily tapering over 6–8 weeks.

> Steroid side effect can be overcome by using budesonide a potent synthetic corticosteroid which reduces mucosal inflammation. Following absorption of the drug undergoes extensive first pass metabolism in the liver so adrenocortical axis suppression and side effect are minimum.

- **Azathioprine**—1.5–2 mg/kg/day.
- **Cyclosporin A (CsA)**—2–4 mg/kg/day in severe UC that is refractory to IV glucocorticoid and can be considered alternative to colectomy. Maintenance dose 2 mg/kg/day.
- **Tacrolimus**—A macrolide which is 100 times more potent than CSA and is effective in both UC and CD.

  Those who respond inadequately to steroid and azathioprine can be treated by—
- **Infliximab** (monoclonal antibody against TNF-α) induces clinical remission in 80% patients with Crohn's disease who are refractory to corticosteroid and are particularly helpful in healing fistula associated with Crohn's disease and moderate to severely active ulcerative colitis.

  Unfortunately most patient relapse within 12 weeks of infliximab infusion and 2nd time infusion may cause anaphylactic reaction. Current practice is periodic infusion at 8 weeks interval. Antibodies to infliximab associated complication can be managed by increasing the dose and decreasing the dose interval or switching over to adalimumab or certolizumab pegol.
- **Adalimumab** and **certolizumab** are humanized antibody to TNF and **natalizumab** is an antibody to intregrins which prevents trafficking lymphocyte to gut mucosa.

  All have promising trial report in Crohn's disease.

Management of Metabolic Bone Disease

Inflammatory bowel disease (IBD) patient particularly who require frequent course of steroid and malnourished have significant risk of developing osteopenia and osteoporosis and fracture.

They should be treated with bisphosphonate:

- Alendronate—7 mg daily/70 mg weekly
- Risedronate—5 mg daily
- Ibandronate—150 mg once monthly. To be taken in the morning in empty stomach with a glass of water
- Zolindronate—150 mg IV yearly.

NUTRITIONAL THERAPY

Elimination diet—Best advice for the majority of patients is to eat a well-balanced healthy diet and to avoid only those foods which by experience are poorly tolerated.

Specific nutritional therapy *can induce remission in active Crohn's disease but not in ulcerative colitis.*

Parenteral hyperalimentation should be done at the stage of 'toxic megacolon'.

Unfortunately nutritional therapy is expensive and often poorly tolerated and unusually followed by relapse on return to normal diet.

SURGICAL TREATMENT

Nearly 50% of UC with extensive disease require surgery within 10 years.

Nearly 80% of CD with small bowel disease require surgery and nearly 50% of colonic disease with CD require surgery.

Indications of Surgery in Ulcerative Colitis

- Intractable disease
- Fulminant disease
- Toxic megacolon
- Colonic perforation
- Massive hemorrhage
- Extracolonic disease
- Colon cancer
- Prophylaxis for colon cancer.

Surgery of ulcerative colitis:

- Removal of colon and rectum
- Panproctocolectomy with ileostomy
- Proctocolectomy with ileoanal pouch anastomosis.

Indications of Surgery in Crohn's Disease

- Stricture and distraction
- Fistula
- Abscess
- Massive hemorrhage
- Perianal disease not responding to medical therapy
- Cancer prophylaxis
- Intractable or fulminant disease.

Surgery in Crohn's disease in complicated with recurrence and surgical intervention should therefore be as conservative as possible in order to minimize loss of viable intestine and to avoid creation of short bowel syndrome.

Ileoanal pouch formation should be avoided because of high-risk of *disease recurrence* within the pouch with subsequent *fistula*, *abscess formation* and *pouch failure*.

Patients who have perianal Crohn's disease are managed as *conservatively* as possible by *drainage of abscess* and *avoidance of resection* and *reconstructive procedure*. Multiple and recurrent strictures are managed by stricturoplasty where strictures are not resected but incised on longitudinal axis and sutured transversely.

MANAGEMENT OF FULMINANT COLITIS (TOXIC MEGACOLON)

It is a life-threatening complication which demands intensive medical and surgical intervention.

Clinical Features of Toxic Megacolon

- Fever.
- Tachycardia.
- Increased number and volume of the stool.
- Increase blood loss.
- Clinical signs of peritonitis.
- X-ray abdomen—Dilated colon diameter >6 cm with loss of haustration.
- Evidence of preparation.
- Triggered by electrolyte imbalance and narcotics.

Treatment of Toxic Megacolon

- Stop oral feeding.
- Parenteral hyperalimentation.
- IV methylprednisolone (60 mg daily)/hydrocortisone 300 mg/day.
- Steroid/mesalamine enema.
- IV antibiotics.
- Blood transfusion.
- Subcutaneous LMWH for prophylaxis against thromboembolism.
- Avoidance of opiates/antidiarrheal agent.
- Improvement is seen in 50% patients with conservative medical therapy.
- Frequent monitoring for sign of toxic dilatation of colon (>6 cm) and perforation of gut (gas under diaphragm) by clinical parameter and abdominal X-ray. If improvement does not occur within 5–7 days or if patient deteriorates urgent colectomy should be undertaken and subsequent ileoanal pouch reconstruction on recovery.

Perianal Diseases in Crohn's Disease

Patients who have painful or discharging perianal disease are managed jointly by surgeon and physician.

- **Metronidazole and ciprofloxacin**—to eliminate sepsis and relieve pain.
- **Abscess**—Require drainage but radical procedure risk injury to anal sphincters.
- **Infliximab**—May be used in resistant cases.

Risk of Cancer in Ulcerative Colitis

Risk of neoplasia in chronic UC increase with duration. It is 0.5–1% per year after 8–10 years of disease. Yearly or biyearly colonoscopy is recommended in patient >10 years of pancolitis.

Risk of Cancer in Crohn's Disease

Risk factors for cancer in CD are:

- Long-standing disease
- Extensive disease
- Bypass colon segment
- Colon stricture
- Primary sclerosing cholangitis
- Family history of colon cancer.
- *Other malignancy in IBD are non-Hodgkin lymphoma (NHL), leukemia and myelodysplastic syndrome (MDS).*

EXERCISE

Write short notes on

1. Clinical features of UC and CD.
2. Extraintestinal manifestation of IBD.
3. Treatment of UC and CD.
4. Complications of UC and CD.
5. Management of toxic megacolon.
6. Indication of surgery in UC and CD.

SECTION VI

RHEUMATOLOGY

- Approach to a Patient of Monoarthritis
- Approach to a Patient of Polyarthritis
- Approach to a Patient of Low Back Pain
- Gout
- Rheumatoid Arthritis
- Felty's Syndrome
- Still's Disease
- Sjögren's Syndrome
- Juvenile (Rheumatoid) Idiopathic Arthritis
- Systemic Lupus Erythematosus
- Antiphospholipid Antibody Syndrome
- Seronegative Spondyloarthritis
- Ankylosing Spondylitis
- Reactive Arthritis
- Psoriatic Arthropathy
- Progressive Systemic Sclerosis
- Mixed Connective Tissue Disorder
- Hemolytic Uremic Syndrome
- Thrombotic Thrombocytopenic Purpura
- Vasculitis Syndrome (Vasculitides)
- Antineutrophil Cytoplasmic Antibody

Chapter 52

Approach to a Patient of Monoarthritis

CAUSES OF ACUTE MONOARTHRITIS

A. In an healthy individual

Monoarthritis is seen in following situation:

- Rheumatoid arthritis.
- Monoarticular presentation of oligo or polyarthritis, e.g. reactive, enteropathic, psoriatic seronegative spondyloarthritis.
- Septic arthritis.
- Crystal arthritis (gout and pseudogout).
- Juvenile idiopathic arthritis.
- Hemarthrosis-associated clotting factor abnormality.
- Trauma.
- Foreign body reaction.

B. Causes of acute arthritis in a previously abnormal joint

- Septic arthritis
- Bone problem (e.g. avascular necrosis, subchondral collapse or fracture)
- Pseudogout in association with osteoarthritis
- Hemarthrosis

C. Causes of chronic single joint synovitis

- Chronic infection TB and fungi
- RA, seronegative spondyloarthritis and juvenile idiopathic arthritis
- Foreign body
- Monoarticular presentation of oligo/pauciarticular disease
- Enteropathic arthritis mainly Crohn's diseases
- Amyloidosis
- Synovial sarcoma
- Chronic sarcoidosis

D. Causes of inflammatory oligoarthritis/pauciarticular diseases—(disease affecting two to four joints)

- Seronegative spondyloarthritis
  - Ankylosing spondylitis
  - Reactive arthritis
  - Psoriatic arthritis
  - Enteropathic arthritis
  - Juvenile idiopathic arthritis
  - Erythema nodosum
  - Oligoarticular presentation of polyarthritis.
- Infection—Bacterial endocarditis, *Neisseria* and mycobacteria

APPROACH TO A PATIENT OF MONO OR OLIGOARTICULAR PAIN

All patients of mono or oligoarthritis should be evaluated properly to arrive at correct diagnosis. Many such patients exhibit a definite predictable pattern of onset, localization and progression and associated with some extraarticular manifestations and some selected maneuvers and tests help to arrive at a diagnosis of such patients.

Involvement of Hand Joints

- **Focal or unilateral hand pain results from**
  - Trauma
  - Professional overuse
  - Infection
  - Reactive arthritis
  - Crystal-induced arthropathy.
- **Bilateral hand complain suggest**
  - Degenerative disorder (osteoarthritis)
  - Inflammatory or autoimmune disorder (rheumatoid etiology)
    - History may suggest trauma or overuse.
    - Local and systemic sign of inflammation—Short history and rapid onset, swelling of joint and surrounding tissue, redness, pain, tenderness and fever suggest *infection* or *crystal-induced arthropathy*.
    - Past history of UTI or diarrhea suggest reactive arthritis.
    - Involvement of DTP or PIP with bony hypertrophy (**Heberden's and Bouchard's node**) suggests osteoarthritis.
    - Pain with or without swelling of the base of thumb suggest of osteoarthritis.
    - Involvement of PIP, MCP, intercarpal and carpo-metacarpal and wrist joint with pain, prolonged stiffness and synovial hypertrophy suggest RA.

- Involvement of PIP, DIP and carpal joint with extraarticular manifestation like nail pitting or onycholysis and characteristic skin lesion suggest **psoriasis**.
- Soft tissue swelling over the dorsum of the hand and wrist suggests inflammatory extensor tenosynovitis due to gonococcal gout or other inflammation.
- The diagnosis of *tenosynovitis* may be suggested by local warmth, edema which is confirmed when pain appears on maintaining flexion of wrist or neutral position after flexing the digit distal to MP joint to stretch the extensor tendon sheath.
- Focal wrist pain localized on the radial aspect of the joint may be due to **de Quervain's tenosynovitis** resulting from inflammation of the tendon sheaths involving abductor pollicis longus or extensor pollicis brevis. It is suggested by **Finkelstein's test**—positive test is represented by focal wrist pain after the thumb is flexed across the palm and placed inside the clenched fist the patient actively deviates the hand downward with ulnar deviation at the wrist. It is due to overuse or following pregnancy.
- **Carpal tunnel syndrome**—It is commonly associated with edema, pregnancy, trauma, osteoarthritis, inflammatory and infiltrative disorder (amyloidosis) diagnosed by **Tinel's sign** or **Phalen's sign** in which paresthesia is elicited by thumping volar aspect of wrist (Tinel's sign) or pressing the dorsal aspect of both flexed wrist against each other (Phalen's sign).

Differential Diagnosis of Shoulder Pain

- History of trauma, infection and inflammatory diseases, occupational history and history of liver, gallbladder, and diaphragmatic diseases to be taken carefully.
- Shoulder pain may be frequently referred from cervical spine, Pancoast tumor, gallbladder, hepatic and diaphragmatic disease.
- Subacrominal bursitis (frequent cause of shoulder pain) is diagnosed by direct pressure over subacrominal bursa that lies lateral to and immediately beneath the acromion.
- Bicipital tendinitis is diagnosed by pain from direct pressure over the tendon in the bicipital groove anterior to subacromial bursa as the patient rotates humerus internally and externally.
- Palpation of acromioclavicular joint reveals local pain, bony hypertrophy and/or (rarely) synovial swelling diagnostic of osteoarthritis and rheumatoid arthritis.
- Pain and swelling of glenohumeral joint suggest effusion and is diagnostic of RA.
- Acute tear of rotator cuff can be palpated by (anteriorly) by placing the thumb over the humeral head (just medial and inferior to coracoid process) and rotate the humerus externally and internally.
- Rotator cuff tendinitis (formed by supraspinatus, infraspinatus, teres minor, subscapularis) is suggested by pain on active abduction, pain over lateral deltoid muscle, night pain and impingement sign (passive forced flexion of shoulder preventing the rotation of scapula). A positive sign is indicated by appearance of pain before 180° of force flexion.
- **Rotator cuff tear**—It is common in elderly from trauma and manifests in the same manner as rotator cuff tendinitis but drop arm test is positive (i.e. patient is unable to hold the arm up once 90° abduction is reached).

  Tendinitis or tear of the rotator cuff can be confirmed by MRI or arthrography.

Differential Diagnosis of Knee Pain

- RA, gout, Reiter's syndrome involving knee joint produce significant pain, stiffness, swelling and warmth.
- *Baker's cyst* on the back of knee is inspected while patient is standing with knee extended and palpated with the knee partially flexed.
- Osteoarthritis of patellofemoral joint is diagnosed by anterior knee pain while climbing stairs.
- Most common malalignment of knee is
  - Genu varum (bow leg)
  - Genu valgum (nock knee) due to hypertrophic osseous changes diagnostic of osteoarthritis and neuropathic arthropathy.
- Patellar tap is positive in small to moderate effusion <100 mL.
- Periarticular bursitis may present as knee pain.
  - Anserine bursitis present as joint tenderness over inferior and medial to the patella.
  - Prepatellar bursitis—Present as pain and tenderness located superficially over the inferior portion of patella.
  - Infrapatellar bursitis—Present as pain and tenderness located beneath the patellar ligament before its insertion to the tibial tubercle.
- Damage of meniscal cartilage is suggested by the symptom of locking, clicking or giving way of the knee joint with a history of trauma or athletic activity.
- Meniscal (semilunar) cartilage damage is diagnosed by—
  - Eliciting pain during direct palpation over the medial and lateral joint line.
  - Ipsilateral joint line pain when the knee joint is stressed laterally or medially.
  - Positive McMurray test—Pain during medial or lateral rotation of leg while extending the knee from

90° flexed position. Painful clicking during inward rotation indicates *lateral meniscus tear* and pain during outward rotation suggests *medial meniscus injury*.

- Damage to cruciate ligament is suggested by pain and swelling of knee joint due to gross bloody effusion with a history of trauma.
- **Drawer tests**—Anterior movement of tibia over femur suggests anterior cruciate ligament tear and posterior movement of tibia over femur suggests posterior cruciate injury.

Differential Diagnosis of Hip Pain

- The most common *hip pain* is located posteriorly over gluteal musculature which is usually associated with low back pain with a radiation to the posterolateral aspect of thigh along L_5, S_1 dermatome is due to *degenerative arthritis* of lumbosacral spine.
- *Hip pain located laterally* overlying trochanteric bursa is due to *trochanteric bursitis* confirmed by eliciting point of tenderness over trochanteric bursa (due to depth of the bursa, swelling and warmth are usually absent).
- *Hip pain located anteriorly* over the inguinal ligament is least common and is due to true *disease of the hip joint* which may radiate medially to the groin or along the anteromedial aspect of thigh.
- Pain due to iliopsoas bursitis may mimic pain due to true hip joint involvement—it is suggested by worsening on hyperextension of hip joint. So, patient preferred flexion and external rotation of hip to reduce the pain.

LABORATORY INVESTIGATION

- **Blood**
  - Full blood count is helpful in rheumatic fever, viral arthritis and SLE.
  - Anemia is due to chronic inflammation or due to chronic blood loss for NSAID and autoimmune hemolytic anemia in SLE.
  - Raised ESR and CRP are seen in SLE and RA.
  - Serology for viral polyarthritis.
  - Rheumatoid factor positive suggests RA.
  - Anti-CCP-positive confirms RA.
  - HLA typing—$HLAB_{27}$ positivity suggest ankylosing spondylitis and reactive arthritis.
  - ANA and anti-dsDNA positive in SLE.
  - Serum uric acid raised in gout.
  - LFT.
- **Radiology**
  - X-ray for exclusion of fracture
  - CT
  - MRI of pelvis for ankylosing spondylitis and RA.
- **Synovial fluid study**—Infective and RA.
- **Synovial membrane biopsy**—Tuberculosis.

EXERCISE

Write short notes on

1. Approach to a patient of monoarthritis.
2. Approach to a patient with hand pain.

Chapter 53

Approach to a Patient of Polyarthritis

RA—Rheumatoid arthritis
RF—Rheumatoid factor
SLE—Systemic lupus erythematosus
PIP—Proximal interphalangeal joint
DIP—Distal interphalangeal joint
MCP—Metacarpophalangeal joint
MTP—Metatarsophalangeal joint
HSP—Henoch schonlein purpura
JRA—Juvenile rheumatoid arthritis
Anti-CCP—Cyclic citrullinated peptide
ANCA—Antineutrophil cytoplasmic antibody.

CAUSES OF POLYARTHRITIS

A. Inflammatory
B. Noninflammatory.

Inflammatory

- **Viral**—Parvovirus—B_{19}, HBV, HCV, mumps, rubella, chickenpox, infectious mononeucleosis, *Neisseria gonorrhoeae* and tuberculosis.
- Rheumatoid arthritis and SLE.
- **Seronegative spondyloarthritis**—Ankylosing spondylitis, psoriatic, reactive and enteropathic arthritis.
- Chronic gout and pseudogout.
- Juvenile idiopathic arthritis.
- Chronic sarcoidosis.
- Scleroderma and polymyositis.
- Hypertrophic osteoarthropathy.

Noninflammatory

- Generalized osteoarthritis
- Hemochromatosis
- Acromegalic arthropathy.

Patient with musculoskeletal complain should be evaluated from history and physical examination as about

- Whether it is intraarticular or extraarticular disorder?
- Is it acute (<6 weeks) or chronic (>6 weeks)?
- Whether the signs of inflammation is present?
- How many joints are involved?
- Which joints or joint groups are involved?

A. If it is nonarticular (extraarticular) then the diagnosis may be the followings:
- Trauma or fracture
- Fibromyalgia
- Polymyalgia rheumatica
- Bursitis
- Tendinitis.

B. If it is articular whether the complain persisting for more than 6 weeks or not.

Table 53.1 Duration of illness in different form of arthritis

	Persisting <6 weeks		Persisting >6 weeks
1.	Infectious arthritis	1.	RA
2.	Gout	2.	SLE
3.	Pseudogout	3.	Scleroderma
4.	Reiter's syndrome	4.	Polymyositis
5.	Initial presentation of chronic arthritis	5.	Osteoarthritis
		6.	Osteonecrosis
		7.	Charcot arthritis
		8.	Psoriatic arthritis
		9.	Chronic infective arthritis
		10.	Pauciarticular JA

C. The next question is whether the signs of inflammation is present or not as evidenced by erythema and pain: warmth and swelling.
- Prolonged morning stiffness
- Presence of soft tissue swelling
- Presence of systemic symptoms
- Elevation of acute phase reactant—ESR and CRP.

If signs of inflammation is not present, then it is chronic noninflammatory arthritis. The causes are

a. Osteoarthritis
b. Osteonecrosis
c. Charcot arthritis.

D. Then we have to see which joint or joint groups are involved
- If DIP, 1st CMC, hip or knee joint are involved then it is a case of osteoarthritis.

- If these joints are not involved then it is a case of osteonecrosis or Charcot arthritis.

E. If signs of inflammation is present then it is chronic inflammatory arthritis and we have to look for how many joints are involved.

- *If less than 3 joints are involved then it is a chronic oligo-or monoarthritis causes are*
  1. Chronic infective arthritis (TB)
  2. Psoriatic arthritis
  3. Reiter's syndrome/reactive arthritis
  4. Pauciarticular JA.
- *If more than 3 joints are involved,* it is chronic inflammatory polyarthritis and we have to see whether the involvement is symmetric or asymmetric.
  1. **If the involvement is asymmetric** then it is
     - » Psoriatic arthritis
     - » Reiter's syndrome/reactive arthritis.
  2. **If the involvement is symmetrical** then whether PIP and MCP or MTP joints are involved.
     - » If they are involved—Rheumatoid arthritis.
     - » If they are not involved—SLE, scleroderma and polymyositis.

HISTORY: IMPORTANT POINTS IN HISTORY

Age

- Child—Rubella, rheumatic fever, HSP and JRA.
- Young adult—SLE and gonococcal and Reiter's syndrome.
- Old age—Osteoarthritis.

Sex

- Rubella—F > M
- SLE—F : M = 9 : 1
- Reiter's syndrome—M : F = 15 : 1

Mode of Presentation

- Acute or chronic
- Symmetric/asymmetric
- Lower limb/upper limb
- Large joint/small joint
- Periarticular involvement present or not
- Extraarticular involvement present or not.

Onset

- *Acute onset*—viral fever, rheumatic fever, reactive arthritis and HSP.
- *Chronic onset*—RA, SLE, osteoarthritis and psoriatic arthritis.
  Polyarthritis that persists more than 6 weeks unlikely to be of viral etiology.

Symmetry

- *Symmetric involvement*—Viral fever, SLE, RA and osteoarthritis.
- *Asymmetric involvement*—Rheumatic fever, psoriatic arthritis and reactive arthritis.

Limb

- *Lower limb*—Mostly involved in seronegative spondyloarthritis (ankylosing spondylitis) and reactive arthritis.
- *Upper limb*—Mainly hand joints are involved in rheumatoid arthritis.

Joint

- *Large joints* are involved in rheumatic fever, seronegative spondyloarthritis (ankylosing spondylitis).
- *Small joints* are involved in the early stage of RA.
  Both large and small joints are involved in RA, JRA and generalized osteoarthritis.

Periarticular manifestation

- *Tenosynovitis and bursitis*—RA.
- *Tenosynovitis (wrist extensor) and arthralgia*— SLE.
- Enthesitis and diffuse periarticular swelling—Seronegative spondyloarthritis and ankylosing spondylitis.

Extraarticular features associated with polyarthritis

- **Skin, nail and mucous membrane**
  - **Nail pitting** and ridging seen in psoriatic arthritis.
  - **Raynaud's phenomenon**—Scleroderma and SLE.
  - **Increased photosensitivity**—SLE.
  - **Livedo reticularis**—SLE.
  - **Splinter hemorrhage and nail fold infarct**—Vasculitis.
  - **Oral ulcer**—SLE, reactive arthritis, Behçet's syndrome.
  - **Large nodule on the extensor surface hand and forearm**—RA, gout and rheumatic fever.
  - **Clubbing**—Enteropathic arthritis, metastatic lung cancer and endocarditis.
- **Eye**
  - **Scleritis and episcleritis**—Vasculitis and RA
    - **Conjunctivitis**—Reactive arthritis
    - **Uveitis**—seronegative spondyloarthritis.
- **Heart and Lung**
  - Pleuropericarditis seen in SLE and RA.
  - Fibrosing alveolitis seen in RA and SLE.
- **Abdominal organ**
  - Hepatosplenomegaly found in SLE and RA.
  - Hematuria and proteinuria found in SLE, PSS, reactive arthritis and vasculitis.
  - Urethritis seen in reactive arthritis.

- **Fever and lymphadenopathy seen in**
  - Infective arthritis, rheumatic fever and systemic JRA.

Pattern of Joint Involvement

- Rheumatoid arthritis (RA)—Symmetrical inflammatory involvement of small joints of hand (carpal, metacarpophalangeal and PIP) and elbow, wrist, ankle, knee with morning stiffness and characteristic deformity without involvement of DIP joint in a lady are suggestive of rheumatoid arthritis.
- **Ankylosing spondylitis**—Inflammatory sacroiliitis and lumbosacral involvements with asymmetric involvement of root joint mostly of lower limb associated with enthesitis in young male.
- **Reactive arthritis**—Inflammatory spondylosis with involvement of knee, ankle, subtalar, MTP, IP joint with facial involvement in the sole and foot, with history of urethritis GI and respiratory tract infection along with recent evidence of urethritis and conjunctivitis.
- **Acute rheumatic fever (RF)**—Migratory polyarthritis with asymmetric involvement of large joint of both upper and lower limb without any residual joint damage.
- **Psoriatic arthritis**—Inflammatory asymmetrical large/small joint involvement of upper and lower limb with typical skin lesion and features of dactylitis and nail changes seen.
- **Generalized osteoarthritis**—Symmetrical small and large joint involvement with Heberden's node at DIP usually in elderly.
- **Viral arthritis**—Very acute self-limiting with characteristic rash and fever.

Past History

- Dysentery, urethritis and respiratory tract infection suggest reactive arthritis and HSP.
- Valvular heart disease—Acute rheumatic fever (ARF) and infective arthritis.
- Recurrent acute attack associated with chronic gout.

Drug history

- Anticonvulsant, hydralazine, procainamide and INH associated with SLE.
- Dramatic response to salicylate seen in rheumatic fever.

Personal history

- Sexual overactivity is associated with gonorrhea and Reiter's syndrome (reactive arthritis).
- Drug addicts suffer from infective arthritis.

INVESTIGATION

- **Blood**
  - **Complete blood count**.
  - **Acute phase reactant**—ESR and C-reactive protein, help in discrimination of inflammatory from noninflammatory disorder. Elevated in infectious arthritis, inflammatory arthritis, autoimmune disorder and neoplasia.
  - **Serum uric acid** elevated in gout.
  - **Serological test**
    - **Rheumatoid factor and anti-CCP** positive in RA.
    - **Antinuclear antibody (ANA)** positive in SLE.
    - **ANCA**—Diffuse and speckled patterns are least specific whereas a peripheral or rim pattern is highly specific and suggestive of autoantibodies against double-stranded DNA and diagnostic of SLE.
    - ASO positive in acute rheumatic fever.
    - **Viral serology**—Infectious arthritis.

    This test should be carried out only when clinical diagnosis points to a particular diseases.
  - **Synovial fluid analysis**—Indicated in acute or chronic monoarthritis, e.g. infectious or crystal-induced arthropathy and helps in distinguishing inflammatory from noninflammatory arthritis.

Points to be noted in the examination of synovial fluid

- Appearance
- Viscosity
- Cell type and count
- Crystal identification.
  - **Normal synovial fluid**—Clear or pale straw-colored and viscous due to high level of hyaluronate.
  - Viscosity is assessed by seeing the stringing effect behind each drop when expressing the fluid from syringe needle one drop at a time.
  - **Noninflammatory synovial fluid**—Clear or ambar-colored, viscous with a WBC count <2000/mL with a predominance of mononuclear cell—effusion caused by osteoarthritis or trauma.
  - **Inflammatory synovial fluid**—Turbid or yellow with a WBC count 2000–50,000/mL with a neutrophilic predominance. Viscosity is reduced due to diminished hyaluronate. Effusion is caused by septic arthritis, rheumatoid arthritis, gout and other inflammatory arthritis.
  - **Infectious synovial fluid**—Opaque or purulent with low viscosity and WBC count >50000/mL with predominance of neutrophil (>75%)—typical septic arthrites but rarely seen in sterile inflammatory arthritis, e.g. RA and gout.

- **Hemorrhagic synovial fluid**—Seen in
  - Trauma
  - Coagulopathy
  - Neuropathic arthritis.

Special points to be examined in synovial fluid

- Presence of crystal by light and polarizing microscopy.
- Gram stain and culture for bacteria, tuberculosis and fungus.
  - **Gout**—Large needle-shaped, negatively-birefringent, usually intracellular crystal of monosodium urate seen in gout.
  - **Pseudogout and chondrocalcinosis**—Short, rhomboid envelop-shaped, positively-birefringent crystal seen in chondrocalcinosis and pseudogout.

IMAGING IN MUSCULOSKELETAL DISORDER

- **X-ray is helpful in detecting**
  - Fracture.
  - Soft tissue swelling.
  - Juxtaarticular demineralization.
  - Calcification of soft tissue, cartilage and bone.
  - Joint space narrowing.
  - Erosion of bone and cartilage.
  - Bony ankylosis.
  - New bone formation—Sclerosis, osteophytes and periostitis.
  - Subchondral cyst.
- **Ultrasonography (limited use)**—For diagnosis of
  - Synovial cyst—Baker's cyst.
  - Rotator cuff tear, tendinitis tendon injury and synovitis.
- **Radionucleotide scintigraphy**—
  - 99m TC pertechnetate for survey of bone metastasis and Paget disease of bone.
- **CT (computed tomography) scan**—Provide most useful information in the assessment of the axial skeleton specially zygapophyseal, sacroiliac, sternoclavicular and hip joints. CT has been useful in diagnosis of low back pain syndrome, sacroiliitis osteoid osteoma, herniated intervertebral disk, sacroiliitis, spinal canal stenosis, spinal trauma, stress fracture.
- **MRI (magnetic resonance imaging)**—It can image fascia, vessel, nerve, muscle, cartilage ligament, tendon, pannus, synovial effusion and bone marrow. Visualization of particular structure can be enhanced by altering the pulse sequence to produce either T_1 or T_2-weighted spin echo, gradient echo or inversion recovery images. It is more sensitive than arthrography or CT images in soft tissue injury like meniscal or rotator cuff tear, intraarticular derangement, spinal cord damage and subluxation or synovitis.

  Indication—Avascular necrosis, osteomyelitis, intraarticular derangement and soft tissue injury, derangement of axial skeleton and spinal cord, herniated intervertebral disk, marrow abnormality like myeloma and osteonecrosis, ankylosis spondylitis.

EXERCISE

Write short note on

1. Approach to a patient of polyarthritis.

Chapter 54

Approach to a Patient of Low Back Pain

NCV—Nerve conduction velocity
EMG—Electromyogram
ANA—Antineutrophil antibody
PID—Prolapsed intervertebral disk
SSA—Seronegative spondyloarthritis.

Low backache is very common symptom. About 80% of population experience back pains at some time of his/her life. Fortunately, 70% of these subside within a month without any treatment but may recur at any point of time.

The specific etiology of most of the back pain is very difficult to diagnose.

The common causes of low backache are as follows:

- **Degenerative**
  - Osteoarthritis.
- **Inflammatory causes**
  - Seronegative spondyloarthritis
  - Tuberculosis.
- **Traumatic causes**
  - Prolapsed intervertebral disk (PID)
  - Vertebral fracture
  - Sprain and strain.
- **Neoplastic**
  - **Benign**—Osteoid osteoma
    Eosinophilic granuloma.
  - **Malignant**
    - *Primary*—Multiple myeloma and others.
    - *Secondary*—From any sites (most common — breast and prostate).
- **Congenital causes**
  - Spondylosis
  - Spondylolisthesis
  - Lumbar scoliosis and kyphosis
  - Spina bifida.
- **Metabolic**
  - Osteoporosis
  - Osteomalacia.
- **Referred pain form viscera**
  - Genitourinary disease
  - Gynecological disease.
- **Miscellaneous**
  - Hysterical.
  - *Defective posture*—Protuberant abdomen and bad posture.

DIAGNOSTIC APPROACH OF LOW BACK PAIN

- **Age**—Some diseases are common in particular age group, e.g.
  - **Children**—Congenital or traumatic cause.
  - **Adolescents**—Hysterical and traumatic or faulty posture.
  - **Adult**—Ankylosing spondylitis and disk prolapse.
  - **Old age**—Osteoporosis, degenerative arthritis and metastatic bone disease.
- **Sex**—Low back pain is more common in women with multiple pregnancies due to
  - Poor muscle tone
  - Nutritional osteomalacia
  - Overweight.
- **Occupations**—Patients with sedentary jobs which involve prolonged standing or sitting are also at the risk of developing back pain, e.g. surgeons, dentists and truck drivers.
- **Past history**—Previous history of tuberculosis and trauma or malignancy is very important for etiological diagnosis of low back pain.

Features of Pain

The following features are very suggestive:

- **Location**—The pain located in the upper or middle of the back may be due to infection or trauma.
  Pain located in the lower back is due to disk prolapse and degenerative spondylitis or ankylosing spondylitis.
- **Onset**
  - If onset preceded by trauma—Suggest fracture, ligament sprain and muscle strain.
  - Sudden forceful flexion, extension or twisting of spine suggest disk prolapse and is present in 40% of patients. Trauma may be subtle resulting from a routine activity.
- **Localization of pain**—Pain arising from muscle or tendon injury is localized.
  Pain arising from deeper structure are diffuse.
  Pain referred to a particular dermatome of lower limb with associated neurological sign point to nerve root involvement.

Table 54.1: Clinical features of nerve root compression

Level	Root affected	Motor	Sensory loss	Reflex
L_3–L_4	L_4	Weakness of extensor of knee of leg	Over medial side of shin bone	Knee jerk—Sluggish or absent Ankle jerk—Brisk Plantar—Extensor
L_4–L_5	L_5	Weakness of extensor hallucis longus and dorsiflexors	Over dorsum of foot and lateral aspect of leg	Knee jerk—Normal Ankle jerk—Brisk Plantar—Extensor
L_5–S_1	S_1	Weakness of plantar flexor of foot	Over posterior aspect of ankle and sole	Knee jerk—Normal Ankle jerk—Sluggish or absent Plantar—Not elicitable

- **Progress/course of the pain**
  Traumatic or PID—Pain is maximum at onset, then gradually subsides.
  Morning pain and stiffness of back—Suggest inflammatory nature.
  PID—Period of remission and acute exacerbation.
  Arthritis and spondylosis—Constant pain aggravated by activity.
  Pain due to infection or tumor—Progressive course.
- **Aggravating/relieving factor**
  Most low back pain worsen by activity relieved by rest.
  Ankylosing spondylitis and SSA—Aggravated by rest and relieved with activity.
  Spinal canal stenosis—Pain started on walking or standing and relieved by rest.
  Pain increases during menstruation—Indicate endometriosis.
- **Associated symptoms**
  - *Stiffness*—Early morning stiffness and associated with limitation of chest movement—ankylosing spondylitis or seronegative spondyloarthritis.
  - *Pain in other joints*—Low back pain associated with asymmetrical large joint involvement more in the lower limb suggests ankylosing spondylitis and reactive arthritis.
  - *Low back pain associated with neurological symptom*—Suggest thecal sac compression or nerve root compression, e.g.
    - Pott's disease
    - Spinal canal stenosis
    - Prolapse intervertebral disk
  - *Extraskeletal symptoms*
    - LBP with conjunctivitis and urethritis—Suggest reactive arthritis.
    - LBP with gynecological symptoms—Suggest extraskeletal cause.
  - *Psychological status*—To rule out malingering and hysteria.
    But patient suffering from chronic organic disease may have psychological disturbances.

Physical Examination

- **Examination in standing position**
  - Look for scoliosis, kyphosis, lordosis, pelvic tilt and forward flexion of spine.
  - *Muscle spasm*—It may be present with acute back pain and can be seen as prominence of paravertebral muscle at rest or on mild movement.
  - *Swelling*—Nontender fluctuating swelling indicates caries spine.
  - *Range of movement*—There is limitation of the range of movement of spine in disease of vertebra and for accurate diagnosis, one must carefully differentiate between movement of spine from movement of adjacent joints, e.g. hip and sacroiliac joint.
- **Examinations in Supine position**
  - Straight leg rising test—This test helps in diagnosing root compression.
  - Neurological examination—Sensation, motor power and reflexes of lower limb are examined. This helps in localizing site of spinal pathology.
  - Peripheral pulse in femoral and brachial artery should be palpated to detect any vascular cause of low back pain.
  - Adjacent joints—Often pain arising from hip joint may mimic low back pain; hence this joint should be examined routinely.
  - Abdominal, rectal and vaginal examination should be done routinely and chest expansion in full inspiration and expiration should be recorded.

Investigation

Etiological diagnosis can be made in most of the cases by clinical examination. But in some cases X-ray and other investigations are very helpful.

- **Radiological examination**
  - Routine X-ray of lumbosacral spine (AP and lat) and pelvis (AP) should be done in all cases of low back pain persisting for more than three weeks after proper bowel preparation with laxative. This is helpful in diagnosing metabolic inflammatory and neoplastic diseases.
- **CT Scan**—It is very much helpful in detecting bone lesion.
- **MRI** of spine is helpful in diagnosing soft tissue disease around spine and spinal canal stenosis (and have replaced myelography). PID, ankylosing spondylitis and malignancy.
- **Blood**—TC, DC, ESR, rheumatoid factor, serum uric acid, HLAB 27 and ANA. protein electrophoresis for 'M' band.
- **Other tests**
  - Mantoux test and chest X-ray (PA).
  - NCV and EMG—If root compression is a possibility
  - Bone scan—It may be helpful for multiple myeloma and skeletal metastasis.

EXERCISE

Write short note on

1. Approach to a patient of low back pain.

Chapter 55

Gout

The term gout indicate a heterogeneous group of diseases that include the following characteristics:

a. Elevated serum urate concentration >6.8% mg/dL.
b. Recurrent attacks of acute arthritis in which monosodium urate monohydrate crystal are demonstrable in synovial fluid leukocyte.
c. Aggregates of sodium urate monohydrate crystal (tophi) deposited chiefly in and around joints which sometimes leads to deformity and crippling.
d. Renal disease involving glomerular, tubular and interstitial tissues and blood vessels.
e. Uric acid nephrolithiasis.

Hyperuricemia denotes an elevated level of urate in the blood >**6.8 mg/dL at 37° C**.

For men it has been rounded off at **7 mg/dL** and for women it has been rounded off at **6 mg/dL**.

The prevalence of gout ranges from 1–15% with clear increase in incidence in recent years perhaps related to the consumption of Western diet and obesity.

Serum urate levels are low in children and increase in men at puberty and women at menopause.

Hyperuricemia are directly related to *age, blood pressure, alcohol intake, body mass index and serum creatinine*.

Comparatively low level of serum urate in women is a consequence of **concentration of sex hormone and higher fractional excretion of urate**, secondary to lower tubular reabsorption.

Many factors are associated with gout:

- Consumption of *alcohol (beer), seafood and red meat aggravate gout*.
- Consumption of *milk and yogurt are protective.*
- *Polymorphism in several candidate gene encoding urate transporter in the renal proximal tubules as determinants of serum urate level and risk of gout*.

CLINICAL FEATURES

There are four stages of gout:

1. Asymptomatic hyperuricemia
2. Acute gout
3. Intercritical gout
4. Chronic gouty arthritis.

Asymptomatic Hyperuricemia

Asymptomatic hyperuricemia may last up to 20 years before the initial attack of gout or nephrolithiasis develop.

*First attack of acute gout usually occurs at the age of 40–60 in male and after 60 in female. Many drug raises serum urate level and predisposes to gout of which **diuretic** is notorious but **cyclosporin** and **heparin** are others. Other provocative factor include **trauma, alcohol ingestion, surgery, dietary excess, hemorrhage, foreign protein therapy**, **infection** and **radiographic contrast**. The gout may precipitated after initiation of antihyperuricemic therapy, the more potent the urate lowering effect the more likely the chance of precipitation of acute attack.*

Acute Gout

*Usually, the first attack of gout are monoarticular with a predilection for the **first metatarsophalangeal joint** (80–90% **podagra**) which usually have a characteristic abrupt and painful onset. Next in order of frequency are the **in step of foot, ankle, heel, knee, wrist, fingers and elbow**. Acute gouty bursting tendinitis or tenosynovitis can also occurs. Urate deposition and subsequent gout appear to have a predilection for a previously damage joint such as Heberden's node in the older women.*

The differential diagnosis is usually **septic arthritis** or other **crystal-induced arthritis** but broader differential are given below. Mild attack may persist for several hours to a few days but severe attack may last for weeks. The skin over the joint often may desquamates as the erythema. Subside with resolution and become asymptomatic and enter the intercritical period.

Differential diagnosis of acute gouty arthritis

- Other crystal arthritis, e.g. CPPD (pseudogout) and basic calcium phosphate (hydroxy apatite).

- Septic arthritis including gonorrhea.
- Trauma.
- Cellulitis.
- Lyme arthritis.
- Reactive arthritis.
- Psoriatic arthritis.
- Sarcoidosis.
- Unusual presentation of rheumatoid arthritis.

Intercritical Gout

The term intercritical gout and interval gout is applied to the period between two acute gouty attack. Some patient may never have a second attack. Usually, the second attack comes within 6 month to 2 years after acute attack.

About 7% patient never had a second attack.

Later attack are less explosive, polyarticular, more severe, last longer, abate more slowly but recovery is usually complete. The diagnosis of intercritical phase of gout is sometimes difficult but can be accomplished by demonstration of urate crystal in 12.5–90% of joint fluid.

Chronic Gouty Arthritis

During this phase, the patient does not have any pain. It develops on an average 11–12 years often the initial acute gouty arthritis.

The rate of formation of tophaceous deposit correlate with both the degree and duration of hyperuricemia. Serum urate concentration of *<9.1 mg have no tophi whereas 10–11 mg/dL have minimal to moderate tophi and greater than 11 mg/dL have extensive tophaceous* involvement. The **rate of Tophus formation** also increases with severity of **renal disease** and use of **diuretics**.

As the urate pool expand, the urate crystal appear in cartilage, synovial membrane, tendon, soft tissue and elsewhere. Tophi are rarely present at the time of initial acute attack of primary gout. They are more likely to be present in gout secondary to **myeloproliferative disease (CML), Lesch-Nyhan syndrome** or after **allograft transplantation** patient treated with **cyclosporine**.

Gout is associated with **obesity, hypertriglyceridemia, glucose intolerance** and **metabolic syndrome, hypertension and atherosclerosis** and **hypothyroidism**. **Renal insufficiency** is frequently associated with hyperuricemia and gout.

Hyperuricemia is the common cause of nephrolithiasis and rarely chronic hyperuricemia may cause urate nephropathy and acute hyperuricemia may lead to uric acid nephropathy in the tumor lysis syndrome.

Chronic alcohol use, lead intoxication and **cyclosporin treatment** are associated with hyperuricemia and gout.

A diagnosis of gout should prompt a search for the coexistence of these associated condition.

Treatment

Asymptomatic hyperuricemia in generally not treated but its identification should lead to a search for the cause and/or associated condition.

Episodes of acute gouty arthritis can be treated with colchicine, NSAID, systemic or intraarticular steroid and adrenocorticotropic hormone.

Prophylaxis against acute attack with colchicine or NSAID can be effective but does not change the underlying process in the absence of concomitant urate lowering therapy.

Starting of urate lowering therapy after a single attack *of gout remains* ***debatable*** *but—(a)* ***recurrent attack*** *of gout, (b)* ***urate nephrolithiasis****, (c)* ***tophaceous gout*** *and/or (d)* ***evidence of gout-induced joint damage*** *are all* ***strong indication for urate lowering therapy***.

Xanthine oxidase inhibitors and uricosurics are effective agent for lowering serum urate level.

Uricases with **pegloticase** are reserved for refractory tophaceous gout.

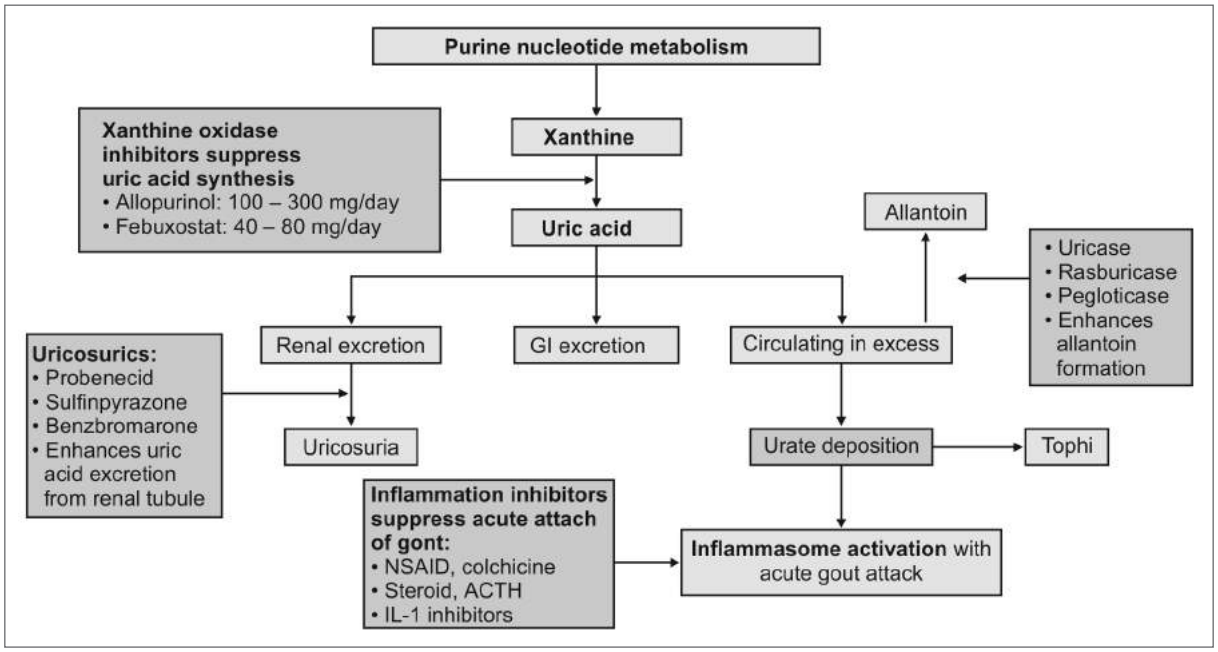
Target urate level is 6 mg/dL.

Prophylaxis with colchicine, NSAID *or less preferably systemic steroids should continued for* ***6 months after initiation of urate lowering therapy***.

Long term complication with the treatment regimen remains a major controversy.

Lifestyle modification is also helpful in the control of gout like—(a) **reduction of alcohol** consumption, (b) **management of obesity** and (c) **hyperlipidemia**.

Flowchart. 55.1: Purine metabolism and development of gout and drug interfering at different level preventing the development of gout



Chapter 56

Rheumatoid Arthritis

DEFINITION

Rheumatoid arthritis (RA) is a chronic multisystem disease with symmetrical arthritis of unknown etiology.

Although there are variety of systemic manifestation, characteristic features of RA is p**ersistent inflammatory synovitis involving peripheral joints in a symmetric distribution**.

Pathogenesis

- Rheumatoid arthritis is a disease of unknown etiology
- Importance of genetic susceptibility comes from the high concorda nce rate in the monozygotic twin and increased frequency of the disease among the 1st degree relative of RA patient
- HLA-DR4 is the major susceptibility haplotype but HLA-DR1 and HLA-DW15 are common among Indians
- More specifically susceptibility is associated with a shared epitope of specific amino acid sequence on the B–I chain (of a number of Class–II alleles located in 3rd allelic hypervariable region) of HLA–DR B–I between amino acid residue 67 and 74 which flank the 'T' cell recognization site
- Female gender is at increased risk specially during post-partam and breastfeeding. No infectious agent could be incriminated. Cigarette smoking is a risk factor
- Whatever be the initiating stimulus, RA is characterized by persistent cellular activation, autoimmunity and immune complex at articular and extraarticular lesions

Pattern of onset with clinical features

Typical presentation of RA are as follows:

a. **Palindromic**—Monoarticular attacks lasting for 24–48 hours. 50% progress to other types of RA, particularly those with HLA-DR4
b. **Transient**—Self-limiting disease lasting <12 months living no permanent joint damage. Usually sero-negative for IgM rheumatoid factor

Contd...

Contd...

c. **Remitting**—There is a period of several years during which the arthritis is active but then remits living minimal damage
d. **Chronic persistent**—The most typical form either seropositive/seronegative for IgM RF. The disease follows a relapsing and remitting course.
   seropositive patient develops greater joint damage and greater long-term disability
   - *Arthritis robustus*—It is not an unusual presentation characterized by proliferative synovitis often with deformity which causes little pain and less disability. Patient are either manual labor or athlete. Osteopenia is unusual. New bone formation is common. Bulky subcutaneous nodule or subchondral cyst may develop
   - *Rheumatoid nodulosus*—Clinical picture include recurrent pain and swelling of different joint. Radiologically there is subchondral bone cyst and rheumatoid nodule present
e. **Rapidly progressive**—Disease progresses rapidly over a few year develops joint damage and disability within a short period of time. Usually seropositive with high incidence of systemic complication
   - Pain, swelling and tenderness initially poorly localized to joint and which is aggravated by joint movement. It is the most common manifestation of RA
   - Generalized stiffness is frequent and greatest after inactivity. Morning stiffness >1 hour duration is one of the important diagnostic criteria
   - RA is a chronic polyarthritis and in two-third patient it begins insidiuously with fatigue, weakness, anorexia and vague musculoskeletal symptoms which may persist for few weeks/months.
   - Specific symptoms appear gradually, as joints of hands, knee, wrist and feet are involved in symmetrical fashion

Hand and Wrist Deformities in Rheumatoid Arthritis

With persistent inflammation a variety of characteristic deformitis are seen in hand which include the followings:

a. *Radial deviation at wrist with ulnar deviation of digits—Often with palmar subluxation of proximal phalanges called* **'Z' deformity**.
b. *Hyperextension of PIP joint with compensatory flexion of DIP joint called* **'Swan-neck' deformity Fig. 56.2**.

Fig. 56.2: Rheumatoid arthritis hyperextension of PIP with flexon of DIP/Swan neck deformity

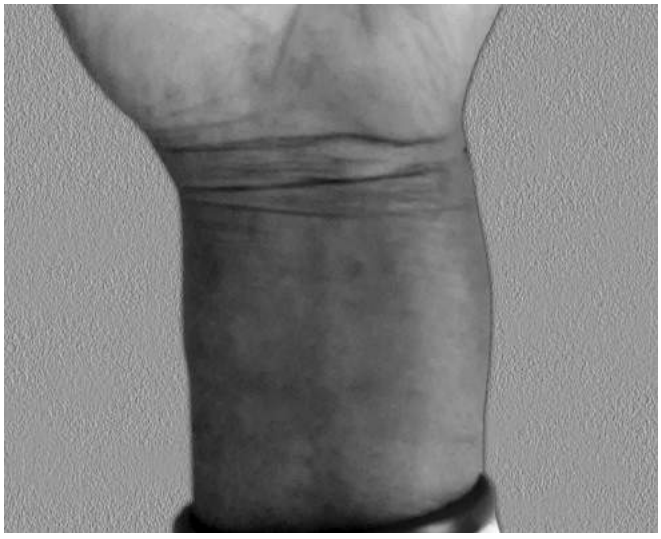


Fig. 56.1: Swelling above wrist due to synovitis

Fig. 56.3: Swelling of MCP and PIPgt in rheumatoid arthritis

c. *Flexion contracture of PIP joint and extension of DIP joint called* **'Boutonniere deformity'** *or* **'button-hole deformity'.**
d. *Hyperextension of 1st IP joint and flexion of 1st MP joint* with a consequent loss of thumb mobility and pinch.
e. *Dorsal subluxation of ulnar styloid process* contributes to the rupture of 4th and 5th extensor tendon.
f. *Triggering of fingers* is due to nodule on flexor tendon sheath.
g. *Synovial swelling* on the dorsum of hand and wrist (56.1).
h. *Carpal tunnel syndrome*.

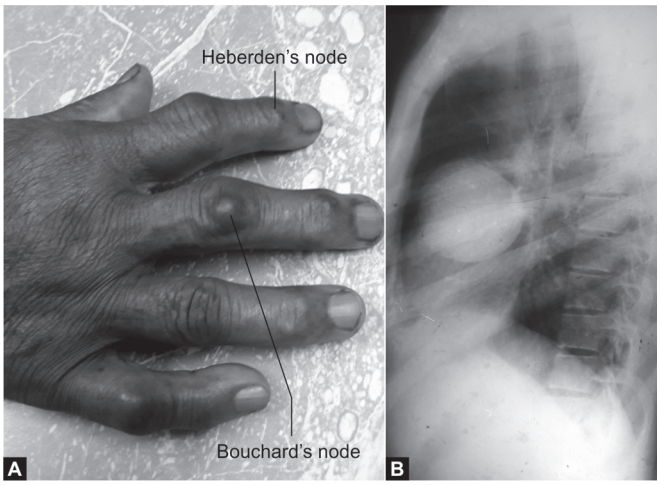


Fig. 56.4A and B: Heberden's node and Bouchard's node

Shoulder Joint

Initially RA can mimic *tendinitis and painful arc syndrome*, later *global stiffness* occurs or the rotator cuff may tear.

Elbow Joint

Synovitis may result in painful fixed flexion deformity.

Knee Joint

Massive synovitis and effusion in the knee joint which responds to aspiration and steroid injection. A persistent effusion leads to formation of popliteal cyst (**Baker's cyst**).

Foot and Leg

In the forefoot there is dorsal subluxation of MP joint results in '**cock-up deformity**'.

In the hind foot **calcaneovalgus (eversion)** deformity is most common due to **damage of ankle** and **subtalar joint**. This is often associated with loss of longitudinal arch (**flatfoot**) due to **rupture of tibialis posterior tendon**.

Spine

Usually upper part of cervical spine is involved resulting in **subluxation of atlantoaxial joint** with **features of cord compression**. Lumbar spine is not involved.

Hip Joint

Hip joint is rarely involved. Juxtaarticular osteoporosis which permits medial migration of acetabulum (**protrusio acetabuli**).

Rare joints involved in rheumatoid arthritis

- Atlantoaxial.
- Temporomandibular joint
- Cricoarytenoid joint
- Sternoclavicular joint
- Manubriosternal joint
- Hip joint producing protrusio acetabuli.

EXTRAARTICULAR MANIFESTATION OF RA

1. **Musculoskeletal manifestation**
   - Muscle waisting
   - Tenosynovitis and bursitis
   - Osteoporosis.
2. **Vasculitic manifestatio**n
   - Digital arteritis.
   - Ulcer.
   - Pyoderma gangrenosa.
   - Mononeuritis multiplex due to involvement of vasa nervosum.
   - Visceral arteritis.
3. **Hematological manifestation**
   - Anemia
   - Thrombocytopenia
   - Eosinophilia.
4. **Lymphoreticular manifestation**
   - Splenomegaly
   - Felty's syndrome
5. **Cardiac complications**
   - Pancarditis—Pericarditis, myocarditis and endocarditis.
   - Pericardial effusion.
   - Conduction defect.
   - Coronary vasculitis.
6. **Pulmonary manifestation**
   - Nodule—Rheumatoid nodule with/without cavity.
   - Broncheolitis.
   - Fibrosing alveolitis.
   - Pleural effusion—with low glucose <10 mg/dL.
   - Granulomatous pneumonitis.
   - **Caplan's syndrome**—Coexistence of seropositive RA and a rounded fibrotic peripherally located pulmonary nodule (0.5–5 cm in diameter) in patient with coal miner's pneumoconiosis following silica exposer is called *Caplan syndrome*.

     Pulmonary nodule may appear singly or in cluster that coalesces. Single nodule may appear as coin lesion. *Caplan's syndrome* in which pneumoconiosis and RA synergistically produces a violent fibroblastic reaction with obliterative granulomatous fibrosis which has now become rare due to improved mining operation of the present time. Nodule may cavitate producing bronchopleural fistula.
7. **Neurological manifestation**
   - Cervical cord compression
   - Compressive neuropathy
   - Peripheral neuropathy
   - Mononeuritis multiplex.
8. **Ocular manifestation**
   - Episcleritis
   - Scleritis
   - Scleromalacia
   - Keratoconjunctivitis sicca.
9. **Systemic manifestation**
   - Fatigue
   - Weight loss
   - Fever.
10. **Rheumatoid nodule**—Causing sinus and fistula on the overlying skin.
11. **Amyloidosis**.

Table 56.1: Classification criteria for rheumatoid arthritis (ACR-EULAR criteria)

Joint involvement	Type of joint	Score
	1 large joint (shoulder, elbow, knee, hip and ankle)	**0**
	2–10 large joints	**1**
	1–3 small joints (MCP, PIP, MTP, wrist, thumb and IP)	**2**
	4–0 small joints	**3**
	>10 joints with at least one small joint	**5**
Serology	**Negative RF and negative anti- CCP**	**0**
	Low positive RF and anti-CCP (<3 times of upper limit of normal)	**2**
	High positive RF and anti-CCP (>3 times of upper normal limit)	**3**
Acute phase reactant	**Normal ESR/CRP**	**0**
	Abnormal ESR/CRP	**1**
Duration	<6 weeks	**0**
	>6 weeks	**1**

DIAGNOSIS OF RHEUMATOID ARTHRITIS

A score ≥6 fulfils the requirements of diagnosis of RA.

Investigation

- **RF—**Rheumatoid factor (IgM type) positive in 75–80% patient.
- **Anti-CCP** positive is 80% but specificity is 95%. Positive anti-CCP (cyclic citrullinated peptide) associated with worst outcome.
- **Synovial fluid**—Cell count 5,000–50,000 WBC/cmm with neutrophil predominance. Synovial fluid is positive for RF and anti-CCP but does not contain urate or oxalate crystal.
- High ESR and CRP.

X-ray

The typical radiographic picture of RA are as follows:

- Periarticular osteopenia (within 6 months) with marginal nonproliferative erosions within 1 year.
  - **USG** is useful to visualize periarticular structure, soft tissue and tendon.
    It also helps to guide local injection of steroid.
    Quantitative bone density estimation.
  - **MRI**—Most sensitive for diagnosis specially with gadolinium bone scan for detecting synovitis, effusion and bone marrow change which develop before they are detected in X-ray.
  - **Bone scintigraphy**—With TC99 for abnormal bone tumor and differentiate among areas of inflammation, infection and malignancy.
  - **Dexas scan**—Measures bone density used for screening and monitoring osteoporosis.

Rheumatoid Factor

- It is an autoantibody of either IgG/IgM or IgA class against the Fc portion of a IgG antibody (antibody against antibody).
- IgM rheumatoid factor is commercially used for detection of rheumatoid arthritis.
- RF is present in almost 80% of patients with RA but it can also be present in many other conditions related or unrelated to musculoskeletal disorder.

KEY POINT IN THE PLAN OF TREATMENT OF RHEUMATOID ARTHRITIS

- Diagnose RA as early as possible and initiate DMARD therapy at the point of diagnosis.

A. RF present in musculoskeletal disorder
1. RA—80%
2. Sjögren's syndrome—75–95%
3. Mixed connective tissue disorder—50–60%
4. Type II essential mixed cryoglobulinemia— 40–90%
5. PSS—20–30%
6. SLE—15–30%

B. RF associated with other unrelated conditions
1. Age >60 years (1–5%)
2. Infection—Mumps, TB, SABE (sub-acute bacterial endocarditis and syphilis
3. Chronic liver disease (HBV and HCV)
4. Sarcoidosis
5. ILD (interstitial lung disease)
6. Primary biliary cirrhosis
   - Presence of RF is one of the seven criteria for diagnosis of RA laid by ARA (American Rheumatological Association)
   - RF is also a good screening test for Sjögren's syndrome and cryoglobulinemia
   - Titer of RF correlates with extraarticular manifestation/disease severity but does not correlate with disease progression

- For most patient **methotrexate in the cornerstone of DMARD therapy**.
- Many effective biologic DMARD are available, all **are more effective with methotrexate**.
- Treat all patient to a disease activity—remission or low disease activity.
- NSAID may provide useful symptom control but are rarely indicated without DMARD.
  - **NSAID**—Once it was viewed as the core of all other therapies but its use has been restricted due to side effects like gastritis, peptic ulcer and renal impairment. All NSAID are almost equivalent in their efficacy.
  - **Glucocorticoid**
    - It may be administered to achieve rapid disease control as bridge up therapy before the onset of effective DMARD therapy.

- 1–2 weeks brust of glucocorticoid may be prescribed for the management of acute disease flair.
- Chronic administration 5–10 mg/day prednisolone may be warranted in patient with inadequate response to DMARD therapy. Benefit of this approach must be weighted against risk of osteoporosis and other long-term complications. Osteoporosis can be prevented by bisphosphonate who are receiving prednisolone (5 mg/day) for more than 3 months.

– **Conventional DMARD (disease-modifying antirheumatoid drug, Table 56.2)**—They include —(a) Methotrexate, (b) hydroxychloroquine, (c) sulfasalazine, (d) leflunomide. They exihibit a delayed onset of action (6–12 weeks).
  - **Methotrexate** (MTX) (10–25 mg/week oral or IM) is the DMARD of choice for treatment of RA. It is the anchor drug for most combination therapy.
  - **Leflunomide** (LEF) (inhibitor of pyrimidine synthesis)—Clinical efficacy is similar to methotrexate (10–20 mg/day).
  - **Hydroxychloroquine** (HCQ) (200–400 mg)—For treatment of mild and early disease. It does not delay the radiographic progression of disease.
  - **Sulfasalazine** (SSZ) (1–3 gm/day) can reduce the radiographic progression of disease.

    Other DMARDS are *goldsalt*, *penicillamine*, *azathioprine*. *Cyclosporin* are sparingly used due to inconsistent efficacy and toxic effect.
– **Biological DMARD** (Table 56.2)
  - **Anti-TNF agent** *(antibody to TNF receptor protein ETAN)* —
    - » *Infliximab*—3 mg/kg IV at 0, 2, 6 then 8 weeks interval.
    - » *Etarnacept TNF type-II receptor fused with IgG-1* —50 mg SC weekly.
    - » *Golimumab*—50 mg SC monthly.
    - » *Adalimumab (Fully human antibody to TNF)*—40 mg SC alternate week.
    - » *Cetrolizumab (pegylated fab fragment)*—400 mg SC on 0, 2, 4 weeks, then 200 mg every alternate week.
  - **Abatacept (kill/inhibit 'T' cell)**—Fusion protein of CTLA-4 with modified human IgG. (500–750 mg IV 0, 2, 4 weeks then 4 weekly).
  - **Rituximab**—Antibody against CD-20 mature lymphocyte (1000 mg IV on day 0, 14).
  - **Anakinra (kill CD-20)**—Recombinant IL-1 receptor antagonist (100 mg SC daily) should not be combined with other anti-TNF drug.
  - **Tocilizumab**—Monoclonal antibody against IL-6 (8 mg/kg IV monthly).

Table 56.2: List of DMARD

	Conventional DMARD		Biologic DMARD
1.	Methotrexate	1.	Infliximab
2.	Hydroxychloroquine	2.	Etanercept
3.	Sulfasalazine	3.	Golimumab
4.	Leflunomide	4.	Adalimumab
5.	Azathioprine	5.	Certolizumab
6.	Minocycline	6.	Abatacept
7.	Cyclosporine	7.	Rituximab
8.	Penicillamine	8.	Anakinra
9.	Gold salt	9.	Tocilizumab
10.	Glucocorticoid (should never be used without DMARD)		

Plan of Treatment

Methotrexate is the drug of first choice can be started as monotherapy. If adequate improvement cannot be achieved with monotherapy, triple therapy with various type of combination DMARD are used in the treatment of RA.

- **Group 1—Sequential DMARD monotherapy**— Initial MTX 15 mg/week → MTX 25–30 mg/week → SSZ → LEF → (MTX + Infliximab).
- **Group 2—Step-up combination therapy**—Initial MTX 15 mg/week →MTX 25–30 mg/week → (MTX + SSZ) → (MTX + SSZ + HCO) → (MTX + SSZ + HCQ + Prednisolone) → (MTX + Infliximab).
- **Group 3—Initial combination therapy**—Initial MTX 7.5 mg/week + SSZ 2000 mg/day + Predniso- lone 60 mg/day (tapered to 7.5/day by 7 week) → MTX 25 mg/week to 30 week + SSZ + Prednisolone →MTX + CSA + Prednisolone → MTX + Infliximab.
- **Group 4**—Initial MTX 25–30 mg/week + Inflximab 3 mg/kg → Infliximab 6 mg/kg every 8 week → Infliximab 7.5 mg/kg every 8 week → Infliximab 10 mg/kg every 8 week.

CSA – Cyclosporin.

Criteria for remission of RA—It is defined as total absence of all articular and extraarticular inflammation and immunological activity related to RA.

Boolean-based definition—RA patient may be considered in remission if he/she meets the clinical and laboratory criteria listed in the table set at any point of time—

Index-based definition—At any point of time patient must have a disease activity index score ≤3.3.

- Number of tender joint ≤1
- Number of swollen joint ≤1
- CRP <1 mg/dL
- Patient global assessment ≤1 (on 0–10 scale)
  Or
- At any point of time, patient must have a simplified disease activity index score (SDAI) ≤3.3

DIFFERENTIAL DIAGNOSIS OF RHEUMATOID ARTHRITIS

1. SLE
2. Psoriatic arthritis
3. Reactive arthritis
4. Postinfections arthritis
5. Osteoarthritis (Table 56.3)
6. Crystal-induced arthritis.

FACTORS ASSOCIATED WITH POOR PROGNOSIS IN RA

1. Presence of rheumatoid factor at high titer.
2. Presence of anti-CCP antibody at high titer.
3. Presence of shared epitope (HLA DR alleles) and member of copies.
4. Presence of erosive disease at presentation.
5. Disease activity at presentation.
6. Magnitude of ESR and CRP elevation.
7. Presence of nodule or other extraarticular feature.
8. Female gender.
9. Smoker or exsmoker.
10. Obesity.

DIFFERENTIAL DIAGNOSIS OF FEVER WITH POLYARTHRITIS

- **Temperature >40°C**
  - Still's disease
  - Bacterial arthritis
  - SLE.
- **Fever preceding arthritis**
  - Viral arthritis
  - Lyme disease
  - Reactive arthritis
  - Still's disease
  - Bacterial endocarditis
- **Migratory arthritis**
  - Rheumatic fever
  - Gonococcemia
  - Meningococcemia
  - Viral arthritis
  - SLE
  - Acute leukemia
  - Whipple's disease
- **Effusion greater than pain**
  - TB arthritis
  - Bacterial endocarditis
  - IBD
  - RN
  - Giant cell arthritis
  - Lyme disease.
- **Pain greater than effusion**
  - Rheumatic fever
  - Acute leukemia

Table 56.3: Features differentiating RA from osteoarthritis

	RA	Osteoarthritis
• **Age of onset**	Childhood and adult Peak incidence in 50s	Increase with age
• **Predisposing factor**	HLADR4, HLADR1 PTPN PAD14 Polymorphism and smoking	Congenital abnormality Shallow acetabulum
• **Early symptom**	Pain increase after rest with morning stiffness	Pain increases through day and with use
• **Joints involved**	Metacarpophalangeal joint } commonly involved PIP joint wrist Distal interphalangeal joint—never	DIP with Heberden's node, hip and knee (weight bearing joint) are commonly involved
• **Physical finding**	Soft tissue swelling and warmth	Bony osteophytes minimal Soft tissue swelling
• **Radiologic finding**	Periarticular osteopenia and marginal erosion	Subchondral sclerosis and osteophytes
• **Laboratory finding**	Increased CRP, RF, anti-CCP antibody anemia and leukocytosis	Normal

  - ARDS
  - Familial mediterranean fever.
- **Positive test for RF**
  - RA
  - Viral arthritis
  - TB arthritis
  - Bacterial endocarditis
  - SLE
  - Sarcoidosis
  - Systemic vasculitis
- **Morning stiffness**
  - RA
  - Polymyalgia rheumatica
  - Still's disease
  - Some viral and reactive arthritis
- **Symmetric small joint arthritis**
  - RA
  - SLE
  - Viral arthritis
- Leukocytosis >15,000/cmm
  - Bacterial arthritis
  - Bacterial endocarditis
  - Still's disease
  - Systemic vasculitis
  - Acute leukemia
- **Leukopenia**
  - SLE
  - Viral arthritis
- Episodic occurrence
  - Lyme disease
  - Crystal-induced arthritis
  - IBD
  - Whipple's disease
  - Mediterranean fever
  - Still disease
  - SLE.

EXERCISE

Write short notes on

1. Hand changes in rheumatoid arthritis.
2. ACR–EULAR criteria for diagnosis/classification of rheumatoid arthritis.
3. Rheumatoid factor.
4. Treatment of rheumatoid arthritis.
5. Felty's syndrome.
6. DMARD.

Chapter 57

Felty's Syndrome

It refers to a subgroup of rheumatoid arthritis patient, who is chronically seropositive for nodular RA associated with splenomegaly and neutropenia and seen in <1% of RA patient.

CLINICAL FEATURES

The special clinical features are as follows:

- Splenomegaly
- Lymphadenopathy
- Skin pigmentation
- Keratoconjunctivitis sicca
- Subcutaneous nodule
- Vasculitis
- Recurrent infection and chronic leg ulcer
- Carpal tunnel syndrome
- Weight loss.

These features are present in association with the classical features of RA.

T-cell large granular lymphocyte leukemia (T-LGL) may have a similar presentation and often develop in association with RA, but it usually develops early in the course of RA.

RISK FACTORS

- Age >60 years
- Female > Male
- Black < Caucasian
- Long-standing RA
- Strongly positive RF
- <1% of RA patients develop Felty's syndrome
- Deforming but inactive disease.

DIAGNOSIS

- High titer of RF
- Neutropenia <1500/cmm with leukopenia
- Anemia
- Thrombocytopenia
- Abnormal LFT
- Abnormal cell-mediated and humoral immunity.

TREATMENT

- **Splenectomy** should be done along with treatment of RA.
- **Special**
  - **Splenectomy is indicated in case of**
    - *Hypersplenism as evidenced by*
      - » Severe granulocytopenia <500/cmm.
      - » Severe anemia.
      - » Severe persistent thrombocytopenia with or without hemorrhage.
    - *Chronic leg ulcer.*
    - *Recurrent serious infection.*

EXERCISE

Write short note:

1. Felty's syndrome

Chapter 58

Still's Disease

It is a seronegative variant of RA in children and young adult presenting with high fever associated with:

- Arthralgia
- Arthritis
- Myalgia
- Hepatosplenomegaly
- With or without pleurisy or pericarditis.
- Lymphadenopathy
- Evanescent skin rash
- Anemia
- Leukocytosis.

CLINICAL FEATURES OF ADULT ONSET STILL'S DISEASE

Adult onset Still disease have the following features:

- High spiking fever of quotidian variety temperature (touches the baseline at least once in 24 hours).
- Evanescent salmon/pink colored rash over trunk and extremity during febrile episode.
- Involvement with cervical spine with loss of neck mobility.
- Severe abdominal pain.
- Abnormal LFT consistent with hepatitis.
- Hypergammaglobulinemia (60%).
- Serum complement is high or normal.
- Serum ferritin >10,000 mg/mL. Glycosylated form of serum ferritin is low <16% which is normally >50%.

LABORATORY FEATURES

- Anemia
- Leukocytosis with neutrophilia
- Thrombocytosis
- Raised ESR >100 mm/hour
- Negative for rheumatoid factor.

DIAGNOSTIC CRITERIA FOR STILL'S DISEASE

Major Criteria

- Temperature >39°C for >1 week
- Leukocytosis >10,000/mm^3 with 80% PMN
- Typical rash
- Arthralgia >2 week.

Minor Criteria

- Sore throat
- Lymph node enlargement
- Splenomegaly
- Liver dysfunction (raised SGOT/SGPT).

For diagnosis of Still's disease 5 criteria of which at least one from major criteria must be present.

TREATMENT

- Good prognosis
- Responds to NSAID or steroid or DMARD.

EXERCISE

Write short note:

1. Still's disease.

Chapter 59

Sjögren's Syndrome

INTRODUCTION

The clinical hallmark of Sjögren's syndrome (SS) are **keratoconjunctivitis sicca** (KCS) (dry eye), **xerostomia** (dry mouth) and **parotid gland swelling**.

Sjögren syndrome is divided into primary and secondary form. The primary form occurs in approximately 0.1–0.6% of the general population.

Extraglandular features of primary Sjögren's syndrome include **fatigue**. **Raynaud's phenomenon, polyarthralgia/polyarthritis, ILD, neuropathy and purpura**.

Classification Criteria for Sjögren's Syndrome

- **Ocular symptoms**
  - Dry eyes for more than 3 months
  - Sensation of sand and gravel in the eye
  - Use of tear substitute more than 3 times/day.
- **Oral symptoms**
  - Dry mouth for more than 3 months.
  - Recurrently or persistently swollen salivary gland.
  - Frequently drink liquid to aid in swallowing dry food.
- **Ocular sign**—Positive result for one of the following tests:
  - Schirmer's-1 test performed without anesthesia ≤5 mm in 5 minutes.
  - Rose Bengal score or other ocular dye score ≥4.
- **Histopathology of minor salivary gland**—Focal lymphocytic sialoadenitis >50 lymphocyte/4 mm^2 of glandular tissue.
- **Salivary gland involvement**
  - Unstimulated whole salivary flow <1.5 mL in 15 minutes.
  - Parotid sialography show diffuse sialectasis without any obstruction in the major duct.
  - Scintigraphy shows delayed uptake, reduced concentration and delayed excretion of tracer.
- **Autoantibodies—**Presence of antibody to Ro (SSA) or LA (SSB) antigen or both.

Any four out of six items along with item IV and VI or any three of item no. III, IV, V and VI are diagnostic of primary SS.

Diagnosis of Primary Sjögren's Syndrome

A diagnosis of primary Sjögren syndrome is made by subjective and objective assessment of **dry eyes** and **dry mouth** and by the presence of:

- Serum antinuclear antibodies
- Anti-RO/SSA antibodies
- Anti-La/SSB antibodies
- Labial salivary gland biopsy.

Diagnostic Criteria for Secondary Sjögren's Syndrome

Presence of well defined connective tissue disease with item I or II plus any two of the III, IV and V are diagnostic of secondary SS.

Treatment of Sjögren's Syndrome

Treatment of Sjögren's syndrome aims to provide symptomatic improvement in the symptoms of dry eyes and dry mouth and control of extraglandular manifestation of the disease.

- **Dry eye (KCS)**—Avoid dry environment
  - Tear supplement
  - Punctal occlusion
  - Ophthalmic cyclosporin.
- **Dry skin**—Avoid abrasive soap
  - Skin moisturizers
  - Emollient with urea/lactate.

- **Vaginal dryness**—
  - Vaginal moisturizer
  - Vagina lubricant
  - Estrogen cream.
- **Xerostomia (dry mouth)**
  - Topical fluoride for teeth
  - Sugarless candy/gum
  - Saliva substitute
  - Pilocarpine/cevimeline
  - Treatment of oral candidiasis.
- **Extraglandular disease**
  - Mild diseaseNSAID and HCQ
  - Moderate/severe disease Corticosteroid ±
  - MTX, AZA, MMF and CYC.

EXERCISE

Write short note on:

1. Dianostic criteria and treatment of Sjögren's syndrome.

Chapter 60

Juvenile (Rheumatoid) Idiopathic Arthritis

INTRODUCTION

Juvenile (Rheumatoid) idiopathic arthritis (JIA/JRA) have three types of clinical presentation:

1. Pauciarticular onset (60%)
2. Polyarticular onset (30%)
3. Systemic onset (10%).

PAUCIARTICULAR JRA [<4 JOINTS ARE INVOLVED (60%)]

Type 1

- Female predominate over male.
- Onset in between 3–5 years.
- Knee, ankle and elbow are most commonly involved.
- Joint swelling is greater than joint pain.
- About 25% patients develop iridocyclitis which may lead to blindness.
- Blindness preventable.
- Good prognosis but with asymmetric limb growth and localized deformity.

Type 2

- Male predominate over female.
- Onset above 8 years.
- Large joints of lower extremity are usually involved.
- Joint swelling is greater than joint pain.
- Those who are HLA B_{27} positive develop ankylosing spondylitis in later life.
- Iritis may develop but not so severe.

POLYARTICULAR JRA

[>5 JOINTS ARE INVOLVED (30%)]

- Joint pain is greater than joint swelling.
- Fever and malaise are significant.
- More than 5 joints are involved within first 6 months.

This can be subdivided into two subtypes:

a. Polyarticular JRA with positive rheumatoid factor.
b. Polyarticular JRA with negative rheumatoid factor.

Polyarticular JRA with Positive Rheumatoid Factor

- Age of onset—Late.
- Clinical features are that of adult rheumatoid arthritis.
- Rheumatoid nodule indicates severe diseases.
- Produces erosive deforming arthropathy if not aggresively treated early.
- Respond to treatment is unpredictable.

Polyarticular JRA with Negative Rheumatoid Factor

- It can develope at any age.
- Knee, wrist and hip are commonly involved.
- Rheumatoid nodule usually absent.
- Good prognosis with minimal residual joint involvement.

SYSTEMIC ONSET JRA (10%)

- Age of onset—Any age.
- Acute onset with systemic features precede joint involvement.
- Common in male.
- Usually present with PUO with double pick (39°–40°C).
- Maculopapular rash with central clearing.
- Hepatosplenomegaly with lymphadenopathy.
- Pericarditis with interstitial lung disease.
- ANA—Positive
- RF—Negative.
- Course—Variable—in 50% patients remission with minor residual damage.

Those who are HLA DR4 positive have progressive arthritis or recurrent episode of systemic disease.

EXERCISE

Write short note on:

1. Juvenile idiopathic arthritis.

Chapter 61

Systemic Lupus Erythematosus

DEFINITION

It is an *autoimmune inflammatory multisystem connective tissue disease* characterized by presence of *numerous autoantibodies, circulating immune complexes* and *widespread immune-mediated tissue damage.*

Onset is more common in 2nd and 3rd decade of life with F : M ratio of 9 : 1.

Etiology and pathogenesis

- The exact pathogenetic mechanism is unknown and caused by interaction between susceptibility gene and environmental factor resulting in abnormal immune response
- Susceptible genes are HLA-D8, DR3 and DR2. In addition to that there is inherited deficit of C_2, C_4 which are in linkage disequlibrium with HLA-DR2 and DR3
- Functional deficiency of C_{1q} is also associated. This genetic abnormalities lead to hyporeactivity and hypersensitivity of T and B lymphocyte to self-antigen results in polyclonal T and B cell activation, which leads to formation of autoantibody against intracellular and intranuclear (component) antigen
- Although the trigger which leads to autoantibody production against nuclear antigen in SLE are unknown but the possible mechanism may be the spill over of intranuclear and intracellular antigen during apoptysis. This hypothesis is supported by the fact that environmental factors (exposure to sunlight, UV ray, pregnancy and infection) that are associated with flair of SLE which causes increase oxidative stress and subsequent apoptysis

CLINICAL FEATURES

A. Systemic manifestations
- Fatigue
- Malaise
- Fever
- Anorexia
- Weight loss.

B. Musculoskeletal manifestations
- Nonerosive polyarthritis (mild to severe)
- Arthralgia and myalgia
- Myopathies and myositis.

Jaccoud's like arthropathy

- This joint deformity of hand such as ulnar drift of metacarpophalangeal joints, swan neck and Boutonniere deformities and hyperextension of interphalangeal joint of thumb closely resemble the deformities seen in rheumatoid arthritis or that develop in patient with a history of rheumatic fever are caused by laxity of joint capsule and ligament are also seen in SLE

C. Mucocutaneous manifestations
- Photosensitivity (80%)
- Malar rash (50%)
- Oral ulcer (40%)
- Discoid rash (DLE) (20%)
- Alopecia (40%)
- Vasculitis (20%)
- Articaria and SCLE (15%)
- Raynaud's phenomenon
- Livedo reticularis.

- **DLE (discoid lupus erythematosus)**—Discoid lesions are roughly circular encircled with slightly raised scaly hyperpigmented erythematous rim with depigmented atrophied center in which all dermal appendages are permanently destroyed. Lesions are disfiguring particularly on face and scalp.
  Treatment
  1. Local corticosteroid
  2. Systemic antimalarial

Contd...

Contd...

- **Butterfly malar rash—**Slightly raised erythema occasionally scaly on face specially on cheeks and nose—butterfly rash; also involves ears, chin, V regions of neck, upper back and extensor surface of arm. Worsening of rash accompanies flairs of SLE. Many other rashes seen infrequently with SLE include
  a. Recurrent urticaria
  b. Lichen planus-like dermatitis
  c. Bulae
  d. Panniculitis (lupus profundus)

  Rashes of SLE may be minor to very severe and may be the major disease manifestations.
- **SCLE (subacute cutaneous lupus erythema)**—Consists of scally red patches similar to psoriasis or circular red rimmed lesion.
- **Others**—Small painful ulceration on oral or nasal mucosa (oral ulcer resembles aphthous ulcer indicative of disease activity)

D. Renal manifestations—It is the most serious manifestation of SLE and leading cause of death in the first decade of SLE.

– As SLE nephritis may be asymptomatic, urine analysis must be done in all cases of SLE at diagnosis and thereafter at an interval of 6–12 months.

- **WHO histopathologically classified SLE nephritis into six classes**
  – **Classes I**—No histologic changes by light microscope but **mesangial immune deposit** by immunofluorescence
  – **Class II—Proliferative changes** confined to **mesangium either cellular proliferation or matrix deposition**
  – **Class III—Focal proliferative changes** in the tuft of 10–50% glomeruli with **focal subendothelial immune deposit**
  – **Class IV—Diffuse proliferative glomerulonephritis** (DPGN) affecting >50% glomeruli with **diffuse sub-endothelial immune deposit**
  – **Class V**—Predominantly **membranous change** with various degrees of proliferation with segmental/global **subepithelial immune deposit**
  – **Class VI**—End stage—sclerotic glomeruli
- **Clinical manifestations of SLE nephritis**
  a. **Nephritic syndrome** accounts for 30–40% patient
  b. **Subnephrotic proteinuria** (30–50%) (>300 mg –3.5 g/24 hour with pus cell and RBC)
  c. **Nephrotic syndrome** (25%) (>3.5 g/24 hour)
  d. **RPGN** present in 10%
  e. **End-stage renal disease (ESRD)**—[5–10%]

Contd...

- **Correlation between histopathological classification and clinical manifestation**
  – **Mesangial nephritis** (stage I and II) have proteinuria <1 g/day with or without hematuria but no cellular cast
  – **Proliferative lupus nephritis** (stage III and IV) have nephritic urine sediment (various degree of proteinuria often at nephrotic range) low C_3 and high anti-ds DNA
  – **Membranous glomerulopathy** (stage V) have nephrotic range proteinuria with unremarkable urine sediment C_3 normal anti-ds DNA is low

E. Hematological manifestations

1. The most frequent hematological manifestation is **anemia** (70%) of normocytic and normochromic variety.

   Causes of anemia are—
   a. Anemia of chronic infection.
   b. Coombs' positive hemolytic anemia—which can be treated by high dose steroid.
2. **Leukopenia** (<4000/mL)—It is present in 65% patient and almost always associated with lymphopenia but not granulocytopenia. It rarely predisposes to infection and does not per se require any therapy.
3. **Lymphopenia (<1500/mL)**—It present in 50% SLE patients.
4. **Thrombocytopenia (<100,000/mL)**—It present in 15% patients.

   It may be a recurring problem—if count > 40000 abnormal and spontaneous bleeding is absent. High dose glucocorticoid (prednisolone 1 mg/kg/ day) is effective for first few episodes of thrombocytopenia.
5. **Lymphadenopathy** is present in 15% patients.

- Recurring or prolonged anemia with thrombocytopenia who is nonresponder to high dose steroid; requires additional therapy of cyclosporin (3–5 mg/kg/day). Though nephrotoxic but cyclosporin may have to be used for resistant pancytopenia unresponsive to steroid or when pancytopenia is a serious complication of other cytotoxic drugs used in the treatment of SLE

6. **Splenomegaly** is also present in 15% patients.

F. Neuropsychiatric manifestations of SLE (NPSLE)—It is one of the major causes of morbidity and mortality in SLE patient.

Risk factor for neuropsychiatric manifestations

– Generalized SLE.

- Previous major NPSLE manifestations.
- Moderate to high titer of aPL antibody.

Most neuropsychiatric manifestation develop at the onset within first 2–4 years after diagnosis of SLE and common with generalized lupus activity.

- **Cognitive disorder**—Associated with 50% patients. Difficulty with memory and reasoning.
- **Mood disorder**—Present in 40% patients.
- **Headache (25%)**—When excrutiating indicates SLE flair.
- **Seizure of any type**—Present in 20% patients.
- **Mono/polyneuropathy**—Present in 15% patients.
- **Strokes and TIA**—Usually seen in 10% of SLE patients.

Causes of TIA

1. Focal occlusion (either noninflammatory or with associated vasculitis)
2. Embolization from carotid artery plaque or fibrinous vegetation of Libman-Sacks endocarditis

- **Acute confusional state and movement disorder**—(5%).
- **Aseptic meningitis and myelopathy**.

Diagnosis of neuropsychiatric manifestation is done by—

- **MRI** which helps to identify—Ischemic, thrombotic and demyelinating or infectious process.
  T_2 weighted bihemispheric white matter lesions ≥5 in number ≥6–8 mm in size is diagnostic of SLE.
  CSF study—Exclude CNS infection (but mild abnormalities are common in NPSLE).
- **EEG** to diagnose seizure disorder.
- **NCV** for peripheral neuropathy.
- Neuropsychologic test for cognitive's dysfunction.

G. Cardiopulmonary manifestations—(60%)

- Pleurisy and effusion
- Pericarditis and effusion
- Myocarditis
- Endocarditis (Libman-Sacks fibrinous endocarditis)
- Lupus pneumonia
- Coronary artery diseases and AMI (due to accelerated atherosclerosis without
  a. Hypertension
  b. Dyslipidemia
  c. APLA syndrome
  d. Younger age group
- Interstitial lung diseases
- Pulmonary hypertension and ARDS.

H. Gastrointestinal manifestations

- Nausea.
- Abdomen pain.
- Diarrhea.
- Abnormal liver enzyme → indicates active disease.
- Vasculitis leads to perforation, ischemia, bleeding and sepsis.
- Ascites.
- Budd-Chiari syndrome.

I. Thrombosis can occurs both in vein and artery

- Venous (15%)
- Arterial (10%).

J. Ocular manifestations

- Sicca syndrome (Sjögren's syndrome)
- Conjunctivitis
- Episcleritis
- Vasculitis

DIAGNOSIS

ACR Criteria for Diagnosis of SLE

1. **Malar rash**—Fixed erythema, flat or raised, over the malar eminences and sparing nasolabial fold.
2. **Discoid rash**—Erythematous raised patches with adherent keratotic scale and follicular plugging, atropic scarring may occur in older lesion.
3. **Photosensitivity**—Skin rash due to unusual reaction to sunlight.
4. **Oral ulcer**— Painless oral or nasopharyngeal ulcer.
5. **Arthritis**—Nonerosive arthritis involving two or more peripheral joints characterized by tenderness, swelling and effusion.
6. **Serositis**
   a. *Pleuritis*—History of pleuritic chest pain/clinically rub/CXR-pleural effusion.
   b. *Pericarditis*—Documented by ECG, rub and echo evidence of effusion.
7. **Renal disorder**
   a. Persistent proteinuria >0.5 g/day/>3+ if quantification cannot be done.
   b. Urinary cast—It may be RBC/Hb/granular/WBC tubular or mixed.
8. **Neurologic**
   a. Seizure in absence of offending drug or known metabolic derangement.
   b. Psychosis —In absence of offending drug or known metabolic derangement like uremia, acidosis and electrolyte imbalance.
9. **Hematologic disorder**
   a. Hemolytic anemia with reticulocytosis
   b. Leukopenia <4000/cmm
   c. Lymphopenia <1500/cmm
   d. Thrombocytopenia <100,000/cmm.
10. **Immunologic disorder**
    a. Presence of anti-ds-DNA antibody.
    b. Presence of anti-Smith antibody to Sm nuclear antigen.
    c. Presence of antiphospholipid antibody

i. Presence of anticardiolipin antibody
ii. Presence of lupus anticoagulant.
iii. Presence of anti $\beta_2$microglobulin.

d. False-positive—Treponema pallidum immobilization test or fluorescent Treponemal antibody absorption test.

11. **Positive test for antinuclear antibody**—Raised titer of ANA by immunofluorescence (HEP-2 method) in the absence of drug known to cause drug-induced SLE.
    - *A person diagnosed as having SLE if any four out of this eleven criteria either serially/simultaneously present on two separate occasions.*
      – Specificity—95%
      – Sensitivity—75%.

LABORATORY INVESTIGATIONS IN SLE PATIENT

Investigations to diagnose SLE

Various antibodies are present in SLE

a. **ANA**—(specially by HEP–2 method) (for diagnosis of SLE)
   – It has 98% sensitivity
   – It is the best screening test
   – Repeated negative test rules out SLE.
b. **Anti-ds DNA antibody** (for diagnosis of SLE)
   – It is highly specific
   – It has 70% sensitivity
   – It correlates with disease activity.
c. **Anti-Sm antibody** (for diagnosis of SLE)
   – It has 25% sensitivity
   – It is specific for SLE.
d. **Anti-Ro (SS-A) antibody** (for diagnosis of SLE)
   – It is not specific for SLE
   – It is associated with
     – Sicca syndrome.
     – SCLE.
     – Neonatal lupus with congenital heart block.
     – Decreased risk of nephritis.
e. **Anti-La (SS-B) antibody**—Same as *Anti-Ro (SS-A)*.
f. **APLA**—(Antiphospholipid antibody) Present in 50% SLE patient.
   (Three test are available for detection of anti-phospholipid antibody).
   – ELISA for *anticardiolipin* antibody.
   – ELISA for *anti-β_2 GP-1* (glycoprotein) antibody estimation.
   • Increase APTT with DRVVT. (diluted Russell viper venom) for *lupus anticoagulant*.

APLA syndrome is associated with fetal loss, increased arterial/venous thrombosis and thrombocytopenia

- APLA is considered positive if two of the three above antibody are positive.

g. **Antiribosomal-P antibody** (for diagnosis of SLE)
   – It has 20% sensitivity.
   – It correlates with depression and psychosis in CNS lupus.
h. **Antineuronal antibody** (for diagnosis of SLE)
   – It has 60% sensitivity
   – It correlates with active lupus.
i. **Antihistone antibody (70%)**—More frequent in drug-induced SLE.
j. **Anti (U-1) RNP antibody (40%)**—Not specific for SLE and high titer associated with overlap syndrome.
k. **Antierythrocyte antibody (60%)**—Measured by direct Coombs test.
l. **Antiplatelet antibody (30%)**—Associated with thrombocytopenia but sensitivity and specificity are not good.

INVESTIGATIONS FOR DETECTION OF COMPLICATION OF SLE

Blood is Examined

- For evidence of anemia, leukopenia, lymphopenia, thrombocytopenia.
- Raised ESR and CRP.
- Coombs test is done for diagnosis of autoimmune hemolytic anemia.

Histopathology

Biopsy from skin and kidney demonstrate the diagnostic features of SLE skin manifestation and SLE nephropathy described previously.

CT/MRI

CT/MRI of brain to detect infarct, hemorrhage, cerebral atrophy or white matter disease as complication of SLE.

Chest X-ray, Echo and ECG

For detection of cardiopulmonary involvement.

MANAGEMENT

There is 'no-cure' for SLE and complete sustained remission is rare.

So our aim is to control acute severe flair and develop maintenance strategy.

SPECIFIC TREATMENT FOR SLE MANIFESTATION

- **Skin manifestation of SLE respond to**
  – Sun exposure prophylaxis.
  – Topical glucocorticoids (fluocinonide 0.05%)—In refractory to topical therapy for skin disease.
  – **Hydroxychloroquine (antimalarial) (HCQ—6.5 mg/kg)** alone or in combination with oral glucocorticoid 20 mg/day may be used. HCQ was

HCQ – 6.5 mg/kg will reduce
i. Skin and joint manifestation
ii. Adjuvant treatment for achieving remission
iii. Moderate reduction is glucocorticoid dose
iv. Greater than 50% reduction is general SLE disease activity and reduced organ damage accurial
v. Moderate reduction is severe flares

equally effective and has more favorable safety profile than oral retinoid "acitretin".

- **Second line agents**—Alternative choice for mucocutaneous and joint diseases are —
  a. **Retinoids**
  b. **Dapsone**
  c. **CYC** (cyclophosphamide) **IV**
  d. **Thalidomide**
  e. **Rituximab**.

  The last two are reserved drug for their high cost and serious neurotoxicity.

INDICATIONS FOR IMMUNOSUPPRESSIVE THERAPY IN SLE (TABLE 61.1)

A. General indications
- Involvement of major organ
- Extensive involvement of nonmajor organ (skin)
- Failure to respond or inability to taper corticosteroid.

B. Lupus nephritis—Require immune-suppressive therapy.
- **Histologically** they are subdivided into
  - Proliferative nephritis
  - Membranous nephritis.

  (clinically nephritic or nephrotic syndrome).

Classification of lupus nephritis—Severity of lupus nephritis patient are stratified based on Renal pathology demographic, clinical and laboratory data in to two categories (proliferative/membranous). This enables the identification of lupus nephritis patient at high-risk for renal dysfunction who may benefit from aggressive cytotoxic therapy.

I. Proliferative lupus nephritis
1. **Mild**—Class III nephritis with normal renal function with nonnephrotic range proteinuria without cresent or fibrinoidnecrosis.
2. **Moderate**
   - Mild disease with partial or no response after initial induction therapy for 12 months.
   - Class III nephritis (focal proliferative nephritis) with adverse histologic feature.
   - Class IV nephritis without adverse histologic feature.
3. **Severe**
   - Moderately severe as defined above but not responding despite 6–12 months of therapy.
   - Class IV nephritis (proliferative disease) with impaired renal function (fibrinoid necrosis or crescent >25% glomerule).
   - Proliferative nephritis with high chronicity.
   - Mixed membranous and proliferative nephritis.
   - Class V nephritis (rapidly progressive glomerulonephritis)

II. Membranous lupus nephropathy
1. **Mild**—Nonnephrotic range proteinuria with normal renal function.
2. **Moderate**—Nephrotic range proteinuria with normal renal function.
3. **Severe**—Nephrotic range proteinuria with impaired renal function

Table 61.1: Immunosuppressive therapy for major organ involvement in SLE

	Induction therapy	Maintenance therapy
Mild	Prednisone (0.5–1 mg/kg/day x 4 –6 week tapered to 0.125 mg/kg every other day x 3 month or in combination with AZA (1–2 mg/kg/day)	Low dose prednisone < 0.125 mg/kg on alternate day or with AZA (1–2 mg/kg/day)
Moderate	MMF 2 g/day or AZA with GC as above If no remission after 6–12 month treat as severe	MMF tapered to 1.5 gm/day for 1 year then 1 gm/day for 1 year and consider further tapering at each year Alternatively AZA 1–2 mg/kg/day
Severe	Monthly pulse of CYC – 0.5–1 gm/m^2 x 7 month or in combination with monthly pulse IV MP (0.5–1 g) x 6 months with background GC 0.5 mg/kg/day for 4 week then taper. If no response consider adding RTX or switch to MMF	Quaterly pulse of CYC for 1 year beyond remission Alternatively— AZA 1–2 mg/kg/day Alternatively MMF 1–2 g/day

Abbreviations: AZA, Azathioprine; MP, Methylprednisolone; RTX, Rituximab; MMF, Mycophenolate mofetil; CYC, Cyclophosphamide; Gc, Glucocorticoid.

C. **Hematologic** manifestation that require immune-suppressive therapy are
   - Thrombocytopenic <20,000/cmm
   - Thrombotic thrombocytopenic purpura
   - Severe hemolytic or aplastic anemia/neutropenia not responding to GC.

D. **Pulmonary**—Manifestation like lupus pneumonitis or alveolar hemorrhage require immune-suppressive therapy.

E. **Cardiac** manifestation that require immune-suppressive therapy are—Myocarditis with depressed LV function or pericarditis with tamponade.

F. **Gastrointestinal**—Manifestation of abdominal vasculitis require immune-suppressive therapy.

G. **Nervous system**— Manifestation like transverse myelitis, optic neuritis, cerebritis, mononeuritis multiplex and peripheral neuropathy refractory to corticosteroid require immune-suppressive therapy.

TREATMENT OF NEUROPSYCHIATRIC MANIFESTATIONS

- **Control of aggravating factors like**
  a. Infection
  b. Dehydration
  c. Hypertension
  d. Metabolic abnormalities.
- **Control of symptoms by**
  a. Anticonvulsants
  b. Antidepressant
  c. Antipsychotic.
- **Glucocorticoid and/or immunosuppressive therapy in case of**
  a. Acute confusional state
  b. Aseptic meningitis
  c. Myelitis
  d. Optic neuritis
  e. Refractory seizure disorder
  f. Peripheral neuropathy
  g. Severe psychosis.
- **Control of generalized non-CNS lupus activity**.
- **Antithrombotic or antiplatelet therapy in case of**
  a. aPL associated CVA
  b. Ischemic optic neuropathy
  c. Chorea
  d. Vascular thrombosis.

SUMMARY OF THE TREATMENT PROTOCOL OF SLE

- **Skin manifestation in SLE usually respond to**
  i. Sun exposer prophylaxis
  ii. Topical glucocorticoid [fluocinonide (0.05%)
  iii. Systemic antimalarial.
- **In moderately severe proliferative lupus nephritis mycophenolate mofetil** may be preferred as induction regimen specially when gonadal toxicity is concern. Failure to achieve response after initial 6 months of therapy, should evoke decision about intensifying or altering immunosuppressive therapy.
- Combination of monthly pulse of **IV CYC** and **pulse IV methylprednisolone** is the treatment of choice for **severe lupus nephritis**.

  If substantial improvement occurs after first 6 months, **maintenance therapy with azathioprine** or **mycophenolate mofetil may be started**.
- **Glucocorticoid alone or in combination with immunosuppressive** agent are recommended for neuropsychiatric events.
- **Antiplatelet or anticoagulation therapy** or **both** are recommended for events related to **antiphospholipid antibody syndrome** to prevent recurrent event. The intensity of such therapy remain controversial.

EXERCISE

Write short notes on

1. Diagnostic criteria of SLE patient.
2. Hematological complication of SLE patient.
3. Renal complication of SLE patient.
4. Investigations in a patient of SLE.
5. Treatment of SLE patient.

Chapter 62

Antiphospholipid Antibody Syndrome

INTRODUCTION

- *Antiphospholipid antibody syndrome (APLS) are a family of autoantibodies directed against phospholipid binding plasma proteins, mostly β_2 glycoprotein–1 (β_2 GP–I).*
- Clinical manifestation ranges from asymptomatic to catastrophic antiphospholipid syndrome (APS).
- Stroke is the most common presentation of arterial thrombosis.
- Deep vein thrombosis is the most common presentation of venous thrombosis.
- Pregnancy losses typically occur after 10 weeks of gestation.
- Earlier embryonic losses (<10 weeks of gestation) can occur.
- Catastrophic APS is a rare form of APS where multiple thrombosis of medium and small size arteries develop over days.
- Diagnosis is made in the presence of characteristic clinical manifestation with persistently positive aPLS antibody measured at 3 months apart.

The mechanism by which the antibody predisposes to thrombosis is unclear but it may be related to either **maintaining platelets in an activated state within the circulation or inhibiting fibrinolytic activity of endothelial cells**.

There are two types of APLA syndrome:

1. **Primary APLA**—Patient without clinical evidence of other autoimmune disease.
2. **Secondary APLA**—When it occurs in association with other autoimmune disease like SLE.

CLINICAL FEATURES

The clinical features are mostly associated with arterial/venous thromboembolism in various organs/systems producing following manifestations in different organ.

A. CVS manifestations are
- Thrombosis in any artery or vein
- Angina
- AMI
- Valvular disease
- Hypertension.

B. Pulmonary complications
- Pulmonary embolism
- Pulmonary hypertension.

C. CNS manifestations
- TIA
- Stroke
- Multiinfarct dementia
- Epilepsy
- Chorea
- Migraine
- ATM (acute transverse myelitis)
- Mononeuritis multiplex
- Multiple sclerosis.

D. Gastrointestinal manifestations
- Budd-Chiari syndrome
- Hepatic infarction
- Splenic infarction
- Intestinal infarction
- Pancreatitis.

E. Renal complications—Thrombosis of renal artery/vein leading to renal *infarction, hematuria* and *ARF*.

F. Skin manifestations are
- Ulcers
- Infarction of skin/digital gangrene/leg ulcer
- Livedo reticularis.

G. Ophthalmological complication—Retinal artery and venous thrombosis

H. Obstetric complications
- Recurrent spontaneous abortion
- IUD of fetus
- Preeclampsia/eclampsia.

I. Hematological
- Thrombocytopenia
- Autoimmune hemolytic anemia.

LABORATORY INVESTIGATION

- Coombs positive autoimmune hemolytic anemia.
- Thrombocytopenia in 40–50% patient (50,000–1,00,000/mL).
- Features of DIC – FDP, D-dimer present in blood.
- APLA antibodies presence of
  - **Lupus anticoagulant (LA)**—Lupus anticoagulants are antibodies that are identified by coagulation assay—prolongation of APTT by DRVVT (dilute Russell viper venom test).
  - **Anticardiolipin antibodies (aCL)**
  - **Anti-β_2 GPI antibodies** detected on 2 occasions 12 weeks apart.
- Anticardiolipin antibodies and anti-β_2 GPI antibody are assessed by ELISA.

Documentation of lupus anticoagulant requires four step testing.

a. Demonstration of prolong APTT (which is phospholipid-dependent) with dilute Russell's viper venom.
b. Failure to correct the prolong APTT after mixing patient's plasma with normal plasma (indicating the presence of inhibitor).
c. Correction of prolong APTT by addition of excess phospholipid.
d. Exclusion of other inhibitor.

The lupus anticoagulant test is *more specific but less sensitive predictor* of thrombosis than anticardiolipin antibody test.

The *anticardiolipin ELISA is more sensitive* but not specific for diagnosis of APS.

Patient with *negative test for lupus anticoagulant and anticardiolipin* IgG and IgM but has high suspicion for APS should be *tested for the presence of IgA anticardiolipin* and IgG, IgM and IgA *anti-β_2 GPI*.

Low titer anticardiolipin and anti-B_2 GPI and transient aPLs and antibody to noncardiolipin phospholipid have no or less proven relationship APS.

A false-positive test for syphilis is not diagnostic of APS.

CRITERIA FOR CLASSIFICATION OF CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME (APS)

- Evidence of **involvement of three or more organ system or tissue**.
- Development of **manifestations simultaneously** or **in less than 1 week time**.
- **Confirmation by histopathology of small vessel occlusion** in at least one organ/tissue.
- Laboratory confirmation of the presence of anti-phospholipid antibody (to be confirmed by double testing at 12 weeks apart).
  - Lupus anticoagulant.
  - Anticardiolipin antibody.
  - Anti-B_2 glycoprotein–1 antibody.

DIAGNOSIS OF DEFINITE CATASTROPHIC APS

When all four above criteria are present.

DIAGNOSIS OF PROBABLE CATASTROPHIC APS

- Criteria (2) + (3) + (4) and two organ, system or tissue involved.
- Criteria (1) + (2) + (3) and except no confirmation at 6 week apart due to early death of the patient.
- Criteria (1) + (2) + (4).
- Criteria (1) + (3) + (4) and development of third event of organ involment after more than 1 week but less than 1 month after the first despite anticoagulation.

DIAGNOSIS OF THE APS REQUIRE

- Positive lupus anticoagulant test.
- Moderate to high titer for anticardiolipin antibody.
- Moderate to high titer for anti-β_2 GP-I (IgG or IgM). Along with characteristic clinical manifestation.

Positive APL results require a confirmation after 12 weeks to exclude transient rise.

SUMMARY OF TREATMENT OF ANTIPHOSPHOLIPID SYNDROME (TABLE 62.1)

- To prevent fetal loss in aPL positive patient with a history of fetal loss is low dose aspirin and low molecular weight heparin (LMWH).
- Primary thrombosis prevention in persistently aPL positive patient requires
  - Risk stratification approach.
  - Elimination of reversible risk factor for thrombosis.
  - Prophylaxis during high-risk period.
- Effectiveness of aspirin in persistently aPL positive patient without vascular events is not supported by controlled studies.

Table 62.1: Summary of treatment for persistent aPL antibody positive patient

1.	Asymptomatic	No treatment
2.	Venous thrombosis	Warfarin to keep INR 2.5 indefinitely
3.	Arterial thrombosis	Warfarin to keep INR 2.5 for indefinite period
4.	Recurrent thrombosis	Warfarin to keep INR 3–4 ± low dose aspirin
5.	Pregnancy	
	a. First pregnancy	No treatment
	b. Single pregnancy loss at <10 week	No treatment
	c. ≥1 fetal or ≥1 embryonic loss without thrombosis	Prophylactic LMWH (0.5 mg/kg SC) with low dose aspirin throughout pregnancy continue up to 6–12 weeks after delivery
	d. Thrombosis regardless of pregnancy	Therapeutic LMWH (1 mg/kg SC bid or 1.5 mg/kg SC od) Alternatively Low dose aspirin throughout pregnancy, warfarin in the post-partum period
6.	Heart valve nodule or deformity	No treatment (Full anticoagulation if history of embolism or intracardiac thrombus is present)
7.	Thrombocytopenia	
	>50,000/cmm	No treatment
	<50,000/cmm	Prednisolone and IVIG
8.	Catastrophic APLS	Anticoagulation + Corticosteroid + IVIG or plasmapheresis

Abbreviations: LMWH, low molecular weight heparin; IVIG, intravenous immunoglobulin.

- No evidence indicate that anticoagulation is effective for nonthrombotic manifestation of aPLS, e.g. thrombocytopenia and heart valve disease.
- Catastrophic APS patient usually received a combination of *anticoagulation*, *corticosteroid*, *IVIG* or *plasma exchange*.

EXERCISE

Write short notes on

1. Diagnosis of APLA syndrome.
2. Treatment of APLA syndrome.

Chapter 63

Seronegative Spondyloarthritis

INTRODUCTION

Seronegative spondyloarthritis (SpA) is applied to a group of inflammatory joint disease distinct from rheumatoid arthritis (rheumatoid factor—negative) that are thought to share similar pathogenesis and show considerable overlap and similarity of articular and extraarticular clinical features.

The members of this group are

- Ankylosing spondylitis
- Reactive arthritis including Reiter's syndrome
- Psoriatic arthritis
- Enteropathic arthritis (Crohn's disease, ulcerative colitis) with spondylitis.
- Undifferentiated and juvenile onset spondylo-arthritis.

COMMON CLINICAL FEATURES

- Sacroiliitis and inflammatory spondylitis.
- Asymmetrical inflammatory oligoarthritis of lower limb > upper limb.
- Inflammatory enthesitis.
- Positive family history.
- Seronegative for RF (rheumatoid factor).
- Absence of rheumatoid nodule.
- Overlapping extraarticular features typical of this group are
  - **Mucosal surface inflammation**
    - **In Reiter's syndrome**—*Conjunctivitis, buccal ulceration, urethritis and prostatitis*.
    - **In IBD**—*Bowel ulcer*.
    - **In psoriatic arthropathy**—*Skin lesion and nail dystrophy*.
  - **Anterior uveitis**.
  - **Aortic root fibrosis**—Leading to AR, CCF and conduction defect.
  - **Erythema nodosum**.
  - In addition to their clinical similarity they share a common pathology and a striking genetic association with **HLA-B_{27} antigen**.

PATHOLOGY

Pathology is often indistinguisable from RA however the distinctive features are

a. **Marked extrasynovial inflammation** and specially of enthesitis.
b. I**nflammation of capsule, periarticular periosteum, cartilage and subchondral bone**.

   Large central cartilaginous joints are involved, e.g. **sacroiliac joint, intervertebral joint** and **symphysis pubis**.

   Sometime synovial joints are also involved, e.g. **spinoapophyseal joint, hip, knee** and **shoulder joint**.
c. Resolution of inflammation is associated with **extensive fibrosis**.
d. Tendency of resultant scar tissue to **calcify and ossify**.

Table 63.1: Amor criteria for spondyloarthritis

A. Clinical symptom or past history of	Score
• Lumbar or dorsal pain during night	1
• Morning stiffness of lumbar and dorsal spine	1
• Asymmetric oligoarthritis	2
• Buttock pain	1
• Alternating buttock pain	2
• Dactylitis of finger and toes	2
• Heel pain or other enthesopathy	1
• Iritis	2
• Nongonococcal urethritis/cervicitis within	
• 1 month of arthritis	2
• Acute diarrhea within 1 month of arthritis	1
• Psoriasis, balanitis or inflammatory bowel disease	2
B. Radiology	**Score**
• Sacroiliitis (grade ≥2, if bilateral; grade ≥3 if unilateral).	3
C. Genetic background	**Score**
• HLA-B_{27} positive family history of ankylosingpondylosis	2

Contd...

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• Reactive arthritis, uveitis, psoriasis and inflammatory bowel disease	2
D. Respond to treatment	**Score**
• Good response to NSAID within 48 hours	2
• Relapse within 48 hour if NSAID is withdrawn	

For definite diagnosis spondyloarthritis ≥ 6

For probable diagnosis spondyloarthritis ≤ 5

EXERCISE

Write short notes on

1. Clinical features of seronegative spondyloarthritis.

Chapter 64

Ankylosing Spondylitis

DEFINITON

It is an inflammatory joint disease of unknown etiology that primarily affects the axial skeleton (peripheral joints and extraarticular structures may also be involved) which begins at 2nd–3rd decade of life with a male : female ratio of 3 : 1.

The disease has a striking correlation with HLA-B27 gene currently believed that susceptibility to ankylosing spondylitis entirely depends on genetic factor of which HLA-B27 comprises about one-third of genetic components.

PATHOLOGY

- The enthesis (means the tendon, joint capsule and ligamentous attachment of bone) is thought to be the site of primary pathology in ankylosing spondylitis which is associated with edema of adjacent bone marrow and eventual erosion of joint margin and followed by ossification.
- Sacroiliitis is one of the earliest manifestation of ankylosing spondylitis. In the spine junction of annulus fibrosus of disk cartilage and margin of vertebral bodies are the common sites with formation of bony syndesmophytes bridging the adjacent vertebra. Ascending progression of this process leads to '**Bamboo spine**'. Other lesions in the spine include
  - *Diffuse osteoporosis*
  - *Erosion of vertebral bodies at disk margin*
  - *Squaring of vertebra*
  - *Inflammation with destruction of bone at disk border*.

CLINICAL FEATURES

1. Involvement of sacroiliac joint and lumbar spine results in low back pain with nocturnal exacerbation is characteristically associated with early morning stiffness that improves with movement and recurs after a period of inactivity.
2. Physical signs of involvement of lumbar spine
   - Failure to obliterate the lumbar lordosis on forward flexion.
   - Restriction of movement of lumbar spine in all directions.
   - Restriction of forward flexion of lumbar spine is demonstrated by **Schober test**, in which two points are marked—one 10 cm above and the other 5 cm below LS joint on midline. On forward flexion, the distance between these two points is longer by ≤4 cm (normally ≥5 cm).
   - Involvement of SI joint also causes low back pain which can be demonstrated by direct pressure over the joint or by maneuvers **(Figure of 8 test)** that stress the joint.
   - Bony tenderness is also present over the iliac crest, greater trochanter, ischial tuberosities, tibial tuberosity, heel and costochondral junction.
   - Involvement of thoracic spine, costovertebral and sternocostal joints results in **diminished chest expansion (<5 cm)** with chest pain ultimately resulting in thoracic kyphosis.
   - Involvement of cervical spine results in **neck pain** and **forward stoop of the neck**.
   - Progression of the disease is assessed by
     - Measuring patient's height (gradual diminution of height).
     - Measuring patient's chest expansion (<5 cm) when measured at the 4th ICS or just below breast in case of female.
     - Limitation of spinal flexion by Schober test (<4 cm).
     - Occiput to wall distance (gradually increasing).
     - Occasionally patient may report with advanced physical finding without significant symptom.
     - Peripheral arthritis is usually late and asymmetric with involvement of hip and shoulder (root joint) leads to flexion contracture.

EXTRAARTICULAR MANIFESTATIONS

- **Eye**—Acute anterior uveitis and iritis in 40% patients.
- **Heart**—Aortic regurgitation with CCF and 3rd degree heart block.
- **Lungs**—Apical pulmonary lobe fibrosis with cavitation.
- **CNS**
  - Compressive myelopathy secondary to atlanto-axial subluxation and spinal fracture.
  - Cauda equina syndrome following lumbar-canal stenosis.
- **General**—Osteoporosis and amyloidosis.

LABORATORY DIAGNOSIS

No laboratory test is diagnostic for AS.

- Increased ESR and C-reactive protein are often present.
- RF—negative, ANA—negative, Anti-CCP— negative.
- **HLA-B_{27} present in 80–90% patients**. Presence of B_{27} is neither necessary nor sufficient for diagnosis of AS. But positive B_{27} is helpful in patient with suggestive clinical features who has not yet developed sacroiliitis.
- MRI bone scan—It demonstrate early SI joint involvement. *Dynamic MRI is the procedure of choice for diagnosis of sacroiliitis.*
- *X-ray change in AS*
  - *Fuzziness of SI joint followed by erosion* and *sclerosis***.**
  - *Squaring of lumbar vertebra***.**
  - *Erosion* and *sclerosis of anterior corners of vertebra***.**
  - *Syndesmophyte formation***.**
  - *Bamboo spine* and *loss of lumbar lordosis***.**
  - *Diffuse osteoporosis of spine***.**
  - *Atlantoaxial subluxation and vertebral fracture***.**
  - *Erosive changes in symphysis pubis, ischial tuberosity and peripheral joints***.**

The sequential change of SI joint on standard radiograph shows—

a. **Blurring of cortical margin** of subchondral bone.
b. **Erosion of subchondral bone—pseudowidening** of joint space.
c. **Later sclerosis** develops **due to fibrosis** and bony ankylosis—later joint space become obliterated. The lesion is usually symmetrical.

Diagnosis of AS based on the modified New York Criteria

- **History of inflammatory back pain**
  - Age of onset <40 years
  - Insiduous onset
  - Duration >3 months
  - Morning stiffness
  - Improvement with action or exercise.
- **Limitation of motion of lumbar spine** both in sagittal and frontal plane.
- **Limited chest expansion** (relative for standard value of age and sex).
- Radiological evidence of definite sacroiliitis.
  - *The presence of radiographic sacroiliitis plus any one of the other three criteria is sufficient for diagnosis of definite AS.*

ASAS classification criteria for axial spondyloarthritis (SPA) in patient with back pain ≥3 month and age of onset <45 years.

A. Sacroiliitis on imaging plus ≥1 SPA feature
Alternatively
B. $HLAB_{27}$ positive plus ≥2 other SPA features

Features of sacroiliitis

- Active inflammation on MRI highly suggestive of sacroiliitis alternatively.
- Definite radiological features of sacroiliitis according to modified New York criteria.

SPA features

- Inflammatory back pain
- Arthritis
- Heel enthesitis
- Uveitis
- Dactylitis
- Psoriasis
- IBD (Crohn's disease/ulcerative colitis)
- Good response to NSAID
- Family history of SPA
- $HLAB_{27}$ positive
- Elevated CRP.

DIFFERENTIAL DIAGNOSIS

DISH (diffuse Idiopathic Skeletal Hyperostosis)

Shows marked calcification and ossification of paraspinous ligament (mainly anterior spinal ligament) and gives the appearance of flowing wax on the anterior surface of vertebral bodies.

But DISH has the following features

- IV disk space—preserved.
- Sacroiliac and apophyseal joints are normal.
- Occurs in middle age and elderly.
- Frequently asymptomatic (but stiffness may be present).
- Radiological picture is much more dramatic than symptoms.

TREATMENT

- AS is a chronic progressive disease with wide spectrum of syndrome.
  In mild AS—**NSAIDs** can control the pain combined with exercise program and is helpful in maintaining the posture and range of motion (NSAID—Indomethacine/cox-2 inhibitor).
- **Sulfasalazine**—(2–3 g/day) Shows modest benefit primarily for peripheral arthritis.

- Recent study suggests potential benefit of two diverse agents—
  a. **Bisphosphonate**—Pamidronate (60 mg IV monthly) for axial osteoporosis.
  b. Thalidomide (200 mg/day)—Perhaps by acting through inhibition of TNF-α.
- Introduction of anti-TNF-α-therapy heralded a revolutionary change in management of AS.
  a. **Infliximab (***chimeric human/mouse anti-TNF -α antibody*).
     – 5 mg/kg IV stat and repeated at 2 weeks, 6 weeks, and then 8 weeks intervals.
  b. **Etanercept** (soluble P^{75} TNF-α receptor–IgG fusion protein)
     – 25 mg SC twice weekly/50 mg once weekly.
  c. **Adalimumab**—40 mg biweekly SC.
  d. **Golimumab**—50/100 mg SC every 4 week.

  All anti-TNF antibody have shown rapid, profound and sustained effects in all clinical and laboratory measures of disease activity. Patients with long-standing disease even complex spinal ankylosis have shown striking improvement in both subjective and objective indicators of disease activity and function including morning stiffness, spinal mobility, peripheral joint swelling, CRP and ESR. Even MRI shows sustained resolution of bone marrow edema, enthesitis, joint effusion in SI joint, spine and peripheral joint.

Adverse Effects of anti-TNF Agent

- Disseminated tuberculosis
- Pancytopenia
- Demyelinating disorder
- Exacerbation of CCF
- SLE-related syndrome may appear
- Hypersensitivity reaction/injection site reaction
- Severe liver disease.

EXERCISE

Write short notes on

1. ASAS diagnostic criteria for axial spondyloarthritis.
2. Modified New York criteria for diagnosis of ankylosing spondylitis.
3. Treatment of ankylosing spondylitis.
4. Treatment of different complication of systemic sclerosis.

Chapter 65

Reactive Arthritis

DEFINITION

It refers to an acute, sterile, nonpurulent arthritis triggered by a particular infection outside the joint (except chlamydia).

- Reactive arthritis (ReA) usually follows **enteric or urogenital** infection.
- The disease predominately involve individuals who are **HLA-B_{27} positive** (75% cases).
- Reiter's syndrome is the combination of a classical triad of
  a. **Nonspecific urethritis**
  b. **Conjunctivitis**
  c. **Reactive arthritis**.

  Often there may be additional mucocutaneous lesion.

The term reactive arthritis was previously used loosely to mean any form of arthritis that comes after some kind of infection and that include Lyme diseases, rheumatic fever and postviral form of arthritis but they should called **postinfections arthritis**.

Common enteric pathogen that triggers the disease are *Shigella, Salmonella, Yersinia, Campylobacter* and *Clostridium difficile*.

Urogenital pathogen—*Chlamydia, Neisseria gonorrhoeae, Streptococcus pyogenes* and *ureaplasma.*

Pathogenesis

Most, if not all, of the triggering organisms have the common features
- To produce LPS
- To attack mucosal surface
- To invade host cell
- To survive intracellularly

- ReA may be a form of chronic infection rather than solely reactive where the T cell that specifically responds to

Contd...

Contd...

antigen of the inciting organism has been in the inflamed synovium but not in peripheral blood of patient with ReA This 'T' cell is predominantly CD_4 'T' cell
- The role of HLA-B_{27} in ReA also remains obscure. Probably presence of HLA-B_{27} *significantly prolongs the intracellular survival of Yersinia, Shigella and permits trafficking of the infected leukocytes from site of primary infection to joints* where 'T' cell response to persistent bacterial antigen may then promote arthritis
- HLA-B_{27} positive patients have worst outcome while Yersinia-induced arthritis seems to be less chronic than *Shigella*-induced ReA

CLINICAL FEATURES

Clinical picture ranges from isolated, **transient monoarthritis to severe multisystem disease** with or without evidence of antecedent infection (1–4 weeks) before the onset of symptoms.

1. **Constitutional symptoms**—Fatigue, malaise, fever and weight loss.
2. **Musculoskeletal symptoms**
   - Acute in onset
   - Asymmetric arthritis, usually additive in nature over a period of days to weeks.
   - With a special predilection to joints of lower extremity with k**nee, ankel, subtalar, MP and IP joint**.
   - Rarely fingers and wrist may be involved.
   - **Spinal and low back pain** are quite common caused by insertional inflammation, muscle spasm and sacroiliitis.
   - Tendinitis, fasciitis–enthesitis may produce pain at several sites **(Achilles tendon, plantar fascia and axial skeleton)**.

3. **Urogenital lesion**
   - Urethritis—Marked or asymptomatic.
   - Prostatitis, Cervicitis, Salpingitis } Either by triggering infection or sterile reactive process
4. **Ocular lesion**—It may range from symptomatic conjunctivitis to aggressive anterior uveitis which result in blindness.
5. **Mucocutaneous lesion/extra articular manifestation of ReA**
   - Asymptomatic **oral ulcer**.
   - **Keratoderma blennorrhagica** in HIV patient is extensively severe lesion consisting of vesicles which **turns hyperkeratotic** and becomes **crusted** before disappearing from **palms and soles** or elsewhere. Histologically identical with psoriasis.
   - **Circinate balanitis**—Over glans penis.
   - **Erythema nodosum**—It is usually seen in *Yersinia* infection but may be associated with other infection.
   - Nail changes—**Onycholysis, distal yellowish discoloration and hipped up hyperkeratosis**.
     - In 30–60% patients—Joint symptoms become chronic with only 25% patients showing recurrence.
     - Arthritis can persist from 3 months to 1 year.

MASES enthesitis score provide list of tender 13 major enthesis.

	Score
1st and the 4th costochondral joint	Left + Right = 4
Anterior and posterior iliac spine	Left + Right = 4
Iliac crest	Left + Right = 2
5th lumbar spinous process	= 1
Calcaneal insertion of plantar fascia	Left + Right = 2
	13

LABORATORY DIAGNOSIS

- **Mild anemia**.
- **Increased ESR and CRP** with elevated other phase reactants.
- **HLA-B_{27} positive in 50–85% patients**—It is helpful for prognostic significance in terms of severity, chronicity and propensity for spondylitis and uveitis and helpful diagnostically in atypical cases.
- **Synovial fluid**—Culture, serology and molecular method helps to identify the triggering infection and exclude septic and crystal arthropathy.
- HIV testing is necessary to select appropriate therapy.
- Difference from psoriatic arthropathy
  - Gradual onset.
  - Psoriasis primarily affect joint of upper extremity.
  - In psoriatic arthritis there is less periarthritis.
  - Psoriatic arthritis is not associated with urethritis and bowel symptoms or oral ulcer.

DIAGNOSIS OF REACTIVE ARTHRITIS

Patient can be confidently diagnosed with reactive arthritis if they have

- **Classic clinical features**
  - Asymmetric oligoarthritis (predominantly lower limb).
  - Enthesitis.
  - Extra articular sign.
  - Proven infection by salmonella, campylobacter, yersinia, shigella, chlamydia, *Clostridium difficile, Mycobacterium bovis*, Bacillus Calmette-guérin (whether symptomatic or not).
- Any acute inflammatory arthritis including mono-arthritis and/or axial inflammation and proven in- fection by reactive arthritis-associated bacteria.
- Classic clinical features as listed in no-1 and diarrhea or urethritis, cervicitis within previous 6 weeks.

TREATMENT OF REACTIVE ARTHRITIS

Control of Symptoms

Most patient (80–90%) have self-limiting disease.
For relief of pain

- **NSAID**
  - Nonselective (risk of GI Hge)
  - Selective (Cox-2 inhibitor) (risk of cardiovascular disease) (etoricoxib)
- **Antibiotic therapy** for acute chlamydeal urethritis. **Rifampicin 300** mg/day + **azithromycin** 500 mg od × 5 day then twice weekly.
  Or

Rifampicin 300 mg/day + **doxycycline** 200 mg twice weekly × 6 months.

- **Intraarticular corticosteroid** very much effective but prior to injection infective arthritis is to be excluded and local steroid injection at the site of enthesitis including plantar fascia (except Achilles tendon in view of the tendency of the tendon to rupture).
- Patient may require a short course of **oral steroid** for control of acute symptom.
- Physiotherapy.
- **Conventional DMARD**
  - **Sulfasalazine**—It should be started in those who have severe, persistent and recurrent disease particularly those who are HLA-B_{27} positive.
  - **Methotrexate or leflunomide** (or a combination of two) who fail to improve with sulfasalazine.

- **Biologics DMRD**
  - **TNF blocking agent** has been used in reactive arthritis.

    Till date there is no evidence of recurrence of infection in view of persistence of chlamydia or yersinia in the joint.
  - **Inhibitor of IL-23 ustekinumab** is effective in reactive and psoriatic arthritis.
  - **Tocilizumab**—It helps in generating T-helper (Th –17) cell.

EXERCISE

Write short note on

1. Treatment of reactive arthritis.
2. Clinical features of reactive arthritis/Reiter's syndrome.

Chapter 66

Psoriatic Arthropathy

INTRODUCTION

Psoriatic arthropathy (PsA) is a inflammatory arthritis that cha- racteristically occurs in individuals with psoriasis.

Incidence of PsA is about 10–30% amongst the patients of psoriasis.

PATHOGENESIS

- Pathogenetic mechanism is not well-understood but mostly immune-mediated.
- It is possible that the interaction of environmental factor such as those derived from pathogen or expressed after trauma with "Toll"–like receptor in a genetically susceptible individual may set in chain of intracellular signalling events leading to cytokine release, immune activation and release of destructive enzyme such as MMPs.

PATHOLOGY (FLOWCHART 66.1)

- Synovitis resembles RA although DIP of fingers, spine and sacroiliac joint are more commonly involved with less hyperplasia and cellularity than RA but with greater vascularity.
- There is greater tendency of synovial fibrosis than RA and prominent enthesitis is similar to spondyloarthritis.
- Seronegative for RF/ANA.

SKIN CHANGES

Involved psoriatic skin is characterized by

- Epidermal hyperplasia
- Neutrophil in stratum corneum
- Increase in various subset of dendritic cell
- CD_8 'T'-cell in epidermis
- Mononuclear leukocyte in papillary dermis
- Mixture of CD_8 and CD_4 cell in dermis.

Most of the 'T' cell in skin lesion express addressin, a cutaneous lymphocyte antigen in contrast to circulating 'T' cell and 'T' cell found in psoriatic synovium. Finally vascular changes are prominent in psoriasis with impressive growth and dilatation of blood vessel.

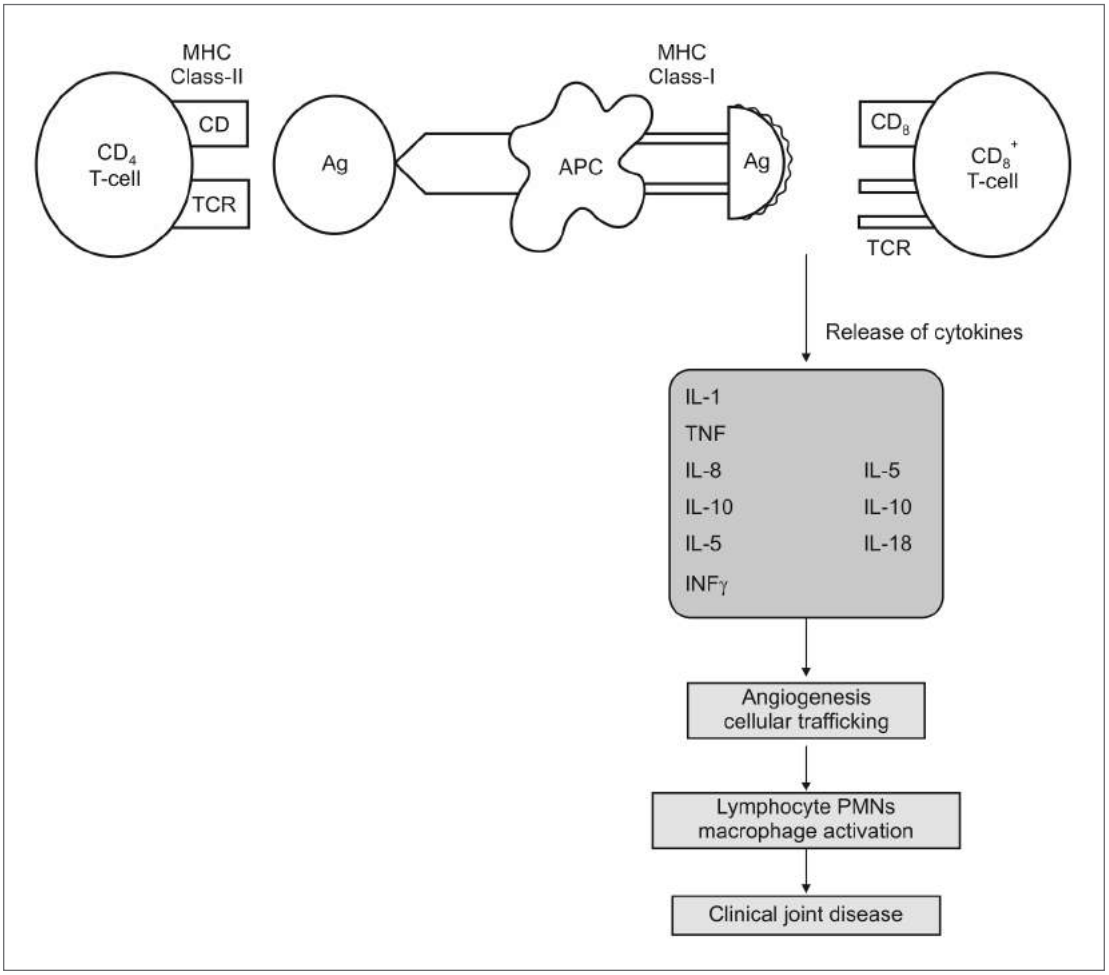
CLINICAL FEATURES

- In 60–70% cases, skin changes in psoriasis precedes joint disease.
- In 15–20% cases, these two manifestations appear within 1 year of each other.
- In 15–20% cases arthritis precedes skin changes and possess a serious diagnostic challenge.
- Male : Female → 1 : 1
- Disease may start in the childhood or late in life but average onset is 37 years.
  - **Spectrum of arthropathy**
    - Asymmetric oligoarthritis (40%)
    - Symmetric polyarthritis similar to RA (25%)
    - Arthritis of DIP joint (15%)
    - Axial involvement (spine and SI joint)—(15%)
    - Arthritis mutilans (5%)

  Simpler scheme in recent use contain three patterns
    - **Oligoarthritis**
    - **Polyarthritis**
    - **Axial arthritis**.

    But the *pattern is not fixed* and may change later from initial presentations. *Pustular psoriasis* is said to be *associated with most severe arthritis.*
  - Nail changes in finger and toes occur in **90% of PsA patients** compared to 40% patients with psoriasis without arthritis.
    - Pattern of nail involvement are of five types. These are
      - » Pitting
      - » Horizontal ridging
      - » Onycholysis
      - » Yellowish discoloration of nail margin
      - » Dystrophic hyperkeratosis
      - » Combination of all these findings.
    - Dactylitis occurs in >30% patients.
    - Enthesitis and tenosynovitis are more common.
    - **About 5% of patients of PsA have arthritis mutilans** with shortening of digits (due to telescoping) with coexistent ankylosis and contracture of other digits.

Flowchart 66.1: Pathogenesis of psoriatic arthritis



- **Arthropathy confined to DIP joint** is found in 15% of patients with accompanying nail changes.
- **About 30% of patients have asymmetric oligoarthritis** commonly of knee or another large joint and few small joints in finger or toes.
- **Symmetric arthritis occurs in about 40%** patients of PsA may be indistinguishable from RA. Peripheral joints are somewhat less tender.
- **Axial arthropathy is present in 5% of patients**.
- **Eye changes**—Conjunctivitis or uveitis is noted in 10–30% of patients.
- **Aortic valve** involvement is seen in 4% of patients.

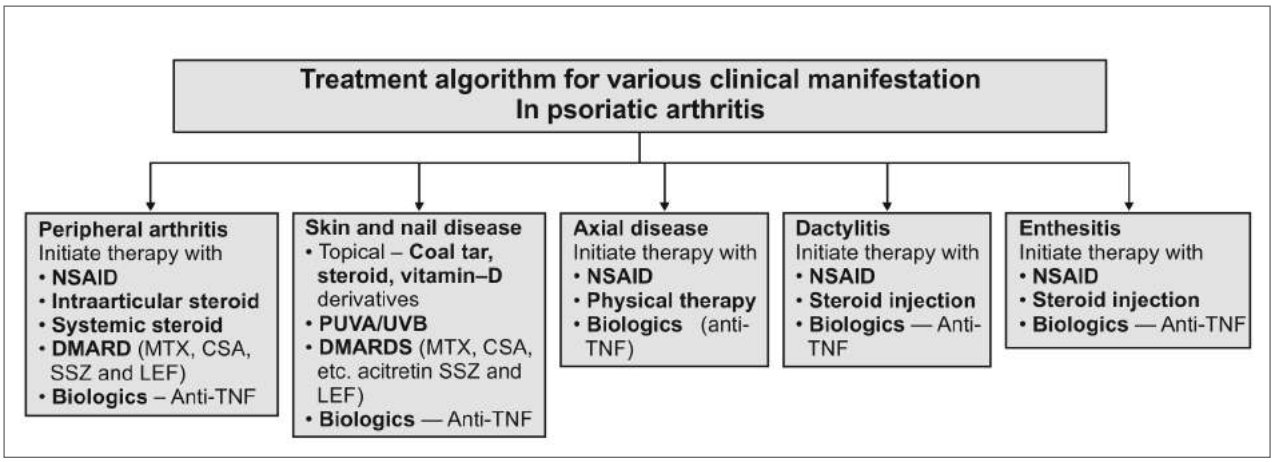
LABORATORY DIAGNOSIS

- ESR and CRP are not always elevated.
- Small percentage of patients have low titer of RF and ANA.
- Uric acid level is elevated.
- HLA-B_{27}—It is found positive in 50–70% of patients with axial disorder but 15–20% with peripheral joint involvement.
- **X-ray findings**
  - **DIP involvement** with **pencil in cup deformity**.
  - **Marginal erosion** and bony proliferation.
  - Small joint ankylosis.
  - **Osteolysis of phalanges** and **metacarpal bone with telescoping of digits**.
  - **Periostitis and proliferation of new bone** at the **site of enthesitis**.
  - Axial PsA shows **asymmetric sacroiliitis** and less zygapophyseal joint arthritis.
  - **Cervical spine is severely involved with atlantoaxial subluxation sparing thoracolumbar spine**.

CASPAR (CLASSIFICATION CRITERIA FOR PSORIATIC ARTHRITIS)

- Evidence of *current psoriasis* or *personal history* or *family history of psoriasis.*
- Presence of *psoriatic nail dystrophy*.
- A *negative* test result for *rheumatoid factor*.
- Present or past history *dactylitis* recorded by rheumatologist.
- *Radiographic evidence of new bone formation* in the hand and foot.

Flowchart 66.2: Treatment algorithm of psoriasis



Abbrevations: CSA, Cyclosporin A; DMARDs, Disease modifying antirheumatic drugs; I.A., Intraarticular; LEF, Leflunomide; MTX, Methotrexate; PT, Physical therapy; PUVA, Psoraten-plus ultravolet A; SSZ, Sulfasalazine; TNF, Tumor necrosis factor; UVB, Ultraviolet-B; NSAID, Nonsteroidal antiinflammatory

To meet *CASPAR criteria* a patient must have *inflammatory articular disease* (spine joint and entheseal) *with more than 3 points from the above 5 criteria.*

TREATMENT (FLOWCHART 66.2)

- **PUVA therapy** (psoralin and UVA rays). } For skin lesion
- **Cyclosporin**. }
- Retinoic acid derivative (**tretinoin**).
- **Leflunomide**—Also tried in PsA. } Do not halt the progression of erosive joint disease
- **MTX**—15–25 mg/week }
- **Sulfasalazine**—2–3 g/day }
- **Anti-TNF-α agents** (*infliximab, etanercept, adalimumab and golimumab*)—*Promise to revolutionize the treatment for PsA and skin lesion in psoriasis.*
- **Anti-'T' cell biologic agent**
  - **Alefacept** with **methotrexate**—It has shown benefit in both arthritis and psoriasis.
  - **Ustekinumab** A monoclonal antibody to shared IL-23/IL-12 P40 has shown promise in treating psoriasis and PSA.
- Surgical intervention for joint deformities require in 7% patient.
- Physical therapy.

Use of immunosuppressive therapy is contraindicated in HIV-associated PsA.

EXERCISE

Write short notes on

1. Clinical features of psoriatic arthritis.
2. Treatment of psoriatic arthritis.

Chapter 67

Progressive Systemic Sclerosis

DEFINITION

Progressive systemic sclerosis (PSS) is a chronic multisystem disorder of unknown etiology clinically *characterized by thickening of skin due to accumulation of connective tissue and by structural and functional abnormality of internal organ like heart, lung, gastrointestinal tract and kidney due to accumulation of excessive fibrous tissue.*

CLASSIFICATIONS OF PROGRESSIVE SYSTEMIC SCLEROSIS

- **Diffuse cutaneous systemic sclerosis (dc-SSC)**—Rapid development of skin thickening on trunk, face, proximal and distal extremities.
- **Limited cutaneous systemic sclerosis (lc-SSC)**—Symmetric skin thickening limited to face and distal extremities. Later developes the features of CREST syndrome.
  CREST syndrome consist of
  C—Calcinosis cutis
  R—Raynaud's phenomenon
  E—Esophageal dysmotility
  S—Sclerodactyly
  T—Telangiectasia.
- **Sine scleroderma**—Characterized by Raynaud's phenomenon with involvement of internal visceral organ and vascular and serologic abnormality with- out clinically detectable skin changes.
- **Overlap's syndrome/MCTD/lupoderma/scleroderm-atomyositis**—It consists of any of the three previous classifications (dc-SSC, lc-SSC and sine scleroderma) along with a diagnosis of SLE, RA, polymyositis with very high titer of anti-U1 RNP.
- **Undifferentiated**—Raynaud's phenomenon with clinical and serologic features of systemic sclerosis but without skin thickening and internal organ involvement—who do not have the diagnostic criteria of anyone connective tissue disease.
- **Localized scleroderma**—May be of three types
  1. Morphea—Guttate morphea and diffuse morphea
  2. Linear scleroderma
  3. En Coup de sabre or hemifacial atrophy.
- **Secondary scleroderma due to chemical and toxin**
  - Vinyl chloride
  - Bleomycin
  - Pentazocin
  - Epoxy and aromatic hydrocarbon.

PATHOGENESIS

Etiology is unknown, no consistent genetic, geographic and racial association could be detected. In small percentage of cases exposure to silica dust, vinyl chloride, trichloroethylene, epoxy resin can be correlated.

Infiltration of skin by T-lymphocyte which causes abnormal fibroblast activation that leads to increased production of extracellular matrix in the dermis (primarily collagen type-1) that collagen result in symmetrical thickening, tightening and induration of skin (sclerodactyly).

In addition to skin, there is arterial and arteriolar narrowing due to intimal proliferation and inflammation—this endothelial injury causes release of vasoconstrictor and platelet activation resulting in further ischemia.

PATHOGENESIS OF SCLERODERMA

The hallmark of pathogenesis of SSC are

- Autoimmunity.
- Inflammation.
- Functional and structural alteration of small blood vessel.
- Interstitial and vascular fibrosis in the skin and internal organ.

Fibrosis is due to sustained mesenchymal cell activation by growth factor, cytokine, chemokines, hypoxia and reactive oxygen species and aberrant reactivation of developmental pathway.

Immune dysregulation is manifested by autoantibodies and interferon but it's role as a primary factor in the pathogenesis has not yet been established. Genetic association studies implicate HLA and other immune regulatory gene that are also associated with SLE.

GENERAL FEATURES

Skin and Digital Manifestation

In patient with diffuse cutaneous form of systemic sclerosis *skin changes* will *become generalized initially* involving extremity *followed by face and trunk over 6 months to few years*. In some patients, skin changes gradually develop over several years. *Rapid progression* of skin involvement over 1–3 years is *associated with visceral disease of lung, heart and kidney*. Skin changes *peak over 3–5 years* then *slowly improve to some extent but does not return to normal*.

In limited cutaneous scleroderma skin lesions have a more gradual progression which are restricted to fingers and distal extremity and face but continue to worsen.

In both the subsets (diffuse/limited) **skin thickening** is **greater in the distal extremity**.

Digital changes

- Fingers and hand are swollen.
- Swelling gradually involve forearm, feet, leg and face.
- Lower extremity relatively spared.
- Edematous phase persists for several weeks to months—edema may be pitting or nonpitting in character with erythema.
- Skin changes begin distally in the extremities and advance proximally.
- The skin becomes firm, thick and tightly bound to underlying subcutaneous tissue.
- **Acroosteolysis**—Resorption of terminal phalanges.

Cutaneous changes

- **Raynaud's phenomenon** (90–100%) It in universally present and preceed other clinical features. Differential diagnosis of *Raynaud's phenomenon are*
  - *Thoracic outlet syndrome* due to scalenus anticus or cervical rib.
  - *Shoulder-hand syndrome*.
  - *Trauma*—Vibratory machine operator (air hammer) operator.
  - *Cold injury*.
  - *Vinyl chloride* exposure.
  - *Circulating cryoglobulin*.
- **Nonpitting edema of fingers** and flexor tendon sheath causing carpal tunnel syndrome.
- **Sclerodactyly**—Skin becomes shiny and taught, skin creases also disappear.
- **Erythema and tortuous dilatation of capillary loops** in nail fold bed readily visible by ophthalmoscope. More common in limited SSC.
- **Pulp atrophy**—Soft tissue loss at fingertips.
- **Nail fold thrombi, digital infarct, digital ulceration** rarely **digital gangrene** can develop.
- Skin may be *pigmented or depigmented* producing **salt pepper** appearance. Specially over **scalp, upper back and chest**.
- Skin is dry, **coarse** with **loss of hair follicles, sweat gland and sebaceous gland**.
- **Calcinosis cutis**—*Deposition of calcium* in the subcutaneous tissue with superficial ulceration. Over PIP joint fingertips, elbows and malleoli.
- **Face**—Microstomia with radial furrowing, pinched up nose with beek-like appearance and expressionless masked facies.

Respiratory System

(Major cause of morbidity and mortality)

- Exertional **dyspnea, fatigue, reduced exercise tolerance** are the presenting respiratory symptoms.
- **ILD** (interstitial lung disease) is present in 85% by HRCT and 90% by autopsy.
- **Pulmonary artery** hypertension (6 times more common in limited disease than diffused one). Pulmonary artery pressure >25 mm Hg.
- **Fibrosing alveolitis** more common in dc-SSC.
- **Aspiration pneumonia**.
- Malignant **alveolar or bronchial cell neoplasm**.
- Rarely **pleurisy and restriction of chest movement**.
- **Velcro crackles** at lung bases.
- **PFT is a sensitive** test for detecting early pulmonary involvement.

Cardiovascular System

Common manifestations are

- Features of *right ventricular failure* and *chronic cor pulmonale*.
- *Heart block and arrhythmias*.
- *Restrictive caridomyopathy* with left ventricular failure.
- *Pericarditis*.

Gastrointestinal System (affected in 90% patients)

- Smooth muscle atrophy and *fibrosis of lower two-thirds of esophagus*.
- *Reflux and erosive esophagitis*.
- *Dysphagia*.
- *Odynophagia*.

- Early satiety and *gastric outlet obstruction* due to involvement of stomach.
- *Gastric antral vascular ectasia* (watermelon stomach).
- *Impaired intestinal motility* may result in malabsorption and chronic diarrhea secondary to bacterial overgrowth.
- *Intermittent bloating and constipation*.
- *Dilatation of large and small bowel* may cause pseudo-obstruction.

Musculoskeletal

- *Arthralgia* and *morning stiffness*.
- *Flexor tenosynovitis*.
- *Restriction of hand movement* is mostly due to skin stiffness rather than joint involvement.
- *Erosive arthritis* is rare.
- *Muscle wasting and weakness* due to myositis.

SCLERODERMA RENAL CRISIS

It is the most dreaded complication of SSC and develop in 10–15% patients within 4 years of onset of the disease.

Patient present with *accelerated hypertension, progressive renal insufficiency* but in 10% of patients *BP may remain normal, headache, blurred vision* and *chest pain are the common symptoms*.

Urine shows *proteinuria, hematuria* and *granular cast*.

Blood shows *thrombocytopenia* with *microangiopathic hemolysis* (differential diagnosis–TTP).

- Risk factor for development of scleroderma renal crisis are
  - *Early diffuse skin disease*
  - *Use of corticosteroid*
  - *Presence of anti-RNA polymerase-III antibody*. Early pharmacological intervention with short-acting ACEI is crucial to control and possibly reverse the disease process.

PATHOLOGY OF SCLERODERMA RENAL CRISIS

Pathogenesis include *obliterative vasculopathy with luminal narrowing leads to increased renin secretion which causes further renovasoconstriction*.

Black Race, male sex, **dc-SSC** with **extensive and progressive disease** are associated with bad prognosis.

Skin involvement and antibody to RNA polymerase I and III, palpable tendon friction rub, pericardial effusion, anemia and thrombocytopenia are harbinger of scleroderma renal crisis. *Oliguria and creatinine >3 mg* are badmarker.

LABORATORY INVESTIGATION

1. Anemia is due to
   - Hypoproliferation of bone marrow.
   - Iron deficiency.
   - B_{12} and folic acid deficiency.
2. Hypergammaglobulinemia.
3. **ANA**—Positive.
4. **Antitropoisomerase-1 (Scl–70)** antibody present in 40% of patients with diffuse disease and 60% with limited disease.
5. **Anticentromere antibody** present in 80% with limited cutaneous scleroderma or CREST syndrome.
6. **Antinuclear antibody** (RNA–1) specific for SSC present in 40% patient.

DIAGNOSTIC CRITERIA FOR SCLERODERMA

ACR criteria for Diagnosis of Scleroderma

Must have (1) or any two of the three criteria (2), (3) and (4) for diagnosis of scleroderma (specificity 98%).

- *Proximal SSC (proximal to MCP/MTP joint)*
- *Digital pits*
- *Sclerodactyly*
- *Pulmonary fibrosis (chest X-ray/HRCT)*.

ACR criteria for Diagnosis of CREST Syndrome

Must have three of the five features:

1. *Calcinosis*.
2. *Raynaud's phenomenon*.
3. *Esophageal dysmotility*.
4. *Sclerodactyly*.
5. *Telangiectasia*.

Raynaud's Phenomenon (RP)

- RP is *common in general population* and usually have *benign clinical course*.
- In *scleroderma RP is more symptomatic* and may be associated with digital ischemia.
- *Abnormal vasomotor regulation and progressive endothelial and structural vessel disease* occur in RP associated with scleroderma.
- Treatment of RP include suppression of *excessive vasoreactivity, modification of structural vascular disease and prevention of microthrombotic* events.

Minor Criteria for Diagnosis of Systemic Sclerosis

Sine scleroderma

Must have all three criteria:

1. *Definite Raynaud's phenomenon*.
2. *Abnormal capillary loop (nail fold changes only)*.
3. *Specific scleroderma autoantibody*:
   - *Anticentromere antibody*
   - *Antitopoisomerase antibody* (Scl-70)
   - *Anti-RNA polymerase III antibody*.

Some expert continues to classify patient with minor criteria only as undifferentiated connective tissue disease with scleroderma features.

Differential Diagnosis of Scleroderma like Fibrosing Skin Disorder

- **Immune-mediated inflammation**
  - Eosinophilic fasciitis
  - GVHD (graft vs host disease)
  - POEM syndrome
  - Overlap syndrome (with SLE and dermatomyositis).
- **Metabolic**
  - PKU (phenyl ketonuria)
  - Porphyria cutanea tarda
  - Hypothyroidism.
- **Deposition**
  - Scleromyxedema
  - Systemic amyloidosis
  - Lipodermatosclerosis.
- **Occupational**
  Exposer to
  - Polyvinyl chloride
  - Organic solvent
  - Silica
  - Epoxy resin
- **Genetic**—Progeroid disorder
- **Toxic/iatrogenic**
  Exposer to
  - Bleomycin
  - Pentazocin
  - Carbidopa
  - Postradiation fibrosis
  - Aniline-denatured rapeseed oil
  - L-tryptophan-induced eosinophilic myalgia syndrome.

TREATMENT (TABLE 67.1)

General treatment of progressive systemic sclerosis:

- **Glucocorticoid**—It may be helpful for reducing stiffness and aching in early stage of dc-SSC but does not influence the progression of skin and internal organ involvement. On the contrary high dose glucocorticoid is associated with increased risk of scleroderma renal crisis.
- **Cyclophosphamide**—Reduce the progression of ILD in SSC with modest improvement of HRCT and pulmonary function test after 1 year of therapy along with skin induration. But the beneficial effect regresses after discontinuation of therapy.
- **Methotrexate and mycophenolate** is associated with modest improvement in skin score and skin induration.
- **D-penicillamine**—Stabilize and improve skin induration, prevent new internal organ involvement and improve survival.

Vascular Therapy

To control Raynaud's phenomenon:

- *Use gloves and stocking.*
- *Avoid exposer to cold and stress.*
- *Nifedipine and diltiazem.*
- *Losartan.*
- *Prazosin.*
- *Sildenafil.*
- *Fluoxetine.*
- *Topical nitroglycerine and intravenous prostaglandins are commonly used.*
- *Low dose aspirin/dipyridamole.*
- *Statin and antioxidant may be used as adjunctive agent and delay the progression of vascular damage.*
- a. *Digital sympathectomy.*
  b. *Local injection of botulinum type A toxin (botox) into the digit may be done in severe Raynaud's phenomenon.*

Treatment of Pulmonary Arterial Hypertension (PAH)

When PAH is symptomatic:

- **Sildenafil** in combination with **bosentan**.
- Prostacycline analogue **epoprostenol** or **treprostinil** throug IV, SC or inhalation. The combination of sildenafil with epoprostenol has become popular. Patient also requires diuretic, oral anticoagulant, digoxin and O_2 inhalation (to avoid hypoxia-induced vasoconstriction in lung).
- Lung transplant is an alternative.

Treatment of Gastrointestinal (GI) Complications

Patient with GI reflux:

- Elevate the head end of the bed
- Frequent small meal
- PPI in high dose.
  - **Recurrent GI bleeding**—From watermelon stomach require laser photocoagulation.
  - **Bacterial overgrowth**—Treatment with short course of broad spectrum antibiotics by rotation such as metronidazole, erythromycin and tetracycline.
  - **Chronic hypomotility**—It may respond to octreotide/lesuride.

Treatment of Renal Crisis

It is a medical emergency and managed by

- Monitor blood pressure regularly.
- Withdrawal of nephrotoxic drug.
- **Glucocorticoid**—To be used when absolutely necessary with low dose (5–10 mg/day).
- Prompt treatment with **short-acting ACEI** for normalization of BP.

Table 67.1: Comprehensive current recommendation for treatment of scleroderma

	Manifestation	Primary therapy	Alternative therapy
1.	Raynaud's phenomenon	Vasodilator (CCB) Antiplatelet (aspirin)	Phosphodiesterase 5-inhibitor Prostacycline and endothelin antagonist
2.	Hypertensive renal crisis	Short-acting ACE inhibitors	ARB, CCB, prostacycline and renal transplant (after 24 month)
3.	GI involvement – Upper GI – Lower GI	 Dental care, prokinetics and PPI Probiotic and rotational antibiotics	 EGD scopy to treat stenosis and gast, i.e. gastric antral vascular ectasia Total parenteral nutrition
4.	Skin	Mycophenolate mofetil Cyclophosphamide	IVIG (intervenous immunoglobulin) and ATG (antithymocyte globulin)
5.	ILD	Cyclophosphamide and mycophenolate mofetil azathioprine	
6.	Pulmonary arterial hypertension	Phosphodiesterase 5 inhibitor Endothelin antagonist Prostacycline	Atrial septostomy and lung transplant
7.	Cardiac involvement	Heart failure therapy Diuretic CCB	Immunosuppression for myocardial inflammation
8.	Joint	Prednisone and methotrexate TNF inhibitor	IVIG and physical therapy
9.	Muscle	Prednisone, methotrexate Azathioprine	IVIG

Abbreviations: ILD, interstitial lung disease; PPI, proton pump inhibitors; CCB, calcium channel blocker; ARB, angiotensin-receptor blocker; EGD, esophagogastroduodenoscopy.

- Two-thirds of patients require dialysis.
- About 50% of patients recover who need dialysis.

Kidney transplantation in necessary for remaining 50% patients.

Skin Care in Scleroderma

Skin involvement is not life-threatening and it usually stabilizes or regresses overtime. The agents commonly used are

1. Hydrophilic ointment and bath oils.
2. Short-term and low-dose prednisolone (5 mg/day).
3. D-penicillamine (750 mg/day).
4. Cyclophosphamide and methotrexate have modest effect on skin induration.
5. **Pulse dye laser** for telangiectasia of face.

PROGNOSIS

Five years survival is approximately 70%.

Risk factors are

- *Old age*
- *Diffuse skin disease*
- *Proteinuria*
- *High ESR*
- *Low TLCO*
- *Pulmonary hypertension*.

EXERCISE

Write short notes on

1. Classification of prognosis systemic sclerosis.
2. Skin and finger changes in PSS.
3. Scleroderma renal crisis.
4. Treatment of different complication of systemic sclerosis (pulmonary and GI complication).

Chapter 68

Mixed Connective Tissue Disorder

DLE—Discoid lupus erythematosus
PHTN—Pulmonary hypertension
RA—Rheumatoid arthritis
SSC—Systermic sclerosis

It is an overlap syndrome characterized by combination of clinical features of **SLE, RA, polymyositis** and **SSc** along with presence of **very high titer of anti-U1 RNP antibody**.

CLINICAL FEATURES

The usual presenting symptoms are

- Raynaud's phenomenon (most common clinical feature).
- High fever (occasional).
- Synovitis.
- Edema of hands—followed by sclerodactyly.
- Arthralgia and arthritis.
- Myalgia.
- Polymyositis.
- Neurological features like
  - **Trigeminal neuralgia**
  - **Aseptic meningitis.**

The other various clinical features that may develop over months to years are as follows:

- Sclerodermal changes usually limited to distal extremities and face sparing trunk.
- Telangiectasia and calcinosis.
- SLE features—Malar rash, photosensitivity, DLE, alopecia and painful oral ulcer.
- Pulmonary involvement (85%)— PHTN and pleurisy.
- Renal involvement (25%)—MGN (Membranous glomerulonephritis).
- GI involvement (70%)—Esophageal dysmotility.
- CVS involvement (30%)—Pericarditis.

Majority of patient develop within 5 years of presentation one of the connective tissue disease like systemic sclerosis (SSc) or SLE.

LABORATORY DIAGNOSIS

- Anemia (due to chronic inflammation and is Coombs positive).
- Leukopenia.
- Thrombocytopenia.
- RF (rheumatoid factor) is present in 50% patient.
- Anti-U1 RNP antibody—Strongly positive.

TREATMENT

- Same as for respective connective tissue diseases.
- More than half of the patients have a favorable course.
- 10-year-survival is possible in 80% patients.
- Ultimate fate depends on the type of connective tissue diseases that may eventually develop.

EXERCISE

Write short notes on

1. MCTD

Chapter 69

Hemolytic Uremic Syndrome

Hemolytic uremic syndrome (HUS) is characterized by **microangiopathic hemolytic anemia, thrombocytopenia, acute renal insufficiency** which may progress to acute renal failure.

Two broad subgroup of HUS are as follows:

1. D plus HUS (associated with diarrheal prodrome).
2. D minus HUS (not associated or preceded by diarrheal illness). It is due to familial deficiency of factor 'H'.

D PLUS HUS

Enterotoxin-producing *E. coli* (0157:H7) and *Shigella* dysenteriae type–1 cause this diarrheal prodrome.

PATHOGENESIS

The cytotoxin of *E. coli* and *Shigella* causes bloody diarrhea and cytotoxin-mediated injury to endothelium of the renal microvasculature that leads to localized coagulation and fibrin deposition on vessel wall which subsequently damages RBC that are sequestrated by spleen. The major site of microvascular injury is in the kidney but brain may be involved.

CLINICAL FEATURES

Children <2–3 years.

Onset is preceded by acute diarrhea/dysentery. Sudden development of

- Oliguria.
- Pallor.
- Prostration.
- Hypertension may be there.
- Focal or generalized seizure and alteration of level of consciousness.

LABORATORY DIAGNOSIS

Blood

- Moderate to severe anemia with fragmented red blood cell (RBC) and numerous schistocytes.
- Reticulocytosis
- Plasma haptoglobin low
- Serum bilirubin (unconjugated) level raised
- Lactate dehydrogenase (LDH) increased
- Coombs test negative.
- White blood cell (WBC) normal.
- Thrombocytopenia <100,000.
- Prothrombin time may be mildly elevated.
- FDP (fibrin degradation product) may be present.
- Creatinine may be increased.
- Circulating immune complex may be seen.

Urine

Hematuria, proteinuria, granular/hyaline cast may be present.

Kidney Biopsy

Endothelial cells are swollen and separated from basement membrane by accumulation of foamy material in subendothelial space.

Renal capillary lumen is narrowed by swollen endothelial cells and blood cells.

Patchy or extensive renal cortical necrosis is seen.

D MINUS HUS

- Onset is insidious.
- Occurs in older child/adult.
- Resembles severe progressive nephritis.

PREDISPOSING FACTORS

- It has autosomal inheritance.
- There is abnormality in complement regulatory pathway.
- Infection with *neuraminidase-producing organism (pneumococci) precipitate HUS.*
- Drugs—*Mitomycin, cisplatin, bleomycin, gentamycin, cyclosporine also* can cause HUS.
- Gastric, colorectal and breast carcinoma is associated with HUS.
- Minor febrile or viral illness can also predispose HUS.

The factor H, a protein in complement pathway, normally protect cell from damage by alternate complement pathway. Deficiency of factor 'H' allow C_3 to potentiate autoantibody-mediated injury to glomerular cell leading to exposer of subendothelial cell and activation of both platelet and coagulation.

CLINICAL FEATURES

- Same as D plus HUS
- Insidious in onset
- Not preceded by diarrhea/dysentery.

TREATMENT

- Supportive care and management of acute renal failure.
- Management of hypertension.
- Correction of anemia.
- Correction of dyselectrolytemia.
- Renal replacement therapy—peritoneal or hemodialysis is required.
- Plasma exchange should be initiated as early as possible but renal failure is not reversed in most of the patients.
- Overall mortality is <5% in D plus HUS and 25% in D minus HUS.

EXERCISE

Write short note on

1. HUS

Chapter 70

Thrombotic Thrombocytopenic Purpura

Although Thrombotic thrombocytopenic purpura (TTP) and hemolytic-urenic syndrome (HUS) were previously considered as overlap syndrome but it is now clear that at least idio- pathic TTP is completely different from HUS.

The pathogenesis of idiopathic TTP is due to deficiency to metalloprotease ADAMTS-13 which cleaves VWF. Normally, VWF is secreted as very large multimers from endothelial cells which are cleaved by ADAMTS-13 to smaller multimers. In TTP, the activity of this ADAMTS-13 is inhibited either due to deficiency or antibody to ADAMTS-13 and the ultralarge molecular weight multimers of VWF initiates platelet aggregation and thrombosis.

PREDISPOSING FACTORS

- Common in women.
- More common in HIV and pregnancy.
- Medication (ticlopidine, clopidogrel, cyclosporin, mitomycin C, tacrolimus and quinine) related micro-angiopathy may be secondarily to antibody against ADAMTS-13.

CLINICAL FEATURES

- Fever
- Microangiopathic hemolytic anemia
- Thrombocytopenia
- Renal failure
- Neurological finding.

DIAGNOSIS

- Increased LDH.
- Increased indirect bilirubin.
- Decreased haptoglobin.
- Increased reticulocyte count or antibody.
- Negative direct globin test.
- Schistocyte and polychromasia, nucleated red blood cell (RBC) in peripheral blood is due to infarction of bone marrow.

TREATMENT

a. **Plasma exchange** is the mainstay of treatment in TTP.
b. When TTP is due to anti-ADAMTS-13 antibody **glucocorticoid** can be used as adjuctive therapy.
c. Other immunomodulatory drugs like **rituximab, vincristine, cyclophosphamide and splenectomy** can be tried in refractory TTP with variable success.

Relapse occurs in 25–45% cases within 30 days of remission and late relapse occurs in 15–40% of cases.

Relapse in more frequent with severe ADAMTS-13 deficiency.

EXERCISE

Write short notes on

1. TTP.

Chapter 71

Vasculitis Syndrome (Vasculitides)

DEFINITION

Vasculitis is etiologically a heterogeneous group of disorder in which all have a common features is inflammation and damage of the vessel wall and is usually associated with compromised vessel lumen and ischemia of the tissue supplied by the involved vessel.

CAUSES OF SECONDARY FORMS OF VASCULITIS

- Connective tissue disorder (rheumatoid vasculitis, SLE, Sjögren's syndrome and inflammatory myopathies).
- Inflammatory bowel disease.
- Paraneoplastic syndrome.
- Infection.
- Drug-induced vasculitis.

CLASSIFICATION ON VASCULITIDES (PRIMARY VASCULITIDES)

- **Large vessel vasculitides**
  - Giant cell arteritis (temporal arteritis)
  - Takayasu's arteritis.
  - Cogan syndrome
  - Behçet's disease
- **Medium-sized vessel**
  - Polyarteritis nodosa (PAN)
  - Kawasaki disease
  - Cutaneous polyarteritis
  - Berger's disease
  - Primary angiitis of the central nervous systems
- **Predominantly small-vessel vasculitis**
  - Immunocomplex-mediated vasculitis
    - Good pasture's disease
    - Cutaneous leukocytoclastic angiitis
    - Henoch-schönlein purpura
    - Hypocomplementemic urticarial vasculitis
    - Essential cryoglobulinemia
    - Erythema elevatum diutinum.
  - ANCA-mediated vasculitis
    - Wegener's granulomatosis
    - Microscopic polyangiitis
    - Churg-Strauss syndrome (CSS)
    - Renal limited vasculitis.

Some small and large vessel vasculitides may involve medium-sized artery but large and medium vessel vasculitides do not involve vessel smaller than artery.

SUMMARY OF THE CLINICAL MANIFESTATION OF LARGE, MEDIUM AND SMALL VESSEL VASCULITIS (TABLE 71.1)

Constitutional symptoms: Fever, weight loss, malaise arthralgia/arthritis are common for vasculitides of all vessel sizes apart from that other manifestation can be subdivided according to size of the vessel involved.

Table 71.1: Manifestation of different form of vasculitis

	Large vessel		Medium vessel		Small vessel
1.	Limb claudication	1.	Cutaneous nodule	1.	Purpura
2.	Asymmetric blood pressure	2.	Ulcer	2.	Vesiculobullous lesion
3.	Absence of pulses	3.	Livedo reticularis	3.	Urticaria

Contd...

Contd...

	Large vessel		Medium vessel		Small vessel
4.	Bruits	4.	Digital gangrene	4.	Glomerulonephritis
5.	Aortic dilation	5.	Mononeuritis multiplex	5.	Alveolar hemorrhage
6.	Renovascular hypertension	6.	Microaneurysm	6.	Cutaneous extravascular necrotizing granuloma
		7.	Renovascular hypertension	7.	Splinter hemorrhage
				8.	Uveitis/episcleritis/scleritis

WEGENER'S GRANULOMATOSIS

- It is a necrotizing vasculitis affecting small to medium-sized vessel together with granuloma formation which may be either intravascular or extravascular involving upper and lower respiratory tract and glomerulonephritis.
  - **Necrotizing granuloma of URT/LRT**—The lesion may vary from inflammatory sinusitis and mucosal granuloma to ulcerative lesions of the nose, palate, pharynx rimmed by vasculitis. In lungs, zone of fibroblastic proliferation with giant cell and leukocytic infiltrate may be seen. Dispersed focal necrotizing granuloma may fuse together to form radiologically visible nodule that undergoes cavitation.
  - **Renal involvement**
    - Focal and segmental glomerulonephritis (FSGN)
    - Crescentic glomerulonephritis (RPGN).
- Males are predominantly involved with average age of involvement is 40.
- C-ANCA present in 95% of the patients is serum and is a good marker of disease activity and its rising titer indicates relapse.

CLINICAL FEATURES

- **The most common site** of involvement is upper respiratory tract with the features of sinusitis, nasal discharge, otitis media, hearing loss, stenosis of upper airway.
- **Pulmonary involvement is seen** in the form of nodule, infiltrate and hemoptysis (in 90% patients).
- **Renal disease** is seen in (75%). It is the next common manifestation and is the cause of mortality in this disease.

  Focal and segmental glomerulitis that may evolve rapidly into progressive crescentic glomerulonephritis. Once clinically detectable renal functional impairment occurs, rapidly progressive renal failure develops unless appropriate treatment is instituted.
- Apart from *kidney, LRT* and *URT, eye* (50%) and *skin* (45%) are also affected.

LABORATORY CRITERIA FOR DIAGNOSIS

- Anemia, leukocytosis, thrombocytosis raised ESR, mild elevation of IgA with raised RF (rheumatoid factor) is seen.
- In 90% of patients, **P-ANCA** (antimyeloperoxidase type) is **positive** but however in absence of active disease the sensitivity drops to 65%.
- Demonstration of **necrotizing granulomatous vasculitis from lung tissue and pauci-immune glomerulonephritis in kidney** biopsy specimen is confirmatory.

TREATMENT

Combined treatment with

- **Prednisolone**—1 mg/kg × 1 month then gradually tapering the dose over 6 months.
- **Cyclophosphamide**—2 mg/kg × 1 year.
  The dose of cyclophosphamide to be adjusted to keep TLC >3000/mL and PMN >500/mL.

Improvement is seen in 90% and complete remission in 75% but 50% who have initial remission later associated with relapse.

Relapse are treated with the same above regimen.

COMPLICATIONS

- Renal insufficiency.
- Hearing loss.
- Tracheal stenosis.
- Saddle nose deformity due to erosion of nasal spine.
- Chronic impaired sinus function.

CHURG-STRAUSS SYNDROME/ ALLERGIC GRANULOMATOUS ANGIITIS

- This disease has a strong association with allergic sinusitis, asthma or eosinophilia points towards immunological phenomenon.
- It is also a necrotizing vasculitis affecting small and medium-sized muscular artery. Pathologically, it is

characterized by granuloma formation with eosinophilic necrosis.
- P-ANCA is positive in 50% of cases.
- Prominent involvement seen in pulmonary vasculature and coronary vessel.
- Coronary artery involvement and myocarditis are the principal causes of morbidity and mortality apart from *skin, kidney, PNS* and *GI tract involment*.

CLINICAL FEATURES

Nonspecific symptoms are fever, malaise, anorexia, weight loss points towards multisystem involvement.

Pulmonary finding predominates the picture with **asthmatic attack** and presence of pulmonary infiltrate.

Mononeuritis multiplex (70%), **allergic rhinitis** and **sinusitis** (60%) and **skin lesion** (50%) are the next common manifestation in Churg-Strauss than Wegener's granulomatosis.

LABORATORY MANIFESTATION

Eosinophilia >1000 cell/mL in (80%), with raised ESR fibrinogen and α_2-globulin (in 80%).

P-ANCA is present (50%) of antimyeloperoxidase type.

DIAGNOSIS

Evidence of asthma with eosinophilia and clinical and histopathological features of vasculitis are suggestive of Churg-strauss syndrome.

TREATMENT

Glucocorticoid alone is sufficient in ordinary disease, but combined treatment with cyclophosphamide and prednisolone (as in Wegener's granulomatosis) is necessary for fulminant multisystem disease. Seven-years survival with this therapy in 75%. The most common cause of death is myocardial involvement.

MICROSCOPIC POLYANGITIS (MPA)/ HYPERSENSITIVITY VASCULITIS

- Necrotizing vasculitis with few or no immune complex affecting small vessel (capillaries, venules or arterioles).
- Glomerular lesion is identical to that of Wegener's granulomatosis.
- Pulmonary capillary are often involved.
- Vascular lesion is histologically similar to PAN.
- Absence of granuloma formation differentiates it from Wegener's granulomatosis.
- Antineutrophil cytoplasmic antibodies (ANCA) is strongly positive which may play a role in pathogenesis.

Clinical Features

Microscopic polyangiitis and Wegener have some common clinical features.

Gradual onset—*fever, weight loss and musculoskeletal pain.*

Glomerulonephritis is seen in 80% leading to rapid onset renal failure.

Hemoptysis is seen in 10% but upper airway disease and pulmonary nodule are absent.

Other manifestations are *mononeuritis multiplex, cutaneous vasculitis and GI tract involvement.*

Laboratory Features

Anemia, leukocytosis and thrombocytosis with raised ESR ANCA of antimyeloperoxidase type (P-ANCA) is presents in 75% of patients.

ANCA positive necrotizing vasculitis with pauci-immune glomerulonephritis and without granuloma formation but evidence of multisystem disease is diagnostic of microscopic polyangiitis.

Treatment

Patient with life-threatening disease should be treated with prednisolone and cyclophosphamide as in Wegener's.

Five-year-survival seen in 75% but relapse occurs in 35%. Treatment of relapse is same as initial treatment.

POLYARTERITIS NODOSA

Polyarteritis nodosa (PAN) is a *necrotizing vasculitis of small and medium-sized renal and visceral vessels (mesenteric vessels) sparing pulmonary circulation.*
- It is characterized by transmural involvement of arterial wall with infiltration of PMN, eosinophil and mononuclear cell and accompanied by fibrinoid necrosis of wall of the vessel with thrombosed lumen. Later, the vessel wall may show fibrous thickening.
- Special predilection for PAN vasculitis is the branching point or at the bifurcation of vessel.
- Vasculitis may cause segmental weakening of arterial wall with aneurysmal dialation or rupture.
- All stages of inflammation may be seen in different vessels/different parts of the same vessels.
- About 30% of patients have HBSAg in their serum.
- **PAN is Not associated with ANCA**.

Clinical Features

- **Nonspecific signs and symptoms** are *fever, weight loss, malaise, weakness, myalgia, headache, abdominal pain and arthralgia*.
- Renal involvement may present as hypertension, hematuria and renal insufficiency.

- Musculoskeletal manifestations are *arthritis, arthralgia myalgia* and *weakness*.
- Neurological manifestations are *CVA, neuropathy, seizure and mononeuritis multiplex.*
- Skin manifestations are *rash, purpura, cutaneous infarct, livedo reticularis, Raynaud's phenomenon.*
- Cardiac symptoms are CCF, AMI, pericarditis and hypertension.

Laboratory Features

No specific diagnostic test is available for PAN.

- Raised ESR.
- Increased neutrophil count.
- HBsAg present in 30% patients.
- Demonstration of vasculitis on HP examination is the hallmark of diagnosis.
- ANCA negative.

Treatment

1. **Prednisolone** 1 mg/kg for 1 month; then gradual tapering and discontinuation within 6 months. Improvement seen in 90% patient and complete remission in 75% patient.

   Alternatively, intermittent intravenous **cyclophosphamide 10–15 mg/kg/month** is less toxic and equally effective.
2. Cyclophosphamide 2 mg/kg to be continued for 1 year after induction of remission. Other agents that are used are chlorambucil, azathioprine and methotrexate. Intravenous immunoglobulin and interferon alfa are useful especially in vasculitis secondary to hepatitis B.

KAWASAKI DISEASE (MUCOCUTANEOUS LYMPH NODE SYNDROME)

- Kawasaki disease affect infant and young children (<4 years of age) (80%).
- It is characterized by c**ongested mucous membrane** (**conjunctiva, lips, oral mucosa**, cutaneous erythema of palm, sole and **cervical lymphadenopathy**.

Clinical Features

- Fever.
- Hemorrhagic edema of conjunctiva, lips and oral mucosa.
- Erythema of palm and sole with edema of hand and feet.
- Cervical lymphadenopathy.
- It is also a medium vessel vasculitis like PAN. The pathogenesis is almost same as PAN but fibrinoid necrosis usually less prominent here.
- The major cause of morbidity (25%) and mortality (28%) is due to coronary artery vasculitis and aneurysm formation, but aspirin may reduce the coronary artery aneurysm formation and death related to it. Other cardiac manifestations are pericarditis and myocarditis.

Treatment

Early treatment with high dose IV gamma globulin 2 g/kg as a single infusion over 10 hours together with aspirin 100 mg/kg/day × 14 days; then 5 mg/kg/day for several weeks is effective in reducing coronary artery abnormality.

Overall mortality is 2.5% and is due to coronary artery involvement causing myocardial ischemia and infarction.

TAKAYASU'S ARTERITIS

It is an inflammatory vasculitis with stenotic lesion of aortic arch and its branches (also called aortic arch syndrome).

The disease involves medium and large size artery (aortic arch and its branches).

Pulmonary artery may be involved.

It is a panarteritis with inflammatory mononuclear cell infiltration of all three layers, marked proliferation of intima with fibrosis, scarring, disruption and degeneration of the elastic lamina.

Narrowing of lumen due to thrombosis is also seen. Etiology is uncertain although circulating immune complex have been demonstrated.

Clinical Features

Common among adolescent and young ladies.

General symptoms are fever, malaise, night sweats and arthralgias.

Hypertension is seen up to 90% of patients and responsible for renal, cardiac and cerebral injury.

Vascular occlusion is manifested as

a. Involvement of subclavian (90%) manifested as Raynaud's phenomenon, claudication with unequal or absent radial pulse.
b. Involvement of common carotid (60%) manifested as syncope, TIA, CVA and visual change.
c. Involvement of renal artery (40%) manifested as hypertension and renal failure.
d. Occlusion of coronary artery (10%) manifested as AMI and angina.
e. Involvement of aortic root and arch (35%) causes AR and CCF.

Laboratory Features

- **Nonspecific**—Anemia, raised ESR and with elevated immunoglobulin.

Diagnosis

Young ladies with decrease or absent peripheral pulse, unequal blood pressure, presence of arterial bruits with arteriographic pattern of irregular vessel wall, arterial

stenosis and poststenotic dilatation and aneurysm formation is diagnostic of Takayasu's is disease.

Prognosis

Mortality is due to CCF, CVA, AMI, renal failure and rupture aneurysm.

Treatment

- **Medical therapy**
  - Prednisolone 40–60 mg/day.
  - Methotrexate 25 mg/week in steroid refractory cases.
- **Surgical therapy**
  - *Surgical correction of stenosed artery and stenting when vascular inflammation is well-controlled with medical therapy*.

HENOCH-SCHÖNLEIN PURPURA

Henoch-Schönlein purpura (HSP) or anaphylactoid purpura is a small vessel systemic vasculitis characterized by

- **Palpable purpura**—Distributed over the extensor aspect of buttock and lower extremity.
- **Arthralgia**.
- **GI sign (70%)**—Colicky abdominal pain, nausea, vomiting, diarrhea mixed with blood and mucus in the stool.
- **Glomerulonephritis** (10–50%)
  - Incidence—M : F (1.5 : 1)
  - Age of onset—4–7 years
  - Peak incidence—Spring season
  - Pathogenesis—It is a immune complex disease.
  - Antigen—Upper respiratory tract pathogen, drugs, food, insect bite and immunization act as antigen
  - IgA antibody is frequently involved in immune complex.

Complications

- **GI complications**
  - Acute abdomen.
  - Ileocolic intussusception
- **Rheumatological complication**—Most patients develop polyarthralgia instead of arthritis.
- **Renal complications (present mostly in child >6 years)**
  - Mild glomerulonephritis
  - Mild proteinuria (nephritic/nephrotic range)
  - Microscopic hematuria
  - RBC cast
  - Hypertension.

  Usually resolve spontaneously but may develop RPGN and CRF.
- **Myocardial Infarction**.

Diagnosis

- **Skin biopsy (confirmatory)**—Leukocytoclastic vasculitis along with IgA and C_3 deposition on immunofluorescence.
- **Renal biopsy**—Rarely needed for diagnosis.

Treatment

- It is self-limiting disorder. Mortality is very rare.
- 1–5% of children progress to end-stage renal disease (ESRD).
- In some children and adult with arthralgia, abdominal discomfort, increasing tissue edema treated with prednisolone (1–1.5 mg/kg/day) initially and tapered according to clinical response.

  Glucocorticoid cannot improve renal and skin manifestation and does not affect the duration of the disease and rate of recurrence.
- **Rapidly progressive glomerulonephritis (RPGN)**—Treated with plasma exchange and azathioprine.

Prognosis

- Excellent
- Mortality 1–5% in ESRD
- Recurrence seen in 10–40% patient.

GIANT CELL ARTERITIS AND POLYMYALGIA RHEUMATICA (TEMPORAL ARTERITIS/ CRANIAL ARTERITIS)

It is the most common form of systemic vasculitis in adult.

Inflammation of large and medium-sized artery characteristically involve carotid or any of its branches especially temporal artery.

Pathology

It is panarteritis involving large and medium-sized artery.

There is infiltration of inflammatory mononuclear cell in all layers of artery with giant cell formation.

There is **proliferation of intima and fragmentation of internal elastic lamina**.

There is restricted clonal expansion of 'T' cell suggesting antigen residing in arterial wall.

Clinical Features

Age of onset over 50 years. Female > Male.

General symptoms are fever, headache, malaise, fatigue, anorexia, weight loss, sweating, arthralgia and polymyalgia rheumatica.

Polymyalgia rheumatica is manifested as stiffness and aching with pain in the muscle of neck, shoulder, lowback,

hip and thigh. Usually polymyalgia occurs in isolation but in 40–50% patients with giant cell arteritis. 10–20% patients initially present as polymyalgia but later develop feature of giant cell arteritis. This strong clinical association together with pathophysiological data suggests that polymyalgia and giant cell arteritis are different clinical spectrum of the same disease.

Scalp pain with claudication of jaw and tongue with tender thick nodular temporal artery are the most common and specific manifestation.

Visual symptom with blindness and claudication of extremity, stroke, myocardial infarction, dissecting aneurysm are other manifestation.

Laboratory Investigation

Raised ESR with anemia with elevated IgG, complement and abnormal LFT are the common laboratory findings. Serum creatinine kinase are not elevated.

Diagnosis

GCA is diagnosed from the syndrome complex of fever, headache, jaw, claudication and visual symptoms anemia, high ESR with or without symptoms of polymyalgia rheumatica.

Long segment **biopsy (3–5 cm) of temporal artery is confirmatory**, where vasculitis can be detected even 2 weeks after starting glucocorticoid therapy. A dramatic response to glucocorticoid also supports the diagnosis.

Treatment

- **Prednisolone**—40–60 mg/day may have to be continued for >2 years. ESR can serve as guide to steroid therapy.
- **Methotrexate**—As a glucocorticoid-sparing agent is controversial.

ESSENTIAL MIXED CRYOGLOBULINEMIA

Cryoglobulin is cold precipitable monoclonal or polyclonal immunoglobulin.

Cryoglobulinemia may be associated with

- Lymphoproliferative disorder
- Multiple myeloma
- Connective tissue disease.
- Liver disease and infection but in vast majority of patient, it is related to an aberrant immune response to (5% of) chronic hepatitis-C infection.

Cryoglobulinemia may be manifested as systemic vasculitis characterized by **palpable purpura, arthralgia, weakness, neuropathy and glomerulonephritis**.

Essential mixed cryoglobulinemia occurs when an aberrant immune response to HCV infection leads to the formation of immune complexes consisting of **hepatitis-C antigen, polyclonal hepatitis C-specific IgG and monoclonal IgM rheumatoid factor**.

The deposition of these immune complex in blood vessel trigger inflammatory cascade that results in a clinical syndrome which is called essential mixed cryoglobulinemia.

Clinical Features

Is characterized by cutaneous vasculitis (palpable purpura), arthritis and arthralgia, peripheral neuropathy and glomerulonephritis.

Renal involvement seen in only 20% patient but it is life threatening.

RPGN or vasculitis of CNS, GI and heart is rare.

Laboratory Investigations

- RF is positive in almost all patient
- Hypocomplementemia is present in 90% patient
- Elevated ESR
- HCV RNA or antibody is present.

Treatment

Glomerulonephritis is a poor prognostic sign seen in (15%) patient. About 40% patient have fatal disease of CVS and liver failure.

Treatment with **INF-α and ribavirin** is beneficial; however many patient have relapse of viremia and disease after withdrawal of antiviral therapy.

Plasmapheresis and **cytotoxic agent** are helpful.

EXERCISE

Write short note on

1. PAN, Wegener's granulomatosis and EMC.

Chapter 72

Antineutrophil Cytoplasmic Antibody

INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA) is closely associated with three forms of vasculitis:

- Hypersensitivity vasculitis, microscopic polyangiitis (MPA).
- Granulomatous polyangiitis (GPA) and Wegener's granulomatosis (WG).
- Eosinophilic granulomatous angiitis (EGPA) and Churg-Strauss syndrome (CSS).

Antineutrophil cytoplasmic antibody (ANCA) is of two types:

- **P-ANCA**—Perinuclear antineutrophil cytoplasmic antibody.
- **C-ANCA**—Cytoplasmic antineutrophil cytoplasmic antibody.

  Antigen responsible for P-ANCA is myeloperoxidase granule (MPO) and is now called **MPO-ANCA**.

  Antigen responsible for C-ANCA is proteinase 3(PR–3) is now called **PR-3 ANCA**.

  Other antigen responsible for P-ANCA reactivity include *elastase, azurocidin cathepsin lysozyme, lactaferrin, BPI and ANA.*

DISEASE ASSOCIATED WITH ANCA

Vasculitis

- Microscopic polyangiitis (MPA).
- Wegener's granulomatosis or granulomatous polyangiitis (GPA).
- Churg-Strauss syndrome or eosinophilic granulomatous polyangiitis (EGPA).
- Renal limited idiopathic necrotizing crescentic vasculitis.

Other diseases associated with ANCA (but these are non-MPO or non-PR3 ANCA)

- Rheumatoid arthritis
- SLE
- Myositis.

Infectious diseases (occasionally positive non-PR 3/ non-MPO ANCA)

- Cystic fibrosis
- Endocarditis
- HIV
- IBD (UC > CD)
- Sclerosing cholangitis
- Autoimmune hepatitis.

Drugs responsible for ANCA positivity (MPO ANCA)

- Hydralazine
- Propylthiouracil
- D-penicillamine
- Minocycline.

PATHOGENESIS

Both MOP and PR3 antigen are transported from primary granule of neutrophil to the cell membrane of neutrophil during activation by TNFα and IL-8.

The binding of PR3 ANCA, MPO ANCA and other ANCA to their cognate target on neutrophil surface augments a variety of activation related neutrophilic function including **degranulation, respiratory burst, nitric oxide production, chemotaxis, adhesion molecule expression and binding to endothelial cell surface**. Such binding of ANCA with a antigen binding site and engagement of the Fcy receptor, collectively contribute to vascular damage. ANCA also stabilizes cell adhesion molecule, promote migration of neutrophil through endothelium.

Whether PR3 is synthesized and expressed on endothelial cell is controversial but PR3 is capable of passive binding to the endothelial cell surface and thus serve as a target for PR3 ANCA. Binding of PR3 ANCA to endothelial cell surface

leads to upregulation of adhesion molecule expression and IL-8 production both of which might contribute to vessel inflammation and injury. ANCA are able to regulate proteolytic activity positively and negatively depending on epitope restriction. In this way, ANCA play a modulatory role in inflammatory response.

In ANCA, positive vasculitis 92% flares are associated with rise in ANCA level. The predective value are higher for ELISA than IFA method with regard to both PR3 and MPO.

EXERCISE

Write short notes on

1. ANCA.

SECTION VII

HEMATOLOGY

- Approach to a Patient of Anemia
- Hemolytic Anemia and Its Investigations
- Thalassemia
- Hypoproliferative Anemia
- Myelodysplastic Syndrome
- Leukemias
- Lymphoid Cells Malignancy (Lymphoma)
- Approach to a Patient with Bleeding Disorder
- Thrombocytopenic Purpura
- Hemophilia
- von Willebrand Disease
- Disseminated Intravascular Coagulation
- Thrombotic Disorder/Thrombophilia
- Kikuchi Disease

Chapter 73

Approach to a Patient of Anemia

HISTORY

Evaluation of a patient of anemia requires a careful history and examination.

- Complain related to the anemia
  - Increased fatiguability
  - Decreased effort tolerance
  - Shortness of breath.
- If anemia is associated with pancytopenia then other relevant histories
  - **Signs of infections**—Skin infections, cough, left respiratory tract infection (LRTI), pneumonia, ischiorectal abscess and fever related to WBC series dysfunction.
  - **Bleeding from various sites**—Epistaxis, gum bleeding, hematemesis, melena, menorrhagia, purpura, easy bruising with ecchymosis—all point towards platelet dysfunction.
- Other important relevant points in history
  - **Nutritional history**—Nutritional deficiency.
  - **Drug history**—History of intake of bone marrow suppressant drug.
  - **History of exposure to radiation**.
  - **Personal history**—History of alcohol consumption.
  - **Occupational history**—History of exposure to lead, chemical solvents, benzene dye, insecticides.
  - **Familial history**—History of similar illness among family members suggests genetic inheritance—Thalassemia, sickle cell, hemophilia.
  - **Geographic background and ethnic origin**—Suggest inherited disorder of Hb molecule or intermediary metabolism, e.g. thalassemia, sickle cell anemia, G-6-PD deficiency.

EXAMINATION

General Examination

For examination of pallor, inspect mucous membrane where venules and capillary are very close to nonkeratinized transparent surface through which we can actually visualize blood in the capillary, venules and make an eye estimation about the amount of hemoglobin.

- **Pallor**—Examination of areas where blood in veins and capillary are closed to surface, e.g. mucous membrane (lower palpebral conjunctiva, oral mucous membrane) nail bed, palmar crease.

  Skin and mucous membrane may be pale when hemoglobin level is inbetween 8–10 g/dL.

  If palmar creases are lighter in color than surrounding skin (when the hand is hyperextended) hemoglobin level is below 8 g%.
- **Lymphadenopathy**—If present with severe anemia suggest malignancy of lymphoreticular system.
- **Edema**—If present with severe anemia suggest CVS decompensation (right heart failure).
- **Neck vein**—If pulsatile with severe anemia it suggest CCF.
- **Bone pain and tenderness** is present in anemia with lymphoproliferative disorder.

Systemic Examination

1. Cardiovascular system
   Presence of hyperdynamic circulatory features, e.g. forceful peripheral pulse.
   Forceful/accentuated heartbeat. } Suggest severe
   Systolic flow murmur. } anemia
2. Gastrointestinal system
   a. Splenomegaly—Seen in:
      - Chronic hemolytic anemia, hypersplenism.
      - Anemia associated with lymphoproliferative disorder, CML, AML and is very rare in ITP and iron deficiency anemia.

   b. Hepatomegaly—Found in chronic hemolytic anemia with extramedullary erythropoiesis, e.g. thalassemia and granulocytic sarcoma in CML.

LABORATORY TEST IN DIAGNOSIS OF ANEMIA

Complete Blood Count (Flowchart 73.1 and Table 73.1)

- Red cell count
  - Hb
  - Hematocrit
  - Reticulocyte count.

Table 73.1: Stand hemoglobin for age and sex

	Hb	Hematocrit%
At birth	17	52
Childhood	12	36
Adolescent	13	40
Adult	16 (±2)	47 (±6)
Women (menstruating)	13 (±2)	40 (±6)
Women (nonmenstruating)	14 (±2)	42 (±6)
Pregnancy	12 (±2)	37 (±6)

These tests are to be done for diagnosis of anemia. A number of physiological factors affect this value include age, gender, pregnancy, smoking and altitude, e.g. high normal Hb% are seen in persons living at high altitude and smoke heavily.

If reticulocyte production index <2.5 in face of established anemia, it indicates a defect in the erythroid marrow proliferation and maturation whereas if the reticulocyte production index ≥2.5, it indicates a normal marrow response which is normally present in hemorrhagic and hemolytic anemia.

- Red blood cell (RBC) indices
  - MCV = (Hematocrit × 10)/RBC count × 10^6 [90 ± 8 fL].
  - MCH = (Hemoglobin × 10)/RBC count × 10^6 [30 ± 3 pg].
  - MCHC = (Hemoglobin × 10)/hematocrit [33 ± 2%].

The component of RBC indices that helps in classification of anemia is **microcytosis** and **macrocytosis**. The mean corpuscular hemoglobin (MCH) and mean corpuscular

Reticulocyte count provides us the information about the number of new RBC adding to the circulation/day. This percentage of reticulocyte appears higher when the total number of RBC/mL falls. Hence reticulocyte index is important.

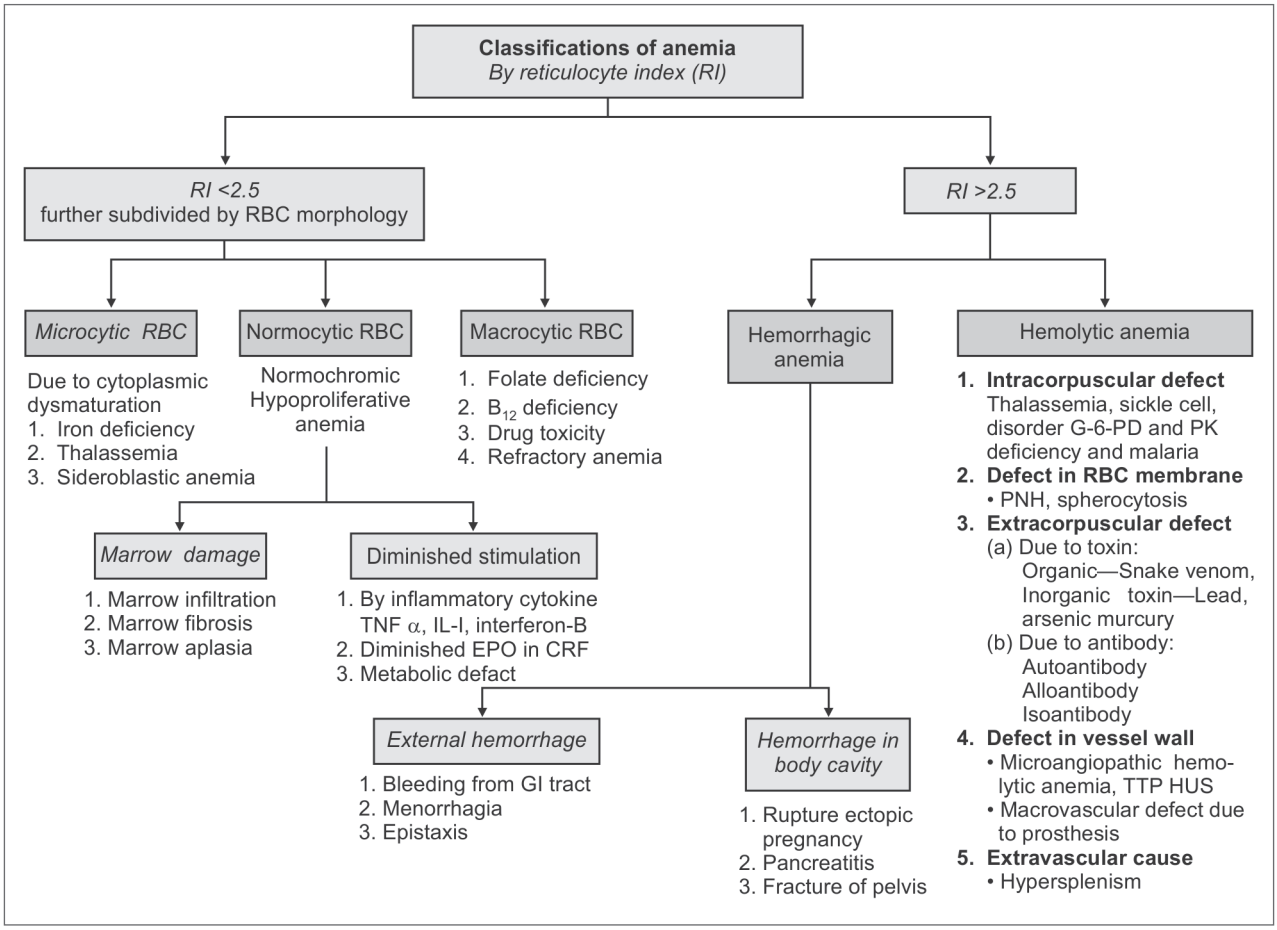
With anemia percentage of reticulocyte may be increased while absolute number is unchanged. To correct this effect reticulocyte parcentage is multiplied by the ratio of patient's Hb% for that age, sex.

A further correction is required as because reticulocyte is released prematurely from marrow in severe anemia. This permaturely released reticulocyte survive in the circulation for more than one day providing a falsely high estimate of daily reticulocyte production. If polychromasia is increased the corrected reticulocyte count should be again divided by a factor of 2 to account for prolonged reticulocyte maturation time

Hence, **Reticulocyte index** =

$$\frac{\text{Reticulocyte percentage} \times \text{Patients hemoglobin}}{\text{Standard Hb for that age and sex}} \times \frac{1}{2}$$

Flowchart 73.1: Etiopathological classification of anemia



hemoglobin concentration (MCHC) reflect the defect in hemoglobin synthesis whereas microcyte and macrocyte reflect the defect in maturation of red cell.

Microcytosis reflects defect in cytoplasmic maturation. **Macrocytosis** reflects defect in nuclear maturation.

When anemia is associated with disturbance in the myeloid lymphoid or megakaryocytic lineage it will be evident from WBC and platelet count

- White blood cell (WBC) count— (a) TC, (b) DC and (c) nuclear segmentation of neutrophil.
  Helpful in diagnosis of leukemia.
- Platelet
  - Count
- RBC morphology
  - Cell size
  - Hb content
  - Anisocytosis (variation in cell size)
  - Poikilocytosis (variation in cell shape)
  - Polychromasia.

Poikilocytosis—Suggest a defect in maturation of RBC in the marrow/fragmentation of circulating RBC.

Polychromasia—In this disorder, RBC of slightly larger size with grayish blue coloration on Giemsa stain represents, residual amount of ribosomal RNA. These are reticulocyte prematurely released from marrow, appears in circulation in response to excess EPO stimulus or architectural damage of marrow by fibrosis/infiltration of malignant cell.

Microcytic hypochromic RBC—Seen in Fe-deficiency anemia and thalassemia.

Macrocytosis—Seen is nuclear maturation disorder in folate, B_{12} deficiency and due to drug.

Howell-Jolly bodies—Suggest functional absence of spleen (remnant of nucleus seen as homogeneously stained blue inclusions).

Teardrop cell, nucleated RBC—Seen in myelofibrosis with extramedullary erythropoiesis.

Target cell—Seen in thalassemia, liver disease (having a bull's eye appearance).

Fragmented RBC—Seen in foreign body in circulating, e.g. prosthetic valve or thermal injury (burn).

Burr cell/echinocyte—Regularly-spaced small spiny projection on the surface of RBC seen in uremia.

- **Acanthocyte or spur cell**—Several irregular thorn-like projection on the surface of RBC. Seen in chronic liver diseases.
- **Schistocyte**—Seen in TTP and HUS (microangiopathic hemolytic anemia).
- **Iron-supply study**
  - Serum iron—(50–150 μg/dL).
  - TIBC—(300–360 μg/dL).
  - Serum ferritin (and marrow Fe stain)—Average 100 μg/dL.
    Serum iron and ferritin is low in iron deficiency anemia but total iron binding capacity (TIBC) is high.

Table 73.2: Classification of anemia based on reticulocyte index

Reticulocyte index (RI)	
RI <2.5	RI ≥2.5
1. Hypoproliferative anemia 2. Maturation disorder	1. Hemorrhagic anemia 2. Hemolytic anemia

Transferrin saturation = Serum iron × 100 ÷ TIBC
Serum iron = 50–150 μg/dL, TIBC = 300–360 μg/dL
Transferrin saturation is 25–50%
Transferrin saturation <20%.
Suggest iron deficiency state
Male—Ferritin 100 μg/L
Female—Ferritin 30 μg/L
Serum ferritin <15 μg suggest absent body iron store.

Amount of total iron needed by an anemic patient = Body wt × 2.3 × (15–patient's Hb g/dL) + 500– 1000 mg (for iron store)

Sodium ferric gluconate and iron sucrose have much lower side effect.

- **Bone marrow examination**
  - Bone marrow aspiration is done to have an idea about
    - M/E ratio
    - Cell morphology
    - Iron stain.
  - Bone marrow biopsy for
    - Cellularity
    - Morphology.

Bone marrow aspirate/needle biopsy is useful in the diagnosis of myelofibrosis, RBC maturation defeat, infiltrative disorder like lymphoma and leukemia.

M/E ratio of 2 or 3 : 1 with a reticulocyte index <2.5 suggests a hypoproliferative anemia.

M/E ratio 1 : 1 with a reticulocyte index >3 suggests hemolytic or hemorrhagic disorder which can be differentiated from history.

Either marrow smear/biopsy stained for presence of iron store/iron in developing RBC gives an idea about body iron store.

Even small ferritin granule can be normally seen in 20–40% of developing erythroblast which are called sideroblast. **Transferrin saturation** ranges from 25–50%.

Ferritin level of 100 mg/L corresponds to iron store of about 1 g. Serum ferritin level of 10–15 mg/L represents depletion of body iron store. However, ferritin is also an acute phase reactant and may rise several fold in acute and chronic inflammation. Serum ferritin >200 mg/L suggests there is at least some iron in tissue store.

EXERCISE

Write short notes on

1. Classification of anemia.
2. Classification of hemolytic anemia.
3. Investigations of hemolytic anemia.
4. Approach to a patient of anemia.

Chapter 74

Hemolytic Anemia and Its Investigations

CLASSIFICATION OF HEMOLYTIC ANEMIA

- **Abnormalities of the red blood cell (RBC) interior responsible for hemolytic anemia**
  - Disorder of hemoglobin synthesis—Thalassemia and sickle cell anemia.
  - Defective RBC enzyme—G-6-PD deficiency and PK deficiency.
  - Malaria.
- **RBC membrane abnormality responsible for hemolytic anemia**
  a. Congenital—Hereditary spherocytosis and elliptocytosis.
  b. Acquired—PNH (paroxysmal nocturnal hemoglobinuria).
- **Extracorpuscular defect responsible for hemolytic anemia**
  - Entrapment—Hypersplenism
  - Immune
    - Warm reactive antibody (IgG).
    - Cold reactive antibody(IgM)—Cold agglutinin diseases.
    - Cold reactive antibody (IgG)—Paroxysmal cold hemoglobinuria.
    - Drug dependent antibody—(i) Autoimmune and (ii) hapten.

  c. Traumatic hemolytic anemia
    - Impact hemolysis
    - Macrovascular defect—Prosthesis
    - Microvascular causes—Thrombotic thrombocytopenic purpura (TTP), Hemolytic-uraemic syndrome (HUS), Disseminated intravascular coagulation (DIC).

  Other causes of microvascular abnormality:

  d. Hemolytic anemia due to toxic effect on RBC membrane.
    - Spur cell anemia.
    - External toxin—Snake venom and spider venom.
    - Heavy metal
      - Copper and lead
      - Organic compound
      - Malaria parasite.

Causes of Warm Antibody Hemolytic Anemia

1. Idiopathic
2. Lymphoma: CLL, NHL and HD
3. SLE and other collagen vascular diseases
4. Drugs
   a. α–Methyldopa—Warm antibody to RH antigen
   b. Penicillin—Stable hapten
   c. Quinidine—Unstable hapten
5. Postviral infection
6. Other tumor

Causes of Cold Antibody Hemolytic Anemia

1. Cold agglutinin diseases:
   a. Acute—Mycoplasma, infectious mononucleosis
   b. Chronic—Idiopathic lymphoma
2. Paroxysmal cold hemoglobinuria

INVESTIGATION OF HEMOLYTIC ANEMIA

- **Hemolytic anemia is diagnosed by**
  - Increase reticulocyte count and reticulocyte index.
  - Increased unconjugated bilirubin.
  - Decreased haptoglobin level.
  - Urine shows presence of hemoglobinuria after massive hemolysis and hemosiderinuria for 6 weeks after hemolysis.
  - Methemoglobinemia.
- **To establish the cause of hemolytic anemia**
  - Peripheral blood smear.
    - Spherocyte present in hereditary spherocytosis.
    - Sickled RBC present in sickle cell anemia.
    - Target cell present in thalassemia.
    - Acanthocyte (spur cell) suggest chronic liver disease.
    - Heinz body present in precipitated hemoglobin suggest unstable hemoglobin and oxident stress.
    - Malaria parasite.
  - HPLC (high performance liquid chromatography) for diagnosis of thalassemia and sickle cell anemia.
- Chromosomal study for diagnosis of thalassemia and sickle cell anemia.

- G-6-PD enzyme estimation for diagnosis of G-6-PD deficiency.
- Flow cytometry for diagnosis of PNH (CD 55, CD 59 deficiency).
- Coombs test (both direct and indirect) for immunohemolytic anemia.
- FDP and D-dimer increase level suggest of DIC.
- ANA and anti-dsDNA present in SLE.
- Biopsy for lymphoma.
- Serological test for viral infection.
- Fever, microangiopathic hemolytic anemia. Thrombocytopenia, renal failure, CNS symptoms—suggest microangiopathic hemolytic anemia—TTP and HUS.

EXERCISE

Write short notes on

1. Classification of hemolytic anemia.

Chapter 75

Thalassemia

INTRODUCTION

Thalassemia syndromes are inherited disorder of diminished α or β-globin chain synthesis.

It is a recessively inherited disorder leading to reduced/absent production of globin chain of **hemoglobin**.

Imbalance between production of α-and β-polypeptide chain of hemoglobin is the main pathology of thalassemia.

- **In α-thalassemia** → α-globin chain submit synthesis is depressed or absent.
  In β-thalassemia → β-globin chain submit synthesis is depressed or absent.
  In δβ-thalassemia → both δ-and β-globin chain submit synthesis is depressed or absent.
- **Excess α/β**: is α-thalassemia excess β-chain and is β-thalassemia excess α chain precipitate in red cell membrane causing damage and premature destruction of red blood cell (RBC) either in bone marrow or peripheral circulation causing ineffective erythropoiesis or hemolysis.
  - Frequency of thalassemic gene in Indian population average 3%. Vary between 0–17%.
  - Most common in North-West India.
  - About 10,000 thalassemic children born every year in India.
- **Due to hemolysis and ineffective erythropoiesis**—HbF level remains high still after fetal life.

  Increased O_2 affinity of Fetal hemoglobin (HbF) causes decreased released of O_2 for tissue and leads to tissue hypoxia which stimulate-erythropoiesis and responsible for expansion of marrow space and gives rise to characteristic facial appearance.

β-THALASSEMIA

- The gene responsible for β-chain synthesis is present on the short arm of chromosome 11p.
- β-chain production is totally, minimally/partially depressed depending upon the type of mutation and designated β° and β+ respectively.
- Severity of thalassemia depends on various factors:
  - Type of mutation affecting β-chain synthesis.
  - Associated presence of α-chain mutation.
  - Increase of γ-chain synthesis produces increased HbF which will reduce the severity of the disease.
  - Concomitant presence of other hemoglobinopathies.

CLINICAL MANIFESTATION

- The spectrum of the disease varies from severe homozygous form (**thalassemia-major**) present in early infancy (6–18 months) with progressive pallor, hepatosplenomegaly, bony changes and if left untreated die with 1–2 years of life.

  Heterozygous form (**thalassemia-minor**)—in which patient can lead a practically normal life with normal life expectancy except for a persistent mild anemia.
- In between the two very extremes a relatively intermediate form with varying degree of clinical manifestation of anemia, hepatosplenomegaly and bone changes who maintains the lifestyle more comfortably and not dependent on blood transfusion is called → **thalassemia intermedia**.

  Diagnosis may be made at 4–5 years to the second decade because of an intercurrent infection or illness will cause exaggeration of anemia or persistence of jaundice. Normally produced α-chain combines with γ/δ-chain to produce increased level of HbF ($\alpha_2\gamma_2$) or HbA_2 ($\alpha_2\delta_2$).

  The tetramer of α deposit on the RBC cell membrane of normoblast and the immature RBC are destroyed within bone marrow called (in effective erythropoiesis). In **HbH** disease production of HbA is only 25–30%. In fetal life, some unpaired γ-chain accumulate [causing tetramer of γ (**Hb Barts**)]. But in adult tetramer of β–chain accumulate called **HbH** which is soluble and forms few inclusion and are characterized by milder ineffective erythropoiesis with moderate anemia.

  In **hydrops fetalis**—Tetramers of γ-chain accumulate called Hb Barts which has very high affinity to O_2. It delivers no O_2 to fetal tissue causing edema and hydrops fetalis.

α thalassemias are of four types—α region is controlled by four gene.

- If one gene is absent → **Silent thalassemia**: 0 α / αα

- If two gene is absent → **Thalassemia trait**: 0 0/αα or αu/α0
- If three gene is absent → **Hemoglobin H disease:** α 0/0 0
- If all four gene is absent → Hydrops fetalis: 0 0/0 0
- The liver and spleen are enlarged as a result of extramedullary erythropoiesis and transfusional hemosiderosis causing malfunctioning of liver, spleen, heart and endocrine glands.
- The hemosiderosis is due to the iron released from the breakdown of endogenous/transfusional RBC and excess iron absorbed due to anemia that cannot be further utilized.

- Typical clinical features of β-thalassemia major—Patients who survive the 1st year of life shows Mongoloid facies with the characteristics of
  - *Frontal bossing*
  - *Flattened vault with prominent eminences of skull*
  - *Straight forehead*
  - *Hypertrophy of maxilla*
  - *Prominent malar eminence*
  - *Depressed bridge of nose*
  - *Puffy eyes with pallor and icteric tinge.*

  Following features cannot be found in very early stages as sufficient time has not yet elapsed for compensatory hypertrophy of the marrow causing such appearance:
  - **Hepatosplenomegaly** is due to hemolysis and extramedullary erythropoiesis.
  - **Physical growth** is markedly retarded. Teeth get malform pathological fracture of long bones and vertebra may be present.
  - **Mild icteric change** in the sclera is usually present.
  - Patient usually suffer from irregular fever due to increased metabolic activity and intercurrent infection.
  - Sometimes episodes of aplastic crisis may be there.

FATE

- Death may occur in the first few years of life.
- Death is mostly caused by anemia, heart failure, hepatic failure.
- With repeated blood transfusion they succumb to iron overload in the 2nd decade of life.

DIAGNOSIS

- Hb-electrophoresis is the diagnostic test **(done by HPLC) method to detect abnormal hemoglobin**.
- Routine examination of blood shows **microcytic, hypochromic** picture.
  - Hb level is reduced, between 2–6 g/dL
  - Cells—RBC are microcytic and hypochromic
    - Count is low → 2–3 million/cmm.
    - Hematocrit → decreased.
    - MCV<80 fL.
    - Reticulocyte index ≥2.5.
    - Microcytic, hypochromic.
    - Anisocytosis, poikilocytosis.
    - Variable number of target cell/teardrop cell.
    - Large number of normoblast.
    - Erroneous increased count of leukocyte.
    - Small number of immature myelocyte, metamyelocyte may be present.

BONE MARROW

a. **Marrow is hypercellular**.
b. **Erythroid hyperplasia** (M : E = 1 : 1).
c. Increased number of **sideroblast or stippled erythroblast**.
d. Granulopoiesis, thrombopoiesis is preserved.
e. **Increased hemosiderin pigment** in the marrow.

FRAGILITY OF RED BLOOD CELL

Fragility of RBC is decreased on exposure to hypotonic saline as the cells are thinner so they can accommodate increased amount of water before being hemolyzed.

SERUM BILIRUBIN (UNCONJUGATED)

Moderately elevated between 1–3 mg/dL. The bilirubin level depends on the rate of hemolytic activity and the capacity of liver. Urinary urobilinogen and fecal stercobilinogen is increased.

Ferrokinetic study shows:

- *Increased serum iron level*
- *Decreased TIBC*
- *Increased ferritin*
- *Increased transferrin saturation*
- Decreased plasma haptoglobin
- Decreased plasma hemopexin
- Increased urinary hemosiderin.

RADIOLOGICAL APPEARANCE OF SKULL (LATERAL VIEW)

- Though skull picture is diagnostic, **earliest radiographic change occurs in small bones of hands**, giving them **rectangular appearance with widening of medullary cavity**. Cortex is thinned out resulting pathological fracture of the bones.
- Diploid spaces of skull bones are widened. Bony trabeculae traversing perpendicularly from inner to outer table **gives hair on end** appearance. Outer cortex is thinned out.
- Frontal bone is thickened from nasal region to parietotemporal region spearing occiput → gives the appearance of frontal bossing.
- Pneumatization of sinuses are delayed.
- Maxilla appears overgrown with prominent malar eminence.

MANAGEMENT OF THALASSEMIC CHILD

- Confirmation of diagnosis.
- **Correction of anemia by repeated transfusion**.
- **Folic acid supplement** (1–2.5 mg/day) for increased erythropoiesis.

Transfusional Therapy

• Goals of therapy	Prevent anemia (HB ~ 10 g) which suppress endogenous erythropoiesis to prevent ineffective erythropoiesis.
• Transfusion is required for	β thalassemia major β thalassemia intermedia who cannot maintain Hb level >7 g/dL or show evidence of growth retardation.
• Transfusional material	Triple saline washed, Coombs crossmatched RBC or cold centrifuged packed cell.
• Transfusional amount	In low transfusion regimen (Hb is maintained at 6–10 g/dL) In hypertransfusion regimen (Hb level is maintained at 10–12 g/dL) In supertransfusional regimen (Hb level is maintained at 12–14 g/dL).

Neocyte transfusion with gerocyte removal

Neocyte has longer survival/lifespan—average 90 days.

Removal of gerocytes by pheresis causes decrease iron load.

The regimen which is used, should permit:

- Normal growth/physical activity.
- Suppress endogenous erythropoiesis thus preventing skeletal changes and G-I iron absorption.
- Suppress extramedullary erythropoiesis to inhibit hepatomegaly and splenomegaly.

The popular regimen is hypertransfusional regimen to maintain pretransfusional Hb level at least above 10 g% and mean at least at 12.5 g% in this regimen

- About 10–15 mL of packed cell/kg every 3rd week is sufficient to manage pretransfusional Hb level above 10 g/dL
- Rate of transfusion is 5–7 mL/kg/h to avoid sudden increase in blood volume
- Patient with cardiac insufficiency, the transfusion should be given every 2nd week with a rate of 1–3 mL/kg/h not more than 5 mL/kg/h

- Average annual blood requirement—180–200 mL of blood/kg → *if the annual blood requirement level exceed that level then hypersplenism or development of anti-RBC antibody should be considered.*
- Blood should be screened for HIV, HBV, HCV(ab), malaria, syphilis, CMV.

Chelation Therapy is Required

To reduce Fe-overload and transfusional hemosiderosis.

- Iron-overload is due to increased GI absorption and from transfusion
- Normal body iron → 3–5 g
- Normal baby requires 1 to 1.6 mg of iron/day
- Thalassemia baby can absorbe up to 10 mg of iron/day
- Each unit of blood contains 250–300 mg of iron
- Ill effects of iron overload:
  a. Cardiomyopathy and arrhythmias
  b. Diabetes is due to pancreatic iron deposition (Bronze diabetes) with bronze color of skin
  c. Hepatomegaly, hepatic fibrosis and cirrhosis
  d. Growth retardation and delayed puberty due to pituitary Fe-deposition
  e. Increase *Yersinia* infection due to increased iron load
  (Increase infection is due to blockage of macrophage phagocytosis by excessive broken RBC)
- Increase ferritin which should be >1000 μg/L (>7500 μg/L → prove to be fatal)

For patient who has already received > 100 U of packed RBC and usually develop hemosiderosis.

- **Deferoxamine (DFO)** is the drug of choice for chelation therapy.
  - DFO is a hydroxylamine compound.
  - 1 g DFO chelates 85 mg of Fe.
  - DFO therapy should not be started before 3–5 years.
  - Dose—30–70 mg/kg for a minimum of 5–6 times a week over 8–12 hours subcutaneously by an infusion pump.
  - Goal → to keep ferritin level – <1000 μg/L.

Toxicity–relatively nontoxic

- Liberation of histamine cause bradycardia, hypotension, rigor, headache, photophobia, feeling of cold.
- Rarely sensorineural deafness, cataract, local skin reaction and urticaria.
- Delayed growth.

Deferasirox is an oral analog of deferoxamine.

- Dose—20–50 mg/kg.
- It has 70–100% effectivity as compared to DFO.
- It decrease eye and ear toxicity.
- It increase urinary clearance of Ca, Cu, Mn, Mg.
- No renal/hepatic involvement.
- ANA, Anti-DS-DNA may be positive in few cases due to drug-induced SLE.
- About 20–30% patients present with arthropathy with synovial effusion and thickening.
- Absolute neutropenia, thrombocytopenia may develop.

Splenectomy

- Indications
  - Increase yearly requirement of packed cell >200 cc/kg/year.
  - Features of hypersplenism as evidenced by decreased platelet and WBC count with splenomegaly.
- Precautions
  - The child who will undergo splenectomy should be >5 years of age.
  - All children before splenectomy should receive *pneumococcal*, *H. influenzae*, *meningococcal* vaccine 4–6 weeks prior to surgery.

    In splenectomized patients prophylactic antimalarial treatment should be continued whenever the patient enters malaria.

    Prophylactic penicillin therapy should be endemic zone also continued life long in these patients.
  - Episodes of infection should be treated with broad spectrum antibiotic.

Bone Marrow Transplant (BMT) is Curative in 80–90% of Patients

Bone marrow transplant is to be done, early in the course of the disease before end organ damage occurs.

- Allogenic SCT can cause permanent cure.
- Principles
  - Destroy defective stem cell.
  - Sufficient immunosuppression for good engraftment.
  - SCT is done with normal β-chain production gene containing cell from sibling or parent.
  - High dose of immunosuppressant is required for GVHD (graft vs host disease).
- Adverse prognostic factors
  - Hepatomegaly (>2 cm)
  - Portal fibrosis
  - Iron overload
  - Increased age.

Gene Therapy and Manipulation of HbF

- Gene therapy in thalassemia proved to be an elusive goal. Uptake of gene vector into the nondividing hematopoietic stem cell has been inefficient. **Lenteviral type of vector** that can transduce nondividing stem cell may solve this problem but still it is unresolved problem.
- Re-establishing high level of fetal hemoglobin synthesis could ameliorate the symptom of β-thalassemia to some extent. This is done by cytotoxic agent.
  - **Hydroxyurea** and **cytarabin**, promote high level of HbF synthesis probably by stimulating proliferation of primitive HbF-producing progenitor cell. Unfortunately, this regimen is not effective in β-thalassemia.
  - **Butyrate** stimulates HbF production but only transiently.

PREVENTION

- **Mass screening**—Hb-electrophoresis for detection of HbF by HPLC. (a) Screening should be premarital/newly married couple.
- **Genetic counseling**—If one of the parents have thalassemia minor and the other have normal hemoglobin, less than 50% chance of having a thalassemia minor child with 50% chance of getting a normal child.

  If both of them have thalassemia minor then
  - 25% chance to have thalassemia major
  - 50% chance to have thalassemia minor
  - 25% chance to have normal child.
- **Antenatal diagnosis**—Antenatal diagnosis of thalassemia syndrome is now widely available. DNA diagnosis is based on PCR amplification of fetal DNA obtained by amniocentesis or chorionic villus biopsy followed by hybridization with allele-specific oligonucleotide probe or direct DNA sequencing.
  - Chorionic villous sampling between 9th–11th week can be done without anesthesia.
  - Amniocentesis/cordocentesis between 16th–18th week of gestation and determining β/α ratio in fetal blood.
  - If the fetus is affected, MTP is advised.

EXERCISE

Write short notes on

1. Management of thalassemia
2. Gene therapy for thalassemia.

Chapter 76

Hypoproliferative Anemia

INTRODUCTION

Hypoproliferative anemia associated with marrow damage include:

- Aplastic anemia
- MDS
- Pure red cell dysplasia
- Myelophthisis.

Anemia in this disorder is normocytic, normochromic but may be macrocytic and characterized by low reticulocyte count, associated with leukopenia and thrombocytopenia in varying combination, results from deficient hematopoiesis.

Hemopoietic failure syndrome are classified as:

- Pancytopenia with hypocellular bone marrow
- Pancytopenia with cellular bone marrow
- Hypocellular bone marrow ± cytopenia.

PANCYTOPENIA WITH HYPOCELLULAR BONE MARROW

- Constitutional aplastic anemia (Fanconi's anemia and **Dyskaratosis** congenita).
- Acquired aplastic anemia.
- Some myelodysplasia syndrome (MDS).
- Myelofibrosis.
- Some acute lymphocytic leukemia (ALL).
- Lymphoma of bone marrow.

PANCYTOPENIA WITH CELLULAR MARROW

There are causes of pancytopenia with cellular marrow described in Table 76.1.

Table 76.1: Causes of pancytopenia with cellular marrow

Primary bone marrow disease	Secondary to a systemic disease
• MDS • PNH • Myelofibrosis • Aleukemic leukemia • Myelophthisis • Bone marrow lymphoma	• SLE • Hypersplenism • B_{12} and folic acid-deficiency • Sarcoidosis • Alcoholism • Overwhelming infection • Brucellosis • TB • Leishmaniasis

HYPERCELLULAR MARROW WITH OR WITHOUT CYTOPENIA

- Q-fever
- **Legionnaires** disease
- *Mycobacterium* infection
- Anorexia nervosa and starvation.

APLASTIC ANEMIA

DEFINITION

In aplastic anemia, there is pancytopenia with bone marrow hypocellularity.

ETIOLOGY

- **Congenital disorders**
  - Fanconi's anemia
  - Dyskeratosis congenita.
- **Idiopathic** (most common)
- **Postradiation**
- **Secondary to drugs and chemicals**.

  Chemicals
  - Benzene
  - Insecticides.
  - Heavy metals—Gold, As, Bi and Hg.

  Drugs
  - Sulfonamides.
  - Anticonvulsants—Phenytoin, carbamazepine
  - Cytotoxic antineoplastic drugs.
  - Chloramphenicol
  - Antihistaminics—Chlorpheniramine
  - Antiprotozoal—Chloroquine
  - NSAIDs—Phenylbutazone, ibuprofen and aspirin
  - D-penicillamine
  - Estrogen/pregnancy.
- **Viral infection**
  - EBV (infectious mononucleosis)
  - Seronegative viral hepatitis (Non-A, Non-B, Non-C)
  - Parvovirus-B_{19}
  - HIV.

- Immune-mediated disease
  - Thymoma/thymic carcinoma
  - Graft-versus-host disease (GVHD)
  - Paroxysmal nocturnal hemoglobinuria (PNH)
  - Eosinophilic fasciitis.

CLINICAL FEATURES

- Symptoms may be abrupt or insidious in onset.
- Striking feature of aplastic anemia is restriction of symptoms to hematologic systems and patient even feel and look remarkably well despite drastically reduced blood count. If associated weight loss is present, it points to other etiologies of pancytopenia.
- *Family history* of hematologic disease, prior *drug use, chemicals exposure, proceeding viral illness, hepatitis* must be elicited.
- Bleeding is most common and early symptom: It is suggesting by
  - Easy bruising
  - Gum bleeding
  - Epistaxis
  - Heavy menstrual flow
  - Sometime with petechiae
  - Rarely intracranial/retinal hemorrhage.
- Second common symptom related to anemia:
  - Lassitude
  - Shortness of breath
  - Pounding sense in the ear.
- Infection is the unusual first symptom of aplastic anemia. If present usual manifestations are pharyngitis, anorectal infection and frank sepsis.

SIGNS

- Pallor.
- Petechiae, ecchymosis are typical along with retinal hemorrhage on fundoscopy.
- Lymphadenopathy and splenomegaly are highly atypical for aplastic anemia.
- Café-au-lait spot and short stature suggest Fanconi's syndrome.
- Peculiar nail and leukoplakia suggest dyskeratosis congenita.

INVESTIGATION

Blood

- Smear show large red blood cell (RBC), paucity of platelets and granulocyte.
- Reticulocyte are few or absent.
- Lymphocyte may be normal or reduced.
- MCV commonly increased in.
- Nucleated RBC seen in — Marrow fibrosis or tumor invasion.
- Immature myeloid cell seen in leukemia or MDS.
- Abnormal platelet seen in peripheral destruction or MDS.

Bone Marrow

- Marrow aspirate—appears dilute on smear and shows only RBC, residual lymphocyte and stromal cells.
- Marrow biopsy specimen—appears grossly pale due to fatty infiltration with hemopoietic cell occupying <25% of marrow space. It may be 100% fat cell.
- Dry tap suggests myelofibrosis/myelophthisis. Residual hemopoietic cell should have normal in appearance except—mildly megaloblastic erythropoiesis mega-karyocytes are invariably reduced or absent.
- Granuloma in cellular specimen may indicate infectious etiology.

Special Test

- Chromosomal breakage study of peripheral blood using di-epoxy-butane (DED) and mitomycin C for Fanconi's anemia.
- Chromosomal study for MDS:
  - Flow cytometry assay for diagnosis of PNH (absent CD55, CD59).
  - Serologic studies for viral infection like EBV and HIV.
  - Aplastic anemia is difficult to distinguish from hypocellular MDS which has the finding of morphologically abnormal megakaryocyte and myeloid precursor cell with typical cytogenetic abnormality.
  - Posthepatitic aplastic anemia is seronegative (non-A, non-B and non-C).
  - MRI to assess fat content of vertebral body to differentiate between aplastic anemia and MDS.
  - Splenic size should be determined by USG.
  - Tests to exclude—TB, kala-azar, SLE as an etiology of aplastic anemia.

Combination of pancytopenia with fatty empty bone marrow is diagnostic of aplastic anemia.

PROGNOSIS

Severe untreated aplastic anemia rapidly deteriorates to death but with appropriate treatment like

- RBC and platelet transfusion
- Antibiotic therapy
- Bone marrow transplantation (BMT)
- And immunosuppression has changed the picture dramatically. A few patient may go spontaneous recovery. Bad prognostic parameter is defined as presence of any 2 of the 3 following criteria.
  - *Absolute neutrtophil count* <500/mL
  - *Platelet* **<20,000/µL**

– *Reticulocyte count* **<1%**.
Absolute reticulocyte count **<60,000/µL**.
Severe disease is defined as *absolute neutrophil count is* **<200/µL**.

TREATMENT

- Avoidance of exposure to drugs, chemicals, radiation.
- Supportive care.
- Hemopoietic growth factor has limited, usefulness and glucocorticoid are of no value.
- *Severe aplastic anemia can be cured by SCT*.
- *Aplastic anemia can be ameliorated by suppression of immune system to* allow the recovery of patient's residual bone marrow function.
  – **BMT**—It is the best form of therapy for young patient with full HLA matched sibling donor.
  – **Immunosuppression is the treatment of choice** where suitable marrow donor is lacking.

Immunosuppression Therapy

- **ALG/ATG (antilymphocyte/antithymocyte globulin)** IV for 5/4 days respectively along with.
  – **ATG (antithymocyte globulin)** → 40 mg/kg/day × 4 days IV.
  Rabbit ALG (antilymphocyte globulin) → 3.5 mg/kg/day × 5 days IV with
    – Methylprednisolone → 1 mg/kg/day for 2 weeks for suppression of immune consequence of heterologous protein infusion.
- **Cyclosporine** → Addition of cyclosporine increases the response rate to 70% especially in children who are severely neutropenic.
  Orally 12 mg/kg/day for adult, 15 mg/kg/day for children with subsequent adjustment of dose according to blood count every 2 weekly.
  Side effects of cyclosporine:
  – *Nephrotoxicity*.
  – *Hypotension*.
  – *Seizure*.
  – PCP pneumonia (prophylactic treatment with monthly inhaled pentamidine.
- Effectiveness of androgen are variable.
- Splenectomy often increases blood count in relapse/refractory cases.
- **Supportive care**
  – Prompt initiation of broad spectrum antibiotic therapy when required.
  – Platelet and packed cell transfusion are given as and when necessary to maintain platelet count >10,000 and Hb% – ≥7–9 g/L which require 2 unit every 15 days.

EXERCISE

Write short notes on

1. Treatment of aplastic anemia.
2. Diagnosis of aplastic anemia.
3. Causes of pancytopenia.

Chapter 77

Myelodysplastic Syndrome

DEFINITION

Myelodysplastic syndrome (MDS) is a heterogeneous group of stem cell disorder characterized by cytopenia associated with dysmorphic bone marrow (usually cellular) and ineffective hematopoiesis.

Subtypes (Table 77.1)

Seven entities are defined in FAB classification of MDS:

- **Refractory anemia (RA)**.
- **RA with ringed sideroblast (RARS)**.

Table 77.1: FAB classification of myelodysplastic syndrome

Disease	Frequency	Blood finding	Bone marrow finding	Prognosis
1. a. Refractory anemia (RA) b. Refractory neutropenia (RN) c. Refractory thrombocytopenia (RT)	10–20% <1% <1%	Anemia ± Blast	Erythroid dysplasia <5% blast <15% ringed sideroblast	Protracted course LTN 6%
2. Refractory anemia with ring sideroblast (RARS)	10–15%	Anemia No blast	Erythroid dysplasia <5% blast ≥15% ringed sideroblast	Protracted course LTN 1–2%
3. Refractory cytopenia with multilineage dysplasia (RCMD)	35%	Cytopenia (2–3 lineage) ± Blast No Auer rod <10^9 monocyte/L	Dysplasia ≥10%, ≤2 lineage dysplasia. No Auer rods <15% ringed sideroblast	Variable course LTN 11%
4. Refractory anemia with excess blasts (RAEB)–1 and RAEB–2	40%	Cytopenia No Auer rod <10^9 monocyte/L RAEB-1→ <5% blast, RAEB-2 → 5–19% blast	Unilineage/multilineage dysplasia RAEB-1→ 5–9% blast No Auer rod RAEB-2 → 10–19% blast ± Auer rod	RAEB-1 → Progressive BM failure with Lt~25% RAEB-2 → Progressive BM failure with LTN 33%
5. MDS with isolated del (5q)	Unknown	Anemia <5% Blast platelet → Normal or increased	Normal/increased megakaryocyte Hypolobulated nuclei of megakaryocyte <5% blast No Auer rod	Long survivor
6. Childhood MDS/refractory cytopenia of childhood (RCC)	10%	Pancytopenia	<5% marrow–blast RCC- marrow hypocellular	
7. MDS unclassified (MDSU)	Unknown	Cytopenia ± Blast No Auer rod	Dysplasia in myeloid/ platelet lineage <5% blast No Auer rod	Unknown

- **Refractory cytopenia with multilineage dysplasia (RCMD)**.
- **Refractory anemia with excess blast**.
- **Childhood MDS/refractory cytopenia of childhood (RCC)**.
- **MDS with isolated Del (5q)**.
- **Myelodysplastic syndrome unclassified (MDS-U)**.

EPIDEMIOLOGY

- MDS has slight male preponderance.
- Idiopathic MDS is a disease of elderly—mean age 68.
- MDS is rare in children except childhood MDS/RCC.
- Therapy related MDS develop in 15% patient which is seen within a decade after intensive chemotherapy.

ETIOLOGY AND PATHOPHYSIOLOGY

MDS is a clonal hematopoietic stem cell disorder leading to impaired cell proliferation and differentiation.

ETIOLOGY

- Radiation.
- Benzene.
- Combination of radiation and radiomimetic alkylating agents—busulfan, nitrosourea, procarbazine and topoisomerase-II inhibitors.
- Acquired aplastic anemia can develop following immune suppression therapy.
- Fanconi's anemia can evolve into MDS.
- Multiple genetic abnormality, loss of tumor suppressor gene and activation of protooncogene leads to MDS.

CLINICAL FEATURES

Signs and symptoms are referable to specific cytopenias usually megaloblastic anemia with dyserythropoiesis. Alcohol abuse and nutritional deficiency of vitamin B_{12} and folate deficiency may have similar clinical picture.

Symptoms

Symptoms of anemia dominates the picture.

- It is asymptomatic in 50% cases and may be detected in routine check-up.
- Anemia, weakness, dyspnea, pallor, fatigue are the main cardinal symptoms of MDS.
- Past history of radiation and chemotherapy may be present.
- Family history of Fanconi's anemia or sideroblastic anemia may be present.

Signs

- Pallor.
- Unusual skin lesion including sweet syndrome (febrile neutropenic dermatosis) can develop.
- Splenomegaly present in 20% patient.

LABORATORY INVESTIGATION

Blood

- RBC series
  - Anemia—Seen in majority of patients.
    - Macrocytosis—Commonly dimorphic with distinctive population of large RBC.
  - PNH may be present.
- WBC series
  - TC is usually normal or low except CMML.
  - Neutrophil is **hypogranular, hyposegmented, ringed** or **abnormally segmented nuclei** with **Döhle** bodies and functionally deficient.
  - Circulatory myeloblast usually correlates with marrow blast and their quantitation is important for classification and prognosis.
- Platelet series
  - Thrombocytopenia is usual
  - Platelet is large and lack of granules.
- Bone marrow is either
  - Normal/hypercellular
  - But in 20% cases—It is hypocellular (differential diagnosis of aplastic anemia).

RBC lineage

- Dyserythropoietic changes (especially nuclear abnormality).
- Ringed sideroblast.
- Megaloblastic nuclei with defective hemoglobinization.

WBC lineage

- Hypogranular, hyposegmented granulocyte precursor may be present.
- Increase in myeloblast.

Platelet lineage

- Reduced number of megakaryocyte showing decreased number of disorganized nuclei.

DIFFERENTIAL DIAGNOSIS

- Vitamin B_{12} and folic acid deficiency—Diagnosed by appropriate blood test or therapeutic trial with B_{12} and folate.
- B_6 deficiency in ringed sideroblast—Differentiated by therapeutic trial of pyridoxin.
- Marrow dysplasia in acute viral infection, drugs and chemical toxicity—all are transient.

- Bone marrow aplasia should be differentiated from hypocellular MDS.
- Early acute leukemia to be differentiated from RAEB.
- AML to be differentiated from MDS by presence of more than 20% blast in marrow.

TREATMENT

- Therapy of MDS is generally unsatisfactory.
- **SCT** is the only curative therapy.
  Survival up to 3 years is seen in 50% patient.
- **ATG and cyclosporine** improves blood count and employed in the same way as in aplastic anemia.
- **Azacitidine** improves blood count and survival in a minority of MDS.
- **Decitabine** (by continuous IV infusion every 12 hours for 3 days). It is chemically related to azacitidine but 20% patient show improvement of blood count which last for more than one year. **Azacitidine—**SC OD for 7 days with decitabine IV for 3 days at 6 weeks interval have a response rate ranges from 25–65% but the response may be delayed. So at least 4 cycle may be required to determine the efficacy.
- **Lenalidomide** (a thalidomide derivative) is particularly effective in **Del 5q** syndrome. It is administered orally and improvement is seen after 3 months of therapy. It not only improves anemia but cytogenetics also become normal.
- **Campath** (anti-CD52 monoclonal antibody) is especially effective in younger MDS (age <60 years). It can be used alternative to ATG and cyclosporin with HLA-DR-15.
- Erythropoietin—Alone or in combination with G-CSF can improve Hb level specially in those who have low serum erythropoietin.
- Supportive care—Blood, blood product and appropriate antibiotics.

PROGNOSIS

The poor prognostic factors are
- Precipitous worsening of pancytopenia
- Acquisition of new chromosomal abnormality
- Increase in number of blast.

EXERCISE

Write short notes on
1. Classification of MDS.
2. Treatment of MDS.
3. Laboratory feature of MDS.

Chapter 78

Leukemias

ACUTE MYELOID LEUKEMIA (AML)

It is a **heterogeneous group of disease where peripheral blood and bone marrow (sometimes soft tissue) are infiltrated with malignant cells of hemopoietic system**.

ETIOLOGY

Exact etiology is not known but the common association are as follows:

1. **Hereditary disorder associated with AML**
   - Down's syndrome
   - Klinefelter's syndrome
   - Ataxia telangiectasia
   - Fanconi's syndrome
   - Patau syndrome
   - Kostmann's syndrome.
2. **Radiation is associated with higher incidence of AML**
   - Therapeutic radiation with alkylating agents
   - Survivors of atom bomb explosion.
3. **Drugs**
   - Anticancer drugs (used for treatment of HD or NHL) are the leading cause of treatment associated AML.
   - Chloramphenicol
   - Chloroquine
   - Phenylbutazone
   - Methoxypsoralen

   } Exposure to these drugs are rare causes of AML
4. **Chemicals**
   - Benzene
   - Petroleum product
   - Herbicide
   - Pesticide
   - Ethylene oxide

   } Exposure to these chemicals sometime associated with AML

CLASSIFICATION

The categorization of AML into biologically distinct groups is based on morphology, cytochemistry, immunophenotype as well as cytogenetic and molecular technique.

The most widely used FAB classification is as follows: At present this classification is done by the identification of **cell surface molecule by flow cytometry**.

- M_0—Minimally differentiated leukemia (2–3%).
- M_1—AML without maturation (20%).
- M_2—AML with maturation (30%).
- M_3—Hypergranular promyelocytic leukemia (5–10%).
- M_4—Myelomonocytic leukemia.
- M_4E_0—Variant, eosinophil in bone marrow.
- M_5—Acute monoblastic/monocytic leukemia (10%).
- M_6—Acute erythroleukemia (Di Guglielmo's disease) (5%).
- M_7—Acute megakaryoblastic leukemia.

CLINICAL PRESENTATION

History

- Increased fatigue and decreased exercise tolerance is due to anemia.
- Excess bleeding and bleeding from unusual sites in case of DIC and thrombocytopenia present in M_3.
- Fever and recurrent infection suggest granulocytopenia.
- Headache, visual change, nonfocal neurologic abnormality are associated with CNS leukemia and bleeding.
- Family history of AML if present suggest **Fanconi syndrome, ataxia telangiectasia, Kostmann's syndrome**.
- History of cancer with exposures to topoisomerase-**II inhibiting alkylating agent and radiation** to be enquired for.
- Occupational history of exposure to radiation, benzene, petroleum product, paint, pesticide should be searched for.
- Personal history of smoking. Usually present in AML.

Physical Examination

- **Fever, tachycardia** are signs of infection.
- **Ecchymosis, oozing from injection sites**—Suggest DIC in M_3.
- **Poor oral hygiene** is due to infection and present in M_4 leukemia.
- Gum hypertrophy associated with M_4 leukemia.

- **Oral ulcer, Cancrum oris** (fistula tract connecting oral cavity with paranasal sinus), agranulocytic **angina or neutropanic ulcer** are present in AML (specially M_4).
- **Skin infiltrate and nodule** found in M_4 leukemia.
- Soft tissue mass in breast, retroorbital tissue—called granulocytic sarcoma (chloroma) may be present.
- **Back pain, lower extremity weakness** associated with spinal granulocytic sarcoma.
- **Splenomegaly, hepatomegaly** found in all subtype of AML.
- **Papilledema, retinal infiltrate and cranial nerve abnormality** suggest CNS infiltration by leukemia cell.
- **Bone pain, sternal tenderness** is due to periosteum and marrow involvement by leukemic cell.

Laboratory and Radiological Studies

- Peripheral blood picture: Anemia is due to
  - Diminished erythropoiesis
  - Increased destruction
  - Increased blood loss.
- **Total count of WBC**
  Average—15000/mL
  In 25–40% patient it is <5000/mL (subleukemic/aleukemic leukemia).
  In 20% patient it is >1,00,00/mL—Mostly in M_6 leukemia.
  In 5% patient—No detectable leukemia cell in peripheral blood and is called aleukemic leukemia.
- **Leukocytes**—Nuclear chromatin is fine lesh like, large nucleoli with nuclear folding and clefting.
- **Platelet**—
- In 75% patient platelet count is <1,00,000/mL
- In 25% patient platelet count is <25,000/mL
  - Platelet are of bizzare size with abnormal granulation and inability to aggregate and adhere with one another.
- **Bone marrow**
  In bone marrow myeloblast is >20%.
  - Cytochemistry
  - Cytogenetics
  - Flow cytometry
  - Molecular studies are to be done to determine exact subtype of acute leukemia (M_0–M_7)
- **Coagulation studies**
  - P time
  - APTT
  - Fibrinogen
  - D-dimer is to be done to know the coagulation status of the patient (specially M_3).
- Routine blood biochemistry: Sugar, urea, creatinine, Ca^{+2}, PO^{-3}, uric acid, hepatic enzyme, bilirubin, LDH, amylase, lipase.
- Viral serology for presence of
  - CMV
  - HSV-1
  - VZV.
- Cryopreservation of leukemic cells for future reference.
- **Chest X-ray**—PA and lateral for detection of lung infiltrate and mediastinal granulocytic sarcoma.
- **USG of abdomen**—To detect granulocytic sarcoma in ovary, prostate, retroperitoneal space.
- **Lumbar puncture**—For those with CNS symptoms.
- **MRI of spine**—For patient with low back pain and paraparesis to determine the exact etiology.
- Thorough dental checkup to eliminate focus of gum infection.

TREATMENT

A. Pretreatment evaluation
1. Subtyping by flow cytometry
2. Assessment of functional integrity of CVS/CNS/ hepatic/renal/respiratory system
3. Leukemic cells should be cryopreserved for future references
4. Patient with evidence of anemia and thrombocytopenia should receive appropriate blood product
5. Patient with hyperuricemia and high lysosome should be treated with allopurinol or rasburicase (recombinant uric oxidase) and maintenance of adequate hydration
6. Appropriate treatment for infection should be early instituted

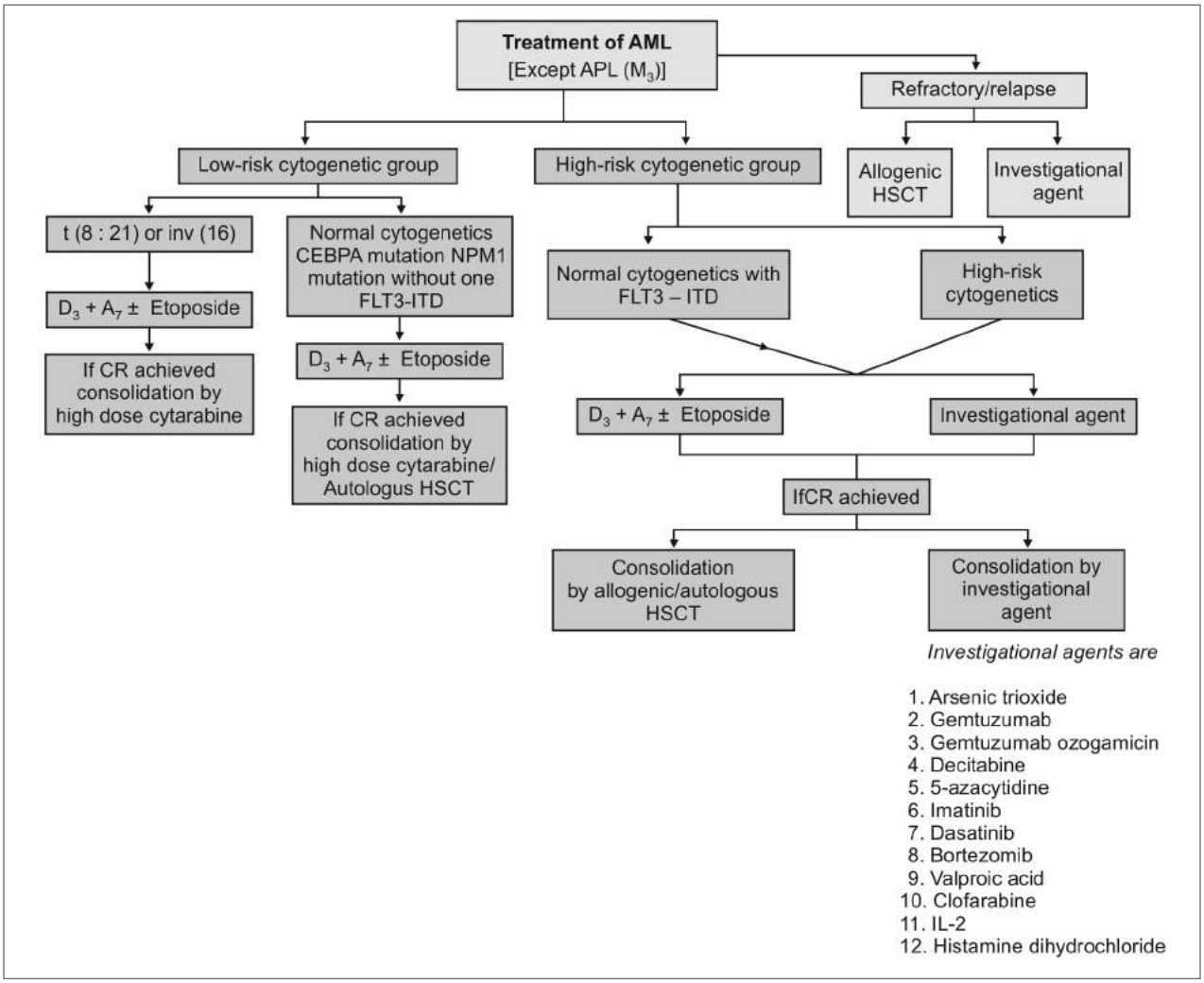
B. Bad prognostic factors
1. **Age** (at diagnosis): Is inversely correlate with prognosis
2. **Prolonged symptomatic interval preceeding diagnosis** (with cytopenia) associated with lower CR rate and shorter survival time
3. Secondary AML or development of AML after treatment with cytotoxic agents for malignancy is extremely difficult to treat and carries poor prognosis
4. Hyperleukocytosis (>100,000/mL) have CNS bleeding and pulmonary leukostasis and relapse.
5. Chronic intercurrent disease or acute medical problem at diagnosis: Carries poorer prognosis.
6. Genetic marker: Patient with t (8 : 21), inv (16), t (15 : 17) have good prognosis, while those with no cytognic abnormality—moderate prognosis
   Patient with complex karyotype [inv (3) or inv (7)] have poor prognosis

Induction Chemotherapy (Flowchart 78.1)

The commonly used CR (clinical remission) induction regimen for all AML except APL (M_3) consists of combination therapy with **cytosine arabinoside for 7 days** (cytarabine) and **daunorubicin/idarubicin for initial 3 days (D_3A_7)**.

- **Daunorubicin** (45–60 mg/m^2/day) IV on day D_1, D_2, D_3. or **idarubicin** (12–13 mg/m^2/day) IV on day D_1, D_2, D_3 (is superior in younger patient).
- **Cytarabine** (100–200 mg/m^2/day) for 7 days from D_1– D_7 by continuous intravenous infusion.
- **Etoposide** can be added to this regimen but in that condition dose of daunorubicin to be increased to 90 mg/m^2.

Flowchart 78.1: Treatment of AML except APL (M_3)



For patient with APL (M_3) induction of CR is done by **daunorubicin** with **tretinoin** (all trans retionic acid) and the Arsenic trioxide followed by consolidation with **Daunorubicin** and maintenance with **tretinoin**. After first cycle of chemotherapy bone marrow and peripheral blood is reexamined for residual leukemia.

Criteria for complete remission (CR)

- Peripheral neutrophil count >1500/mL.
- Platelet count >100,000/mL.
- Hb%/hematocrit is not a criterion for CR.
- Circulating blast cells should be absent. If a few is detected on first exam that should disappear on subsequent studies.
- Bone marrow cellularity >20% with trilineage maturation.
- Blast cells in bone marrow should be less than 5%.
- Auer rods should be absent.
- Extramedullary leukemia should not be present.
- RT-PCR and FISH and flow cytometry are currently used to detect residual disease.
- Patient who achieve CR undergo postremission **consolidation therapy** which include
  - **High dose cytarabine**.
  - **Allogenic SCT** (stem cell transplant/autologous SCT).
  - Novel investigational agents **decitabine**/**clofarabine** for the high-risk patient without compatible donor for allogenic SCT or who did not achieve CR as stated in the above figure.

Supportive Care

- Patient with granulocytopenia should receive G- CSF, GM-CSF or blood transfusion.
- Patient with thrombocytopenia should receive **platelet transfusion** to maintain platelet count in between 10,000–20,000/mL if possible from HLA matched donor.
- Patient with anemia—packed cell transfusion to maintain hemoglobin around 8 g/dL.
- Blood product should be **irradiated** to prevent graft versus host disease (GVHD).

- **CMV negative blood product** should be used for CMV seronegative patient.

TREATMENT OF INFECTION

- Infection to be detected and treatment to be instituted as early as possible.
- **Oral nystatin/clotrimazole** is recommended for oral candidiasis.
- For AML patient—**quinolones** and **fluconazole** prophylaxis in absence of fever is beneficial.
- For HSV seropositive patient—**Acyclovir prophylaxis** to be started.
- For fever—(in 50% patient,) the actual infection could not be documented.
- Acceptible regimen for emperical antibiotic therapy should include anyone of the initial 3 regiment
  - **Imipenem—Cilastatin/piperacillin—tazobactum** with **aminoglycoside**/3rd generation cephalosporin with antipseudomonal activity (**ceftazidime/cefepime**).
  - Double B-lactam combination (**ceftazidime with piperacillin**).
  - If patient is hypersensitive to B-lactam **aztreonam with aminoglycoside or quinolone.**
  - If fever does not subside within 3 days and gram-positive organism is suspected then **vancomycin** can be added—1 g 12 hourly.
    Or
  - If temperature does not subside within 7 days, antifungal like **amphotericin** B/**caspofungin/voriconazole** should be used.
- Antibiotic should be continued so long as the patient remains neutropenic.

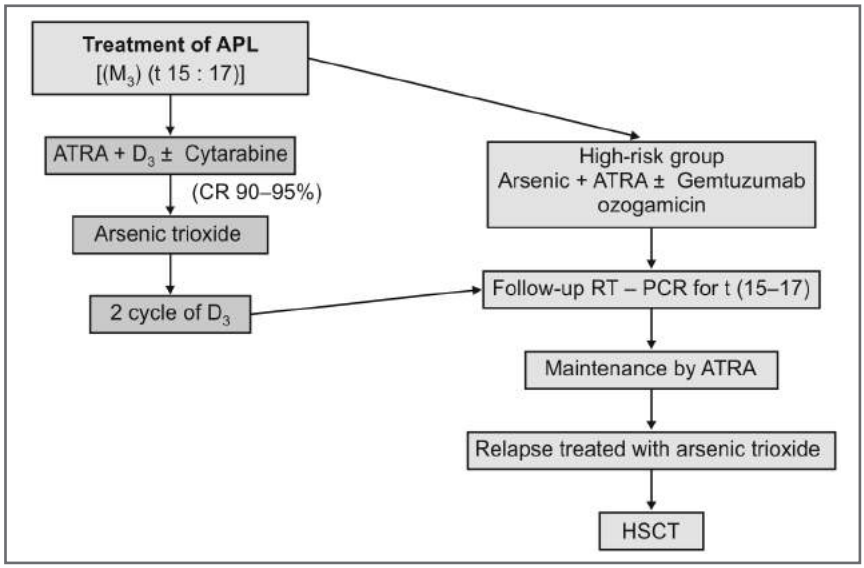
TREATMENT OF ACUTE PROMYELOCYTIC LEUKEMIA (APML–M_3) (FLOWCHART 78.2)

- It is responsive to cytarabine and daunorubicin therapy but 10% of patients die of DIC induced by release of granule component of dying tumor cells.
- **All-trans retinoic acid (ATRA)** or **tretinoin** does not produce DIC and is the drug of choice for treatment of M_3.
- **In *PML,* ATRA (45 mg/m²/day)** until remission is documented along with **daunorubicin (45–60 mg/ m²/day**) IV on day 1, 2, 3 for induction of CR.
- It is the safest and most effective treatment of acute promyelocytic leukemia.
- ATRA can produce **APL differentiation syndrome** characterized by **fever, dyspnea, chest pain, edema, pulmonary infiltrate, pleural and pericardial effusion and hypoxia** which can be managed by glucocorticoid.
- Tretinoin refractory cases are treated with arsenic trioxide. Combination of tretinoin with arsenic trioxide in refractory APL are under trial. Combination of **arsenic trioxide** with **tretinoin and/or daunorubicin/gemtuzumab ozogamicin** (monoclonal antibody to CD_{33} combined with cytotoxic agent calicheamicin) show favorable response.

POSTREMISSION THERAPY

- High dose cytarabine is similar to achieve CR by standard dose cytarabine but **duration of CR is more prolong with high dose cytarabine**.
- **High dose—3 g/m²/every 12 hourly on D_1, D_3, D_5.**
- **Intermediate dose—400 mg/m²/day for 5 days by continuous infusion**.

Flowchart 78.2: Treatment of acute promyelocytic leukemia APL (M_3)



- **Standard dose—100 mg/m²/day for 5 days by continuous infusion**.
- In APL, the role of cytarabin in induction of remission and consolidation is controversial.
- Toxicity of high dose cytarabin
  - Myelosuppression
  - Pulmonary toxicity
  - Cerebellar toxicity.

MYELOPROLIFERATIVE DISORDER

It consists of a clonal stem cell disorder—results in excess production of myeloid element in the bone marrow.
These consist of
- Essential thrombocythemia
- Polycythemia vera
- Chronic myeloid leukemia
- Myelofibrosis.

ESSENTIAL THROMBOCYTHEMIA

It is a chronic myeloproliferative disorder characterized by over production of platelet. Average age of onset is 5th–6th decade of life with platelet count >600,000/mL. About 30% of patient have this disorder in 3rd decade of life.

CLINICAL FEATURES

Splenomegaly present in 40% patient.

Hepatomegaly present in 20% patient.

About 50% patient remain asymptomatic and detected incidentally. Hyperuricemia and hyperphosphatemia and hyperkalemia (due to released from aggregated platelet) may be present.
Symptoms are due to thrombosis causing:
- **TIA/scotoma**
- **Amaurosis fugax**
- **Migraine**
- **Renal vein thrombosis**
- **Budd-Chiari syndrome**.

Patient with extremely high platelet count >1 million/mL may have hemorrhagic complication that are due to acquired von Willebrand syndrome.

DIAGNOSIS

For diagnosis platelet count must be >600,000/mL on two different occasion one month apart after exclusion of iron deficiency, infection and malignancy is diagnostic of essential thrombocythemia.

Bone marrow shows hypercellular marrow with morphologically abnormal megakaryotic hyperplasia with megakaryocytic cluster. About 50% patient have JAK-2 mutation (a gain of functional mutation on chromosome 9) that may be present in all the myeloproliferative disorder. CML is excluded by absence of Philadelphia chromosome. Polycythemia is excluded by hematocrit and erythropoietin level.

TREATMENT OF ESSENTIAL THROMBOCYTHEMIA

Treatment depends on the age of patient, degree of thrombocytosis and medical history.
- In case TIA, stroke, myocardial infarction, two episode of GI bleeding quick reduction of platelet count is done by **platelet apheresis** and **high dose hydroxyurea**.
- In case of less urgent symptom myelosuppression is done by lower dose **hydroxyurea, anagrelide or INFα plus aspirin**.
- Smoking should be stopped.
- Erythromelalgia respond rapidly to aspirin.
- Asymptomatic patients are managed with low dose aspirin and close observation.

POLYCYTHEMIA VERA

It is characterized by over production of RBC although WBC and platelet may also be affected.

CAUSES OF SECONDARY POLYCYTHEMIA

- Tumor-related increase in serum erythropoietin level Renal cell carcinoma, hepatocellular carcinoma, uterine fibroid.
- Hypoxemia—COPD, sleep apnea, obesity, high altitude.
- Increase carboxyhemoglobin—Smoking.
- High O_2 affinity Hb.

CLINICAL FEATURES

Symptoms—Headache, sweating, weight loss paresthesia, dizziness—generalized pruritus after hot bath (in 50%).

Sign—Ruddy cyanosis, hypertension, splenomegaly.

Thrombotic disorder—Erythromelalgia, TIA, MI, stroke, DVT, Budd-Chiari syndrome develops in two-thirds patient.

Thrombosis is due to increased RBC mass, increased viscosity aggravated by thrombocytosis (50%) and leukocytosis in (75%).

Postoperative patients are at increased risk of thrombosis and hemorrhage.

DIAGNOSIS

Hematocrit >60% in male and 56% in female.

However patient with slightly higher hematocrit and Budd-Chiari syndrome should be evaluated for polycythemia by nuclear medicine and depressed level of erythropoietin. JAK2 V 617F mutation should always be searched for as 40% of Budd-Chiari syndrome have polycythemia.

Secondary polycythemia is excluded by measuring baseline erythropoietin, carboxy Hb level, arterial O_2

saturation and oxygen partial pressure at which 50% Hb is saturation.

TREATMENT

- **Phlebotomy** to lower PCV <42% in female and <45% in male.
- Low dose **aspirin** is given to all patient.
- Hyperuricemia is treated with **allopurinol**.
- **Antihistaminic** for pruritus.
- **INFα, anagrelide** and/or **hydroxyurea** for older symptomatic patient. Death is due to thrombosis, bleeding, AML and myelofibrosis.

CHRONIC MYELOID LEUKEMIA (CML)

It is a disease of clonal expansion of hemopoietic stem cell possessing a reciprocal translocation between chromosomes 9 and 22.

This t (9 : 22) results in head to tail fusion of BCR gene on chromosome (22) with the Abl (named after abalson murine leukemic virus) gene located on chromosome (9) resulting in formation of BCR-Abl chimeric gene. Which produces excessive tyrosine kinase. This tyrosine kinase cause excessive proliferation of hemopoietic stem cell of granulocytic series and result in chronic myeloid leukemia.

ETIOLOGY—EXACT ETIOLOGY IS NOT KNOWN

- Large dose radiation can induce CML.
- No clear correlation with exposure to cytotoxic drugs, alkylating agent or viral etiology could yet be established.
- Cigarette smoking accelerates the progression to blast crisis.

  The disease has three clinical phases:
  1. Chronic phases
  2. Accelerated phase
  3. Phase of blast crisis.

CLINICAL FEATURES

Symptoms

- Usually onset is insiduous.
- A small percentage of patient is detected in routine health check-up.
- Other presents with features of hypercatabolic symptoms (**fatigue, malaise, weight loss, fever, sweating**) or features of splenomegaly are **early satiety or LUQ mass** and pain.
- Less common symptoms are related to granulocyte/platelet dysfunction—**infection, thrombosis, bleeding**.
- Occasionally, patient may present with leukostatic manifestation due to leukocytosis and thrombocytosis, e.g. **vaso-occlusive disease, CVA, AMI, venous thrombosis, priapism, visual disturbances, pulmonary insufficiency**.
- About 10–15% of patients present with accelerated phase or blast crisis.
- Onset of accelerated or blast crisis phase is usually heralded by **unexplained fever, significant weight loss, bone and joint pain, bleeding-thrombosis and features of infection**.
- Histamine production secondary to basophilia in accelerated or blast crisis phase is manifested as **pruritus, diarrhea, flushing**.

Signs

- Mild pallor.
- Moderate to **huge splenomegaly**.
- **Mild hepatomegaly**.
- **Myeloid sarcoma** (chloroma) at various sites and lymphadenopathy presents in the late stage of the disease and carries poor prognosis.

HEMATOLOGICAL FINDING

Blood and Bone Marrow Findings

- **Blood**
  - High WBC count ranges from 1–3 lacks with various degree of immaturity of granulocytic series in chronic phase.
  - Usually circulatory blast <5% combination of circulatory blast and promyelocyte is <10%.
    Blast—10–20% seen in accelerated phase
    Blast >20% seen in blast crisis.
  - Blood basophil, eosinophil, monocyte count is high.
  - Platelet count is always elevated.
  - Mild degree of normocytic normochromic anemia.
  - LAP score (leukocyte alkaline phosphatase) is low.
  - Serum B_{12} and B-binding protein is elevated.
- **Bone marrow**
  - Blast percentage is generally normal or slightly elevated.
  - *Myeloid and megakaryocyte lineage greatly supercede the erythroid precursor with alternation of myeloiderythroid ratio (7 : 1).*
  - *50% patients show increased marrow collagen.*
- Accelerated phase is defined by
  - Increasing degree of anemia unaccounted for bleeding and chemotherapy.
  - *Blood/marrow blast between 10–20%.*
  - *Blood and marrow basophil ≥20%.*
  - *Platelet count <100,000/mL.*
- Blast crisis is defined by
  - *Acute leukemia like picture blood/marrow blast ≥20%.*
  - *Hyposegmented neutrophil (Pelger-Huët nuclear anomaly).*

  Blast can be classified as
  - Myeloid (50%)

- Lymphoid (33%)
- Erythroid (10%)
- Rest—Undifferentiated.

CHROMOSOMAL FINDINGS

- All the patients should have the evidence of translocation either by cytogenic, molecular or FISH study.
- Cytogenetic hallmark of CML is the presence of reciprocal translocation of long arm in between 9 and 22 chromosomes [Philadelphia chromosome] present in 90–95% patient.
- Some patients have more complex translocation involving three, four or five chromosomes including translocation of chromosome 9, 22. However molecular consequences of this changes is similar to those resulting forms t (9 : 22).

TREATMENT

The treatment of CML has undergone a dramatic change from busulfan to and allogenic HSCT through hydroxyurea, IFN, imatinib in the last couple of years.

- **Allogenic SCT**—It is currently the only curative therapy of choice where feasible.

Outcome depends on
a. Age of the patient
b. Phase of the disease (early chronic phase has a good prognosis than late accelerated/blastic phase)
c. Type of donor (syngenic or HLA compatible allogenic related/unrelated donor)
d. Preparative regimen (myeloablative/reduced intensity myelosuppression)
e. Graft versus host disease (GVHD)
f. Posttransplant treatment

- **Imatinib mesylate**—It works through
  - Competitive inhibition of ATP binding site of Ablkinase in the inactive conformation which leads to inhibition of tyrosine phosphorylation of proteins involved in BCR-Abl signal transduction leading to **apoptosis of cell expressing BCR-Abl chimeric gene**.
  - **Dose—400 mg/day** for life long.

    Progression of CML to accelerated or blastic phase of disease is 3% in patient treated with imatinib which is much less than 8.5% of patient treated with INF.

    Patient who achieve major molecular response by 1 year, no accelerated/blastic phase is seen among them.
  - Those who do not achieve major cytogenic remission following 3 months of therapy has a higher risk of progression to accelerated/blastic phase.
  - In newly diagnosed CML –

    Percentage of *complete hematological remission is 97% with imatinib while it is only 69% with IFN-α* and cytarabine therapy.
  - Side effects—Nausea, diarrhea, skin rash, fluid retension, muscle cramps.
  - **Dasatinib**—100 mg/day.

    Nilotinib— 400 mg twice daily.

    These two are newer homolog of imatinib and are now recommended for *chronic or accelerated phase of CML who are resistant or intolerant to imatinib therapy*.
- **Interferon (IFN)**
  - It was once the treatment of choice before introduction of imatinib.
  - Patient treated with IFN-α survive longer than patient treated with hydroxyurea or busulphan.
  - **Dose**—1.5 million U SC on alternate day.
  - Acute side effects like flu-like symptoms develop within 1–3 weeks.
  - Chronic side effects of INF are neurologic (fatigue, lethargy, depression, weight loss, myalgia, arthralgia develops in 50% of patient).
  - Cough.
  - Postnasal drip.
  - Dryness of skin.
  - Immune thrombocytopenia.
  - Anemia.
  - Hypothyroidism.

EXERCISE

Write short notes on

1. Stages with clinical features of CML.
2. Treatment of CML.

Chapter 79

Lymphoid Cells Malignancy (Lymphoma)

Previously, it was called '**Lymphoma**' meaning swelling of lymph node but as later our knowledge expands about the etiology and origin of this disease, it seems that these are actually malignancy arising either from 'B' or 'T' lymphocyte (cells of immune system at different stages of differentiation and maturation).

- Lymphoma are considered as the clonal proliferation of immune cell.
- Lymphoma ranges from most indolent to most aggressive human malignancies.
- Some malignancy of lymphoid cell present as leukemia [involvement of bone marrow and blood, i.e. acute lymphoblastic leukomia (ALL)].
- While others present as lymphoma (solid tumors of immune systems, i.e. diffuse large B-cell lymphoma).
- Some lymphoid malignancy may have features of lymphoma and leukemia both (SLL/CLL).
- While some other lymphoid malignancy may initially present as lymphoma in course of time develops the manifestation of leukemia.

ETIOLOGY

Etiology is poorly understood.

Following factors have a strong association with lymphoid malignancy:

- Infection—The following viral infections have close association with lymphoma.
  - **Epstein-Barr virus (EBV)**—Burkitt's lymphoma, Hodgkin's disease.
    Posttransplant lymphoma. Diffuse large β-cell lymphoma of CNS. Extranodal NK/T-cell lymphoma.
  - **HTLV-1**—Adult T-cell lymphoma/leukemia (ATLL)
  - **HIV**—Diffuse large B-cell lymphoma, Burkitt's lymphoma.
  - **HCV**—Lymphoplasmocytic lymphoma.
  - **HHV-8**—Primary effusion lymphoma, multicentric Castleman's disease.
  - *Helicobactor pylori*—Gastric MALT (mucosa associated lymphoid tissue) lymphoma.
  - **Borrelia species**—MALT lymphoma of skin.
  - *Chlamydophila psittaci*—Malt of eye.
  - *Compylobacter jejuni*—Malt of small intestine.
- Inherited immune deficiency disease
  - Klinefelter
  - Ataxia telangiectasia
  - Wiskott-Aldrich syndrome
  - Chédiak-Higashi syndrome.
- Acquired immune deficiency
  - Iatrogenic immune suppression (organ transplant)
  - HIV-I
  - Acquired hypogammaglobulinemia.
- Autoimmune diseases
  - Sjögren's syndrome
  - Rheumatoid arthritis
  - SLE.
- Drugs and chemicals
  - Phenytoin, digoxin
  - Phenoxy herbicide.
- Radiation—Therapeutic and accidental exposure.

CLASSIFICATIONS

- Lymphoid cell malignancy are traditionally classified in the first half of last century as Hodgkin's disease and non-Hodgkin's lymphoma after recognition of RS cell (Reed-Sternberg cell) at the beginning of 20th century.
- Histologic classification of lymphoma is the most controversial issue in the field of malignancy is proved by the fact that it has been changed 6 times in last 40 years.
- Rappaport classification (1966)
  a. Nodular non-Hodgkin's lymphoma (NHL)
  b. Diffuse NHL
- Lukes–Collins classification (1972)
  a. B-cell lymphoma
  b. T-Cell lymphoma
  c. Histiocytic lymphoma
  d. Undifferentiated lymphoma
- Kiel's classification (1981)
- Working formulation (1982) by international study group
  a. Low grade
  b. Intermediate grade
  c. High grade
- REAL classification (1984) (revised European American classification)
- WHO classification (1999) [most accepted worldwide]

WHO CLASSIFICATION OF LYMPHOID MALIGNANCY

Common B-cell neoplasm

About 75% of all lymphoid leukemias and 90% of all lymphoma are B-cell origin.

- **Precursor B-cell** neoplasm Precursor B-cell lymphoblastic leukemia/lymphoma (acute lymphoblastic leukemia). (HLADR$^+$, TOT, HCR, CD10, 19, 20, 21, CD5 and CD38 are the B-cell marker).
- **Mature B-cell neoplasm**
  - **B-cell CLL/SLL.**
  - B-cell prolymphocytic leukemia.
  - Lymphoplasmocytic lymphoma.
  - Splenic marginal zone B-cell lymphoma.
  - **Hairy cell leukemia.**
  - **Plasma cell myeloma/plasma cytoma.**
  - **Externodal marginal zone B-cell lymphoma (MALT).**
  - **Mantle cell lymphoma.**
  - **Follicular lymphoma.**
  - **Nodal marginal zone B-cell lymphoma.**
  - **Diffuse large B-cell lymphoma (DLBL).**
  - **Burkitt's cell lymphoma—leukemia**.
  - Hodgkin's disease.

Common T-cell neoplasm are

Cell surface marker of T-cell differentiation are CD 1, 2, 3, 4, 5, 6, 7, 8, 38, 71.

- **Precursor T-cell neoplasm**
  - Precursor T-cell acute lymphoblastic leukemia/lymphoma.
- **Mature T-cell neoplasm**
  - T-cell polymorphocytic leukemia
  - T-cell granular lymphocytic leukemia
  - Aggressive NK cell leukemia
  - Adult T-cell lymphoma/leukemia (ATLL)
  - Extranodal NK/T-cell lymphoma
  - Enteropathic T-cell lymphoma
  - Hepatosplenic gamma-delta T-cell lymphoma
  - **Mycosis fungoides (Sezary syndrome)**
  - Peripheral T-cell lymphoma
  - Angioblastic T-cell lymphoma
  - Anaplastic large cell lymphoma.
  - Hodgkin disease.

Hodgkin's Disease (B-cell Neoplasm)

Subtypes

- **Nodular sclerosis**
- **Mixed cellularity**
- **Lymphocytic predominant**
- **Lymphocytic depletion**.
  - Our focus will be on the subset of neoplasm which together constitute 95% of lymphoid malignancies.

These are as follows:

- ***Acute lymphoblastic leukemia/lymphoma*** (Precursor T and B-cell type) (3.8%).
- CLL/SLL (9%).
- Multiple myeloma (16%).
- Diffuse large B-cell lymphoma (31%).
- Burkitt's lymphoma (2.4%).
- Follicular lymphoma (22%).
- Mantle cell lymphoma (6%).
- Hodgkin's disease (3.2%).

Table 79.1: Subdivision of B-cell lymphoma according to clinical progression

Indolent tumor	Aggressive tumor	Highly aggressive tumor
• Small lymphocytic lymphoma • Follicular lymphoma • Marginal zone lymphoma • MALT lymphoma • Splenic lymphoma • Nodal lymphoma	DLBL Mantle cell lymphoma	Burkitt's lymphoma Lymphoblastic leukemia AIDS-related lymphoma

- Indolent lymphoma are incurable except in few patient with stage-I disease and median survival in 9–10 years.
- Patient with aggressive or highly aggressive NHL are potentially curable with combination chemotherapy.
- All B-cell derived NHL are CD 19 and CD 20 positive.

STAGING EVALUATION OF NONHODGKIN/ HODGKIN LYMPHOMA

Staging of lymphoma is done with the help of physical examination and the following investigations:

- Physical examination.
- Documentation of B-symptom.
- Laboratory evaluation—CBC, LFT, uric acid calcium, serum protein electrophoresis, serum B_2 microglobulin and lactate dehydrogenase, urea, creatinine.
- CT of abdomen, pelvis, chest.
- Bone marrow biopsy.
- Lumbar puncture with CSF study—in lymphoblastic, Burkitt's and diffuse large B-cell lymphoma with positive marrow biopsy.
- *Gallium scans or PET scan in diffuse large B-cell lymphoma*.

ANN-ARBOR STAGING FOR LYMPHOMA BOTH HODGKIN'S AND NHL

- **Stage I**—Involvement of a single lymph node or lymphoid structure (e.g. spleen, thymus and Waldeyer's ring).
- **Stage II—**Involvement of two or more lymph node on the same side of the diaphragm (the mediastinum is a single site, hilar lymph nodes should be considered "lateralized" and, when involved on both sides, consider stage II disease).

- **Stage III**—Involvement of lymph node or lymphoid structures on both side of the diaphragm.
  - III_1—Subdiaphragmatic involvement limited to spleen, splenic hilar nodes, celiac or portal lymph nodes.
  - III_2— Subdiaphragmatic involvement include paraaortic, iliac, or mesenteric lymph nodes plus structures in III_1.
- **Stage IV**: Involvement of extranodal site(s) beyond that designated area E.
  More than one extranodal deposit at any location any involvement of liver or bone marrow.
  - E signify: Localized solitary involvment of extralymphatic tissue, excluding liver and bone marrow.
  - **A signify**: No symptom
  - **B signify**:
    - Unexplained weight loss of >10% of the body weight during the last 6 months.
    - Unexplained persistent, or recurrent fever with temperatures >38°C during the last month.
    - Recurrent drenching night sweats during the last month.

IPI SCORE

- **International prognostic index for NHL**—Patients are subdivided into 5 groups depending on the presence of 5 adverse prognostic factors. There are:
  - **Age ≥60 years**
  - **Serum LDH → elevated**
  - **Performance status ≥2 [ECOG]**
  - **Ann-Arbor stage—III/IV**
  - **>1 site of extranodal involvement**.

  Based on the presence of risk factor lymphomas are classified into 4 groups:

		Risk group	5 years survival
0–1 risk factor	→	Low-risk group (35%) patient	75%
2 risk factor	→	Low-intermediate risk group (27%) patient	51%
3 risk factor	→	High-intermediate risk group (22%) patient	43%
4/5 risk factor	→	High-risk group (16%) patient.	26%

ACUTE LYMPHOBLASTIC LEUKEMIA

PRECURSOR B-CELL/T-CELL LEUKEMIA

It is the most common (25%) cancer of childhood and 75% all newly diagnosed leukemia in child.

- This disorder rarely present as lymphoma either in child or in adult.
- Malignant cells are of precursor B-cell or T-cell in origin.
- Age of onset
  - 4 years for pre-B phenotype.
  - 15–20 years for pre-T phenotype.

CLINICAL FEATURES

Both AML and ALL share some common features.

- *Features due to suppression of RBC series*
  - Malaise
  - Pallor
  - Fatigue
  - Diminished effort tolerance.
- *Features due to suppression of WBC series*
  - Fever due to infection/septicemia
  - Common sites for infection
    - Lung
    - Gum/upper respiratory tract
    - Urinary tract
    - Skin
    - Perirectal tissue.
- *Features due to suppression of platelet lineage: Bleeding from*
  - Skin (ecchymosis, petechiae, easy bruising, purpura), nose (epistaxis), gum bleeding, vaginal bleeding, retinal hemorrhage. Intracranial hemorrhage is a dreadful complication usually associated with headache, fundal hemorrhage, focal neurodeficit.
- *Features due to expanding mass in bone marrow*:
  - Sternal tenderness
  - Bone pain.
- *Features due to leukemic infiltration are as follows*
  - Hepatomegaly
  - Splenomegaly
  - Lymphadenopathy.

  These are present in 60% patient at diagnosis.
- Leukemic infiltrate in CNS (seen in 2–5%) occurs in brain parenchyma, spinal cord and meninges giving rise to the picture of leukemic meningitis.
- Other areas of leukemia cell infiltration are gum, testis, ovary, eye, bone, skin and joint.

Table 79.2: Immunophenotype and genetic marker for low grade NHL

	CD5	CD10	CD20	CD23	Chromosomal marker	Oncogeny
Follicular lymphoma	–	+	+	–	Z (14 : 18)	bel –2
SLL/CLL	+	–	Dim	+	Trisomy 12	–
Mantle cell lymphoma	+	–	+	–	Z (11 : 14)	bel –1 (cyclin D1)
MZL/MALT lymphoma	–	–	+		Z (1 : 18)	API –2
					(1 : 14)	MALT bel –10

INVESTIGATIONS

- Anemia is of normocytic, normochromic type.
- Increased TLC (10,000–50,000/mL seen in 50% patient. In 50% patient TLC <10,000/mL).
- Circulating blast is usually 60–100%.
- Platelet count <100,000/mL.
- Rarely there may be pancytopenia with few blast in the blood which is called aleukemic leukemia.
- But the marrow is flooded with blast cell resulting in aplastic anemia.
- Lumbar puncture is required for diagnosis of CNS leukemia. A single blast cell in CSF is sufficient to diagnose CNS leukemia.
- Bone marrow biopsy for genetic and immunologic study.
- Immunophenotype **(Table 79.2)**
  - Pre B-cell express – CD 19 with TdT
  - Pre T-cell express – CD 2 with TdT

  (TdT—Terminal desoxynucleotidyl transferase)
- TdT is positive for both pre B/pre T-cell type.
- **Karyotype**—Major cytogenetic subgroups include t (9 : 22) seen in acute lymphoblastic leukemia, t (8 : 14) seen in Burkitt's lymphoma—Associated with poor prognosis.

Table 79.3: Classification of acute lymphoid leukemia

Immunologic subtype	FAB subtype	Cytogenetic abnormality
Pre B ALL – 75%	L_1 L_2	t (9 : 22) t (4 : 11) t (1 : 19)
T-cell ALL – 20%	L_1 L_2	(14 q 11) or (7 q 34)
B-cell ALL – 5%	L_3	t (8 : 14), t (8 : 22), t (2 : 8)

LEUKEMIA (TABLE 79.3)

- L_1—Small uniform blast seen in acute lymphoblastic leukemia in child.
- L_2—Large round and more variable size blast.
- L_3—Uniform size blast with vacuolated basophilic cytoplasm—seen in Burkitt's lymphoma.

PROGNOSIS

1. Children (2–10 years) with pre-B leukemia have best prognosis and can be cured in 90% patient.
2. Poor prognostic parameters
   - Chromosomal abnormality t (9 : 22)
   - Elderly age
   - Very high WBC count
   - Patient clinical status
   - Major organ function.

   Overall cure rate in children is (90%) but 50% in adult. This reflects bad cytogenetic abnormality seen in adult B-cell lymphoblastic leukemia.

DIFFERENTIAL DIAGNOSIS

- Aplastic anemia.
- Idiopathic thrombocytopenic (ITP).
- Juvenile rheumatoid arthritis (JRA) for joint pain, neuroblastoma, NHL. Rhabdomyosarcoma, Ewing's sarcoma, retinoblastoma.

TREATMENT

Treatment consist of three steps:
- Supportive therapy
- Bone marrow transplant/stem cell transplantation (BMT/SCT)
- Specific therapy.

Supportive therapy
- Anemia → is managed by packed cell transfusion.
- Bleeding → is managed by platelet transfusion.
- Infection → is managed by identification of viral/bacterial/fungal/protozoal cause and appropriate chemotherapy.
- Barrier nursing.
- Maintenance of fluid-electrolyte balance.
- Evidence of hyperuricemia is managed by
  - Hydration
  - Urine alkalization
  - Allopurinol—100 mg 8 hourly
  - Rasburicase/febuxostat.

BMT/SCT—*Allogenic bone marrow transplant.*Considered to be curative among the young patients with ALL in 1st/2nd or subsequent remission. Success rate is 20–40%.

Treatment protocol of ALL (Table 79.4)

Combination chemotherapy with limited cranial irradiation is the main treatment protocol for ALL.

Current treatment of ALL has been divided into four phases:
- **Remission induction**—By *vincristine, prednisolone, daunorubicin, L-asparaginase.*
- **CNS prophylaxis**—By *methotrexate*
- **Intensification/consolidation**—By *cyclophosphamide, vincristine, cytarabin, 6 MP.*
- **Maintenance therapy**—By *vincristine, prednisolone, daunorubicin, L-asparaginase.*
  - **Remission induction**—It is done with *vincristine, prednisolone, L-asparaginase, and/or daunorubicin* with a remission rate of 92–98% and therapy lasts for 4–6 weeks.
  - **CNS prophylaxis**—It is based on the fact that most children with ALL have subclinical CNS involvement at the time of diagnosis—this leukemic cells are protected from systemic chemotherapy because of blood brain barrier. So early institution of CNS prophylaxis is essential to increase the survival rate. It is done with—
    - **Intrathecal MTX** with low dose cranial irradiation—1800 cGy.

Table 79.4: Treatment protocol of acute lymphoblastic leukomia

Induction-1 (I_1) →	Prednisolone Vincristine Daunorubicin L-asparaginase MTX	40 mg/m² oral (Day 1–28) 1.4 mg/m² IV (Day 1, 8, 15, 22, 29 30 mg/m² IV (Day 8, 15, 29) 60,000 mg/m² IM. OD × 10 doses in between Day 2–20) 6 mg (<1 year) 8 mg (1–2 years) 10 mg (2–3 years) 12 mg (>3 years) } Intrathecally on day 1, 8, 15, 22
Induction-2 (I_2) →	6-mercaptopurine Cyclophosphamide MTX Cranial irradiation	75 mg/m² oral (Day 1–7 and Day 15–21) 750 mg/m² IV (Day 1 and 15) Same as before 200 cGy × 9 days
Consolidation →	Cyclophosphamide Vincristine Cytarabine 6-mercaptopurine	Same as before Same as before (Day 1 and 15) 70 mg/m² SC × BD × 3 days (Day 1–3 and 15–17) Same as before
Maintenance (6 cycle) with 2–2.5 years	Prednisolone Vincristine Daunorubicin L-asparaginase 6-mercaptopurine MTX	Same as before (Day 1 to 7) 1.4 mg/m² IV (Day 1) 30 mg/m² IV (Day 1) 60,000/m² IM (Day 1, 3, 5, 7) 75 mg/m² oral OD × 3 weeks out of 1 month for a total of 12 weeks 15 mg/m² oral once a week missing every 4th weeks for a total 12 weeks begin on day 15

  - Other alternative regimes are triple chemotherapy (intrathecal) with **MTX, hydrocortisone, cytarabine**.
  - Combination of **intrathecal MTX with moderate dose of intravenous MTX**.
  - Only **high dose MTX**. In this regimen cranial irradiation is reserved for very high-risk features like—
    - » WBC >100,000/cmm.
    - » Philadelphia chromosome with ALL.
    - » Presence of CNS involvement at the time of diagnosis.
    - » T-cell ALL.
- Consolidation—Cranial prophylaxis is followed by another dose of chemotherapy meant to decrease the leukemic burden to minimum. It is done with **L-asparaginase, epipodophyllotoxin, cyclophosphamide, cytarabine and high dose methotrexate**. This consolidation therapy is the main reason for improvement in survival.
- **Maintenance therapy**—It is continued for additional 2–2.5 years without which relapse occur within 2–4 months. [Except B-cell ALL—which can be treated with short-term (6 months) high dose chemotherapy like NHL]. Maintenance dose include:
  - **Daily 6-mercaptopurine for 3 weeks**.
  - **Once a week oral MTX**.
  - **Monthly pulse therapy of vincristine and daunorubicin**.
  - **Prednisolone for first 7 days** or with other cytotoxic drugs. For better outcome MTX and 6-mercaptopurine should be given to the limit of tolerance as determined by absolute neutrophil count.

SIDE EFFECTS OF TREATMENT

- Due to cranial irradiation—Cognitive and intellectual impairment and CNS neoplasm.
- Due to etoposide and tenoposide—Secondary acute myeloid leukemia.
- Daunorubicin cause cardiac toxicity.
- Endocrine dysfunction cause—Short strature, growth retardation obesity, precocious puberty, osteoporosis thyroid dysfunction.

TREATMENT OF RELAPSE

Despite successful treatment relapse occurs in 20–30% of children. Most common sites are bone marrow (20%), CNS (5%) and testis (3%). Relapse in extramedullary site have a better progonosis.

The treatment of relapse must be done more aggressively than the first line therapy with induction of new drug to overcome the problem of drug resistance.

FOLLICULAR LYMPHOMA

It is the most common indolent lymphoma and constitute 40% of NHL. It is subdivided into 3 grades. It is CD 10+ CD

20+ (immunophenotypically) positive. Most patient are asymptomatic at diagnosis although having disseminated disease with bone marrow involvement.

Median survival 8–12 years.

It is incurable except in those with localized disease by irradiation.

TREATMENT IS CONTROVERSIALS

- Wait and watch for early stage disease.
- Patient with IA and IIA (early) stage disease are treated with local field radiation and 50% remain disease free at 10 years.
- Patient with disseminated disease need systemic treatment.
- Emerging data suggest that rituximab as a maintenance treatment prolong progression free and overall survival.

MALT LYMPHOMA

These are classified as marginal zone lymphoma. Indolent form are localized at extranodal site, e.g. **stomach, lung, thyroid, salivary gland, breast** and **eye**. Gastric malt are associated with ***H. pylori*** infection which is treated by metronidazole, amoxycillin, clarithromycin and PPI to eradicate the antigenic drive for lymphocytic proliferation. This treatment often induces complete remission in 75% with localized gastric malt. However, this approach is less well-established outside stomach except a conflicting role of chlamydial infection is orbital MALT lymphoma. Radiation is often used to treat MALT lymphoma when antibiotic approach is not successful or sites other than stomach.

For more extensive disease treatment is similar to used in follicular lymphoma.

Marginal zone lymphoma can also present as more aggressive lymphoma with large cell and higher mitotic rates than indolent marginal zone NHL and treated in the same line of DLBL.

CHRONIC LYMPHOID LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

- Chronic lymphocytic leukemia and small lymphocytic lymphoma are identical tumors that differ in peripheral blood involvement.

  Those with large number of circulatory lymphocyte is called CLL.

  Those without large number of circulatory lymphocyte but with lymphadenopathy is called SLL (it is thought to be aleukemic phase of CLL) and accounts for 7% of NHL.

  So the clinical presentation may be either leukemia or lymphoma.
- Together CLL and SLL constitute 9% of lymphoid malignancy.

IMMUNOPHENOTYPE

- Malignant lymphocyte express pan B-cell marker — CD5, 19, 20, 23 with surface IgM, IgD.
- CD5 is a marker of monoclonal T-cell (shared by Mantle cell lymphoma).

CLINICAL FEATURES

- Age of onset >50 years (peak around 65 years), children are rarely involved.
- Male—Female ratio is 2 : 1.
- In this disease, there is accumulation of *long lived nonfunctioning B-lymphocyte* that infiltrate bone marrow/blood/lymph node and other tissue.
- About 25% patients remain asymptomatic and diagnosed incidentally when CBC is done for other reasons.
  B symptom seen in 33% patients.
- Generalized lymphadenopathy without splenomegaly is the most common presentation.
- The diagnosis of B-cell CLL should be considered in an elderly patient presenting with
  - *Autoimmune hemolytic anemia*
  - *Autoimmune thrombocytopenia*
  - *Red cell aplasia*: Molecular analysis of immunoglobulin gene sequence in CLL has shown that
    - *About 50% patients have mutated immunoglobulin gene sequence with negative CD38. Who have good prognosis.*
    - *About 50% patients have unmutated immunoglobulin gene sequence with positive CD38 who have poor prognosis.*
- **Hepatosplenomegaly**—Present in 50–60% patients. Bone marrow involvement present in 70–75% patients.
- Suppression of lymphocytic series leads to hypogamsglobulinemia and infection.
- Anemia may be due to autoimmune hemolysis or pure red cell aplasia.
- Thrombocytopenia is due to antoimmune response. About 5 years survival seen in 50% patients.

INVESTIGATIONS

- TLC is usually between 20,000–200,000/mL.
- About 95% of cells are mature looking small lymphocyte.
- Mild to moderate anemia (autoimmune hemolytic anemia) is usually present.
- Direct Coombs test may be positive.
- Thrombocytopenia—autoimmune in nature or due to hypersplenism.
- Lymph node biopsy shows well-differentiated small/noncleaved lymphocyte.
- Serum folic acid level is low.
- Cytoplasmic expression of ZAP-70 protein and presence of CD38 on cell surface caries poor prognosis.

Table 79.5: Staging of typical B-cell lymphoid leukemia

Stage		Clinical features	Median survival years
Rai system			
0	Low risk	Lymphocytosis in blood and bone marrow	>10 years
I	Intermediate risk	Lymphocytosis + lymphadenopathy	7 years
II	Intermediate risk	Lymphocytosis + lymphadenopathy + splenomegaly ± hepatomegaly	1.5 years
III	High risk	Lymphocytosis + anemia+ thrombocytopenia	
Binet system			
I	Less than three areas of clinical lymphadenopathy; no anemia or thrombocytopenia		>10 years
II	Three or more involved node areas; no anemia or no thrombocytopenia		7 years
III	Hemoglobin ≤10 g/dL and/or platelets <100,000/μL		2 years

TREATMENT

Criteria for starting treatment in CLL patient include B symptom (fever, weight loss and night sweats) and symptoms due to lymph node enlargement, hepatosplenomegaly and worsening cytopenia.

- **Binet stage A or RAI stage O** require **no specific treatment**. Only follow-up is necessary. Median survival >10 years.
- **Stage B require no treatment** is required if the patient is at initial stage who has adequate number of circulating blood cell and is asymptomatic, with only lymphadenopathy and hepatosplenomegaly. Median survival is 7 years but most will require therapy in the follow-up.
- **Stage C**—Patients of stage 'c' who present with features of bone marrow failure like anemia and thrombocytopenia with Binet stage C or RAI stage III and IV require initial therapy in almost all cases. These patients have median survival of 1.5 years.
- Only **allogenic stem cell transplant** has curative potential with CLL but this form of treatment is applicable only to few patient because the median age of CLL patient in 70 years.
- **Specific therapy constitute** combination of
  Fludarabine—25 mg/m^2 on D2D3 × 3 cycle
  Rituximab—375–500 mg/m^2 on D1
  Cyclophosphamide—250 mg/m^2 yield highest response in CLL (69%) with half of them achieve molecular remission.
- Therapy may be complicated with high infection rate including opportunistic infection requiring prophylaxis against pneumocystis species and herpes virus infection.
- Patient with p53 mutation respond better to anti CD52 monoclonal antibody (alemtuzumab).
- Hemolytic anemia occurs in 3–37% patient with advanced CLL and treated with high dose corticosteroid, Iv Ig, splenectomy and treatment of CLL.
- Patient with CLL may develop ITP which should be distinguished from thrombocytopenia secondary to malignant infiltration. Treatment of this condition include **corticosteroid, IvIg** and **aggressive chemotherapy** for CLL.

Supportive Therapy

- Immune manifestation of typical B-cell CLL should be managed independently of specific antileukemia therapy.
  Autoimmune hemolytic anemia is managed by **glucocorticoid**.
  Thrombocytopenia is managed by **glucocorticoid**.
- **Hypogammaglobulinemia** is managed by infusion of **gammaglobulin**.
- **When anemia and thrombocytopenia** are due to hypersplenism—**splenectomy** is the treatment of choice.
  Patients presenting with lymphoma are treated with combination chemotherapy (**CHOP/COP regimen**).
- **CHOP—Cyclophosphamide, doxorubicin, vincristine, prednisolone + rituximab.**
- **CVP—Cyclophosphamide, vincristine, prednisolone**.

DIFFUSE LARGE B-CELL LYMPHOMA

Diffuse large B-cell lymphoma (BLBCL) is the most common type of non-Hodgkin lymphoma (33%) and is a heterogenous entity which includes several form of NHL.

COMMON FEATURES

- B-cell phenotype
- Diffuse growth pattern
- Aggressive clinical course.

IMMUNOPHENOTYPE

- Express pan—B-cell antigen CD 19, 20, 23, 79.
- IgM and IgG kappa and lambda light chain formation.
- CD 10 variably expressed.

GENOTYPE

- About 30% patients have (14:18) with rearrangement of BCL2-Ig and BCL-6 gene.
- Overexpression of BCL-2 protein is associated with relapse.

CLINICAL FEATURES

- M > F.
- Median age 60 years but constitute about 25% of childhood NHL.
- B-symptoms present in 33% patients.
- At the time of diagnosis—
  - 54% patient have stage I and II disease.
  - 46% patient have stage III and IV disease.
- DLBCL usually presents with rapidly enlarging nodal or extranodal (50% cases) mass.
- Involvement of GI tract (15%), bone marrow (20%), brain, skin may be present.
- Liver and spleen involvement is uncommon at diagnosis.
- Leukemic picture is also uncommon.

Overall 46% patients survive up to 5 years.

SPECIAL SUBTYPE

- *EBV is associated with DLBL* in immune compromised individual.
- *DLBCL in young female (median age 37 years) with pleural effusion is very difficult to diagnose and carries poor prognosis.*
- *Intravascular DLBL have bad prognosis* and difficult to diagnose.
- *Diffuse large B-cell lymphoma of pancreas have better prognosis* than pancreatic carcinoma.
- *Primary diffuse large B-cell lymphoma of brain* are now frequently encountered.

PROGNOSIS

- DLBCL is a rapidly fatal disease if untreated, but extensive combination chemotherapy can achieve complete remission.
- IPI risk score 0 present in 10% patient who have 5 years survival around 95%.
- IPI risk score 1–2 present in 45% patient who have 5 years survival around 80%.
- IPI risk score 3/4/5 present in 45% patient who have 5 years survival around 55%.

TREATMENT

- **For stage I and stage II disease**—3–4 cycles of combination chemotherapy with **CHOP** along with local field **radiation** for localized bulky gland.

  Cure rate is 80–90% in stage I and 70–80% in stage II.
- **For bulky stage I, stage III and IV**—6–8 cycles of CHOP + rituximab. 70% of patient can be expected to achieve remission and 50–70% of complete responder will be cured.

Large number of diffuse large 'B' lymphoma are either refractory to treatment or relapse after chemotherapy.

For them two forms of therapy is available:

1. **Autologous bone marrow transplant**—Long-term disease-free survival is 40%.
2. **Salvage chemotherapy**—Long-term disease survival <10%.

Late complication of high dose chemotherapy are AML and MDS need to be balanced against potential benefit of the treatment.

HAIRY CELL LEUKEMIA

Hairy cell leukemia consist of atypical lymphocyte with thread-like cytoplasmic projection from cell surface which is common in older adult and Male : Female ratio (5 : 1).

This disease is characterized by **significant bone-marrow involvement, pancytopenia** and **splenomegaly** but no **lymphadenopathy**. Hairy cell leukemia has B-cell immunophenotypic features with SIg+; CD20+, CD11 and CD103+ on flowcytometry.

TREATMENT

The mainstay of treatment of hairy cell leukemia is **cladribine** continuous infusion for 7 days which induces complete remission in 82% patient. Combination of **interferon, fludarabine** and **rituximab** can also be used in this patient.

MYCOSIS FUNGOIDOSIS

CD4+ T cell leukemia is characterized by major skin involvement when leukemic phase is prominent it is referred to as **Sezary syndrome**. The cells of mycosis fungoides have a **folded or cerebriform nucleus morphology**, skin involvement is **patchy area of diffuse erythroderma** like that of **benign skin disease**. Infection of skin lesion is common and is the leading cause of death.

TREATMENT

Treatment of early stage of mycosis fungoides consist of **corticosteroid, mechlorethamine**, and **carmustine** and **retinoids** such as **bexarotene gel**. More extensive skin involvement responds well to **electron beam radiation, phototherapy with U-V rays** and **oral psoralen** is also effective, combination chemotherapy or immunotherapy with purine nucleoside based on **CHOP like regimen, monoclonal antibody based treatment denileukin diftitox (an antiinterleukin-2 receptor monoclonal antibody linked to diphtheria toxin), interferon alfa or alemtuzumab (anti-CD52 monoclonal antibody)** are useful in disseminated disease. **Vorinostal or suberoylanilide hydroxamic acid** has been approved by FDA for treatment of mycosis fungoidosin.

MANTLE CELL LYMPHOMA

It is characterized by indolent to aggressive lymphoma. This disease is considered incurable but has a shorter median survival (than disseminated indolent lymphoma) of approximately 3 years. Mantle cell lymphoma usually present with disseminated disease including GI involvement. In these patient cell cycle protein cyclin D1 is expressed as a result of an 11:14 chromosomal translocation activating the bcl1gene. More intensive regimen with **cyclophosphamide, vincristine, doxorubicin, dexamethasone, cytarabine and methotrexate** (hyper C- VAD-AM) combined with **rituximab** have improved both response rate and duration of response but cannot cure the patient. Stem cell transplant during first remission have encouraging results.

PLASMA CELL DYSCRASIA

- It is a group of B-cell neoplasm that have common expansion of a single clone of immunoglobulin-secreting cell and a resultant increase in serum level of single homogeneous immunoglobulin or its fragment referred to as **'M' component (monocomponent)**.
- Monoclonal antibody must be present >0.5 g/dL which can be accurately detected by electrophoresis.
  This corresponde to 10^9 cell producing this antibody.
- **Immunoelectrophoresis is used for qualitative assessment** of 'M' component.
- Electrophoresis is used for quantitative assessment of M component.
- M component may be seen in otherwise normal individual called **monoclonal gammopathy of undetermined significance**.
- Collectively this disorder accounts for 15% of death of malignant white cell disorder.
- Plasma cell disorder has 6 major variants
  1. **Multiple myeloma**.
  2. **Localized plasmacytoma (solitary myeloma)**.
  3. **Lymphoplasmocytic lymphoma**.
  4. **Heavy chain disease (Waldenström's macroglobulinemia)**.
  5. **Primary/immunocyte associated amyloidosis**.
  6. **MGUS (monoclonal gammopathy of unknown significance)**.

MULTIPLE MYELOMA

It represents malignant proliferation of plasma cell derived from a single clone.

ETIOLOGY

Exact etiology not known. The common associations are:
- Exposure to radiation in World War II with a 20 years latency.
- Exposure to petroleum product.
- Farmer, woodworker, leatherworker who are exposed to many chemical substances.

GENOTYPE

Deletion of 13q14, 17p13 and 11q.
t (11 : 14) (q 13 : q 32).

Error in splicing and switch recombination of immunoglobulin gene due to overexpression of Myc and Ras gene and mutation of the p53, Rb1 and IL-6 plays a driving role in plasma cell proliferation.

INCIDENCE

- Median age of onset 68 years
- Rare before 40 years of age
- Male > female
- Black > white
- 1% of all malignancy in white
- 13% of hemopoietic malignancy in white
- 2% of all malignancy in black
- 35% of hemopoietic malignancy in black.

PATHOGENESIS AND CLINICAL FEATURES

- **Bone marrow is infiltrated heavily with atypical plasma cells** results is anemia, thrombocytopenia, leukopenia.
- **Localized tumor formation within the bone marrow** results in punched out lesion in radiograph.
- **Uric acid level in serum is elevated** (breakdown product of DNA catabolism).
- **Activation of osteoclast** by OAF (Osteoclast-activating factors) IL-1, VEGF, TNF, MIP-1 and B-lympotoxins results in **punched out bony lesion and hyperuricemia**.
- **Mobilization of Ca^{++} from bone resulting in hypercalciuria, nephrocalcinosis**.
- **Bence-Jones proteinuria, amyloidosis, hypercalcemia, hyperuricemia** results in renal damage and renal failure.
- **Hyperviscosity** of plasma is due to increase level of globulin in serum results in hyperviscosity syndrome.

CLINICAL FEATURES

- **Bone marrow involvement results in**
  - Anemia
  - Leukopenia
  - Thrombocytopenia.
- **Bone involvement results in**
  - Localized swelling over vertebra, skull, sternum, ribs, clavicle and pathological fracture.
- **Renal involvement is due to**
  - Nephrocalcinosis
  - Amyloidosis
  - Hyperuricemia

  - Hypercalcemia
  - Bence-Jones proteinuria.
- **Neurologic symptoms**
  - Cord compression due to collapse of vertebra with radiculopathy.
  - Amyloid peripheral neuropathy and carpal tunnel syndrome.
- **Features of hyperviscosity syndrome** are blurred vision, papilledema, headache, vertigo, fatigue.
- **Suppression of immune system cause**: LRTI and UTI.
- **Clotting problem** present as purpura which is due to interference with clotting factor, platelet dysfunction and amyloid damage of endothelium.

DIAGNOSTIC CRITERIA FOR MULTIPLE MYELOMA/ MGUS/OTHERS PLASMA CELL-RELATED DISORDER

- **Multiple myeloma**
  - M-protein present in serum >30 g/L.
  - Marrow plasma cell >10% with neoplastic phenotype.
  - Myeloma-related end organ damage/bone lesion present.
- **MGUS**
  - M-protein <30 g/L in serum
  - Bone marrow plasma cell <10%
  - No bony lesion/end organ damage.
- **Solitary plasma cytoma**
  - No M-protein in serum
  - Marrow plasma cell <10%
  - Normal skeletal survey apart from solitary bone lesion. No end organ damage.
- **Asymptomatic myeloma**
  - M-protein in serum >30 g/L
  - Marrow plasma cell ≥10%
  - No bony lesion/end organ damage.
- **Nonsecretory myeloma**
  - No M-protein in serum/urine
  - Marrow plasma cell >10%
  - Bone lesion present
  - End organ damage present.

INVESTIGATIONS

- Hemogram shows *anemia*, *leukopenia, thrombocytopenia* with *markedly raised ESR*, and *peripheral Rouleaux formation*.
- **Bence-Jones protein** may be present (20%).
- **Serum Ca^{+2}** level raised (>12 mg/dL).
- **Serum uric acid** level raised.
- **Total protein level** → increased with alteration of A : G ratio.
- **Serum B_2 microglobulin** level correlates with prognosis. (<4 μg/dL → good prognosis, >4 μg/dL → bad prognosis).
- Radiological examination shows generalized **osteoporosis, punched out osteolytic lesion in skull, ribs, axial skeleton** with/without collapse of vertebra.
- **Immune electrophoresis**: Provide qualitative estimation of M-component, which are monoclonal in origin.
- **Electrophoretic study**: Provide quantitative estimation of M-component. Demonstrate paraproteins as M bands (M for monoclonal).
- **Bone marrow** shows infiltration by **plasma cell** >10%.

Conditions associated with increased M-component:

1. Plasma cell disorder
2. Other lymphoid neoplasm: CLL, lymphoma
3. Nonlymphoid neoplasma: CML, breast cancer
4. Nonneoplastic condition
   a. Cirrhosis
   b. Sarcoidosis, Gaucher, parasitic disease
   c. Rheumatoid arthritis
   d. Myasthenia gravis, cold agglutinin disease, lichen myxedematosus, papular mucinosis, necrobiotic xanthogranuloma

TREATMENT

- Supportive therapy
  - Prompt treatment of **infection**.
  - **Fluid intake** >3 L/day to prevent hyperviscocity syndrome and excretion of calcium and light chain.
  - In compromised renal function with acidosis—managed by **Na-bicarbonate** orally.
  - **Allopurinol** (300 mg/day)—For management of uricemia.
  - **Analgesics** for bone pain and pathological fracture.
  - Physiotherapy and orthopedic assistance for osteolytic manifestation.
  - **Renal failure**—managed by **medical therapy** for **CRF or RRT** in last stage.
  - **Hypercalcemia**—Treated by **rehydration, oral prednisolone, bisphosphonate**.
  - **Hyperviscosity** syndrome—Managed by plasmapheresis and hydration.
  - **Anemia**—Managed by iron, folate, cobalamine and orythropoietin.
  - **Chemotherapy for multiple myeloma**—
    For candidate of BMT the induction of remission is done by anyone of the combination chemotherapy regimen.
    - *Lenalidomide + Bortezomib + Dexamethasone.*
    - *Thalidomide + Bortezomib + Dexamethasone.*
    - *Cyclophosphamide + Bortezomib + Dexamethasone.*

      Combination chemotherapy to be continued until maximum cytoreduction is achieved (90–100%) which is followed by **autologous stem cell transplant**.

Lenalidomide—It is an immune modulatory derivative of thalidomide.
Bortezomib—It is a proteosome inhibitor.
Those who are not a BMT candidate melphalan in combination with other agents are used:
» *Melphalan + Prednisolone*
» *Melphalan + Bortezomib + Prednisolone*
» *Melphalan + Lenalidomide + Prednisolone*
» *Melphalan + Thalidomide → followed by lenalidomide* maintenance therapy.
» *High dose Melphalan + Prednisolone*
Allogenic HSCT has 40% mortality. For this high mortality **nonmyeloablative allogenic HSCT is now under evaluation to allow immune vs. myeloma effect**.

- **Radiotherapy** is indicated
  - **For local bone problem** in spine causing neurologic symptom in lower limb or back pain or bladder bowel disturbances.
  - For **solitary bone plasma cytoma**—A single lytic bone lesion without marrow plasmacytosis.
  - For **extramedullary plasmacytoma** which involve submucosal lymphoid tissue of nasopharynx or paranasal sinuses without marrow plasmacytosis.
- Both the above tumors are highly responsive to local radiation therapy.
- **Solitary bone plasmacytoma** may recur in other bony sites or evolve into myeloma.
- **Extramedullary plasma cytomas** rarely recur or progress.

WALDENSTROM'S MACROGLOBULINEMIA

It is a malignancy of lymphoplasmocytoid cell that **secrete IgM** and associated with **lymphadenopathy** and **hepatosplenomegaly**. Major clinical manifestation is *hyperviscosity syndrome and not associated with lytic bone lesion, pathological fracture, hypercalcemia and kidney involvement.*

MIXED CRYOGLOBULIN

It is composed of IgM or IgA complex with IgG seen in rheumatoid arthritis and other autoimmune disease but not with malignancy.

CLINICAL FEATURES

The disease resembles chronic lymphocytic leukemia or small lymphocytic lymphoma and myeloma.

Symptoms

Weakness, fatigue, epistaxis, visual disturbances, peripheral neuropathy, headache, dizziness, Raynaud's phenomenon.

Signs

Hepatosplenomegaly, lymphadenopathy, vascular segmentation and dilatation of retinal vein on ophthalmoscopy.

LABORATORY INVESTIGATIONS

- **Normocytic, normochromic anemia** with Rouleaux formation.
- **Positive Coombs test**.
- About 10% macroglobulin are pure cryoglobulin and are pure M-component and are associated with **vascular phenomenon like Raynaud's phenomenon** on exposure to cold.

TREATMENT

Many patients those who have indolent form of the disease do not require any treatment.

- Plasmapheresis for control of hyperviscosity symptom, e.g. altered state of consciousness and paresis.
- Those who have cytopenia, male sex and older patients require treatment with
  - **Fluderabine**—25 mg/m^2/day for 5 days every 4 weeks. Can be used singly.
  - **Cladribine**—0.1 mg/kg for 7 days every 4 weeks are highly effective single agent and response rate is 80%.
  - **Rituximab** (anti-CD20 antibody) can be used alone or in combination with any above two drug.
  - Introduction of **lenalidomide, bortezomib** and **bendamustine** have improved the outcome.

HODGKIN'S DISEASE

Hodgkin's disease (HD) is a highly curable tumor. HD is a tumor composed of inflammatory cell (T-cell, eosinophil, plasma cell) with rare malignant cell of B-cell origin. The accumulation of inflammatory cells are possibly due to cytokines produced by malignant cell.

The histologic hallmark of Hodgkin's disease is the presence of **Reed-Sternberg cell which are large binucleate malignant cell of B-cell origin** and are surrounded by reactive 'T' cell, eosinophil, plasma cell and differ from NHL in several respect. Clinical differentiation between NLL and HD is discussed in Table 79.6.

- In contrast to NHL, HD arise in single lymph node/chain of node region and spread to anatomically contiguous site.
- In contrast to NHL, *in HD neoplastic cell makes up only (1–5%) of the total cell mass.*
- It is one of the most common malignancy in young adult (average age of diagnosis is 32 years).

PATHOLOGICAL SUBTYPES OF HODGKIN'S DISEASE

- **Nodular sclerosis** (CD-15, 30 positive) present in (70%) patients have very good prognosis.

- **Mixed cellularity** (CD-15, 30 positive) present in (25%) patients have good prognosis.
- **Lymphocyte predominant variety** (CD-20, 45 positive) present in (5%) patients with excellent prognosis.
- **Lymphocyte depleted variety** (CD-15, 30 positive) present in (1%) patient have poor prognosis.

CLINICAL FEATURES

- Hodgkin's disease usually presents with painless enlargement of lymph node with rubbery consistency and may fluctuate in size and usually involves **neck, axilla** and **supraclavicular fossa**. In nodular sclerosing variety large mediastinal mass which is surprisingly asymptomatic may be present in 50% patients. Isolated subdiaphragmatic nodes found in less than 10% cases (common in elderly).
- Spread is contiguous from one node to next node.
- Extranodal (bone, brain, skin) involvement is rare.
- One-third of patient presents with B-symptoms (more common in mixed cellularity group).
- Hepatosplenomegaly is rare.
- **Unusual manifestations of Hodgkin's lymphoma**
  - *Severe unexplained itching*
  - *Erythema nodosum*
  - *Ichthyosiform atrophy*
  - *Paraneoplastic cerebellar degeneration*
  - *Nephrotic syndrome*
  - *Immune hemolytic anemia*
  - *Thrombocytopenia*
  - *Hypercalcemia*
  - *Pain in the lymph node on alcohol ingestion.*

DIFFERENTIAL DIAGNOSIS

- Inflammatory lymphadenopathy.
- EBV-associated lymphadenopathy infectious mononucleosis.
- NHL.
- Phenytoin-induced lymphadenopathy.

INVESTIGATIONS

- Blood
  - **Normocytic, normochromic anemia**
  - **Lymphopenia**—bad prognostic factor
  - **Eosinophilia** } May be present
  - **Neutrophilia** } May be present
  - **Raised ESR**
  - **Raised LDH**—Level is a poor prognostic factor.
- **Renal function test**—Usually normal prior to treatment.
- **LFT**—If abnormal indicate hepatic infiltration or node at porta hepatis.
- **Chest X-ray**—May show mediastinal mass.
- **CT scan**—Of abdomen, pelvis and chest.
  It has replaced laparotomy as a staging procedure.
  (Bulky disease >10 cm in a single node—poor prognostic variable).
- **Lymph node biopsy**—For confirmation of disease.
- **Bone marrow biopsy**.
- **PET and gallium scan** are used to document remission of the disease.

MANAGEMENT

Three forms of therapy available—Radiotherapy, chemotherapy and HSCT.

- *Radiotherapy*
  - Indications of radiotherapy
    - Stage-I disease.
    - Stage-II disease with ≤3 areas involved.
    - After chemotherapy, radiotherapy to site where there is original bulk disease.
    - Lesion causing serious pressure symptoms.
  - Complications of radiotherapy
    - Breast carcinoma
    - Lung carcinoma
    - Hypothyroidism
    - CAD
    - Infertility
    - Secondary malignancy
    - Lhermitte's syndrome (15%)— A electric shock like sensation down the spine on flexion of neck who receive neck/thoracic radiotherapy.

Table 79.6: Clinical differentiation between Hodgkin's disease and Non Hodgkin lymphoma

Non Hodgkin lymphoma	Hodgkin disease
1. More frequent involvement of multiple peripheral nodes	1. More often localize to a single axial group of nodes (cervical, mediastinal, para-aortic)
2. Noncontiguous spread	2. Orderly spread by contiguity
3. Waldeyer's ring and mesenteric nodes are commonly involved	3. Mesenteric nodes and Waldeyer's ring rarely involved
4. Extranodal involvement is common	4. Extranodal involvement is less common
	5. Immunophenotypically positive for CD15 and CD30 but negative for CD 45 in nodular sclerosis and mixed cellularity group. Lymphocyte predominance type is positive for CD 45, 20 but negative for CD 30, 15

- *Chemotherapy*
  - Indications
    - All patients with B-symptoms
    - Stage-II disease >3 sites involvement
    - Stage-III, IV disease.

REGIMEN

- **MOPP**—Nitrogen mustard (**mechlorethamine**), **Oncovin**, (Vincristine), Vinblastine, **prednisolone, procarbazine**.
- **ABVD—Adriamycin** (doxorubicin), **bleomycin**, **vinblastine, dacarbazine** administered weekly.
- **Stanford-V regimen**—Includes radiation with ABVD regimen.
  - About 80% patients respond to this combination chemotherapy.
  - Drugs are delivered as OPD basis every 3–4 weeks for a total of 6–8 cycles, with supportive treatment such as G-CSF.
  - Patient with high-risk disease is treated with **bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisolone (BEACOP)** regimen.

PROGNOSIS

- About 90% patients with stage IA disease are cured with radiotherapy alone.
- Patients with stage IIA disease have a reduced cure rate from radiotherapy.
- About 70% patients treated with chemotherapy are cured.
- About 15% of patients who fail to respond to initial chemotherapy have a poor prognosis but some may achieve long-term survival after high-dose therapy and autologous SCT.
- Patients relapsing after local radiotherapy have a good cure rate after subsequent chemotherapy but with an increased long-term toxicity.
- Patients relapsing within a year of initial chemotherapy have a good salvage rate with high-dose therapy and autologous SCT.
- Patients relapsing after 1 year may obtain long-term survival with further chemotherapy.
- Lymphocyte predominant varient of Hodgkin with early stage disease are treated with regional/involved field radiation.
- Patient with B-symptom or disseminated disease are treated in the same line as classical disease.
- Rituximab may be used in selected paient who are not candidate for chemotherapy because this type of lymphoma express CD20 differentiating it from other type of Hodgkin lymphoma (more like low grade NHL).

EXERCISE

Write short notes on

1. Ann-Arbor staging of lymphoma.
2. Short notes on Hodgkin, SLL/CLL, DLBCL, multiple myeloma.
3. Clinical features of multiple myeloma and Hodgkin with treatment.

Chapter 80

Approach to a Patient with Bleeding Disorder

HISTORY AND CLINICAL EXAMINATION

History and clinical examination should focus on the following points:

- Bleeding disorder due to **platelet abnormality usually manifests later in life** whereas **factor deficiency manifests early in life**.
- If a patient develops **petechial or superficial spontaneous** ecchymosis or mucosal bleeding without preceding significant history of trauma or injury—consider **platelet disorder or vWD**.
- Platelet-related bleeding starts immediately after injury and affects skin or mucous membrane in the form of petechiae, epistaxis, menorrhagia and GI bleeding.
- Muscular hematoma or palpable purpura (smaller muscular hematoma may reach subcutaneous tissue and gives the picture of palpable purpura or palpable ecchymotic spot) is suggestive of plasma **clotting factor deficiency (mainly factor VIII and IX)**.
- Coagulation factor-related bleeding are usually delayed in onset and manifest as muscle hematoma, hemarthrosis, deep tissue bruises/ecchymoses.
- If there is prolonged bleeding from umbilical cord at birth or bleeding from gum during eruption of teeth or following circumcision or bleeding in joints favors **hereditary coagulation factor deficiency (factor VIII and IX)**.
- Joint deformities are particularly common in patient with deficiency of factor VIII and IX—the two sex-linked coagulation disorders refer to **hemophilia**.
- **vWD** is the most common factor deficiency but clinical presentation is like that of platelet disorder with purpura, bruise and ecchymosis.
- Positive family history is present in coagulation factor deficiency —If male members are only affected—suggestive of hemophilias (factor VIII and IX deficiency).

Following laboratory investigations are useful in distinguishing bleeding from coagulation disorder that from platelet defect (Table 80.1):

- **When history suggestive of platelet defect** (Flowchart 80.1) first test to be done in
  - **Bleeding time** (a sensitive measure of platelet function).

Table 80.1: Basic investigations in a patient of bleeding disorder

Investigation for suspected platelet disorder	Investigation for suspected coagulation factor deficiency
1. Bleeding time	1. Prothrombin time
2. Platelet count	2. Activated partial thromboplastin time
3. Platelet aggregation assay	3. Thrombin time
4. Peripheral smear examination	4. Mixing study with normal serum and absorbed plasma
5. Bone marrow study	5. Clot solubility test with 5 mole urea solution

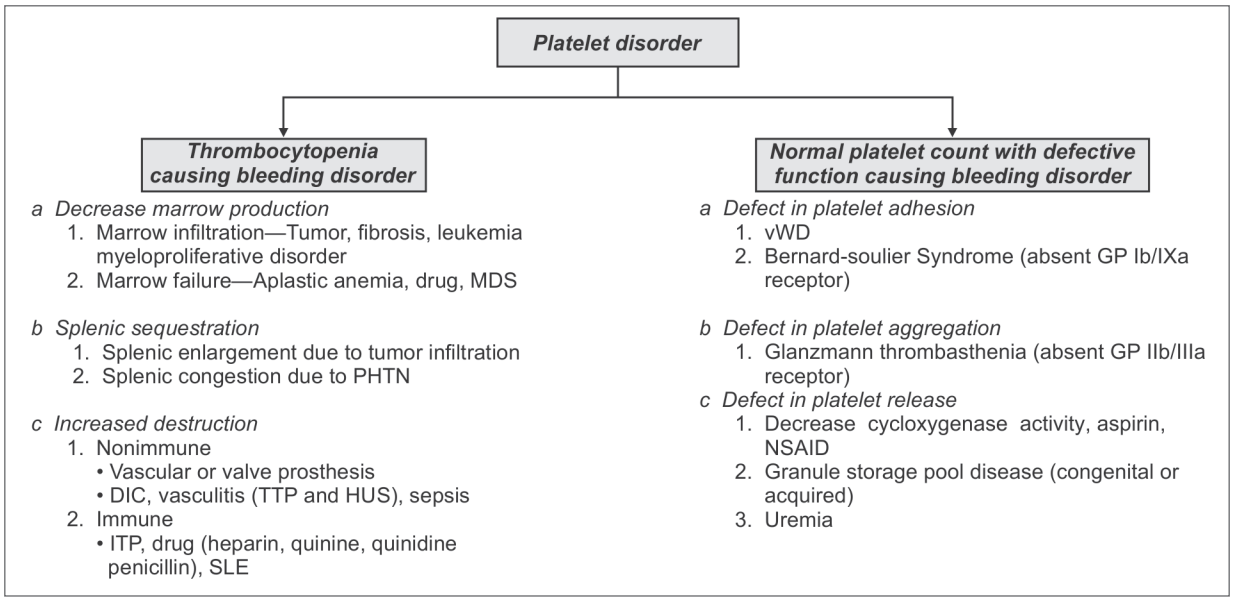
Technique—The time period of bleeding (noted by a stop watch) from an incised wound 9 mm long and 1 mm dip made by an automated scalpel on the flexor aspect of forearm and a sphygmomanometer cuff inflated to 40 mm Hg to distend the capillary bed of the forearm uniformly.

- Patient with BT >10 minutes has an increased risk of bleeding.
- Patient with BT >15 minutes to 20 minutes has high chance of spontaneous bleeding.
- Occasionally patient with vWD have normal bleeding time due to cyclical variation in the level of vMF. In that condition repeated testing may be necessary to establish the accurate diagnosis of vWD.

– **Platelet count** (second test to be done when platelet disorder is suspected from history and BT is prolonged).
(Normal platelet count is 1,50,000-4,00,000/μL).
- Count >100,000/μL—Bleeding time normal patient asymptomatic.
- Count 50,000–100,000/μL—Mild prolongation of bleeding time and bleeding occurs after severe trauma.
- Count <50,000/μL—Easy bruising manifested by purpura after minor trauma and bleeding from mucous membrane.
- Count <20,000/μL—Chance of spontaneous bleeding is high.

– **Peripheral smear and platelet aggregation assay**.
– **Bone marrow study**.

Flowchart 80.1: Platelet abnormality causing bleeding disorder



- **Other study**—Coombs test, ham test, coagulation study.

- **When history suggestive of coagulation factor deficiency**. As evidenced from family history or past history, e.g.
  - Prolong bleeding from umbilical cord at birth or from gum during dental eruption or circumcision.
  - Hemarthrosis.
  - Muscle, hematoma at injection site during primary immunization.
  - Bleeding into the body cavity.

  In that condition the test to be done are as follows:
  - **Prothrombin time**—(Which in a measure of extrinsic pathway and common pathway). When prolonged— suggestive of factor VII deficiency or vitamin. K deficiency or (warfarin) anticoagulant ingestion or II, V and X deficiency.
  - **APTT—When prolonged** (measure of intrinsic and common pathway) suggestive of deficiency of VIII, IX, X, XI, XII. HMWK or PK and II, V and X.
  - **APTT—When prolong but**
    - No clinical bleeding suggest XII, high-molecular-weight kininogen (HMWK), PK deficiency.
    - Mild or rare bleeding suggest factor XI deficiency.
    - Frequent severe bleeding suggest factor VIII or IX deficiency.
  - **When both activated partial thromboplastin time (APTT) and prothrombin time (PT) are prolong but corrected with addition of normal plasma**: Suggest factor II, V, X deficiency.
  - **Prolong PT/APTT not corrected with addition of normal plasma** suggest presence of specific or nonspecific antibody.

    They are infrequent cause of bleeding and require special diagnostic testing of antibodies against specific coagulation factor develop in four situations.

	Test to be done for diagnosis
– Postpartum women – Patient with SLE	i. Anticardiolipin antibody ii. APTT with DR VVT and iii. Anti-β_2 microglobulin estimation

  - Penicillin and streptomycin
  - Otherwise healthy elderly individual
  - After multiple transfusion, e.g. hemophilia
  - **PT and APTT are normal but strong history of bleeding** suggest factor XIII deficiency. Diagnosed by clot solubility test with 5 m urea solution
  - **Prolong thrombin time**—(measure clottable fibrogen level).

    With history of mild or rare bleeding suggest afibrinogenemia. With history of severe bleeding suggest dysfibrinogenemia or heparin-like inhibitor/ heparin administration.

- Most common inherited factor deficiency:
  - Factor VIII deficiency (hemophilia A)
  - Factor IX deficiency (hemophilia B)
  - von Willebrand factor deficiency.

- Rare coagulation abnormality are (defect in fibrinolytic system)
  1. α_2 plasmin inhibitor deficiency
  2. PAI-1 (plasminogen activator inhibitor–1) deficiency (major inhibitor of plasminogen activator).
     a. Measuring the rate of clot lysis with the euglobulin lysis
     b. Measuring the level of α_2 plasmin inhibitors and PAI-1
  3. Scott's syndrome—Measuring the serum PT which assess the amount of residual prothrombin

EXERCISE

Write short notes on

1. Approach to a patient with bleeding disorder.

Chapter 81

Thrombocytopenic Purpura

IMMUNE THROMBOCYTOPENIC PURPURA

PATHOGENESIS

Thrombocytopenia results from increased destruction of antibody-coated platelet by RE system in spleen and possibly inhibition of platelet release from megakaryocyte. The antibodies are usually IgG but rarely IgM class or in combination directed against GP IIb/IIIa platelet membrane antigen rarely against GP1b/ IX a or Ia/IIa platelet membrane antigen.

Spleen is the major site of destruction of IgG-coated platelet.

Liver is the major site of destruction of IgM-coated platelet.

Antibody also acts on megakaryocyte and thereby interferes with the production and maturation of platelet.

CLASSIFICATIONS

- **Acute Immune thrombocytopenic purpur (ITP):** Clinically presented with sudden onset symptom associated with severe thrombocytopenia and preceded by viral infection in 50% cases. More than 80% cases resolve spontaneously within 1–2 months. Relapse may occurs following initial remission.
- **Chronic ITP:** There is insidious onset of symptom, thrombocytopenia is not so severe, usually associated with other autoimmune disorder like SLE, rheumatoid arthritis or collagen vascular disease or CLL. Only 10 to 20% have spontaneous remission.

CLINICAL FEATURES OF ACUTE ITP

Common age group 2–8 years.

Boys and girls are equally affected in acute ITP but females are 3 times more commonly affected in chronic ITP. Children with HLA-B8 and B_{12} are at higher risk of developing ITP.

Symptoms

Easy bruisability and spontaneous subcutaneous hemorrhage and petechiae are the most common presenting symptom.

Ecchymoses are usually present over the bony prominence and anterior aspect of lower limb.

Bleeding from mucosal surface is seen in one-third cases.

Hematemesis, melena and bleeding in joint are rare.

Anemia is always proportionate to the degree of bleeding.

Spleen is usually not palpable (palpable only 5–15% in ITP).

Significant anemia and splenomegaly suggest secondary purpura.

Hematuria, GI bleeding, severe epistaxis, menorrhagia in adolescent girls are manifestations of severe ITP.

Intracranial bleeding is present in 1–2%.

Laboratory Investigations

- **Bleeding time is prolonged but prothrombin time** and **activated partial thromboplastin time** (**APTT) are normal**.
- **Thrombocytopenia** <100,000/μL in peripheral smear.
- **Capillary fragility** test is positive.
- **Platelet antibody** can be demonstrated in 70–90% cases but not helpful due to low sensitivity.
- **Bone marrow shows**—Increased number and size of megakaryocyte with diminished budding with normal myeloid erythroid ratio with eosinophilia. Suggest ITP.

It is also helpful for exclusion of other causes of thrombocytopenia like leukemia (CLL), aplastic anemia, tumor cell infiltration.

Laboratory testing for HIV, HCV, HBV, SLE, serum protein elecrophoresis to be done. Serum immunoglobulin level for diagnosis of hypogammaglobulinemia. If autoimmune hemolytic anemia is present (detected by direct Coombs test) along with ITP. It is called Evans syndrome.

DIFFERENTIAL DIAGNOSIS

- Chronic ITP.
- Secondary thrombocytopenia, seen in leukemia, aplastic anemia, tumor cell infiltration.
- Drug-induced thrombocytopenia seen with quinine, heparin, NSAID, anticonvulsant, sulfonamide.
- Giant platelet suggests congenital platelet defect.
- TTP, HUS and HSP also present with thrombocytopenia.

MANAGEMENT

- Supportive care
- Specific treatment.
- Usually patients require no specific treatment as long as the platelet count is above 40,000/μL.

Supportive Care

- Restriction of physical activity and outdoor games.
- Avoidance of drugs like aspirin, NSAID.
- Avoidance of intramuscular injection.
- Patients are admitted in hospital when platelet count falls below 20,000/cmm as there is high risk of serious bleeding.
- **Platelet transfusion are usually not given** as platelet are destroyed soon but can be given in life-threatening situation and prior to surgery.

Specific Treatment

- **Corticosteroids**—Prednisolone 1 mg/kg/day for 2–3 weeks followed by gradual tapering of dose over next 2–3 weeks.

  Prednisolone inhibits production of antibody and interferes with the interaction of antibody with platelet.
- **Intravenous immunoglobulin (IV-IgG)**—This antibody block the Fc receptor in RE cell of spleen and thereby prevent it from attaching with the platelet antibody.

  Total dose 2 g/kg either 0.4 g/kg daily × 5 days or 1 g/kg of IV-Ig × 2 days.

  Acute ITP cases respond within 48 hours.
- **Anti-Rh(D) therapy**—Anti-Rh(D) result in blockade of Fc receptors of cells of RE system by the antibody-coated RBC in place of antibody-coated platelet.

  Dose—25 μg/kg × 3 days.

  These above two measure IV/IgG and anti-Rh (D) therapy are used as a bridge up therapy before splenectomy.
- **Splenectomy**
  - Indications
    - Chronic ITP
    - Uncontrolled bleeding
    - Recurrence of bleeding after steroid withdrawal
    - Not responding to steroid or IV Ig.

Splenectomy results in immediate rise in platelet count as antibody is produced in spleen and spleen is the major site of destruction of platelet.

Prior to splenectomy the patient should be immunized with ***pneumococcal, meningococcal***, and ***H. influenzae*** vaccine at least 3 weeks before hand.

Management of Intracranial Hemorrhage/ Emergency Management in ITP

- IVIg
- IV methylprednisolone—1 g/day × 3 days
- Platelet transfusion.

  If all these measures fail emergency splenectomy should be considered.

Management of Chronic ITP

- **Corticosteroid** to be started as acute ITP and to be continued with very small daily or alternate day dose for 4–6 months.
- **Immunoglobulin** 0.4–1 g/kg/every 2–6 weeks. Sometime cure chronic ITP by its immunomodulatory effect.
- **Rituximab (anti-CD 20)** has shown efficacy is the treatment of refractory ITP.
- **Recombinant human thrombopoietin** (romiplostim SC once weekly or eltrombopag orally daily).

HEPARIN-INDUCED THROMBOCYTOPENIA

Heparin-induced thrombocytopenia (HIT) is the most common drug-induced immune thrombocytopenia. In HIT antibodies directed against heparin-platelet factor 4 (PF4–a protein released from platelets) complex bind to FCγ-receptor on platelet and result in platelet activation and release of prothrombotic microparticles.

HIT occurs in 5% of patient treated with unfractionated heparin (**UFH)** for 5 days and 1% of patient with low molecular weight heparin (**LMWH)** and almost nonexistent in patient receiving **fondaparinux**. The risk of developing HIT is highest in open heart surgery and minimum in medical and obstetric patient.

DIAGNOSIS

The criteria for diagnosis of HIT include:

- Thrombocytopenia (count <15,000/cmm or 50% decrease in platelet count from baseline is the presence of heparin or its use over past 3 months.
- Exclusion of other causes of thrombocytopenia.
- Reversal of thrombocytopenia on cessation of heparin.
- Positive laboratory test result.

CLINICAL FEATURE

HIT is associated with high risk of thrombotic events especially venous thrombosis (66%). Arterial thrombosis occurs in 33% cases.

TREATMENT

- Heparin must be stopped immediately.
- Start direct thrombin inhibitors, e.g. **lepirudin** (in liver disease), **argatroban** (in renal disease) through IV route with close monitoring.
- Once the platelet count is above 100,000/cmm start warfarin.
- Platelet transfusion may be necessary in life-threatening cases.

EXERCISE

Write short notes on

1. Clinical features of ITP.
2. Management of ITP.
3. HIT.

Chapter 82

Hemophilia

INTRODUCTION

Hemophilia is due to congenital deficiency of plasma coagulation **factor VIII or IX**.

Hemophilia-A is due to deficiency of factor VIII.

Hemophilia-B (Christmas disease) is due to deficiency of factor IX.

It is an X-linked recessive disease, so females are carrier and males are sufferer.

But sporadic mutation of gene on the X chromosome is responsible for 20–39% cases and in those condition, family history is absent.

PATHOGENESIS

Factor VIII has two components:

1. **Factor VIII-related antigen (F VIII Ag)**—Helps in binding of platelet to vessel wall [deficiency produce von *Willebrand disease (vWD)*].
2. **Factor VIII coagulant activity (F VIII C)**—Exerts procoagulant activity (deficiency produce *hemophilia-A*).

Normally these two component are present in blood in equal proportion.

In hemophilia A—*F VIII C* activity is reduced while *FVIII Ag* remains normal.

In vWD *F VIII—Ag* component is decreased preventing attachment of platelet to capillary wall.

Based on the concentration of VIII hemophilia can be divided into:

- Mild disease, where factor level >5–30% of normal.
- Moderate disease, where factor level <1–5% of normal.
- In severe disease factor level is <1% of normal.

CLINICAL FEATURES

- In mild and moderate disease, individuals remain asymptomatic and only develop prolonged bleeding following surgery, tooth extraction and severe trauma.
- In severe disease, child or infant presents with muscle hematoma or hemarthrosis or prolonged bleeding from umbilical cord or following circumcision and teeth eruption/extraction.
- As the baby starts walking, there is repeated hemarthrosis, especially in weight-bearing joints, e.g. knee, hip and ankle.
- Recurrent hemarthrosis leads to synovial thickening, chronic arthropathy and ankylosis.
- Retroperitoneal bleeding may present with severe abdominal pain, anemia with even shock and features of femoral nerve compression.
- Hematuria and gastrointestinal hemorrhage are difficult to control.

  Intracranial bleeding are common and is the major cause of death. It may be of extradural, subdural, or intracerebral in type.

INVESTIGATIONS

- Bleeding time is normal and platelet count is normal.
- Clotting time is prolonged.
- Activated partial thromboplastin time (APTT) is prolonged.
- Estimation of factor VIII and IX—grossly diminished (from less than 1 to 30%).
- Mixing study with normal plasma or absorbed plasma.
  - *Normal serum contain factor IX, X, XI, XII.*
  - *Absorbed plasma contain factor V, VIII, XI, XII.*
    - Correction of patients APTT after mixing with normal serum but not with absorbed plasma suggest factor IX deficiency (hemophilia-B).
    - Correction of patients APTT after mixing with absorbed plasma but not with normal serum suggest factor VIII deficiency (hemophilia-A).

MANAGEMENT

Management consist of three steps:

1. Control of bleeding
2. Treatment of complication
3. Rehabilitation.

CONTROL OF BLEEDING

Prompt replacement of factor VIII and IX is the key to control bleeding. It can be done by

- **Fresh frozen plasma**—Each unit contain 200 U factor VIII and IX.

- **Cryoprecipitate**—Each unit contain 100 U of factor VIII.

One unit of VIII concentrate per kilogram raises factor VIII by 2% but the half-life is short whereas one unit per kilogram of factor IX concentrate raises factor IX by 1% but half-life is 18–20 hours. So hemophilia-A patient requires twice daily infusion whereas hemophilia-B require once daily infusion.

Dose of FVIII = (Target level of FVIII – Baseline level of FVIII) × Body weight × 0.5 unit/kg.

Dose of FIX = (Target level of FIX—Baseline level of FIX) × Body weight × 1 unit/kg.

Administration of FFP/cryoprecipitate carries the risk of HCV, HBV, CMV transmission. This can be avoided by

- Porcine factor.
- Monoclonal purified factor VIII.
- Heating of lyophilized factor VIII concentrate under careful condition.
- Recombinant factor VIII/factor IX concentrate.
- Prothrombin complex concentrate—These are useful in treatment of factor VIII and IX deficiency but is very costly.

MANAGEMENT OF HEMARTHROSIS

Prompt treatment of hemarthrosis is essential for prevention of chronic arthropathy and limiting morbidity.

Factor VIII – 25 U/kg every 12 hours for 1 day.

- **Check APTT** to ensure AHG is corrected or not.
- **Immobilize the joint** for 48 hours.
- **Do not try to aspirate** from the joint.
- **Start ambulation** and physiotherapy as soon as acute stage is over.
- **Paracetamol pethidine, tramadol, diazepam** to be used as analgesic.
- To relieve pain NSAID to be avoided.
- Children and parents are ***trained for home therapy*** with factor concentrate as because sooner the initiation of therapy better the outcome. Factor concentrate can be stored at home.

Table 82.1: Complications of blood transfusion

Immunological reaction	Infections	Nonimmunological reaction
1. Febrile reaction	1. HCV	1. Fluid overload
2. Allergic reaction	2. HBV	2. Potassium overload
3. Anaphylactic reaction	3. HIV I and II	3. Iron overload
4. ARDS	4. HTLV I and II	4. Hypocalcemia
5. Hemolytic reaction	5. CMV	5. Hypothermia
a. Acute	6. Malaria	6. Hypotensive reaction
b. Delayed	7. Parvovirus B_{19}	
c. Fatal		
6. RBC alloimmunization		
7. HLA alloimmunization		
8. GVHD		

Abbreviations: ARDS, acute respiratory distress syndrome; RBC, red blood cell; HLA, human leukocyte antigen; GVHD, graft versus host disease; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HTLV, human T-lymphotropic virus; CMV, cytomegalovirus

PROPHYLACTIC THERAPY

- It prevents morbidity and hemophilics are able to lead normal life and even participate in sports. Factor VIII 10–20 U/kg twice or thrice weekly.
- **For major surgery and intracranial hemorrhage**—Factor VIII level to be kept > 50% for 10–14 days by factor VIII infusion every 12 hourly.
- **For joint replacement**
  Therapy should be continued for 3 weeks.
- **For tooth extraction and oral surgery**
  Therapy starts just before surgery and to be continued for 2–3 days.

OTHER AGENTS

- Epsilon aminocaproic acid **(EACA)**—Loading dose 200 mg/kg followed by 100 mg/kg every 6 hourly.
- **Tranexamic acid**—25 mg/kg 3–4 times/day.
  These two drugs should not be used in hematuria because of formation of clot in bladder.
- **Desmopressin acetate (DDAVP)**—It increase the level of FVIII and vWF but not FIX by releasing it from store (endothelial cell).

  It can cause thrombosis and hyponatremia and more than three dose become ineffective as the body store is depleted by this time.
- **Danazol (synthetic testosterone)** also helps in increasing factor VIII and IX level.

  Inhibitors of fibrinolytic system inhibit clot lysis and promote thrombosis.
- **Fibrin glue**—Can stop bleeding after dental extraction or surgical operation. It acts by activation of thrombin which converts fibrinogen to fibrin.

Antenatal Diagnosis of Hemophilia

- Fetal blood sampling at 18–20 weeks of gestation and procoagulant portion of VIII are assessed by radioimmunoassay.
- Using DNA probe in amniotic fluid fibroblast.
- Chorionic villus sampling using oligonucleotide primer and PCR.

CARRIER DETECTION

- Estimation of F VIII C—F VIII Ag ratio which is (1 : 1) in normal person.
  If the ratio <0.6, it is suggestive of carrier state.
- DNA study can identify the mutation in carrier. Clinical trial by gene therapy are in progress for correction of factor VIII deficiency.

EXERCISE

Write short notes on

1. Complication of blood transfusion.
2. Hemophilia.
3. Treatment of Hemophilia.

Chapter 83

von Willebrand Disease

INTRODUCTION

von Willebrand Disease (vWD) is the most common inherited bleeding disorder due to factor deficiency. **vWF** is also called factor **VIIIAg**. Although clinically, it simulate platelet disorder (due to presence of purpura) **vWD** is actually due to deficiency of a plasma protein **vWF** released by endothelial cell.

This factor forms a bridge between subendothelial collagen and platelet at the site of injury by binding with platelet (Ib/IXa) receptor.

vWF is also a carrier for factor **VIIIc** when **VIIIc** cannot bind to defective or deficient **vWF**, half-life and concentration of this **VIIIc** factor are reduced which may result in a coagulation defect.

vWD is of two type:

1. Type—I is due to deficiency of vWF.
2. Type—II is due to defect in polymerization of vWF subunit.

CLINICAL FEATURES

- Spontaneous severe bleeding
- Bleeding after minor trauma
- Ecchymosis
- Menorrhagia
- Bleeding from oral and nasal mucosa and GI tract.

INVESTIGATIONS

- Prolong bleeding time.
- Prolong activated partial thromboplastin time (APTT) due to concomitant factor VIIIc deficiency.
- Variable level of vWF (repeated measurement is required as there is diurnal variation of the level of vWF).
- Ristocetin cofactor (a measure of the role of vWF in platelet function).
- Multimeric analysis of the VW protein.

TREATMENT

The goal of treatment is to increase vWF level by:

- Administration of *desmopressin (DDAVP)*
- Infusion of *cryoprecipitate or factor concentrate* that contain vWF.

Acquired vWD is due to lymphoproliferative or myeloproliferative disorder, nonhematologic malignancies, aortic stenosis, cardiac defect or drugs like valproic acid.

Management in same as that of inherited disorder along with treatment of underlying associated disease.

EXERCISE

Write short note on

1. vWD.

Chapter 84

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) is due to widespread activation of coagulation that leads to formation of fibrin clot within the blood vessel.

ETIOLOGY

- **Infection**—Gram-negative sepsis rarely Gram-positive infection, viruses, HIV, mycotic and parasitic infection.
- **Cancer**—Especially mucus producing adenocarcinoma, $AML M_3$.
- **Obstetrics**—Missed abortion.
- **Trauma with extensive injuries, acute respiratory distress syndrome (ARDS), snake bite, burn**.
- **Acute or chronic liver diseases**.
- Drugs—**Fibrinolytic, warfarin, aprotinin**.

CLINICAL FEATURES

- Some patient have a **thrombotic disorder** characterized by deep vein thrombosis or pulmonary embolism, arterial thrombi and infarction.
- Some patient present with bleeding due to consumption of platelet and coagulation factor.
- Erythrocyte consumption is manifested by microangiopathic hemolytic anemia with fragmented red blood cell (RBC).

DIAGNOSIS

It is based on

- Prolong P-time, aPTT and thrombin time.
- High D-dimer level.
- Reduced fibrinogen level.
- Reduced platelet count.
- Fragmented RBC suggesting microangiopathic hemolytic anemia.

A scoring system with sensitivity 91% and specificity 97% has been developed for diagnosis of DIC.

TREATMENT OF DISSEMINATED INTRAVASCULAR COAGULATION

- Correction of the underlying cause.
- Transfusion of fresh frozen plasma when P-time >1.5 times of normal.
- Transfusion of platelet when platelet <20,000/cm.
- Cryoprecipitate can also be used.

Replacement of fresh frozen plasma (FFP) is indicated when P time >1.5. One unit of FFP will increase most coagulation factor by 3% without DIC.

Low level of fibrinogen <100 mg/dL will require infusion of *cryoprecipitate, (which is a plasma fraction enriched for fibrinogen, F VIII and vWF. A replacement of 10 U of cryoprecipitate for every 2–3 U of FFP is sufficient to correct the hemostasis. Platelet concentrate at a dose of 1–2 U/10 kg body weight in sufficient for most DIC patient with severe thrombocytopenias)*.

- Antithrombin and activated protein C is partially effective.

Low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) which were used previously are nowadays obsolete.

EXERCISE

Write short notes on

1. DIC.

Chapter 85

Thrombotic Disorder/Thrombophilia

Factors that inhibit thrombus formation in normal condition are:

- Rapid blood flow
- Dilution of activated factor
- Nonthrombogenic endothelium
- Inhibitor to coagulation factor
- Fibrinolytic system.

INHERITED DISORDER FAVORING THROMBOSIS

- Antithrombin deficiency
- Protein C deficiency
- Protein S deficiency
- Factor V Leiden
- Prothrombin 20210A mutation
- Dysfibrinogenemia (rare).

UNKNOWN ETIOLOGY FAVORING THROMBOSIS

- Hypohomocysteinemia
- High levels of factor VIII, IX and XI
- Activated protein C (APC) resistance in the absence of factor V leiden
- High level of thrombin activatable fibrinolysis inhibitor (TAFI)
- Low level of TFPI (tissue factor pathway inhibitor).

ANTITHROMBIN

Anti thrombin was previonsly known as antithrombin III deficiency. It is an autosomal dominant disorder present in 0.02% in general population:

Type I: Deficiency of antithrombin

Type II: Defective antithrombin

Antithrombin deficiency is associated with venous thromboembolism (VTE).

FACTOR V LEIDEN

A single mutation in the factor V gene results in substitution of arginine to GlU at position 506 rendering factor V more resistant to cleavage by activated protein C.

This mutation found in approximately 20% of all individual with decpveinthrombosis (DVT) and associated DVT in women with oral pill.

PROTHROMBIN 20210A MUTATION

This is another thrombophilic mutation where G → A mutation at 20210 position of prothrombin gene results in higher prothrombin level in affected individual and confer 3–4 fold increased risk of VTE.

PROTEIN C AND PROTEIN S DEFICIENCY

They are vitamin K dependent protein. *Protein C requires activation by thrombomodulin thrombin on the endothelial surface to neutralize factor VIIIa and Va whereas protein S is a cofactor in this reaction*. It is inherited as an autosomal recessive trait.

Protein C has a half-life of approximately 6 hours and decrease to low level after initiation of warfarin therapy.

Protein S deficiency is inherited as a autosomal dominant trait. (It is bound to C4B binding protein and 40% of which is free and active).

Deficiency of antithrombin, protein C and S all leads to an increase risk for VTE.

Antiphospholipid syndrome—It is the most common acquired cause of thrombophilia. The antiphospholipid **antibody is actually an antibody to a protein bound to phospholipid identified as B_2 glycoprotein 1**. Other protein such as prothrombin or protein C may function as the epitope for binding. The antiphospholipid antibody sometime interfere with coagulation cascade as measured by increased activated thromboplastin time (aPTT) or PT. This prolongation is not corrected after mixing with normal plasma. These antibody although prolong the in vitro coagulation test [(APTT by using dilute Russell's viper venom time (DRVVT)] but are associated with increased risk of venous or arterial thromboembolism. This syndrome has a strong correlation with pregnancy loss presumably due to placental insufficiency.

LABORATORY TEST FOR THROMBOPHILIA

- Testing **should not** be done in the setting of acute thrombotic event.
- Screening for thrombophilia is done in those who are **strongly thrombophilic** as suggested by
  - Idiopathic VTE before 50 years of age.
  - Recurrent thrombotic episode.
  - First degree relative have documented thromboembolism before 50 years of age. Weekly thrombophilic patient with VTE have none or anyone of the above criteria.

The following test is to be done (in case of strong thrombophilic patient).

- Presence of activated protein C resistance
- Presence of factor V leiden
- Presence of prothrombin gene mutation
- Presence of antiphospholipid antibody
- Presence of lupus anticoagulant
- Deficiency of antithrombin present or not
- Deficiency of protein C present or not
- Deficiency of protein S present or not.

In case of weekly thrombophilic patient testing for deficiency of antithrombin, protein C and protein S are not indicated.

EXERCISE

Write short notes on

1. Causes of inherited thrombotic disorder.
2. Laboratory test for thrombophilia.

Chapter 86

Kikuchi-Fujimoto Disease

INTRODUCTION

Kikuchi-Fujimoto disease (KFD) is a rare self-limiting disorder that typically affect the cervical lymph node. Course of the disease is generally benign and self-limiting. Lymphadenopathy most often resolve over several weeks to 6 months. Recurrence rate is 3%. Mortality is extremely rare and is usually due to hepatic, respiratory or cardiac failure.

PATHOPHYSIOLOGY

It is possible that KFD may represent an exuberant 'T' cell-mediated immune response in a genetically susceptible individual to a variety of nonspecific stimuli extending from (a) infectious agent (EBV, HHV_6, HHV_8, HIV_1, HTLV, and Parvovirus B_{19}) (b) chemical, (c) physical, (d) neoplastic agent, and (e) autoimmune disorder like SLE, antiphospholipid syndrome, polymyositis and juvenile idiopathic arthritis, uveitis, cutaneous necrotizing vasculitis have been linked to KFD.

CLINICAL FEATURE

It is a disease of young adult (20–30 years) F > M.

Sign and symptom of Kikuchi's disease are **fever, headache and lymphadenopathy**.

Rarely hepatosplenomegaly and nervous system involvement resembling aseptic meningitis is seen.

The cause of the disease is unknown although infection and autoimmune etiology have been proposed but not yet established.

Differential diagnosis include SLE, disseminated tuberculosis, lymphoma, sarcoidosis and viral lymphadenitis.

DIAGNOSIS

It is done by HP examination of lymph node biopsy. ANA, APLA, anti-dsDNA, RF are usually negative.

Its clinical feature may overlap with Hodgkin's lymphoma.

MANAGEMENT

There is no specific cure, treatment is mostly supportive. nonsteroidal anti-inflammatory drug (NSAID) for fever and tender lymph node.

Corticosteroid are useful for severe extranodal or generalized disease.

If the clinical course is more severe that multiple flare of bulky cervical lymphadenopathy and fever low dose corticosteroid has been suggested.

EXERCISE

Write short note on

1. Etiopathogenesis clinical features and management of Kikuchi's disease.

SECTION VIII

ENDOCRINE

- Thyroid Gland Disorders
- Adrenal Gland Disorders
- Acromegaly
- Syndrome of Inappropriate Antidiuretic Hormone

Chapter 87

Thyroid Gland Disorders

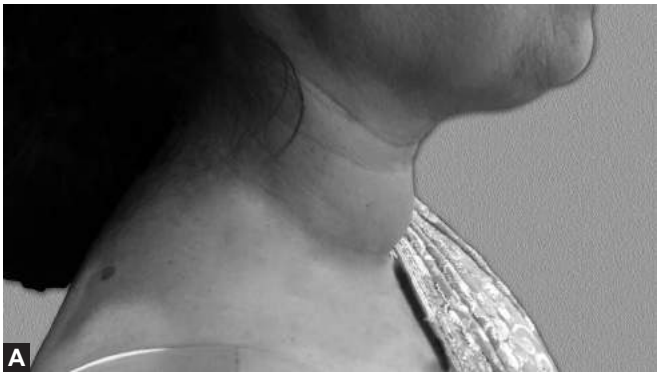
THYROTOXICOSIS (HYPERTHYROID)

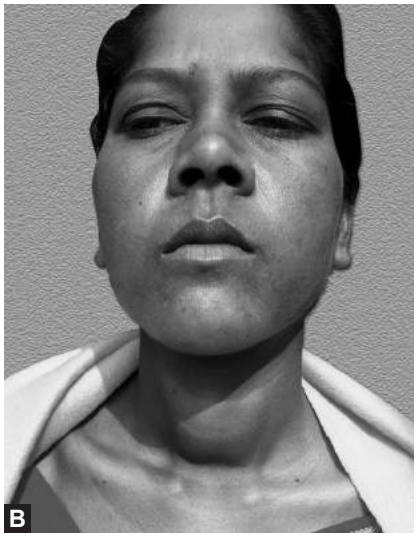
Thyrotoxicosis is defined as a state of excess thyroid hormone.

Hyperthyroidism means excessive thyroid function.

CAUSES OF THYROTOXICOSIS

- **Primary hyperthyroidism**:
  - Graves' disease (Diffuse goiter) (Figs 87.1A and B)
  - Toxic multinodular goiter (TMG)
  - Toxic adenoma (Single nodule)
  - Functioning thyroid carcinoma metastasis
  - Activating mutation of TSH receptor
  - Activating mutation of Gσα (McCune-Albright syndrome)
  - Struma ovarii.
  - Drugs I_2 excess (Jod-Basedow phenomenon).
- **Secondary hyperthyroidism**:
  - TSH-secreting pituitary adenoma
  - Thyroid hormone resistant syndrome
  - Chorionic gonadotropin secreting tumor
  - Gestational thyrotoxicosis.
- **Thyrotoxicosis without hyperthyroidism**:
  - Subacute thyroiditis
  - Silent thyroiditis
  - Other causes of thyroid destruction—Amiodarone, radiation and infarction
  - Thyrotoxicosis factitia.





Figs 87.1A and B: Diffuse goiter; (A) Side view; (B) Front view

GRAVES' DISEASE

- Graves' disease accounts for 70–80% of thyrotoxicosis.
  - **Prevalence varies**
    - Among population.
    - I_2 intake (high I_2 intake is associated with increase incidence of Graves' disease).
    - F : M → 10 : 1
  - The disease typically occurs between 20–50 years of age but may occur in elderly.

PATHOGENESIS

A combination of HLA-DR and CTLA-4 polymorphism and environmental factor contribute to Graves disease susceptibility.

- Stress is an important environmental factor, presumably operating through neuroendocrine effect on immune system.
- Smoking is a minor risk factor for Graves' disease but a major risk factor for development of ophthalmopathy.

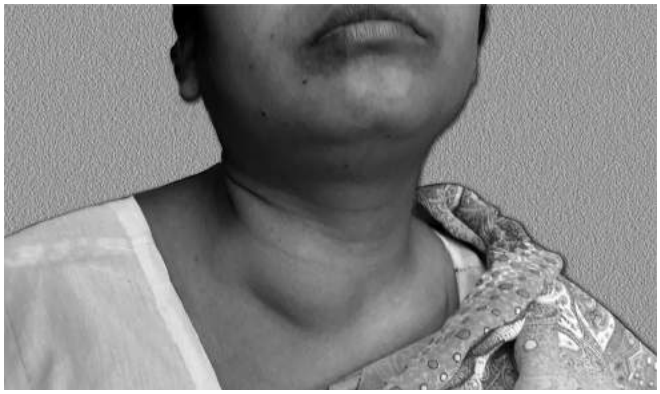


Fig. 87.2: Nodular goiter involving right lobe of thyroid

- Sudden increase in I_2 intake—Precipitate Graves' disease.
- 3-fold increase in Graves disease seen in postpartum period.
- TPO antibody is present in 80% cases and serves as a ready marker of autoimmunity, but hyperthyroidism of Graves disease is caused by TSI that are synthesized in the thyroid gland, bone marrow and lymph node. Pathogenesis of ophthalmopathy remains unclear.
- Cytokines play a major role in ophthalmopathy. Infiltration of extraocular muscle (EOM) by the activated 'T' cell causes release of TNF, IFN-γ, IL-1 results in fibroblast activation and increases synthesis of glycosaminoglycan (GAG) that trap water and leads to muscle swelling. Late in the disease muscle shows evidence of fibrosis.
- There is increased expression of TSH-R in the orbital muscle which may serve as orbital autoantigen. Autoantibody against orbital muscle fibroblast detected in ophthalmopathy are likely secondary phenomenon dependent on 'T' cell-dependent autoimmune response.
- Similar mechanism is also involved in dermopathy.

For clinical features of hyperthyroidism see Table 87.1.

Table 87.1: Clinical features of hyperthyroidism

General symptoms	Signs
• **Goiter**—Diffuse swelling of thyroid	• **Over the thyroid—**Bruit (may or may not present) with goiter
– Heat intolerance – Fatigue – Apathy – Thirst – Lymphadenopathy	
• **Cardiorespiratory**	
– Palpitation – Dyspnea on exertion – Angina – Exacerbation of asthma	– Sinus tachycardia – Atrial fibrillation – Increased pulse pressure with bounding pulse – High output failure – Aortic systolic murmur
• **Neuropsychiatric**	
– Nervousness and hyperreactivity – Irritability – Emotional lability – Psychosis	– Fine tremor – Hyperreflexia – Ill-sustained clonus – Muscle wasting – Proximal myopathy – Bulbar myopathy – Hypokalemic periodic paralysis (in Chinese population) Chorea (rare)

Contd...

Contd...

	General symptoms	Signs
•	**Dermatological** – Increased sweating – Pruritus – Pigmentation – Vitiligo – Alopecia	• **Dermatological** sign usually develops within 1–2 years of development of hyperthyroidism – Digital clubbing (<1%) also called thyroid acropachy. – Pretibial myxedema (<5%). Almost always associated with moderate to severe ophthalmopathy
•	**Ocular**	• **Ocular**
	– Grittiness – Excessive lacrimation – Proptosis	– Lid retraction – Lid lag – Chemosis of conjunctiva } Can occur in any form of thyrotoxicosis and is due to sympathetic overactivity – Exophthalmos – Corneal ulceration – Ophthalmoplegia – Diplopia – Papilledema – Loss of visual acuity } Called **Graves' ophthalmopathy now called thyroid associated ophthalmopathy, as it may be seen in autoimmune hypothyroidism**
		In 75% of Graves' disease patient, the onset of ophthalmopathy appears within a year before or after the diagnosis of thyrotoxicosis but sometimes it may precede or follow by several years. The thyroid-associated ophthalmopathy like features may develop in absence of Graves' disease in 10% cases and sometimes it may precedes thyrotoxicosis by several years accounting for **euthyroid ophthalmopathy**
6.	**Gastrointestinal** – Weight loss despite increased or normal appetite – Diarrhea due to increased peristalsis	
7.	**Reproductive** – Amenorrhea and oligomenorrhea – Infertility – Spontaneous abortion – Loss of libido and impotence – Gynecomastia	

Important Eye Sign

- **Naffziger's sign**—Forward bulging of eyeball.
- **Dalrymple's sign (lid retraction)**—Visibility of the upper sclera (Fig. 87.3).
- **Von Graefe's sign** (lid lag).
- **Joffroy's sign** loss of wrinkle on forehead on looking up (Fig. 87.3)
- **Moebius sign** loss of medial convergence on accommodation.
- **Stellwag's sign** (staring look/infrequent blinking): Many patient with Graves' disease have little clinical evidence of ophthalmopathy but enlarged extraocular muscle typical of the disease and other features can be detected by USG or CT of orbit in almost all patients of Graves' disease.

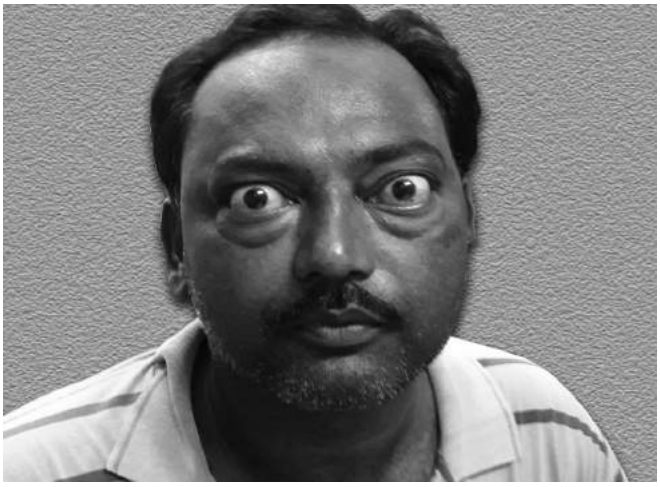


Fig. 87.3: Graves' disease, shows sclera above upper limbus (Called lid retraction)

Investigation

- **For diagnosis of hyperthyroidism**
  - **Estimation of T_3, T_4 and TSH**
    - *In primary thyrotoxicosis*—Usually free T_3 and free T_4 are high with a very low TSH .
    - *In secondary thyrotoxicosis*—Free T_3 and free T_4 are high and TSH will be also high.
    - *In T_3 toxicosis and in borderline I_2 excess*—Only free T_3 is high not T_4.
    - *In T_4 toxicosis and areas of high I_2 intake*—Only free T_4 is high.
- **For etiological diagnosis**
  - **Measurement of TPO antibody**—Increased level of TPO is a marker of autoimmune thyroiditis.
  - **USG of thyroid**—Differentiate between multinodular goiter and toxic adenoma from diffuse enlargement of thyroid.
  - **Radioiodine $^{123}I/^{131}I$ scan**—For detection of toxic nodular goiter/diffuse goiter.
  - **MRI of pituitary fossa**—For diagnosis of secondary hyperthyroidism.
  - **CT/USG of orbit**—For detection of ophthalmopathy.

Other Laboratory Features

- Elevated bilirubin and liver enzyme.
- Ferritin is high with microcytic anemia and thrombocytopenia.

Differential Diagnosis

- *Nodular thyroid disease*
- *Destructive thyroiditis*
- *Ectopic thyroid tissue*
- *Factitious thyroiditis*
  - **Radionucleotide** ^{99}Tc and ^{123}I or ^{131}I scan of thyroid which will distinguish Graves' disease from other disorders.
  - **In secondary hyperthyroidism**—TSH level will be high, which is due to pituitary tumor and is confirmed by MRI scan.
  - **Clinical features of thyrotoxicosis in some aspect can mimic**
    - Panic attack
    - Mania
    - Pheochromocytoma
    - Malignancy-associated weight loss which can be easily excluded by normal TSH and free T_4 in the serum.

Treatment

Hyperthyroidism can be controlled by two ways—

1. **Antithyroid drugs**—By reducing thyroid hormone synthesis.
2. – **Subtotal thyroidectomy**
   – **Radioiodine treatment**.
   } By reducing thyroid tissue

Antithyroid drugs

Reduces oxidation and organification of iodine.

- **Carbimazole**—10–20 mg every 8–12 hourly for initial 6–8 weeks followed by 5–10 mg for 2–3 years.
- **Propylthiouracil**—100–200 mg every 6–8 hourly for 3 months followed by 50–100 mg for 2 or 3 years.

Maintenance phase—More than 50% usually relapse within 2 years after stopping antithyroid drug. Rarely despite good drug compliance, T_4 and TSH level fluctuate between hyper and hypothyroid. In such patient satisfactory control can be achieved by total blocking of thyroid hormone synthesis with carbimazole 30 mg/day with levothyroxine T_4–150 μg daily as replacement therapy.

Common side effect of antithyroid drugs are **rash, urticaria, fever and arthralgia** seen in 5% patient.

Hepatitis, SLE and agranulocytosis are the major side effects and are idiosyncratic and develops abruptly in less than 1% patient. Maximum remission is achieved in 30–50% over 18–24 months.

Adjuvant drugs

- **Propranolol**—20–40 mg 6 hourly or **atenolol**—25–50 mg daily.

  It is helpful in controlling adrenergic symptoms in early part of the disease before the antithyroid drug takes effect.
- **Warfarin**—It should be considered for the patient with atrial fibrillation.

Subtotal thyroidectomy

Indications

- Relapse after antithyroid drugs
- Young individual
- When goiter is very large
- Patient preferring this treatment to radioiodine.

Preoperative: Control of thyrotoxicosis with antithyroid drug followed by 3 drops saturated solution of potassium iodide (SSKI) tid for 10 days to reduce vascularity of the gland and to avoid thyrotoxic crisis. β-blocker is also given.

Radioiodine treatment

Antecedent treatment with antithyroid drug should be considered in all patients to deplete thyroid hormone store before administration of radioiodine.

Antithyroid drug to be stopped 3 days prior to radioiodine administration to achieve optimum iodine uptake.

Dose: ^{131}I—5 to 15 mCi.

Incomplete treatment and early relapse is more common in man below the age of 40.

Most patients progress ultimately to hypothyroidism over 5–10 years, requiring thyroid hormone replacement.

Hyperthyroidism can persist for 2–3 months before radioiodine takes full effect.

Pregnancy and breastfeeding are absolute contraindication, patient can conceive 6 months after radioiodine treatment.

Patient with severe ophthalmopathy: Treated with prednisolone 40 mg/day at the time of radioiodine treatment, tapered over 2–3 months to prevent exacerbation of ophthalmopathy.

Overall risk of cancer is negligible although many physicians avoid radioiodine in children and adolescent because of theoretical risk of malignancy.

Complications of Surgery

- Bleeding
- Laryngeal edema
- Damage to recurrent laryngeal nerve
- Hypoparathyroidism.

Treatment of Ophthalmopathy

- Mild or moderate ophthalmopathy improves spontaneously and requires no treatment.
- Meticulous **control of thyroid hormone level**.
- **Cessation of smoking**.
- Eye discomfort can be relieved by artificial tear (**1% methylcellulose**) and dark glass with side frame.
- **Upright sleeping** position prevents periorbital edema.
- Minor degree of diplopia improves with **spherical lens**.
- Severe degree ophthalmopathy with optic nerve involvement and chemosis of conjunctiva can be treated with **prednisolone** 40–80 mg per day, some time combined with cyclosporin. The prednisolone is tapered by 5 mg every 1–2 weeks. But tapering of steroid often associated with reappearance of congestive symptom.
- Severe congestive symptom sometime requires IV **methylprednisolone**—1 g in 250 mL of saline infused over 1 hour × 7 days followed by **oral prednisolone**.

  Once the eye disease is controlled, surgery may be done for correction of diplopia and appearance of eye. *Orbital decompression is done by removing bone from inferior wall of orbit through maxillary sinus.*
- **External beam radiation** of orbit is an equivocal mode of therapy.

Prognosis

About 15% of patients who enter remission with antithyroid drug later develop hypothyroidism.

Some patients with mild Graves' disease have spontaneous remission and relapse.

Rarely patient may fluctuate between hypo and hyperthyroidism due to change in functional activity of TSH-R antibody.

Ophthalmopathy worsens in the initial 3–6 months followed by a plateau phase over next 12–18 months with spontaneous improvement. Fulminant course is seen in 5% of patients requiring intervention in acute phase if there is optic nerve compression or corneal ulceration.

Probably radioiodine therapy and smoking is associated with worsening of eye disease. Antithyroid drug and surgery have no adverse effect on eye disease.

Dermopathy usually appears within 1–2 years of onset of Graves' disease and may improve spontaneously.

THYROID DERMOPATHY

- Usually does not require any treatment.
- Topical high potency glucocorticoid with occlusive dressing may be used.
- Octerotide may be beneficial.

HYPOTHYROID

Causes of Hypothyroidism

- **Primary:**
  - *Autoimmune*
    - Hashimoto's thyroiditis
    - Atrophic thyroiditis.
  - *Iatrogenic*
    - ^{131}I treatment
    - Subtotal/near total thyroidectomy
    - Irradiation of neck for lymphoma/cancer.
  - *Drugs*
    - Iodine containing contrast media and amiodarone
    - I_2 excess
    - Lithium, PAS, INF-α, aminoglutethimide
    - Antithyroid drug.
  - *I_2 deficiency.*
  - *Infiltrative disorder*—Amyloidosis, sarcoidosis, scleroderma, cystinosis and Riedel's thyroiditis.
  - *Congenital*—Absent or ectopic gland and dyshormonogenesis.
- **Overexpression of type-III deiodinase** in infantile hemangioma.
- **Transient:**
  - Silent thyroiditis.
  - Subacute thyroiditis.
  - Withdrawal of thyroxine treatment with an intact thyroid.
- **Secondary:**
  - *Panhypopituitarism*—tumor, trauma, surgery, irradiation and Sheehan's syndrome.

    Genetic factor—Isolated or combined trophic hormone deficiency.

- *Hypothalamic disorder*—tumor, trauma, idiopathic, infiltrative disease and hydrocephalus.
- Bexarotene treatment.
- Isolated TSH deficiency.

In areas of I_2 excess the leading cause of *hypothyroidism is autoimmune (Hashimoto's thyroiditis) and iatrogenic drug-induced* and *atropic thyroiditis.*

HASHIMOTO'S THYROIDITIS

Autoimmune hypothyroidism may be associated with goiter in the early stage (goitrous thyroiditis) and at a later stage of disease there is minimal residual thyroid function which is called atrophic thyroiditis. As it is a slow compensatory process—the T_4 level remains normal in spite of high or raised TSH level (subclinical or mild hypothyroidism). Later free T_4 level falls in spite of high TSH (>10 mU/L) which is clinically referred to as clinical or overt hypothyroidism.

Clinical Features (Table 87.2)

- Onset is usually insiduous and patient may only be aware of symptoms only when euthyroid is restored.
- Patient of Hashimoto's thyroiditis presents with goiter rather than symptoms of hypothyroidism.
- Goiter is not usually large but irregular, firm in consistency and rarely associated with pain.

Pathophysiology

Environmental factors (high I_2 containing diet) may play role in the background of genetic susceptibility to produce autoimmune hypothyroidism. HLA-DR polymorphism (HLA-DR 3,4,5) and CTLA-4 polymorphism account for half of the genetic susceptibility to autoimmune hypothyroidism.

Female preponderance of thyroid autoimmunity indicates the role of sex-steroid or any X-linked genetic factor (proved by the higher frequency of hypothyroid among Turner's) in the etiology of autoimmune thyroiditis.

Chromosome-21 may be responsible proved by the higher incidence of hypothyroid amongst Down's patient.

In autoimmune thyroiditis, thyroid is infiltrated with CD4 and CD8. CD8 destroys the thyroid cell by perforins or granzyme-B-induced apoptosis. In addition T cell produces cytokine-like TNF, IL-I, IFN-γ that render the thyroid cells more susceptible to apoptosis by Fas-Fas ligand and impair thyroid cell function by expressing proinflammatory molecules like HLA-Class 1, 2, adhesion molecule CD 40 and nitric oxide.

Antibodies to TG and TPO are clinically important marker of thyroid autoimmunity. TPO antibody fixes complement which forms MAC and is responsible for destruction of thyroid cells. But isolated TPO without T cell-mediated injury cannot produce destruction of thyroid is proved by the fact that fetus born of hypothyroid mothers who have TPO antibody are euthyroid. Up to 20% of patients with autoimmune hypothyroidism have antibody against TSH receptor which prevents the binding of TSH with its receptor on the surface of acinar cell. This TSH receptor blocking antibody cause hypothyroidism specially in Asian patients with thyroid atrophy.

Fig. 87.4: Endocrine—hypothyroid facies with scanty eyebrow and puffy appearance of face

Laboratory Diagnosis

- **TSH level** is eleveted except in secondary hypothyroidism.
- **Free T_4** is also low, but it is inferior to TSH when used as screening test.
- Unbound T_3 is normal in about 20% patients. So not indicated for diagnosis.
- **TPO antibody** is present in 90–95% patients of autoimmune (Hashimoto's thyroiditis).
- TSH-R blocking antibody cannot be measured easily. But TSH binding inhibiting immunoglobulin ((TBII) can be measured. TBII elevated level in the context of hypothyroidism indicates Hashimoto's thyroiditis. Measurement of TBII not done routinely as found in only 20% patients of Hashimoto's disease.
- Other abnormal laboratory findings are increased level of **CPK, cholesterol, TG and anemia**.
- **Fine-needle aspiration cytology (FNAC)** can be used to confirm autoimmune thyroiditis and to exclude other causes.
- MRI/CT of pituitary of brain for secondary hypothyroidism.

Differential Diagnosis

Ultrasonography (USG) may be needed to differentiate multinodular goiter and solitary nodule from heterogenous thyroid enlargement of thyroiditis.

TREATMENT

If there is no residual thyroid (tissue function) daily replacement dose of **levothyroxine is 1.6 µg/kg/day** (Typically 100–150 µg). In many patients lower dose

Table 87.2: Clinical features of hypothyroidism

Symptoms	Signs
General	
• Tiredness • Weight gain • Cold feeling • Hoarseness of voice • Neck swelling	• Dry course skin • Cool extremity • Puffy face
Cardiorespiratory	
• Angina • Shortness of breath due to CCF	• Bradycardia • Hypertension • CCF • Xanthelasma • Pericardial and pleural effusion
Neuromuscular	
• Aches and pains • Muscle stiffness • Deafness	• Delayed relaxation of DTR • Deafness • Myotonia • Cerebellar ataxia
Dermatological	
• Dry skin and fall of hair • Purplish leap • Flash • Carotenemia • Vitiligo	• Myxedematous skin
Reproduction	
• Menorrhagia • Galactorrhea • Infertility • Impotence	
Gastrointestinal	
• Constipation • Distension of abdomen due to ileus, ascites	
Psychological	
	• Depression • Psychosis • Somnolence

is required due to presence of residual thyroid tissue. Elderly patient under 60 years without heart disease should be started with 50–100 μg of T_4 of daily dose and adjusted according to the level of TSH which should be measured after two month of starting therapy.

- Patient experiences full relief in 3–6 months time.
- Once full replacement is achieved TSH level is monitored initially annually later at 2–3 years interval.
- Because T_4 has long life—patient who misses the dose can be advised to take up to 3 skipped doses at a time.
- The dose of levothyroxine have to be increase by 50% during pregnancy.
- Elderly patients require 20% less thyroxine than younger patients.
- In elderly patient with heart disease (IHD) starting dose is 12.5–25 μg/day.
- Malabsorption, estrogen therapy, ferrous sulfate, calcium supplements, aluminium hydroxide, rifampicin, amiodarone, carbamazepine, phenytoin therapy causes increased levothyroxine requirement.

EXERCISE

Write short notes on

1. Clinical features of Graves disease and thyroid-associated ophthalmopathy.
2. Diagnosis of thyrotoxicosis/hyperthyroidism.
3. Management of hyperthyroidism.
4. Management of thyroid ophthalmopathy.
5. Clinical features of hypothyroidism.
6. Treatment of hypothyroidism and follow--up management of hypothyroidism.

Chapter 88

Adrenal Gland Disorders

CUSHING'S SYNDROME

Cushing's syndrome is defined as symptoms and signs associated with excessive activation of glucocorticoid receptors of long duration (Fig. 88.1).

Cushing's disease is corticosteroid excess due to pituitary-dependent bilateral adrenal hyperplasia.

Pituitary adenoma is the cause of Cushing's disease. Usually microadenoma (<10 mm in size) does not generally cause symptoms by local mass effect. Pituitary macroadenoma is uncommon in these patients.

CLASSIFICATIONS

- **ACTH-dependent**
  - Cushing's disease—Pituitary-dependent bilateral adrenal hyperplasia.
  - Ectopic ACTH/CRH syndrome—Bronchial carcinoid, small cell carcinoma of lung, pancreatic carcinoma and carcinoid of thymus.
  - Iatrogenic—ACTH therapy.
  - Pituitary—Hypothalamic dysfunction.
- **Non-ACTH-dependent**
  - Adrenal macronodular and micronodular hyperplasia.
  - Adrenal neoplasia
    - Adenoma
    - Carcinoma.
  - Iatrogenic—Prolonged steroid use.
- **Pseudo-Cushing's syndrome**—Cortisol excess as a part of another illness.
  - Alcohol excess—Biochemical and clinical feature—suggestive of Cushing.
  - Major depressive illness—Biochemical and some clinical features overlap with Cushing.
  - Primary obesity—Mild biochemical feature and some clinical features overlap.

CLINICAL FEATURES

- Alopecia.
- Hirsutism—More specific for Cushing's syndrome.
- Psychosis.
- Moon facies with malar flash and acne (Fig. 88.2).
- Cataract with mild exophthalmos.
- Truncal obesity (Buffalo bump) and increases body weight due to insulin resistance and/or high insulin level (exception —cachexia in presence of ACTH/CRH-producing nonendocrinal neoplasm)—
- Decreased skin thickness and purple striae.
- Hypertension.
- **Hyperglycemia**—Due to:
  - Increased hepatic neoglucogenesis
  - Insulin resistance
  - Hypokalemia-related decreased insulin production.
- **Menstrual abnormality**:
  - Oligomenorrhea
  - Amenorrhea.
- Osteoporosis, compression fracture, loss of height with low back pain.
- Weakness and wasting of proximal thigh muscle.
- Easy bruising.
- Tendency of infection with poor wound healing—
  - Myopathy, easy bruising, typical striae and virilizing signs if present suggestive of Cushing's syndrome.
  - Acne, hirsutism and menstrual abnormality is due to increased androgen production from adrenal.

DIAGNOSIS

- Diagnosis of Cushing's syndrome depends on:
  - Demonstration of excess cortisol production.
  - Failure to suppress cortisol production by dexamethasone.
- Once diagnosis is established further testing is needed for etiological diagnosis.

For diagnosis of Cushing's syndrome (Flowchart 88.1)

- **24 hour urinary free cortisol (>50 μg/day)** suggestive of Cushing's syndrome.
- **Plasma cortisol at 8 am more than 8 μg/dL** and evening level of plasma cortisol >75% of morning level.

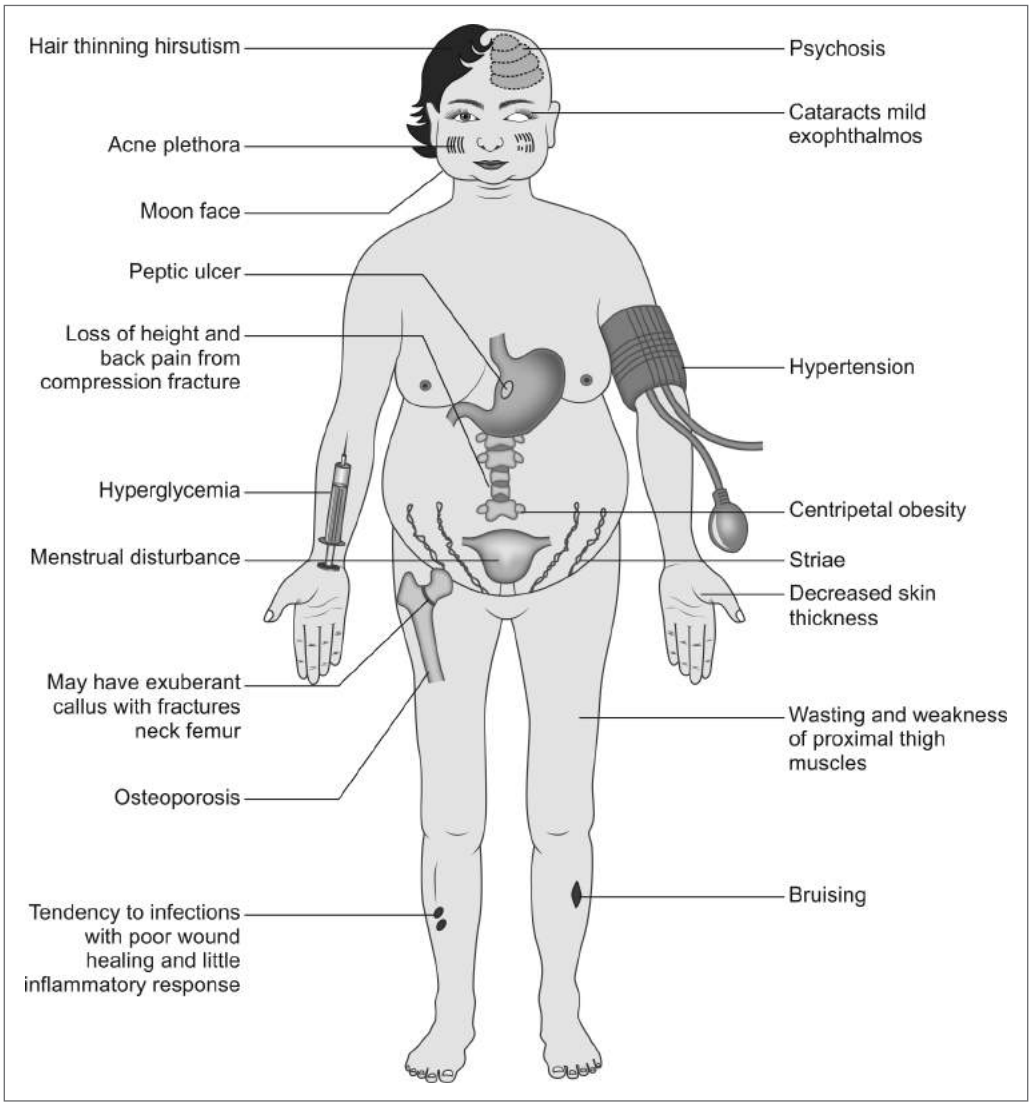


Fig. 88.1: Cushing's syndrome

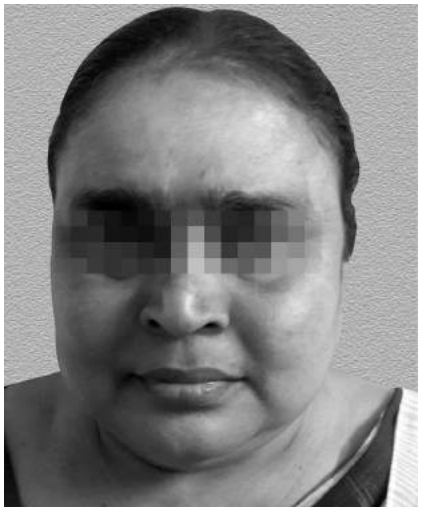


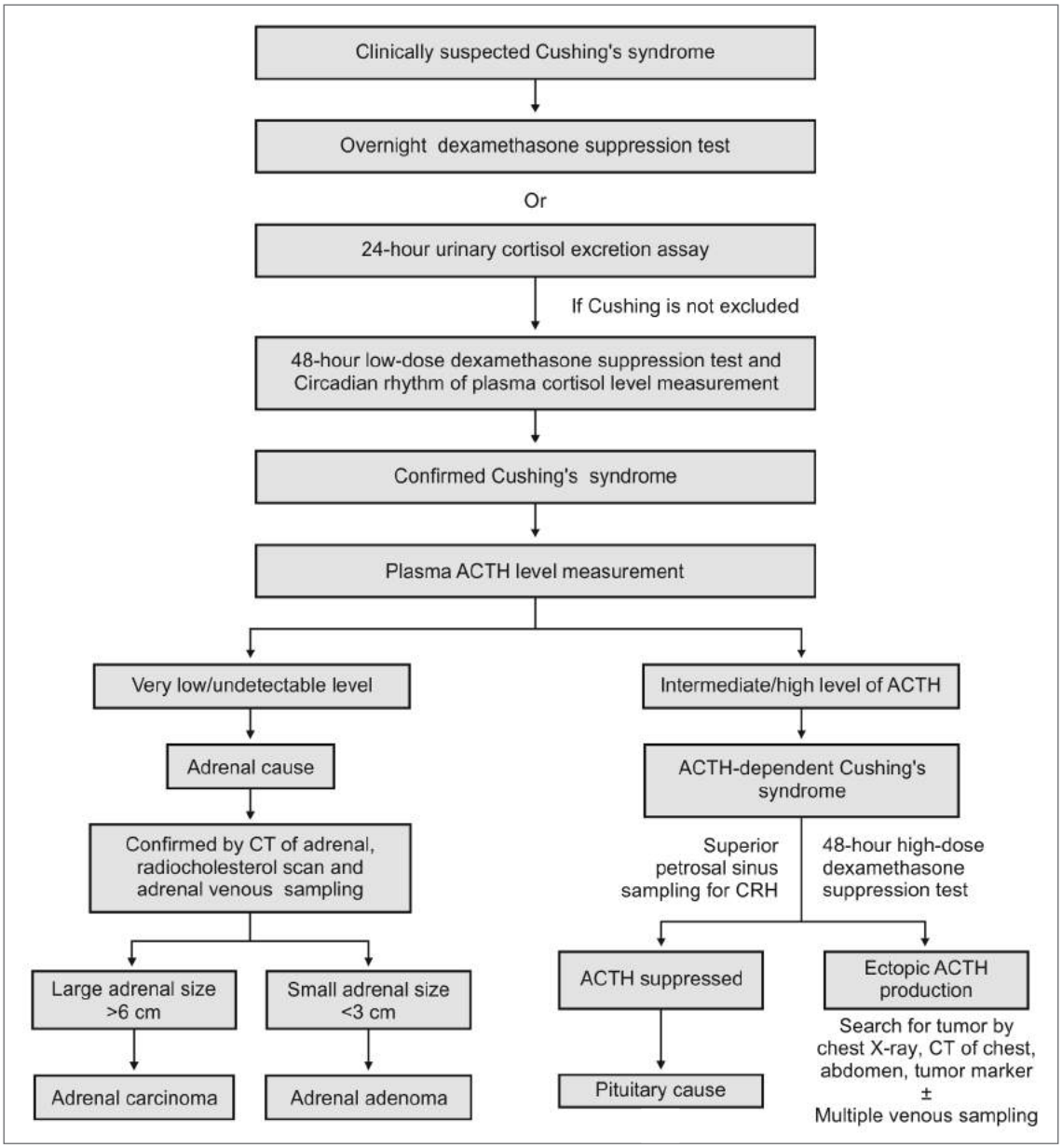
Fig. 88.2: Moon face in Cushing

- **Dexamethasone suppression test**—Definitive diagnosis is established by failure of urinary cortisol to fall below 10 μg/day (or, plasma cortisol less than 5 μg/dL) after low dose dexamethasone (0.5 mg every 6 hourly for 48 hours) therapy.
- **Absence** of normal **fall of plasma cortisol at midnight** is also diagnostic of Cushing's syndrome.

TESTS FOR ETIOLOGICAL DIAGNOSIS

- **Measurement of plasma ACTH**—Normal level is less than 60 pg/mL.
  - ACTH low/undetectable <10 pg/mL—Adrenal tumor (neoplasm).
  - High ACTH level 200–500 pg/mL—It is suggestive of ACTH secreting pituitary macroadenoma or ACTH-producing nonendocrine tumor.

Flowchart 88.1: Diagnosis of Cushing's



– Intermediate ACTH level 50–150 pg/mL—It is suggestive pituitary microadenoma or pituitary hypothalamic dysfunction.

However, the main problem in diagnosis of Cushing's syndrome is that ACTH level may be similar in individual with **hypothalamopituitary axis dysfunction or pituitary microadenoma** and **ectopic CRH** or **ACTH**-producing big tumor.

A useful step for solving this problem is to see the **suppression of cortisol output in response to high dose dexamethasone** (2 mg every 6 hourly for 48 hours). **Suppression of urinary free cortisol** of more than 90% of the normal level by high dose dexamethasone suppression test suggests **ACTH-secreting pituitary microadenoma or hypothalamo-pituitary dysfunction**.

Nonsuppression of cortisol production by high dose dexamethasone suppression test suggests:

– **Pituitary macroadenoma**.
– **ACTH-producing nonendocrine tumor** (carcinoid and pheochromocytoma).

- **Adrenal neoplasia**
  - Nonendocrine tumor, carcinoid and pheochromocytoma are differentiated clinically by
    - » Presence of diarrhea and flushing suggest—**Carcinoid**.
    - » Presence of episodic headache and hypertension suggest **pheochromocytoma**.

- **Those with high ACTH level**—Pituitary MRI and selective petrosal sinus venous sampling for ACTH at basal 2, 5 and 10 minutes after ovine CRH injection (1 μg/kg IV). Peak petrosal : peripheral ACTH ratio >3 confirm pituitary ACTH secreting tumor.

  If peak plasma cortisol > 120% and/or ACTH >150% of basal values, it suggests pituitary-dependent disease. But if the response is lower, it indicate ectopic ACTH production.

  Pituitary MRI with gadolinium demonstrates microadenoma only in half of the patients. Microadenoma is detected in 10–20% of normal persons without pituitary disease. A positive imaging does not prove that pituitary is the source of ACTH.
- **Those with low/undetectable range of ACTH level** in plasma should be evaluated with CT—abdomen specially the adrenals, adrenal venous sampling and radio-cholesterol scan.

  Tumor >6 cm suggest—Adrenal carcinoma.

  Tumor <3 cm suggest—Adrenal adenoma.

TREATMENT

Adrenal Neoplasia

- **Surgical removal of tumor** (may be done by laparoscopy) with irradiation of tumor bed and adrenolytic drug **OP DDD - Mitotane**-prognosis is not very good, expected survival of 3 years.

  Replacement therapy with prednisolone (similar to addisonian patient) undergoing elective surgery till the contralateral adrenal, hypothalamus and pituitary recover.
- **Medical therapy**—Chemical adrenalectomy may be accomplished by administration of inhibitor of steroidogenesis.
  - **Ketoconazole** (600–1200 mg/day)
  - **Aminoglutethimide** (1 g/day)
  - **Metyropone** (2–3 g/day)
  - **Mifepristone**—A competitive inhibitor of glucocorticoid to its receptor may be another treatment option.

Cushing's Disease

- Transsphenoidal surgical removal of the pituitary adenoma is the treatment of choice.
- Metyrapone or ketoconazole given for preoperative preparation for surgery to reduce the effect of hypercortisolism.
- If no tumor is found radical hypophysectomy is done.
- If diagnosis is uncertain bilateral adrenalectomy is done followed by pituitary irradiation with yttrium 90 to prevent development of **Nelson's syndrome**.
- Following adrenalectomy—**Prednisolone and fludrocortisone** replacement therapy is given for variable period.

ECTOPIC ACTH SYNDROME

- If Cushing's syndrome is due to bronchial carcinoid — surgical removal is the treatment of choice.
- If Cushing's syndrome is due to malignant tumor-radiotherapy and chemotherapy are treatment of choice.
- During treatment or palliation (radio or chemo) of other malignancies, severity of Cushing's syndrome is reduced with medical therapy by *ketoconazole*, or *aminoglutethimide or metyrapone*—the dose of which is best titrated depending on 24-hour urinary cortisol excretion.

NELSON'S SYNDROME

It is an aggressive locally invasive pituitary tumor with high level of ACTH and hyperpigmentation of skin.

If develops in patient with Cushing's disease (bilateral pituitary dependent adrenal hyperplasia) treated by bilateral adrenalectomy without any definitive treatment for pituitary.

TREATMENT

Transsphenoidal removal of pituitary followed by radiotherapy.

ADDISON'S DISEASE

ETIOLOGY (FIG. 88.3)

- **Primary (increased ACTH)**
  - **Anatomic destruction of gland**
    - *Idiopathic (common)*:
      - » Autoimmune
        - ▫ Sporadic (30–40%)
        - ▫ PGA-2 (60–70%) (autoimmune polyglandular syndrome)
      - » Adrenoleukodystrophy.

    Rare causes are:
    - *Surgical removal*
    - *Infective*—TB, histoplasma, cryptococcus, coccidioidomycosis and HIV.
    - *Hemorrhage*
      - » Adrenal apoplexy
      - » Waterhouse-Friderichsen syndrome

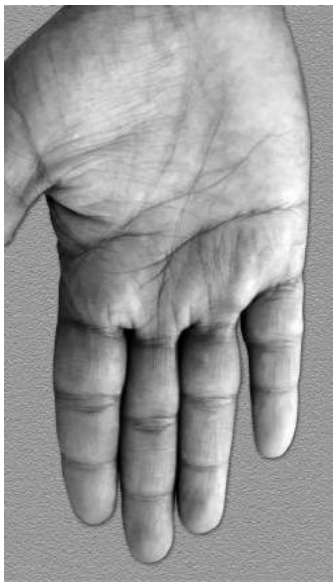


Fig. 88.3: Hyperpigmentation of palmar creases in Addison's disease

  - *Invasion*
    - » Metastatic
    - » Lymphoma.
  - *Adrenal vein thrombosis*
    - » APLA syndrome
    - » Hyperviscosity syndrome.
- **Metabolic failure in hormone production**
  - Congenital adrenal hypoplasia (CAH).
  - Enzyme inhibitors—Ketoconazole and metyrapone.
  - Cytotoxic drugs—Mitotane.
- **ACTH-blocking antibody**
- **Mutation in ACTH receptor gene**
- **Adrenal hypoplasia congenita**.

- **Secondary (decreased ACTH)**
  - **Hypopituitarism**—Due to hypothalamic or pituitary disease.
  - Suppression of hypothalamopituitary axis
    - By endogenous steroid or tumor.

CLINICAL FEATURE (TABLE 88.1)

Gradual destruction of gland is characterized by insidious onset fatigability, weakness, anorexia, nausea, vomiting, weight loss and cutaneous pigmentation or hypotension and hypoglycemia.

More than 90% gland must be destroyed before clinical adrenal insufficiency appears.

DIAGNOSIS

The diagnosis of adrenal insufficiency (Tabale 88.2) is made only with ACTH stimulation testing to access adrenal reserve capacity for steroid production.

In the screening test 250 μg of cosyntropin given IV/IM (synthetic ACTH) and cortisol response is seen at 30–60 minutes after when serum cortisol should exceed 80 μg/dL in normal person. If the response is abnormal primary or secondary adrenal insufficiency is the cause which are differentiated by simultaneous measuring of serum aldosterone and plasma ACTH level.

In secondary but not in primary adrenal insufficiency aldosterone increment will be normal. In primary adrenal insufficiency plasma ACTH level and B-LPT level are elevated (Flowchart 88.2).

ASSESSMENT OF MINERALOCORTICOIDS

- Hyponatremia
- Hyperkalemia (common but not universal)
- High plasma renin activity in supine posture
- Low or subnormal aldosterone level.

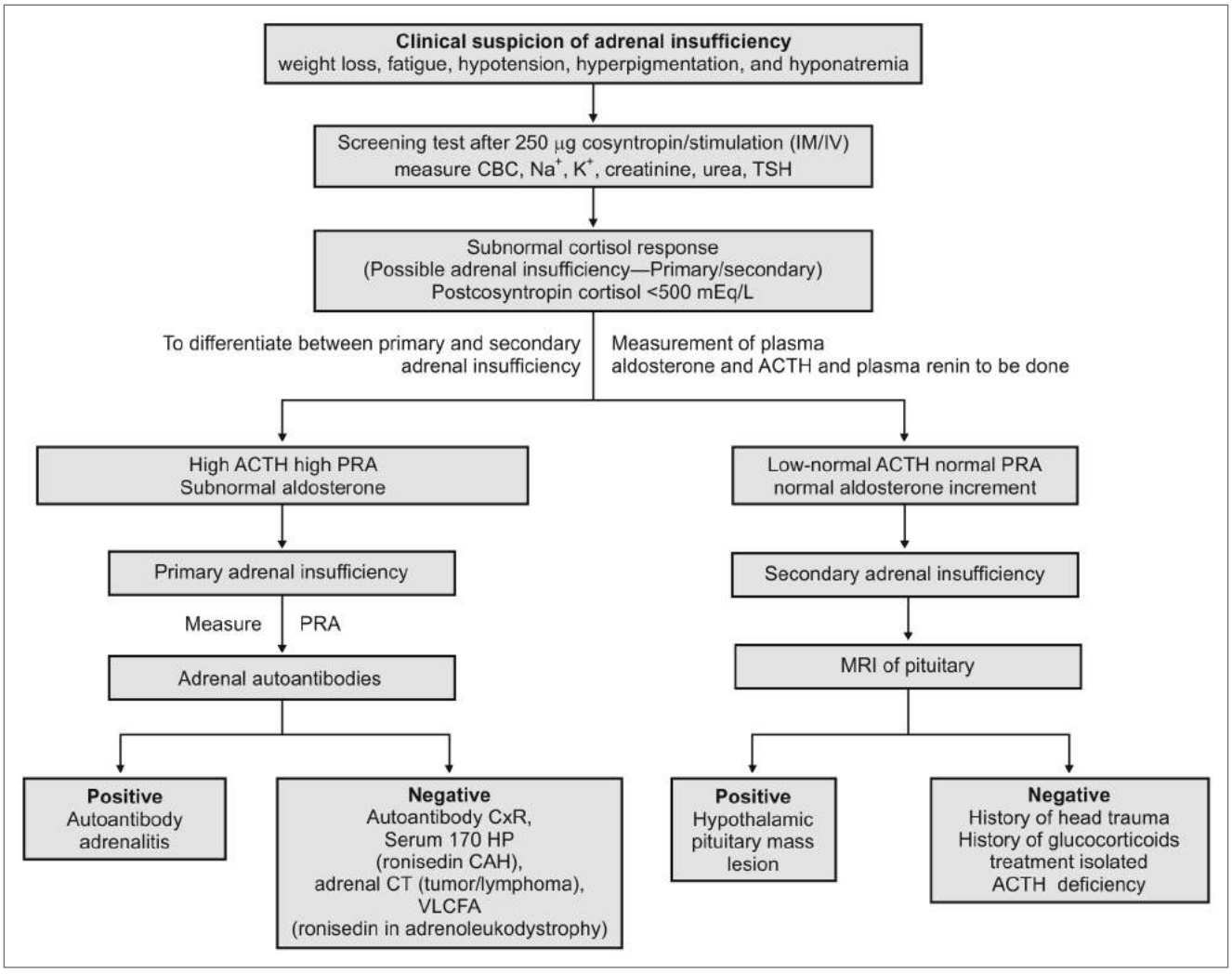
Table 88.1: Clinical features of adrenal insufficiency

Glucocorticoid insufficiency	Mineralocorticoid insufficiency	Androgen insufficiency
• Weight loss anorexia • Myalgias, fever and joint pain • Weakness, fatigue and lack of energy • Anemia • Lymphocytosis • Eosinophilia • Raised TSH • Postural hypotension • Low BP • Hypoglycemia • Hyponatremia	• Hypotension • Shock • Hyponatremia • Hyperkalemia • Increased serum creatinine • Abdominal pain • Nausea and vomiting • Dizziness • Salt craving	• Increased pigmentation • Lack of energy • Loss of libido • Dry itchy skin • Loss of axillary and pubic hair

Table 88.2: Differential diagnosis of adrenal insufficiency

	Withdrawal of exogenous glucocorticoid	Hypopituitarism	Addison's disease	Congenital adrenal hyperplasia (hydrolase defficiency)
Glucocorticoid insufficiency	✓	✓	✓	✓
Mineralocorticoid insufficiency	×	×	✓	✓
ACTH excess	×	×	✓	✓
Adrenal androgen insufficiency	✓	✓	✓	×

Flowchart 88.2: Diagnosis of adrenal insufficiency



Abbreviation: PRA, plasma renin actively; MRI, magnetic resonse imaging CBC, Complete blood count; VLCFA, very long cain fatty acid TSH, Thyroid-stimulating hormone ACTH, adrnocorticotropic hormone

OTHER TESTS TO ESTABLISH THE CAUSE

- Full blood count—To rule out pernicious anemia
- Thyroid function test
- Blood sugar (fasting and PP)
- Test of gonadal function
- Serum Ca^{++}
- Antibody against:
  - Thyroid antigen
  - Pancreatic B cell
  - Gastric parietal cell
  - Steroid-secreting cell (adrenal and gonad).

For PGA_2
- Chest X-ray—to rule out TB.
- CT abdomen/MRI abdomen—Identification of metastatic malignancy.
- ELISA for HIV.

MANAGEMENT

Patient with adrenal insufficiency is best treated with replacement therapy for **glucocorticoid** and **mineralocorticoid**. Replacement therapy with **adrenal androgen, DHEA** improves mood and fatigue in patient with Addison's disease.

GLUCOCORTICOID REPLACEMENT IN (CHRONIC) ADRENAL INSUFFICIENCY

Cortisol (hydrocortisone) is the drug of choice 20–30 mg/day dose is given in two divided doses with 2/3rd dose at 8 am and rest 1/3rd at 4 pm.

If patient is unable to take hydrocortisone orally due to severe vomiting then hydrocortisone may have to be administered parenterally.

Alternatively prednisolone—5 mg at 8 am and 2.5 mg at 4 pm.

Patient having severe infection the dose of glucocorticoid should be doubled with concomitant administration of broad spectrum antibiotics.

Glucocorticoid Replacement in Acute Adrenal Insufficiency

Patient undergoing surgery

Day of operation—Hydrocortisone 10 mg/hour infusion

Postoperative

- 1st post-operative day—Hydrocortisone 5–7.5 mg/hour infusion.
- 2nd to 5th postoperative day—Hydrocortisone 2.5–5 mg/hour infusion.

Mineralocorticoid Replacement

- Fludrocortisone 0.05–0.1 mg/day to be given orally at 8 am. Dose should not be increased during acute infection or stressful condition and supplemental sodium intake 3–4 g/day.

Sex Corticoid Replacement

Dehydroepiandrosterone (DHEA) 25–50 mg/day improves quality of life and bone mineral density.
- Adequacy of glucocorticoid replacement is assessed clinically by weight gain.
- Adequacy of mineralocorticoid replacement is assessed by measuring BP, plasma electrolyte and plasma renin activity.

PHEOCHROMOCYTOMA

It is catecholamine-producing tumor derived from chromaffin cells of sympathetic nervous system usually arises from adrenal medulla (90%) or extraadrenal in 10% patient. Paragangliomas arise from the following sites:
- Abdominal paraaortic gland (75%)
- Thoracic gland (10%)
- Bladder (10%)
- Rarely in the neck or pelvis.

Parasympathetic paragangliomas are located in the head and neck.

Sympathetic paraganglioma are usually located in the abdomen or thorax.
- In 10% patient it is a malignant tumor
- In 10% patient it is bilateral
- In 10% patient it is extra-adrenal.

Pheochromocytoma may be unilateral or bilateral and occurs in association with the following hereditary syndromes.
- **MEN-2A (Sipple's syndrome)**—Comprises of:
  - Medullary thyroid carcinoma (95%)
  - Pheochromocytoma (40%)
  - Hyperparathyroidism (25%)
  - Cutaneous lichen amyloidosis.
- **MEN-2B**—Comprises of:
  - Medullary thyroid carcinoma (100%)
  - Pheochromocytoma (50%)
  - Specific abnormal phenotype
  - Multiple mucosal ganglioneuroma
  - Rarely hyperparathyroidism.
- **Von Hippel-Lindau's diseases**—Autosomal dominant disorder associated with inactivation mutation of von Hippel-Lindau tumor suppressor gene on chromosome 3.
  Pheochromocytomas occur in 10–20% cases of von Hippel-Lindaus' disease.
  Others features are renal cell carcinoma (70%), CNS and retinal hemangioblastoma.
  Pancreatic islet cell tumor. Endolymphatic tumor. Pancreatic and epididymal cyst.
- **Neurofibromatosis type-1 (von Recklinghausen's disease)**—Due to inactivation mutation of NF1 tumor suppressor gene on chromosome 17 (approximately 2% patient have pheochromocytoma. Pheochromocytoma may produce calcitonin, ACTH, VIP and PTHrP.

CLINICAL FEATURES

Patient with pheochromocytoma may be intermittently or continuously symptomatic. **Episodes or paroxysm of hypertension, headache, palpitation and sweating** lasting for minutes to hour are the classic manifestation of pheochromocytoma. 0.1% of hypertensive patients have pheochromocytoma.

Majority (90%) of the patients have hypertension that may be mild to severe, labile and difficult to treat.

Patient may present with cardiovascular collapse arrhythmia during operation under GA or following drugs like opiates, glucagon, metaclopramide, pancuronium and TCAD.

A detailed family history should be taken to exclude hereditary syndrome.

Approximately >50% patients present with the classical triad of—(a) **headache**, (b) **sweating** and (c) **palpitation**. Approximately >20–40% patients present with:

- Pallor
- Nausea
- Tremor
- Anxiety
- Abdominal pain
- Chest pain
- Weakness.

Approximately >20% patient present with:

- Dyspnea
- Weight loss
- Flushing
- Visual disturbances.

INVESTIGATIONS

- Biochemical diagnosis
- Tumor localization.

Biochemical Diagnosis

Measurement of urinary catecholamines and metanephrines/normetanephrines or VMA in acidified 24 hours urine allows confirmation of diagnosis of pheochromocytoma in 95% of patients.

Inaccurate result may be associated with patient taking labetalol or α-methyldopa.

If 24 hours urine metanephrine is borderline then measurement of

- Plasma catecholamine level
- Clonidine suppression test may be helpful.

Tumor Localization

When biochemical diagnosis is confirmed the tumor is localized with the help of—

- CT/MRI of abdomen and thorax.
  - CT diagnose pheochromocytoma with 95% accuracy. Contrast should only be used when the patient has been prepared with α-blocker.
  - MRI is helpful in pregnant women and in whom intracaval extension of tumor is suspected.
- ^{131}I-MIBG (Metaiodobengylguanidine) scan will identify at least 90% of the tumors including extraadrenal disease, multiple tumor and metastasis.

TREATMENT

- **Medical**
  - α-blockers—phenoxybenzamine 20–80 mg in divided dose. The dose may be increased by 10 mg every 48 hours until adrenergic symptom resolves or the patient reports for postural hypotension and stuffy nose.
  - β-blocker is only indicated if tachycardia develops and should only be started when the α-receptors are fully blocked because of the risk of hypertensive crisis.

    If successful can cure the disease but in 10% cases tumor recur.
- **Surgical**—Profound change in blood pressure and pulse rate can occur during surgery. A sudden fall of blood pressure is usual when the venous drainage of the tumor has been ligated. At this point rapid infusion of large volume of fluid and epinephrine may be necessary. Catecholamine excretion measurement should be performed annually to identify recurrence.
- **For malignant pheochromocytoma**
  - Combination of *vincristine, dacarbazine* and *cyclophosphamide* is helpful in symptom control and survival.
  - *Therapeutic ^{123}I-MIBG* is of benefit in 30% of patients but its effects are short-lasting.

    5-year-survival of malignant pheochromocytoma is 50%.

EXERCISE

Write short notes on

1. Clinical features of Cushing's syndrome.
2. Diagnosis of Cushing's syndrome including etiological diagnosis.
3. Treatment of Cushing's syndrome.
4. Clinical features of pheochromocytoma.
5. Diagnosis and treatment of pheochromocytoma.
6. Clinical features and diagnosis of Addison's disease.
7. Management of Addison's disease.

Chapter 89

Acromegaly

INTRODUCTION

Acromegaly is usually caused by the excess growth hormone (GH) secretion usually from the somatotroph adenoma of pituitary, but may also rarely from extrapituitary source.

ETIOLOGY

Excess GH Secretion

- **Pituitary (98%)**
  - *Densely or pursely granulated GH cell adenoma (60%).*
  - *Mixed GH and PRL cell adenoma (25%).*
  - *Mammosomatotroph cell adenoma (10%).*
  - Pleurihormonal adenoma.
  - GH cell carcinoma/metastasis.
  - MEN-1.
  - McCune-Albright syndrome.
- **Extrapituitary**—Pancreatic islet cell tumor.

Excess GHRH Secretion

- **Central**
  - Hypothalamic hamartoma
  - Choriostoma
  - Ganglioneuroma.
- **Peripheral**
  - Bronchial carcinoid
  - Pancreatic islet cell tumor
  - Small cell lung carcinoma
  - Adrenal adenoma
  - Medullary carcinoma of thyroid (MCT)
  - Pheochromocytoma.

CLINICAL FEATURES

- **Protean manifestation** of GH and IGF hypersecretion is not clinically diagnosed for 10 years or more. Acral body overgrowth results in:
  - Frontal bossing.
  - Increased hand and foot size (spade-shaped hand).
  - Mandibular enlargement with prognathism.
  - Widened space between lower two incisors.
  - In children and adolescent, if GH hypersecretion is prior to epiphyseal fushion or closure, is associated with development of pituitary gigantism.
  - Soft tissue swelling.
  - Increased heel pad thickness.
  - Increased shoe size.
  - Increased glove size.
  - Ring tightening.
  - Characteristic course facial features.
  - Large fleshy nose.
- **Other features include**:
  - Hyperhidrosis
  - Oily skin
  - Hollow and deep sounding voice
  - Acropathy
  - Kyphosis
  - Carpal tunnel syndrome
  - Proximal myopathy and fatigue
  - Acanthosis nigricans
  - Generalized viceromegaly with cardiomegaly, macroglossia and thyroid enlargement.
- **Cranial nerve involvement in acromegaly**
  - Bitemporal hemianopia (due to pressure on optic chiasma).
  - Blindness due to optic atrophy.
  - External ophthalmoplegia due to 3rd, 4th and 6th nerve involvement.

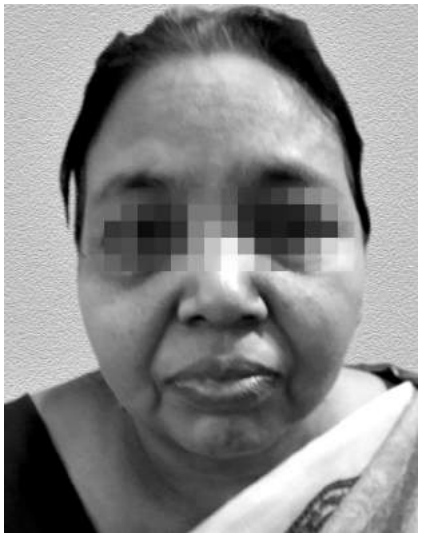


Fig. 89.1: Acromegaly with deep nasolabial furrow and bulky nose

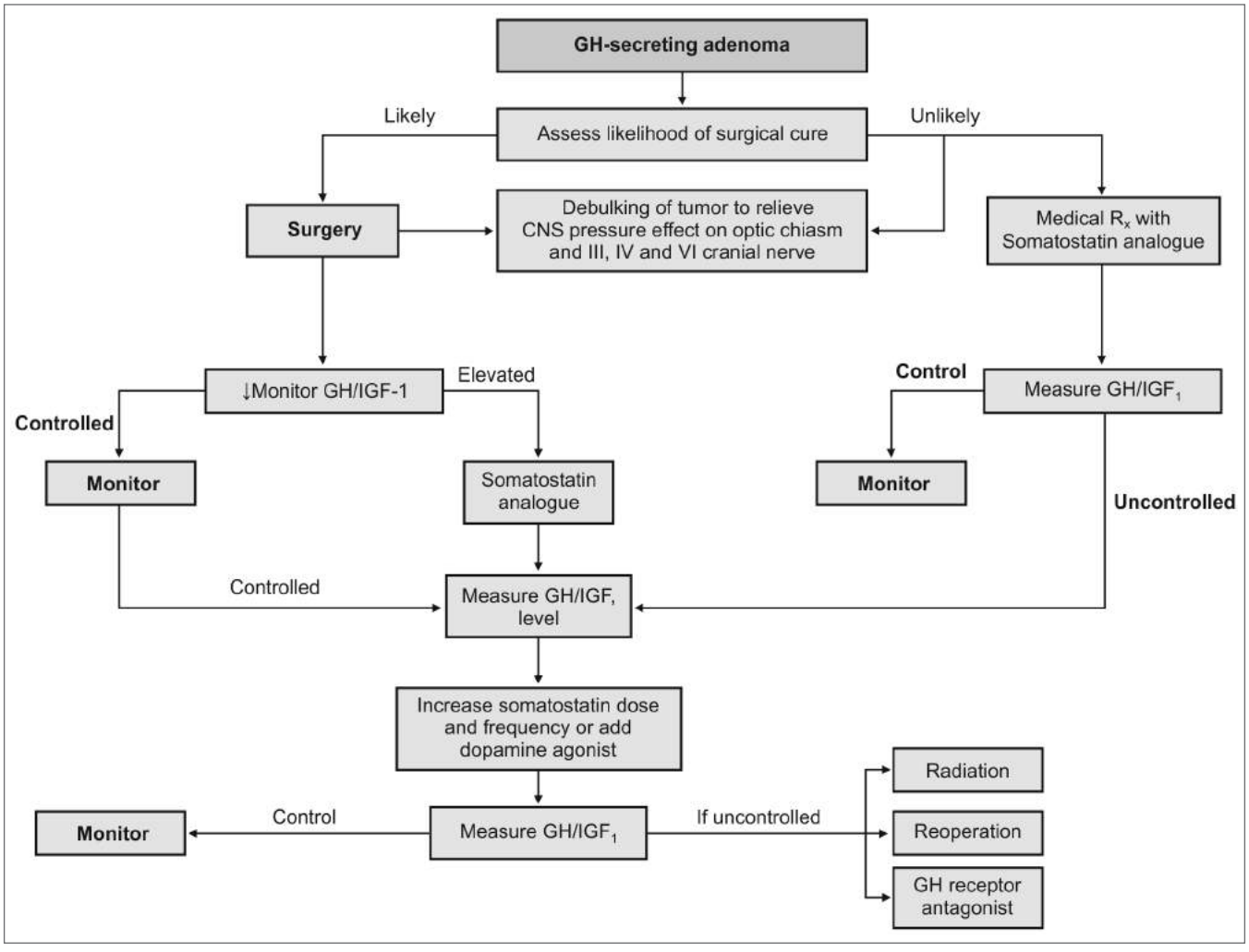
- **Common manifestation of CVS involvement are**:
  - CAD
  - Cardiomyopathy
  - Arrhythmia
  - Left ventricular hypertrophy
  - Hypertension in about 30% patient.
- Sleep apnea occurs in about 60% patients (due to laryngeal obstruction).
- Diabetes mellitus develops in 25% patients.
- Acromegaly is associated with increase in risk of colonic polyp and malignancy.
- Overall mortality is increased by 3 fold due to cerebrovascular disease, coronary artery diseases and malignancy.
- Unless GH level is controlled, survival is reduced by 10 years.

LABORATORY DIAGNOSIS

- IGF level is elevated in age and gender matched population.
- Due to pulsatility of GH secretion, a single measurement of GH level is not useful.

  Diagnosis is confirmed by demonstration of failure of GH suppression below 1 μg/L within 1–2 hours of oral 75 g glucose load.
- Prolactin is elevated in 25% patients.
- Estimation of plasma somatomedin C by RIA.
- X-ray shows: Skull—Lateral view
  - Enlargement of pituitary fossa
  - Double floor of pituitary fossa
  - Erosion of clenoid process
  - Prominent supraorbital ridges and jaw
  - Enlargement of PNS
  - Mandibular enlargement.
- X-ray of hand shows:
  - Tufting of terminal phalanges—Arrowhead appearance.
  - Heel pad thickness:
    - >21 mm in men
    - >18 mm in women.

Flowchart 89.1: Management of acromegaly



- X-ray spine—Kyphoscoliosis and osteoporosis
- Chest X-ray—Cardiomegaly
- USG abdomen shows organomegaly
- CT/MRI to visualize pituitary gland enlargement.

TREATMENT (FLOWCHART 89.1)

Surgical (1st line of treatment)

- Transsphenoidal surgery in pituitary microadenoma.
- If total removal is not possible, surgery serves as a debulking of the tumor and further 2nd line therapy is required according to postoperative imaging and glucose tolerance.

Radiotherapy

External radiotherapy (Gamma knife) is employed as 2nd line treatment if acromegaly persists after surgery. However GH level falls slowly over many (8–18) years and signs of hypopituitarism and hypothalamic damage takes 10 years to develop after therapy (ACTH, TSH and gonadotropin deficiency).

Medical

In patient with persisting acromegaly after surgery medical therapy is applied to lower GH level <2 μg/mL.

- Somatostatin analogue—Octerotide is given by SC injection initially with 50 μg tid–150 μg/day. Rapid relief of headache and diminution of soft tissue swelling occur in 75% patients within days or weeks and subjective improvement occurs more quickly than biochemical remission. Modest pituitary tumor reduction occurs in 40% patient.
- Lanreotide—30 mg IM depot. preparation (cyclic somatostatin octapeptide analogue) suppress GH and IGF secretion for 10–14 days.
- Long-acting somatostatin depot formulations—**Sandostatin LAR** is a sustained release formation incorporated in microsphere (60 mg injection). Suppresses GH and IGF for 4 weeks and also decreases size of the tumor and pituitary size.
- Dopamine agonists are less potent in lowering GH but are helpful in patients with prolactin excess.
  - Dopamine against—Bromocriptine ≥20 mg/ day in 3–4 divided doses given in prolactin excess tumor or carbergolin (0.5 mg/day) achieve modest efficacy.
  - Combined treatment—Bromocriptine and octeritide induce additive biochemical control compared to either drug alone.
- Encouraging trial have been performed with GH receptor antagonist pegvisomant. 10–12 mg SC daily or biweekly normalizes IGF in >90% patients.

  Combined treatment with somatostatin monthly and pegvisomant weekly or biweekly is used in resistant cases.

EXERCISE

Write short notes on

1. Diagnosis of acromegaly.
2. Treatment of acromegaly.

Chapter 90

Syndrome of Inappropriate Antidiuretic Hormone

Excessive secretion or action of AVP results in production of decreased volumes of more highly concentrated urine.

If not accompanied by a concomitant reduction in water intake, the excessive action of AVP results in water retention and a decrease in plasma osmolarity and sodium concentration (hyponatremia).

If hyponatremia develops acutely it is accompanied by symptoms and sign of water intoxication like *headache, confusion, anorexia, nausea, vomiting, coma* and *convulsion*.

If hyponatremia develops more gradually or present for few days it may be asymptomatic.

Severe **hyponatremia may be fatal**.

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE

Hyponatremia in absence of ECF volume contraction or reduction in effective volume or in renal insufficiency is usually due to increased AVP secretion resulting in decreased water excretion.

High level of AVP alone is not sufficient to produce hyponatremia, hence ingestion of extra amount of water is also necessary.

Syndrome of inappropriate antidiuretic hormone (SIADH) remains the most common cause of euvolemic/normovolemic hyponatremia (type–III).

SIADH has many causes:

- **Ectopic production of AVP** by neoplasm of lung, duodenum, pancreas, ureter, bladder and ovary. Other neoplasm are mesothelioma, bronchial adenoma, carcinoid and thymoma may cause SIADH. Abnormal expression of AVP-NP-II gene by primary or metastatic malignancies is responsible for ectopic production of AVP.
- **Eutopic form manifest** in patient with:
  - **Head injury** (penetrating or closed)
  - **Vascular cause**—CVA (hemorrhage and infarction), cavernous sinus thrombosis.
  - **Neurologic cause**—G-B syndrome, multiple sclerosis, amyotropic lateral sclerosis, peripheral neuropathy, hydrocephalus, delirium tremens and psychosis.
  - **Infection**—Meningitis (bacterial or viral), encephalitis, pneumonia (bacterial or viral), TB of lung and brain, lung abscess and AIDS.
  - **Metabolic**—Asthma, pneumothorax and positive pressure ventilations.
  - **Drugs**—Vasopressin or desmopressin and oxytocin (high dose), chlorpropamide, carbamazepine, cyclophosphamide, vincristine, TCAD, MAOI, SSRI amd phenothiazine.

The mechanism by which these diseases disrupt the osmoregulation is not known.

The secondary form of osmotically inappropriate antidiuresis is divided into two groups:

1. Type I (hypervolemic)
2. Type II (sodium-depleted states).

- **Type I SIADH (hypervolemic)** occurs in sodium-retaining and edema-forming states, e.g.
  - CCF
  - Cirrhosis
  - Nephrotic syndrome
- **Type II SIADH (hypovolemic)** occurs is sodium-depleted states, for example,
  - Severe gastroenteritis
  - Diuretic abuse
  - Mineralocorticoid deficiency
  - Reduction in blood/extracellular volume
  - Reduction in blood pressure.

Pathophysiology

In SIADH the abnormal osmoregulation of AVP can take any of the following forms:

- AVP secretion remains fully responsive to change in plasma osmolarity/sodium but the set point of osmoregulation is abnormally low.

  They are able to maximally suppress plasma AVP and dilute their urine if their fluid intake is high enough to reduce their plasma osmolality and sodium to the new lower set point.
- A smaller subgroup (10%) of the total does not have any defect in osmoregulation.

  Their is appropriate antidiuresis is due to enhanced renal sensitivity to the antidiuretic effect of normally

low level of AVP or activation of aquaporin-2 water channels by a mechanism that is independent of AVP and V_2 receptor.

The extracellular volume expansion that results from excessive retention of water produces excess atrial natriuretic peptide and suppression of plasma renin activity which cause urinary loss of sodium that is responsible for hyponatremia but tries to reduce hypervolemia.

Thus hyponatremia is due to decrease in total body sodium as well as increase in total body water.

The acute retention of water and fall in plasma sodium also increase intracellular volume. This results in brain swelling causes increase in ICT and responsible for symptoms of water intoxication.

In type I (edematous) or type-II (hypovolemic and hyponatremia) the osmotic inhibitions of AVP secretion and urine concentration is counteracted by hemodynamic stimulus, that results from a substantial reduction in effective or absolute blood volume.

The resultant antidiuresis is usually enhanced by decreased distal delivery of filtrate that results from increased reabsorption of sodium from proximal tubule secondary to hypovolemia.

If it is not associated with concomitant reduction in water intake, the marked reduction in urine output results in expansion of extracellular volume and symptoms of hyponatremia.

Differential Diagnosis

SIADH is a diagnosis of exclusion that can usually be made from history of physical and laboratory examination.

If the glucose is not elevated enough to account for the hyponatremia (for rise of 36 mg/dL of glucose serum sodium decrease 1 mEq/L) and/or plasma osmolarity, the hyponatremia is true and can be typed or classified by standard clinical indicator of the extracellular fluid volume.

In patient who fulfils the clinical criteria for type III euvolemic hyponatremia plasma cortisol should be measured to rule out unsuspected secondary adrenal insufficiency.

Treatment

In acute SIADH

- The first step is to restrict total fluid intake to less than the sum of insensible water loss and urine output. Total fluid intake should be 500 mL less than urinary output.
  As insensible loss (500 mL) = water derived from food (500 mL).
  This measure usually reduces body water and increases serum sodium by about 1–2%/day.
- If more rapid correction of hyponatremia is desired, fluid restriction is supplemented by intravenous infusion of hypertonic (3%) saline.

  If hyponatremia is present for more than 24–48 hours, too rapid correction has the potential to produce **central pontine myelinolysis** characterized by quadriparesis, ataxia and abnormal extraocular movement.

  The following guidelines minimize the risk of pontile myelinolysis.
  - 3% saline is infused at the rate of <0.05 mL/kg.
  - The infusion should be stopped as soon as serum sodium increased by 12 mmol/L or to 130 mmol/L whichever comes first.
  - Urine output should be monitored as spontaneous remission of SIADH can occur at any time and result in acute diuresis.
- In chronic SIADH
  - Hyponatremia can be corrected by treatment with demeclocycline—150–300 mg orally 3–4 times a day. Action seen 7–14 days after starting of therapy and is due to production of reversible form of nephrogenic diabetes insipidus.
    Side effects—Phototoxicity and azotemia.
  - Fludrocortisone 0.05–0.2 mg twice daily. It also has latent period of 1–2 weeks and is partly due to increase retention of sodium and possibly inhibitions of thirst. It also causes excretion of potassium; so potassium supplementation is required and hypertension precludes therapy.
- When an SIADH-like syndrome is due to protracted nausea and vomiting or isolated glucocorticoid deficiency all abnormalities can be corrected by antiemetic or glucocorticoids.
- Nonpeptide AVP antagonists (Tolvaptan / conivaptan are undergoing clinical trial and has become the treatment of choice of SIADH to both acute and chronic SIADH. They produce a dose-dependent increase in urinary free water excretion which is combined with modest restriction of water intake gradually reduces body water and correction hyponatremia without any side effect.

EXERCISE

Write short notes on

1. Etiology of SIADH.
2. Treatment of SIADH.

SECTION IX

DIABETES (ENDOCRINE)

- Diabetes Mellitus

Chapter 91

Diabetes Mellitus

INTRODUCTION

Diabetes mellitus (DM) comprises a group of metabolic disorders that have the common characteristic hyperglycemia due to absolute or relative deficiency of insulin.

CLASSIFICATION

Though previously diabetes was classified on the basis of age of onset or type of therapy, now it is classified solely on the basis of pathogenic process causing the disease.

Two features of the current classification of DM diverge from previous classification:

- Firstly the term IDDM and NIDDM are obsolete. (As many individuals with type–II DM may require insulin subsequently as a part of their treatment.)
- Secondly age is not a criteria for classification.

ETIOLOGIC CLASSIFICATION OF DIABETES

- **Type-I DM** (B-cell destruction causing absolute in- sulin deficiency).
  - Immune-mediated—Type-IA
  - Idiopathic—Type-IB.
- **Type-II DM** (insulin resistance with relative insulin deficiency or secretory defect).
- **Other specific types of DM**:
  - *Genetic defects in β-cell function*:
    - MODY 1, 2, 3, 4, 5, 6
    - Mitochondrial DNA mutation
    - Proinsulin or insulin conversion defect.
  - *Genetic defects in insulin action*:
    - Type A insulin resistance
    - Lypodystrophy.
  - *Endocrine defects*:
    - Acromegaly
    - Hyperthyroid
    - Glucagonoma
    - Cushing
    - Pheochromocytoma
    - Aldosteronoma.
  - *Diseases of the exocrine pancreas*:
    - Pancreatitis and pancreatectomy
    - Pancreatic neoplasia
    - Cystic fibrosis
    - FCPD
    - Hemochromatosis.
  - *Drugs/chemicals used*:
    - β-adrenergic agonist diazoxide
    - α-interferon
    - Glucocorticoid
    - Pentamidine
    - Phenytoin
    - Protease inhibitor
    - Thiazide
    - Thyroid hormone.
  - *Infections*:
    - Congenital rubella
    - CMV
    - Coxsackievirus.
  - *Uncommon form of immune-mediated DM*:
    - Antiinsulin receptor antibodies.
  - *Other genetc disorders*:
    - Down's, Klinefelter's, Turner's, Friedreich's ataxia, Huntington's chorea, myotonic dystrophy and porphyria.
- **Gestational DM (GDM)**—Insulin resistance related to the metabolic changes of late pregnancy causes increased insulin requirements and may lead to IGT (impaired glucose tolerance).

  It is seen in approximately 4% of pregnancies.

  Most women revert back to normal glucose tolerance but 45–60% of them develop DM in later life.
- **MODY (maturity onset diabetes of the young)**—It is a subtype of DM characterized by:
  - Autosomal dominant inheritances
  - Early onset hyperglycemia
  - Impairment of insulin secretion.

DIAGNOSIS

Criteria for Diagnosis of DM

1. **Symptoms of DM + Random blood glucose** ≥200 mg/dL
2. **Fasting blood sugar** ≥126 mg/dL
3. **PP blood sugar** ≥200 mg/dL during an oral GTT
4. **HbA1C** ≥6.5%

- Revised criteria for diagnosis of DM emphasize the FPG as a reliable and convenient criteria to diagnose DM in asymptomatic individual.
- Random blood sugar (≥200 mg/dL) accompanied by classic symptoms of DM (polyuria, polydipsia and weight loss) is sufficient for diagnosis DM.
- Oral glucose tolerance test (GTT) though a valid test but not considered as a part of routine diagnostic procedure.
- ADA recommends screening of all individuals >45 years of age every 3 years and screening of individuals with additional risk factors (for DM) at an earlier age.

Risk Factors of DM (Type–II)

- Family history of DM
- Habitual physical inactivity
- History of GDM or delivery of baby >4 kg
- History of vascular disease
- HTN (≥140/90)
- BMI >25 kg/m^2 with central obesity
- PCOD/Acanthosis nigricans
- Previously identified IGT/IFG
- Race/ethnicity
- HDL ≤35 mg/dL
- Triglyceride > 250 mg/dL.

PATHOGENESIS OF TYPE-I DM

Type–I DM

- Type-I DM develops as a result of destruction of β-cell of pancreas by a synergistic action of genetic, environmental and immunologic factors.
- Individuals with a genetic susceptibility begin to loose β-cell mass secondary to its destruction by an autoimmune process (thought to be secondary to an environmental or infectious stimuli) over months to years.

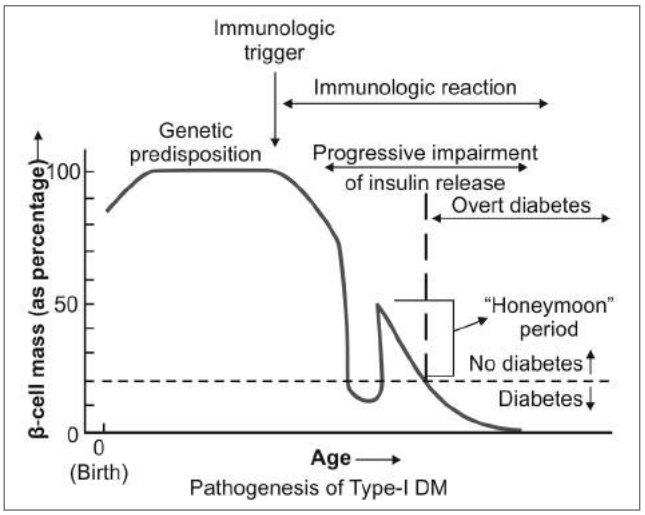


Fig. 91.1: Pathogenesis of type-I DM

- Features of DM do not become evident until a majority of β-cells are destroyed (~ 80%).
- After the initial clinical presentation of type–I DM, a '*honeymoon phase*' (Fig. 91.1) may be seen during which time the glycemic control can be achieved with modest dose of insulin or rarely no insulin is required. This fleeting phase of endogenous insulin production from residual β-cell disappears as the autoimmune process destroys the remaining β-cell and the individual becomes completely insulin deficient.
- **Genetic considerations**
  - Polymorphism of HLA complex account for 40–50% of the genetic risk of developing type–IA DM. In addition to HLA association 17 different loci contribute susceptibility for type–IA DM.
  - HLA DR–3 and/or DR–4 haplotypes are mostly susceptible.
  - The concordance of type–IA DM in identical twin is 30–70%.
  - Risk of developing type–IA DM is increased 10 fold in relatives of individuals the disease.
- **Autoimmune factors**
  - Although α, β, δ and PP cells of pancreas are functionally and embryologically similar but in autoimmune reaction against β-cell, others cells are inexplicably spared.
  - In this autoimmune process—
    - Islet cell autoantibodies are formed
    - T-cell infiltrates the pancreas
    - Release of cytokines (TNF-α, IL-1, INF-γ) takes place.
  - Basically the β-cells are destroyed due to formation of nitric oxide metabolites and direct CD_8 cytotoxicity.
  - The targeted autoantigens are insulin, GAD (glutamic acid decarboxylase), IA-2, ICA-512 and ZnT-8.
- **Immunologic marker**
  - Islet cell autoantibodies that helps us to diagnose T-I DM are against GAD, insulin, IA–2/ICA–512.
- **Environmental agents**
  - Virus (coxsackie and rubella).
  - Bovine milk protein.
  - Nitrosourea.

  } Three agents are so far identified as environmental factor which trigger autoimmune destruction of islet cell in a genetically susceptible individual.

Type–II DM

Insulin resistance and abnormal insulin secretion play the key role in development of type–II DM. But it is seen that insulin resistance precedes its secretory defects and diabetes develops only when its secretion becomes inadequate.

- **Genetic consideration**—Type–II DM is:
  - Polygenic and multifactorial.

  - The concordance rate between identical twins is between 70–90%.
- **Pathophysiology**
  - Central obesity is very common in type–II DM. Adipocytes secrete biologic product like (**leptin, TNF-α, free fatty acids, resistin, adiponectin, retinol binding protein 4**) which modulate insulin sensitivity, appetite and body weight and insulin resistance in liver and skeletal muscles.
  - Three pathophysiologic abnormalities which characterize type–II DM are:
    - Peripheral insulin resistance
    - Impaired insulin secretion
    - Excessive hepatic glucose production.
  - Initially the insulin resistance supervenes which is compensated by hyperinsulinemia. Later the pancreatic β-cells fail to sustain the hyperinsulinemic status and turns into IGT. Later the condition progresses to frank DM.
  - Insulin resistance:
    - Insulin resistance impairs glucose utilization by insulin-sensitive tissues and increases hepatic glucose output—both contribute to hyperglycemia. *Increased hepatic glucose output accounts for increased FPG level; whereas decreased peripheral glucose utilization results in post-prandial hyperglycemia.*
    - The pathogenesis of insulin resistance is currently focused on a *PI-3-kinase* signalling defect, which reduces translocation of GLUT-4 to the plasma membrane.

      Postreceptor defects are also believed to play a predominant role in insulin resistance. Polymorphism in IRS-1 may be associated with glucose intolerance.
    - Elevated free fatty acids in obese persons may:
      - » Impair glucose utilization in skeletal muscles
      - » Promote glucose production in liver
      - » Impair β-cell function.
  - Impaired insulin secretion : Early in the course of the disease the secretion of insulin increases (probably involves glucose-stimulated insulin secretion) but afterwards the secretory defect progresses to a grossly inadequate insulin secretion.

    The cause of decrease in insulin secretion is actually unknown.

    Several theories are postulated:
    - *Amyloid* deposition around the islets in long-standing DM.
    - Chronic hyperglycemia paradoxically impairs insulin secretion (**glucose toxicity**).
    - Elevated free fatty acid may reduce insulin secretion (**lipotoxicity**).
  - Increased hepatic glucose production—Insulin resistance in liver leads to inability to suppress hepatic neoglucogenesis which results in fasting hyperglycemia and decrease hepatic glycogen store during postprandial stage.

CLINICAL FEATURES

In the initial stage most of the diabetic patients both type–I and II may be asymptomatic. Both type–I and II classical patients may presents with:

- *Polyuria*.
- *Polydipsia*.
- *Polyphagia*.
- Sudden loss or gain in weight or may be *detected diabetic on routine examination* or may present with acute complications of diabetes, like *DKA* and *HONK*, *recurrent infections* (*boil*, *curbuncle*, *LRTI* or *UTI* or *pulmonary TB)*. The diabetics may present with features of *chronic complications* like *peripheral neuropathy*, *myocardial infarction* or *visual disturbances* or features of *nephrotic syndrome and kidney failure*. The detail features of chronic complication are described under the respective complications.

INVESTIGATIONS

The following investigations are routinely done in all case of new onset diabetes:

- FBG.
- 2 hours PPBG.
- HbA1C/estimation.
- Blood urea, creatinine and ketone bodies.
- Lipid profile (annual).
- Urine RE/ME.
- 24 hours urine albumin excretion.
- Spot urine ACR (normal up to 30).
- GFR estimation.
- BP recording.
- ECG.
- Fundoscopy (annual).
- Echocardiography (not routinely done).
- NCV and EMG (not routinely done)
- Insulin estimation and C-peptide for differentiation of type I and type II.

ASSESSMENT OF LONG-TERM GLYCEMIC CONTROL

It is done by examining HbA1C which represent mean plasma glucose in last 3 month

HBA1C 6% correspond to mean plasma glucose 126 mg/dL
HBA1C 7% correspond to mean plasma glucose 154 mg/dL
HBA1C 8% correspond to mean plasma glucose 183 mg/dL
HBA1C 9% correspond to mean plasma glucose 212 mg/dL
HBA1C 10% correspond to mean plasma glucose 240 mg/dL
HBA1C 11% correspond to mean plasma glucose 269 mg/dL
HBA1C 12% correspond to mean plasma glucose 298 mg/dL

TREATMENT

Because the complications of DM are related to glycemic control, normoglycemia or near normoglycemia is desired. Regardless of the level of hyperglycemia, improvement of the level of glycemic control will lower the risk of diabetic complications.

The ideal goal for DM patient set by ADA are:

1. **2 hours postprandial plasma glucose** 70–130 mg/dL
2. **Peak postprandial plasma glucose** <180 mg/dL
3. **Hb** A1C <7%

[Plasma glucose values are 10–15% higher than whole blood values]

4. **BP**—130/80 mmHg
5. **LDLC** <100 mg/dL
6. **HDL** >40 mg in men, >50 mg in female
7. **TGL** <150 mg/dL

MANAGEMENT OF TYPE-1 DM

Individuals with type–I DM lack endogenous insulin production. So **insulin** is the main pillar for management of type-I DM. Apart from insulin two other agents can be used for treatment of type-I DM patient.

- **Insulin**
- **Amylin analog—Pramlintide**
- **α-glucosidase inhibitor**—Acarbose, voglibose and miglitol.

DOSE OF INSULIN

Usually type–I DM patients require **0.5–1 U/kg/day of which 50% is given as long-acting (basal) insulin** which is usually given either at breakfast or in the evening and the **residual 50% is broken up and given as short-acting insulin before each meal usuing the formula 1–1.5 U/10 gm of carbohydrate**. To this insulin dose is added the correcting dose for preprandial hyperglycemia. **Two types of formula are used for calculations of the extra doses of insulin** for preprandial hyperglycemia:

- **1 unit of insulin for every 50 mg/dL over the preprandial glucose target**.
- **Body weight in kg × (blood glucose – desired glucose) in mg/dL/1700**.

INSULIN PREPARATIONS

At present insulins are prepared by recombinant DNA technology in *Escherichia coli* or in *yeast cell*.

- **Short-acting insulins—Lispro, regular insulin aspart and glulisine**.
  Lispro—In Lispro molecule 28th and 29th amino acid (lysine and proline) on B-chain are reversed.
- **Intermediate-acting insulins—NPH and lente insulin.**
- **Long-acting insulins—Ultralente, glargine and detemir.**

Glargine—In glargine asparagine is replaced by glycine at 21 position and two arginine residue are added to 'C' terminal of B-chain.

The newer short-acting insulin analogues have full biologic activity but less tendency toward subcutaneous aggregation, resulting in more rapid absorption, shorter onset and duration of action.

Lispro and aspart are to be given just before or just after meal but regular insulins are to be given 30–45 minutes prior to a meal. The shorter duration of action of lispro and aspart causes less number of hypoglycemic episodes.

- Insulin glargine is a long-acting biosynthetic human insulin. Compared to NPH insulin, duration of action of glargine is also longer (>24 hours). No pronounced peak, causing lower incidence of hypoglycemia—specially at night.
- In the management of type-I DM basal insulin requirements are provided by intermediate/long-acting insulin preparation and are usually combined with short-acting insulin formulations to mimic physiologic insulin release after meals. Mixing of human regular insulin with NPH allows production of combinations of insulins that contain NPH and regular in the ratio 70 : 30/50 : 50. These combinations are more convenient for the patient but prevent adjustment of only one component of that insulin formulation.
- The main shortcoming of current insulin regimens is that the **injected insulin immediately enters systemic circulation where endogenous insulin is secreted into portal venous system and thus exogenous insulin exposes liver to subphysiologic dose of insulin**.
- **In general individuals with type-I DM require 0.5–1 U/kg/day of insulin divided in multiple doses**.
- The most commonly used regimen consists of twice daily (BD) injections of NPH/lente mixed with short-acting insulins. Such regimens provide 2/3rd of total daily insulin dose in the morning (with about 2/3rd as intermediate-acting and 1/3rd as short-acting) and 1/3 before the evening meal (with approx half given as intermediate and half as short-acting insulins).

  Though it is simple and effective at avoiding severe hyperglycemia, it does not generate near-normal glycemic control in most people with type-I DM. If the patient's meal pattern/content varies or if the physical activity is increased, hyperglycemia or hypoglycemia may result.
- Moving the intermediate-acting insulin from before evening meal to bedtime may avoid serious nocturnal hypoglycemia and provide insulin at a higher level as glucose level rises in the early morning (so-called **dawn phenomenon**) by the surge of counter regulatory hormone.

MANAGEMENT OF TYPE–II DM (FLOWCHARTS 91.1 AND 91.2)

Three essential pillars for management of type-II DM patients are:

- Glycemic control.
- Treatment of associated condition like dyslipidemia (Flowchart 91.5) hypertension and obesity.
- C. Screen and manage complications like retinopathy, nephropathy, neuropathy and cardiovascular disease.

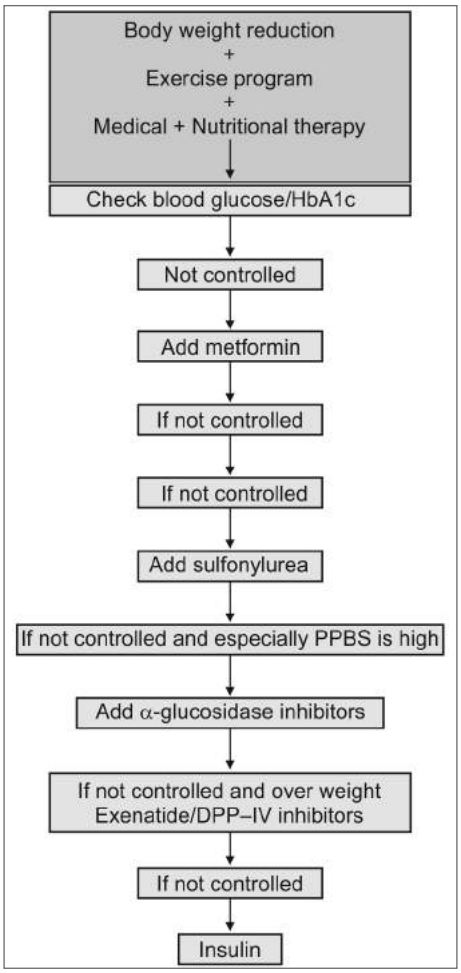
Glycemic control is achieved by:

- **Diet and lifestyle modification**
- **Exercise programe**
- **Drugs**.

Various groups of drugs apart from insulin are used for management of type–II DM.

- **Insulin secretagogues**:
  - **Sulfonylurea**—Glimepiride, glipizide and glyburide.
  - **Nonsulfonylurea**—Repaglinide and nateglinide.
  - **GLP-1 receptor agonist**—Exenatide and liraglutide.
  - **DPP-4 inhibitors**—Vildagliptin, sitagliptin, saxagliptin and teneligliptin.

Flowchart 91.1: Treatment algorithm for type-II DM



Abbreviations:PPBS,plannig, Programming, and Budgeting.

- **Biguanide**—Metformin.
- **α-glucosidase inhibitors**—Acarbose and miglitol voglibose.
- **PPAR-γ stimulant** (thiazolidinediones)—Pioglitazone (withdrawn from market as it aggravates heart failure).
- **Insulin**:
  - Most individuals usually require more than one class of oral drugs or insulin for optimal glycemic control.
  - Insulin secretagogues, biguanides, GLP-I agonist and thiazolidinediones improve glycemic control to similiar degree (HbA1c reduction 1–2%) and are more effective than α-glucosidase inhibitors and DPP-IV inhibitors.
  - Insulin secretagogues, GLP-I agonist, DPP-IV inhibitors and α-glucosidase inhibitors begins to lower plasma glucose immediately.
  - Whereas action of biguanide and thiazolidinediones are delayed by several weeks.
  - Apart from insulin and insulin secretagogues all other class of drug do not directly cause hypoglycemia.

But if the initial FBG is very high insulin can be started early which rapidly lowers the blood glucose and reduces the glucose toxicity to islet cells and improves endogenous insulin secretion and permits other oral glucose lowering agent to be more effective.

INSULIN SECRETAGOGUES

They preferably stimulate insulin secretions by interacting with the ATP-sensitive K^+ channel on β-cell of pancreas.

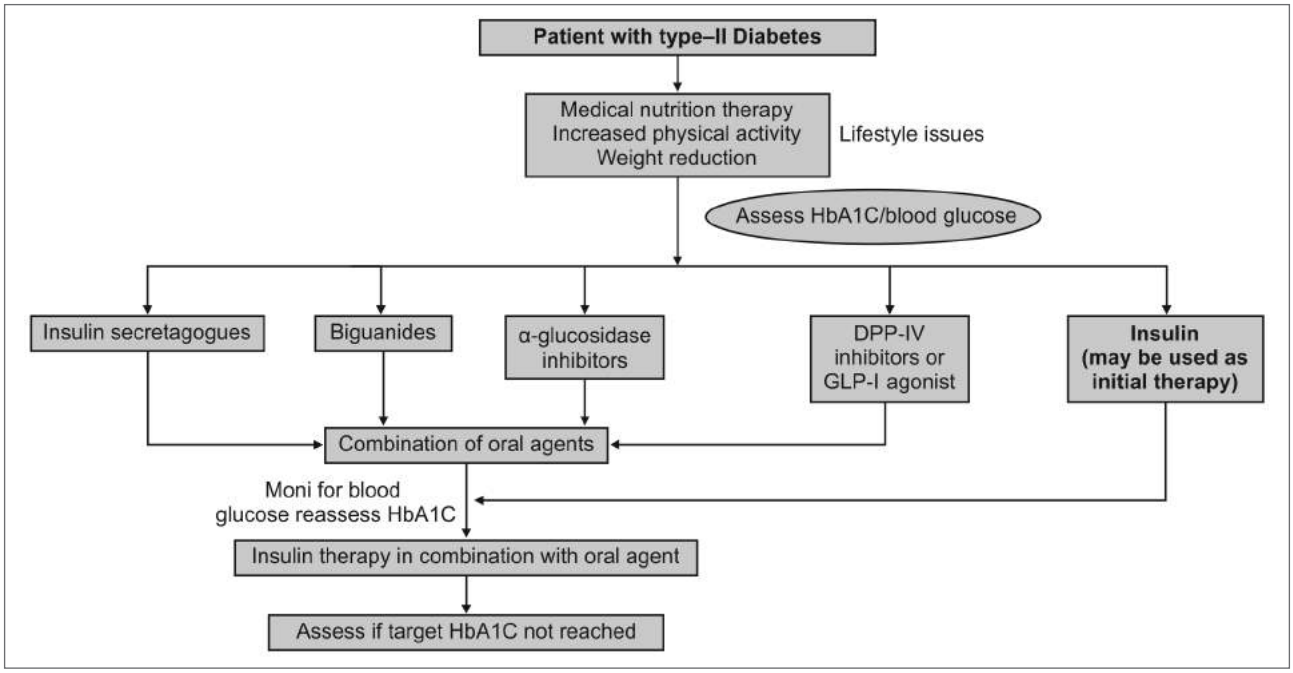
- These drugs are most effective in recent onset type-II DM (<5 years) [who have residual β-cells mass for endogenous insulin production] and in obese patient.
- Two groups of insulin secretagouges are:
  - **Sulfonylureas**:
    - First-generation—Chlorpropamide, tolazamide and tolbutamide (not in use).
    - Second-generation—Glimepiride, glipizide and glyburide.
  - **Nonsulfonylureas**—Repaglinide and nateglinide.
- The second generation drugs have more rapid onset of action and better coverage.
- Sulfonylureas reduce both fasting and PPBS and should be initiated at low dose and increased at 1–2 week. intervals. Repaglinide and Nateglinide though not sulfonylureas but also interact with ATP-sensitive K^+ channel. Because of their shorten half-life these agents are given with each meal/immediately before to reduce PPBS.

  Sulfonylurea interacts with alcohol, aspirin, warfarin, ketoconazole and α-glucosidase inhibitors.

BIGUANIDES

- Metformin is the only representative of this class and decreases hepatic glucose production through an

Flowchart 91.2:Treatment algorithm for type II diabetes



undefined mechanism. It reduces FBS, improves lipid profile, promotes modest weight loss.

- Initial starting dose is 500 mg od/bd and can be increased up to 1000 mg bd. The dose to be increased every 2–3 weeks based on SMBG.
- Main toxicity is lactic acidosis and should not be used in **renal compromised** patient, **CCF** patients and in any type of acidosis.
- Drug is metabolized in liver; so should not be used in patients with liver disease or heavy **ethanol intake**.

α-GLUCOSIDASE INHIBITORS

They are not very potent oral agent to decrease HbA1C but they can reduce PPBS even in patients with type-I DM.

- Acarbose, voglibose and miglitol are the members of this group reduce PPBS by delaying glucose absorption and they do not affect glucose utilization or insulin secretion.
- These drugs should be taken just before each meal to reduce glucose absorption by inhibiting the enzyme that cleaves oligosaccharides into simple sugars in the intestinal lumen.
- Therapy should be initiated at a low dose [acarbose (50–100 mg) voglibose (0.2–0.3 mg) and miglitol (25 mg)], with evening meal and may be increased to a maximum dose over weeks to months.
- Major side effects are diarrhea, flatulence, abdominal distention related to increased delivery of oligosaccharides to large bowel.
- It may increase the level of sulfonylureas and may cause hypoglycemia.
- α-glucosidase inhibitors are contraindicated in-IBD, gastroparesis and renal insufficiency.

THIAZOLIDINEDIONES

- It preferentially reduce insulin resistance by binding with PPAR-γ (peroxisome proliferator-activated receptor γ) nuclear receptors. These are found mostly in adipose tissue.
- Pioglitazone (only member of this group) promotes adipocyte differentiation and may reduce insulin resistance indirectly because of enhanced fatty acid uptake and storage.
- Dose of pioglitazone—15–45 mg/day in a single daily dose.
- It increase LDL and HDL but lower TG.
- It is associated with minor weight gain, small reduction in hematocrit and mild increase in plasma volume.
- It is contraindicated in liver disease and CCF.

INSULIN

- It should be considered as the initial therapy in type-II DM, particularly in:
  - **Lean individuals or those with severe weight loss**.
  - **In individuals with underlying renal or hepatic disease**.
  - **Hospitalized/acutely ill patient**.
  - **GDM**.
- **Insulin dose**—Single dose of intermediate/long-acting insulin (0.3–0.4 U/kg/day) given either before breakfast or before bedtime.

Since fasting hyperglycemia and hepatic neoglucogenesis is the cardinal character of type-II DM; bedtime insulin (single dose) is preferred.

Low fixed starting dose of intermediate-acting insulin (~15–20 U in morning, 5–10 U at bedtime) may be used to avoid hypoglycemia.

CHOICE OF INITIAL GLUCOSE-LOWERING AGENT (FLOWCHARTS 91.1 AND 91.2)

- Patients with mild to moderate hyperglycemia (FBS 200–250 mg/dL)—respond well to single OHA.
- Patients with severe hyperglycemia (FBS –>250 mg/dL)— stepwise combined therapy can be taken to achieve normoglycemia.
- **Insulin** can be started as initial therapy in severe hyperglycemia for more rapid glycemic control and to decrease glucose toxicity to islet cells of pancreas and to improve endogenous insulin production. This will allow glucose- lowering agents to be more effective and later insulin may be discontinued.
- **Metformin** is the usual drug of choice for obese type–II diabetic patient.
  - It promotes mild weight loss
  - Lowers insulin level
  - Improves lipid profile
  - Lowers secondary failure rate
  - Relatively cheap.

  Sulfonylurea may also be used.

  Based on SMBG and HbA1C the dose of sulfonylurea/metformin should be adjusted.
- Thiazolidinediones are alternative initial agents but very costly but α-glucosidase inhibitors are least potent drug and should not be used as initial agent.

COMBINATION THERAPY (FLOWCHART 91.2)

- The combination therapy may be given in the form of:
  - Insulin secretagogues + metformin/thiazolidinediones.
  - Sulfonylureas + α-glucosidase inhibitor.
  - Insulin + metformin/thiazolidinediones.
- If adequate control is not achieved with two oral agents, bedtime insulin or a third oral agent may be added in a stepwise approach.
- When a long-standing DM patient enters the phase of relative insulin deficiency, exogenous insulin is required because glycemic control cannot be achieved with two OHA. Insulin can be used in combination with any of the four oral agents.
- **Daily insulin requirement in type-II DM** is (1–2 U/kg/day), very high in comparison to type-I DM patients. Because in long-standing type-II DM the endogenous insulin production falls but insulin resistance persists.

EMERGING THERAPIES

- **Whole pancreas transplantation** (performed with a renal transplant)—in type-I DM and late type-II DM.
- **Pancreatic islet transplantation**.
- **Inhaled insulin** and additional insulin analogues are under trial.
- **Aminoguanidine**, an inhibitor of the formation of advanced glycosylation end products and inhibitor of protein kinase C may inhibit DM-related complications.
- **Closed loop pumps** that infuses appropriate amount of insulin in response to changing glucose level are potentially feasible now—as continuous glucose monitoring technology has been developed.

CAUSES OF COMA IN DIABETIC PATIENT

- **Hypoglycemia**
- **DK**
- **Hyperglycemic, hyperosmolor, nonketotic (HHONK)**
- **CVA**
- **Uremia**
- **Lactic acidosis**
- **Dyselectrolytemia**.

DIABETIC KETOACIDOSIS

Diabetic ketoacidosis (DK) was formerly considered as a hallmark complication of type-I DM. There is either absolute/relative insulin deficiency with hyperglycemia, volume depletion and acid-base abnormalities.

PATHOPHYSIOLOGY

DK results from absolute/relative insulin deficiency combined with counterregulatory hormone excess—glucagon, catecholamine, cortisol and growth hormone.

Decreased ratio of insulin—Glucagon promotes neoglucogenesis, glycogenolysis, keton body formation in liver and increases amino acid and fatty acid delivery from fat and muscle to liver. Insulin deficiency also reduces the level of GLUT-4 glucose transporters which impair glucose uptake by skeletal muscle and fat cells.

Altered ratio of insulin—Glucagon favors increased fatty acid release from peripheral adepocyte due to increased lipase activity which is normally converted to TG and VLDL in liver but in state of relative hyperglucagonemia, there is activation of the carnitine-palmitoyltransferase-1 in the mitochondria of liver which converts free fatty acid to ketone bodies (acetone, acetoacetic acid and β-hydroxybutyric acid).

Conditions of Precipitating DK

- Complete omission of insulin.
- Failure to increase the dose of insulin during the stress (infection, MI, CVA and surgical operation).

- Drugs (cocaine).
- Pregnancy.

CLINICAL FEATURES

Symptoms

- Nausea, vomiting; thirst and polyuria.
- Abdominal pain-mimicking pancreatitis or rupture of hollow viscus.
- Shortness of breath (Kussmaul's breathing to counteract metabolic acidosis by making respiratory alkalosis).

Signs

- Sinus tachycardia.
- Dry skin and mucous membrane with dehydration.
- Hypotension.
- Tachypnea with Kussmaul's respiration with a fruity odor in patients breath.
- Respiratory distress.
- Lethargy and obtundation.
- Features of cerebral edema—headache and vomiting.
- Ultimately coma and death.

LABORATORY DIAGNOSIS

- Blood glucose—250–600 mg/dL.
- Na^+—Low (125–135 mEq/L.)
- K^+—Normal/slightly increased
- Mg^+—Normal
- Cl^-—Normal
- PO_4—Diminished
- Creatinine—Slightly increased
- Osmolality—300–320 mosmol/mL
- Plasma ketone bodies—++++
- $NaHCO_3$—low (<15 mEq/L)
- Arterial pH → 6.8–7.3
- Arterial pCO_2 → low (20–30 mm Hg)
- Anion gap $\{Na^+ - (Cl^- + HCO_3^-)\}$ mEq/L—Increased.

MANAGEMENT

- **Admit** the patient to hospital if pH < 7 or if the patient is unconscious.
- **Assess serum electrolyte, acid-base status** and **renal function**.
- **Fluid replacement**—2–3 L of normal saline over first 1–3 hours (5–10 mL/kg/hour).

  Subsequently the rate of infusion of normal saline @150–300 mL/hour—when blood glucose reaches 250 mg/dL. Normal saline is replaced by dextrose with normal saline @ 100–200 mL/hour) to maintain blood glucose around 200 mg/dL.
- **Insulin**—Initial dose (0.1U/kg IV bolus) followed by 0.1 U/kg /hour by continuous IV infusion. The dose may have to be increased by 2–10 fold depending on the response is seen by 2–4 hours.
- If initial serum K^+ is <3.3 mmol/L—*Do not administer insulin before correction of potassium*. Potassium deficit is corrected by infusion of intravenous 10% KCl.
- **Measure capillary glucose** every 1–2 hours and serum electrolyte (K^+, HCO_3^-, PO_4^{-3} and anion gap) every 4 hours for the first 24 hours.
- **Monitor pulse, respiration, mental status**, **fluid intake and output** every 1–4 hours.
- If the pH is too low <7.2 infusion of sodi-bicarb (30–50CC) slowly through IV route.
- Usually a broad spectrum β-lactum antibiotic is started to present infection.

MORTALITY/PROGNOSIS

- With appropriate therapy mortality is low (<5%) and is related more with underlying precipitating event such as infection, MI or venous thrombosis, upper GI bleeding and ARDS.

GESTATIONAL DIABETES MELLITUS (FLOWCHART 91.3)

There has been a lot of controversies about the concept of gestational diabetes mellitus (GDM), the importance of this condition and appropriateness of screening for it. ADA recommends either universal or selective screening. Identification and treatment of GDM will avert some of the adverse outcomes such as—pregnancy-induced HTN, macrosomia, perinatal mortality and neonatal metabolic disorders.

HYPERGLYCEMIC, HYPEROSMOLAR, NONKETOTIC COMA

This is usually seen in elderly individual with type-II DM with a several week history of polyuria, weight loss, dehydration, diminished oral fluid intake that results in mental confusion, lethargy and coma.

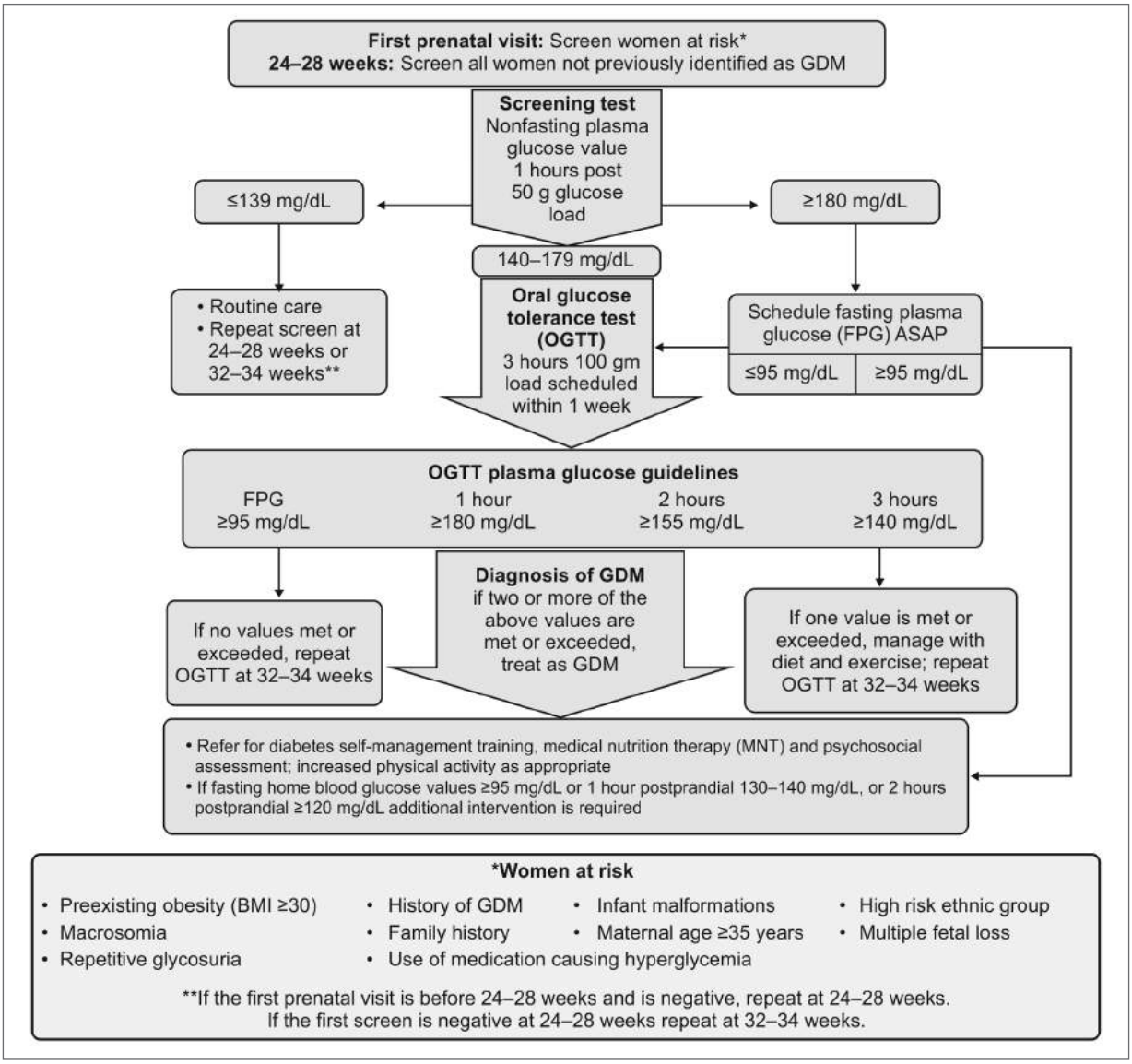
PRECIPITATING FACTORS

- Serious intercurrent illness (MI, stroke, pancreatitis, subdural hematoma and burn).
- Infection (sepsis, pneumonia and severe UTI).
- Debilitating condition (prior stroke/dementia that compromises water intake).
- Chronic use diuretic, phenytoin, glucocorticoid, hemodialysis, peritoneal dialysis and tube feeding with high protein diet.

CLINICAL FEATURES

- Profound dehydration and hypotension.
- Altered mental state, mental confusion, lethargy and coma.
- Significantly absent nausea, vomiting, Kussmaul's breathing and abdominal pain.

Flowchart 91.3: Algorithm for gestational diabetes (GDM) screening, diagnosis and management



PATHOPHYSIOLOGY

- Relative insulin deficiency with inadequate fluid intake is the underlying pathology behind HHONK.
- Insulin deficiency increases glycogenolysis and neoglucogenesis and impaired glucose utilization by muscle and adipose tissue.
- Hyperglycemia leads to osmotic diuresis with contraction of intravascular volume which is exacerbated by inadequate fluid intake and excess fluid loss (in diuretic users).
- **Absence of ketosis in HHONK is ill understood**.
  Possible mechanisms are:
  - Insulin deficiency in only relative and less severe than DK.
  - Lower level of counterregulatory hormone (glucagon, etc.).
    Insulin-glucagon ratio is not much lowered and does not favor ketogenesis.
  - Liver is less capable of ketone body synthesis from free fatty acid.

LABORATORY DIAGNOSIS

- Blood glucose—Usually 600–1200 mg/dL.
- Na^+—Normal (135–145 mEq/L).
- K^+, Mg^{+2}, PO_4^{-3} and Cl^-—Normal.
- Creatinine→Moderately raised and BUN—30–40 mg%.
- Osmolality→330–380 mosmol/mL (raised) [normal—280–300 mosmol/mL].
- Plasma ketone →Usually absent/normal.
- Serum HCO_3^- → Normal/slightly depressed.
- $PaCO_2$ → Normal.
- pH → >7.3.
- Anion gap is normal/slightly raised.

MANAGEMENT

- The most important point in management of HHONK:
  - Fluid replacement.
  - Insulin infusion.
  - Search for precipitating problem which should be aggressively managed.
- **Fluid replacement**—1–3 L of normal saline over first 2–3 hours—too rapid reversal may worsen the neurologic function.
  If serum Na^+ >150 mEq/L—then half-strength saline is used.
  After hemodynamic stability is achieved normal saline is to be replaced by half-strength saline and then 5% dextrose.
  The total fluid deficit should be corrected over 1–2 days with a infusion rate—200–300 mL/hour by half-strength saline.
- **Insulin infusion**
  - Initially 5–10 U IV bolus to be followed by 3–7 U/h. IV to continue.
  - 5% dextrose to be added to the IV fluid when plasma glucose level falls <250 mg/dL and insulin infusion is to be decreased by 1–2 U/h.
  - Insulin infusion is to be continued until patient resumes eating and then it can be switched over to SC insulin.
- **K^+ replacement**
  - K^+ deficit is quite large when patient is taking diuretic. Usually accompanied by Mg deficiency.
  - It is dictated by repeated measurement of serum K^+. Potassium deficit is corrected by infusion of KCl—10 mEq/500 mL of fluid.
  - Hypophosphatemia is evident during therapy and improved by infusing K_3PO_4
  - $NaHCO_3$ (8.5%)—100 mL infused over 1 hour if pH < 7.2.
- The HHONK patients are usually older, more likely to have altered mental status and more likely to have life-threatening precipitating illness with accompanying comorbidities. Even with proper treatment HHONK have substantially higher mortality than DK (up to 15%).

CHRONIC COMPLICATIONS OF DM

Vascular Complications

- **Microvascular complications**
  - *Eye disease—*
    - Retinopathy
      - » Nonproliferative
      - » Proliferative.
    - Maculopathy.
  - *Neuropathy—*
    - Polyneuropathy
    - Mononeuropathy
    - Radiculopathy
    - Autonomic neuropathy.
  - *Nephropathy*.
- **Macrovascular complications**
  - CAD
  - CVA
  - Peripheral vascular disease.

Other Systems

- GI complications—
  - Gastroparesis
  - Diarrhea.
- Genitourinary complications—
  - Uropathy
  - Sexual dysfunction.
- Dermatologic
- Infectious
- Cataract
- Glaucoma.

DIABETIC RETINOPATHY

Three important factors in the development of diabetic retinopathy (DR) are:

- Duration of DM
- Degree of glycemic control
- Presence of hypertension and dyslipidemia
  - Nonproliferative retinopathy found in almost all patients with DM >20 years.
  - Incidence of diabetic retinopathy is more with T_1DM but the severity of maculopathy is more with T_2DM.

Diabetic retinopathy is divided into:

- **Preproliferative diabetic retinopathy**:
  - Mild preproliferative retinopathy
  - Severe preproliferative retinopathy.
- **Proliferative diabetic retinopathy**
- **Advanced diabetic eye disease**.

FEATURES OF MILD PREPROLIFERATIVE RETINOPATHY

- Microaneurysm
- Dot-blot hemorrhage
- Flame-shaped hemorrhage
- Hard exudate.

FEATURES OF SEVERE PREPROLIFERATIVE RETINOPATHY

- Numerous microaneurysm.
- Large dark blot hemorrhage.
- Numerous cotton-wool exudate
- Venous dilatation—Bending, looping and segmentation
- IRMA (intraretinal microvascular abnormality).

FEATURES OF PROLIFERATIVE RETINOPATHY

(Develop within 5 years of severe preproliferative diabetic retinopathy. This window period of 5 years give us excellent opportunity for treatment of diabetic retinopathy)

- Hemorrhage—Preretinal or vitreal hemorrhage.
- Neovascularization
  - NVD (neovascularization at disk)
  - NVE (neovascularization elsewhere).
- Posterior vitreous detachment.

ADVANCED DIABETIC EYE DISEASE

- Recurrent vitreous hemorrhage
- Tractional retinal detachment
- Burnt out diabetic retinopathy
- Neovascular glaucoma (Rubeosis iridis).

Diabetic maculopathy
All features of background diabetic retinopathy are present here plus:

1. **Focal diabetic maculopathy**:
   a. Visual acquity severely impaired
   b. Focal area of leakage
2. **Diffuse diabetic maculopathy**:
   a. Cystoid macular edema in long-standing case
   b. Diffuse leakage in posterior pole arranged in flower petal pattern
   c. Ischemic—Gross capillary nonperfusion in macular and paramacular area

MANAGEMENT OF DIABETIC RETINOPATHY

- **General management**
  - Metabolic control.
  - Control of hypertension.
  - Correction of anemia.
  - Antiplatelet agent.
  - Control of hyperlipidemia by clofibrate/atorvastatin.
- **Specific management at different stages**
  - Background diabetic retinopathy
    - No treatment required.
    - Annual checkup to detect the progression of retinopathy.
  - Preproliferative diabetic retinopathy
    - Watch very carefully.
    - Photocoagulation in case of massive area of hypoperfusion.
  - Proliferative diabetic retinopathy
    - Photocoagulation with YAG/agron/diode laser.
  - Diabetic maculopathy
    - Focal laser photocoagulation is the treatment of choice.
  - Advanced diabetic eye disease
    - Pars plana vitrectomy with panretinal photocoagulation in vitreal hemorrhage and tractional retinal detachment.

DIABETIC NEUROPATHY

- Diabetic neuropathy (DN) develops in 50% of diabetic patients with long-standing type-I or type-II diseases. Both myelinated and unmyelinated fibers are involved.
- Occurrence of diabetic neuropathy correlates with:
  - Duration of DM
  - Adequacy of glycemic control.

Diabetic neuropathy are of four types:

- *Polyneuropathy* (most common)
- *Mononeuropathy/mononeuropathy multiplex*
- *Radiculopathy*
- *Autonomic neuropathy*.

POLYNEUROPATHY

- It is the most common form of diabetic neuropathy.
- It frequently presents with distal sensory loss/paresthesia and dysesthesia.
- Symptoms of polyneuropathy also include numbness, tingling, sharpness and burning that begin at the feet and spread proximally.
- Neuropathic pain developed in some individual preceded by improvement in glycemic control which is usually present at rest and worsen at night mainly found in lower extremities. This neuropathic pain may be of two types—acute or chronic. As neuropathy progresses the pain subsides but the sensory deficit increases.
- Physical examination reveals both small and large fiber involvement along with autonomic involvement.

a. Features of large fiber involvement (posterior column):
- Vibration sense is lost early. Loss of joint sense results in Charcot joint. Other senses like fine touch, muscle sense, position and pressure sense, cortical senses are also lost at a later stage which is called diabetic pseudotabes

b. Features of small fiber involvement (anterior spinothalamic tract):
- Dysesthesia
- Numbness
- Painless foot
- Loss of temperature sense
- Loss of crude touch and pressure sense which results in trophic ulcer

MONONEUROPATHY

Involves isolated cranial or peripheral nerve and is less common than polyneuropathy.

Clinical Features

- Pain and motor weakness in the distribution of a single nerve.
- Pathogenesis is unknown; probably vascular in origin.
- Involvement of 3rd cranial nerve manifested by diplopia due to ophthalmoplegia with preservation of normal light reflex.
- Sometimes 4th, 6th and 7th cranial nerves are affected.

- Peripheral mononeuropathy/mononeuropathy multiplex is rare.
- Polyradiculopathy (Diabetic amyotrophy)
  - Asymmetric involvement with severe pain in the distribution of one or more nerves over thorax, abdomen, hip and thigh.
  - Mainly proximal group of muscle is involved.
  - Most evident weakness seen in muscle innervated by femoral and obturator nerve (diabetic amyotrophy) involving *quadriceps, iliopsoas* and *adductor magnus*.
  - Ipsilateral loss of knee jark.
  - Objective sensory deficit is minimal but pain in the hip and anterior thigh, thorax and abdomen may be prominent.
  - Loss of function is usually partly or completely recovered within 6–12 months.

DIABETIC AUTONOMIC NEUROPATHY

It is characterized by:

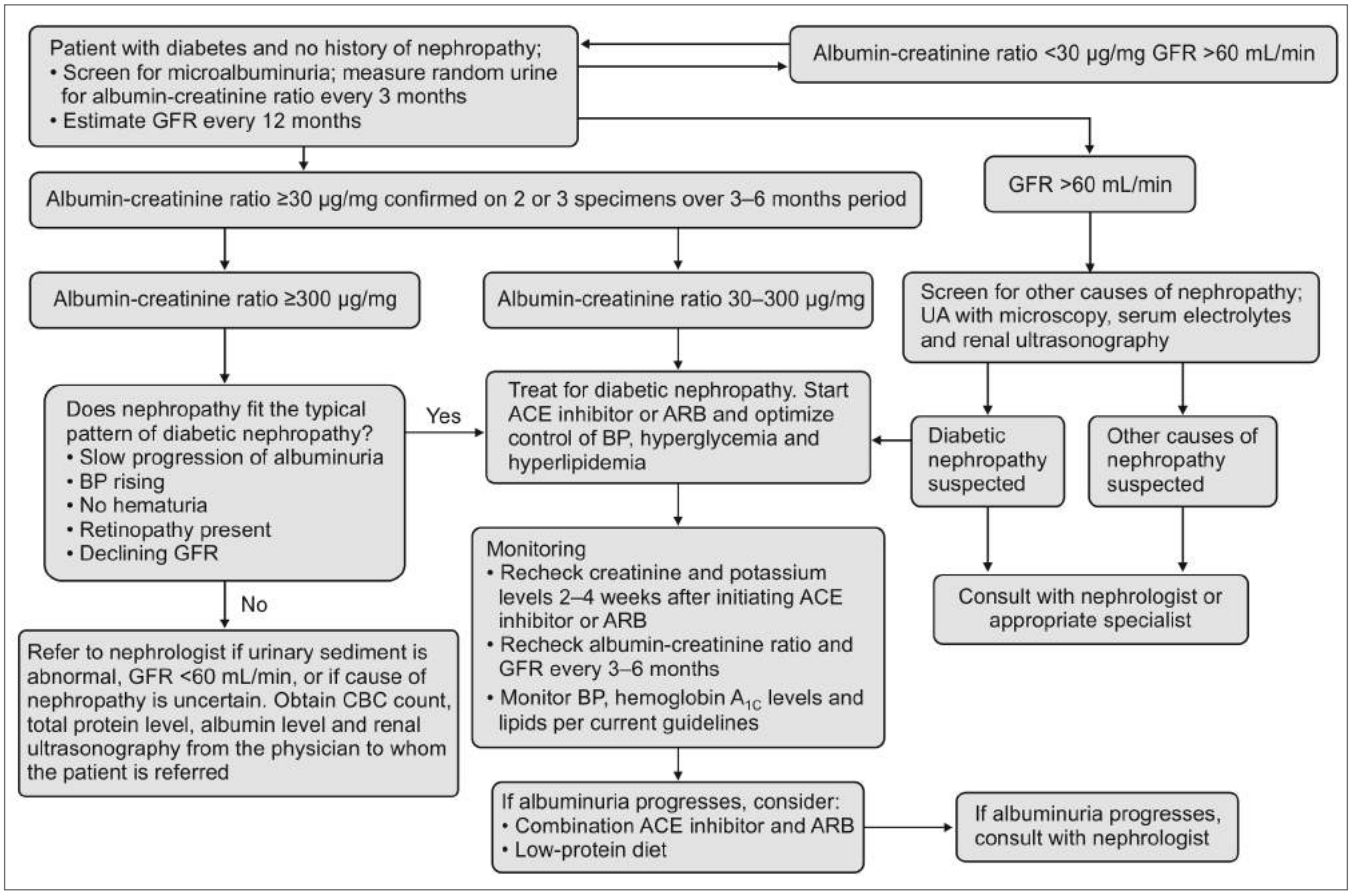
- Postural hypotension.
- Tachycardia or bradycardia.
- Signs and symptoms of hypoglycemia may not be marked.
- Disorder of bladder emptying.
- Painless myocardial infarction.
- Hyper or anhidrosis.
- Impotence, diminished libido and erectile dysfunction.
- Intermittent claudication.
- Crack, fissure and callus formation in the sole.

DIABETIC NEPHROPATHY

It is one of the leading cause of ESRD and DM related mortality and morbidity. Only ~ 40% patient with diabetes develop diabetic nephropathy.

- Proteinuria in a patient with DM reduces survival and is an increased risk of CAD.
- DM nephropathy patient always has DM retinopathy.
- Pathogenesis:
  - Effects of soluble factors—Growth factor, angiotensin II, endothelin and AGES.

Flowchart 91.4: Algorithm on management of diabetic nephropathy



Abbreviations: GFR, Glomerular filtration rate; CBC, Complete blood cell; ACE, Angiotensin-converting enzyme; ARB, Angiotension receptor blocker; BP, Blood pressure; UA, Urine analysis

Source: Veterans Health Administration/Dept. of Defence. Management of diabetes mellitus in primary care. Clinical Practice Guidelines 2003

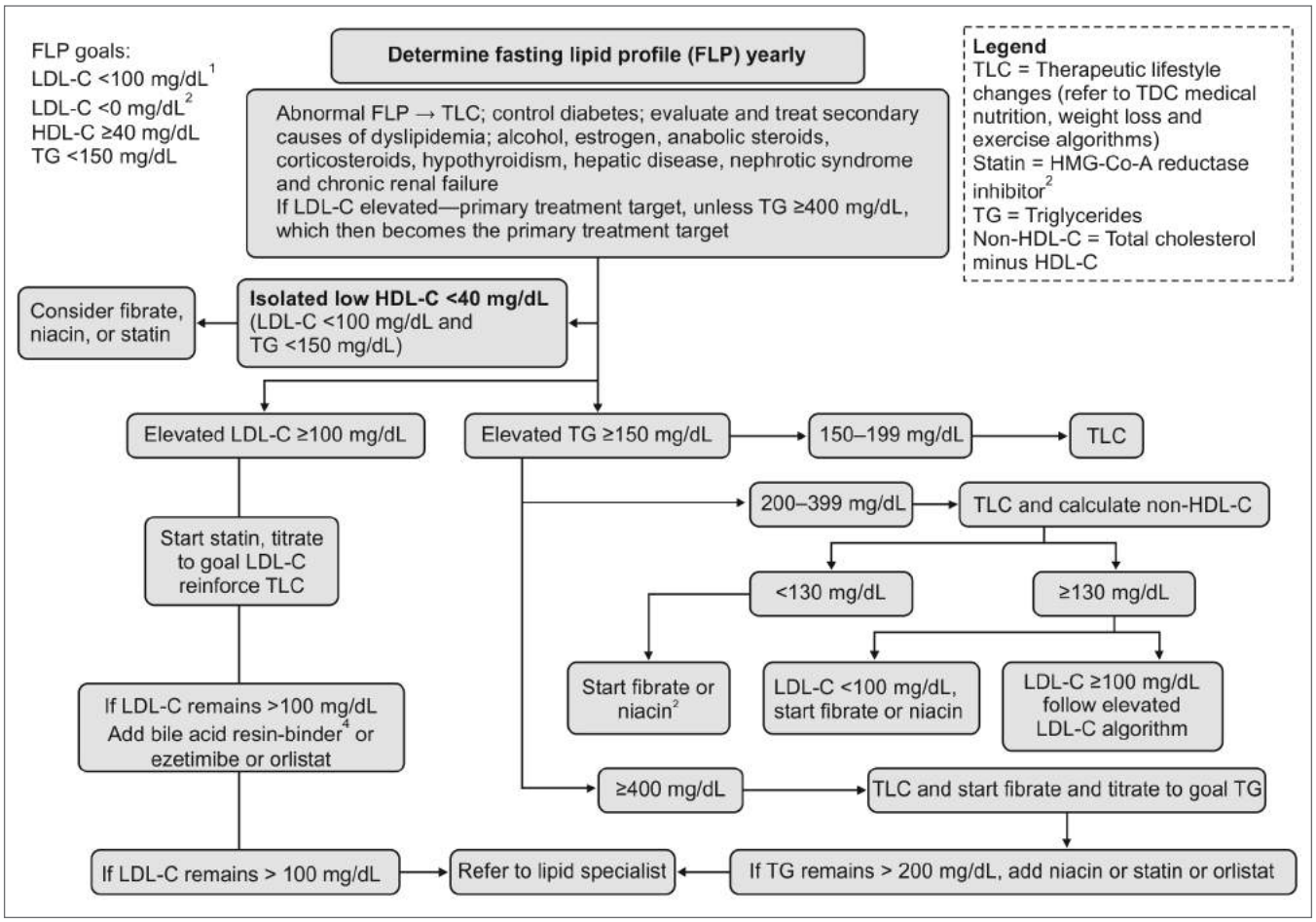
- Hemodynamic alteration in renal microcirculation:
  - Increase glomerular capillary pressure
  - Glomerular hyperperfusion/hyperfilteration.
- Structural changes of glomerulus:
  - Increase thickening of GBM
  - Increase extracellular matrix
  - Mesangial hypertrophy and fibrosis
    - » All the changes are due to chronic hyperglycemia.
    - » Some of the changes are mediated via AT_2 receptor.
    - » Smoking accelerates the decrease in renal function.

STAGES

- **Stage I (stage of hyperfiltration)**—GFR >150 mL/min. In this stage renal reserve to protein challenge is lost. This stage appear within 1 year of onset of diabetes but GFR returns to normal within 5 years.

  Pathological changes at this stages are:
  - Thickening of basement membrane
  - Glomerular hypertrophy
  - Mesangial volume expansion.
- **Stage II (stage of microalbuminuria)**—It develops in 40% patients within 8–10 years of onset of type–I DM. In this stage patient excrete 30–300 mg of albumin/day in urine or albumin—creatinine ratio is 30–300 µg/mg of creatinine in spot urine sample. About half of the patients with microalbuminuria progress to the stage of macroalbuminuria. In some type–I DM patients the microalbuminuria regresses but it is a risk factor for cardiovascular disease.
- **Stage III (stage of macroalbuminuria)**—This is an irreversible stage. From this stage GFR steadily declines and reaches ESRD within 7–10 years in about 50% type–I DM patients.
- **Stage IV (stage of ESRD)**—GFR <10 mL/min and serum creatinine >5 mg/dL blood pressure rises slightly and pathological changes in glomerulus are irreversible.

Flowchart 91.5: Lipid treatment algorithm of dyslipidemia for type-I and type-II diabetes mellitus in adults



DIFFERENCE IN NEPHROPATHY IN TYPE–II WITH THAT OF TYPE–I DM

- Microalbuminuria or overt proteinuria may be present at the time of diagnosis of type–II DM as there is prolonged asymptomatic period.
- HTN is usually associated with type–II DM nephropathy.
- Microalbuminuria is less predictive of overt proteinuria or ESRD in type–II DM nephropathy as proteinuria may be due to HTN, CCF and infection or BHP.

TREATMENT OF DIABETIC NEPHROPATHY (FLOWCHART 91.4)

- **Strict control of blood glucose** with insulin or OHA but the once overt nephropathy/ESRD develops, doses of insulin should be reduced and OHA are contraindicated.
- **Strict control of BP** by ACEI or ARB but if BP cannot controlted with ACEI/ARB, β-blocker, diuretic and CCB can be added.

  Target BP in DM without proteinuria is 130/80. Target BP in DM with proteinuria is 120/80.

  However *control of BP with any of these agent is extremely important* **but drug-specific benefit in diabetic nephropathy independent of BP control is seen with ACEI in type–I DM and ARB in type–II DM nephropathy**.
- **Treatment for dyslipidemia by statin (Flowchart 91.5)**
- **Protein restriction**
  - In microalbuminuria—0.8 g/kg/day.
  - In overt DN—<1.0 g/kg/day.

  RDA (recommended daily allowance)—10% of daily calorie.
- Chances of complication in hemodialysis in DN is more than unrelated condition.
- Renal transplantation from living related donor is acceptable but require chronic immune suppression.
- Combined pancreas kidney transplantation hold promise.

> Type IV renal tubular acidosis may develop in type-I or type-II DM patient which may be exacerbated by ACEI and ARB that are usually used for treatment of diabetic nephropathy

EXERCISE

Write short notes on

1. Diagnostic criteria of DM.
2. Classification of DM.
3. Risk factor for DM.
4. Target goal of glycemic control in DM.
5. Diagnosis and management of diabetic ketoacidosis.
6. Diagnosis and management of HHONK.
7. Diabetic neuropathy.
8. Diabetic retinopath.
9. Diabetic nephropathy.

SECTION X

DERMATOLOGY

- Scabies
- Fungal Infection of the Skin
- Psoriasis
- Vitiligo and Leukoderma
- Acne Vulgaris
- Leprosy

Chapter 92

Scabies

INTRODUCTION

Scabies is caused by the acarus sarcoptes scabiei and is a global health problem.

SITE OF AFFECTION

It affects the whole body except the scalp and face in adult but in infant it can affect the whole body.

MODE OF SPREAD

It spreads by intimate personal contact and sharing of clothings and bedding specially in overcrowded environment.

PATHOGENESIS

Gravid female mite 0.3–0.4 mm in length burrow superficially beneath the stratum corneum of skin and remain there for a month depositing 2–3 eggs/day. The nymphs that hatch from the egg within 2 weeks mature after a series of molting and thereafter emerge as adult mite on the surface of the skin where they mate and the newly fertilized female mite reinvades the skin. The typical burrow are difficult to find because they are few in number and obscured by excoriation. Burrows appear as dark wavy line in the skin, 3–15 mm in length, end in a small pearly bleb which contain the female mite. Such lesions are generally seen on the flexor aspect of wrist, intertrigo, penis and elbow.

CLINICAL FEATURES

The infestation causes intense itching resulting in considerable discomfort specially at night after putting off clothes and hotbath. The itching leads to ulceration of skin which may be secondarily infected by pyogenic bacteria and can lead to poststreptococcal glomerulonephritis and eczematous changes. [The itching and the rash associated with the scabies derived from a sensitization reaction directed against the excreta that the mite deposit in its burrow.] For this reason the initial infestation remains asymptomatic for 4–6 weeks and a reinfestation produces a hypersensitivity itching without delay. Scratching and immune reaction destroys the burrowing mite as a result most of the patients usually do not have more than 10–15 mites. Hyperinfestation with thousands of mites produce crusted scabies or called **Norwegian scabies** which occurs in immune deficiency state like AIDS, diabetes, glucocorticoid therapy, HTLV-1 infection. Small papules, vesicles, pustules, nodules or eczematoma plaques are seen on the flexor aspect of wrist, in between figures, elbow, shaft of penis, scrotum, buttocks, upper thigh, axilla, lower abdomen. Except in infants face, scalp, neck, palm and sole are spared. Bacterial superinfection alter the appearance of the rash. Atypical presentation of scabies are bullous lesion resembling pemphigoid and vesicular lesions resembling dermatitis herpetiformis.

DIAGNOSIS

Pruritic, symmetric polymorphic skin lesion in characteristic location with history of contact is suggestive of scabies. Burrows should be sought and unroofed with a sterile needle and the scrapping should be examined microscopically for the mite, egg and its fecal pellets. A drop of mineral oil facilitates the examiniation. In the absence of mite or mite product the diagnosis is based on the clinical presentation and history.

TREATMENT

Scabicide

- **Permethrin cream (5%)**.
- **Lindane preparation (1%)**.
- **Crotamitone cream (10%)**.
- **Benzyl benzoate**. **emulsion (25%)**.
- **Gamma benzine**. **hexachloride (1%)**.

Applied thinly but thoroughly all over the whole body except head and face from behind the ear and neck down to toes after bathing and removed 12 hours later with soap and water.

Successful treatment of crusted scabies require application first of a keratolytic agent such as 6% salicylic acid ointment to improve the penetration of scabicides and then of scabicides to scalp, face and ears and whole body with care to avoid the eyes. Repeated and sequential use may be necessary.

- A single dose of ivermectin 200 μg/kg effectively treats scabies. Two or more doses separated by one week may be required for crusted scabies. Although the patient becomes noninfectious within a day, itching and rash due to hypersensitivity frequently persist for months.

Supportive Treatment

- Antihistaminic and calamine lotion relieve itching during treatment.
- Oral antibiotic may be necessary for bacterial superinfection.
- Asymptomatic family members should be treated simultaneously.

EXERCISE

Write short notes on

1. Scabies.
2. Treatment of scabies.

Chapter 93

Fungal Infection of the Skin

Superficial fungal infections
- Dermatophytic infection
- Pityriasis versicolor
- Candidiasis.

Deep fungal infections
- Mycetoma
- Sporotrichosis
- Chromoblastomycosis
- Subcutaneous phycomycosis.

Dermatophytosis or ringworm.

The causative fungi are
- Trichophyton
- Epidermophyton
- Microsporum.

The clinical forms of cutaneous infection are
- Tinea corporis—Involvement of body/trunk
- Tinea capitis—Involvement of scalp
- Tinea cruris—Involvement of groin
- Tinea pedis—Involvement of feet
- Onychomycosis—Involvement of nail (tinea unguium)
- Tinea manuum—Involvement of palm and sole.

TINEA CORPORIS

Infection of relatively hairless skin of the body (glabrous skin).

Clinical features are variable. Classical lesions are erythematous, annular and scaly with well-defined edge and central clearing. These are usually asymmetrical, may be single or multiple, associated with inflammatory reaction or deep inflammatory granuloma or nodule.

Causative Agents

- Microsporum carvis—From dog
- Trichophyton verrucosum—From cattle.

TINEA CRURIS

Itchy erythematous plaque extend from groin flexures on to the medial aspect of thigh sparing scrotum.

Causative Agent

Trichophyton rubrum.

TINEA PEDIS

It is the most common dermatophyte infection and is often chronic in nature characterized by variable erythema, scaling, pruritus and invariably involve the webspace between the 4th and 5th toes.

It presents as itchy rash between the toe with fissuring, maceration and peeling of skin.

Causative Agents

- Trichophyton rubrum
- Trichophyton mentagrophytes
- Epidermophyton floccosum.

TINEA MANUUM

It presents with itchy lesion with fine scaling—when caused by Trichophyton rubrum. It presents with vesiculation or frank blistering.

Causative Agent

- Trichophyton mentagrophytes.

Tinea unguium or **onychomycosis** occurs in many patients with tinea pedis and is characterized by opacified yellowish thickened nail with sublingual debris.

Diagnosis

- Skin scraping and nail clipping with KOH preparation.

Treatment

- **Topical**—Terbinafine or miconazole cream, clotrimazole and ketoconazole cream.
- **Systemic**—Terbinafine, griseofulvin, fluconazole and itraconazole.
- **Griseofulvin (micronized)**—125 mg twice daily × 4 weeks. Ultramicro sized—350 mg/day with fatty meal. Contraindicated in pregnancy, SLE and liver failure.
- **Fluconazole**—150–200 mg weekly × 4 weeks.
- **Onychomycosis**—Treatment has to be continued for 6–9 months.
- **Itraconazole**—Daily therapy 200 mg/day or 200 mg twice daily for 1 week/month.
  For finger nail—2 months continuous therapy or 2 pulses.
  For toe nail—3 months of continuous therapy or 3 pulses.
- **Terbinafine**—200 mg/day × 6 weeks for fingure nail.
  200 mg/day × 12 weeks for toe nail.
  Side effects—GI upset, taste disturbance and hepatotoxicity.

TREATMENT FOR DIFFERENT TYPES OF TINEA

a. **Tinea corporis**
   - Localized—Topical therapy × 4 weeks.
   - Extensive— Terbinafine × 2 weeks.
     Griseofulvin × 4–6 weeks.

b. **Tinea cruris**
   - Short duration—Topical therapy × 4 weeks.
   - Chronic— Terbinafine × 4–6 weeks.
     Griseofulvin × 6–8 weeks.

c. **Tinea capitis**—Terbinafine × 12 weeks.
   Griseofulvin × 12 weeks.

d. **Tinea unguium**
   - Finger nails—Terbinafine × 8 weeks.
     Itraconazole × 2 pulses.
     Griseofulvin × 24 weeks.
   - Toe nails—Terbinafine × 12–16 weeks
     Itraconazole × 3–4 pulses
     Griseofulvin × 36 weeks.

EXERCISE

Write short notes on

1. Different from of cutaneous fungal infection.
2. Treatment of different types of Tinea.

Chapter 94

Psoriasis

INTRODUCTION

Psoriasis is a noninfectious chronic dermatosis characterized by well-demarcated erythematous plaque with silvery scales with a predilection for extensor aspect of body and scalp and have a chronic fluctuating course.

AGE OF ONSET

It has a bimodal peak.

- First peak in the late teen and early adulthood—(type I).
- Second peak in 5th and 6th decades—(type II).

The first group has an association with HLACW6 gene and to a lesser degree with HLADR7 and frequently has a family history of psoriasis with earlier age of onset, more severe is the presentation and more longer the lifetime course.

ETIOLOGY

Exact etiology is not known. Two pathophysiological aspects are

1. Infiltration by polymorphs, T-cell and other inflammatory cell in the dermis with dilated tortuous capillary loop.
2. Keratinocytes hyperproliferation in the stratum corneum layer of epidermis with grossly increased mitotic index and preservation of nuclei causing irregular thickening of epidermis.

Psoriatic lesions are characterized by infiltration of the skin by activated T-cells which appear to have a role in the pathology of psoriasis. Presumably cytokines from activated T-cells elaborate growth factors that stimulate keratinocytes to hyperproliferate.

Disordered cell proliferation in psoriasis is reflected by increased number of mitosis in the psoriatic plaque and diminished transit time (time taken for passage of cell from basal layer to superficial layer of skin is reduced from 28 days to 5 days).

Contd...

Contd...

The evidence of immunological involvement in pathogenesis are:

1. Association with HLACW6
2. Clinical improvement with ciclosporin (an immunosuppressive agent)
3. Development of psoriasis in recipients of bone marrow transplant

FACTORS PRECIPITATING OR FLARING UP OF PSORIASIS

- **Trauma**—Scratch or surgical wound often develops lesion of psoriasis (Koebner or isomorphic phenomenon).
- **Infection**—β-hemolytic streptococcal throat infection often precedes guttate psoriasis.
- **Sunlight**—Rarely UV rays, worsen psoriasis.
- **Drugs**—Antimalarial, β-blockers, lithium may cause psoriasis or rebound of psoriasis can occur after stopping systemic or potent local steroids.

CLINICAL FEATURES

Clinical course is variable. Earlier the age of onset, more severe is the initial presentation and more severe is the course of the disease.

Psoriasis have the following morphological types:

- Stable plaque psoriasis
- Guttate psoriasis (eruptive psoriasis)
- Rupoid psoriasis.

5–10% of patients with psoriasis have associated joint complaints and these are often found in patients with finger nail involvement.

TYPES OF PSORIASIS

1. **Stable plaque psoriasis**
   - Most common type of psoriasis.
   - Lesions are well-demarcated.
   - Lesions vary from few millimeters to several centimeters in diameter.
   - Lesions are red, dry and covered with silvery white scales.
   - Plaque psoriasis develops slowly and runs an indolent course.
   - Common sites are extensor aspect of body, elbow, knee, lower back, gluteal cleft and scalp, umbilicus.
2. **Guttate psoriasis**
   - Common in children and adolescents.
   - Usually preceded by streptococcal sore throat.
   - Lesion usually appears on trunk.
   - Lesion appears in several crops of small erythematous papules.
   - Size of the lesion vary from droplet to few millimeter.
   - Clear up spontaneously or respond well to phototherapy.
   - Later may develop stable plaque psoriasis.
3. **Rupoid psoriasis**
   - Patch with heapedup scale.
   - Scales are firmly adherent to skin.
   - Giving the patch a conical appearance.
   - Such lesions are seen in patient with Reiter's syndrome who are HLA B27 positive.

- **Other features of Reiter's syndrome are**
  a. Preceded by chlamydial genital tract infection or infectious diarrhea by Salmonella/Shigella
  b. Acute asymmetric, additive ascending inflammatory arthritis including sacroiliitis
  c. Circinate balanitis
  d. Keratoderma blenorrhagicum
  e. Iridocyclitis

OTHER COMMON SITE

1. **Flexural psoriasis**
   - Lesion involve submammary and axillary fold, groin, genital fold.
   - The lesions are not scaly but red, shiny and symmetrical.
   - Depth of the fold may be fissuring.
   - Differential diagnosis from candidal intertrigo.
2. **Psoriasis of palm and soles**
   - Bilateral, symmetrical, thickened plaque.
   - Silvery scales are minimal or adherent to palm and soloes.
   - Erythema are minimal because of thickness of stratum corneum.
3. **Scalp psoriasis**
   - May be sharply defined or diffused involvement may be present.
   - Scaling may be massive, asbestos-like firmly adherent.
   - Differential diagnosis—Pityriasis amiantacea or seborrheic dermatitis.
4. **Penile psoriasis**
   - In uncircumcised patient, scaling is absent but the lesion is well-defined.
   - In circumcised patient, the lesion over the glans is similar to lesions of the other parts of the body.

COMPLICATIONS OF PSORIASIS

1. **Erythrodermic psoriasis**
   - It is a common complication.
   - It is due to use of irritant agent like tar or dithranol or withdrawal of systemic or potent topical steroid.
   - The plaque loose their boarder, skin become uniformly red and shiny with marked scaling.
   - Involvement is generalized.
   - Complications are hypothermia, hyperthermia, water and electrolyte imbalance.
2. **Pastular psoriasis**—It can also be precipitated by irritant topical therapy or steroid withdrawal.
   Two forms are usually encountered—
   a. *Localized*—Seen in palmoplantar psoriasis.
   b. *Generalized* (**von Zumbusch's pustular psoriasis**)
      - A rare serious complication.
      - Accompanied by high fever, tachypnea, chills.
      - Characterized by appearance of generalized erythema followed by appearance of superficial pustules, which become confluent to form circinate lesion with lakes of pus. New lesions appear as old one are crusting.

JOINT INVOLVEMENT

About 10% of patients with psoriasis have joint involvement. Four patterns of joint involvement are recognized:

1. **Polyarticular variety**—Multiple DIP are involved and there are marked nail changes.
2. **Monoarticular variety**—Single large joint involved.
3. **Rheumatoid arthritis like**—Joints may be mutilated.
4. **Axial variety**—Sacroiliac joint and spine are involved and have strong association with HLA B27.

NAIL CHANGES

About 10–50% of psoriatic patients have nail involvement (Fig. 94.1). The following nail changes are seen:

- **Pitting**.
- Nail plate **thickening**.

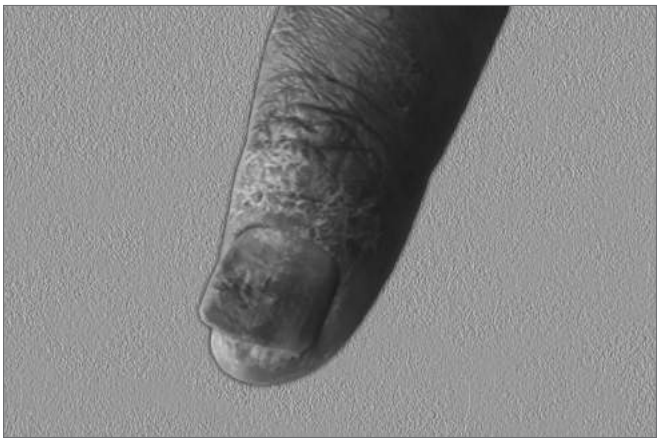


Fig. 94.1: Psoriatic nail change

- **Subungual hyperkeratosis**—Accumulation of keratinous material under nail plate.
- **Onycholysis**—Separation of nail plate from bed.
- **Discoloration** of nail plate.
- **Oil spot** or staining of nail bed.

BEDSIDE TEST

Two bedside tests can be done to confirm clinical diagnosis of psoriasis.

a. **Grattage test**—Scales of a psoriatic plaque can be accentuated by grating with a glass slide.
b. **Auspitz sign**—
   - *Step I*—Gently scrap the lesion with a glass slide to accentuate the scale.
   - *Step II*—A glistering white membrane (Burkley's membrane) appears.
   - *Step III*—On removing the membrane punctate bleeding spot becomes visible.

TREATMENT OF PSORIASIS

1. **Plaque psoriasis**:
   - *Localized*—**Coal tar**
     Dithranol (short period)
     Topical steroid + Salicylic acid
   - *Extensive > 30% of body surface*
     UVB (narrow band)
     PUVA / PUVA + SUN exposer
     Systemic—**Methotrexate, cyclosporin and acitretin**.
2. **Guttate psoriasis**
   - **Antibiotic** + PUVA/PUVA + SUN, coal tar and **tacrolimus**
3. **Flexural psoriasis**
   - Mild to moderate potency topical steroid plus antifungal agent.
4. **Pustular psoriasis**
   - **Hand and feet**
     - Moderate potency topical steroid + Salicylic acid
     - Topical PUVA / PUVA + SUN exposer
     - Methotrexate.
5. **Erythrodermic psoriasis**
   - **Methotrexate**
   - **Acitretin**
   - **Cyclosporin A**.

BIOLOGICAL RESPONSE MODIFIER

As it is a T-cell-mediated disorder the following drugs are found effective:

- **Etanercept**
- **Alefacept**
- **Infliximab**
- **Efalizumab**.

EXERCISE

Write short notes on

1. Type of psoriasis
2. Complication of psoriasis
3. Treatment of psoriasis.

Chapter 95

Vitiligo and Leukoderma

HYPOPIGMENTATION

It may be due to
- Primary cutaneous disorder
- Systemic disease.

Hypopigmentation is of two types:
1. Diffuse
2. Localized.

Causes of Hypopigmentation

Primary Cutaneous Disorder Associated with Hypopigmentation

- **Diffuse**—Generalized vitiligo (absence of melanocyte).
- **Localized**:
  - Idiopathic guttate hypomelanosis
  - Postinflammatory
  - Tineal pityriasis versicolor
  - Vitiligo
  - Chemical leukoderma
  - Nevus depigmentosus
  - Piebaldism.

Systemic Disorder Associated with Hypopigmentation

- **Diffuse**
  - Oculocutaneous albinism.
    - Hermansky Pudlak syndrome
    - Chédiak-Higashi syndrome.
  - Phenylketonuria.
  - Homocystinuria.
- **Localized**
  - Vogt-Koyanagi-Harada syndrome
  - Scleroderma
  - Melanoma-associated leukoderma
  - Tuberous sclerosis
  - Hypomelanosis of ISO
  - Sarcoidosis
  - Tuberculoid leprosy
  - Indeterminate leprosy
  - Cutaneous T-cell lymphoma.

Diffuse hypopigmentation are of two types:
1. **Type I**—Oculocutaneous albinism (OCA due to mutation of tyrosinase gene).
2. **Type II**—Due to deletion of 'P' gene which encodes ion channel protein in the melanosome.

Patients with type IA OCA have a total lack of enzyme activity. At birth different forms of OCA can appear with white hair, gray blue eyes, pink white skin. Patients with no tyrosinase activity maintain this phenotype throughout the life whereas those with decreased activity or P gene mutation will acquire some pigmentation of the eye, hair and skin as they become order. The ocular finding in OCA correlates with the degree of hypopigmentation and include decreased visual acquity, nystagmus, photophobia and monocular vision. OCA are at grossly increased risk of skin burn and skin cancer.

OCULOCUTANEOUS ALBINISM

It is a autosomal recessive disorder.

Two main varients of oculocutaneous albinism (OCA) are:
1. Tyrosinase positive (less severe)
2. Tyrosinase negative (more severe).

Molecular Defect

Absent or sparse production of melanin.

Clinical Features

Total absence of melanin in skin, hair, eyes since birth eye with decreased visual acquity, nystagmus, photophobia, monocular vision red reflex.

Skin Complication

Skin malignancy specially squamous cell carcinoma produced by UV rays on the exposed parts due to lack of protective melanin.

Developmental Abnormalities

Small stature, mental retardation.

Hair Bulb Test

To differentiate tyrosinase positive from tyrosinase—negative albinism, plucked hairs are incubated with dihydroxyphenylalanine. Hair of patient with tyrosinase positive albinism turn black.

Differential Diagnosis (Tables 95.1 and 95.2)

Table 95.1: Differential diagnosis of OCA from vitiligo

OCA	Vitiligo
• Present at birth	• Begins later in life
• Freckling may develop on photoexposed parts	• Depigmentation may progress or regress
• Eye changes always present	• Eye changes absent
• No response to treatment	• Partial response to treatment

Table 95.2: Differential diagnosis of OCA from piebaldism

OCA	Piebaldism
• Present at birth	• Present at birth
• All hairs are depigmented	• White forelock of hair • Rest of the hair are pigmented
• Skin, hair and eyes show no pigmentation or some pigmentation	• Localized area of depigmentation present symmetrically on central area of face, trunk and limbs with acral sparing

Treatment

There is no effective treatment.

- Eye protection by photoprotective sunglass.
- Skin photoprotection—by opaque clothing and broad spectrum sunscreens.
- Regular surveillance for cutaneous malignancy.

Prenatal Diagnosis

Skin biopsy at 4th month examined by electron microscopy for arrest of development of melanosomes.

Causes of Localized Hypopigmentation (Hypomelanosis)

In this group of diseases, the areas of involvement are macules or patches with decreased or absence of pigmentation.

VITILIGO

It is an acquired autoimmune condition in which circumscribed depigmented patches develop and affect 1% of population.

Etiology

In albinism—where melanocyte are present but the production of melanin is abnormal. **In vitiligo,** it is caused by focal or local loss of melanocyte which is possibly a cell-mediated autoimmune phenomenon that results in destruction of the melanocyte. Alternative hypothesis is self-destruction of melanocytes and the circulating autoantibody and cytotoxic 'T' cells are secondary phenomenon. The melanocytes are the target of cell-mediated autoimmune attack, is supported by the strong coexistence of other autoimmune diseases like hypothyroidism, Graves disease, diabetes, pernicious anemia, Addison's disease with vitiligo (uveitis, alopecia ereata, chronic mucocutaneous candidiasis and polyglandular autoimmune syndrome type I and II). Disease of thyroid are the most frequent associate disorder (up to 30% of patients) with vitiligo. Trauma and sunburn may precipitate the appearance of vitiligo but why focal areas are involved remain unexplained.

Clinical Features

Two Types

1. Segmental vitiligo
2. Generalized vitiligo

Segmental vitiligo

Restricted to one part of the body but not necessarily one dermatome.

- Develop in young individual.
- Restricted to one dermatome or multidermatomal.
- Half of the patients have lesion over trigeminal nerve distribution.
- Stable course.
- Leukotrichia over the lesion.
- Response to treatment less satisfactory.

Generalized vitiligo

It is often symmetrical in distribution and sequentially involves hand, knee, wrist and areas around body orifices. The hair of scalp or beard are also depigmented. The patch of depigmentation are sharply defined and may be surrounded by light brown 'café au lait' hyperpigmentation. In Caucasian perihair follicular pigment may be seen with in the depigmented patch and may be the first sign of repigmentation. Sensation in the depigmented patch is normal (differential diagnosis of leprosy).

- Extensive lesion.

- Variants
  - Acrofacial vitiligo—Involve eyelid on the face, periungual area, palms and soles.
  - Lip and tip vitiligo—lip, tip of penis, vulva and nipple are involved.
  - Vitiligo universalis.
- Widespread vitiligo.
- Associated with multiple endocrinopathies.
- Begins before the age of 20 years.
- Spontaneous repigmentation is seen in 10–20% cases.
- Poor prognostic indicators
  - Long-standing disease
  - Leukotrichia
  - Acrofacial lesion
  - Lesion on ankle, wrist, elbow, periungual area, nipple, areola, lips and genitalia.

Prognosis

The course of the disease is unpredictable but most patches remain static or enlarged. A few repigment spontaneously.

Management

- Protecting the patches from sunexposer by clothing or sunscreen—helpful is reducing sunburn and development of skin cancer in long-term.
- Camouflage cosmetic may be helpful in dark skin person.
- **Localized lesions**
  - New lesion—Topical steroid
  - Old lesion—Topical PUVA.

  Extensive lesions—Systemic PUVA sometimes combined with oral steroid (if rapidly progressing).
  Generalized lesions—Monobenzyle solution of hydroquinone.

  Repigmentation is seen as small foci of dark areas of skin surrounding hair follicle within the vitiliginous area. The absence of whiteness of hair is a good prognostic sign).
- Skin transplantation when depigmentation is widespread.

Differential Diagnosis

- **Vogt-Koyanagi-Harada syndrome**—History of aseptic meningitis, nontraumatic uveitis, tinnitus, hearing loss or dysacusis. Face and scalp are the most common site of the pigment loss.
- **Scleroderma**—Vitiligo-like leukoderma seen in patient with scleroderma has a clinical resemblance to idiopathic vitiligo which begins to repigment with treatment.
- **Melanoma-associated leukoderma**—It begins on trunk. Its appearance promt a search for metastatic disease. The destruction of normal melanocyte is the result of an immune response against malignant melanocyte.

IDIOPATHIC GUTTATE HYPOMELANOSIS

Commonly acquired disorder 1–4 mm in diameter usually located over shins or extensor forearm.

Wood's lamp—Shows less enhancement than vitiligo. Skin biopsy shows abrupt decrease in epidermal melanin content.

Pathogenesis

Possibly exposure to UV rays as a reflection of aging.

Treatment

No treatment.

POSTINFLAMMATORY HYPOPIGMENTATION

It can develop within active lesion as a subacute lupus or after the lesions fades.
Wood's lamp—Shows less enhancement than vitiligo. Skin biopsy shows different types of inflammatory infiltrate depends on the specific disease.

Pathogenesis

Block in transfer of melanin pigment from melanocyte to keratinocyte secondary to edema or decrease in contact time.

Destruction of melanocyte if inflammatory cells attack basal layer.

Treatment

Management of underlying skin disease.

TINEA (PITYRIASIS) VERSICOLOR

Common disorder in warm climate. Involved upper trunk and neck of young adult. Macules have fine white scale when scratched.

Wood's lamp—Shows golden fluorescence.

Skin Biopsy

It shows hyphae and budding yeast in stratum corneum.

Pathogenesis

Invasion of stratum corneum by yeast. Pityrosporum yeast which is lipophilic and produce C_9, C_{11} dicarboxylic acid which is in vitro inhibit tyrosinase.

Treatment

- **Topical**
  - Selenium sulfide 2.5%
  - Imidazole.

- **Systemic**
  - Imidazole
  - Triazoles.

CHEMICAL LEUKODERMA

Similar appearance to vitiligo. Often begins in hands. Satellite lesion in areas not exposed to chemical.

Wood's lamp—More apparent chalk white.

Skin Biopsy

Decreased number and absence of melanocyte.

Pathogenesis

Exposure to chemical that selectively destroyed melanocyte particularly phenolol and catichol (germicide and adhesive). The release of cellular antigen and activation of circulating lymphocyte may explain satellite lesion.

Management

Avoid exposure to offending agent and then treat as vitiligo.

PIEBALDISM

- Lesions are present at birth.
- Congenital autosomal dominant disorder.
- White forelock.
- Areas of hypomelanosis contain normally pigmented or hypopigmented macules of various size.
- Symmetric involvement of central forehead ventral trunk and midregion of upper and lower extremity.

Wood's lamp—Enhancement of leukoderma and hyperpigmented macules.

Skin Biopsy

Hypomelanotic areas show few to no melanocyte.

Pathogenesis—Defect in migration of melanoblast from neural crest to ventral skin or failure of melanoblast to survive or differentiate in these areas. Mutation within e-kit proto-oncogene that encodes tyrosine kinase receptor for mast/stem cell growth factor.

Treatment

- Photoprotection
- PUVA therapy can be tried
- Skin transplant.

EXERCISE

Write short notes on

1. Classify hypopigmentation.
2. OCA and vitiligo.

Chapter 96

Acne Vulgaris

INTRODUCTION

It is a disease of late teenage but may occur up to third decade and beyond particularly in female.

ETIOLOGY

Excessive Sebum Excretion

- Rate of sebum excre- tion correlates with the disease activity but acne usually improves in the 3rd and 4th decade despite a high sebum secretion. The main stimulus for sebum secretion is hormonal, accounting for the onset of acne in the late teenage. Androgen are the principle sebotrophic hormone but progesterone also increase the sebum excretion. Androgen specially testosterone is converted by 5 α reductase to dihydrotestosterone which is directly responsible for sebaceous gland activity.

Infection

- Propionibacterium acnes colonize in the pilosebaceous duct and act on the lipid to produce proinflammatory factor. Other bacteria are
  - *P. granulosum*
  - Malassezia furfur
  - Coagulase negative micrococci.

MODIFYING FACTOR

Blockage of pilosebaceous unit.

- Genetic predisposition is there but exact mode of inheritance is not known.
- Diet plays very little or no role.
- Cosmetic—Oil based cosmetic predisposes acne.
- Premenstrual aggravation of acne occurs in 70% of female.
- Psychological factor—Probably related to anxiety and anger.

CLINICAL FEATURES

- **Site of lesion**—Face, shoulder, upper chest and back. Seborrhea or greasy skin are obvious.

The most pathognomonic lesion is comedon.

- **Black head (open comedon)**—Due to plugging of pilosebaceous orifice by keratin or sebum.
- **White head (closed comedon)**—Due to accretion of sebum and keratin in the pilosebaceous duct.

Inflammatory papule, nodule, cyst also occur with one or two types of lesion predominating.

- **Conglobate acne**—Refers to severe acne with many abscess, cyst, marked scarring and intercommunicating sinus formation.
  - Comedones are typically multiporus.
  - Takes long time to heal and on healing leaves behind pitted or hypertrophic scar (sometime keloid) and joined by keloid ridges.
- **Acne fulminans**—Refers to severe acne with fever, joint pain, raised ESR and marker of systemic inflammation.
- **Acne excorice**—Refers to the effect of scratching and picking particularly on the face of teenaged girl.
- **Infantile acne**—Rarely seen and is due to sebotrophic effect of maternal hormones on the infant.
- **Chloracne**—Caused by industrial chemical like tar, chlorinated hydrocarbon and oily cosmetic.
  - Lesions are predominantly comedons.
  - Unusual site of involvement—forearm and leg.
  - Middle-aged males are affected.
- **Drug-induced acne**—Glucocorticoid, anabolic steroid, oral contraceptives, antitubercular drug, iodides, bromides and anticonvulsant can cause an acniform lesion.
- **Polycystic ovarian** diseases present with acne and feature of virilism and others features of androgen secreting tumors.

MANAGEMENT

Topical Therapy

1. **Retinoic acid or tretinoin (vitamin A analogue)**
   - Effective against comedones.
   - To be used at night as causes photosensitivity.
   - Gradual higher concentration are used.
   - Avoid application around eye, nose and mouth may cause irritation.

Table 96.1: Principles of treating acne

		Topical agent	Systemic agent
1.	Mild acne	Retinoids or Benzoyl peroxide	Not required
2.	Moderately severe acne	Retinoids and Benzoyl peroxide and Antibiotic	Antibiotics
3.	Severe acne	Benzoyl peroxide and Retinoids	Antibiotics or Antiandrogen or Retinoids

2. **Benzoyl peroxide**—This is useful for minor disease particularly with comedons. They are antimicrobial and have irritant activity, so initially they are applied for short time with low dilution later the strength and duration gradually increased.

Antibiotic Therapy (Table 96.1)

- **Clindamycin/erythromycin**—Topical preparation are useful in patient with relatively minor disease.
- **Oxytetracycline**—1.5 g/day single dose in empty stomach. It has a good safety profile on long-term use. Useful for moderate to severe disease.
- **Minocycline**—It can be used as an alternative to oxytetracycline because of the care of dosing. Side effect is autoimmune hepatitis. So it is not the drug of choice.
- **Erythromycin**—250 mg 6 hourly can be used if good response is not seen with oxytetracycline for 3 months.

Hormone Therapy

Cyproterone acetate (an antiandrogen) with ethinyl estradiol (2 mg + 35 μg/day) from 5th to 14th day of the cycle for its sebum reduction effect. If these topical and systemic measures fail to produce satisfactory response within 3–6 months then.

Systemic Therapy

- **Isotretinoin (13 cis-retinoic acid)**—0.5–1 mg/kg inhibit sebum excretion >90% over 3–4 months. Although the sebum secretion gradually return to normal over years after the drug is stopped the clinical benefit is much more prolonged. Many patients do not require any further treatment for acne except a very few who require a second course of isotretinoin. Side effects are dry skin and mucous membrane and may elevate serum triglyceride level and may precipitate depression and suicide. It has teratogenic potential so all female patients must receive effective contraceptive starting from one month prior to one month after the finishing of the course of isotretinoin.
- **Physical measure**
  - Cyst can be incised drained under local anesthesia.
  - Intralesional injection of triamcinolone acetonide 0.1–0.2 mL of (10 mg/mL solution) for resolution of stubborn cyst.
  - **Cryotherapy**—for nodulocystic lesion and scar.
  - **Laser therapy**—Carbon dioxide laser for skin resurfacing.
  - **Dermabrasion**—Superficial planing with high speed rotating wire brush.
  - **Collagen injection**—Injection of purified bovine collagen are undergoing trial.

EXERCISE

Write short notes on

1. Etiology and clinical features of acne.
2. Treatment of acne.

Chapter 97

Leprosy

INTRODUCTION

A chronic granulomatous disease affecting skin and peripheral nerves caused by *Mycobacterium leprae*.

CLINICAL SUBTYPE

The clinical subtype is determined by the degree of CMI (cell-mediated immunity) expressed by the individual toward the bacteria *M. leprae*. If the host has good cell-mediated immune response, the infection is localized and does not spread. If the patient cannot express an immunological response to *M. leprae* a generalized infection of the skin along with visceral involvement is seen.

Absent CMI with plenty of bacilli results in lepromatous leprosy whereas high level of CMI with elimination of leprosy bacilli produce tuberculoid leprosy.

Clinical subtypes are

- Lepromatous leprosy (LL)
- Borderline lepromatous leprosy (BL)
- Borderline variety (BB)
- Borderline tuberculoid leprosy (BT)
- Tuberculoid leprosy (TT).

The clinical features and complications of the disease are due to

- Bacillary infiltration
- Immunological reaction
- Nerve damage.

TRANSMISSION

- Untreated lepromatous patients discharge bacilli from their nose and infection enters the body also through the nostrils followed by hematogenous spread to skin and nerve.
- Contact microinoculation from infected soil can occure.
- Insect vectors (bedbug and mosquito) are considered by some authority as mode of spread.

Skin-to-skin contact is generally not considered an important route of transmission.

Incubation period is 2–5 years for tuberculoid cases and 8–12 years for lepromatous cases.

CLINICAL FEATURES

- **Skin lesion**—Hypopigmented and anesthetic lesion. Vary from macule, nodule, plaque or diffuse infiltration of skin. The skin appendages, hair and sweat glands are reduced.
- **Peripheral neuropathy**—Peripheral nerves are usually thickened, tender with sensory and motor impairment. Affected special sites of predilection are
  - Ulnar nerve at elbow.
  - Median nerve at wrist.
  - Radial nerve at radial groove of humerus.
  - Radial cutaneous nerve at wrist.
  - Common peroneal nerve at knee around neck of fibula.
  - Posterior tibial and sural nerve at ankle.
  - Facial nerve as it crosses the zygomatic arch.
  - Great auricular nerve at posterior triangle of neck.

  All these nerves should be examined for
  a. Thickening
  b. Tenderness
  c. Test for motor and sensory function.

  CNS is not affected in leprosy.
- **Eye involvement**—Anesthesia of cornea and conjunctiva due to 5th nerve involvement causes corneal ulcer.

CLINICAL FEATURES OF DIFFERENT TYPES OF LEPROSY

1. **Tuberculoid variety (TT)**
   - It is the localize form of the disease.
   - One to three asymmetrically located lesion.

- Characterized by well-defined, hypopigmented anesthetic macules or plaque with loss of hair and impairment of sweating.
- Cutaneous nerve is usually thickened and nodular.

2. **Borderline group**—It consists of
   a. Borderline tuberculoid (BT)
   b. Mid borderline (BB)
   c. Borderline lepromatous (BL).
      - **Borderline tuberculoid (BT)**
        » Lesions are large hypopigmented macules or plaque.
        » Lesions are less sharply demarcated having satellite lesion.
        » Lesions are more numerous.
        » Lesions are less asymmetrical.
        » Lesions are less hypoesthetic.
        » Few nerves may be asymmetrically thickened.
      - **Mid borderline (BB)**
        » Lesions are erythematous raised plaques with central clearing and sloping edge (inverted saucer appearance).
        » Lesions are hypoesthetic.
        » Lesions are numerous, distributed symmetrically.
        » Multiple nerves are thickened.
      - **Borderline lepromatous (BL)**—They look like lepromatous leprosy (LL) but differ from it by the points
        » Lesions are larger, resembling BB.
        » Lesions are less symmetrical.
        » Lesions are hypoesthetic.
        » Peripheral nerve involvement is asymmetrical.
3. **Lepromatous leprosy (LL)**—It is a systemic disease with extensive cutaneous, neural and systemic involvement.
   - **Facial lesion**
     - Diffuse infiltration of face, ear lobules and alae nasi.
     - Loss of lateral 1/3rd of eyebrow (madarosis).
     - Depressed bridge of nose (now rare).
   - **Skin lesion**
     - Lesions are symmetrical and numerous.
       Three types of skin lesions are seen.
       1. *Macules*—Small hypopigmented or erythematous ill-defined confluent macule, hypoesthesia is minimal.
       2. Papulonodules—Most frequent type of lesion in LL.
          Lesions are papules, nodules or diffuse infiltrate and are dull red in color.
       3. Histoid leprosy—A distinct variant of LL.
          Well-demarcated juicy cutaneous or subcutaneous nodules on normal looking skin.
   - **Nerve involvement**
     - Bilaterally symmetrical thickening of nerve.
     - Nerves are tender.
     - Gloves and stocking anesthesia with motor deficit (foot drop and wrist drop).
   - **Systemic involvement**—Common manifestations are
     - Lymphadenopathy
     - Hepatosplenomegaly
     - Ocular involvement
     - Testicular atrophy.
4. **Indeterminate leprosy (LL)**
   - Seen on the face of children in endemic areas.
   - Always an ill-defined macule.
   - Usually hypoesthetic, atrophic, hypopigmented or slightly erythematous lesion with or without nerve thickening.

PURE NEURAL LEPROSY

It occurs principally in India and accounts for 10% of patient. There is only asymmetric involvement of peripheral nerve trunk with no visible skin lesion.

Always consider leprosy as a possible cause of peripheral neuropathy or neuropathic ulcer in India unless proved otherwise.

LEPROSY REACTION

These are events superimposed on the cardinal features of leprosy. Two types of lepra reactions are seen:

1. **Type-I lepra reaction**—It occurs in ~50% of borderline patients (BT, BB and BL) and is absent in lepromatous form and is of delayed cell-mediated hypersensitivity reaction and Arthus phenomenon.
   It is due to alteration of host CMI and are of two types—
   When **type-I lepra reaction** precede the initiation of appropriate antimicrobial therapy they are termed **down grading reaction** and histologically move towards lepromatous form.
   When **Type-I Lepra Reaction** occures after initiation of therapy they are termed reversals reaction, the case become more tuberculoid. **Reversal reaction** usually occur with one month of starting therapy but may develop several year later.
   Clinical manifestations are:
   - Erythema, edema and scaling and signs of inflammation of the preexisting lesions.
   - Appearance of new lesion.
   - New nerve involvement characterized by nerve thickening, new areas of sensory and motor impairment. The nerve commonly involve is ulner nerve at elbow which is extremely tender and if not treated promptly with glucocorticind, the nerve may be damaged with 24 hour leading to wrist drop, foot drop.
   - Fever (low grade).

This type of reaction can occur:
a. Spontaneously
b. After starting treatment
c. After completion of treatment.

Management
- Mild cases—Aspirin
- Severe case—Prednisolone 40–60 mg/day tapered 5 mg over each month for 3–9 months.

Indications for starting glucocorticoid
- Lesion with intense inflammation with a threat of ulceration.
- Lesion at cosmetically important site—face.
- Lesion with neuritis.

2. **Type-II lepra reaction**—(erythema nodosum leprosum)—This type of lesion is due to immune complex deposition and occurs in 50% of patients of BL and LL subgroup. It may continue intermittently for several years and starts in 90% of patients within 2 years of starting chemotherapy.
   - **Clinical features**—Clinical features are fever, malaise, new crop of small pink nodules on face, flexures and leg that resolve spontaneously in a few days to weeks.
     Apart from it, uveitis iritis, acute neuritis, orchitis, lymph-adenitis, bone pain, dactylitis, glomerulonephritis, proteinuria may be present. leukocytosis and elevated aminotransferase may be present.
   - **Management**
     - Mild cases—Aspirin 600 mg TDS.
     - Severe cases.

     Indications—many skin lesion, fever, malaise and other tissue involvement.
     - **Prednisolone**—80 mg tapered down rapidly over 1–6 months.
       Thalidomide—If despite two course of prednisolone, ENL appears to be recurring and persisting, treatment with thalidomide is indicated.
       Dose—It has teratogenic potential, but can be used safely in nonchildbearing age group. Thalidomide 100–300 mg at bedtime.
       Clofazimine—300 mg at bedtime has some efficacy against ENL but its use permits only a moderate reduction of dose of glucocorticoid.
       Chloroquine—250–500 mg/day.
       » Eye involvement—1% hydrocortisone drop ointment.
       » 1% atropine drop.

Diagnosis

Three most important diagnostic criteria are:
1. Anesthetic skin lesion.
2. Nerve involvement.
3. Demonstration of acid-fast bacilli from skin smear.

Bacterial load is assessed by scraping dermal material or from slit skin smear specimen from nose, ear lobule, buttock, and other suspected site on a glass slide.

Smear is useful for diagnosis and monitoring response to treatment.

Differential Diagnosis

Tuberculoid and BT lesions have to be differentiated from fungal lesion, vitiligo, psoriasis and eczema by the presence of acid-fast bacilli.

Lepromatous lesion have to be differentiated from onchocerciasis, Kaposi sarcoma, PKDL by AFB from slit skin smear.

Treatment (Who Recommended MDT Regimen)

1. **Paucibacillary single skin lesion**—ROM regimen.
   - Rifampicin—600 mg
   - Ofloxacillin—400 mg
   - Minocycline—100 mg

   } Single dose
2. **Paucibacillary [Multiple lesion (2–5 skin lesion)]**
   - Rifampicin—600 mg monthly
   - Dapsone—100 mg daily

   } For 6 months to 1 year
3. **Multibacillary (More than 5 skin lesion)**
   - Rifampicin—600 mg
   - Clofazimine—300 mg

   } Monthly
   - Dapsone—100 mg
   - Clofazimine—50 mg

   } Daily

   } 1–2 years

Treatment of Complications

1. **Trophic ulcer**—Rest, antibiotic and nonweight bearing splint.
2. **Motor deficit**—Physiotherapy, splint surgical correction (transposition of ulnar nerve).
3. **Iridocyclitis**—
   - Topical corticosteroid
   - Oral corticosteroid.
4. **Orchitis**—Oral corticosteroid.

EXERCISE

Write short notes on
1. Classification of leprosy.
2. Treatment of leprosy.
3. Complication of leprosy.
4. Lepra reaction and its management.

SECTION XI

INFECTIVE DISEASES

- Dengue
- Rabies
- Tetanus
- Diarrhea
- Typhoid and Paratyphoid (Enteric) Fever
- Leptospirosis (Weil's Disease)
- Malaria
- Leishmaniasis (Kala-azar)
- Approach to a Patient of Fever with Rash
- Management of *Helicobacter pylori* Infection
- Human Immunodeficiency Virus, Acquired Immunodeficiency Syndrome
- Tuberculosis

Chapter 98

Dengue

INTRODUCTION

The dengue flavivirus is a common cause of fever in the tropics. It is endemic in Caribbean, Central America, South-East Asia and India.

Aedes aegypti and Aedes albopictus are the principle vectors.

Four serotypes of dengue virus produce similar clinical syndrome. Homotypic immunity is lifelong but heterotypic immunity between serotype lasts only few months. Dengue and yellow fever viruses are antigenically related but do not result in cross immunity.

CLINICAL FEATURES

Clinical disease starts 2–10 days after bite of infective mosquito.

Onset of fever may be sudden or with prodromal symptoms of malaise, chills and headache, backache, generalized pain, retroorbital pain, pain on eye movement, lacrimation, scleral injection anorexia, nausea, vomiting, relative bradycardia, lymphadenopathy.

For severe bodyache and pain in the prodormal phase it is often called 'break bone fever'.

Fever is continuous or 'saddle back' with first peak on 4th or 5th day and a second peak 5–8 days after the first one.

Maculopapular or scarlatiniform rash may appear on 3rd/4th day and last for 2–3 days, then fades with desquamation.

Convalescence is usually slow.

In young children dengue is a mild febrile illness lasting for 1–3 days but can cause two severe syndrome.

- **Dengue hemorrhagic fever (DHF)**
- **Dengue shock syndrome (DSS)**.

It usually occurs in individuals who are having antibody against one serotype of dengue virus subsequently infected by a different serotype of dengue virus (children may passively acquire antibody from mother during breastfeeding).

Although initial symptoms simulate normal dengue, the patients condition abruptly worsens characterized by shock and hemoconcentration.

This altered manifestation of dengue may occur in epidemic form in regions where several dengue serotypes are regularly present and mortality rate is usually 1–10% but may reach up to 40%.

Circumstantial evidence suggest that second infection with dengue type-2 virus may be associated with severe disease. It is postulated that virus–antibody complex are formed *within a few days of the second dengue infection and that the nonneutralizing enhancing antibody promote infection of higher number of mononuclear cells followed by the release of cytokines, vasoactive mediators and (TNF-α, INF-γ) procoagulants leading to increased vascular permeability and disseminated intravascular coagulation* responsible for **dengue shock syndrome and dengue hemorrhagic fever (DSS and DHF)**.

The induction of vascular permeability and shock depends on multiple factors—

- Presence of nonneutralizing, enhancing antibody:
  - Antibody elicited by previous heterologous dengue infection.
  - Transplacental maternal antibody in infants <9 months.
- Age—Incidence of DHF/DSS more common below 12 years.
- Sex—Female > Male.
- Race—Caucasian > Black.
- Nutritional status—Healthy children are vulnerable. Malnutrition is protective.
- Sequence of infection—Serotype 1 followed by serotype 2 seems more dangerous than serotype 4 followed by serotype 2.
- Infective serotype—Type 2 is apparently more dangerous than other serotypes.

Mild DSS/DHF is diagnosis by
- Hemorrhagic sign
- Restlessness and lethargy
- Petechiae
- Overt bleeding from GI tract in absence of ulcer
- Positive tourniquet test
- Thrombocytopenia <100,000/μL
- Hemoconcentration results from increased vascular permeability leading to shock.

It is usually detected 2–5 days after the onset of typical dengue fever usually at the time of defervescence.

Maculopapular rash that often develops in dengue fever may also appear in DHF and DSS.

DSS is much more serious than DHF and more severe DSS/DHF is diagnosed by the following signs:
- Low BP
- Cyanosis
- Hepatomegaly
- Pleural effusion
- Ecchymosis
- GI bleeding.

The period of shock last for 1–2 days. Most patients respond to treatment. Mortality is <1%.

LABORATORY DIAGNOSIS

- Leukopenia with relative lymphocytosis and thrombocytopenia <100,000/μL.
- Isolation of virus is very difficult and can be done by RT-PCR-based method for identification and subtyping.
- Defection NSI antigen in the blood can be done as early as D1.
- Neutralizing and hemagglutination—inhibiting antibody IgM by IgG, ELISA, appear within 7 days of infection. But serologic test may detect cross-reacting antibody from other flavivirus including yellow fever. Multiple flavivirus infections lead to a broad immune response to several members of this group and lack of virus specificity of IgM and IgG immune response. IgG antibody require 16–20 days to appear.

MANAGEMENT OF DHF/DSS

There is no specific treatment
- O_2 inhalation.
- Bodyache and pain can be relieved by paracetamol not aspirin.
- Volume replacement is done by crystalloid for DSS. In severe hypotension colloid and Dopamin, Dobutamin or Noradrenaline can be added.
- For DHS—Blood or blood product transfusion is required.
- Glucocorticoid have no role in the management of DHF/DSS. On the contrary it enhances the chance of bleeding from GI tract.

There is as yet no vaccine but a tetravalent live-attenuated version is at an advanced stage of development.

EXERCISE

Write short notes on
1. Clinical features and management of dengue shock syndrome/dengue hemorrhagic fever.
2. Management of dengue.

Chapter 99

Rabies

It is an acute lethal viral infection of CNS that affects all mammals and is transmitted by infected secretion.

Most common human transmission takes place through exposure to saliva of infected animals during a bite or very rarely by infected organ transplant (corneal transplant).

ETIOLOGY

Rabies is caused by a bullet-shaped enveloped single-stranded RNA virus of negative polarity. It is in the family Rhabdoviridae within the genus Lyssavirus.

The first event in rabies is the inoculation of virus through the skin by a bite which delivers virus laden saliva.

PATHOGENESIS

Initial viral replication appears to occur within the striated muscle cell at the site of inoculation.

The peripheral nervous system is exposed at the neuromuscular junction (motor end plate) and/or neurotendinous spindle of unmyelinated sensory nerve cell ending with neurotransmitter receptor such as acetylcholine which is implicated in viral attachment and internalization.

The virus is then carried centripetally up along the nerves to the CNS probably via peripheral nerve axoplasm at the rate of 100–400 mm/day via fast axonal transport.

Once the virus reaches the CNS it replicates almost exclusively in the gray matter and passes centrifugally along nerves to other tissues—salivary gland, adrenal medulla, kidney, lung, liver, skeletal muscle, skin and heart.

Incubation period is extremely variable, ranging from 7 days to >1 year, or mean 1–2 months which apparently depends on:

- Amount of virus introduced.
- Amount of tissue involved.
- Loss of defence mechanism.
- Actual distance that the virus has to travel (distance of the site of bite from the brain, e.g. bite over head and neck has shorter incubation period than bite over leg).
- Virulency of the species.

The most characteristic pathologic finding of rabies in the CNS is the formation of cytoplasmic inclusions called '**Negri body**' within neuron which is an eosinophilic mass of 10 nm size and is made up of a finely fibrillar matrix and rabies virus particle. It is found particularly in Purkinje cell of the cerebellum, pyramidal cell in the hippocampus, brainstem, and cortical neurons. It is found in ~80% cases caused by wild rabies virus whereas rarely seen in laboratory variant of the virus. Negri bodies are absent in 20% cases. So the absence of Negri body does not exclude the diagnosis of rabies.

CLINICAL FEATURES

Clinical features of rabies can be divided into four stages:

- Nonspecific prodrome.
- Acute nonspecific viral encephalitis.
- Profound dysfunction of brainstem centers (that produces classic feature of Rabies encephalitis).
- Death or rare cases recovery.

Nonspecific Prodrome

Very similar to other viral fevers and last for 1–4 days marked by fever, headache, malaise, myalgias, increased fatiguability, anorexia, nausea, vomiting, sore throat and nonproductive cough. In this stage rabies is suggested by the complaint of paresthesia and/or fasciculation at or around the site of inoculation (bite) of virus. These sensations which may be related to the multiplication of virus in the dorsal root ganglion of sensory nerve or cranial sensory nerve ganglia supplying the area of bite reported by 50–80% of patient.

Acute Encephalitic Phase

It is marked by excessive motor activity, excitation, agitation, confusion, hallucination, combativeness, bizarre aberration of thought, muscle spasm, meningismus, opisthotonus posturing, seizure and focal paralysis.

Characteristically period of mental aberration is interspersed with completely lucid period but as the disease progressess the lucid period gradually gets shorter until the patient becomes comatosed.

Hyperesthesia with excessive sensitivity to bright light, loud noise, touch and even gentle breezes (*aerophobia*) is very common, by which rabies can be differentiated from other viral encephalitis. For this reason rabies patients are nursed in cool dark isolated room.

Temperature may be as high as 105°F.

Unfortunately the presenting signs and symptoms of rabies are indistinguishable from those of other viral and neurologic diseases which cause delay in diagnosis. **Early brainstem involvement and profound dysfunction of brainstem center distinguishes rabies from other encephalitis**.

Cranial nerve involvement causes

- Diplopia
- Optic neuritis
- Facial nerve palsy
- Difficulty in deglutition.

Foaming at the month—Excessive salivation and difficulty in swallowing produce traditional picture of foaming at mouth.

Hydrophobia—It is due to painful, violent, involuntary contraction of the diaphragm, accessory respiratory, pharyngeal and laryngeal muscle initiated by swallowing of liquid (seen in 50% of cases). These symptoms are due to dysfunction of infected brainstem neurons that normally inhibit inspiratory neuron.

Presence of hydrophobia and aerophobia is seen in about two-third of cases. Involvement of the amygdaloid nucleus results in priapism and spontaneous ejaculation. The patient lapses into coma and involvement of the respiratory center produces apneic death.

The median period of survival after the onset of symptom is 4 days with a maximum up to 20 days unless artificial supportive measures are started.

Death or Rare Recovery

If life is prolonged by intensive respiratory support a number of late complications may appear. These include—

- SIADH
- Diabetes insipidus
- Cardiac arrhythmia
- Vascular instability
- ARDS
- Paralytic ileus.

Dumb Rabies

- Rabies rarely may presents as an ascending paralysis resembling the Laundry/Guillain-Barré syndrome alternatively called **dumb rabies, rage tranquille (20%)**
- This clinical pattern was reported most frequently among persons given PEP after being bitten by vampire bats but also seen in Southern Asia with canine exposure or often with infected corneal transplant

LABORATORY DIAGNOSIS

CSF (Nonconfirmatory)

- Mild lymphocytosis >5 cell/mL
- Protein level mildly elevated
- Glucose level normal.

Two laboratory methods are commonly used to detect rabies virus specific antibody in serum.

- **Indirect fluorescent antibody test**—Done by the addition of patient's, serum to the plates with wells containing rabies virus-infected cell. If rabies-specific antibody is present in the serum they bind to the infected cell. The bound antibody is then detected by fluorescein-tagged antihuman antibody.
- **Rapid fluorescent focus inhibition test**—Fixed amount of rabies virus, diluted patient's serum and cell monolayer are incubated together for 20 hours. If antibody is present in the serum it will neutralize the virus and prevent the virus from infecting the cell. Now direct fluorescent focus antibody test of the cell monolayer shows no/or very few infected foci of virus in the same monolayer.

- Rabies-specific antibody may be found in the patient serum due to previous vaccination against rabies but when it is found in the CSF it is diagnostic of the disease rabies since antibody from vaccination does not cross intact blood-brain barrier

- **RT–PCR** can detect presence of rabies virus nucleic acid in fresh saliva.
- **DFA testing and PCR**—PCR on full thickness skin biopsy sample demonstrate viral antigen in the peripheral nerve associated with the hair follicle from the nape of neck. Where virus can be detected very early due to its close proximity to brain.

DIFFERENTIAL DIAGNOSIS

Other common cause of viral encephalitis

- Herpes virus type 1, VZV.

Less common causes of viral encephalitis

- Enterovirus—68–71 including coxsackie, echo, polio
- Arboviruses—West Nile virus.
- G-B syndrome.

TREATMENT

No specific treatment. Rabies is almost uniformly fatal but almost always preventable. Medical management is supportive and palliative.

POSTEXPOSURE PROPHYLAXIS

- Immediate and thorough mechanical cleansing of wound by scrubbing with soap and then flushed with water.
- Chemical cleansing (following mechanical cleansing) is done by
  Quarternary ammonium compound, e.g.
  1–4% benzalkonium chloride.
  1% Citrimonium bromide. Or povidone iodine solution.
- Tetanus toxoid and antibiotic prophylaxis should be administered.
- Active immunization—Human rabies PEP consists of 5 intramuscular (deltoid) injection of 1 mL modern cell culture vaccine on 0, 3, 7, 14 and 28th day.
- Passive immunization—In addition to vaccine, one dose of the human rabies immunoglobulin 20 IU/kg or 40 IU/kg of equine rabies immunoglobulin should be given as early as possible or at least within 7 days of exposure. As much of the dose as possible (anatomically feasible) is given at the site of bite if any excess should be administered in the deltoid opposite to the site of the vaccination.

Where possible, observe the animal for 10 days for clinical sign of rabies. If the animal remains normal and healthy after 10 days, vaccination can be discontinued.

PREEXPOSURE RABIES VACCINATION

1 mL modern cell culture vaccine is given intramuscularly over the deltoid on 0, 7, 21 or 28th day.

During administration of vaccine cloroquine is contraindicated.

Vaccine is always administered in the deltoid or anterior thigh in case of child (not over the buttock).

Once immunized against rabies with potent vaccine individuals are primed against rabies for rest of their lives. If an exposure occurs in previously immunized person, he should receive postexposure boosters consisting of two doses 3 days apart.

Persons with moderate to high risk rabies exposure categories should have their rabies virus neutralizing antibody titer monitored every 2 years and 6 months respectively.

Person in the low exposure category do not require serologic monitoring but like all previously immunized person must receive 2 doses of booster vaccine 3 days apart after exposure to rabies.

EXERCISE

Write short notes on

1. Pre and postexposer prophylaxis of rabies.

Chapter 100

Tetanus

INTRODUCTION

Tetanus is a CNS disorder characterized by increased muscle tone and spasm, that is caused by tetanospasmin, a powerful (protein) toxin elaborated by *Clostridium tetani*.

Tetanus occurs in several clinical forms—

- Generalized tetanus
- Local tetanus
- Neonatal tetanus
- Cephalic tetanus.

GENERALIZED TETANUS

CAUSATIVE AGENT

Clostridium tetani—A gram-positive spore forming bacillus which has a drumstick or tennis racket like appearance. The organism is found worldwide in soil, animal feces. Spores can survive for years in the inanimate environment and is resistant to various disinfectant and boiling for 20 minutes.

PATHOGENESIS

Contamination of wound with spore of *C. tetani* in presence of low oxidation-reduction potential seen within devitalized tissue, foreign body and active infection, cause germination of vegetative forms and toxin production.

This toxin is called tetanospasmin which is a heterodimer consist of a heavy chain that mediates binding of the toxin with the nerve cell receptor and entry of the toxin into the cell and a light chain which acts to block the neurotransmitter release.

The toxin is transported to nerve cell body in brainstem and spinal cord by retrograde intraneuronal transport.

The toxin then migrates across the synapse to presynaptic terminal where it *blocks the release of inhibitory neurotransmitter, glycine and γ-arninobutyric acid. With diminished inhibition the resting firing rate of the α-motor neuron increases and produces rigidity*. With diminished activity of reflexes that limits polysynaptic spread of impulses, (a glycinergic activity), agonist and antagonist may be recruited rather than inhibited with consequent production of spasm.

Loss of inhibitor may also affect preganglionic sympathetic neuron in the lateral gray column of the spinal cord and produce sympathetic overactivity and high circulating catecholamine level. Tetanospasmin may block neurotransmitter release at neuromuscular junction producing weakness and paralysis.

In local tetanus—Nerves supplying the affected muscle are involved.

In generalized tetanus—Toxin released from the wound enters the lymphatics and bloodstream and spreads widely to distant nerve terminals. Blood-brain barrier blocks direct entry into CNS. As intraneuronal transport time is equal in all nerves, short nerves are affected before long nerves. This fact explains sequential involvement of nerve of the head, neck, trunk and extremities in generalized tetanus.

CLINICAL MANIFESTATION OF GENERALIZED TETANUS

- **Trismus or lock jaw**—Due to increased tone of masseter.
- **Dysphagia**—Due to spasm of pharyngeal muscle.
- **Neck rigidity** due to spasm of neck extensor muscle.
- **Risus sardonicus (a grimace or sneer)**— Due to sustained contraction of facial muscle.
- **Opisthotonus**—Due to spasm of back muscle (erector spinae).
- **Generalized convulsion**—Paroxysmal violent painful generalized muscle spasm that may cause cyanosis and threaten ventilation.
- **Autonomic dysfunction**—Labile or sustained HTN tachycardia, dysarrhythmia, hyperpyrexia, profuse sweating, peripheral vasoconstriction and increased plasma catecholamine level. Sudden cardiac arrest.
- **Complications**—Aspiration pneumonia, fracture, muscle rupture, deep vein thrombophlebitis, pulmonary emboli, decubitus ulcers and rhabdomyolysis.

TETANUS NEONATORUM

It occurs due to contamination of umbilical cord in neonates born to nonimmunized mother. Onset usually occurs within first 2 weeks of life. Poor feeding, rigidity and spasm are typical features of neonatal tetanus. Mortality is very high close to 100% if not treated early.

LOCAL TETANUS

It is an uncommon form in which manifestations are restricted to muscle near the wound. The prognosis is excellent.

CEPHALIC TETANUS

It is a rare form of local tetanus which develop following head injury or ear infection.

Trismus and dysfunction of one or more cranial nerve (often 7th cranial nerve) are found. Incubation period is few days and mortality is very high.

DIFFERENTIAL DIAGNOSIS

Includes local condition producing trismus, e.g.

- Alveolar abscess.
- Tonsillitis.
- Strychnine poisoning.
- Dystonic drug reaction—Phenothiazine metoclopramide.
- Hypocalcemic tetany.
- Meningitis, encephalitis, rabies, acute peritonitis (because of rigid abdomen).

Marked increased tone of central muscle (face, neck, chest, back, abdomen) with superimposed generalized spasm of proximal limb muscle sparing hand and feet in a patient with unimpaired mentation confirm tetanus.

TREATMENT

General Measure

- **Nursing**—In a quite dark room to avoid minor stimuli which can precipitate spasm.
- **Wound care to eliminate source of toxin and require consideration of prophylaxis**—
  - Passive immunization with TIG—250 U (human) or TAT 3000–6000 unit (horse).
  - Active immunization with vaccine—3 doses of intramuscular injection on 0, 4 weeks and 24 weeks.
- **Antitoxin**—To neutralize circulating or unbound toxin.
  - Human tetanus immune globulin (TIG) (Given promptly)—3000 U to 6000 U IM in divided doses. Some authority consider 500 U dose is as effective as higher dose.
  - Equine tetanus antitoxin (TAT) (50000 U) given intramuscular after skin test (as because it can cause anaphylaxis).

Control of Muscles Spasm

1. Injection diazepam (GABA agonist) IV maximum daily dose < 250 mg/day by continuous infusion.
   Lorazepam—Larger duration of action } Other
   Midazolam—Shorter duration of action } option
2. Injection Barbiturates
   Injection Chlorpromazine } Consider 2nd line agent
3. Therapeutic paralysis with a nondepolarizing neuromascular blocking agent and mechanical ventilation may be required to control spasm in unresponsive cases.
4. Alternative agents are—
   - Propofol.
   - Dantrolene.
   - Baclofen (intrathecal).
   - Succinylcholine (side effect—hyperkalemia).
   - Magnesium sulfate (measurement of magnesium level).
5. Laryngeal intubation or tracheostomy with or without mechanical ventilation to overcome hypoventilation due laryngospasm or oversedation.
6. Autonomic dysfunction—Optimal therapy not known. Labetalol, esmolol (short half-life) clonidine (a central-acting antiadrenergic drug), morphin sulfate, parenteral $MgSO_4$ and continuous spinal or epidural anesthesia may be used but are very difficult to monitor.

PROPHYLAXIS

Patients recovering from the tetanus should be actively immunized because immunity is not developed by the disease.

- Tetanus neonatorum can be prevented by immunizing mother with two doses of 1 mL tetanus toxoid IM given 1 month apart in the 3rd trimester.
- Infant and children are immunized with triple antigen containing tetanus, diphtheria and pertussis vaccine given at 6, 10, 14 weeks of age with a booster at 18th month and 5 years and thereafter with tetanus and diphtheria (double antigen) at 10 years interval at 15, 25, 35, 45, 55 ..... years of age.

EXERCISE

Write short notes on

1. Clinical manifestation of tetanus.
2. Treatment of tetanus.
3. Prophylaxis of tetanus.

Chapter 101

Diarrhea

DEFINITION

Diarrhea in loosely defined as passage of abnormally liquid or unformed stool with an increased frequency.

For an adult on a Western diet, stool weight >200 g/day can generally be considered as diarrhea.

Diarrhea can be classified as:

- **Acute diarrhea**—Diarrhea that begins acutely but lasts less than 14 days with passage of loose watery stool. Fluid-electrolyte imbalances is more in this form of diarrhea.
- **Persistent diarrhea**—Diarrhea that persists for 2–4 weeks.
- **Chronic diarrhea**—Diarrhea that may begin acutely but persists for more than 4 weeks duration. Nutritional impairment is more common with this type of diarrhea.
- **Dysentery**—It is the term used for diarrhea with visible mucus and blood in the stool and often associated with fever and tenesmus.

Two clinical conditions that may minimic diarrhea are—

1. **Pseudodiarrhea**—Frequent passage of small volume of stool totalling <200 g/day, often associated with rectal urgency and accompanies the irritable bowel syndrome or proctitis.
2. **Fecal incontinence**—Involuntary discharge of rectal contents caused by neuromuscular disorder or structural anorectal problem.

ACUTE DIARRHEA

ETIOLOGY (TABLE 101.1)

- Infectious agent
- Medication
- Toxin ingestion
- Ischemia
- Miscellaneous.

Infectious agent is responsible for ~90% of acute diarrhea, 10% are caused by others.

- **Infectious agent**—Most infectious agents are acquired by fecal—oral transmission either by personal contact or by ingestion of food or water contaminated with pathogens from human or animal feces.

  Infective agents are

  Virus—Rotavirus and Norwalk agent.

  Bacteria—*E. coli*, *Shigella*, *Vibrio*, *Clostridia* and *Yersinia*.

  Protozoa—Giardia and *Entamoeba histolytica*.

> Normal rectum contains more than 500 taxonomically distinct species of resident microflora which play an important role in suppression of the growth of ingested microorganism

Acute infection or injury occurs when the ingested agent overwhelms the host's immune and nonimmune defences like

- Gastric acid
- Digestive enzyme
- Mucus secretion
- Peristalsis
- Suppressive resident flora.

CLINICAL FEATURES

Clinical features that are usually associated with acute diarrhea by infectious agent may help in clinical diagnosis.

- Profuse watery diarrhea secondary to small bowel hypersecretion occurs with ingestion of preformed bacterial toxin, enterotoxin-producing bacteria or enteroadherent pathogen. *B. cereus*, *S. aureus Clostridium*, *Vibrio*, enterotoxigenic *Escherichia coli* (ETEC), *Klebsiella*.
- Diarrhea associated with marked vomiting and minimal or no fever may occur abruptly within a few hours of ingestion.
  - Preformed bacterial toxin.
  - Enterotoxin-producing bacteria, *B. cereus*, *S. aureus* and *Clostridium*.
- Minimal vomiting but profound abdominal pain and bloating and high fever is associated with 'enteroadherent pathogen'. enterotoxigenic *Escherichia coli* (EPEC), enteroaggregative *Escherichia coli* (EAEC), Giardia and Cryptosporidiosis).

Table 101.1: Causative agents and clinical features of acute infectious diarrhea

Name/pathology	Incubation period	Vomiting	Abdominal pain	Fever	Diarrhea
1. Toxin Producer					
A. Preformed toxin					
• *Bacillus cereus*	1–8 hours	+ + +	+ +	±	+ + + +
• *S. aureus*					watery
• *Clostridium perfringens*	8–24 hours				
B. Enterotoxin					
• *Vibrio cholerae*	8–72 hours	+ + +	+ +	±	+ + + +
• ETEC					watery
• *Klebsiella pneumoniae*					
• *Aeromonas* species					
2. Cytotoxins Producer					
• *Clostridium difficile*	1–3 days	±	+ + +	+ +	+ + watery/ bloody
• Hemorrhagic *E. coli*	12–72 hours	±	+ + +	+ +	+ + watery/bloody
3. Enteroadherent					
• EPEC and EAEC	1–8 days	±	+ +	+ +	+ + watery
• Giardia					
• Cryptosporidiosis					
• Helminths					
4. Invasive Organisms					
A. Minimal inflammation					
• Rotavirus/Norwak agent	2–3 days	+ +	+ + +	+ + +	+ + + watery
B. Variable inflammation					
• Aeromonas/Campylobacter	12 hours–10 days	+ +	+ + +	+ + + +	+ + + watery/
• *Vibrio parahemolyticus*					bloody
• *Yersinia*					
C. Severe Inflammation					
• *Shigella*/EIEC (enteroinvasive *E. coli*)	12 hours–8 days	±	+ + +	+ + + +	+ + bloody
• *Entamoeba histolytica*					

- Cytotoxin-producing and invasive microorganism cause high fever and abdominal pain—*Shigella*/ EIEC.
- Yersinia invades terminal ilium and asending colon causes severe abdominal pain and tenderness mimicking acute appendicitis.

SOME SPECIAL FEATURES ASSOCIATED WITH DIARRHEA

- **Reiter's syndrome** (Syndrome complex of arthritis, urethritis and conjunctivitis) may be associated with diarrhea due to *Salmonella*, *Shigella*, *Campylobacter* and *Yersinia*.
- **Hemolytic uremic syndrome** with high mortality is associated with diarrhea due to enterohemorrhagic *E. coli* (0157 : H7) and *Shigella*.
- **Autoimmune thyroiditis, pericarditis, glomerulonephritis** may be associated with diarrhea due to *Yersinia*.
- Viral hepatitis, toxic shock syndrome, listeriosis, legionellosis may be associated with acute diarrhea.

OTHER CAUSES OF ACUTE DIARRHEA

- Medication that causes diarrhea are
  - Antibiotics (ampicillin) and chemotherapeutic agent.
  - Antiarrhythmic.
  - Antihypertensive.
  - NSAID.
  - Antidepressant.
  - Bronchodialators.
  - Mg-containing antacid.
- Ischemic colitis—It causes acute lower abdominal pain with watery and bloody diarrhea.
- Colonic diverticulitis and graft vs host disease may cause acute diarrhea.
- Acute diarrhea is often associated with organophosphates, amanita and other mushroom, arsenic, environmental toxin and seafood.
- Early stage of abrupt onset chronic diarrhea may be confused with acute diarrhea.

MANAGEMENT

Most episodes of acute diarrhea are mild and self- limiting. Indications for evaluation include

- Profuse diarrhea with dehydration
- Gross bloody diarrhea
- Fever >38.5°C
- Duration more than 48 hours
- Age >50 years and specially over 70 years
- Diarrhea associated with abdominal pain.

INVESTIGATION

A. **Microbiological analysis of stool**
   1. **Microscopy of stool**—For ova, parasite and cyst.
   2. **Immunoassay for**
      a. Bacterial toxin—*Clostridium difficile*
      b. Viral antigen—Rotavirus and Norwalk agent.
      c. Protozoal antigen—Giardia and *E. histolytica*.
   3. Culture for bacterial and viral pathogen. Special culture may be necessary for enterohemorrhagic and other type of *E. coli*, *Vibrio* species and *Yersinia*. Persistent diarrhea is commonly due to giardia but additional causative agent that should be considered include *C. difficile* (specially if diarrhea develops after antibiotic therapy), *E. histolytica*, *Cryptosporidium*, *Campylobacter*.

B. **Other investigations**
   1. Flexible sigmoidoscopy
   2. Upper GI endoscopy.
      For structural evaluation, biopsy and duodenal aspiration.
   3. CT scan of abdomen to exclude IBD.

   These investigations are important in suspected non-infectious diarrhea due to ischemic colitis diver- ticulitis and partial bowel obstruction.

TREATMENT OF ACUTE DIARRHEA

Fluid and electrolyte replacement play the central role in all forms of acute diarrhea.

- *In mild case*—Oral fluid replacement composed on sugar electrolyte or ORS (oral rehydrating solution) should be instituted promptly to limit dehydration which is the major cause of death.
- *In moderately severe* nonfebrile nonbloody diarrhea, antimotility antisecretory agents (loperamide) may be used, but such agents should be avoided in febrile dysentery.
- *Profoundly dehydrated* patients specially infants and elderly require intravenous rehydration.
- Bismuth subsalicylate may reduce symptoms of vomiting and diarrhea but should not be used in immunocompromised patient because of the risk of bismuth encephalopathy.
- Racecadotril (a chloride channel blocker) can be used in acute watery diarrhea as an adjacent therapy.
- *Use of antibiotics* in selected cases will reduce the Severity and duration of diarrhea quickly pending laboratory evaluation
  - **Febrile dysentery** in moderate to severely ill patient—quinolone (ciprofloxacin—500 mg bid for 3–5 days).
  - In suspected giardiasis—metronidazole 400 mg tid for 7 days.
  - Antibiotic coverage is indicated in
    - Immunocompromised patient
    - Patient with mechanical heart valve
    - Recent vascular grafts
    - Elderly patient.

Even if a causative agent is not discovered after investigation.

- Antibiotic prophylaxis with trimethoprim/ sulfamethoxazole or ciprofloxacin is indicated in
  - Persons travelling to high-risk countries
  - Immunocompromised patient
  - Inflammatory bowel disease
  - Gastric achlorohydria.

CHRONIC DIARRHEA

DEFINITION

Diarrhea lasting for more than 4 weeks.

Most of the causes of chronic diarrhea are non-infectious in origin.

ETIOLOGICAL CLASSIFICATION OF CHRONIC DIARRHEA

1. Secretory diarrhea
2. Osmotic diarrhea
3. Inflammatory diarrhea
4. Infectious diarrhea
5. Radiation diarrhea
6. GI malignancy
7. Dysmotility
8. Factitious diarrhea.

ETIOLOGY OF CHRONIC DIARRHEA

Secretory Diarrhea

It is due to derangement in fluid and electrolyte transport across the enterocolic mucosa.

The stool is watery, large volume (may be as high as 20 L/ day), that are typically painless and persist even with fasting.

As there is no malabsorbed solute, stool osmolality is due to normal endogenous electrolyte with no fecal osmotic gap.

It is due to

- Exogenous stimulant laxative—Senna, cascara bisacodyl, castor oil.
- Endogenous laxative (dihydroxy bile acid)
- Other drug and toxin
- Chronic ethanol ingestion

- Idopathic secretory diarrhea
- Gut resection or partial bowel obstruction
- Hormone producing tumor—Carcinoid, VIP-oma, medullary cancer of thyroid, gastrinoma, colorectal villous adenoma, Addison's disease.

Osmotic Diarrhea

Osmotic diarrhea occurs due to poorly absorbed osmotically active solute, which draws too much fluid into intestinal lumen that exceeds the reabsorption capacity of colon. It may be due to

- Osmotically active laxative, e.g. Mg^{+2}, sulfate and phosphate.
- Nonabsorbable carbohydrates, e.g. sorbitol, lactulose and polyethylene glycol.
- Due to lactase/disaccharidase deficiency which affects 3/4th of the noncaucasian worldwide.

Steatorrhea

Fat malabsorption leads to diarrhea caused by osmotic effect of fatty acids (after bacterial hydroxylation) and neutral fat often associated with weight loss and nutritional deficiencies due to concomitant nonabsorption of amino acids and vitamine.

- Normal stool fat does not exceed 7 g/day.
- In rapid transit diarrhea fecal fat up to 14 g/day.
- In steatorrhea due to small intestinal disease.
  It is usually in between 15–25 g/day.
- When it is due to pancreatic enzyme deficiency it may exceed 32 g/day.

Steatorrhea may be due to

- Intraluminal maldigestion, e.g. pancreatic enzyme deficiency, bacterial overgrowth and liver disease–Cirrhosis or biliary obstruction.
- Mucosal malabsorption—Celiac sprue, tropical sprue and Whipple's disease.
  Infection—MAI in AIDS and giardia.
  Medication—Colchicine, cholestyramine and neomycin abetalipoproteinemia.
- Postmucosal lymphatic obstruction—congenital intestinal lymphangiectasia, acquired due to trauma, surgical operation, tumor, infection.

PATHOGENESIS OF INFLAMMATORY CHRONIC DIARRHEA

Usually accompanied by fever, pain, bleeding and other manifestation of inflammation.

The mechanisms of inflammatory diarrhea are—

- Exudation
- Fat malabsorption
- Disrupted fluid electrolyte absorption
- Hypersecretion
- Hypermotility due to release of proinflammatory cytokines.

Stool analysis shows leukocyte and leukocyte derived protein such as fecal calpronectin.

ETIOLOGY OF INFLAMMATORY CHRONIC DIARRHEA

- IBD (Crohn's disease and ulcerative colitis)
- Eosinophilic gastroenteritis
- Microscopic and collagenous colitis
- Food allergy
- Graft versus host disease (GvHD)
- Immune-related mucosal disease
- Radiation colitis
- Behçet's syndrome.

OTHER CAUSES OF CHRONIC DIARRHEA

- IBS (irritable bowel syndrome).
- Dysmotile causes
  - Visceral neuromyopathy—Diabetes, scleroderma
  - Hyperthyroid, carcinoid
  - Prokinetic drugs—Itopride.
- Factitial cause.

EXERCISE

Write short notes on

1. Definition of acute diarrhea, persistent diarrhea, chronic diarrhea, dysentery, pseudodiarrhea and fecal incontinence.
2. Etiology of chronic diarrhea and acute diarrhea.
3. Special disease associated with diarrhea.

Chapter 102

Typhoid and Paratyphoid (Enteric) Fever

It is an important cause of fever transmitted by fecal-oral route in the developing countries of tropics.

ETIOLOGY

It is caused by *Salmonella typhi* and *S. paratyphi* A and B. The bacilli live in the gallbladder of the carrier for months to years after clinical recovery from the diseases and pass intermittently in the stool and less commonly in the urine. Incubation period is about 10–14 days for *S. typhi* but for *S. paratyphi* it is somewhat shorter.

PATHOLOGY

After entry through oral route the organism initially settle in Peyer's patches and lymphoid follicles of small intestine. These lymphoid structures swell due to congestion and then ulcerate. During this stage they may perforate and bleed causing perforation of the gut.

CLINICAL FEATURES

The fever is insidious in onset and rises in a stepladder fashion. For the 1st week it ranges from 102°–105°F.

There is associated headache, myalgias, drowsiness and aching in the limb. Constipation (15%) is usual in the first week followed by diarrhea, abdominal distension from early 2nd week. Vomiting (18%) and diarrhea (25%) is prominent in children.

There is *relative bradycardia* (the pulse is often slower than what is expected from the height of temperature).

At the end of 1st week a sparse slightly raised red spot (**rose spot**), which fades on pressure, appears on the chest and upper abdomen and back which is usually visible in white skinned person.

At the beginning of 2nd week spleen becomes palpable in 6% cases, cough, bronchitis and delirium may develop. By the end of 2nd week the patient is profoundly ill and in the 3rd week toxemia increases and the patient may pass into coma and die unless course of the disease is modified by treatment.

COMPLICATIONS

- **Bowel**—Perforation (2%) and hemorrhage (10–20%), cholecystitis.
- **Systemic**—Septic arthritis, osteomyelitis, meningitis.
- **Endotoxin liberated from dead bacteria causes**: Encephalitis, myocarditis and nephritis.
- **Typhoid state (not seen at present)**—When effective chemotherapy was not available an encephalitis like picture was commonly seen in typhoid patients usually from 2nd week onwards caused by inflammation of cortical neurons by the endotoxin liberated from dead bacteria clinically characterized by
  - Comavigil
  - Picking at bed cloth
  - Carphology
  - Semiconsciousness or unconsciousness
  - Convulsion
  - Low muttering delirum.

INVESTIGATIONS

- **Blood**—
  - Leukopenia with neutropenia is common.
  - Leukocytosis is more common in children during first 10 days of illness or when complicated by perforation.
- Demonstration of rising antibody titer against Salmonella by **widal reaction** from 2nd week onward is widely practised but not specific for diagnosis.
- **Culture of blood, bone marrow, urine, stool, duodenal aspirate** *to demonstrate Salmonella typhi, S. paratyphi A and B is the gold standard for diagnosis of enteric fever.*

DIFFERENTIAL DIAGNOSIS

Malaria, dengue, leptospira, amebic liver abscess, acute HIV infection, rickettsial infection.

MANAGEMENT

- Ciprofloxacin—500 mg bid for 7 days.
- Ofloxacin—400 mg BD × 7 day.

Alternatively

- Cotrimoxazole—one double strength tab bid (oral) × 14 days.
  Intravenous preparations are also available.
- **Amoxycillin**—750 mg 6 hourly × 14 days.
- **Chloramphenicol**—25 mg/kg tid × 14 days IV or oral.

Resistance to the above drugs is very common and are managed by—

- 3rd generation cephalosporin
  - **Ceftrixone**—2 g twice daily
  - **Cefotaxime**—1 g every 4 hourly
  - **Cefixime**—400 mg BD.
- Azithromycin—
  - 1 g × 5 days (oral), or
  - 1 g on 1st day then 500 mg daily × 6 days (oral).

Therapy for enteric fever to be continued for 10 days or for 5 days after resolution of fever which reduces the relapse and fecal carrier state to <2%.

In case of severe typhoid fever (fever with an abnormal state of consciousness (typhoid state) delirium, obtundation, stupor, coma, or septic shock with a positive culture or *S. typhi* or *S. paratyphi A* dexamethasone is added as adjunctive therapy.

Dexamethasone—

- 1st dose—3 mg/kg IM/IV followed by 1 mg/kg × 8 dose given every 6 hours interval.
- Intestinal perforation is managed by prompt surgical intervention.

Prophylaxis—Three types of vaccine are currently available—

1. **Ty21a—Live attenuated** *S. Typhi* vaccine (four oral dose on D1, D3, D5, D7 and a booster every 5 years). Starting from 6 years of age. Effective in 51% case up to 3 years.
2. **ViCPS**—Purified Vi-polysaccharide from the bacterial capsule (one parenteral dose) with booster every 2 years. Starting from 2 years of age. Effective in 55% up to 3 years.
3. **Acetone killed whole cell vaccine**.
   It is a Whole cell vaccine and is effective for 3 years (73%) and is superior to other —but not available commercially.
4. **A fourth vaccine vir EPA** is under development have 91% efficacy.

Even with effective chemotherapy there may be recrudescence and development of carrier state for which **ciprofloxacin may have been continued for 4 weeks and** cholecystectomy may be necessary.

EXERCISE

Write short notes on

1. Treatment and prophylaxis of enteric fever/typhoid fever.

Chapter 103

Leptospirosis (Weil's Disease)

INTRODUCTION

Leptospira are tightly coiled thread-like organisms 5–7 micron in length with hooks at both ends. *Leptospira interrogans* is pathogenic for human.

This pathogen appears to be ubiquitous in wildlife and domestic animals. The most frequent host is rodent where the organism persists in the convoluted tubules of the kidney without causing apparent disease and are shed into the urine in massive numbers.

The organism can enters the human body through intact skin and mucous membrane (but entry is facilitated by cuts and abrasion) from infected water.

CLINICAL FEATURES

The disease is caused by pathogenic leptospira and characterized by a broad spectrum of clinical manifestations varying from inapparent infection to fulminant fatal disease.

Many leptospira-infected persons may remain asymptomatic. In 90% of symptomatic cases clinical manifestation may be very mild and is usually anicteric without meningitis. Severe leptospirosis with jaundice (Weil's syndrome develops in 5–10% of cases.

Incubation period ranges from 1–2 weeks. Four main clinical syndrome can develop:

1. Bacteremic leptospirosis
2. Aseptic meningitis
3. Icteric leptospirosis (Weil's diseases)
4. Pulmonary disease.

1. **Bacteremic leptospirosis**—It produces nonspecific illness characterized by fever, weakness, muscle pain and tenderness, diarrhea, headache, nausea, vomiting with notable conjunctival congestion which persist for about 1 week, then either the patient recovers or ends in other form of clinical syndrome.

   Most of the patients become asymptomatic within one week. After an interval of 1–3 days again the illness recurs in a number of cases.

   The start of the second phase (immune phase) coincides with the development of antibody. Usually the symptoms (fever, myalgia) last for few days but occasionally develop at this stage:
   - **Aseptic meningitis** (15%)
   - **Weil's disease**
   - **Pulmonary syndrome**.
2. **Aseptic meningitis**—Classically associated with L. canicola infection present in 15% of patients, mostly in children.

   This illness is very difficult to distinguish from viral meningitis. The *conjunctiva is usually congested* but there is no other differentiating sign from viral meningitis.
3. **Icteric leptospirosis (Weil's disease or syndrome)**—Less than 10% of patients develop Weil's disease. The syndrome is usually but not exclusively associated with serovars icterohemorrhagiae/Copenhagen. It is a life-threatening disease characterized by **fever, hemorrhage, jaundice, renal impairment**.
   - *Conjunctiva is hyperemic, purpura, large areas* of *bruising* may appear.
   - *Epistaxis, hematemesis and melena* may be present.
   - *Bleeding into pleural, pericardial or subarachnoid spaces* with *thrombocytopenia* is probably related to *activation of endothelial cell which causes platelet adhesion and aggregation*.
   - *Liver is enlarged with deep jaundice* but *hepatic failure and encephalopathy are rare*.
   - *Acute renal failure* with *oliguria* and *anuria* is due to hypovolemia, *impaired renal perfusion* and *acute tubular necrosis* with presence of albumin, blood and cast in urine. Mortality 5–15%.
4. **Pulmonary syndrome**—It is characterized by *cough, dyspnea and chest pain, hemoptysis, patchy lung infiltrates on chest X-ray, respiratory failure and ARDS*. Other syndromes associated with leptospirosis are

encephalitis, uveitis, iritis, CCF, cardiogenic shock, myocarditis, pericarditis, hemolysis, rhabdomyolysis which are very rare.

Iritis, iridocyclitis and **chorioretinitis** are late complications and usually appear at 3rd week but may persist up to a year.

Mortality in anicteric leptospirosis is nil but 2.5% death have been reported from pulmonary hemorrhage and aseptic meningitis.

DIFFERENTIAL DIAGNOSIS

It is a flu-like disease with disproportionate myalgia.

Other diseases producing fever with muscle ache are

a. Dengue
b. Malaria
c. Enteric fever
d. Viral heptitis
e. Hantavirus infection
f. Rickettsial disease.

There is a strong similarity in clinical features and epidemiology of Hantavirus and leptospirosis which can only be differentiated by serologic testing.

DIAGNOSIS

Blood

- Polymorphonuclear leukocytosis.
- Thrombocytopenia in severe cases.
- Elevated level of CPK.
- Elevated bilirubin and transaminases and prolonged P-time.
- Seroconversion detected by MAT (microscopic agglutination test) and ELISA.
- CSF shows variable cellular response (pleocytosis) with moderately elevated protein with normal glucose level.
- Blood or CSF culture are positive if taken before 10th day of illness.
- ELISA for leptospira antibody IgM and IgG.
- Urine culture becomes positive from 2nd week onward in untreated patient.
- PCR is a rapid and specific investigation for diagnosis in reference laboratory.

TREATMENT

The effectiveness of antimicrobial therapy for mild febrile form of leptospirosis is controversial but such treatment is indicated for more severe form of disease.

A. **Mild leptospirosis (oral treatment)**
   1. Doxycycline—100 mg 12 hourly.
   2. Ampicillin—500 to 750 mg 6 hourly.
   3. Amoxycillin—500 mg 8 hourly.

B. **Moderate or severe leptospirosis (intravenous therapy)**
   1. Penicillin-G—1.5 M unit 6 hourly
   2. Ampicilin—1 g IV 6 hourly
   3. Ceftriaxone—1 g IV 12 hourly
   4. Cefotaxime—1 g 6 hourly
   5. Erythromycin—500 mg IV 6 hourly.

C. **Jarisch–Herxheimer** reaction may develop but is usually mild.

D. Uveitis is treated with systemic antibiotic and local corticosteroid eyedrop.

E. Blood transfusion or platelet transfusion may be required if hemorrhage is severe.

F. ARF in leptospirosis is reversible and managed by hemodialysis or peritoneal dialysis.

PROPHYLAXIS

Infection with *L. interrogans* can be prevented by doxycycline 200 mg weekly.

EXERCISE

Write short notes on

1. Clinical features of leptospirosis
2. Typhoid state.

Chapter 104

Malaria

It is a protozoan disease transmitted by the bite of infected anopheles mosquito. Four species of the genus 'plasmodium'—*P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae* cause malarial infection in human.

Almost all deaths are caused by falciparum malaria.

PATHOGENESIS

Human infection begins with the bite of an infected female anopheles mosquito which introduces plasmodium sporozoites during a blood meal. This sporozoites invade hepatic parenchymal cells and begin asexual reproduction. A single sporozoite produces 10000–30000 daughter merozoites. This merozoites invade RBC and multiply producing 6–30 daughter merozoites within 48–72 hours. When parasite density reaches 50/mL of blood usually the symptomatic stage begins.

In *P. vivax* and *P. ovale* a portion of intrahepatic forms remain dormant for a period of 6 weeks to a year or longer which are called hypnozoites and cause relapse which is characteristic of this two species. After entry into the bloodstream the merozoite rapidly invade RBC which is mediated by attachment to specific RBC receptors. In case of *P. vivax* the receptor is related to Duffy blood group antigen—Fy a and Fy b. West African people who are Duffy negative are resistant to *P. vivax* malaria.

After a series of asexual cycle in falciparum and immediately after relase from liver in vivax, ovale, malariae species, some of the parasites develop morphologically distinct long-lived sexual forms called gametocyte that can transmit malaria to mosquito.

Epidemiology—Endemicity in an area is determined by parasitemia or palpable spleen rate in children of 2–9 years
Hypoendemic—Parasitemia or palpable spleen in children of 2–9 years, <10% of population
Mesoendemic—Parasitemia or palpable spleen rate in children < 11–50% of population
Hyperendemic—Parasitemia or palpable spleen in children = 51–75% of population
Holoendemic—Parasitemia or palpable spleen in children >75% of population
Stable transmission—Frequent year-round infection
Unstable transmission—Infection is low, eratic or focal and full protective immunity is not acquired

CHANGE IN RBC

P. vivax and *P. ovale* invade young RBC
P. malariae → invades older RBC
P. falciparum invades RBC of all age.

Parasite consume the globin part of hemoglobin and the heme is polymerized to biologically inert hemozoin or malaria pigment.

PATHOGENESIS OF FALCIPARUM MALARIA

In falciparum infection, membrane protuberance appears on RBC surface at the end of 1st day of asexual cycle. This knob expresses a high molecular weight strain-specific adhesive protein (PfEMPI) plasmodium falciparum extramembranous protein 1 that mediates attachment to receptor on venule and capillary endothelium, an event termed as cytoadherence.

The parasitized RBC also adheres with the uninfected RBC to form **agglutination. Cytoadherence, rosetting** which play the key role in the pathology of falciparum malaria. **This cytoadherence makes falciparum a fatal disease**.

The endothelial receptors that mediate the adhesion are ICAM-1 in brain, Chondroitin sulfate-B in placenta and CD-36 in other organs

Sickle cell disease, thalassemia, G6PD deficiency confer protection against falciparum malaria.

CLINICAL FEATURES

Common symptom is fever but initial symptoms are—

- Lack of well-being
- Headache
- Fatigue
- Muscle ache
- Abdominal discomfort.

There is no neck rigidity/stiffness, photophobia like that of meningitis.

Nausea, vomiting and orthostatic hypotension is common.

The classical untreated chronic malaria paroxysms has three phases—cold phase, hot phase, sweating phase.

Cold phase—In which fever spike with chill and rigor, occurs at 48–72 hours interval as in vivax.

Hot phase—Temperature usually rises to ≥105° and persists for 4–6 hours.

Sweating phase—Fever subsides with sweating. Patient is usually afebrile in-between the typical paroxysms.

MANIFESTATION OF ACUTE SEVERE FALCIPARUM MALARIA

SIGNS

Major Manifestation

- **Unarousable coma or cerebral malaria**—Failure to respond appropriately to noxious stimulous or coma persisting for more than 30 minutes after convulsions with deep labored breathing.
- **Acidemia**, pH <7.25
  Plasma HCO_3 <15 mmol/L. Plasma lactate >5 mmol/L.
- **Severe normocytic normochromic anemia** (Hb <5 g/dL)
  Hematocrit <15%/Hemoglobin <5 g. Parasitemia >1 lac per mL.
- **Renal failure**—
  24 hours urine output <400 mL
  12 mL/kg in children
  Serum creatinine >3 mg/dL
- **Pulmonary edema/ARDS**—Noncardiogenic pulmonary oedema aggravated by hydration.
- **Hypoglycemia**—Glucose level <40 mg/dL.
- **Hypotension**—
  SBP <50 mm in child
  SBP <80 mm in adult
  Core-skin temperature difference >10°C
- **Bleeding due to DIC**—
  Hemorrhage from gum, nose GIT with presence of D-Dimer in blood.
- **Convulsion**— >2 generalized seizure/24 hours.
- **Hemoglobinuria (Black-water fever)**—Black, brown or red urine not associated with oxidant drug or G6PD deficiency.

Minor Manifestation

- Jaundice—Bilirubin >3 mg/dL
- Impair consciousness—Obtunded but arousable
- Extreme weakness—Inability to seat unaided
- Hyperparasitemia—Parasitemia >5% in nonimmune patient and >20% in any patient.

FEATURES INDICATING POOR PROGNOSIS IN FALCIPARUM MALARIA

Clinical

1. Marked agitation
2. Hyperventilation
3. Hypothermia
4. Bleeding
5. Deep coma
6. Repeated convulsion
7. Anuria
8. Shock.

Laboratory Features of Severe Falciparum Malaria

A. **Biochemistry**
   1. Hypoglycemia <40 mg/dL
   2. Hyperlactatemia >5 mmol/L
   3. Acidosis pH <7.3
   4. Bicarbonate <15 mmol/L
   5. Serum creatinine >3 mg/dL
   6. Serum bilirubin >3 mg/dL
   7. AST, ALT >3 times of the normal.

B. **Hematology**
   1. Total count >12000/cmm
   2. Hemoglobin <5 g/dL
   3. Coagulopathy—
      - Platelet <50,000/cmm
      - P-time >3 sec of control
      - Diminished fibrinogen <200 mg/dL.
   4. Paracytology
      - Hyperparasitemia causing increased motality when paracitisized RBC >1 lac/mL.
      - High mortality when paracitisized RBC >5 lac/mL.
      - >5% neutrophil with pigment.
      - >20% of parasites are trophozoites and schizonts.

DIAGNOSIS OF MALARIA

1. **Thick blood flim**—Stained by Giemsa or Romanowsky stain for identification of parasitemia (sensitive 0.0001% parasitemia).
2. **Thin blood flim**—Stained by Giemsa or Romanowsky stain for species identification.
3. **PfHRP2 (plasmodium falciparum histidine-rich protein-2) dipstick test**—Robust in expensive rapid test, sensitivity similar or superior to thick flim.
4. **Plasmodium LDH dipstick or card test**—Rapid test, sensitivity similar to thick flim.
5. **Microtube concentration method with acridine orange staining**—Sensitivity superior to thick flim (0.001% parasitemia) ideal for screening large number of simple. Do not identify species and require fluorescence microscopy.

CHRONIC COMPLICATIONS OF MALARIA

TROPICAL SPLENOMEGALY (HYPERREACTIVE MALARIAL SPLENOMEGALY—HMS)

Some patients exhibit abnormal immunologic response to repeated or chronic malarial infection.

This immunologic process stimulates RE cell hyperplasia and clearance activity which eventually produces:
a. Massive splenomegaly
b. Hepatomegaly
c. Marked elevation of serum IgM and malarial antibody
d. Hepatic sinusoidal lymphocytosis
e. Peripheral B-cell lymphocytosis (in Africa)
There is production of cytotoxic IgM antibody to CD8 and CD5 T-cell with increase in the ratio of CD4: CD8 T-cell. It leads to B-cell proliferation with production of IgM and cryoglobulin, producing immune complexes.

Patient with HMS presents with abdominal mass and dragging sensation in LUQ due to huge splenomegaly and occasional sharp abdominal pain suggesting perisplenitis. Anemia, pancytopenia and hepatomegaly are also seen but parasite is not usually present in the peripheral blood.

Vulnerability to respiratory and skin infection is increased in HMS and patient may *die of sepsis*. In small percentage of cases it may transform to *malignant lymphoprolipherative disorder*.

Patient with HMS should receive chemoprophylaxis against malaria.

QUARTAN MALARIAL NEPHROPATHY

Chronic repeated infection with *P. malariae* and other species may cause production of soluble immune complex, which cause injury to renal glomeruli in a small proportion of patients resulting in **nephrotic syndrome**.

The histologic appearance is that of **membranoproliferative glomerulonephritis** with splitting of capillary basement membrane and subendothelial dense deposit on EM study. Course granular pattern of deposit on the basement membrane with selective proteinuria carries a better prognosis than fine granular deposits.

Quartan nephropathy responds poorly to treatment by antimalarial, glucocorticoid and cytotoxic agents.

IMMUNE SUPPRESSION

Immune dysregulation caused by parasite malaria increases the *chance of EBV—infection* and *Burkitt's lymphoma* among children in Africa.

TREATMENT

Specific Measures

1. **Artesunate**—
   In case of severe malaria 2.4 mg/kg IM or IV × 6 days at 24 hours interval only the second dose is 1.2 mg/kg at 12 hours.
   a. Artesunate 4 mg/kg (oral) × 3 day + single dose of Sulphadoxine 25 mg/kg and pyrimethamine 1.25 mg/kg on 1st day.
   b. Artesunate + Amodiaquine (4 mg + 10 mg/kg oral) od × 3 days.
   c. Artesunate—4 mg/kg for 3 days post+ Mefloquine 25 mg/kg to prevent emergence of resistance (15 mg/kg on 2nd day and 10 mg/kg on 3rd day.
2. **Quinine**—
   20 mg/kg IV dissolved in 10% dextrose as initial loading dose to be transfused over 4 hours in case of severe malaria followed by 10 mg/kg dissolved in 10% dextrose to be transfused over 4 hours every 8 hourly for 7 days.

- Side effects—Hypotension and arrhythmia, cinchonism (high tone hearing loss), nausea, vomiting, dysphoria

   Quinine to be combined with— Tetracycline 4 mg/kg qid, or doxycycline 3 mg/kg od, or clindamycin 10 mg/kg bid for 7 days.
   (Tetracycline or doxycycline should not be used in pregnancy and child).
3. **Chloroquin**—(For Chloroquin sensitive *P. vivax*, *P. ovale*, *P. malaria*). 10 mg base/kg on 1st day and 2nd day then 5 mg base/kg on 3rd day.
   Primaquine—0.25 mg/kg/day for 14 days for radical cure.
   For *P. falciparum* malaria which have no extra-erythrocytic phase but to eliminate gammetocyte from blood—primaquine 0.75 mg/kg (single dose).
4. **Sulfadoxine-pyrimethamine**—(25/1.25 mg/kg) single dose for adult).
5. **Mefloquine**—(Complications—headache and psychiatric disorder).
   15 mg/kg on the 1st day followed by 10 mg/kg (8–12 hours later) for 2 days.
6. Artemether or Arteether are oil-based and given intramuscularly.
   3.2 mg/kg IM for 3 days.
   Only the 2nd dose is 1.6 mg/kg at 12 hours.
7. **Artemether-lumifantrine**—(For uncomplicated malaria) adult >35 kg. Each tablet containing artemether 80 mg and lumifantrine 480 mg—one tab twice daily for 3 days.
8. **Atovaquone + Prognanil**—(For uncomplicated malaria) (Each tablet containing atovaquone 250 mg and prognanil 100 mg.)
   Adult >40 kg—4 tab. daily for 3 days with food.

IMMEDIATE MANAGEMENT OF SEVERE MANIFESTATION AND COMPLICATIONS OF MALARIA

1. **Coma**
   – Maintain airway.
   – Intubate if necessary.

- Nursing of comatosed patient.
- Exclude other treatable causes of coma like hypoglycemia and bacterial meningitis.
- Avoid corticosteroid, adrenalin and heparin.

2. **Convulsion**
   - Maintain airway.
   - Treat promptly with lorazepam, phenytoin, phenobarbitone and midazolam.
3. **Hyperpyrexia**
   - Tepid sponging
   - Cooling blanket
   - Antipyretics—Paracetamol.
4. **Hypoglycemia**
   - Measure blood glucose. 50 mL 50% dextrose IV followed by continuous 10% dextrose infusion.
5. **Severe anemia**—Transfusion of fresh screened whole blood or packed cell.
6. **Acute pulmonary edema**
   - Prop-up at 45°.
   - Oxygen inhalation.
   - Venesection to drain 50 mL of blood in the donor's bag.
   - Diuretic—Frusemide.
   - Stop IV fluid.
   - Intubate—start PEP/CPAP. Mode of ventilation.
   - Hemofiltration.
7. **Acute renal failure**
   - Exclude prerenal cause.
   - Check fluid balance and urinary sodium. If urine output is inadequate despite fluid replacement and BUN and creatinine rise, renal replacement therapy by hemodialysis or hemofiltration.
8. **Spontaneous bleeding and DIC**
   - Blood transfusion/cryoprecipitate/fresh frozen plasma/platelet transfusion.
   - Injection vitamin K—10 mg/day IV.
9. **Metabolic acidosis**
   - Exclude and treat hypoglycemia, hypovolemia, gram-negative septicemia.
   - Give oxygen.
10. **Shock**
    - Exclude gram–negative septicemia by blood culture.
    - Give prophylactic antimicrobials.
    - Correct hemodynamic disturbances.
11. **Aspiration pneumonia**
    - Give (appropriate) parenteral antimicrobials
    - Frequent change of posture
    - Oxygen
    - Physiotherapy.

CHEMOPROPHYLAXIS AGAINST MALARIA

1. **Chloroquine sensitive areas**: **Chloroquine base** 300 mg once weekly or proguanil 100–200 mg od (Chloroquine is safe in pregnancy).
2. **Partial chloroquine resistance areas**: **Chloroquine + Proguanil**.
3. **High chloroquine resistant areas**: **Mefloquine** 250 mg once weekly, or **Doxycycline** 100 mg daily, or Tab. Malarone (**atovaquone 250 + proguanil** 100 mg one tablet daily.

All of these drugs are to be started 1–2 days prior to entering into malaria endemic zone and to be continued for 2 weeks after return.

EXERCISE

Write short notes on

1. Pathogenesis of falciparum malaria.
2. Manifestation of severe falciparum malaria.
3. Diagnosis of malaria.
4. Chronic complication of malaria.
5. Treatment of malaria.

Chapter 105

Leishmaniasis (Kala-azar)

INTRODUCTION

The term 'leishmaniasis' refers collectively to various clinical syndromes caused by obligate intracellular protozoa of the genus Leishmania.

It is a vector born Zoonosis with rodents and canids as common reservoir host and human as incidental host.

In human three forms of leishmaniasis occurs:

(i) Visceral, (ii) cutaneous and (iii) mucosal.

As a result of infection of macrophage throughout the RE system, in the skin and nasopharyngeal mucosa respectively.

ETIOLOGY

The organism that causes various forms of leishmaniasis in human are in the subgenus Leishmania or subgenus Viannia.

Visceral leishmaniasis is typically but not exclusively caused by Leishmania donovani complex.

Old world cutaneous leishmaniasis is caused by *L. tropica, L. major* and *L. aethiopica*.

New world American cutaneous leishmaniasis is caused by *L. mexicana* complex and Viannia subgenus.

Mucosal leishmaniasis is caused by Viannia subgenus and *L. amazonensis*.

LIFE CYCLE

Leishmania parasite is transmitted by the bite of female Phlebotomus sandfly (old world) and Lutzomyia sandfly (New world).

As the flies attempt to feed, they regurgitate the parasite's flagellated promastigote form into the skin. Promastigote attach to receptors on macrophage and phagocytisized and transform within the phagolysosome into the nonflagellated amastigote stage which multiply by binary fission. After rupture of infected macrophage, amastigote are phagocylized by other macrophages.

If ingested by feeding sand fly amastigotes transform back into promastigotes which require at least 7 days to become infective.

IMMUNOLOGY

Healing and resistance to reinfection are associated with intact T_{HI} cell response with production of IFN-γ and activation of macrophages to kill intracellular amastigotes.

In visceral leishmaniasis IL-10 which deactivates the T_{HI} cell response appears particularly important in progession of the disease.

VISCERAL LEISHMANIASIS

90% of world's case of visceral leishmaniasis occur in Bangladesh, northeastern India particularly Bihar, Nepal, Sudan, northeastern Brazil.

Causative species typically are *L. donovani* complex. Mode of transmission:

- Sand flies (most common)
- Vertical (from mother to child)
- Transfusion or needle sharing.

CLINICAL FEATURES

- Many patients remain subclinical. Asymptomatic infection outnumbers clinically overt cases and may become symptomatic with acute, subacute, chronic course.

Incubation period—Ranges from weeks to months but can be as long as years.

Visceral leishmaniasis covers a broad spectrum of severity and manifestation but the term kala-azar refers to classic image of profound cachectic febrile patients who are heavily infected with parasite and have life-threatening disease.

- Splenomegaly—It is massive, most often soft and non-tender.
- Hepatomegaly : It is present but less impressive.
- Lymphadenopathy is common in some setting in Sudan (not in India).
- PKDL is manifested by skin lesion of macules, papules, nodules and patches that is typically present over face.

The lesion can develop during therapy or within few weeks (in East Africa) to years later (in India).

In India PKDL patients are the primary reservoir host who maintain transmission of infection. Even relapse of viseral diseases can occur from PKDL.

DIAGNOSIS

- Blood—Leukopenia with neutropenia.
- Patient with florid kala-azar have high titer of anti- body to Leishmania which is diagnostically useful but not protective for the patient.

  Aldehyde test—(Appearance of egg white-like opacity on addition of 1 drop of formalin to the patient's serum) once very popular bedside test but has too much false-positive result and do not become positive before 3 months of illness.

  Serology—(Sensitivity is low in HIV-infected individual).
  - Direct agglutination test with freeze-dried antigen.
  - Immunochromatographic dipstick testing of finger prick blood for antibody to recombinant antigen or synthetic peptide (rK-39) *is now widely used and specificity is ~100%*.

  Leishmanin skin test—Test for Leishmania-specific cell-mediated immunity. Usually develops after recovery. Useful for clinical purpose in the diagnosis of cutaneous and mucosal leishmaniasis.
  - Leishmanin skin test is helpful in leishmaniasis recidivans.

Definitive diagnosis is made by demonstration of amastigote form of the parasite on stained slide or promastigote form in culture of a tissue aspirate or biopsy specimen of spleen (98%), bone marrow (90%), liver (80%) and lymph node (<75%).

- **Smear**—It is made from blood and skin or tissue specimen and stain by Giemsa or Romanosky stain and examine under oil emersion lens for the presence of the amastigote form of the parasite containing nucleus and kinetoplast which is nothing but specialized mitocondrial structure that contains extranuclear DNA.
- **Culture**—Culture of parasite is done in the water of condensation of Novy-Macneal–Nicolle, (NNN) medium at 22°C from which promastigote form of the parasite can be demonstrated.
- PCR may be even more sensitive.

DIFFERENTIAL DIAGNOSIS OF VISCERAL LEISHMANIA

- Includes other tropical and infectious diseases that cause fever or organomegaly, e.g. typhoid fever, miliary tuberculosis, brucellosis, histoplasmosis, malaria, tropical splenomegaly syndrome and schistosomiasis.
- Myeloproliferative diseases like leukemia, lymphoma.
- PKDL should be differentiated from syphilis, yaws, leprosy.

TREATMENT

- First Line Therapy
  - **Pentavalent antimony**—20 mg/kg/day, IV or IM × 28 days.
  - **Amphotericin B lipid formulation**—2–5 mg/ kg/ day IV up to a total dose 15–21 mg/kg (usually 3 mg/ kg on day 1to 5, 14th and 21st day total 21 mg/kg).
- Alternatives
  - **Amphotericin B deoxycholate**—0.5–1 mg/kg IV daily or alternate day total 15–20 mg/kg.
  - **Paramomycin sulfate**—15–20 mg/kg/day IV or IM × 21 day.
  - **Pentamidine isethionate**—4 mg/kg/day IV or IM or thrice weekly × 15–30 doses.
  - **Miltefosin** (oral) 2.5 mg/kg daily × 28 days (100–125 mg/day) *except anorexia and nausea there is no side effect and is now the drug of choice*.
  - Sitamaquin (oral) under trial.

CUTANEOUS LEISHMANIASIS

Cutaneous leishmaniasis is classified into new world and old world disease.

90% cutaneous leishmaniasis occurs in Afghanisthan, Algeria, Iran, Iraq, Saudi Arabia, Seria, Brazil and Peru.

Etiological agent of:

New world cutaneous disease are *L. mexicana* complex and L. viannia subgroup and also *L. major* and *L. chagasi*.

Old world cutaneous disease are *L. tropica*, *L. major* and *L. aethiopica* and *L. infantum* and *L. donovani*.

CLINICAL FEATURES

Incubation period ranges from weeks to months. Clinical manifestation is usually a papule at the site of sand fly bite or a regional lymphadenopathy (specially in *L. braziliensis*).

Most of the skin lesions envolve from papule to nodule and ultimately ulcerate with a central depression which can be several centimeter in diameter surrounded by a raised indurated boarder. Some lesions persist as nodule or plaques.

Multiple primary lesion, satellite lesion, regional lymphadenopathy, sporotrichoid subcutaneous nodules, with pain or pruritus and secondary bacterial infection are variably present.

The infecting species, host resistance and location of lesion are the determinant of the clinical manifestation and chronicity of untreated disease. For example in New world, cutaneous disease caused by *L. mexicana* tend to be smaller and less chronic than caused by *L. braziliensis*.

Old world lesion caused by *L. major* tends to be wet and exudative and are less chronic whereas lesion caused by *L. tropica* are dry with central crusting seen in Afghanistan.

Spontaneous resolution of the lesion does not preclude reactivation or reinfection.

Diffuse cutaneous leishmaniasis (DCL)—The polyparasitic cutaneous lesion.

DCL—Caused by *L. aethiopica* (old world), *L. mexicana* (New world)—develop leishmania specific anergy and manifested by chronic disseminated nonulcerative skin lesion.

Leishmania recidivans—Oligoparasitic cutaneous lesion.

Both (DCL and recidivans) are rare and represent the two ends of the same spectrum of the diseases and are notoriously difficult to treat.

Leishmania recidivans—caused by *L. tropica* manifested by chronic solitary plaque on the cheek that expands slowly despite central healing.

DIAGNOSIS

Examination of histologic section of biopsy specimen with special stain can help to establish the diagnosis. As the lesion age very few amastigote form seen.

Serologic testing are usually negative. Leishmanin skin test is diagnostic of leishmaniasis recidivans.

Differential Diagnosis

Lepromatous leprosy, lupus vulgaris, tropical, traumatic and venous stais ulcer.

TREATMENT

A. Parenteral
   1. Pentavalent antimony—Same as visceral disease × 20 days.
   2. Pentamidine—2 mg/kg × 7 days.
   3. Amphotericin B—0.5–1 mg/kg (total dose 20 mg/kg).

B. Oral
   1. Fluconazole for *L. major* (in Saudi Arabia)—200 mg qd or bid × 6 weeks.
   2. Ketoclonazole for *L. mexicana, L. (V) panamensis* (better than itraconazole)—600 mg/day × 28 days.
   3. Miltefosine—2.5 mg/kg daily × 28 days.

C. Local/Tropical
   1. Paromomycin ointment
   2. Topical immunomodulators
   3. Intralesional administration of antimony
   4. Heat therapy
   5. Cryotherapy.

MUCOSAL LEISHMANIASIS

Mucosal lesion is usually clinically evident within several years after the healing of the original cutaneous lesion but mucosal lesion can coexist with the skin lesion or may appear decades later of healing of skin lesion.

Typically the original cutaneous lesion of the patients who develop mucosal disease were not treated or suboptimally treated.

CLINICAL FEATURES

Mucosal involvement is generally manifested by nasal symptoms (e.g. epistaxis) with erythema and edema of nasal mucosa and progressive ulcerative, nasopharyngeal destruction.

Causative agents—Viannia subgenus typically *L. (V). braziliensis, L. (V) panamensis* and *L. (V) guyanensis* and common in South America.

DIAGNOSIS

- Positive serological test only in DCL
- PCR
- Parasitological confirmation difficult except DCL
- Skin test—Positive except DCL.

Differential Diagnosis

- Sarcoidosis, midline granuloma, neoplasm, rhinoscleroma, paracoccidioidomycosis histoplasmosis, leprosy, tertiary syphilis and jaws.

TREATMENT

1. Pentavalent antimony—20 mg/kg/day IM/IV × 28 days.
   Patients who develop respiratory compromise after initiation of therapy due to inflammatory reaction may benefit from concomitant administration of glucocorticoid.
2. Amphotericin B (deoxycholate)—1 mg/kg/day total (20–40 mg/kg).
3. Pentamidine—2–4 mg/kg daily or thrice weekly × 15 doses.
4. Miltefosine (oral)—Shows promise.

EXERCISE

Write short notes on

1. Laboratory diagnosis of kala-azar.
2. Treatment of kala-azar.
3. Cutaneous and mucocutaneous leishmaniasis.

Chapter 106

Approach to a Patient of Fever with Rash

Diseases with fever and rash may be classified depending on the type and site of eruption. They are as follows:

1. **Centrally distributed maculopapular eruption**
2. **Peripheral eruption**
3. **Confluent desquamative erythematous eruption**
4. **Vesiculobullous eruption**
5. **Urticarial eruption**
6. **Nodular eruption**
7. **Purpuric eruption**
8. **Ulcerated lesion or eschars.**

CENTRALLY DISTRIBUTED MACULOPAPULAR ERUPTION WITH FEVER

ETIOLOGY

- **Measles**—Rash starts at hairline at 2–3 days of fever move down the body, sparing palm and sole. It begins as discrete erythematous lesion which becomes confluent as the disease spreads. Koplik's spot (1–2 mm white or bluish lesion) with an erythematous halo on the buccal mucosa are pathognomonic for measles and seen on initial 1–2 days.
- **German measles**—Spreads from hairline downwards, cleaning as it spread, may be pruritic associated with palpable **petechiae** (For chheimers spot) with lymphadenopathy and **arthritis**.
- **Erythema infectiosum (caused by human parvovirus)**—Rash follows resolution of fever. Bright red blanchable erythema on the cheeks (slapped-check appearance) followed by lacy reticular rash that waxes and wanes over 3 weeks. Common in children (3–12 years) in winter and spring. Mildfever and arthritis seen in adult.
- **Primary HIV**—Nonspecific diffuse macules and papules may be urticarial associated with oral and genital ulcer in some cases with pharyngitis, adenopathy and arthralgias.
- **Infectious mononucleosis (EBV)**—Diffuse maculopapular eruption in 10–15% cases and 90% if ampicillin is given. Urticaria in some cases periorbital edema (50%), palatal petechiae (25%).
- **Dengue**—Rash in 50% cases, initially diffuse appear midway through illness of maculopapular rash which begins on trunk and spreads centrifugally to face and extremity, pruritus, hyperesthesia and petechiae are present in some cases. Associated features are headache, musculoskeletal pain (breakbone fever), saddle backfever, leukopenia.
- **Exanthematous drug eruption** (commonly following antibiotic, anticonvulsants and diuretics).
- **Leptospirosis**—Maculopapular eruption with conjunctivitis and scleral hemorrhage. As a result of exposure to contaminated water with animal urine. Associated with myalgia or aseptic meningitis.
- **Lyme disease** (Borrelia burgdoferi)—Papules expanding to erythematous annular lesion with central clearing (erythema chronicum migrance) average diameter—15 cm.
- **Typhoid fever**—Transient blanchable erythematous macular and papular rash (2–4 mm in diameter usually on upper trunk) due to consumption of contaminated food and drink. Variable abdominal pain, diarrhea, headache, myalgias, hepatosplenomegaly are usually present.
- **Relapsing fever** (Borrelia species)—Central rash at the end of febrile episode petechiae in some cases due to exposure to tick and bodylice. Recurrent fever, headache, myalgias and hepatosplenomegaly are usually present.
- **Erythema marginatum**—Erythematous annular or papule or plaque occurring as polycyclic lesion coming in waves over trunk and proximal extremity evolving and resolving within hours. Past history of rheumatic fever, pharyngitis preceding polyarthritis, carditis, subcutaneous nodule, chorea are present.
- **SLE**—It is an autoimmune disorder characterized by malar rash, discoid rash, increased photosensitivity, oral ulcer, associated with polyserositis, arthritis, renal, neurologic and hematologic disorder. ANA and anti-dsDNA are positive in serum.
- **Still's disease**—Autoimmune disease. Transient 2–5 mm erythematous papule appearing at the height of fever on trunk and proximal extremities. Evanescent

lesion common in children and young adults. Associated with high spiking fever, polyarthritis, splenomegaly ESR > 100 mm/hour. Serum ferritin level—very high.

PERIPHERAL ERUPTION WITH FEVER

ETIOLOGY

- **Chronic meningococcemia**—A rare syndrome of episodic fever, rash, arthralgias that can last for weeks to months.

  The rash may be maculopapular occasionally petechial. Splenomegaly may develop.

  If untreated or treated with glucocorticoids, chronic meningococcemia may evolve into meningitis. Fulminant meningococcemia or endocarditis.
- **Disseminated gonocoeal infections**—(skin lesions are seen in 75% of patients). Papules, pustules often with hemorrhagic component are seen on the extremity and 5–40 in number.
- **Rocky mountain spotted fever** (Rickettsia rickettsii)—Rash beginning on wrist and ankle and spreading centripetally appears on the palm and sole later in disease.
- **Secondary syphilis**—It is caused by Treponema pallidum.

  Copper colored, diffuse scaly papular eruption, prominent on palm and soles.
- **Atypical measles** (paramyxovirus)—Maculopapular eruption beginning on distal extremity and spreading centripetally may evolve into vesicle or petechiae edema may be present.

  Koplik's spot absent.
- **Hand-foot-and-mouth disease** (Coxsackie-A16)—Tender vesicles, erosion in mouth 0.25 cm papuler on hand and feet with rim of erythema evolving into tender vesicles. Transient fever occurs in other children < 10 years of age in the family.
- **Erythema multiforme**—Due to drug, infection and other causes.

  Target lesions—central erythema surrounded by areas of clearing and another rim of erythema up to 2 cm in diameter symmetric on knee, elbow, palm, soles may become diffuse, may involve mucosal surface.
- **Bacterial endocarditis**—Subacute course (*S. viridans*)—Osler's node—Tender pink nodule on finger or toe pad, petechiae on skin and mucous membrane. splinter hemorrhage.

  Acute coarse (*S. aureus*)—Janeway lesion-painless erythematous or hemorrhagic macules usually on palms and sole.

  Associated features—Abnormal heart valve, IV drug abuser, new heart murmur.

CONFLUENT DESQUAMATIVE ERYTHEMA WITH FEVER

ETIOLOGY

- **Scarlet fever**—Group A streptococcus pyrogenic exotoxin—A, B, C.

  Diffuse blanchable erythema beginning on face and spreading to trunk and extremities circumoral pallor, sandpaper texture to skin, accentuation of linear erythema in skin fold—Pastia's line, erythema of white evolving into red, strawberry tongue, desquamation in 2nd weak.

  Most common between 2–10 years follows streptococcal pharyngitis.
- **Kawasaki disease** (idiopathic cause)—

  Rash similiar to scarlet fever or erythema multiforme, fissuring of lips, strawberry tongue conjunctivitis, edema of hand and feet, desquamate later. Common in children <8 years. Associated with cervical adenopathy, pharyngitis, coronary artery vasculitis.
- **Streptococcal toxic shock syndrome**—Group A streptococcus associated with pyrogenic exotoxin A or B or certain M type.

  When present rash often scarlatiniform. Associated with multiorgan failure, hypotension. Streptonecrotizing fasciitis, bacteremia and pneumonia. Mortality—30%.
- **Staphylococcal toxic shock syndrome**—(It is caused by *Staph. aureus*)—TSS Toxin–1, Enterotoxin B, C). Diffuse erythema involving palms, mucosal surface, conjunctiva which desquamate 7–10 days later. Associated with fever (102°F), hypotension and multiorgan failure.
- **Staphylococcal scalded skin syndrome** (*Staphylococcal aureus* phage—II)—

  Diffuse tender erythema often with bullae and desquamation, Nikolsky's sign. Associated with nasal or conjunctival secretion and irritability. Renal dysfunction seen in adults.
- **Exfoliative erythroderma syndrome**

  (Associated with underlying psoriasis, eczema, drug eruption, mycosis, fungoides)—

  Diffuse erythema often scaling interspersed with lesion of underlying condition usually occur over 50 years age M > F.

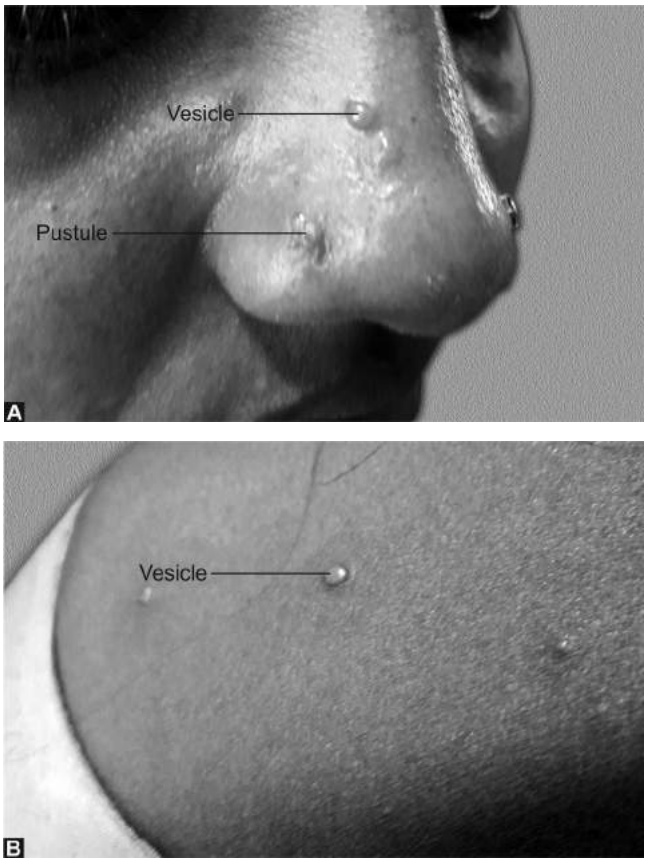
  Associated features—Fever, chill with difficulty in thermoregulation, lymphadenopathy.
- **Toxic epidermal necrolysis** (Drugs, infection, neoplasm and graft-vs-host disease)—Diffuse erythema or target-like lesion progressing to bullae with sloughing and necrosis of entire epidermis. Nikolsky's sign present. Common in children, HIV infection, graft-vs-host disease.

  Dehydration and sepsis due to lack of skin integrity, mortality 25%.

VESICULOBULLOUS ERUPTION WITH FEVER

- **Varicella** (chickenpox) caused by varicella zoster virus)—Macules (2–3 mm)—evolving into papule then vesicles (sometimes umbilicated) dew drop on rose petal appearance as it have an erythematous background). Then quickly transform into pastules and crusting.
  Lesions appearing in crops may involve trunk scalp, mouth and intensely pruritic.
  Affects predominantly children but 10% patients are adults. Common in late winter and spring.
- **Variola** (variola major virus)—Red macule on tongue, palate evolving to papules and vesicles. Skin macule evolving to papules then transform into vesicles then pustules over 1 week with subsequent crusting. Initially appear on face and spread centrifugally from trunk to extremities.
  - Skin lesion in any given area are at some stage of development.
  - There is a prominent distribution of lesions on face and extremities including palm and sole as opposed to prominent rash on trunk in varicella.

  Associated features—Fever, headache, backache, myalgias, vomiting.



Figs 106.1A and B: Vesical and pustula at different stages of chickenpox

- **Disseminated herpes infection** (both HSV and VZV) (Figs 106.1A and B)— Individual lesion similiar for VZV or HSV. In zoster cutaneous dissemination > 25% lesion extend outside the dermatome.
  HSV—Extensive, progressive mucocutaneous lesion.
  HSV lesion may disseminate in eczematous skin—called eczema herpeticum.
  HSV visceral (liver) dissemination may occur with only limited skin diseases.
  Associated with immunocompromised individual and eczema.
- **Rickettsial pox** (*Rickettsia akari*)—
  Eschar found at the site of tick bite, generalized rash involving face, trunk and extremities including palm and sole.
  Seen in Urban setting—Transmitted by mouse bite.
  Associated features—Headache, myalgias, regional adenopathy.
- **Ecthyma gangrenosum—Pseudomonas aeruginosa** and other gram-negative rod and fungi.
  Indurated plaque evolving into hemorrhagic bullae or pustule that sloughs resulting in eschar formation with erythematous halo most common in axilla, groin, perianal region.
  Associated features—Sepsis, usually affects neutropenic patient.
- **Hand-foot-and-mouth disease**—Staphylococcal scalded skin syndrome, toxic epidermal necrolysis—Previously discussed (all produce vesiculobullous eruption).

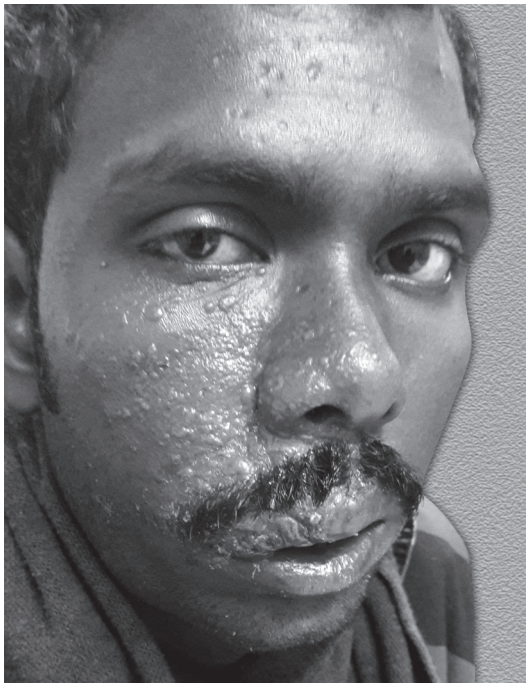


Fig. 106.2: **Herpes zoster** involving maxillary division of trigeminal nerve

URTICARIAL VASCULITIS

Serum sickness often due to infection like HEP-B , enteroviral toxin, parasitic. Infestation drugs like—Penicillin, sulfosalicylate and connective tissue disease.

Erythematous circumscribed areas of edema, indurated, pruritic or purpuric lesion lasting up to five days.

Associated features—Lymphadenopathy, myalgia and arthralgias.

It occurs 8–14 days after antigen exposure in non-sensitized individual but may occur within 36 hours in sensitized individual.

NODULAR ERUPTION WITH FEVER

- **Disseminated infection with fungus and mycobacteria**—Candidiasis, histoplasmosis, cryptococcosis, sporotrichosis, coccidioidomycosis, and mycobacteria.

  Associated with immunocompromised host, HIV, alcoholics.
- **Erythema nodosum**—Infection with streptococcal, fungal, mycobacterial, yersinial infection. Drugs (sulfar, penicillin, contraceptive, sarcoidosis, idiopathic) can cause this type of lesion.

  Large violaceous, nonulcerative subcutaneous nodule, exquisitely tender, usually on legs but may be also on upper extremity.

  More common in 15–30 years of age.

  A common associated feature—Arthralgias in 50% cases.
- **Sweet syndrome** (acute, febrile neutrophilic dermatosis)—Yersinial infection, lymphoproliferative disorder, idiopathic).

  Tender, red or blue edematous nodule, giving impression of vesiculation usually on face, neck, upper extremity.

  When on lower extremity mimic the appearance of erythema nodosum.

  Common in women 30–60 years of age.

  20% cases are associated with malignancy.

  Associated features—Headache, arthralgias, leukocytosis.

PURPURIC ERUPTION WITH FEVER

- Rocky mountain spotted fever.
- Rat-bite fever.
- Endocarditis.
- Epidemic typhus.
- Dengue.
- Acute meningococcemia.
- Purpura fulminans.
- Chronic meningococcemia.
- Disseminated gonococcal infection.
- Enteroviral petechial rash.
- Viral hemorrhagic fever.
- Thrombotic thrombocytopenic purpura or hemo- lytic uremic syndrome.
- Cutaneous small vessel vasculitis.
  - **Purpura fulminans** (Severe DIC)—Large ecchymoses with sharply irregular-shaped evolving in to hemorrhagic bullae and black necrotic lesion. Associated with *N. meningitidis*, malignancy, or massive trauma, after splenectomy.
  - **Enteroviral petechial rash** (Echovirus-9 or Coxsackievirus A9)—Disseminated petechial lesion may be maculopapular, vesicular, urticarial. Associated with pharyngitis, headache, aseptic meningitis.
  - **Viral hemorrhagic fever** (Arbo/arenavirus)—Petechial rash. History of travel to or resident of an endemic zone. Associated features—fever, shock, hemorrhage from mucosa or GI tract.
  - **Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome**—Etiology—*Escherichia coli* 0.157; H7 (shiga toxin) Petechial rash.

    Individual with *E. coli* 0157—H7 gastroenteritis are usually children. It can also be seen in HIV infection, autoimmune diseases, pregnancy and postpartum lady.

    Fever not always present, hemolytic anemia, thrombocytopenia, renal dysfunction, neurologic abnormality are the associated features. Coagulation study are normal.
  - **Cutaneous small vessel vasculitis** (Leukocytoclastic vasculitis): Etiology—Group A streptococcus infection, viral hepatitis, drugs, chemical, food allergen and idiopathic.

    Clinical features—Palpable purpuric lesion appearing in crops on legs or other dependent areas may become vesicular or ulcerative usually resolve over 1 month.

    Associated features—Connective tissue disease or cryoglobulinemia, malignancy, Henoch-Schönlein purpura more common in children.

    Fever, myalgias, arthralgias, systemic vasculitis with involvement of kidney, joint and GI tract seen in HSP.

ERUPTION WITH ULCER AND/OR ESCHARS WITH FEVER

- Scrub typhus
- Rickettsial spotted fever

- Rat-bite fever
- Rickettsial pox
- Ecthyma gangrenosum
- Tularemia—Causative agent *Francisella tularensis*
- Anthrax—Bacillus anthrax.
  Various types of lesion may appear.
  - Ulceroglandular form—Erythema, tender papule evolve into necrotic tender ulcer with raised boarder in 1/3rd cases.
  - Other types of lesions are maculopapular, vesiculopapular, acniform, lesion urticarial, erythema nodosum, erythema multiforme. Due to exposure to ticks, biting flies or infected animal.

  Associated features—headeche, fever, lymphadenopathy.
- **Anthrax** (Bacillus anthrax)—Pruritic papule, enlarging and evolving into 1–3 cm painless ulcer surrounded by vesicle, and then developing into a central eschar with edema.

  It is Due to exposure to infected animal or animal product with spore of anthrax.

  Associated features—Lymphadenopathy and headache.

EXERCISE

Write short note on

1. Approach to a patient of fever with rash.

Chapter 106

Approach to a Patient of Fever with Rash

Diseases with fever and rash may be classified depending on the type and site of eruption. They are as follows:

1. **Centrally distributed maculopapular eruption**
2. **Peripheral eruption**
3. **Confluent desquamative erythematous eruption**
4. **Vesiculobullous eruption**
5. **Urticarial eruption**
6. **Nodular eruption**
7. **Purpuric eruption**
8. **Ulcerated lesion or eschars.**

CENTRALLY DISTRIBUTED MACULOPAPULAR ERUPTION WITH FEVER

ETIOLOGY

- **Measles**—Rash starts at hairline at 2–3 days of fever move down the body, sparing palm and sole. It begins as discrete erythematous lesion which becomes confluent as the disease spreads. Koplik's spot (1–2 mm white or bluish lesion) with an erythematous halo on the buccal mucosa are pathognomonic for measles and seen on initial 1–2 days.
- **German measles**—Spreads from hairline downwards, cleaning as it spread, may be pruritic associated with palpable **petechiae** (For chheimers spot) with lymphadenopathy and **arthritis**.
- **Erythema infectiosum (caused by human parvovirus)**—Rash follows resolution of fever. Bright red blanchable erythema on the cheeks (slapped-check appearance) followed by lacy reticular rash that waxes and wanes over 3 weeks. Common in children (3–12 years) in winter and spring. Mildfever and arthritis seen in adult.
- **Primary HIV**—Nonspecific diffuse macules and papules may be urticarial associated with oral and genital ulcer in some cases with pharyngitis, adenopathy and arthralgias.
- **Infectious mononucleosis (EBV)**—Diffuse maculopapular eruption in 10–15% cases and 90% if ampicillin is given. Urticaria in some cases periorbital edema (50%), palatal petechiae (25%).
- **Dengue**—Rash in 50% cases, initially diffuse appear midway through illness of maculopapular rash which begins on trunk and spreads centrifugally to face and extremity, pruritus, hyperesthesia and petechiae are present in some cases. Associated features are headache, musculoskeletal pain (breakbone fever), saddle backfever, leukopenia.
- **Exanthematous drug eruption** (commonly following antibiotic, anticonvulsants and diuretics).
- **Leptospirosis**—Maculopapular eruption with conjunctivitis and scleral hemorrhage. As a result of exposure to contaminated water with animal urine. Associated with myalgia or aseptic meningitis.
- **Lyme disease** (Borrelia burgdoferi)—Papules expanding to erythematous annular lesion with central clearing (erythema chronicum migrance) average diameter—15 cm.
- **Typhoid fever**—Transient blanchable erythematous macular and papular rash (2–4 mm in diameter usually on upper trunk) due to consumption of contaminated food and drink. Variable abdominal pain, diarrhea, headache, myalgias, hepatosplenomegaly are usually present.
- **Relapsing fever** (Borrelia species)—Central rash at the end of febrile episode petechiae in some cases due to exposure to tick and bodylice. Recurrent fever, headache, myalgias and hepatosplenomegaly are usually present.
- **Erythema marginatum**—Erythematous annular or papule or plaque occurring as polycyclic lesion coming in waves over trunk and proximal extremity evolving and resolving within hours. Past history of rheumatic fever, pharyngitis preceding polyarthritis, carditis, subcutaneous nodule, chorea are present.
- **SLE**—It is an autoimmune disorder characterized by malar rash, discoid rash, increased photosensitivity, oral ulcer, associated with polyserositis, arthritis, renal, neurologic and hematologic disorder. ANA and anti-dsDNA are positive in serum.
- **Still's disease**—Autoimmune disease. Transient 2–5 mm erythematous papule appearing at the height of fever on trunk and proximal extremities. Evanescent

lesion common in children and young adults. Associated with high spiking fever, polyarthritis, splenomegaly ESR > 100 mm/hour. Serum ferritin level—very high.

PERIPHERAL ERUPTION WITH FEVER

ETIOLOGY

- **Chronic meningococcemia**—A rare syndrome of episodic fever, rash, arthralgias that can last for weeks to months.

  The rash may be maculopapular occasionally petechial. Splenomegaly may develop.

  If untreated or treated with glucocorticoids, chronic meningococcemia may evolve into meningitis. Fulminant meningococcemia or endocarditis.
- **Disseminated gonocoeal infections**—(skin lesions are seen in 75% of patients). Papules, pustules often with hemorrhagic component are seen on the extremity and 5–40 in number.
- **Rocky mountain spotted fever** (Rickettsia rickettsii)—Rash beginning on wrist and ankle and spreading centripetally appears on the palm and sole later in disease.
- **Secondary syphilis**—It is caused by Treponema pallidum.

  Copper colored, diffuse scaly papular eruption, prominent on palm and soles.
- **Atypical measles** (paramyxovirus)—Maculopapular eruption beginning on distal extremity and spreading centripetally may evolve into vesicle or petechiae edema may be present.

  Koplik's spot absent.
- **Hand-foot-and-mouth disease** (Coxsackie-A16)—Tender vesicles, erosion in mouth 0.25 cm papuler on hand and feet with rim of erythema evolving into tender vesicles. Transient fever occurs in other children < 10 years of age in the family.
- **Erythema multiforme**—Due to drug, infection and other causes.

  Target lesions—central erythema surrounded by areas of clearing and another rim of erythema up to 2 cm in diameter symmetric on knee, elbow, palm, soles may become diffuse, may involve mucosal surface.
- **Bacterial endocarditis**—Subacute course (*S. viridans*)—Osler's node—Tender pink nodule on finger or toe pad, petechiae on skin and mucous membrane. splinter hemorrhage.

  Acute coarse (*S. aureus*)—Janeway lesion-painless erythematous or hemorrhagic macules usually on palms and sole.

  Associated features—Abnormal heart valve, IV drug abuser, new heart murmur.

CONFLUENT DESQUAMATIVE ERYTHEMA WITH FEVER

ETIOLOGY

- **Scarlet fever**—Group A streptococcus pyrogenic exotoxin—A, B, C.

  Diffuse blanchable erythema beginning on face and spreading to trunk and extremities circumoral pallor, sandpaper texture to skin, accentuation of linear erythema in skin fold—Pastia's line, erythema of white evolving into red, strawberry tongue, desquamation in 2nd weak.

  Most common between 2–10 years follows streptococcal pharyngitis.
- **Kawasaki disease** (idiopathic cause)—

  Rash similiar to scarlet fever or erythema multiforme, fissuring of lips, strawberry tongue conjunctivitis, edema of hand and feet, desquamate later. Common in children <8 years. Associated with cervical adenopathy, pharyngitis, coronary artery vasculitis.
- **Streptococcal toxic shock syndrome**—Group A streptococcus associated with pyrogenic exotoxin A or B or certain M type.

  When present rash often scarlatiniform. Associated with multiorgan failure, hypotension. Streptonecrotizing fasciitis, bacteremia and pneumonia. Mortality—30%.
- **Staphylococcal toxic shock syndrome**—(It is caused by *Staph. aureus*)—TSS Toxin–1, Enterotoxin B, C). Diffuse erythema involving palms, mucosal surface, conjunctiva which desquamate 7–10 days later. Associated with fever (102°F), hypotension and multiorgan failure.
- **Staphylococcal scalded skin syndrome** (*Staphylococcal aureus* phage—II)—

  Diffuse tender erythema often with bullae and desquamation, Nikolsky's sign. Associated with nasal or conjunctival secretion and irritability. Renal dysfunction seen in adults.
- **Exfoliative erythroderma syndrome**

  (Associated with underlying psoriasis, eczema, drug eruption, mycosis, fungoides)—

  Diffuse erythema often scaling interspersed with lesion of underlying condition usually occur over 50 years age M > F.

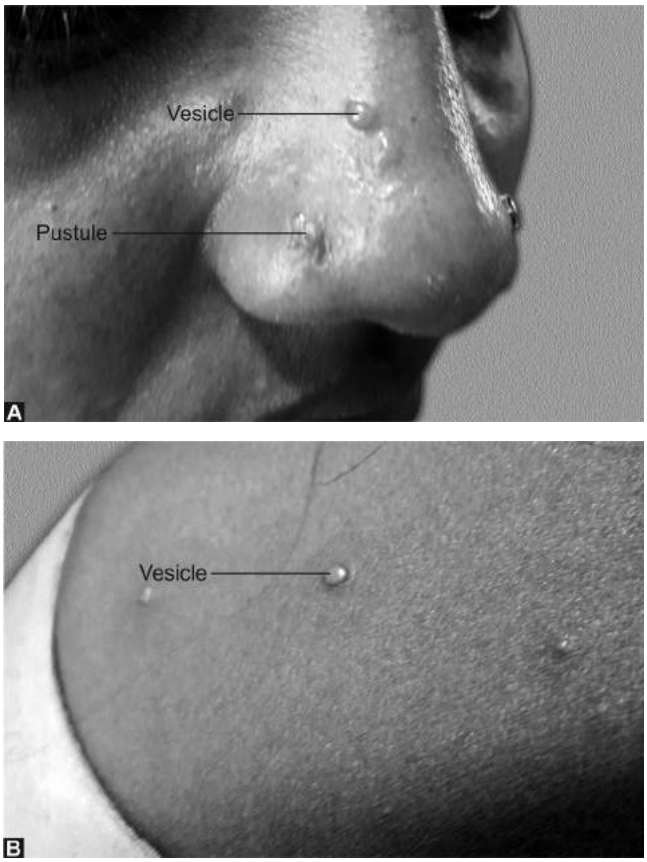
  Associated features—Fever, chill with difficulty in thermoregulation, lymphadenopathy.
- **Toxic epidermal necrolysis** (Drugs, infection, neoplasm and graft-vs-host disease)—Diffuse erythema or target-like lesion progressing to bullae with sloughing and necrosis of entire epidermis. Nikolsky's sign present. Common in children, HIV infection, graft-vs-host disease.

  Dehydration and sepsis due to lack of skin integrity, mortality 25%.

VESICULOBULLOUS ERUPTION WITH FEVER

- **Varicella** (chickenpox) caused by varicella zoster virus)—Macules (2–3 mm)—evolving into papule then vesicles (sometimes umbilicated) dew drop on rose petal appearance as it have an erythematous background). Then quickly transform into pastules and crusting.
  Lesions appearing in crops may involve trunk scalp, mouth and intensely pruritic.
  Affects predominantly children but 10% patients are adults. Common in late winter and spring.
- **Variola** (variola major virus)—Red macule on tongue, palate evolving to papules and vesicles. Skin macule evolving to papules then transform into vesicles then pustules over 1 week with subsequent crusting. Initially appear on face and spread centrifugally from trunk to extremities.
  - Skin lesion in any given area are at some stage of development.
  - There is a prominent distribution of lesions on face and extremities including palm and sole as opposed to prominent rash on trunk in varicella.

  Associated features—Fever, headache, backache, myalgias, vomiting.



Figs 106.1A and B: Vesical and pustula at different stages of chickenpox

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  HSV—Extensive, progressive mucocutaneous lesion.
  HSV lesion may disseminate in eczematous skin—called eczema herpeticum.
  HSV visceral (liver) dissemination may occur with only limited skin diseases.
  Associated with immunocompromised individual and eczema.
- **Rickettsial pox** (*Rickettsia akari*)—
  Eschar found at the site of tick bite, generalized rash involving face, trunk and extremities including palm and sole.
  Seen in Urban setting—Transmitted by mouse bite.
  Associated features—Headache, myalgias, regional adenopathy.
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  Indurated plaque evolving into hemorrhagic bullae or pustule that sloughs resulting in eschar formation with erythematous halo most common in axilla, groin, perianal region.
  Associated features—Sepsis, usually affects neutropenic patient.
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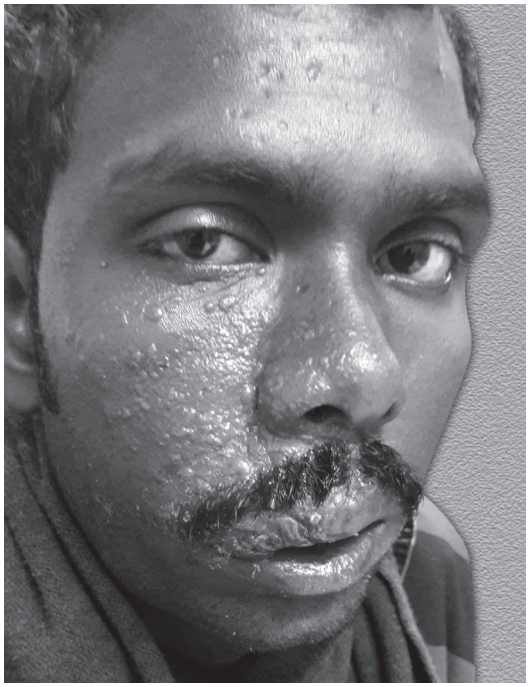

Fig. 106.2: **Herpes zoster** involving maxillary division of trigeminal nerve

URTICARIAL VASCULITIS

Serum sickness often due to infection like HEP-B , enteroviral toxin, parasitic. Infestation drugs like—Penicillin, sulfosalicylate and connective tissue disease.

Erythematous circumscribed areas of edema, indurated, pruritic or purpuric lesion lasting up to five days.

Associated features—Lymphadenopathy, myalgia and arthralgias.

It occurs 8–14 days after antigen exposure in non-sensitized individual but may occur within 36 hours in sensitized individual.

NODULAR ERUPTION WITH FEVER

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  Associated with immunocompromised host, HIV, alcoholics.
- **Erythema nodosum**—Infection with streptococcal, fungal, mycobacterial, yersinial infection. Drugs (sulfar, penicillin, contraceptive, sarcoidosis, idiopathic) can cause this type of lesion.

  Large violaceous, nonulcerative subcutaneous nodule, exquisitely tender, usually on legs but may be also on upper extremity.

  More common in 15–30 years of age.

  A common associated feature—Arthralgias in 50% cases.
- **Sweet syndrome** (acute, febrile neutrophilic dermatosis)—Yersinial infection, lymphoproliferative disorder, idiopathic).

  Tender, red or blue edematous nodule, giving impression of vesiculation usually on face, neck, upper extremity.

  When on lower extremity mimic the appearance of erythema nodosum.

  Common in women 30–60 years of age.

  20% cases are associated with malignancy.

  Associated features—Headache, arthralgias, leukocytosis.

PURPURIC ERUPTION WITH FEVER

- Rocky mountain spotted fever.
- Rat-bite fever.
- Endocarditis.
- Epidemic typhus.
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- Acute meningococcemia.
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- Disseminated gonococcal infection.
- Enteroviral petechial rash.
- Viral hemorrhagic fever.
- Thrombotic thrombocytopenic purpura or hemo- lytic uremic syndrome.
- Cutaneous small vessel vasculitis.
  - **Purpura fulminans** (Severe DIC)—Large ecchymoses with sharply irregular-shaped evolving in to hemorrhagic bullae and black necrotic lesion. Associated with *N. meningitidis*, malignancy, or massive trauma, after splenectomy.
  - **Enteroviral petechial rash** (Echovirus-9 or Coxsackievirus A9)—Disseminated petechial lesion may be maculopapular, vesicular, urticarial. Associated with pharyngitis, headache, aseptic meningitis.
  - **Viral hemorrhagic fever** (Arbo/arenavirus)—Petechial rash. History of travel to or resident of an endemic zone. Associated features—fever, shock, hemorrhage from mucosa or GI tract.
  - **Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome**—Etiology—*Escherichia coli* 0.157; H7 (shiga toxin) Petechial rash.

    Individual with *E. coli* 0157—H7 gastroenteritis are usually children. It can also be seen in HIV infection, autoimmune diseases, pregnancy and postpartum lady.

    Fever not always present, hemolytic anemia, thrombocytopenia, renal dysfunction, neurologic abnormality are the associated features. Coagulation study are normal.
  - **Cutaneous small vessel vasculitis** (Leukocytoclastic vasculitis): Etiology—Group A streptococcus infection, viral hepatitis, drugs, chemical, food allergen and idiopathic.

    Clinical features—Palpable purpuric lesion appearing in crops on legs or other dependent areas may become vesicular or ulcerative usually resolve over 1 month.

    Associated features—Connective tissue disease or cryoglobulinemia, malignancy, Henoch-Schönlein purpura more common in children.

    Fever, myalgias, arthralgias, systemic vasculitis with involvement of kidney, joint and GI tract seen in HSP.

ERUPTION WITH ULCER AND/OR ESCHARS WITH FEVER

- Scrub typhus
- Rickettsial spotted fever

- Rat-bite fever
- Rickettsial pox
- Ecthyma gangrenosum
- Tularemia—Causative agent *Francisella tularensis*
- Anthrax—Bacillus anthrax.
  Various types of lesion may appear.
  - Ulceroglandular form—Erythema, tender papule evolve into necrotic tender ulcer with raised boarder in 1/3rd cases.
  - Other types of lesions are maculopapular, vesiculopapular, acniform, lesion urticarial, erythema nodosum, erythema multiforme. Due to exposure to ticks, biting flies or infected animal.

  Associated features—headeche, fever, lymphadenopathy.
- **Anthrax** (Bacillus anthrax)—Pruritic papule, enlarging and evolving into 1–3 cm painless ulcer surrounded by vesicle, and then developing into a central eschar with edema.

  It is Due to exposure to infected animal or animal product with spore of anthrax.

  Associated features—Lymphadenopathy and headache.

EXERCISE

Write short note on

1. Approach to a patient of fever with rash.

Chapter 107

Management of *Helicobacter pylori* Infection

WHOM TO BE TREATED FOR *H. PYLORI* ERADICATION

1. In endemic areas (all 3rd world countries)—
   a. All GERD patient.
   b. Uncomplicated peptic ulcer disease.
   c. Nonspecific dyspepsia.

   } They should be tested for *H. pylori* and if positive treat for eradication of *H. pylori*
2. All complicated peptic ulcer disease like bleeding peptic ulcer or perforation must be treated.

TESTS FOR PRESENCE OF H. *PYLORI*

1. Serology—Presence of antibody against *H. pylori* in blood is nondiagnostic because once positive always positive throughout the life.
2. Stool for *H. pylori* antigen— Most widely used test→ highly sensitive and specific.
3. Urease breath test with C_{14}—Can be done very quickly.
4. *Endoscopy with rapid urease test (RUT).*
5. *Endoscopy with biopsy and H/E stain: Gold standard test for detection of H. pylori.*

Before any test other than serology–

a. Antibiotic should stopped for 2 weeks.
b. PPI should be stopped for 4 weeks.

TREATMENT OF *H. PYLORI*

1. Triple regimen (OCA)/OCM
   O—Omeprazole—40 mg bd × 4 week → od × 2 months
   C—Clarithromycin (500) – bd
   A—Amoxicillin (500)—tds } For initial 2 weeks
   or
   O—Omeprazole 40 mg bd × 2 week
   C— Clarithromycin 500 mg bd × 2 week
   M— Metronidazole 400 mg tds × 2 week
2. Sequestial regimen
   Clarithromycin 500 mg bd for one week
   ↓ followed by
   Amoxicillin (500—1 capsule tds × 1 week
   } Omeprazole 40 mg bd × 2 weeks
3. Quadriple regimen (OBTM)
   O—Omeprazole (40 mg) bd × 2 weeks
   B—Bismuth 250 mg bd
   T—Tetracycline (500) ods
   M—Metronidazole (400) tds } × 3 weeks

   Although 70% *H. pylori* is resistant to metronidazole but it is till used in combination therapy.

EXERCISE

Write short notes on

1. Management of *Helicobacter pylori* infection.

Chapter 108

Human Immunodeficiency Virus, Acquired Immunodeficiency Syndrome

INTRODUCTION

The etiological agent of acquired immune deficiency syndrome (AIDS) is a retrovirus designated as human immune dificiency virus (HIV) the CD4+T lymphocyte is the primary target of HIV virus because of the affinity of the virus for CD4 surface protein. The CD4+T lymphocyte coordinate all immunologic function result in a progressive impairment of immune response. Studies of the natural history of HIV infection have documented a wide spectrum of disease manifestation ranging from asymptomatic infection to life-threatening condition characterized by severe immunodeficiency. Serious opportunistic infection and cancer. Studies have shown a strong association between life-threatening opportunistic infection and the absolute number or percentage of CD4+T lymphocyte. Measure of CD4+T lymphocyte are used to guide clinical and theraputic management of HIV infected person. Antimicrobial prophylaxis and antiretroviral therapy have been shown to be most effective with certain level of immune dysfunction. As a result antiretroviral therapy should be considered for all person with CD4+T lymphocyte count less then 200/μL.

Acquired immunodeficiency syndrome is casued by human immunodeficiency virus (HIV-I) infection.

A similar but less aggressive illness is caused by HIV-2 which is restricted to Western Africa.

By genomic study it has been confirmed that both virus originated from Simian monkey. Immunodeficiency virus invaded humans in early 1930.

Immunodeficiency is a consequence of continuous high level HIV replication leading to virus and immune- mediated destruction of CD_4 lymphocyte, a key effector in immune system.

MODE OF TRANSMISSION

HIV is present in blood, semen and other body fluids like breast milk, saliva. Exposure to infected fluid leads to a risk of acquiring infection which is dependent on:

- The integrity of the exposed site
- The type and volume of body fluid
- The viral load of the infected fluid.

The major mode of transmission are (in our country):

- **Sexual contact** >85%.
- **Parenteral transmission**
  - Blood or blood product recipient
  - Injection drug abuser
  - Occupational injury.
- **Vertical transmission from mother-to-child**.

DIAGNOSIS

- ELISA antibody testing using immunodominant protein gp-160, gp-120, p-24 p-17/18 is the initial screening test or detection of HIV.
- False-positive results are exceedingly rare and all positive results must be confirmed by using different

Table 108.1: Revised classification for HIV infection and AIDS—(CDC 1993)

Depending on the CD4+ lymphocyte count the disease is sub- divided into:	Clinical categories of HIV infection depending on the prescence of associated condition:
Category I— CD4+T lymphocyte >500/μL	**Category A**: Depending on the presence of one or more condition—(a) A symptomatic infection, (b) acute HIV syndrome and (c) Persistent generalized lymphadenopathy
Category II — CD4+T lymphocyte 200–499/μL	**Category B**: Consist of a symptomatic condition of an HIV infected person indicative of defect in cell mediated immunity
Category III CD4+T lymphocyte <200/μL	**Category C**: It consist of development of specific opportunistic infection or tumor in HIV infective person. This condition is called AIDS defining illness

commercial kit and Western blot technique. False-negative results are also rare but may occur with HIV-2 infection.

BASIC INVESTIGATIONS

These tests to be done in all HIVs infected person:

- History and physical examination
- Blood biochemistry and hematology
- Bilirubin, SGOT and SGPT
- FBS and lipid profile
- CD_4 count
- Blood HIV RNA level
- HIV resistance testing
- HLA-B5701 screening
- VDRL
- Minimental score
- Serology for HAV, HBV, HCV.

SPECIAL INVESTIGATIONS

- For patients whose CD_4 count is <200
  - Chest X-ray
  - Stool for OPC
  - HCV—RNA
  - Cryptococcal antigen.
- For patient whose CD_4 count is <100
  - Dilated fundoscopy
  - ECG
  - CMV antigen by PCR
  - Blood culture for mycobacteria.

CATEGORY-A DISEASE

- Asymptomatic infection
- Acute HIV syndrome
- Persistent generalized lymphadenopathy.

Asymptomatic Infection

Asymptomatic infection persists for a variable period (6–12 weeks) during which the infected individual remains well and no external evidence of disease is present except persistent generalized lymphadenopathy (>2 extrainguinal sites).

Acute HIV Syndrome (Acute Seroconversion)

Approximately 50–70% of individuals with HIVs infection experience an acute clinical syndrome about 6–12 weeks after acquiring primary infection which persists for 3–6 weeks which is called acute HIV syndrome.

Varying degrees of clinical severity have been reported but there is no correlation between the severity of symptoms and subsequent course of the disease.

At this stage, antibody against HIV (detected by ELISA and Western blot) appear in the patients blood.

Typical clinical findings are as follows:

- **General features**
  - Fever (80%)
  - Pharyngitis
  - Lymphadenopathy (70%)
  - Headache/retroorbital pain (40%)
  - Arthralgia/myalgia (50%)
  - Lethargy/malaise
  - Anorexia/weight loss
  - Nausea/vomiting/diarrhea.
- **Neurologic features**
  - Encephalitis
  - Meningitis
  - Myelopathy
  - Peripheral neuropathy.
- **Dermatologic features**
  - Erythematous maculopapular rash over trunk (60%).
  - Mucocutaneous ulceration.

They occur along with a burst of plasma viremia. The plasma HIV RNA level is usually $>10^6$/mL with CD_4 count drops to 300–400/mL rarely below 200/mL. Several symptoms of acute HIV syndrome, e.g. fever, skin rash, pharyngitis, myalgia occur less frequently in those infected by intravenous route versus those acquired by sexual contact.

Symptoms usually persist for one to several weeks and gradually subside as immune-response to HIV develops and the levels of plasma viremia decrease to less than 10^4/cmm and CD_4 count rises to near normal level. The syndrome is typically of acute viral syndrome and has been linked to acute infectious mononucleosis. Approximately 10% of patients manifest a fulminant course of immunologic and clinical deterioration following acute HIV syndrome.

Persistent Generalized Lymphadenopathy (PGL)

In most patients primary infection with or without acute HIV syndrome is followed by period of clinical latency.

At this stage bulk of virus replication takes place within the follicular dendritic cell of lymphoid tissue. There is sustained viremia with a steady decline in CD_4 count usually at the rate of 50–150 cells/year. No clinical sign except persistent generalized lymphadenopathy (> 2 extrainguinal site) is detected.

CATEGORY-B DISEASE

Mildly Symptomatic Disease

Category 'B' diseases include minimally symptomatic constitutional disease—It develops in majority of patients, indicating some impairment of cellular immune system. These diseases are called **AIDS-related complex**. But by definition these are not AIDS-**defining conditions**. The median interval from primary infection to the development

of symptoms is around 7–10 years. The list of diseases are given below:

- Bacillary angiomatosis.
- Bacterial meningitis, sepsis, endocarditis.
- Candidiasis of
  - Oropharyngeal mucosa (thrush)
  - Vulvovaginal area persistent and poorly responsive to therapy.
- Cervical dysplasia (of moderate/severe grade), cervical carcinoma in situ.
- Constitutional symptoms
  - Fever >385°C
  - Diarrhea >1 month duration
  - Weight loss >10% of body weight.
- *Herpes zoster* >two episodes/two dermatomes.
- ITP (idiopathic thrombocytopenic purpura).
- Listeriosis.
- Oral hairy leukoplakia.
- Pelvic inflammatory diseases (PID) with T-O mass (Tubo-ovarian mass).
- Peripheral neuropathy.

CATEGORY-C DISEASE (AIDS DEFINING ILLNESS)

AIDS (Acquired Immunodeficiency Syndrome)

AIDS is defined by development of **specified opportunistic infections or tumors in an HIV-infected patient**.

When the number of CD_4 cells falls below a certain level the patient is at high risk of developing a variety of specific opportunistic diseases particularly infection and neoplasm that are called AIDS-defining illness.

- Category 'C' include the following disease (AIDS-defining condition)
  - Candidiasis of bronchial, tracheal, lung, esophageal mucosa.
  - Invasive cervical cancer.
  - Coccidioidomycosis—Disseminated or extrapulmonary.
  - Cryptococcosis—Extrapulmonary.
  - Cryptosporidiosis >1 month duration.
  - CMV disease
    - CMV retinitis with loss of vision.
    - CMV diseases other than liver, spleen and nodes.
  - HIV—Encephalopathy.
  - Herpes simplex ulcer (chronic >1 month), bronchitis, pneumonia.
  - Histoplasmosis—Extrapulmonary or disseminated.
  - Isosporiasis of intestine >1 month.
  - Kaposi's sarcoma.
  - Primary CNS lymphoma (non-Hodgkin).
  - MAI (*Mycobacterium avium intracellulare*).
  - Burkitt's lymphoma.
  - Lymphoma-Immunoblastic.
  - Miliary or disseminated tuberculosis.
  - Pneumocystis carinii pneumonia.
  - Recurrent pneumonia.
  - Progressive multifocal leukoencephalopathy.
  - Salmonella septicemia (nontyphi).
  - Toxoplasma of brain.
  - Wasting syndrome due to HIV (>10% body weight loss).

CORRELATION OF CD4 COUNT AND HIV-RELATED DISEASE

Diseases common with CD_4 >500 cell/ mm^3

- Acute primary infection
- Progressive generalized lymphadenopathy (PGL)
- Recurrent vaginal candidiasis.

Diseases common with CD_4 200–500 cell /mm^3

- Pulmonary tuberculosis
- Oropharyngeal candidiasis
- Salmonellosis
- *Herpes zoster*
- Oral hairy leukoplakia
- ITP
- Kaposi's sarcoma
- CIN-II and III (cervical intraepithelial neoplasia)
- Lymphoid interstitial pneumonia.

Diseases common with CD_4 <200 cell /mm^3

- Pneumocystis carinii pneumonia
- Cryptosporidium infection
- Microsporidium infection
- Candidiasis of oropharyngeal mucosa
- Miliary/extrapulmonary tuberculosis
- Mucocutaneous herpes (both simplex and zoster)
- HIV-associated wasting
- Peripherial neuropathy.

Diseases Common with CD_4 <100 cell /mm^3

- Cerebral toxoplasma
- Cryptococcal meningitis
- Primary CNS lymphoma
- HIV-associated dementia
- Progressive multifocal leukoencephalopathy
- Non-Hodgkin lymphoma.

Diseases common with CD_4 <50 cell/mm^3

- CMV retinitis
- Disseminated *Myocobacterium avium intracellulare*
- GI disease due to CMV.

BRIEF SYSTEMWISE ACCOUNT OF HIV-RELATED DISEASES

HIV-related Skin Disease

- Early HIV

  - Infectious disease
    - Herpes simplex and zoster
    - HPV—infection
    - Impetigo
    - Scabies
    - Dermatophytes.
  - Others—(noninfectious)
    - Itchy folliculitis
    - Xeroderma
    - Pruritus
    - Seborrheic dermatitis
    - Psoriasis
    - Acne.
- Late HIV
  - Kaposi's sarcoma
  - Chronic mucocutaneous herpes simplex
  - Molluscum contagiosum.

HIV-RELATED GASTROINTESTINAL DISEASES

- **Esophagus**—Candidiasis, Herpes simplex, CMV, Aphthous ulcers and Kaposi's sarcoma.
- **Small bowel**—Cryptosporidium, microsporidium giardia, disseminated mycobacterium avium intracellulare and CMV.
- **Biliary tract**—Cryptosporidium and microsporidium CMV.
- Liver—HBV, HCV, CMV and drug toxicity.
- Large bowel—Salmonella, CMV, campylobacter and *Clostridium difficile*.

HIV-RELATED PULMONARY DISEASES

X-ray Changes

- Diffuse infiltrate—TB, PCP, Kaposi's sarcoma, NHL, atypical bacterial pneumonia and lymphoid interstitial pneumonia.
- Nodule/ focal consolidation—TB, NHL, cryptococcus, bacterial pneumonia and Kaposi's sarcoma.
- Hilar lymphadenopathy—TB, NHL, cryptococcus, Kaposi's sarcoma and histoplasmosis.
- Pleural effusion—TB, bacterial pneumonia, cavitary lymphoma and Kaposi's sarcoma.

HIV-RELATED DISEASES OF CNS

- **SOL**—Toxoplasma, primary lymphoma of brain, tuberculoma of brain, progressive multifocal leukoencephalopathy.
- **Encephalopathy**—HIV, CMV, VZV and HSV.
- **Meningitis**—HIV, TB and cryptococcus.
- **Spastic paraparesis**—HIV vacuolar myelopathy and transverse myelitis (VZV, HSV, HTLV-1).
- **Nerve root and peripheral neuritis**—CMV, non-Hodgkin lymphoma, HIV, AIDP and CIDP.
  Mononeuritis multiplex and distal symmetric polyneuropathy.
  Peripheral neuropathy may be due to drugs—Stavudine, zalcitabine and didanosine
- **Retinitis**—CMV, HIV and toxoplasma.

NEUROLOGICAL DISEASES WITH HIV

- Opportunistic infection
  - Toxoplasma
  - Cryptococcus
  - Cytomegalovirus
  - Syphilis
  - *Mycobacterium tuberculosis*
  - PML
  - HTLV-1.
- Neoplasm
  - Primary CNS lymphoma
  - Kaposi's sarcoma.
- Due to HIV infection
  - Aseptic meningitis
  - HIV encephalopathy
  - AIDS dementia complex
  - HIV myelopathy
  - Pure sensory ataxia
  - Paresthesia.
- Peripheral neuropathy
  - AIDP
  - CIDP
  - Mononeuritis multiplex
  - Polyneuropathy.

BRIEF ACCOUNT OF THE IMPORTANT OPPORTUNISTIC INFECTIONS

- **Tuberculosis**—Clinical picture of PTB with CD_4 count >350 cell/mm^3—Gradual onset fever, weight loss, cough upper lobe infiltrate and cavitary lesion. Leison with advanced AIDS have an atypical presentation like diffuse pulmonary lesion hilar lymphadenopathy and positive blood culture but **absence of cavitary lesion**.
  Treated by INH, RIF, PZA, ETB for 9 month (with usual dose).
- **Pneumocystis carinii pneumonia (PCP)**—Usually have CD_4 count <200 cell/mm^3, clinically charac- terized by nonproductive cough of gradual outset, dyspnea, fatigue and fever.
  Chest X-ray—30% have normal chest X-ray early in the course.
  Others have diffuse reticulonodular pattern predominantly in the perihilar region.
  Definitive diagnosis is made by sputum microscopy by silver methramine stain.
  Treatment (TMP/SMX), 15–20 mg/kg/day oral or IV in 3–4 divided dose × 21 days.

Table 108.2: Primary or secondary prophylaxis for prevention of opportunistic infection

Diseases	Indications	Drugs
1. *Pneumocystis carinii*	i. CD_4 <200 ii. Oropharyngeal candidiasis iii. PUO >2 weeks iv. Prior documented disease	TMP-SMX—1 ds tab daily Alternatively dapsone 200 mg + pyrimethamine 75 mg + leucovorin 25 mg/weekly oral
2. *Mycobacterium tuberculosis*	i. Skin test >5 mm induration ii. Contact with active TB iii. Prior positive test without treatment	a. INH sensitive: INH 300 mg + pyridoxin 50 mg daily × 9 months b. INH resistance: Rifabutin 300 mg/day × 4 months or rifampicin 600 mg/day × 4 months
3. *Toxoplasma gondii*	i. IgG antibody positive ii. CD_4 <100/cmm	TMP-SMX—1 ds tab/day or Dapsone 200 mg/weekly + pyrimethamine 50 mg/weekly + leucovorin 25 mg/ weekly
4. *Vericella zoster*	Exposure to chickenpox with no history of immunization	Varicella zoster immunoglobulin 6.25 mL IM within 96 hours/acyclovir 800 mg 5 times/ day × 5 days (Oral)
5. *Cryptococcus neoformans*	Prior documented disease	Fluconazole 200 mg/day Itraconazole 200 mg/day oral
6. *Histoplasma capsulatum*	Do	Itraconazole 200 mg/12 hourly. Fluconazole 800 mg/ day
7. *Coccidioides immites*	Do	Fluconazole 400 mg/day
8. Salmonella species	Prior bacteremia	Ciprofloxacin 500 mg/bid
9. Cytomegalo virus	Prior endorgan disease when CD_4 count below 100	Valganciclovir 900 mg bid oral or Ganciclovir implant
10. Hep-B		3 doses of vaccine
11. Hep-A		2 doses of vaccine
12. Influenza		Inactivated trivalent influenza vaccine one dose yearly
13. *Streptococcus pneumoniae*		Pneumococcal vaccine 0.5 mL IM × one dose and reimmunized when CD_4 >200
14. MAC	IgG antibody with CD_4 count <50	Azithromycin 1200 mg/weekly oral Clarithromycin 500 mg/bid oral

Corticosteroid—(whose PaO_2 <70 mmHg or $PaCO_2$ >35 mmHg) 40 mg twice daily × 5 days; then 40 mg daily × 5 days then 20 mg daily for 11 days.

The treatment may have to be continued till CD_4 count is persistently >200/cmm.

- **CNS toxoplasmosis**— (only when CD_4 <100/cmm) clinical features—Fever, headache, seizure, altered thought process.

  Diagnosis is established by
  - Serology.
  - CT/MRI—Multiple ring enhancing lesion (the most common cause of ring enhancing lesion in brain in AIDS patient).

  Treatment—Pyrimethamine and sulfadiazine. Pyrimethamine 100–200 mg loading dose then 50–100 mg/day. Sulfadiazine—1.5–2 g qid + leucovorin 15–20 mg qid/ Clindamycin 600–900 mg qid/ Azithromycin 1200 mg qd/ Clarithromycin 1.0 g bid/Atovaquone 750 mg bid.
- **Cryptococcal meningitis**—(when CD_4 <100/mm^3) Clinical presentation is subacute meningoencephalitis very similar to that of toxoplasma encephalitis.

Less than 25% patients have neck rigidity and photophobia.

Usually presents with fever, nausea, vomiting, headache, loss of memory and altered mental status personality changes. A high initial CSF pressure >250 mmHg is associated with increased focal signs and decreased survival.

Diagnosis —(a) Positive serum cryptococcal antigen, (b) Identification and isolation of cryptococcal neoformans from CSF by India ink examination. Treatment—Amphotericin B 1 mg/kg/day IV and flucytosine 100 mg/kg/day oral × 14 days followed by fluconazole 400 mg/day × 10 weeks followed by low dose fluconazole 200 mg/day until CD_4 >200/cm for 6 months with HAART.

Fluconazole can be initial therapy only in persons with normal mental status. Management of raised ICT is essential. Repeated lumbar puncture should be performed to keep CSF pressure <200 mmHg.

- **MAC (disseminated mycobacterium avium complex)**— (Usually with CD_4 <50 cell/cmm) clinical features—Vague constitutional symptoms fever, night

sweats, fatigue, weight loss, abdominal pain diarrhea.
Diagnosis—Blood culture.
Treatment—Clarithromycin 500 mg bid + ethambutol 15 mg/kg/day +/– rifabutin 300 mg/day or ciprofloxacin 500 mg tid.

- **Cytomegalovirus**—(Usually with CD_4 < 50 cell /cmm) Visual symptoms are floaters, flashing of light, visual field defect.
  Diagnosis—Characteristic finding in ophthalmoscopy
  Treatment—Prompt treatment is essential to minimize visual loss.
  Ganciclovir 5 mg/kg IV bid × 2–3 weeks, then 5–6 mg/kg IV.
  Foscarnet 60 mg/kg/8 hourly IV × 2–3 weeks. Then 90–120 mg/kg/day.
  Intraocular ganciclovir pellet + ganciclovir 1000 mg oral/8 hourly.
  Cytomegalovirus can also affect upper and lower GI tract and CNS.
  Intravitreal implantation of Fomivirsen.

TREATMENT OF HIV/AIDS

The aims of HIV treatment are
- Reduce the viral load.
- Improve the CD_4 count <200/ cmm thereby preventing opportunistic infection.
- Reduce vertical transmission.

Management of HIV includes
- Prevention of opportunistic infection (discussed early).
- Treatment of HIV virus.

CHARACTERISTICS OF IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

- It is frequently seen associated with tuberculosis.
- There is paradoxical worsening of clinical condition following initiation of antiretroviral therapy.
- Sign, symptom appear within 2 weeks to 2 years after initiation of ART and include prolong fever, lymphadenitis, uveitis, pulmonary infiltrate, raised ICT sarcoidosis and Grave's disease and is due to type IV hypersensitivity reaction and reflex immediate improvement in immune function that happen when HIV RNA level drops.
- It is seen weeks to months following initiation of antiretroviral therapy.
- It is most commonly encountered when CD4 >50/cmm and experience a precipitous drop in viral load.
- It can be fatal.

To avoid IRIS start glucocorticoids to blunt the inflammatory component.

TREATMENT OF HIV VIRUS

Drugs

- Nucleoside reverse transcriptase inhibitors (NRTIs)
  - Zidovudine (ZDV)—300 mg bid.
  - Lamivudine (3TC)—150 mg bid.
  - Stavudine (d4t)— more than >60 kg–40 mg bid. Less than < 60 kg–30 mg bid.
  - Zalcitabine (ddc)—0.75 mg tid
  - Didanosine (ddi)—<60 kg–125 mg bid
    > 60 kg–200 mg bid
  - Abacavir—300 bid
  - Tenofovir—300 mg qd
  - Emtricitabine—200 mg qd.
- Nonnucleoside reverse transcriptase inhibitors (NNRTIs)—
  - Nevirapine—200 mg once daily for 2 weeks then 200 mg bid.
  - Efavirenz—600 mg 8 ghs (c) Delaviridine—400 mg tid (d) Etravirine—200 mg bid (e) Rilpivirine—25 mg qd.
- Protease inhibitor (PI)
  - Indinavir
  - Ritonavir
  - Saquinavir
  - Nelfinavir—1200 mg bid
  - Lopinavir
  - Aprenavir
  - Fosamprenavir
  - Atazanavir
  - Tipranavir
  - Durunavir.

Pharmacological boosting (Table 108.3) *Low dose ritonavir significantly increases the trough level of other protease inhibitors and combination of ritonavir with other protease are being used in the clinical practice (pharmacokinetic booster).*

- Others—
  - Fusion inhibitors : Enfuvirtide—90 mg SC bid entry inhibitors : Maraviroc—150–600 mg bid.
  - Integrase inhibitors—Raltegravir—400 mg bid Elvitegravir—150 mg bid

Antiretroviral drugs are always given in combination *to prevent emergence of resistant. Different combination regimen are follows. They are called HAART* (highly active antiretroviral therapy).

The treatment regimen are
- 2 NRTI + PI
- 2 NRTI + NNRTI
- 2 NRTI + 2 PI
- 3 NRTI (ZDV + 3TC + abacavir).

Indications to start HAART
- Seroconversion reaction: Recommendation of HAART is controversial.

Table 108.3: Ritonavir boosted PI Regimen

Ritonavir	Other PI	Comments
100 mg bid +	Lopinavir 400 mg bid	Excellent potency
400 mg bid +	Saquinavir 400 mg bid	Highly effective combination but intolerance to ritonavir is common
100 mg bid +	Saquinavir 1000 mg qd	Possible once daily combination
100 mg bid +	Indinavir 800 mg bid	Very potent, indinavir toxicity at this dose
400 mg bid +	Indinavir 800 mg bid	Very potent regimen but intolerance to ritonavir
100 mg bid +	Amprenavir 600 mg bid	Preliminary data suggest once daily dose is also effective
200 mg qd +	Amprenavir 1200 qd	Very potent regimen with reduced Amprenavir pill burden
100 mg bid	Fosaprenavir 700 mg bid	
100 mg bid	Atazanavir 300 mg qd	
200 mg bid	Tipranavir 500 mg bid	
100 mg bid	Durunavir 600 mg bid	

- **When CD_4 count >350/cmm. HAART is recommended provided viral load > 55000/cmm** but if viral load < 55000/cmm. HAART is not recommended—Monitor CD_4 count every 2 monthly.
- **When CD_4 count 200–350/cmm**—Monitor CD_4 count every 2 monthly.
- **When CD_4 <200**—HAART is recommended.

MANAGEMENT OF AIDS ASSOCIATED KAPOSI'S SARCOMA

Optimum HAART.

Single of or Limited Number of Lesion

- Radiation
- Intralesional vincristine
- Cryotherapy.

EXTENSIVE DISEASE

Interferon α if CD4 >150 liposomal daunorubicin. Subsequent therapy—
- Liposomal daunorubicin.
- Paclitaxel.
- Combination chemotherapy with doxorubicin, bleomycin and vinblastine.
- Targated radiation.

POSTEXPOSURE PROPHYLAXIS OF HIV

Combination therapy is now recommended for occupational postexposure prophylaxis (PEP) when the risk is deemed to be significant.

The first dose should be given as soon as possible. Not effective if started 24 hours after exposure.

- Basic regimen (containing two NRTI)—Zidovudine + lamivudine for 4 weeks for routine exposure.
- For high risk exposure and complicated exposure—Basic regimen + indinavir 800 mg tid or nelfinavir (750 mg tid) for 4 weeks.

PREVENTION OF PERINATAL TRANSMISSION

The overall risk of vertical transmission is 25% in untreated patient. The infection occurs:
- During vaginal delivery
- Through breastfeeding.

The transmission rate varies with:
- Maternal viral load
- Antiretroviral therapy during late pregnancy
- Type of delivery (vaginal/cesarean section).

The risk of transmission is <1% if the viral load of the material <50 copies/mL.

Current recommendations are—
- Indentify HIV positive mother by antenatal screening.
- Start HAART during pregnancy from 14th week avoiding efaviranz (have teratogenic potency).
- Careful obstetric management including cesarean section and intravenous zidovudine during labor and delivery.
- For neonate—oral zidovudine therapy 2 mg/kg for 6 weeks.
- Bottle-feeding to the infant born of HIV mother avoiding breastfeeding.

EXERCISE

Write short notes on

1. Acute HIV syndrome.
2. AIDS defining illlness.
3. HIV related skin diseases/GI diseases/pulmonary diseases and CNS diseases.
4. HAART.
5. Postexposure prophylaxis of HIV.

Chapter 109

Tuberculosis

INTRODUCTION

Mycobacterium tuberculosis is most commonly transmitted by droplet nuclei which are aerosolized by coughing, sneezing or speaking.

Other (uncommon/rare) route of transmission are through skin and GI tract.

Patient with cavitary pulmonary disease or a endobronchial or laryngeal tuberculosis produces sputa containing as many as 10^5 AFB/mL.

The tiny droplet dry rapidly, the smallest one may remain suspended in air for several hours and may gain direct access to terminal air passage when inhaled.

The majority of inhaled bacilli are trapped in upper airway and are expelled by ciliated mucosal cell, only <10% reach the alveoli where nonspecifically activated alveolar macrophages ingest the bacilli.

The balance between the bactericidal activity of macrophage and the number and virulence of the bacilli determine the fate of the bacilli following phagocytosis.

The virulence of *M. tuberculosis* confer by the *kat g gene* which encode for *catalase*—a protective enzyme for *M. tuberculosis* against oxidative stress and ***rpov-gene*, the main *sigma factor* which *initiates transcription of several gene*. The defect in this two gene results in loss of virulence of *M. tuberculosis*. In addition to that erp-gene encode a protein required for multiplication also contribute to the virulence**.

Nramp-1 (neutral resistance associated macrophage protein-1) located in chromosome—2q has regulatory role in resistance/susceptibility to mycobacteria in human.

Survival of mycobacteria within the macrophage is associated with *lipo arabino mannan (LAM)* a bacterial cell surface molecule which inhibit intracellular increase of Ca^{++} thus fusion of phagosome—lysosome resulting survival of bacilli within the phagosome.

In the initial stage of host-bacterial interaction, if the bacilli multiply, their growth quickly kill and lyse macrophage. Nonactivated monocyte attracted from the bloodstream to the site by various chemotactic factor relased from the macrophage and ingest the bacilli released from the lysed macrophages.

This initial stages of infection are asymptomatic. After about 4 weeks of infection two additional host response to *M. tuberculosis* develop—

a. Macrophage activating CMI
b. Tissue damaging response.

a. **Macrophage activating response**—A cell-mediated phenomenon resulting in the activation of macrophage that are capable of killing and digesting tubercle bacilli without causing further tissue destruction.

   Large number of activated macrophages accumulate around the site of primary lesion which are then transformed to epithelioid cell and giant cell with necrotic caseous material at the center and the whole thing is called **granuloma or tubercle**.

b. **Tissue damaging response**—A delayed type of hypersensitivity (DTH) reaction to various bacillary antigen, which not only destroys nonactivated macrophages that contain multiplying bacilli but also results in tissue necrosis and caseation.

If the newly developed tissue damaging response is the sole event capable of limiting the bacterial growth within the macrophage, it not only destroys macrophages but also produces early solid necrosis at the center of the tubercle. In spite of that if *M. tuberculosis* can survive its growth is inhibited by low O_2 tension and low pH. At this point, some lesion may heal by fibrosis and calcification.

In minority of cases the macrophage activating response is weak and mycobacterial growth can be inhibited only by intensified DTH which lead to tissue destruction and cavity formation.

The lesion tends to enlarge further and the surrounding tissue is progressively damaged. At the center of the lesion, caseous material liquefies, bronchial wall and blood vessel are invaded and destroyed, the liquefied caseous material containing large number of bacilli are coughed out through bronchus and thereby a cavity is formed.

PRIMARY TUBERCULOSIS

Following formation of subpleural alveolar lesion (known as Ghon's focus) bacilli are rapidly transported to hilar

lymph node and produce hilar lymphadenopathy. Both this two component, *subpleural alveolar lesion and hilar lymphadenopathy and the connecting lymphangitis are jointly called 'primary complex'* which is commonly seen in the mid and lower zone of lung as the inspired air is distributed over this area.

FATE OF PRIMARY COMPLEX

- In 85–90% of cases primary complex heals spontaneously within 1–2 months only the tuberculin skin test becomes positive.
- In 10–15% of cases multiplication of *M. tuberculosis* is not stopped and hilar lymph node enlargement results in—
  - Either pressure effect.
  - Lymphatic spread to pleura, pericardium.
  - Rupture into adjacent bronchus and adjacent pulmonary blood vessel.
- In young child with poor natural (innate) immunity hematogenous dissemination may result in fatal miliary tuberculosis or tuberculous meningitis.

POSTPRIMARY DISEASE ALSO CALLED ADULT TYPE

REACTIVATING OR SECONDARY TUBERCULOSIS

Postprimary disease results from

- Reexposure to smear positive pulmonary tuberculosis (30%).
- Progressive primary disease (30%).
- Reactivation of latent primary complex (40%).

Three common sites of postprimary disease are

- Apical segment of upper lobe
- Posterior segmental of upper lobe
- Superior segment of lower lobe.

The extent of pulmonary disease varies greatly from—Small infiltrate to extensive cavitary disease.

Liquefied necrotic caseous material are ultimately discharged into the airway resulting in satellite lesion that may in turn undergo cavitation.

Massive involvement of pulmonary segment or lobe with coalescence of lesion produce tubercular pneumonia.

Fate of postprimary disease

- Up to 1/3rd of untreated patients sucumb to severe pulmonary disease within months of onset.
- 1/3rd of patients undergo spontaneous remission.
- 1/3rd of patients undergo chronic progressively debilitating course—Individuals with such chronic disease discharge tubercle bacilli into the environment and are the source of infection in the society.

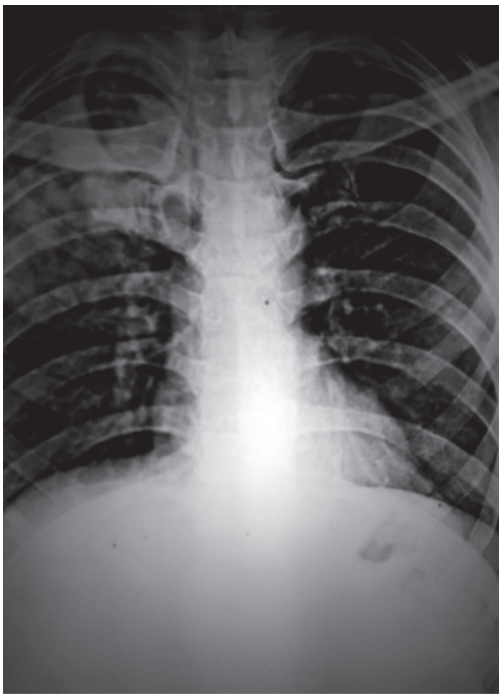


Fig. 109.1: Mass lesion left upper lobe

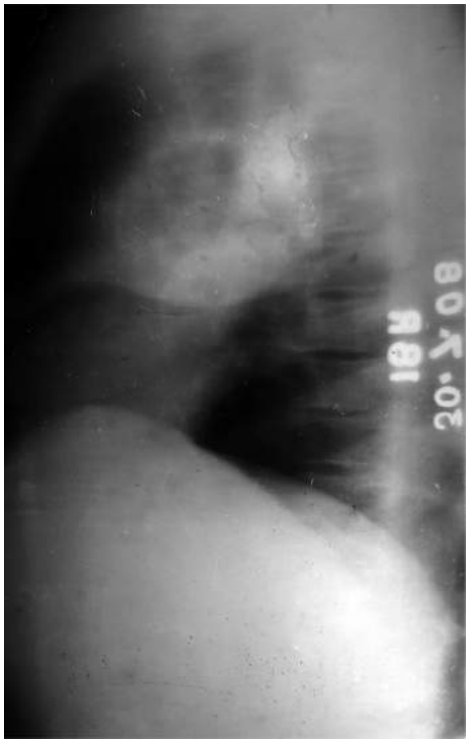


Fig. 109.2: Lung abscess with fluid level in a tubercular cavitary lesion

EARLY SYMPTOMS AND SIGNS OF POSTPRIMARY DISEASE

- **Fever**
- **Night sweat**
- **Weight loss**
- **Anorexia**
- **General malaise**
- **Weakness**
- **Cough** initially nonproductive but subsequently produces purulent sputum.
- **Massive hemoptysis** may result from
  - Erosion of a patent blood vessel in the wall of a cavity.
  - Rupture of a dilated blood vessel in a cavity (*Rasmussen's aneurysm*).
  - From aspergilloma formation in an old cavity.
- Pleuritic chest pain some times develop due to
  - Subpleural parenchymal lesion
  - Muscle strain due to persistent coughing
  - Extensive disease may produce ARDS.

PHYSICAL SIGNS

- **Pallor** due to chronic infection.
- **Clubbing**.
- **Wasting**.
- **Low grade irregular fever**.
- Usually no abnormality detectable on chest examination.
- **Amphoric breath sound** over a large superficial cavity with patent bronchus.
- **Posttussive crepitation**.
- **Rhonchi**—due to partial bronchial obstruction.

INVESTIGATION

- Anemia with leukocytosis due to chronic infection.
- Raised ESR and C-reactive protein.
- Positive tuberculin test.
- Hyponatremia due to SIADH.
- Sputum is positive for AFB both Z–n stain and culture.

EXTRAPULMONARY TUBERCULOSIS

In order of frequency the sites of involvement of extrapulmonary tuberculosis are

- **Lymph node**
- **Pleura**
- **GU tract** (genitourinary tract)
- **Bones and joints**
- **Meninges**
- **Peritoneum**
- **Pericardium**.

However, all organ systems may be affected as a result of hematogenous spread in HIV infected individual.

TUBERCULAR LYMPHADENITIS

It is the most common extrapulmonary tuberculosis usually associated with 25% of postprimary pulmonary tuberculosis.

Causative Agent–*M. Tuberculosis Rarely M. Bovis*

Commonly affected sites are

- Cervical
- Supraclavicular (often called scrofula).

Mode of Presentation

Painless swelling of the gland, lymph node are discreet in the early stage but may be inflamed and may have a fistulous tract draining caseous material to the skin.

Systemic symptoms are usually absent or very minimum in normal individual but may be severe as in HIV-infected individual. Concomitant lung disease may or may not be present.

Laboratory Diagnosis

- FNAC.
- Surgical biopsy.
  AFB is seen in sinear is 50% cases.
  Culture is positive in 70–80% cases of FNAC or surgical biopsy.
  Biopsy specimen. Histologic examination shows granulomatous lesion.

Differential Diagnosis of Lymphadenopathy

- Infectious diseases
- Lymphoma
- Metastatic carcinoma.

PLEURAL TUBERCULOSIS

Involvement is common in primary disease and is due to penetration by tubercle bacilli into pleural space.

SYMPTOMS

- Fever
- Pleuritic chest pain
- Dyspnea.

SIGNS

- Dull on percussion
- Diminished or absent breath sound.
  Chest X-ray is the investigation of choice and 1/3rd cases reveal a parenchymal lesion.
  Thoracocentesis is required to ascertain nature of effusion.

Chest X-ray shows—A homogenous opacity occupying lower part of a hemithorax obliterating costophrenic angle with a concave upper boarder.

PLEURAL FLUID

Appearance—Usually straw colored but at times hemorrhagic. Exudative in nature as evidenced by—

- Protein concentration >50% of that in serum.
- Glucose concentration—low.
- pH <7.2.
- Adenosine deaminase (ADA)—raised.
- WBC 500–2500/ μL. Neutrophil may be predominated in early stage while mononuclear cell are typical later finding, mesothelial cells are rare or absent.
- Smear rarely shows AFB.
- Culture for AFB positive in 1/3rd of cases.
- Needle biopsy of pleura reveals tubercular granuloma and positive culture in 70% cases.

TUBERCULOUS EMPYEMA

It is a less common complication of pulmonary tuberculosis. It usually results from:

- Rupture of a tubercular cavity with delivery of large number of bacilli in to pleural space.
- Bronchopleural fistula from a pulmonary lesion. Chest X-ray shows pyopneumothorax with a horizontal air-fluid level. The effusion is purulent and thick and contains large number of lymphocyte.

TREATMENT

Surgical drainage with wide bore intercostal catheter placed in the dependent part of the hemithorax through the triangle of safety is usually required as an adjunct to chemotherapy for tuberculosis.

COMPLICATIONS

- Pleural fibrosis
- Restrictive lung disease.

GENITOURINARY TUBERCULOSIS

It accounts for 15% of all extrapulmonary diseases. It can affect any region of genitourinary tract. Symptoms depend on the site of involvement.

SYMPTOMS

Common symptoms are

- Frequency
- Dysuria } In case of cystitis and urethritis
- Hematuria—Cystitis and pyelonephritis
- Flank pains—Pyelonephritis.

However, patient may remain asymptomatic and the disease discovered after the destructive lesion of kidney have developed.

Urine analysis and culture—It helps in the diagnosis. Pyuria or hematuria is seen in 90% cases. *Culture negative pyuria (in ordinary media) in acidic urine raises the suspicion of tuberculosis (sterile pyuria).*

Intravenous pyelography and USG—Helps in diagnosis of associated

- Ureteral stricture
- Calcification
- Rarely hydronephrosis and renal damage.

GENITAL TUBERCULOSIS

More common in female than male.
If affects

- Fallopian tube—Produce T-O mass
- Endometrium—Tuberculous endometritis.

SYMPTOMS

- Pelvic pain
- Menstrual abnormality
- Infertility.

DIAGNOSIS

Biopsy and culture of specimen obtained by D and C.
In male it can cause

- Epididymitis
- Orchitis
- Prostatitis.

Half of the patients with genital tract disease have urinary tract disease.

GU tuberculosis responds well to chemotherapy.

SKELETAL TUBERCULOSIS

Responsible for 10% of extrapulmonary tuberculosis.

MODE OF SPREAD

- Reactivation of hematogenous spread
- Spread from adjacent lymph node.

Site of involvement in order of frequency:

- Spine (Pott's disease or tuberculous spondylitis)
- Hip
- Knees.

Upper thoracic spine is involved in children. Lower thoracic and upper lumbar vertebrae are involved in adult.

The infection starts as discitis and then spread along the spinal ligament to involve adjacent anterior vertebral bodies results in *kyphosis or Gibbus*.

A paravertebral cold abscess if forms in the upper dorsal spine may tract to chest wall as a mass. If formed in the lower

thoracic or lumbar spine may present as a swelling above inguinal ligament or as a *psoas abscess*.

DIAGNOSIS

- Needle aspiration for culture and microscopy
- CT/MRI of the spine.

COMPLICATIONS

Paraplegia due to Pott's disease usually due to abscess or compressive lesion of spinal cord.

Paraparesis due to large abscess is a medical emergency and requires surgical drainage.

Tuberculosis of hip presents as—(a) Pain, (b) limping. Tuberculosis of knee presents as—(a) Pain, (b) swelling. If the disease is undiagnosed the joints may be destroyed skeletal TB respond to chemotherapy for 9 months, severe cases may require surgery.

TUBERCULOUS MENINGITIS AND TUBERCULOMA OF BRAIN

TB of CNS accounts for 5% of extrapulmonary cases. It is seen most commonly in young children but may affect adults specially those who are infected with HIV.
It results from:

- Hematogenous spread of primary or postprimary pulmonary disease.
- Rupture of a subependymal tubercle into subarachnoid space.
  Evidence of pulmonary disease is present in chest X-ray in 50% cases.
  Typically the disease evolves over 1–2 months a course longer than that of the bacterial meningitis.

EARLY SYMPTOMS

- Usually chronic headache and mental changes.
- Sometime acutely as confusion, lethargy, altered sensorium with neck rigidity.

COMMON COMPLICATIONS

- Paralysis of cranial nerve, specially ocular nerve.
- Involvement of cerebral arteries may produce focal ischemia causing cerebral infarction.
- Hydrocephalus due to block of CSF passages.

INVESTIGATIONS

- Lumbar puncture and CSF study is the cornerstone of diagnosis.
  - High leukocyte count with a predominance of lymphocyte but in very early stage neutrophil may predominate.
  - Protein—100–200 mg/dL.
  - Glucose—Low glucose content.
    But any of these three parameters may be within normal range.
  - AFB can be demonstrated in 20% by direct smear but in culture it is positive in 80% cases.
  - Adenosine deaminase (ADA) raised in CSF.
- CT/MRI—Abnormal enhancement of basal cistern or ependyma. Rarely hydrocephalus or tuberculoma.

TREATMENT

If untreated it is usually fatal.

- Combination chemotherapy for *M. tuberculosis* for 6–9 months.
- Adjunctive glucocorticoid (dexamethasone 12 mg/day for 4–6 weeks enhances the chance of survival and reduces the neurological complication.
  25% of cases may have residual neurodeficit. Specially if not received adjunctive glucocorticoids.
- Additional measure for treatment of seizure, hydrocephalus or cerebral infarction when present may have to be taken.

TUBERCULOMA

Presents with seizure or focal neurological sign.

CT/MRI

Reveals SOL/contrast-enhanced ring lesion but biopsy is necessary to establish the diagnosis.

DIFFERENTIAL DIAGNOSIS OF TUBERCULOMA

Neurocysticercosis, toxoplasma associated with HIV *cerebral abscess, metastatic deposits*.

GASTROINTESTINAL TUBERCULOSIS

Any part of GI tract may be affected but terminal ileum and cecum are the most common site.

MODE OF SPREAD

- Swallowing of sputum with direct seeding.
- Hematogenous spread.
- Ingestion of unpasteurized milk (although rare nowadays).

CLINICAL FEATURES

- Ascites
- Abdominal pain (at times mimicking appendicitis)
- Diarrhea
- Feature of intestinal obstruction
- Hematochezia
- Palpable mass in the right iliac fossa.

Apart from these fever, weight loss and might sweats are usually presents. There may be abdominal or rectal fistula.

Coexistence of cirrhosis complicates the diagnosis.

DIAGNOSIS

Ascitic fluid must be examined for biochemical, cytological and microbiological evidence of tuberculosis.

- Paracentesis reveals.
  - Exudative fluid—LDH >200 IU
  - High protein content—3 g/dL SAAG <1.1 g
  - Leukocytosis (usually lymphocytosis).
  - Adenosine deaminase level (ADA) raised in ascitic fluid.
- Yield of direct smear and culture for *M. tuberculosis* is relatively low. Culture of large volume of ascitic fluid can yield positive result.
- Peritoneal biopsy or histological examination and culture of specimen obtained intraoperatively or by laparoscopy is the most surest method of diagnosis.

TUBERCULOUS PERICARDITIS

MODE OF SPREAD

- Direct spread from primary focus to the adjacent pericardium.
- Reactivation of a latent focus.
- Rupture of an adjacent lymph node.

MODE OF PRESENTATION

- Acute fever, dull aching retrosternal chest pain and pericardial or pleuropericardial friction rub.
- Subacute unexplained dyspnea, ascites.

  An effusion eventually develops in many cases. Cardiovascular symptoms and signs may ultimately appear. In presence of pericardial effusion on chest X-ray, tuberculosis must be suspected if the patient is coming from high prevalence zone or HIV infected.

DIAGNOSIS

- Echocardiography shows pericardial effusion with thick strand crossing the pericardial space.
- Diagnosis can be facilitated by pericardiocentesis under echocardiographic guidance.

The pericardial fluid must be examined for:

- Biochemical
- Cytological
- Microbiological.

} Evidence of tuberculosis

SPECIAL TEST

- Adenosine deaminase
- INF-γ.

} High level suggests tuberculosis

TREATMENT

If untreated pericardial tuberculosis is usually fatal.

- Combination chemotherapy for 6 months.
- A course of glucocorticoids (prednisone 20–60 mg/day for up to 6 weeks is useful in management of acute cases and prevent the development of complications like—
  - Chronic constrictive pericarditis
  - Pericardial fibrosis
  - Pericardial calcification.

Thus decreasing the mortality.

MILIARY OR DISSEMINATED TUBERCULOSIS

It is due to hematogenous spread of tubercle bacilli. In children it often occurs as a consequence of recent primary infection. In adult it may be due to either recent infection or reactivation of old disseminated foci.

Lesions are yellowish granulomas 1–2 mm in diameter that resemble millet seeds (thus termed as miliary tuberculosis).

CLINICAL FEATURES

Fever, night sweats, anorexia, weakness, weight loss are the general presenting symptoms.

Lungs—Cough, chest pain, dyspnea.

GI tract—Abdominal pain, diarrhea, abdominal mass.

Signs—Hepatomegaly, splenomegaly, lymphadenopathy, ascites and pleural effusion.

Eye examination—Choroid tubercle in 30% cases. Meningismus occurs in 10% cases.

Chest may be normal or with few crepitation and rhonchi.

DIAGNOSIS

A high index of suspicions is necessary for diagnosis of miliary tuberculosis.

CHEST X-RAY

- No abnormality may be evident early in the course and among HIV-infected patients.
- Miliary or reticulonodular pattern (specially in under penetrated film).
- Other radiographic abnormality are large infiltrate, interstitial infiltrate, pleural effusion.

Sputum

Smear is negative in 80% cases.

Blood

- Anemia with leukopenia.
- Neutrophilic leukocytosis.

- Leukemoid reaction.
- Polycythemia.
- DIC—has been reported.
- Abnormal LFT with elevated alkaline phosphatase in severe hepatic involvement.
  - PPD test may be negative up to 50% cases.
  - Bronchoalveolar lavage or tracheobronchial biopsy may be necessary for bacteriological confirmation.
  - Liver biopsy. } may be necessary for demonstration of granuloma
  - Bone marrow biopsy. }

Two rare presentation of miliary tuberculosis are:

1. **Cryptic miliary tuberculosis**: Chronic course characterized by mild intermittent fever, anemia and meningeal involvement preceding death.
2. **Nonreactive miliary tuberculosis**: Rarely occurs due to massive hematogenous dissemination. Pancytopenia is common in this form of disease. Rapidly fatal. At postmortem examination multiple necrotic nongranulomatous lesions are detected.

LESS COMMON EXTRAPULMONARY TUBERCULOSIS

EYE

- Chorioretinitis
- Uveitis
- Panophthalmitis
- Phlyctenular conjunctivitis.

EAR

Tubucular otitis.

SKIN

- Primary infection
- Abscess and chronic ulcers
- Serofuloderma
- Lupus vulgaris
- Miliary lesion
- Erythema nodosum.

ADRENAL TUBERCULOSIS

Presents with signs of adrenal failure.

CONGENITAL TUBERCULOSIS

Transplacental spread or ingestion of contaminated amniotic fluid.

HIV-ASSOCIATED TUBERCULOSIS

Tuberculosis is an important opportunistic infection among HIV-infected persons and documented in 40–60% of all cases of HIV. A person with positive PPD test who acquires HIV infection has a 3–15% annual risk of developing tuberculosis. Presentation of tuberculosis varies with the stages of HIV disease.

- *When CMI is only partially compromised*—Tuberculosis presents as typical like upper lobe infiltrate and cavitation without significant lymph adenopathy or pleural effusion.
- *When CMI is grossly compromised in late stage of HIV*—In thorax the typical pattern of presentation of TB is diffuse intrathoracic lymphadenopathy.

Sputum is less frequently positive for tuberculosis rendering the diagnosis of tuberculosis more difficult.

Extrapulmonary TB is more common in HIV-infected persons. The most common forms are

- Lymphatic tuberculosis
- Disseminated tuberculosis
- Pleural tuberculosis
- Pericardial tuberculosis
- Mycobacteremia
- Meningitis.

Diagnosis of tuberculosis in HIV infected persons is difficult due to

- *Sputum-smear negativity* (up to 40%) in culture positive cases.
- *Lack of typical chest X-ray finding.*
- *Lack of classic granuloma formation* in late stage of HIV disease.
- *Negative result in PPD skin test.*

TREATMENT

First Line Agents

Isoniazid, rifampin, pyrazinamide and ethambutol. The agents are well-absorbed after oral administration with peak serum level at 2–4 hours and nearly complete elimination within 24 hours.

Except ethambutol all these agents are bactericidal (ability to rapidly reduce the number of viable organism and render patient noninfectious) and sterilizer (ability to kill all bacilli and thus sterilize the affected organ measured in terms of the ability to prevent relapse) and low rate of induction of drug resistance.

Second Line Agents

- Injectable—**Streptomycin, kanamycin, amikacin and capreomycin**.
- Oral—**Ethionamide, cycloserine, PAS and fluoroquinolone** like (ofloxacin, levofloxacin, gatifloxacin and moxifloxacin).

Other agents of doubtful efficacy are clofazimine, thiacetazone, amoxycillin/clavulanic acid and linezolid.

Regimen

- *Initial phase (bactericidal phase)*—During this phase majority of the bacilli are killed. Symptoms resolve and patients become noninfectious.
  - Isoniazid—5 mg/kg
  - Rifampin—8–10 mg/kg
  - Pyrazinamide—30 mg/kg
  - Ethambutol—15–20 mg/kg.

  } × 2 months
- *Continuation phase*—It is required to eliminate persisting mycobacteria and prevent relapse.
  - Isoniazid—5 mg/kg.
  - Rifampin—8–10 mg/kg.

  } × 4 months

Treatment may be given either—

- Daily throughout the course or three times weekly throughout the course.
- Initial daily therapy for 2–8 weeks followed by twice weekly.

Treatment Failure

Treatment failure should be suspected when a patient's sputum remains culture positive after 3 months of therapy or AFB-smear remains positive after 5 months of treatment. In the management of such patient add at least two and preferably three new drugs that have never been used previously and to which the bacilli are likely to be susceptible. The patient will continue to take isoniazid and rifampin along with these new agents pending the results of susceptibility test.

Treatment for Relapse

It is wise to begin treatment of all relapse cases (after apparently successful therapy) with all five first line drugs pending the results of susceptibility testing.

Where facilities for culture and drug susceptibility testing are not available a standard regimen is 3 months course of HRZES and a 5 months course of HRE in all cases of relapse and treatment failure.

DRUG-RESISTANT TUBERCULOSIS

DEFINITION

A case of tuberculosis usually pulmonary tuberculosis, excreating bacilli resistant to one or more anti-TB drug.
Resistance may be—

- **Primary resistance**—When the patient has never been treated with any of the ATD in the past, however if there is any doubt regarding this, then the case is to be classified as initial resistance.
- **Secondary or acquired resistance**—When there is a history of previous ATD use, most cases belong to these group.

TREATMENT FAILURE

When a person remains sputum positive after completion of 5 months of any of the regimen or has completed 8 months of retreatment under DOTS scheme. This is usually due to drug resistance.

CHRONIC CASE

It is defined as one who continues to excrete bacilli, despite completion of at least 2 courses of ATD under DOTS scheme.

MDR-TB

When TB bacilli is resistant to at least both of INH and Rifampicin, it is call MDR-TB.

New case—A person who has never been treated with ATD or has received it for less than 1 month.

Old case—A person who has received ATD in the past either completely or incompletely. (After several years of Institution of National Tuberculosis Control Programme in any country) it has been observed that old case represents 10–20% of total TB patient. Of them 20% represent drug resistant strains, 4–10% of these cases are of MDR-TB cases.

PRIMARY VS ACQUIRED RESISTANCE

Rate of primary resistance is lower than that of acquired resistance.

Primary resistance usually involves a single drug while acquired resistance is often MDR-TB.

The level of resistance in primary type is lower than that of acquired type.

In fact prevalence of primary resistance in a community is a reflection of the acquired resistance that existed in it.

PREVENTION OF MDR-TB

New case—Institution of 6 months of ATD under DOTS regimen.

Old case—3 types

- Patient excreting susceptible bacilli.
- Patient excreting bacilli susceptible to refampicin but resistant to INH.
- Patient excreting MDR-TB bacilli.

Those patient who are excreting susceptible bacilli can be successfully treated with ATD for 8 months under DOTS scheme. However, the problem arises with those who remain smear positive despite the completion of 2 courses of ATD of which second one under DOTS SCHEME.

WHEN TO SUSPECT MDR-TB?

- When sensitivity test shows strain resistant to at least INH and rifampicin.

Table 109.1: Dosage schedule of anti-TB-drugs

Drugs	Daily Dose	Thrice Weekly Dose
Isoniazid	5 mg/kg max 300 mg	15 mg/kg max 900 mg
Rifampin	10 mg/kg max 600 mg	10 mg/kg max 600 mg
Pyrazinamide	20–35 mg/kg max 2 G	30–50 mg/kg max 3 G
Ethambutol	15–20 mg/kg	25–30 mg/kg

- When a patient remains smear positive even after receiving retreatment regimen under DOTS.

MANAGEMENT OF MDR-TB

To be done in specialized unit.
Evaluation of patient in respect to
- Which regimen he was taking
- Assess compliance
- Bacteriological, clinical, radiological evaluation
- Reliability of susceptibility testing
- Reliable drug supply.

CRITERIA OF FAILURE OF THE RETREATMENT REGIMEN

- Persistently positive sputum.
- Fall and rise phenomenon.
- Report of drug resistance.
- Radiological deterioration after excluding inter- current pneumonia, pulmonary embolism, cancer, diabetes and HIV.
- Clinical deterioration.

CLASSIFICATIONS OF ATD IN THE TREATMENT MDR-TB

- Highly bactericidal drugs
  - Aminoglycoside
    - Streptomycin
    - Kanamycin
    - Amikacin.
  - Thionamide
    - Ethionamide
    - Prothionamide.
  - Pyrazinamide.
- Low bactericidal drug
  - Fluoroquinolones
    - Ofloxacin
    - Ciprofloxacin.
  - Macrolide
    - Clarithromycin
    - Azithromycin.
- Bacteriostatic drug
  - PAS
  - Cycloserine
  - Ethambutol
  - Thiacetazone.

EXERCISE

Write short notes on
1. MDR-TB.
2. Pathogenesis and treatment of tuberculosis.
3. DOT of tuberculosis.

SECTION XII

MISCELLANEOUS

- Pyrexia of Unknown Origin
- Metabolic Syndrome X and Acanthosis Nigricans
- Emergencies in Clinical Medicine and Its Management
- Acid-Base and Electrolyte Disorder
- Paraneoplastic Endocrine Syndrome

Chapter 110

Pyrexia of Unknown Origin

DEFINITION

Pyrexia of unknown origin (PUO) is defined by the following criteria:

- Fever >101°F on several occasion.
- Fever >3 weeks duration.
- Fever remain undiagnosed despite 1 week of in patient investigation.

Durack and Street classified PUO into 4 categories:

1. Classic PUO
2. Nosocomial PUO
3. Neutropenic PUO
4. PUO associated with HIV.

1. **Classic PUO**—Fever (>101°F) on several occasion of >3 weeks duration where cause or etiology could not be established despite 3 outpatient visits or 3 days of in-hospital investigation or 7 days of intelligent ambulatory investigation.
   Usual causes are
   - Hidden infection
   - Obscure malignancy
   - Chronic inflammatory disease
   - Drug fever.
2. **Nosocomial PUO**—Fever (>101°F) in a hospitalized patient who is receiving acute critical care and in whom infection was not manifest or incubating at the time of admission, and the etiology could not be established on 3 days of investigation including at least 2 days of incubation of culture.
   Causes—Septic thrombophlebitis, sinusitis, *clostridium difficile* colitis and drug fever.
3. **Neutropenic PUO**—Fever (> 101°F) on several occasion in a patient whose neutrophils count <500/μL or is expected to fall to that level in 1–2 days and again the etiology could not be established after 3 days of investigation including 2 days of incubation of culture.
   Causes:
   - Perianal infection
   - Aspergillosis
   - Candidemia.
4. **PUO associated with HIV**—Fever (>101° F) on several occasion over a period of more than 4 weeks or >3 days of hospitalized patient with HIV and the diagnosis could not be established after 3 days of appropriate investigation including 2 days of incubation of culture.
   Causes:
   - MAC/MAI (*Mycobacterium avium* intracellular)
   - TB
   - Non-Hodgkin lymphoma
   - Drug fever.

CAUSES OF CLASSIC PUO

1. **Infections**
   - Extrapulmonary TB.
   - Sepsis—Intraabdominal abscess, renal/retroperitoneal/paraspinal abscess.
   - Osteomyelitis—With or without prosthesis.
   - Infective endocarditis—By HACEK group of organism.
   - Prolonged mononucleosis—By CMV and EBV.
   - UTI with prostatitis.
   - Gingivitis and dental abscess.
   - Sinusitis.
   - Fungal infections
     - Histoplasma involving RE system
     - Cryptococcal meningitis.
   - Malaria and babesia.
2. **Neoplasm**
   - Lymphoma
     - Hodgkin
     - Non-Hodgkin.
   - Leukemia.
   - Solid tumor—Hypernephroma, carcinoma of stomach, colon and pancreas.
3. **Connective tissue disease like**
   - SLE
   - Rheumatoid arthritis (RA)
   - Polyarteritis nodosa (PAN)

- Polymyalgia rheumatica
- Giant cell arteritis
- Adult Still's disease
- Temporal arteritis
- Wegener's granulomatosis.

4. Miscellaneous
   - Drug fever due to
     - B-lactam group of antibiotics
     - Quinidine
     - Phenytoin
     - Antineoplastic drug.
   - Granulomatous disease
     - Sarcoidosis
     - Crohn's disease/ulcerative colitis.
   - Dissecting aortic aneurysm.
   - Gout.
   - Cirrhosis.
   - Hemoglobinopathies.
   - Others
     - Disorders of thermoregulations (increased diurnal variation).
     - Factitious fever.
     - Pulmonary embolism.
     - Familial mediterranean fever.
     - Hyper IgD syndrome.
     - Familial cold-urticaria.
     - Fabry's disease.

APPROACH TO A PATIENT PRESENTING WITH PUO

History

1. Patient present with pulmonary symptoms—Cough, dyspnea, chest pain, expectoration and hemoptysis— TB.
2. Patient present with joint pain and swelling or deformity or bony swelling with discharging sinus or history of implanted prosthesis—chronic osteomyelitis.
3. Multiple joint pain with swelling and skin rash—connective tissue disorder.
4. Patient with urinary symptoms like dysuria, urgency, frequency, hesitancy, strangury suggest cystitis, prostatitis and urethritis—UTI.
5. History of recent blood transfusion or travel to new geographic areas known for endemicity for malaria, babesia, trypanosoma, leishmania, borrelia and HIV.
6. Intake of specific drugs like β-blocker, quinidine, phenytoin and antineoplastic agents.
7. Past history of cardiac and orthopedic surgery tooth extraction—SABE.
8. Personal history of alcohol intake, multiple sexual exposure, IV drug abuse, contact with TB and enquiry about pet animal (cat-toxoplasma) and bird (psittacosis).
9. Family history of collagen vascular disease/connective tissue disease/TB.

Clinical Examination

1. Skin
   - Rash and petechiae—Vasculitis, hematological malignancy.
   - Itchy papular lesion—Fungal.
   - Nodule—Malignancy.
   - Discharging sinus—Chronic osteomyelitis.
   - Evidence of Kaposi's sarcoma and mycosis fungoides—HIV.
2. Lymph nodes (palpable)
   - TB
   - Atypical mycobacteria
   - Systemic fungal infection
   - HIV
   - Infectious mononucleosis
   - Lymphoma
   - Leukemia
   - Sarcoidosis
   - Kikuchi's disease
   - Castleman's disease
   - Wegener's granulomatosis
   - Histiocytosis.
3. Oral cavity
   - Oral thrush } HIV
   - Hairy leukoplakia }
   - Evidence of apical root abscess
   - Gingivitis
   - Cancrum oris
   - Neutropenic ulcer/agranulocytic angina.
4. Nose and PNS
   - Sinusitis
   - Granulomatous disease.
5. Respiratory system : For evidence of
   - TB
   - MAC
   - Systemic fungal infection
   - PCP.
6. CVS : For evidence of
   - Bacterial endocarditis
   - Rheumatic heart disease
   - Congenital heart disease.
7. GIT
   - Hepatomegaly } Infective disorders
   - Splenomegaly } Granulomatous disease
   - Lymphadenopathy } Lymphoma leukemia
   - Kidney lump—Hydronephrosis, renal TB and perinephric abscess.
   - Hypogastric tenderness—PID and cystitis.
8. Per rectal examination (PR) : Ischiorectal abscess.
9. Per vaginal examination (PV) : PID.
10. Genitalia in male : Epididymoorchitis.

Investigations

1. Blood
   a. Complete hemogram
      - Leukocytosis with neutrophilia suggest bacterial infection.
      - Leukocytosis with lymphocytosis suggest TB/salmonellosis/fungal infection/MAC.
      - Leukopenia with neutropenia suggest kala-azar and HIV.
      - Leukocytosis with immature cells suggest lymphoma and leukemia.
      - Anemia with raised ESR suggest chronic inflammatory disease (TB, RA and SLE).
      - Raised ESR with leukocytosis suggest still's disease and anemia.
      - PBS for malaria and kala-azar.
   b. Serological test
      - Salmonellosis by Widal test.
      - Brucellosis.
      - Rickettsial by Weil-Felix test.

      } Rising titer is mostly diagnostic
      - ANF, anti-dsDNA for SLE.
        - APLA is diagnosed by anticardiolipin antibody and lupus anticoagulant, anti-B_2 microglobulin.
      - Rheumatoid factor and anti-CCP for diagnosis of rheumatoid arthritis.
      - ANCA for vasculitis
        - Increase ACE for sarcoidosis
   c. Blood-culture for
      - HACEK group of organisms
      - TB
      - Atypical mycobacteria.
2. Urine (RE, ME and culture) for
   - Bacterial
   - Mycobacterial
   - Fungus infection.
3. CSF (In patient with features of meningitis/meningoencephalitis)—RE and PCR for detection.
   - Virus (nucleic acid).
   - Mycobacteria.
   - Fungus (by India ink preparation).
4. Mantoux test
   - Positive in TB.
   - Negative in AIDS, sarcoidosis, Hodgkin, miliary TB and malnutrition.
5. Chest X-ray for features like cavity, fibrotic lesion, exudative lesion, miliary shadow, hilar, lymphadenopathy, mediastinal widening, bronchiectasis, interstitial infiltrates, pneumonia (atypical), pleural effusion, evidence of localised pleural effusion, subdiaphragmatic collection and hepatomegaly.
6. Sputum (spontaneous or induced) examination or bronchoalveolar lavage for cytology, PAP-stain and culture : For evidence of
   - TB
   - Bacterial infection
   - Fungal infection
   - Atypical carcinoma.
7. HRCT/MRI of chest and abdomen : For evidence of—
   - Hidden malignancy
   - Hidden abscess, e.g.
     - Retroperitoneal abscess
     - Perinephric abscess
     - Paravartebral abscess.
   - Lymphadenopathy.
8. Lower GI endoscopy : For evidence of
   - Colonic TB, malignancy and IBD.
9. Transesophageal echocardiography (TEE) for diagnosis of—
   - Subacute bacterial endocarditis (SABE)
   - Pericarditis/Pericardial effusion
   - Left atrial myxoema.
10. Gallium scan for diagnosis of
    - Sarcoidosis.
    - PCP.
    - Crohn's disease.
11. Liver-biopsy for diagnosis of
    - Granulomatous hepatitis and amoebic liver abscess.
12. Bone-marrow and lymph node biopsy for diagnosis of
    - Leukemia
    - Lymphoma
    - TB
    - Sarcoidosis.

EXERCISE

Write short notes on

1. Approach to a patient of PUO
2. Common etiology of PUO.

Chapter 111

Metabolic Syndrome X and Acanthosis Nigricans

PRESENCE OF ANY THREE RISK FACTORS IS NECESSARY FOR DIAGNOSIS OF METABOLIC SYNDROME X

1. Abdominal obesity
   - Waist measurement
     a. Men—102 cm
     b. Female—88 cm.
2. Triglyceride >1.7 mmol/L (150 mg/dL).
3. HDL
   a. Male <40 mg/dL
   b. Female <50 mg/dL.
4. BP ≥130/85.
5. FBS >110 mg / dL.

DISEASE ASSOCIATED WITH ACANTHOSIS NIGRICANS

- Internal malignancy specially GIT (esophagus).
- Obesity.
- Insulin resistance DM (type-A, type-B) and lipoatrophic form.
- Cushing syndrome.
- Acromegaly.
- Stein-laventhal syndrome.

EXERCISE

Write short notes on

1. Acanthosis nigricans.
2. Metabolic syndrome X.

Chapter 112

Emergencies in Clinical Medicine and Its Management

CARDIOVASCULAR EMERGENCIES

- Management of STEMI
- Management of UA/NSTEMI
- Management of arrhythmia
- Management of acute left ventrticular failure
- Management of hypertensive emergency
- Causes of central chest pain/retrosternal chest pain.

EMERGENCIES IN CNS DISORDER

- Management of status epilepticus
- Management of raised intracranial tension.

EMERGENCIES IN RESPIRATORY SYSTEM

- Management of hemoptysis
- Management of tension pneumothorax
- Management of acute severe bronchial asthma
- Management of acute respiratory distress syndrome
- Causes of lateral chest pain.
- Causes of central chest pain.

EMERGENCIES IN NEPHROLOGY

- Management of hyperkalemia
- Indication of dialysis.

EMERGENCY IN GI DISORDER

- Management of acute upper GI hemorrhage.

EMERGENCIES IN ENDOCRINOLOGY

- Cause and management of coma in diabetes
- Management of diabetic ketoacidosis
- Management of hyperosmolar nonketotic coma
- Management of thyroid storm
- Management of myxedematous coma
- Management of pituitary apoplexy
- Management of addisonian crisis.

MISCELLANEOUS

- Management of snakebite
- Management of organophosphorus poisoning.

MANAGEMENT OF STEMI

- Tab soluble aspirin (350 mg) tablet by chewing.
- Tab GTN (0.4 mg) sublingual × 3 tab at 10 minutes interval.
- Moist O_2 60% inhalation @ 5–6 L/min.
- Injection morphin—4 mg IV × 3 dose + 3 mg IV = 15 mg at interval of 10–15 minutes till the desired level of analgesia is obtained or signs of toxicity develops. Sign of toxicity are
  - Respiratory suppression—managed by naloxone
  - Vomiting— managed by metoclopramide.
  - Hypotension—managed by elevation of foot end of the bed/infusion of one bottle normal saline.
- Injection metoprolol—5 mg IV × 3 dose at 5 minutes interval and wait for 15 minutes after the last dose and search for five adverse effects
  - SBP <90 mm
  - Pulse <60/min
  - Evidence of bronchospasm
  - P-R interval >0.2 second.
  - Rales over lung base more than 10 cm high above diaphragm. If there are absent then

Injection metoprolol—50 mg IV 6 hourly × 48 hours then switch over to oral metoprolol. If adverse effect of metoprolol is present switch over to diltiazem.

- Reperfusion strategy/planning using any one of the following two methods.
  - Thrombolysis—By bolus thrombolytic agent like tenectiplase and alteplase.
  - Primary angioplasty (PCI).

Both thrombolysis and PCI are equally effective if undertaken within 3 hours but angioplasty in superior to thrombolysis as 95–98% recanalization is possible with in a very short time whereas in thrombolysis only 70% recanalization is possible after 3–4 hours.

MANAGEMENT OF UA/NSTEME

INITIAL MANAGEMENT

Antiischemic Therapy

- Tab GTN (0.4 mg) × 3 tab (sublingual) at 10 minutes interval followed by IV GNT (if pain does not subside).
- Moist O_2 (60%) inhalation, 5–6 L/min.
- Injection morphin—4 mg IV × 3 dose + 3 mg IV = 15 mg
- Injection metoprolol—Same as STEMI—5 mg IV × 3 dose followed by 50 mg IV 6 hourly.
- Apart from these four agents
- Atorvastatin—80 mg stat and once daily.
- ACEI /ARB can be started at this stage.

ANTIPLATELET THERAPY

- Oral antiplatelet
- Injectable intravenous antiplatelet.

Oral Antiplatelet

- Soluble aspirin—325 mg by chewing
- Clopidogrel—300 mg by chewing.
  Followed by **enteric-coated aspirin** 75–150 mg/day and **clopidogrel**—75 mg/day.

Intravenous Antiplatelet

- Abciximab—Drug of choice for all type of patient.
- Epitifibatide.
- Tirofiban—Drug of choice for those who do not undergo PCI.

ANTITHROMBIN THERAPY

Low molecular weight heparin (LMWH) is the drug of choice as antithrombin therapy. Any one of the three agent are used.

- Enoxaparin—60 mg SC 12 hourly
- Fondaparinux—5000 u SC daily
- Dalteparin.

During this initial therapy—The patients are evaluated by the following risk factors:

- Age of the patient >65 years.
- Episode of pain more than twice in the last 24 hours.
- Whether aspirin was taken within the last 7 days.
- Previous coronary angio shows >50% block.
- More than 3 coronary risk factor present (diabetes, obesity, dyslipidemia, smoking, alcohol, HTN, Black race, evidence of target organ damage and young age).
- ST-depression more than 1 mV (1 mm)
- Troponin-T strongly positive.
  - If at least the last two points are positive then the patient is considered in the high-risk group.
  - If all the initial five points are positive except the last two point then he is considered in the intermediate-risk group.
  - If only the initial 3 points are positive then the patients are considered in the low-risk group.

For high and intermediate-risk group of patient—Coronary angio is done followed by either CABG or PCI according to indication.

For low-risk group any one of these Trade mill test (TMT)/ dobutamine stress echo (DSE)/ dobutamine stress thallium (DST) are done and the patients are managed conservatively.

If in TMT, ST segment is depressed more than 3 mm small square then the patient is considered high-risk group and managed accordingly.

If in TMT, ST segment is depressed < 2 small square then he is discharged with conservative medical management of IHD (aspirin, clopidogrel, statin, metoprolol and ACEI/ ARB).

If in TMT, ST segment is normal then other than IHD is considered as the cause of chest pain.

MANAGEMENT OF ARRHYTHMIA

BRADYARRHYTHMIA (HEART RATE <60 BEAT/ MIN WITH SYMPTOM)

- Oral orciprenalin/isoprenalin tablet
- Intravenous orciprenalin or atropine infusion
- Temporary/permanent pacemaker implantation.

TACHYARRHYTHMIA

Causes of Atrial Tachyarrhythmia

- Supraventricular tachycardia (SVT)
- Atrial flutter
- Atrial fibrillation.

Supraventricular tachycardia (SVT)

Physical measure

- Carotid massage
- Valsalva maneuver
- Per rectal circumferential digital pressure.

Pharmacological measure

- **Injection adenosine**—6 mg IV bolus in a wide caliber vein (if not controlled), can be repeated twice at 10 minutes interval.
- **Biphasic synchronized DC shock** using 100 J energy can be used to terminate SVT.
- To prevent relapse of SVT **verapamil**, **β-blocker** or **digitalis** can be used as maintenance therapy.

Atrial fibrillation

In acute atrial fibrillation (<24 hours duration) unsynchronized biphasic DC shock with 100 J–150 J–200J energy in successive manner to establised sinus rhythm.

In chronic atrial fibrillation (>24 hours duration) Transesophageal echocardiography is done to detect left atrial thrombus. If thrombus is present start anticoagulation with warfarin to keep INR (2.5–3.5) for 1 month, then repeat transesophageal echocardiography, if thrombus has dissolved DC shock can be tried.

For long duration chronic atrial fibrillation other measures are ventricular rate controlled by

- Digitalis/β-blocker with warfarin.
- AV-node ablation with pacemaker implantation.
- Isolation of atrial musculature entering pulmonary vein in left atrial wall by catheter using different energy source and occlusive device for left auricle to prevent left atrial thrombus formation.

Causes of Ventricular Tachyarrhythmia

a. Ventricular ectopic
b. Ventricular tachycardia
c. Ventricular fibrillation.

Management of ventricular ectopic

If the number of ventricular ectopic is <10 beat/min —wait and watch, no intervention is required but if the number of ectopic is more than 10 beat/min and in the setting of acute myocardial infarction intravenous lignocaine infusion to be continued for 24 hours.

Management of ventricular tachycardia

Three or more than three successive ventricular ectopic is called **ventricular tachycardia**).

Ventricular fibrillation and ventricular tachycardia is managed by—**Biphasic syncronized** (for ventricular tachycardia or **unsyncronized** (for ventricular fibrillation) **DC shock** is used with 200 J–250 J–300 J energy is successive manner till the sinus rhythm is achieved.

If sinus rhythm could not be achieved in spite of 300J energy DC shock then

- **Injection atropine**—1 mg
- **Injection noradrenaline**—1 μg (1 in 1000)

} Intracardiac

- **Sodium-bicarbonate**—50 mL IV infusion.
- **High flow O_2** and is followed by unsyncronized biphasic DC shock using 300 J and 350 J energy output in successive manner.

If in spite of 350 J energy DC shock sinus rhythm could not be achieved or 10 minutes have passed after the onset of ventricular fibriltation patient is considered dead.

MANAGEMENT OF ACUTE LEFT VENTRICULAR FAILURE

Common cause of acute LVF are

a. Acute myocardial infarction
b. Acclerated hypertension.

GENERAL MEASURE FOR ACUTE LVF

- **High flow O_2**
- **Prop-up position**
- **GTN** (0.4) tablet sublingual × 3 at 10 minutes interval
- **Injection frusemide** 40–80 mg IV stat
- **Digitalis** can be used as a last resort.

SPECIAL MEASURE FOR ACUTE LVF

Management of Acute LVF with High BP

If high bood pressure is the cause of acute LVF, emergency lowering of blood pressure to be done by either.

- **Diazoxide** IV
- **Nitroprusside** IV
- **Nitroglycerine infusion**
- **Infusion of labetolol**
- **Injection of enalaprilat**. 1.25 mg IV
  - Diazoxide cause rapid fall of BP so intraarterial monitoring of BP is required.
  - Nitroprusside can cause cyanide toxicity.
  - Nitroglycerin can cause tachyphylaxis.

MANAGEMENT OF ACUTE LVF IN THE SETTING OF ACUTE MYOCARDIAL INFARCTION

Depending on Blood Pressure

- Management of acute LVF with low BP which usually develops in the setting of AMI.
  - If the systolic blood pressure >90 mm Hg then infusion **GTN** starting from 10 μg gradually increased up to 200 microgram/kg/min.
  - If systolic blood pressure 70–90 mm Hg.
    - Infusion of **dopamine or dobutamine** can be used depending on the peripheral perfusion status.
    - If periphery is cold (i.e. vasoconstriction is present) then infusion of **dobutamine** is used.
    - If periphery is warm (i.e. vasodilation is present) then infusion of **dopamine** is used.
  - If systolic blood pressure <70 mm Hg then vaso constrictor, like infusion of **noradrenaline** or levosimendan is used to manage acute LVF.
- If in acute LVF with AMI reperfusion has not yet been done—immediately carry out **bolus thrombolysis/PCI/CABG** according to the situation permit.
- **If AV dissociation with complete heart block is present along with LVF**—then implantation of **dual chamber**

pacemaker is to be done to correct LVF (one lead for atria and the second lead for ventricle for synchronous activation of atria before ventricle. So that the ventricle get the atrial booster which increases LV stroke volume and ejection fraction and correct heart failure.

- **If acute LVF develop in the setting of LBBB**—Then **three chamber pacemaker** implantation is the method of choice so that both the ventricle contract simultaneously and the ejection fraction return to normal level (one lead for atria, 2nd lead for right ventricle and 3rd lead for left ventricle in the coronary sinus).
- **If acute LVF** develop following development of acute **MR or VSD** in the setting of AMI—Surgical repair of the cardiac defect after stabilization of cardiac functional status by intraaortic balloon pulsation (IABP).

MANAGEMENT OF HYPERTENSIVE EMERGENCY (MALIGNANT HTN)

- **Infusion diazoxide**—It lowers BP very rapidly, so intra-arterial monitoring of blood pressure is required.
- **Infusion nitroprusside**—It can cause cyanide toxicity.
- **Infusion nitroglycerin**—It causes tachyphylaxis so gradual higher dose is required in case of continuous infusion or intermittent infusion is used (drug of choice).
- **Injection enalaprilat**— IV or IM lower BP within 20 – 30 minutes.
- **Injection labetolol**—100 mg IV stat follow by continuous infusion is used specially in the setting of pregnancy associated hypertension.

CAUSES AND MANAGEMENT OF CENTRAL OR RETROSTERNAL CHEST PAIN

See Chapter 10, Page No. 90

EMERGENCY IN CENTRAL NERVOUS SYSTEM

MANAGEMENT OF STATUS EPILEPTICUS

Physical Measure

- Loosening of tight garment.
- Putting handkerchief in month to prevent tongue bite.
- Make the patient prone with month rotated to one side and if possible foot end to be raised to prevent aspiration of gastric content.
- Prevention of self-injury.

Pharmacological Measure

- **Injection lorazepam**— 0.1–0.15 mg/kg to be infused over 1–2 minutes wait for 5 minutes.
  ↓ If convulsion is not controlled it can be repeated with same dose after 5 minutes.
- **Infusion valproate**—25 mg/kg IV who is taking valproate in subtherapeutic dose.
  ↓ If seizure not controlled within 20 minutes.
- **Infusion phenytoin** 20 mg/kg IV (at the rate 50 mg/min).
  Infusion fosphenytoin 20 mg/kg IV (at the rate150 mg/min).
  ↓ If seizure not controlled within 20 minutes.

Infusion of **phenytoin/fosphenytoin** can be repeated with half the dose (10 mg/kg).

↓ If seizure not controlled within 20 minutes.

- Infusion of **valproate**—25 mg/kg/IV if not given early.
  ↓ If seizure not controlled within 20 minutes.
- Injection **phenobarbitone** 20 mg/kg IVat the rate 60 mg/min
  ↓ If seizure not controlled

Repeat Injection **phenobarbitone**—10 mg/kg IV at the rate 60 mg/min.

↓ If seizure still not controlled in 20 minutes.

Admit the patient ICU/ITU.

Induction of anesthesia with IV **propofol or midazolam** or **pentothal sodium with ventilatory support**.

MANAGEMENT OF RAISED INTRACRANIAL TENSION

Insert ICP monitor—Ventriculostomy or parenchymal device. General goals—Maintain ICP (intracarnial pressure) <20 mm Hg and CPP (cerebral perfusion pressure) >60 mm Hg pressure. For ICP >20–25 mm Hg for 5 minutes.

- Drain CSF via ventriculostomy (if in place).
- Elevate head of the bed, midline head position.
- Osmotherapy—mannitol 25–100 g q4h as needed (maintain serum osmolality <320 mosmol) or hypertonic saline (30 mL, 23.4% NaCl bolus).
- Glucocorticoids—dexamethasone 4 mg q6h for vasogenic edema from tumor, abscess (aviod glucocorticoids in head trauma, ischemic and hemorrhagic stroke).
- Sedation (e.g. morphine, propofol, or midazolam), and neuromuscular paralysis if necessary (patient will require endotracheal intubation and mechanical ventilation at this point, if not before).
- Hyperventilation to $PaCO_2$ 30–35 mm Hg.
- Pressor therapy—Phenylephrine, dopamine or norepinephrine to maintain adequate MAP to ensure CPP ≥60 mm Hg (maintain euvolemia to minimize deleterious systemic effect of pressure.
- Consider second-tier therapies for refractory elevated ICP
  - High-dose barbiturate therapy ('pentobarb coma')
  - Aggressive hyperventilation to $PaCO_2$ <30 mm Hg
  - Hypothermia
  - Hemicraniectomy.

MANAGEMENT OF SNAKE BITE

GENERAL MEASURE

- Identify the signs of envenomation.
  - Two distinct fangs marks at 1.25 cm apart.
  - Sanguinous fluid coming out of the bite mark.
  - Severe pain.
  - Spreading edema around the site of bite.
  - If the freshly drawn blood sample of the patient does not clot within ½ hour.

  The last two features are the most positive sign of envenomation.
- Infusion of **polyvalent antivenom** 150–300 mL IV over ½ hour. Prior to infusion of antivenom, skin sensitivity is tested by giving 0.1 mL antivenom intradermal injection (as it is prepared from horse serum).

  This antivenom is usually repeated at the rate 50 mL 8 hourly for 1st 24 hour if it is indicated by clinical features.

After infusion of antivenom we have to search for the presence of signs of either hemolytic toxin or neurotoxic toxin.

Hemolytic toxin have the following features:
- Hematuria/hemoglobinuria
- Oliguria
- Anuria/acute renal failure.

If these features are evident then the patient is managed as a patient of acute renal failure and hemodialysis is usually required.

Neurotoxic bite have the following features:
- Ptosis
- Diminution of foward arm abduction time
- Diminution of single breath count test
- Diminution of respiration rate
- Snarling of voice.

If features of neurotoxic bite are present:
- Simultaneous infusion **neostigmine** and **atropine** in the ratio of (5 : 2) via two different IV route.

  Alternatively—

  Infusion of a mixture of **neostigmine** : **pyrogalate** (5 : 2) IV according to the severity of the features of neurotoxicity can also be used.

MANAGEMENT OF HEMOPTYSIS

- First we have to assess whether it is a hemorrhage from GI tract or respiratory tract.

FEATURES OF RESPIRATORY TRACT HEMORRHAGE

- Blood is bright red in color
- Floats in water
- Mixed with air bubble.

FEATURES OF GI TRACT HEMORRHAGE

- Blood is dark red or coffee ground in color
- Sink in water
- Mixed with food particle.

COMMON CAUSES OF RESPIRATORY TRACT HEMORRHAGE (IN INDIA)

- Pulmonary tuberculosis
- Bronchiectasis
- Bronchogenic carcinoma
- Lobar pneumonia
- Pulmonary infarction
- Coagulation disorder/anticoagulant overdose.

PULMONARY TUBERCULOSIS

- History of low-grade irregular fever for 3–6 months
- Anorexia and emaciation.
- History of prolong cough and expectoration.
- Chest pain may be present (due to pleurisy).
- On exam—Bronchial breathing, posttussive crepitations over apex of lung or suspected area.
- Chest X-ray and sputum exam for AFB in confirmatory.

BRONCHIECTASIS

- History of prolong cough or past history pulmonary tuberculosis.
- History of profuse foul smelling expectoration specially in the morning.
- Clinical examination is usually noninformative except few crepitation.
- Confirmed by HRCT of thorax.

BRONCHOGENIC CARCINOMA

- Middle-aged man usually heavy smoker (20 cigarettes a day for 20 years).
- May have chest pain due to erosion of ribs or heaviness of chest due to pleural effusion.
- Clinical examination may be noninformative except dull on percussion over the suspected area and the presence of bronchial breathing.
- Confirmed by chest X-ray and CECT of thorax and for cellular diagnosis CT guided FNAC from suspected lesion.

LOBAR PNEUMONIA

- Patient present with high rise of temperature.
- Cough with streaky hemoptysis.
- Pleuritic chest pain.
- Chest X-ray—Opacity over lobar or segmental distribution.

- On examination—Woody dull on percussion
  - Bronchial breath sound
  - Fine crepitations on auscultation.
- Leukocytosis with high neutrophil count.

PULMONARY INFARCTION

Patient usually complain of sudden onset chest pain, cough with streaky hemoptysis, tachycardia, tachypnea, usually have an embolic source in leg vein or an intravenous drug abuser.

Clinical examination is usually noninformative. Ventilation, perfusion lung scan shows a big nonperfused area over the lung (diagnostic).

COAGULATION DISORDER/ANTICOAGULANT OVERDOSE

It is usually diagnosed from history.

Clinical examination is usually noninformative. Diagnosed by blood exam. TLC DC, platelet count, BT, CT, P- time APTT and presence of D–dimer.

MANAGEMENT

- After taking short relevant history, try to assess the amount of blood loss from pulse, respiration and BP and examination of respiratory system.
- If there is tachypnea with pulse rate more than systolic blood pressure then a significant amount of blood loss have taken place and the patient require blood transfusion.
- Make a IV line during which blood in drawn for grouping and cross-matching and sugar, urea, creatinine TC, DC, ESR, Hb, BT, CT, P-time, INR, APTT and blood gas analysis.
- A slow IV drip with Ringer solution is started and blood transfusion is started as soon as blood is available or as and when required.
- Injection intramascular diazepam is usually given for relief of anxiety.
- A quick chest X-ray (PA) is done which is very much informative in case of tuberculosis, pneumonia and carcinoma lung. Followed by HRCTH or CECT of thorax which is diagnostic of bronchiectasis and carcinoma lung and CT guided FNAC is done for tissue diagnosis in case of carcinoma lung.
- A ventilation perfusion scan is required for suspected cases of pulmonary infarction.

A subsequent definitive treatment is done according to etiology.

MANAGEMENT OF UPPER GI HEMORRHAGE

CAUSES OF UPPER GI HEMORRHAGE

- Peptic ulcer diseases (55%)
- Esophageal varices (40%)
- Gastric carcinoma
- Acute gastric erosion
- de-La-Foys syndrome.

Whenever a patient comes to emergency with hemorrhage from upper GI tract after taking short but relevant history try to assess the amount of blood loss from pulse rate respiration and blood pressure and at the same time jaundice, neck gland, liver and spleen examination also to be done. If there is tachypnea and the pulse rate have crossed systolic blood pressure then it is considered that a significant amount of blood loss have occurred.

Try to establish an IV channel prior to that blood is drawn for grouping cross-matching for blood transfusion and for Hb, TC, DC, S/U/Cr/Na^+/K^+/LFT/P time BT, CT and APTT estimation.

Blood transfusion is started as soon as blood is available. After stabilizing the patient an endoscope is introduced to establish the diagnosis.

- If peptic ulcer with spurting blood vessel is seen in endoscopy then hemostasis is achieved by using cryotherapy and routine investigation for Helicobacter is done.
- Injection omeprazole 80 mg IV 8 hourly is continued till the hemostasis is achieved.
- For eradication of Helicobacter OCA / OCM regimen is most popular.

  In OCA regimen—
  Omeprazole 40 mg bid × 8 week then 40 mg OD for 2 month
  Clarithromycin 500 mg bid × 2 week
  Amoxicillin 500 mg tid × 2 week.

  In OCM regimen—
  Omeprazole 40 mg bd × 8 week then 40 mg OD for 2 month
  Clarithromycin 500 mg bd × 2 week
  Metronidazole 400 mg tds × 2 week.
- If bleeding **esophageal varices** is seen in endoscopy the best method of obtaining hemostasis is—
  - Intravenous infusion of octerotide/terlipresin to be continued for 24–48 hours to obtain early hemostasis.
  - Esophageal tamponade with Sengstaken-Blakemore tube in which first the gastric balloon is inflated followed by esophageal balloon which is kept in esophagus for 4 hours after which it is deflated for 15 minutes to maintain proper circulation of the lower end of esophagus. This inflation and deflation of the balloon is continued for 24–48 hour till complete hemostasis is obtained.

Long-term management of esophageal varices are

- Endoscopic EVL—Esophageal variceal ligation or endoscopic esophageal variceal sclerotherapy.
- Medical therapy by propranolol (40–80 mg 8 hourly) or isosorbide mononitrate. 30–60 mg od.

- Portacaval shunt—End to side/side to side/distal linorenal shunt.
  - TIPS—Transjugular intrahepatic portosystemic shunt.
- If during gastroscopy **large gastric ulcer** near grater curvature with everted margin suggestive of gastric carcinoma is seen then eight quadrant biopsy is taken from the margin of the ulcer for tissue diagnosis and subsequent management is surgical or chemotherapy, after stabilization of the patient by blood transfusion.
- In case of **acute gastric erosion** following NSAID the management is by—
  - Blood transfusion for stabilization of the patient
  - Injection misoprostol—60 mg/day.
- If during endoscopy **spurting arteriole** is seen in the healthy gastric mucosa. It is due to de-La-Foys syndrome and in that condition hemostasis is obtained by cryotherapy.

MANAGEMENT OF TENSION PNEUMOTHORAX

Diagnosis of pneumothorax is made by—

- Gradually increasing respiratory distress over 24–48 hours following the development of pneumothorax.
- Hyperinflation of one hemithorax with buldging of intercostal spaces and supraclavicular fossa with absent respiratory movement.
- Acute shifting of trachea and apex beat to opposite side with absent respiratory movement on the same side.
- Hyperresonant note on percussion on the affected side.
- Silent one hemithorax on auscultation.
- CXR/CT thorax is confirmatory.

MANAGEMENT

- Insertion of a wide bore needle through 2nd intercostal space on the midclavicular line after inducing local anesthesia at the site of needle insertion. Following needle insertion the patient get some relief of the respiratory distress.
- For permanent measure a wide bore intercostal catheter is introduced into the pleural space through 4th intercostal space in the midaxillary line of thorax in the triangle of safety (guarded anteriorly by pectoralis, posteriorly by latis and below by upper board of 6th rib). During the procedure two precautions are taken.
  - Entry point of the intercostal catheter into the hemithorax is tightly secured by a purse string suture to prevent airleak by the side of tube and formation of surgical emphysema.
  - Outer end of the catheter must be fitted with a water-seal drain.

MANAGEMENT OF ACUTE SEVERE BRONCHIAL ASTHMA

- Prop up the head end of the patient.
- Nebulize the patient with salbutamol and budesonide and O_2 for half hour. Then every 2 hourly.
- Injection hydrocortisone—200 mg IV stat and to be repeated every 8 hourly.
- Usually a broad spectrum antibiotic like injection co-amoxyclav 1.2 g IV 8 hourly is started.
- A proton pump inhibitor like Injection pantoprazole is also given.

INDICATIONS OF VENTILATOR THERAPY IN BRONCHIAL ASTHMA

- Patient cannot speak a word
- Central cyanosis
- Silent chest
- Pulse impalpable
- Blood pressure not recordable
- Rising partial pressure of CO_2 >6 kPa
- Falling partial pressure of O_2 <8 kPa.

MANAGEMENT OF ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS) (NONCARDIOGENIC PULMONARY EDEMA)

PULMONARY CAUSES OF ARDS

- Toxic gas/fumes inhalation
- Pneumonia
- Drowning
- Aspiration of gastric content
- Pulmonary contusion.

NONPULMONARY CAUSES OF ARDS

- Acute pancreatitis
- Septicemia
- Multiple blood transfusion
- Multiorgan failure
- Severe trauma
- Burn.

MANAGEMENT

- Minimal intervention, e.g. bronchoscopy.
- Ventilate the patient with low tidal volume of 6 mL/kg of dry body weight to minimize FiO_2 <0.6 maximize PaO_2 88–95%.
- Ventilation is done by PEEP mode with 10–12 mm of pressure, pH to be maintained >7.3. Mean arterial pressure >65 mm Hg.
- Broad spectrum antibiotic like injection piperacillin - tazobactum 4.5 g IV 8 hourly.

- Ventilation may have to be continue for 4–6 weeks.
- Treatment of underlying medical and surgical disorder according to etiology.
- Prophylaxis against venous thrombosis, GI hemorrhage, culture of venous line infection.
- Prompt treatment of nosocomial infection.
- Maintenance of adequate nutrition.

CAUSES AND MANAGEMENT OF COMA IN DIABETES

- Hypoglycemia
- Diabetic ketoacidosis
- Hyperosmolar nonketotic coma
- Uremia
- CVA.
- Lactic acidosis
- Dyselectrolytemia.
  - First measure CBG (capillary blood glucose). If fa- cilities not readily available start emperical IV infusion of 25–50% dextrose 50–100 mL. In case of hypoglycemia patient will regain consciousness immediately.
  - If the patient does not regain consciousness, next step is examination of urine for ketone bodies by dip stick method and thorough neurological examination. If ketone bodies are present in urine then it is a case of diabetic ketoacidosis which is managed accordingly.
  - Other causes of coma with diabetic uremia and CVA dyselectrolytemia are managed according to the etiology.

MANAGEMENT OF DIABETIC KETOACIDOSIS

Condition that predispose diabetic ketoacidosis are—

- Complete omission of insulin.
- Failure to increase the dose of insulin during stress fall condition like infection, CVA, myocardial infarction and surgical operation.
- Drugs—Cocaine addict.
- Pregnancy.

CLINICAL FEATURES

- Nausea, vomiting, increase thrust and polyuria.
- Severe abdominal pain mimicking pancreatitis or rupture of hollow viscus.
- Features of dehydration and hypotension.
- Tachypnea with Kussmaul's respiration with fruity smell and respiratory distress.
- Tachycardia.
- Lethargy, obtundation, coma.

MANAGEMENT

- Draw blood to assess electrolyte, acid-base status and renal function.
- Fluid replacement—Infuse 2–3 liter of normal saline/lacted Ringeres solution over 1–3 hours (15–20 mL/kg/hour)/subsequently reduce the rate of infusion to 250–500 mL/hour (total 3L–5L).

  When the patient is hemodynamically stable and achieve adequate urine output. Normal saline should be replaced by 0.45% saline to prevent hyperchloremia and hypernatremia depending on the volume deficit.

  When the blood glucose reaches 200 mg/dL normal saline to be replaced by dextrose with normal saline to infused at the rate of 150 – 200 mL/hour to maintain blood glucose around 200 mg/dL.
- Insulin—Initial dose 0.1 U/kg IV bolus of regular insulin followed by 0.1 U/kg/hour continuous IV infusion.

  The dose of insulin may have to be increased 2–3 fold depending on the response after 2–4 hours. Insulin have to be continued till ketone bodies disappear from blood which usually takes about 48 hours.
- If initial serum potassium is <3.3 mmol/L do not administer insulin before correction of serum potassium >3.5 mmol/L.
- Measure capillary glucose every 1–2 hours and serum electrolyte (K^+ HCO_3^- PCO^{-3} pH and anion gap every 4 hour for the first 24 hours.
- Monitor pulse, respiration, BP mental status and fluid intake output every hourly.
- Replace K^+ 10 mEq/hour when K <5.0–5.2 mEq. Administer K^+ 40–80 mEq/hour when K <3.0 mEq/L or if HCO_3^- infusion is given.
- Continue the above management till the patient's
  - Blood glucose is stabilized in between 150–250 mg/dL.
  - Acidosis is resolved.
  - Ketone bodies are absent in blood.

  Reduce the dose of insulin infusion to 0.05 U/kg/hour.
- Bicarbonate (when pH <6.9), phosphate (when serum concentration <1 mg/dL) and magnesium replacement may be required in some patient.

MANAGEMENT OF HYPERGLYCEMIC, HYPEROSMOLAR, NONKETOTIC COMA (HHONK)

PRECIPITATING FACTORS

- Serious intercurrent illness, e.g. CVA, AMI, subdural hematoma.
- Infection.
- Debilitating condition.

- Chronic use of diuretic, phenytoin, glucocorticoid, dialysis and tube feeding.

CLINICAL FEATURES

- Profound dehydration, hypotension.
- Altered mental state, confusion, lethargy and coma.
- Nausea, vomiting, Kussmaul's breathing and abdominal pain are significantly absent.

LABORATORY FEATURES

- Blood glucose 600–1200 mg/dL
- Serum osmolality 330–380 mosmol/L
- Plasma ketone body—absent.

MANAGEMENT OF HHONK

- Fluid replacement
- Insulin infusion
- Search for precipitating factor.

FLUID REPLACEMENT

Infuse 1–3 liters of normal saline over 2–3 hours. Too rapid infusion may worsen the neurological sign. If serum Na > 150 mEq/L then half strength (0.45%) saline is used. After hemodynamic stability is achieved normal saline is replaced by half strength saline and then by 5% dextrose. Total fluid deficit (9–10 L) is corrected over 1–2 days by **half strength (0.45%)**, normal saline at the rate of 200–300 mL/hour.

INSULIN INFUSION

- Rehydration and volume expansion lower plasma glucose but insulin is also required.
- Initially 5–10 U IV bolus to be followed by 3–7 U/hour.
- 5% Dextrose to be added to the IV fluid when plasma glucose <250 mg/dL and insulin infusion is decreased to 0.05 U/kg/hour.
- Insulin infusion is to be continued untill the patient resume eating and then switchover to SC insulin.
- K^+ deficit is quite large when the patient is taking diuretic. Usually magnesium deficiency coexist.
- K^+ replacement is done by infusing 10 mEq/500 mL fluid.
- Hypophosphatemia is corrected by infusing K_3PO_4.
- Acidosis if present (pH <7.2) is corrected by infusion of 100 mL $NaCo_3$ (8.5%) over 1 hour.
- HHONK patient are usually older and usually have life-threatening illness or comorbidities. Even with proper treatment HHONK patient have higher mortality (15%) than DK patient (5%).

MANAGEMENT OF PITUITARY APOPLEXY

Acute hemorrhage in the pituitary gland causing substantial damage to pituitary and parasellar structures.

ETIOLOGY

- Spontaneous in preexisting nonfunctioning (usually) adenoma.
- Head trauma.
- Sheehan's syndrome.
- Anticoagulant therapy.
- In association with diabetes, hypertension, shock and sickle cell anemia.

In the setting of macroadenoma, during the rapid growth phase blood vessel may give away producing apoplexy.

Hyperplastic enlargement during pregnancy make the pituitary more vulnerable to ischemia due to PPH or systemic hypotension.

CLINICAL FEATURES

- Bursting headache and signs of meningeal irritation
- Clouding of sensorium—Confusion, delirium and coma
- Ocular symptoms:
  - Diplopia and ptosis
  - Papilledema
  - Bitemporal hemianopia
  - Ophthalmoplegia
- Severe hypoglycemia
- Cerebral hemorrhage in other sites
- Severe hypotension, CVS collapse and death.

DIAGNOSIS

CECT is the investigation of choice as hemorrhage cannot be demonstrated by MRI.

MANAGEMENT

Conservative

- Indications
  - Patient without visual loss
  - Patient without impairment of consciousness.
- Treatment
  - IV 20% mannitol 250–350 mL 6 hourly.
  - Dexamethasone—8 mg IV 8 hourly
  - Maintenance of nutrition
  - Withdrawal of anticoagulant
  - ABC support.

Surgery

- Indications
  - Patient with visual loss
  - Patient with impaired consciousness
  - Nonresponder to medical therapy.
- Evacuation of blood clot by neurosurgical approach (transsphenoidal functional endoscopic surgery).

Follow-up

- Repeat CT/MRI
- Automated perimetry
- Monitoring of tropic hormone.

COMPLICATIONS

- Incomplete visual recovery—Visual recovery is inversely related with time elapsed after acute episode before neurosurgical procedure.
- Hypopituitarism.

MANAGEMENT OF THYROID STORM

It is a rare life-threatening exacerbation of hyperthyroidism.

ETIOLOGY

It develops in noncompliment thyrotoxic patient undergone stress like

- Surgery or radioiodide treatment with inadequate preoperative preparation.
- Infection/sepsis.
- Trauma.
- Stroke.
- Diabetic ketoacidosis.
- Pregnancy.

CLINICAL FEATURES

- Increased sweating.
- Hyperthermia (104°–106° F).
- Tachycardia (SVT/atrial fibrillation) palpitation and heart failure.
- Convulsion, clouding of sensorium–delirium, confusion and coma.
- Vomiting, diarrhea and jaundice (rare).
- Mortality is 30% and it is due to:
  a. Heart failure
  b. Arrhythmia
  c. Hyperthermia.

MANAGEMENT

Intensive monitoring is urgently required.

Specific Management of the symptoms

- Cooling ice bath/ice pack/cooling blankets.
- Basic life support.
- **Propylthiouracil**—600 mg stat (via oral/NG tube/rectally) followed 200–300 mg/6 hours. It also prevent conversion of T_4 to T_3 makes it the drug of choice.
- **Propanolol**—2 mg IV 4 hourly or 60 mg orally 4 hourly—If there is no heart failure (also prevent T_4 to T_3 conversion).
- **Dexamethasone**—2 mg 6 hourly for prevention of shock and prevention of conversion of T_4–T_3.
- SSKI (saturated solution of potassium iodide) 5 drops every 6 hourly.
  or
  Na-Iopodate/Iopanoic acid—500 mg bd.
  or
  Na-Iodide—0.25 g IV 6 hourly.
  Iodine should be administered 1 hour after propylthiouracil. This delay allows antithyroid drugs to prevent the excess 'I' from being incorporated into new hormone (Wolff Chaikoff effect).
- Antibiotics for infection.
- General management of heart failure.

Follow-up

- ECG
- Thyroid hormone status.

MANAGEMENT OF MYXEDEMA COMA

ETIOLOGY

Myxedema coma usually develop in noncompliant and undertreated elderly patient and precipitated by

- Factors that impairs respiration
  - Drugs—Sedative, anesthetic and antidepressant
  - Pneumonia
  - Congestive cardiac failure (CCF)
  - Myocardial infarction
  - Gastrointestinal hemorrhage
  - CVA
- Sepsis
- Exposure to cold
- Hypoglycemia and dilutional hyponatremia.

CLINICAL FEATURES

- Reduced level of consciousness
- Seizure
- Hypothermia. Body temperature may be as low as 23°C
- Other features of hypothyroidism are present.

MANAGEMENT

Replacement therapy

- Levothyroxine—500 μg stat (IV bolus) followed by 50–100 μg / day. If IV preparation is not available then nasogastric route may be used.
- Liothyronine (T_3)—10–25 μg every 8–12 hourly (IV or nasogastric tube—excess liothyronine has the potential to produce arrhythmia.
  - Combination therapy—Initially levothyroxine (200 μg) and liothyronine (25 μg) as a single IV bolus followed by daily treatment with levothyroxine (50–100 μg) and liothyronine (10 μg every 8 hourly).
  - As T4–T3 conversion is inpaired in myxedema coma.

Supportive Therapy

- External warming if temperature <30° as it can produce CVS collapse.
- Space blanket to reduce heat loss.
- Hydrocortisone 50 mg 6 hourly as there is impaired adrenal reserve in profound hypothyroidism.
- Basic life support including ventilatory support.
- Antibiotic coverage for infection.
- 3% hypertonic NaCl and intravenous glucose—If there is hyponatremia and hypoglycemia.
- If seizure develops IV—Phenytoin.
- Precipitation factor to be searched for.

MANAGEMENT OF HYPERKALEMIA

ECG FEATURES OF HYPERKALEMIA (DEPENDING ON THE SERUM POTASSIUM LEVEL)

- Tall-peaked T-wave
- Prolongation of P-R interval
- Absent P-wave
- Prolongation of ORS complex
- ORS and T-wave merges together to form sine wave
- Heart stops in systole.

Steps of Management of Hyperkalemia

It is usually started when serum potassium level >6.5 mEq/L.

- **Infusion of calcium gluconate** (10%) 10 mL solution over 10 minutes. Calcium is a divalent cation which will push back K^+ inside the cell and lower serum K^+ level.
- **Infusion of glucose insulin solution** 100 mL (25%) Dextrose solution mixed with 12–13 U of insulin to be infused slowly. The insulin will push the glucose inside the cell along with Na^+ and K^+ and thereby hyperkalemia is managed.
- **Nebulization with β_2 agonist** helps to manage hyperkalemia without any intervention.
- **Infusion of $NaHCO_3$** (8.5%) (if concomitant acidosis is present) 30–50 mL IV will correct the acidosis and pushback potassium inside the cell. This method can only be applied when hyperkalemia is associated with acidosis.
- **K exchange resign**—This synthetic resign is taken orally with water when it passes through gut there is exchange of Na^+ in resign with K^+ in the blood and the gut wall will act like dialyzer membrane. In this way hyperkalemia can be managed.
- The final solution of hyperkalemic is either any one of the two—
  1. Renal replacement therapy—Dialysis (peritoneal or hemodialysis).
  2. Kidney transplant.

MANAGEMENT OF ORGANOPHOSPHORUS POISONING

FEATURES OF ORGANOPHOSPHORUS POISONING

- Pinpoint pupil
- Bradycardia
- Increased sweating
- Pain abdomen diarrhea
- Increased nasal and oropharyngeal secretion.
  - Remove the cloth that comes in contact with the poison.
  - Wash the suspected area of the skin with soap water that comes in contact with the poison.
  - **Injection atropine**—5–25 mg IV bolus depending on the amount of poison consumed followed by 0.1–2.0 mg/hour continuous intravenous infusion depending on the clinical features.
  - **Injection lorazepum**— Slows IV infusion if there in convulsion.

FEATURES OF ATROPINE OVERDOSE

- Dry and warm skin and mouth
- Dilated pupil
- Tachycardia
- Restless
- Delirium and convulsion.

Atropine overdose is managed by

- Omit injection atropine
- Injection lorazepam/midazolam—Infusion.

CAUSES OF TENDERNESS AND PAIN OVER LATERAL CHEST

- Injury or inflammatory condition of chest wall
- Painful costochondral junction
- Secondary malignant deposit in the rib
- *Herper zoster* before eruption
- Dry pleurisy
- Early hours of pneumothorax.

EXERCISE

Write short notes on

1. Pituitary apoplexy
2. Thyroid storm
3. Myxedema coma
4. Nelson's syndrome
5. Management of hyperkalemia.

Chapter 113

Acid-Base and Electrolyte Disorder

ACID-BASE DISORDER

Four basic parameter are used for assessing acid-base status of a patient.

- Arterial pH—7.4 (standard value).
- Arterial $PCO_2 \rightarrow 40$ mm Hg (standard value)—It indicates volatile acid and respiratory contribution/response to acid-base disorder.
- Serum bicarbonate (HCO_3) or total carbon dioxide (24 mEq/L—standard value) indicate level of fixed acid present in blood.
- Anion gap—It is the difference between the concentration of measured cation (sodium) and anion (chloride and bicarbonate) in plasma $Na^- - (Cl^- + HCO_3^-)$ = 10 mmol/L (standard value).

In assessing the acid-base status of a patient we have to follow four steps:

A. **We have to determine which one is the primary event**—Metabolic cause or respiratory cause.

B. **What is the status of compensation?**
Under compensated, fully compensated and over compensated.
Compensation is to be calculated by the formula given below.
In this connection one must remember that *over compensation does not takes place in our body. If it is seen from the calculated value that there is over compensation then this must be due to a second disorder*.

C. If it is a metabolic acidosis we have to find out whether *it is high anion gap (AG) metabolic acidosis or low/ normal anion gap metabolic acidosis*.

D. Sometime high anion gap metabolic acidosis can musk normal anion gap metalic acidosis or metabolic alkalosis. We have to find out it from $\frac{\Delta AG}{\Delta HCO_3}$ ratio.

I. **Searching the primary event**—It has to be determined from movement of PH and HCO_3 level.
   - If both pH and HCO_3 is decreased then it is metabolic acidosis.
   - If both pH and HCO_3 is increased then it it metabolic alkalosis.
   - If pH has decreased but HCO_3 is increased then it is respiratory acidosis.
   - If pH has increased but HCO_3 is decreased then it is respiratory alkalosis.

II. Status of compensation:
   1. In primary metabolic acidosis we have to find out the ideal level of PCO_2 from the level of HCO_3 by the any one of the following formula.
$$PCO_2 = \Delta HCO_3 \times 1.25 + 8 \pm 2$$
$$\Delta PCO_2 = \Delta HCO_3 \times 1.25$$
$$PCO_2 = HCO_3 + 15$$
   2. In primary metabolic alkalosis we have to find out the ideal level of PCO_2 from the level of HCO_3 by the formula
$$PCO_2 = HCO_3 + 15$$
   3. In respiratory disorder we have to find out the ideal level of bicarbonate from the level of PCO_2.
      - In acute respiratory acidosis for 10 mm rise in PCO_2 there is 1 mmol/L rise in HCO_3 level.
      - In chronic respiratory acidosis for 10 mm rise in PCO_2 level HCO_3 level will rise by 4 mmol/L.
   4. In respiratory alkalosis we have to find out the level of PCO_2 from HCO_3.
      - In acute respiratory alkalosis 10 mm fall in PCO_2 level takes place for decrease of 2 mmol/L of HCO_3 level.
      - In chronic respiratory alkalosis 10 mm fall in PCO_2 level takes place for decrease of 4 mmol/L of HCO_3 level.

III. If it is a metabolic acidosis, one have to find out whether
   - It is a high anion gap (AG) metabolic acidosis or
   - A normal anion gap metabolic acidosis by the formula.

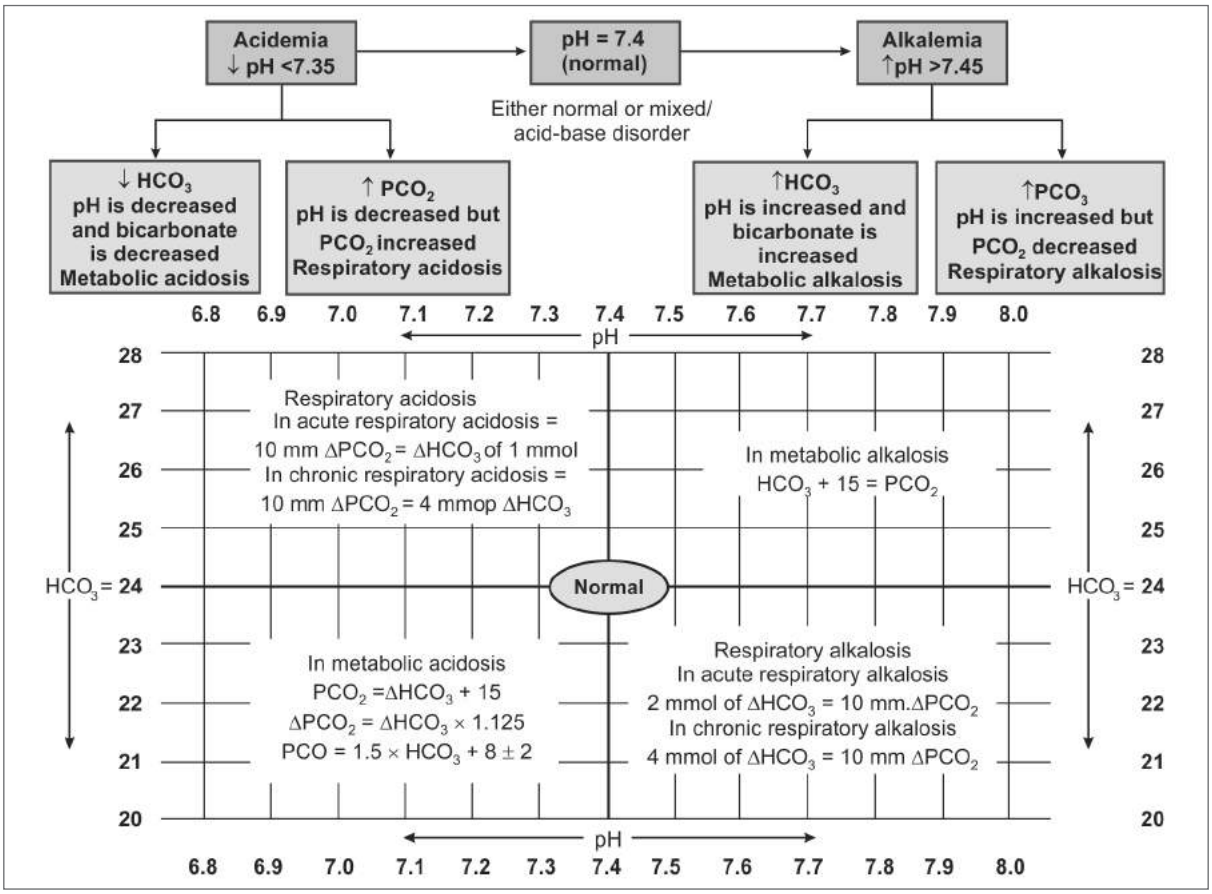
$$\mathbf{Na^+ - (Cl^- + HCO_3^-) = 12 \pm 2\ mmol}$$
$$= (10 - 14 \text{ mmol normal range})$$

If anion gap is > 4 it is called high anion gap acidosis.

Causes of high anion gap metabolic acidosis are remembered by the mnemonic LAMUDPIE

L—Lactic acidosis
A—Aspirin
M—Methanol
U—Uremia
D—Diabetic ketoacidosis
P—Propylene glycol

Flowchart 113.1: Acid-base nomogram



I—Isopropyl alcohol and INH

E—Ethanol

Out of these eight causes of metabolic acidosis, lactic acidosis and diabetic ketoacidosis are the two most common etiology. Again lactic acidosis is of two types.

Type-A—Which is due to ischemia, sepsis and hypotension, profound anemia.

Type-B—Lactic acidosis due to **failure of liver** to metabolize lactate to bicarbonate which occurs in liver disease.

The other causes of high anion gap metabolic acidosis are ethanol, methanol and ethylene glycol toxicity which can be diagnosed from osmole gap in serum.

Measured osmolarity—Calculated serum osmolality by the following formula:

$$\left[2\times Na(mEq)L + \frac{BUN}{3} + \frac{Glucose}{20}\right]$$

Normal osmolar gap is approximately 10

If osmole gap is high then it is due to either ethanol, methanol or ethylene glycol toxicity.

Causes of low or normal anion gap metabolic acidosis are:

a. **Diarrhea**
b. **RTA** (renal tubular acidosis)
c. Lithium
d. *Ingestion of NH_4Cl, HCl* or amino acid like *L-arginine L-Lysine.*

Important Causes of hyperchloremic or nonanion gap acidosis—

a. Bicarbonate loss from GI tract
b. Renal tubular acidosis.

Diarrhea and RTA can be differentiated by the urinary anion gap.

In urine $Na^+ + K^+ + NH_3^+ = Cl^- + HCO_3^-$

So, $NH_3^+ = (Cl^- + HCO_3^-) - (Na^+ + K^+)$

In RTA kidney fails to secrete NH_3 from renal tubule.

So in RTA, $Na^+ + K^+ = HCO_3^- + Cl^-$

But in diarrhea renal tubule secrete NH_3.

So $HCO_3^- + Cl^- > Na^+ + K^+$

D. *Over compensation does not take place in our body and if over compensation is seen in the calculated value then it is due to a second disorder.*

Sometime high anion gap metabolic acidosis can musk normal anion gap metabolic acidosis or metabolic alkalosis. We have to find it out from $\frac{\Delta AG}{\Delta HCO_3}$ ratio.

If the pH is normal or near normal but the ratio $\frac{\Delta AG}{\Delta HCO_3}$ = **Lies between 1–2 then it is a high anion gap metabolic acidosis**.

If the pH in normal or near normal but the $\frac{\Delta AG}{\Delta HCO_3}$ = **>2 then it is due to metabolic alkalosis which is underlying high anion gap metabolic acidosis**.

If the pH is normal or near normal but the $\frac{\Delta AG}{\Delta HCO_3}$ = <1 then it is due to nonanion gap metabolic acidosis which is underlying high anion gap metabolic acidosis.

METABOLIC ALKALOSIS

CHARACTERISTICS

Increased serum HCO_3, increased extracellular pH (may see mild increase in $PaCO_2$ as compensation).

CAUSES

Generally either due to volume contraction (volume loss from GI tract, kidneys, skin, respiratory system, third-spaced fluid and bleeding) or hypokalemia. Also, excessive glucocorticoids or mineralocorticoids, Bartter's syndrome, exogenous alkali ingestion can cause metabolic acidosis.

- **Two types**—Chloride responsive and chloride resistant.
- **Chloride responsive**—Vomiting, diuretics, NG suction, diarrhea, villous adenoma. Spot urine Cl should be less than 10 (except with diuretic use) since the kidney should be conserving Cl. Treatment with 0.9NS should fix the disturbance.
- **Chloride resistant**—Distal exchange site stimulation by aldosterone resulting in increased H^+ and K^+ excretion in exchange for resorption of Na^+ as $NaHCO_3$.

COMPENSATION

Compensation is highly variable and in some cases there may be no or minimal compensation. In chronic metabolic alkalosis, the $PaCO_2$ should increase by roughly 5 mm Hg for every 10 mEq/L increase in serum HCO_3.

HYPONATREMIA

Hyponatremia is characterized by serum Na <135 mEq/L. Free water intake in the setting of that impair free water excretion is needed for hyponatremia to develop.

CLINICAL FEATURES

Symptoms and signs are due to **osmotic swelling of brain**. Early symptoms are **nausea, vomiting** and **headache**. Patient may be asymptomatic as occurs in **cirrhosis** and **CHF**. Worsening of brain swelling causes **confusion, seizure, coma, respiratory arrest** and **death**.

- Diuretic and exercise-induced hyponatremia may have a typical manifestation.
- Diuretic-induced hyponatremia commonly occurs in elderly female with low body weight taking thiazide diuretic.
- Exercise-induced hyponatremia develops in 1–20% of marathon runner is secondary to increase hypotonic fluid consumption in the presence of nonosmotic release of **arginine vasopressin** which impair renal excretion of water. Special clinical features are **nausea, vomiting, seizure, noncardiogenic pulmonary edema** and **respiratory arrest**.

ETIOLOGY (FLOWCHART 113.2)

Most symptomatic hyponatremia develop in the following condition:

- Postoperative setting
- Following diuretic therapy
- Oxytocin treatment
- Menstruant women
- Children
- Hypoxia
- Cortisol deficiency
- Hypothyroidism
- Inappropriate ADH secretion
- GI fluid loss
- ARF/CRF
- Cirrhosis and CHF.

DIAGNOSIS

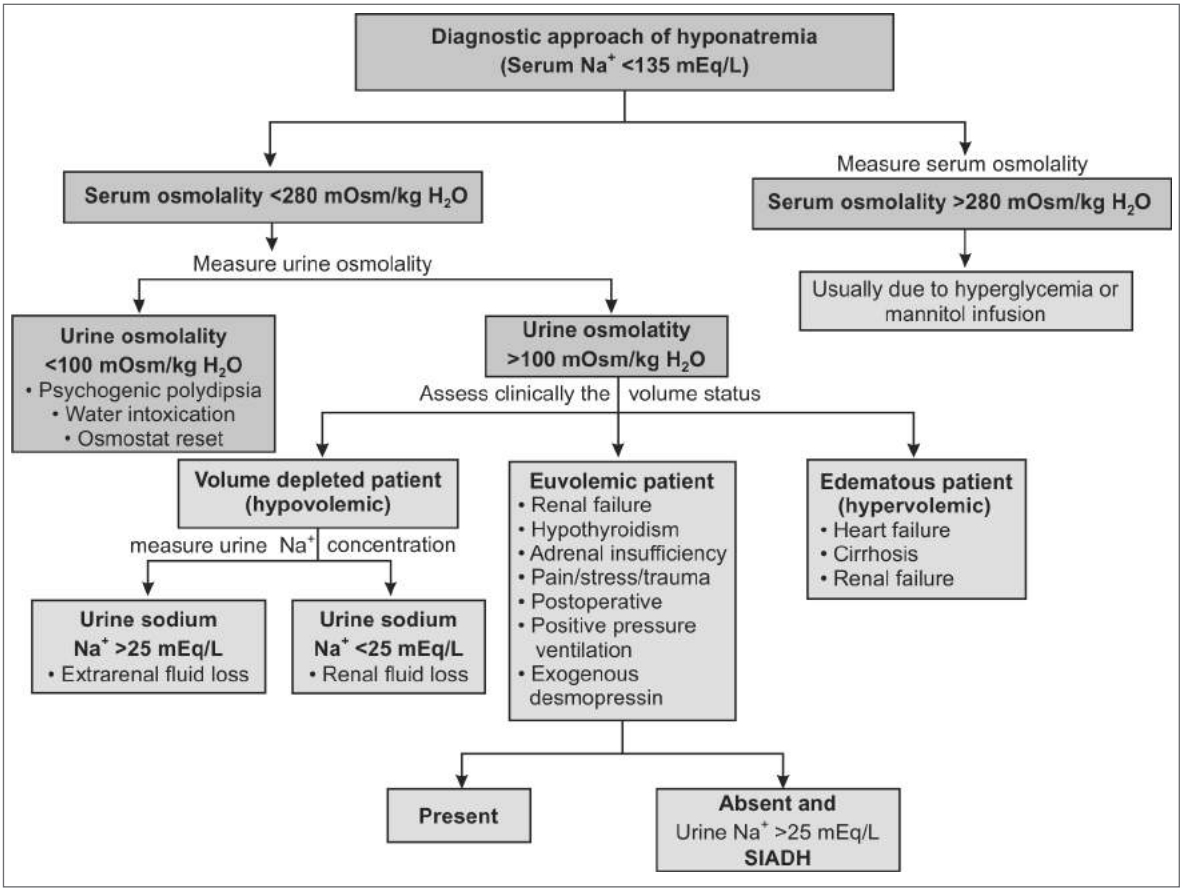
Hyponatremia is characterized by serum Na^+ <135 mEq/L. In hyponatremia exclusion of hyperosmolar hyponatremia is initially indicated which is usually due hyperglycemia or mannitol. **To rectify Na^+ level in the setting of hyperglycemia add 1.6 mEq/L for every 100 mg/dL rise of blood sugar** with the existing serum-Na^+ level. **Hyperproteinemia** and **hyperlipidemia** may cause **spurious low Na^+ concenration** if samples are diluted before measurement.

Hospitalized patient have numerous stimuli for AVP release specially in the postoperative setting, secondary to pain, nausea, narcotic and administration of hypotonic IV fluid (5% dextrose and 0.45% saline).

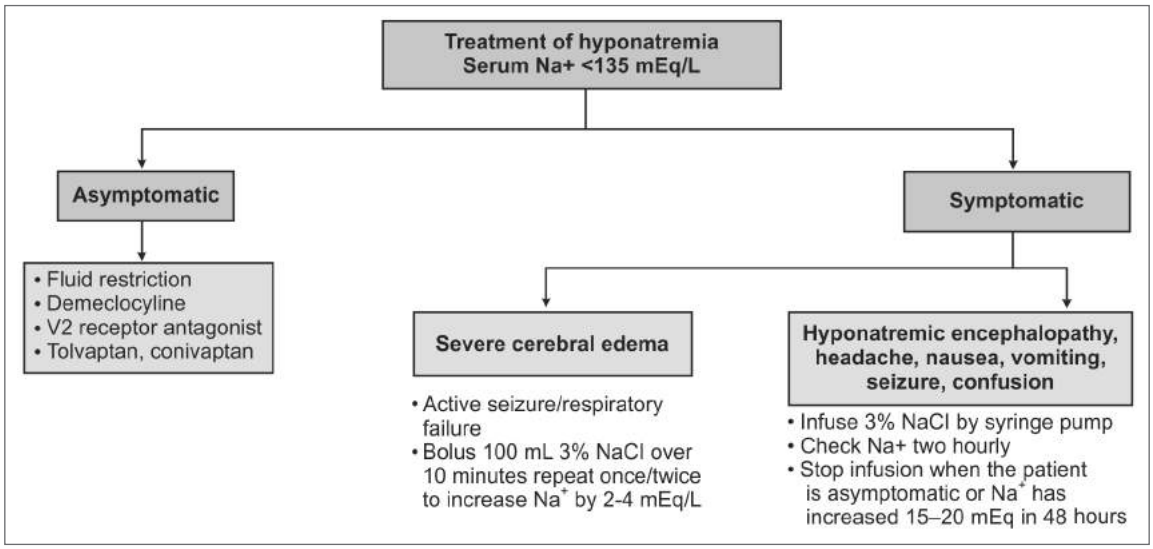
TREATMENT (FLOWCHART 113.3)

Early treatment of symptomatic hyponatremia is indicated. Rapid and aggressive treatment with infusion of hypertonic saline (3% NaCl) with or without a loop diuretic and close monitoring is required. Mortality is high in symptomatic

Flowchart 113.2: Etiological diagnosis of hyponatremia



Flowchart 113.3: Treatment of hyponatremia



patient with hypoxia or who receive delayed treatment regardless of the underlying disorder.

HYPERNATREMIA

DEFINITION

Hypernatremia is characterized by serum-Na^+ >155 mEq/L.

Restricted access to water is the main factor for development of hypernatremia.

COMMON ETIOLOGY

- Solute diuresis secondary to tube feeding or hyperalimentation.
- Nasogastric suction.
- Hyperosmolar nonketotic (HONK).
- Diabetes insipidus.
- Impaired water intake.

CENTRAL DIABETES INSIPIDUS

Insufficient AVP secretion causes central diabetes insipidus (CDI) which present as polyuria and secondary water diuresis.

Common causes are—

- Head injury
- Brain neoplasm
- Pituitary surgery.

In CDI plasma osmolality typically exceed the urine osmlality.

Subcutaneous or intranasal desmopressin is the treatment of choice for CDI. 50% increase in urine osmolality after administration of dDAVP strongly suggest CDI and helps to differentiate from nephrogenic diabetes insipidus.

Hypernatremia causes cerebral dehydration with cell shrinkage.

Patients with liver disease are at high-risk of developing cerebral demyelination when hypernatremia develops.

The goal of hypernatremia treatment is maintaining normal circulatory volume while correcting the serum-Na^+ with free water replacement.

In absence of hypernatremic encephalopathy the serum-Na^+ should not be corrected more quickly than 1 mEq/hour or 15 mEq/24 hour.

CALCIUM HOMEOSTASIS

Intestinal absorption and urinary excretion of calcium is regulated by vitamin D whereas parathormone regulates urinary reabsorption of calcium and reabsorption of calcium from bone.

A reduction in plasma albumin of 1 g/dL decreases serum calcium by 0.8 mg/dL.

CAUSES OF HYPOCALCEMIA

- Hypoparathyroidism/pseudohypoparathyroidism
- Hyperphosphatemia
- Hypomagnesemia
- Vitamin D-deficiency (diet/sunexposure/CLD/CKD)
- Osteoblastic metastasis (prostate and breast)
- Severe pancreatitis
- Citrate overload (usually due to blood transfusion).

Decrease urinary calcium reabsorption and mobilization from bone can occurs in hypoparathyroidism and vitamin D deficiency whereas **increase Ca removal from serum occurs in osteoblastic metastatic disease and severe pancreatitis**.

Clinical Features

Chvostek sign and **Trousseau's sign** and **altered mental status** are the most important sign of hypocalcemia.

Treatment

Calcium chloride or IV calcium gluconate is given in acute symptomatic hypocalcemia. Ionized calcium determine the disease severity so alteration of protein binding of calcium may precipitate the condition. Alkalemia increases the affinity of albumin for calcium by altering the net charges of protein to a more positive state and therefore decreased ionized calcium. Acute increase in total albumin may also cause decrease ionized calcium.

HYPERCALCEMIA

Entry of calcium into the intravascular space in excess of renal calcium excretion cause hypercalcemia.

Intestinal absorption and bone reabsorption causes calcium influx into the intravascular space.

CAUSES OF HYPERCALCEMIA

- Primary hyperparathyroidism (hyperplasia/adenoma).
- Malignancy (multiple myeloma, osteosarcoma, carcinoma by PTH-related peptide called paraneoplastic syndrome).
- Immobilization.
- Granulomatous disease (sarcoidosis and TB).
- Paget's disease.
- Milk alkali syndrome.
- Vitamin D intoxication.
- Thiazide diuretic.
- Familial hypocalciuric hypercalcemia.

Clinical Features

Lethargy, confusion, nausea, constipation, polyuria, HTN volume depletion, nephrolithiasis and nephrogenic diabetes insipidus coma.

Treatment

- IV normal saline.
- IV furosemide.
- Bisphosphonate for hypercalcemia of malignancy (to decrease bone reabsorption).
- Calcitonin has short-term effect with tachyphylaxis.

EXERCISE

Write short notes on

1. Calcium metabolism
2. Hyponatremia
3. Hypernatremia
4. Acid-base disorder.

Chapter 114

Paraneoplastic Endocrine Syndrome

PARANEOPLASTIC ENDOCRINE SYNDROME

- **Hypercalcemia of malignancy due to**
  Ectopic hormone
  PTHrP — From sequamous cell carcinoma of
  by 1, 2, 5 DHCC — (head, neck, lung and skin) GI and
  Prostaglandin — GU and breast carcinoma.
  from lymphoma
  from lung and ovary cancer
  from renal and lung cancer
- **SIADH due to**
  Vasopressin — From small cell and squamous cell cancer of lung, GI, GU and ovarian cancer.
- **Cushing syndrome due to**
  ACTH — Lung cancer (small cell carcinoma carcinoid, adenocarcinoma, squamous cell carcinoma, thymus, pancreatic and medullary thyroid carcinoma.
  CRH — By pancreas, carcinoid, lung and prostatic carcinoma.
- **Hyperglycemia due to**
  IGF II — Mesenchymal tumor, sarcoma adrenal, hepatic, GI and kidney prostatic carcinoma.
  Insulin — Carcinoma cervix.

5. **Male feminization due to**
   From testis — Germinoma, choriocarcinoma
   From lung by — Lung carcinoma.
   hCG — Hepatic and pancreatic carcinoma.
6. **Diarrhea due to**
   Calcitonin — From lung, colon, breast medullary thyroid carcinoma.
   VIP — From pancreas, pheochromocytoma and esophagus carcinoma.

- **Acromegaly due to**
  GnRH — From pancreatic carcinoma and carcinoid tumor.
- **Hyperthyroid due to**
  TSH — From H-mole, embryonal tumor and struma ovarii.
- **HTN due to**
  Renin — From JXT medullary tumor of kidney, lung and pancreas and ovarian carcinoma.

PARANEOPLASTIC HEMATOLOGIC DISORDER

- **Erythrocytosis** by erythropoietin from renal carcinoma, hamartoma, cerebellar carcinoma and hemangioblastoma.
- **Granulocytosis** by GCSF, GMCSF, IL-6, from lung, GI, ovary, GU carcinoma and Hodgkin disease.
- **Thrombocytosis by IL-6** → From lung, GI, breast ovarian carcinoma and lymphoma.
- **Eosinophilia by IL5** → From lymphoma and leukemia.
- **Thrombophlebitis** due to carcinoma lung.

PARANEOPLASTIC NEUROLOGIC SYNDROME

- Encephalomyelitis
- Limbic encephalitis
- Cerebellar degeneration
- Subacute sensory neuropathy
- GI pseudo-obstruction
- Dermatomyositis
- LES (Lambert-Eaton syndrome)
- Carcinoma/melanoma associated retinopathy.

SECTION XIII

PSYCHIATRY

- Psychiatry

Chapter 115

Psychiatry

SLEEP

Sleep is not a continuous process. There are two types of sleep:

Slow eye movement (SEM) sleep

Rapid eye movement (REM) sleep.

SEM sleep has four stages which alternate with REM sleep and makes a sleep cycle. An young healthy adult usually have 3–5 sleep cycles at night. Each cycle persists for about 90 minutes approximately.

Sleep Latency

It is the time taken from going to bed to fell asleep which is approximately <20 minutes in normal person.

Sleep Architecture

Recording of the sleep pattern, i.e. (stage and duration of the stage) with transition from one stage of the sleep to the other with its duration is known as sleep architecture.

Sleep architecture changes with age. Aged men have poor quality of sleep characterized by reduced REM sleep, delta sleep (slow wave in EEG) and total sleep time with increased night time awakening.

Most delta sleep occurs during the first-half of the sleep cycle.

Longest REM sleep occurs in the second-half of the sleep cycle.

Stages of Sem Sleep

SEM sleep has four stages:

- **Stage-1**—It is the lightest and smallest stage of sleep cycle and consists of 5% of total sleep time.

  EEG shows theta activity (4–7 cycles/second). Pulse and respiration gradually slowed down. Episodic body movement may be present.
- **Stage-II**—It is the longest stage of sleep and occupies 45% of the sleep cycle.

  Tooth grinding (bruxism) may be present at this stage. EEG shows sleep spindle or K complex.
- **Stage-III and IV**—It is the deepest and most relaxed stage of sleep cycle.

  Consisting of 25% of total sleep time but decrease with age.

  Night terror, sleepwalking (somnambulism), bedwetting occurs in this stage (paralyzed brain with an active body). EEG shows delta (slow) wave 0–3 cycles/second.

Rapid Eye Movement Sleep

Rapid eye movement sleep (REM) Sleep consists of 25% of total sleep time and decreases with age.

Dreaming, penile erection occurs at this stage.

Pulse, BP and respiration increase at this stage.

Skeletal muscle movement is also absent (active brain in a paralyzed body).

Usually first REM sleep occurs 90 minutes after falling asleep which is known as REM latency.

Duration of REM is 10–40 minutes which occurs at the end of each sleep cycle (at about 90 minutes' interval).

REM rebound—A person who is deprived of REM sleep at one night has increased REM sleep on the next night which is known as REM rebound.

Deprivation of REM or total sleep time may lead to anxiety and psychotic symptom.

Neurotransmitter Associated with Sleep

- Increased amount of acetylcholine in the reticular formation is associated with both total sleep and REM sleep.

  Total sleep time and REM decrease with age, Alzheimer's disease due to low level of acetylcholine in brain.
- Increased level of serotonin increases both total and delta sleep.
- Increased level of dopamine causes decreased sleep time.
- Increased level of norepinephrine decreases both REM and total sleep.

EATING DISORDER

In this eating disorder patient shows abnormal behavior associated with food despite normal appetite and high

interest in food related activities (cooking) [Reverse of viral hepatitis patient].

Anorexia Nervosa

- Patient has significant weight loss (15–20% below ideal body weight) due to self-imposed dietary restriction because of an overwhelming fear of being obese.
- Patient has body image disturbance (feel fat even when very thin).
- Abnormal behavior in dealing with food (simulating eating).
- About 5% of general population and 2% of adolescent female are involved with anorexia nervosa.
- About 95% of anorexia nervosa patients are female.
- Mortality 5–18%.
- Turbulent family history predisposes this condition.
- Two subtypes
  a. Restricting type—Excessive dieting.
  b. Binge eating type—Excessive dieting plus episodic binge eating and purging by laxative.

Clinical Features

- Amenorrhea—Hypogonadotrophic—Hypogonadism (main diagnostic criteria).
- Metabolic acidosis.
- Hypercholesterolemia.
- Hypokalemia.
- Mild anemia and leukopenia.
- Lanugo hair—Downy body hair on trunk.
- Osteoporosis.
- Cold intolerance.
- Syncope.
- Melanosis coli—Blacken area of colon due to laxa- tive abuse.

Treatment

- Usually resistant to treatment—Denial of illness.
- Hospitalization may be required for nutritional therapy and treatment of metabolic abnormalities.
- Family therapy and individual psychotherapy.
- Pharmacologic treatment.
  a. Cyproheptadine
  b. As 40–80% patients with anorexia nervosa have severe depression, they are treated with triple combination antiviral drug (TCAD)—

SSRI amitiyptyline and imipramine.

BULIMIA NERVOSA

Patients usually show compulsive and rapid ingestion of food followed by (in secret) self-induced vomiting or use of laxative or exercise.

Patients usually have relatively normal body weight.

Clinical Features

- Esophageal tear (due to self-induced vomiting).
- Tooth enamel erosion due to reflux of gastric acid in mouth.
- Metacarpal and phalangeal calluses (Russell's sign) due to use of hand for induction of vomiting.
- Enlarge parotid gland.
- Electrolyte disturbances.
- Menstrual irregularities.
- Hypergymnasia (excessive exercise).
- Depression.

Low baseline serotonin concentration in brain is observed in most of these patients.

One-third patients have the history of drug or alcohol abuse.

Treatment

- Cognitive and behavioral therapy—Insight and group therapy.
- Average to high dose antidepressant—TCAD or SSRI are used.

ANXIETY DISORDER

It is a group of disorders which consists of

- Generalized anxiety disorder (GAD)
- Panic disorder
- Phobic disorder
- Obsessive compulsive disorder
- Dissociative disorder.

Generalized Anxiety Disorder

In this type of anxiety disorders symptoms are noticed in day-to-day normal activities and are present on most of the days for at least 6 months.

Panic Disorder

In this type of anxiety disorders symptoms are recurrent and short-lived but the triggering factors are either unknown or unpredictable. Somatic symptoms are more marked.

Phobic Disorder

In this type of anxiety disorder symptoms are noticed by the patient predictably following exposure to certain objects or situations (e.g. by the students before examination or a novice person before speaking a public gathering).

Obsessive Compulsive Disorder

Obsessive compulsive disorder (OCD) this type of anxiety disorder patients experience recurrent intrusive thoughts

Table 115. 1: Symptoms and signs

General Features	Somatic Features	Sympathomimetic Features
Irritability Anxiety Difficulty in concentration Apprehension Recurrent thoughts of fear Weakness and insomnia Repetitive action and ritual (OCD)	Headache Dizziness Nausea, vomiting, bloating chest pain, palpitation and paresthesia	Tremor Tachycardia Sweating Hyperventilation

(obsession) for which they engage themselves in compulsive action (handwashing, door bolting or rituals) to maintain self-control.

Types of Obsessive Compulsive Disorder

There are two types of obsessive compulsive disorders—
a. Obsessive compulsive anxiety disorder
b. Obsessive compulsive personality disorder.

Obsessive Compulsive Anxiety Disorder

Obsessive compulsive anxiety disorder (OCAD) is a type of anxiety disorder in which there is a recurring intrusive feeling or thoughts or images (called obsession) causing anxiety partly relieved by performing repetitive action (called compulsion).

A common obsession—
a. Is avoidance of hand contamination and a compulsive need towards the handwashing after touching things.
b. Repetitive checking of gas jets on the stove or locks in the door or counting objects are also very common symptoms.

These patients are orderly inflexible and perfectionists.

Patients usually have the insight, i.e. they realize that these thought or behaviors are irrational and try to eliminate them.

These obsessions and compulsions are focal and acquired in later life not presence since childhood.

Treatment

Commonly used pharmacological agents are—
1. Fluoxetine 60–80 mg orally once daily
2. Clomipramine.

OBSESSIVE COMPULSIVE PERSONALITY DISORDER

Obsessive compulsive personality disorder (OCPD) is a separate entity in which stubborn perfectionist inflexible humorless orderly and routinely male child have these personality characteristics since his childhood.

In OCPD, genetic factors are involved and increased in first degree relative of **Tourette syndrome** patient.

Treatment

Most effective pharmacological treatment for these patients is an antidepression particularly SSRI with behavioral and cognitive therapy.

Incidence

- OCD 2–5% at 25–30 years of age
- Panic disorder 3–5% at <25 years of age.

Differential Diagnosis

- Myocardial infarction.
- Hypoglycemia.
- Hyperthyroidism.
- Sympathomimetic drug abuse (cocaine and amphetamine).
- Pheochromocytoma.
- Temporal lobe disfunction or epilepsy (specially in dissociative disorder).

Treatment

- Behavioral and cognitive therapy.
- Relaxation technique (yoga)—Especially in panic disorder.
- Desensitization via graded exposure to phobic object or situation.
- Emotive imagery—Imaging anxiety provoking situation while using relaxation technique.
- Family, school or vocational counseling.

Pharmacotherapy

1. GAD
   - Benzodiazepines—Diazepam 5–10 mg tid.
   - Buspirone—15–60 mg po divided tid.
   - Venlafaxine—37.5–75 mg po/day.
   - SSRI—Paroxetine.
2. Panic disorder for acute management
   - Lorazepum—0.5–2 mg.
   - Alprazolam—0.5–1 mg.
   - SSRI—Sertaline 25 mg po/day titrated upward every weekly for long-term management.

3. OCD
   - SSRI—Fluoxetine 60–80 mg po/day.
   - Clomipramine.
4. Phobic disorder
   - SSRI—Paroxetine, sertraline, fluvoxamine.
   - MAO—Inhibitors.
   - Gabapantine—900–3600 mg po divided 8 hourly.
   - Propranolol—20–40 mg po 1 hour before exposure in specific phobic situation (examination or speaking before a public gathering).

SOMATOFORM DISORDER

- Conversion disorder— In this situation psychological stress is converted into physical and neurological symptoms.
- Somatization disorder— A group of symptoms from different systems.
- Hypocondriasis— Fear of having a serious disease based on the misinterpretation of psychological symptom.
- Somatoform pain disorder— Persistent pain in some parts of the body not due to organic cause.
- Dissociative disorder—In this type of anxiety disorder the symptoms and signs are precipitated by emotional crisis (death news of a close person). Here the symptom produce some anxiety reduction and temporary solution of the crisis. The mechanism include repression and isolation as well as particularly limited concentration as seen in hypnotic state.

SPECIAL FEATURES OF DISSOCIATIVE DISORDER

- Sudden unexplained travel away from home with inability to recall past (fugue).
- Amnesia.
- Somnambulism (sleep walking).
- Depersonalization.
- Dissociative identity disorder (multiple personality or split personality).

DEPRESSION

Depression is marked by lack of selfesteem with a sense of guilt or worthlessness. On the contrary, sadness and grief are normal response to loss and are transient.

Dysthymia is a chronic depressive disturbance in which depressive symptoms are milder than major depressive episode.

Incidence

Up to 30% of OPD patients have depressive symptoms.

Symptoms and Signs

- Anxiety.
- Chronic fatigue and somatic complaint which have diurnal variation which is maximum in the morning and improvement as the day progresses.
- Withdrawal from all activities.
- Feeling of guilt.
- Anhedonia—Lack of feeling or enjoying a pleasant situation.
- Poor concentration and cognitive function.
- Vegetative signs—Insomnia, anorexia, constipation, sometimes severe agitation and psychosis.
- Atypical features are hypersomnia, overeating and lethargy.

Diagnosis

- Feeling of worthlessness, hopelessness and intense guilt.
- Lack of interest with diminished involvement in activities.
- Indecision, difficulty in thinking and concentration.
- Sleep—It may be interrupted, reduced and excessive.
- Somatic complaints.
- Lack of energy and initiation, anorexia with dimin- ished sex drive.
- In severe depression
  - Agitation and psychomotor disturbances.
  - Delusion specially hypochondriacal or persecutory.
  - Withdrawal from all social activities.
  - Suicidal ideation.

Differential Diagnosis

- Cyclothymia or bipolar disorder.
- Dysthymia.
- Major depression in the postpartum (usually 2–24 hours).
- After menopause.
- Premenstrual tension.
- Seasonal affective disorders—Carbohydrate craving, lethargy, hyperphagia and hypersomnia.

Investigations

- Complete blood count
- Toxicological screening
- Thyroid function test
- Folate estimation.

Treatment

- TCAD (mainstay of therapy before SSRI)—To start with low dose and gradually increase the dose by 25 mg per week.
- SSRI (now the drug of choice)—Clinical response varies from 2–6 weeks should be given in the morning.
- MAOI—Third line agent, danger of orthostatic hypotension and sympathomimetic crisis.

  If response is inadequate to first agent at 6 weeks of therapy, a second agent from different groups should be added.

PERSONALITY DISORDER (PDS)

A person with personality disorder (PDS) shows lifelong chronic rigid unsuitable pattern of relating to others that causes social and occupational problem (jobless and few friends).

Persons with PDS are not aware that they are the cause of their own problem (does not have the insight) but do not have any psychotic problem.

Personality of a man results from the interaction of a genetic substrate with personal drive and outside influence.

Classification of personality disorder is done according to the predominant symptoms and severity.

Classifications

DSM-IV—TR categorized PDS into three clusters.

1. Cluster-A
   - Paranoid
   - Schizoid
   - Schizotypal.

   Group characteristic—Avoid social relationship, peculiar personality but not psychotic.

   Genetic and familial association—With psychotic illness.
2. Cluster-B
   - Histrionic
   - Narcissistic
   - Borderline
   - Antisocial.

   Group characteristic—Dramatic, emotional and inconsistent.

   Genetic and familial association—Mood disorder, substance abuse and somatoform disorder.
3. Cluster-C
   - Avoidant
   - Obsessive-compulsive
   - Dependent.

   Group characteristic—Fearful and anxious.

   Genetic and familial association—Anxiety disorder.

- **Paranoid**—They are distrustful, suspicious, litigious and hyper alert.

  Attribute responsibility to others for their own problem.
- **Schizoid**—They are shy, introverted, withdrawn, avoid close relationship to any one, detached from society and restricted emotion.
- **Schizotypal**—They are socially isolated and believe in magical thinking (believing that once thought can affect the course of event), superstitious, odd thought pattern and behavior but without psychosis.
- **Histrionic**—These persons are theatrical, extroverted, emotional, sexually provocative cannot maintain interpersonal relationship due to their odd behavior.
- **Narcissistic**—These persons are exhibitionist, grandiose, excessive demand for attention and lack of empathy for others.
- **Antisocial**—They refuse to follow social norm and show no sympathy for others. Associated with conduct disorder in childhood and criminal behavior in adulthood (sociopath or psychopath).
- **Borderline**—They are erratic, impulsive with unstable behavior and mood. Make suicidal attempt or self-mutilation for minor cause and usually associated with eating disorder.
- **Avoidant**—They are socially withdrawn and have low self-esteem, fear rejection, hyper react to rejection and failure.
- **Obsessive compulsive**—These persons are perfectionist, egocentric, indecisive with inflexible and rigid thought.
- **Dependent**—They are passive, lack of self-esteem and self-confidence.

Treatment

- Those who seek help, can be managed by individual or group psychotherapy.
- Pharmacotherapy use to treat symptoms like depression and anxiety.

SCHIZOPHRENIA

It is a chronic, debilitating mental disorder characterized by a period of loss of touch with reality or surrounding (psychosis) with persistent disturbances in thought, behavior and speech and socially withdrawn.

Epidemiology

Prevalent 1% in general population.

- Male : Female = 1 : 1
- Age of onset—Male = 15–20 years
- Female = 25–35 years.

Subtype

- **Paranoid**
  - Age of onset—Elderly

  - Delusion of persecution or grandiose
  - Hallucination of voice often present
  - Less regression of mental faculties.
- **Catatonic**—Complete stupor may be mute.
  - Decrease in spontaneous movement.
  - Rigidity of posture— This can left the patient standing or sitting in ***awkward*** position for long time (waxy flexibility).
  - Brief outburst of violence without provocation.
  - Negativism and echopraxia (repeat movement done by others/doctors).
- **Disorganized**
  - Pronounced thought disorder
  - Explosive laughter
  - Little contact with reality
  - Unorganized behavior and speech
  - Active but aimless
  - Silliness.
- **Undifferentiated**—Psychotic symptoms present but does not fit with paranoid, catatonic and disorganized subtype.
- **Residual**—Past history of schizophrenia present but at present there is no overt psychotic symptom. Mild negative symptoms may be present.

Symptoms

They are of two types and persist for at least six months' duration:

1. Positive symptoms are those that are additional to expected behavior. These are delusion, hallucination, agitation and talkativeness.
2. Negative symptoms are those that are absent from normal expected behavior. These are lack of motivation, social withdrawal, flattened affect, anhedonia (cannot experience or imagine any pleasant emotion or situation).

Disorders of Perception

- Illusion—Misinterpretation of external stimuli—hanging coat in dark perceived as man.
- Hallucination—False sensory perception, can hear voices when alone in a room or voices of dead man.

Disorders of Thought Content

- **Delusion**—False belief, often paranoid in nature—involving perceived threat from others which has no real existence.
- **Idea of reference (thought broadcasting, thought insertion or thought echo)**—False belief of being referred by others. Patient thinks that his friend and neighbors somehow come to know about his idea and are publicly discussing about this.

Disorders of Thought Process

- **Impaired abstruction ability**—When asked what brought him to hospital, the patient replies, 'ambulance'.
- **Magical thinking**—Believe that thought can affect the course of event—once thought, can prevent some- thing from happening.

Forms of Thought

- Loose association (shifting of idea from one object to other)—When answering question about his health, he ends in cricket play.
- Neologism creating new words, i.e. call doctor as medocrat.
- Tangentiality deviated away from the point from where he starts speaking, i.e. start talking about his own health, ends in his sister's abortion.

Other Symptoms

- Motor activity—Generally reduced.
- Social function—Marked withdrawal, deterioration in personal care and interpersonal relationship.
- Speech
  - Neologism—Make new word or phrase
  - Echolalia—Repetition of other's word
  - Verbigeration—Repetition of senseless word or phrase.
- Mood—Usually depressed but rapid swinging of mood may be present.
- Affect—Flat occasionally inappropriate.

Potential Causes

- Trinucleotide repeat amplification
- Birth trauma and hypoxia in case of early onset.

Pathology

Primary pathology is in the limbic system—changes seen in hippocampus, parahippocampus, cingulate gyrus and amygdala. There is also atrophy of the frontal lobe with enlargement of lateral and third ventricle proved by PET scan.

Neurotransmitter Theory

- Excess dopamine activity—Supported by increase number of dopamine receptor and increase concentration dopamine in brain found in schizophrenic patients.
- Serotonin hyperactivity—Seen in schizophrenia, also proved by the fact that clozapine, a 5-HT_2 receptor blocker is used in chronic stage of schizophrenia.

- Glutamate is involved in schizophrenia is proved by the fact that agonist of NMDA receptor alleviate psychotic symptoms.

Differential Diagnosis

- Delusional disorders : Nonbizarre delusion with minimal impairment of daily life.
- Schizo affective disorder: Does not fit with schizophrenia or affective disorder.
- Schizophreniform disorder : Duration <6 months but >a week.
- Brief psychotic disorder—Short lasting arise from psychological stress.
- Atypical psychosis—Arise from cause that become apparent later.
  - Substance abuse.
  - Manic episode.
  - Obsessive compulsive disorder.
  - Psychotic depression.
  - Diseases of endocrine gland like thyroid, adrenal pituitary, hepatic encephalopathy and renal failure.
  - Complex partial schizure and temporal lobe epilepsy.
  - Overdose of antipsychotic drug can cause catatonia.

Investigations

- Sugar, urea, creatinine, electrolyte and liver function test.
- Thyroid function and adrenal function study.
- MRI of brain for pituitary and temporal lobe disorder.

Treatment

- **Pharmacotherapy**
  - Traditional antipsychotic (D_2 blocker) for positive symptoms, e.g. chlorpromazine, thioridazine, haloperidol.
  - Atypical antipsychotic (5-HT_2 receptor blocker) for negative symptom, e.g. olanzapine, quetiapine, ziprasidone and clozapine.

  Because of better side effect profile, these drugs are now treated as firstline drugs.

Side Effects

- Clozapine—Agranulocytosis.
- Ziprasidone—Cause QT prolongation.
- Quetiapine—Associated with cataract.
- Olanzepine—Weight gain and type-II diabetes mellitus.

EXERCISE

Write short notes on

1. Sleep, eating disorder, anorexia nervosa, bulimia nervosa, anxiety disorder, depression, personality disorder and schizophrenia.

SECTION XIV

EXAMINATIONS

- Examination of Cardiovascular System
- Examination of Central Nervous System
- Examination of Upper Gastrointestinal Tract
- Examination of Lower Gastrointestinal Tract
- Approach to a Patient of Lymphadenopathy
- Jaundice
- Cyanosis
- Clubbing
- Arterial Pulse
- Neck Vein
- General Examination/Survey
- Examination of Respiratory System

Chapter 116

Examination of Cardiovascular System

DEFORMITY OVER THE CHEST WALL

SPECIAL POINT IN CHEST

Midline sternostomy, for CABG left posterolateral thoracotomy for operation of coarctation of aorta infraclavicular scar for pacemaker or ICD suggest cardiovascular disease. Scar mark over 5th ICS on left side below nipple or breast for mitral valvotomy.

The common abnormality of chest wall seen in asso-ciation with cardiovascular system (CVS) anomalies are—

- Prominent venous collateral over chest suggest SVC syndrome or subclavian venous obstruction.
- **Barrel-shaped chest** with pursed lip breathing and use of accessory muscle—suggest COPD with sign of right heart failure.
- **Severe kyphosis** with compensatory lumbar lordosis with pelvic and knee flexion—seen in ankylosing spondylitis associated with AR.
- **Spider angioma**—Seen in
  - *Cardiac cirrhosis*
  - *Osler-Rendu-Weber syndrome.*
- **Precordial bulging**—Suggest cardiac enlargement before puberty (before the ossification of ribs).
- **Kyphoscoliosis associated with cor pulmonale seen in rheumatoid arthritis** which is associated with AR.
- **Ankylosing spondylitis and rheumatoid arthritis** is associated with AR.
- **Shield chest**—Broad chest with angle between manubrium and body of sternum with widely separated nipple seen in—
  - *Turner syndrome*
  - *Noonan syndrome.*
- Heavy muscular thorax with less developed lower extremity with collaterals in axilla and back seen in **coarctation of aorta**.
- Upper portion of thorax shows symmetrical bulging with increase inspiratory effort in children seen in **stiff lung syndrome**.
- **Pectus carinatum** (pigeon chest) and **pectus excavatum** (funnel chest) are seen in connective tissue disease and vitamin D and Ca^{++} deficiency in childhood.
- **Pectus excavatum** is associated with
  - Marfan syndrome
  - Homocystinuria
  - Ehlers-Danlos syndrome
  - Hunter-Hurler syndrome
  - Mitral valve prolapse (MVP).
    - This deformity compresses heart and causes rise in systemic and pulmonary venous pressure.
    - May also present with functional systolic murmur over pulmonary area with loud P_2.
- **ack of normal thoracic kyphosis** (straight back syndrome) is associated with—
  - Expiratory splitting of S_2, parasternal mid - systolic murmur and prominence of pulmonary artery in X-ray.
- **Visible pulsation over apex**—It may be physiological which is less than half cm in side MCL.
  a. In LVH (apical pulsation > 2 cm).
     - Systolic retraction of ribs over apex—**Broad-bent's** sign seen in **constrictive pericarditis**.
  b. In thin tall patient and patient with COPD apex may be visible over epigastrium.
- **Systolic retraction of left 2nd ICS** (seen in pulmonary artery enlargement).
- **Systolic pulsation of right 2nd ICS**—Suggest aortic aneurysm.
- **Visible cardiac pulsation lateral to MCL** suggests cardiac enlargement, or there is thoracic deformity or congenital absence of pericardium.
- **Shaking of entire precordium** with each heartbeat suggests hyperkinetic circulatory state like AR, PDA.
- **Pulsation of right sternoclavicular joint** suggests aortic aneurysm.

INSPECTION

Special points to be noted in general survey during examination of CVS are as follows:

1. **Pallor**—It is an important sign in general examination as it aggra vates CHF, IHD and angina.
2. **Cyanosis (central)**—Seen in patient with congenital cyanotic heart disease and in severe LVF (HF can also present with peripheral cyanosis).

- *Peripheral cyanosis (acrocyanosis)*—Seen in severe heart failure, shock, peripheral vascular disease and can be aggravated by β-blocker.
- *Differential cyanosis*—Seen in PDA with coarctation of aorta and reversal of shunt; this can be better seen after leg exercise.
- *Reverse differential cyanosis*—Cyanosis of finger greater than of toes seen in **Taussig-Bing** anomaly which have anomalous origin of great arteries (aorta from RV and pulmonary artery from LV) with PDA and reversal of shunt and coarctation of aorta.

3. Hereditary hemorrhagic telangiectasias on the lip, tongue, mucous membrane as a apart of **Osler-Rendu-Weber** syndrome when present in lung may cause right to left shunt.
   - *Malar telangiectasia*—Seen in mitral stenosis and scleroderma.

   Tan or bronze discoloration seen in hemachro- matosis associated with systolic heart failure.
4. **Clubbing**—The cardiovascular diseases along with clubbing are as following:
   a. Congenital cyanotic heart disease
   b. Infective endocarditis
   c. Pulmonary disease with hypoxia
   d. Left atrial myxoma.

   Unilateral clubbing seen in aortic aneurysm interfering with the arterial supply of the arm.
5. **Other changes seen in the finger in CVS anomaly are**
   - *Osler's nodes*—Small tender, purplish, nodular skin lesion due to infective microemboli in the pad of finger, toe, palm, sole.
   - *Janeway lesion*—Slightly raised, nontender hemorrhagic lesion on palm and sole.
   - *Splinter hemorrhage*—Linear petechial hemorrhage develop under mid-position of nail plate (all three signs are seen in SABE).
6. **Edema**
   - *Bipedal edema* seen in CCF and constrictive pericarditis and IVC obstruction.
   - *Unilateral edema* seen in venous/lymphatic obstruction in DVT filariasis and metastatic deposit.

     Edema of face seen in—
     - SVC obstruction
     - Glomerulonephritis in children.
7. **Respiration**—It is required for NYHA staging of heart failure. Abnormalities of respiration seen in CVS diseases are—
   - Shortness of breath, orthopnea, Cheyne-Stokes breathing seen in heart failure.
   - Paroxysmal nocturnal dyspnea (PND)—Seen in MS, LVF.
8. **Decubitus**
   - *Sitting upright with shortness of breath (orthopnea)*—Seen in HF and COPD.
   - *Sitting upright with leaning forward* → HF with LA enlargement.
   - *Whole body shakes with each heartbeat* (bobbing of head with each heart beat known as de Musset's sign) → Seen in AR.
   - *Platypnea (orthodeoxia)*—SOB increases during upright decubitus seen in left atrial myxoma and hepatopulmonary syndrome.

NYHA Functional Classification:
Class I
- No limitation of physical activity
- No symptom with ordinary exertion

Class II
- Slight limitation of physical activity
- Ordinary activity causes symptom

Class III
- Marked limitation of physical activity
- Less than ordinary activity causes symptom
- Asymptomatic rest

Class IV
- Inability to carry out any physical activity without discomfort
- Symptom at rest

9. **Cardiac cachexia**: Seen in HF due to various cytokines, e.g. TNF and diminished intestinal absorption.
10. **Extensive lentiginoses**: Seen in **carney syndrome** associated with multiple atrial myxomas and a variety of developmental defect of cardiovascular system.
11. **Lupus pernio and erythema nodosum**—Seen in sarcoidosis associated with DCM, heartblock, ventricular tachycardia.
12. **Ecchymosis**—Seen in vitamin K antagonist and antiplatelet over dose.
13. **Subcutaneous xanthomas along tendon sheaths and extensor surface**—Seen in various lipid disorder **eruptive xanthomatosis** and **lipemia retinalis** seen in severe hypertriglyceridemia.

    Palmar crease xanthomas — specific for type III – hyperlipoproteinemia.
14. **Pseudoxanthoma elasticum**—Associated with premature atherosclerosis manifested by leathery cobbled stone appearance of skin in axilla and neck crease associated with angioid streaks on fundo- scopic examination.
15. **Jaundice**—May be due to advanced right heart failure, congestive hepatomegaly or cardiac cirrhosis.
16. **Neck veins**—To be examined in detail as it gives us functional status of the right side of the heart. It has three upstrokes and three downstroke.
    - *Upstrokes are*
      - a-wave → is due to atrial contraction.

- c-wave → is due to carotid artifact or upward displacement of tricuspid valve with cusp during isovolumetric contraction of RV in systole.
- v-wave → is due to passive venous congestion of right atrium during ventricular systole.

– *Downstrokes are*
- x descent → is due to atrial relaxation.
- x-wave → is due to atrial relaxation or downward displacement of tricuspid ring with valve during rapid ejection phase of ventricular systole.
- y-wave → is due to opening of tricuspid valve at the end of ventricular systole when blood from atria rushes to ventricle in the first rapid filling phase of diastole.

– *Common abnormality of neck vein*
- a-wave absent in atrial fibrillation.
- giant a-wave present in tricuspid stenosis, right ventricular hypertrophy, pulmonary artery hypertension (HTN).
- cannon a-wave seen in A-V dissociation or atrial systole against closed tricuspid valve seen in right ventricular pacing.
- c-v wave present in TR.
- stiff 'y' descent seen in pericardial tamponade, COPD.

Abdominojugular reflex is elicited by firm pressure over right upper abdomen for 10 seconds. A positive response is defined by a sustained rise of JVP > 3 cm for at least 15 seconds after release of pressure. Patient should not do Valsalva or breath-holding during the procedure. Positive abdominojugular reflex suggest pulmonary artery wedge pressure > 15 mmHg.

Kussmaul sign—It is defined by either rise or lack of fall of the JVP during inspiration (normally JVP fall by at least 3 mm during inspiration) seen in – constrictive pericarditis, restrictive cardiomyopathy, massive pulmonary embolism and RV infarct, advanced systolic LVF.

17. **Pulse**:

– **Rate**—Normal rate is 60–100/min.
In bradycardia rate is <60/min.
Causes of bradycardia
- Hypothyroid
- Obstructive jaundice
- Vagal hypertonicity.

In tachycardia rate is >100/min.
Causes of tachycardia
- Enhanced automaticity.
- Reentry phenomenon.
- Triggered activity.

– **Rhythm**—The most common abnormalities are
- Ventricular ectopic
- Atrial fibrillation/atrial ectopic.

– **Causes of radioradial and radiofemoral delay and impalpable peripheral pulse are**
- Atherosclerotic occlusion of great arteries
- Takayasu disease
- Coarctation of aorta
- Buerger's disease
- Dissecting aneurysm
- Fibromuscular dysplasia (FMD).

– **Special character of pulse**
- **Water-hammer pulse** also associated with (**Corrigan's sign** – which is vigorous pulsation of the carotid arteries) **Seen in hyperdynamic circulatory state like** AR, PDA, anemia, thyrotoxicosis, pregnancy, exercise, A-V fistula Paget's disease of bone.
- **Pulsus parvus et tardus**—It is a weak and delayed pulse seen in severe aortic stenosis.
- **Anacrotic/plateau pulse** present in AS.
- **Pulsus bisferians** present in AS with AR.
- **Pulsus bigeminy** present in HOCM.
- **Pulsus alternans** present in HF.
- **Pulsus paradoxus/pulsus normalise exaggeratus**—greater than normal (10 mmHg) dip in SBP during inspiration seen in:
  - Cardiac tamponade
  - Constrictive pericarditis
  - COPD.

18. **Distinctive general appearance** → associated with cardiac abnormality:

A. *Marfan syndrome* → Associated with **AS** and **AR**. Features of Marfan's are as follows:
- **High arch palate**.
- **Long extremity** → arm span >height.
- **Lower segment** (pubis to foot) >upper segment (head to pubis).
- **Positive thumb sign, positive wrist sign, Arachnodactyly**—when feast in made over cleanched thumb—the thumb does not extend beyond ulnar side of hand, but usually does so in Marfan.
  Overlapping of thumb and fifth finger around wrist.

B. *Turner syndrome*—Associated with
- Coarctation of aorta
- Bicuspid aortic valve.

Features—*Short stature, cubitus valgus, medial deviation of extended forearm, increase angle between body and manubrium sterni, widely separated nipple, short webbed neck.*

C. *Holt-Oram syndrome*: Associated with:
- **ASD** with skeletal deformity.

- **Thumb with extraphalanges** (fingerized thumb).
- **Deformity of radius and ulna** causing difficulty in supination and pronation.

D. *Noonan's syndrome*—Associated with PS (Hallmark).

Special Point in Head and Neck

- **High arch-palate**—Seen in Marfan syndrome
- **Bifid uvula**—Seen in Loeys-Dietz syndrome.
- **Orange tonsil**—Characteristic of Tangier's diseases.
- **Hypertelorism, low set ear, micrognathia**—are associated with many congenital heart disease.
- **Saddle nose deformity**—seen in Wegener's granulomatosis and when saddle nose is associated with inflamed pinna seen in polychondritis.
- **Ocular manifestation of hyperthyroidism** associated with heart failure.
- **Blue sclera**—features of osteogenesis imperfecta.
- **Fundoscopy**—is diagnostic of hypertension and diabetes.

Special Point in Abdomen

- In advanced COPD point of maximal cardiac impulse may be in the epigastrium.
- Liver is frequently enlarged and tender is CHF.
- Systolic pulsation over liver signify severe TR.
- Splenomegaly may be a feature of infective endocarditis.
- Ascites may be associated with heart failure, constrictive pericarditis and hepatic cirrhosis.

PALPATION OF PRECORDIUM

- Palpation to be done after full exposure of chest and elevated to 30° from lower segment with patient both supine and in left lateral position.
- Subxiphoid region is palpated with breath held in inspiration for right ventricle.
- Precordial tenderness suggests Tietze syndrome which is due to costochondritis.
- **Apex is the downmost and outmost point in the precordium where a definite cardiac thrust can be palpated.** Normal apex is located in the 5th ICS 1.5 inside mid clavicular line or nine centemeter away from midline.

> • During isovolumetric contraction of ventricle, heart rotates counterclockwise and the lower most portion of LV strikes the anterior chest wall cause brief outward motion which is responsible for apex beat followed by medial retraction of ventricle and anterior chest wall during rapid ejection phase of systole

- Location of apical impulse is actually above the anatomical apex.
- **Displacement of apex more than 10 cm** lateral to midsternal line indicates LVH.
- **Diameter of palpable apex ≥3 cm is a sign of LV** enlargement.
- Scoliosis, straight back syndrome and pectus excavatum can cause lateral displacement of apex in normal-sized heart.
  - **Special character of apex**
    - *Forcefull and well-sustained* apex felt in AS.
    - *Forceful but ill-sustained* apex felt in
      - » AR, MR
      - » Asthenic person
      - » Mild LV enlargement
      - » Normal LV with augmented stroke volume.
  - **Palpable thrill over apex**—(Palpable homolog of murmur)

    Timing of thrill is done by placing left thumb over bifurcation of carotid. If the thrill coincide with systolic carotid pulse then it is a systolic thrill. If the thrill does not coincide with apex beat then it is a diastolic thrill.
    - *Systolic thrill* radiating to axilla → found in MR.
    - *Diastolic thrill* localized over apex → found in MS.
    - *Left ventricular heave/lift*

    [Sustained outward motion of an area > 3 cm and persists throughout the systole upto S_2 accompanied by systolic retraction of left parasternal region is the criteria for left ventricular heave or lift].

    It is more prominent in left ventricular hypertrophy than LV dilatation without volume overload.
      - » A double outwards thirst of LV is characteristic of HOCM who may exhibit a parasternal cardiac expansion thus resulting in 3 outward separate motion of the chest wall.
- **Left parasternal thrust**: Suggests RVH or LA enlargement in MR and MS.
- **A palpable and visible thirst** over left/right sternoclavicular joint or suprasternal notch suggest aortic aneurysm.
- **An outward motion of apex** coinciding with the first rapid filling phase and the last rapid filling phase of LV can be palpated in MR, concentric LVH, LVF myocardial ischemia, myocardial fibrosis, during expiration when the patient is examined in left lateral decubitus.
- **Systolic pulsation of pulmonary trunk** in 2nd ICs just left of sternum seen in pulmonary hypertension. This is usually associated with right parasternal pulsation.
- **Palpable shock**: It is due to forceful closure of pulmonary valve – associated with PAH felt over 2nd ICS just left of sternum also called diastolic shock.

AUSCULTATION

FIRST HEART SOUND (S_1)

1st heart sound (S_1) consists of two components.

a. **1st component**—Prominent over apex whose apex is formed by LV (it is due to sudden abrut arrest of motion of more mobile anterior leaflet of mitral valve).
b. **2nd component**—Confined to lower left sternal edge and less commonly heard over apex, seldom heard at the base (it is due to closure of tricuspid valve).

Mechanism of production of 1st major component of S_1—It coincide with sudden abrupt arrest of motion of larger and more mobile anterior cusp of mitral valve (MV).

Causes of loud S_1

- Short PR interval <0.10 sec
- Tachycardia/hyperkinetic state
- Stiff LV
- MS (early phase when the valve is not calcified)
- Left atrial myxoma
- Holosystolic MV prolapse
- Thin chest wall.

Causes of soft S_1

- PR >0.12 sec.
- Depressed LV contraction—LVF/DCM.
- AR/MR.
- LBBB.
- Flail mitral leaflet.
- Extracardiac cause—Thick chest wall, emphysema, pleural effusion, pericardial effusion and pneumothorax.

Widely split S_1 —Complete RBBB

Single S_1—Complete LBBB.

SECOND HEART SOUND (S_2)

Second heart sound is composed of **aortic** and **pulmonic component** and are due to closure of aortic and pulmonary valve respectively.

There is a normal physiological splitting of (0.004 second gap) between A_2 and P_2.

P_2 is considered loud when its

- **Intensity exceeds that of A_2** at the base.
- When it **can be palpated** over left second ICS.
- When **both A_2 and P_2 can be heard at lower left sternal boarder or apex**.
  - This **splitting (A_2–P_2 gap)** increases during inspiration and narrows during expiration.
  - **A_2–P_2 gap also increases in RBBB**, due to late electrical activation of RV and in **MR** due to early closer of aortic valve.
  - **Narrow splitting** or even **single S_2** can be heard in **pulmonary hypertension** due to early closer of pulmonary valve.
  - **Fixed splitting of S_2** (unchanged A_2–P_2 gap in respiratory cycle) heard in **osteum secundum type of ASD** where A_2–P_2 gap is wide and fixed (does not change during respiration).
  - **Reversed or paradoxical splitting** is due to delay in closure of aortic valve due to late activation of left ventricle and can be heard in **LBBB** and in **right ventricular pacing** and **severe AS** and **HOCM** (where left ventricular ejection time has increased).

THIRD HEART SOUND (S_3)

Third heart sound (S_3) occurs during first rapid filling phase of the ventricular diastole. It can be heard in (60%) normal **children**, **adolescent** and **young adult** but in older patient it signifies **heart failure**. Left sided S_3 is a low pitched sound best heard over apex and a right sided S_3 is better heard at
lower left sternal boarder and louder during inspiration.

FOURTH HEART SOUND (S_4)

It is always pathological. It occurs during the last rapid filling phase of ventricular diastole (which is due to atrial systole) and signifies left ventricular presystolic expansion. So it is absent in patient with atrial fibrillation. S_4 is more common in patient who desire significant contribution by atrial contraction to ven- tricular filling such as left ventricular hypertrophy and acute myocardial ischemia.

SYSTOLIC SOUND

- **Early systolic ejection sound (not click)**
  This is associated with
  - Congenital aortic valve stenosis
  - Bicuspid aortic valve
  - Congenital pulmonary valve stenosis.

  Mechanism
  - Abrupt cephalad doming of abnormal semilunar aortic or pulmonary cusp.
  - Opening movement of the leaflet that resonate the aortic trunk or the wall of the dialated great artery (aorta or pulmonary artery).
    - Ejection sound that is heard in bicuspid aortic valve become softer and inaudible as the valve are calcified and become more rigid.
    - Ejection sound that occurs in PS moves closer to S_1 as severity of PS increases and it is the only sound of right sided origin that decrease with inspiration.
- **Midsystolic sound (midsystolic click)**
  - This is associated with MV prolapse.
  - These are high frequency sound coincide with maximal systolic excursion of prolapsed anterior

leaflet or two scallop of posterior leaflet into the left atrium caused by sudden tensening of the redundant leaflet or elongated chordae tendineae.
- Physical/pharmacological intervention that reduces LV volume (valsalva) causes ejection click to occur earlier in systole.
- Physical/pharmacological intervention that increases LV volume (hand-grip) and squatting delays the ejection click.
- Multiple ejection click thought to occur due to asynchronous tensening of different portions of redundant mitral leaflet, specially triscalloped posterior leaflet.

DIASTOLIC SOUND

Opening Snap (OS)

It is a high pitch sound heard in MS patient after S_2.

It is due to sudden abrupt depression of fibrosed mitral cusp from upward position to downward position at the beginning of ventricular diastole.

The **S_2–OS gap** is inversely proportional to the tightness of MS or left artial–left ventricular pressure gradient.

The **intensity of OS** progressively decreases with calcification of the valve.

Loud OS signifies cusp are still pliable and not calcified and no significant AR or MR present.

Pericardial Knock

A high pitch sound due abrupt cessation of ventricular expansion after tricuspid valve opening heard in constrictive pericarditis.

Tumor Plop

A low pitch sound that is rarely heard in patient with left atrial myxoma due to diastolic prolapse of the tumor or mass though mitral valve.

CARDIAC MURMUR

Cardiac murmur are the audible vibrations that are created by increased unusual turbulence of blood. But all murmur are not indicative of structural heart disease. Some murmur are simply due to increased flow of blood as ejection systolic murmur heard in severe anemia or pulmonary flow murmur in ASD. **The intensity of a heart murmur is graded on a scale of 1–6, where a thrill is present with murmur of grade 4 or higher intensity**.

Other parameter that have to be noted in a murmur are
- **Timing of the murmur** whether systolic or diastolic.
- **Location of the murmur**
- **Radiation of the murmur**
- **Response to bedside maneuvers**.

Systolic murmur are usually of three types
- **Holosystolic/pansystolic murmur**
- **Ejection systolic/midsystolic murmur**
- **Late systolic murmur**.

HOLOSYSTOLIC/PANSYSTOLIC MURMUR

It is heard in chronic MR, TR and VSD where the murmur starts with the first sound (S_1) persist throughout the systole, spills over the second heart sound (S_2) and even encroach into protodiastolic period but acute severe MR produces a early systolic decrescendo murmur due to the progressive diminution of pressure gradient between left ventricle and left atrium.

The murmur of MR is best heard over the apex and when the MR is *due to anterior leaflet involvement. It radiates posteriorly toward axilla whereas the murmur of MR that is due to posterior leaflet involvement radiates toward base of the heart* and may be confused with murmur of AS.

Systolic murmur of TR increases in intensity during inspiration and best heard at lower left sternal boarder with regurgitant CV wave visible in the jugular venous pulse.

EJECTION SYSTOLIC/MIDSYSTOLIC MURMUR

It starts *after the isovolumetric contraction phase of ventricle, i.e. during maximum ejection phase of ventricular systole and rapidly reaches its peak in midsystole then gradually fades away before S_2*. Usually this crescendo decrescendo murmur is audible in aortic stenosis which is usually associated with thrill over right second interspace where it is loudest with radiation to carotid and accompanied by soft A_2 and sustained LV-apical impulse and an S_4 but some time patient with aortic sclerosis can have grade 2–3 midsystolic murmur identical to aortic stenosis. Other causes of midsystolic murmur are
- Pulmonary stenosis.
- HOCM.
- Flow murmur of large ASD and several other condition associated with accelerated flow is absence of structural heart disease like. AR fever, thyrotoxicosis, pregnancy, anemia and normal adolescence.

The murmur of HOCM can be differentiated by dynamic auscultation.

It increases in intensity by maneuvers that decrease left ventricular preload or increase left ventricular contractility, i.e. during the strain phase of the Valsalva and after quick standing from squatting.

Murmur become softer in intensity by maneuver that increases left ventricular preload or after load like passive leg rising or squatting.

The murmur of HOCM is best heard between lower left sternal boarder and apex. The murmur of PS is loudest over left second interspaces.

The flow murmur of ASD is loudest over left mid sternal boarder.

LATE SYSTOLIC MURMUR

A late systolic murmur best heard at the apex indicates MVP. This murmur may or not be associated with a click.

With standing LV volume decreases as a result the click and murmur move closer to S_1. Whereas with squatting the click and murmur mover away from S_1 owing to the increases in LV volume and impedance.

DIASTOLIC MURMUR

In contrast to systolic murmur, diastolic murmur always signify structural heart disease.

The diastolic murmur is also of three types:

- **Early diastolic decrescendo murmur** of AR or TR.
- **Middiastolic murmur** of MS is due to increased turbulance at mitral valve during first rapid filling phase of the ventricular diastole.
- **Late diastolic murmur** of MS which is due to increased flow across the mitral valve during atrial systole or last rapid filling phase of ventricular diastole.

EARLY DIASTOLIC DECRESCENDO MURMUR OF AR/TR

The length of the murmur of AR and TR varies inversely with the size of the defect. Large size defect causes short duration murmur due to rapid rise of left ventricular diastolic pressure and the progressive diminition of the aortic—left ventricular pressure gradient.

The decrescendo murmur of chronic severe AR is best heard over **neoaortic area** (left 3rd space close to sternum) with a radiation toward the apex when the defect is primarily in the valve cusp but when AR is due to aortic root dilation the murmur radiates along the right sternal boarder as seen in ankylosing spondylitis and dissecting aneurysms.

The murmur of PR (pulmonary regurgitation) is also heard along the left sternal boarder and is most commonly due to pulmonary hypertension and enlargement of the pulmonary artery annulus. It is associated with right ventricular parasternal lift that is indicative of chronic right ventricular pressure over load and single loud S_2 with palpable pulmonary component.

MID AND LATE DIASTOLIC MURMUR

Mitral stenosis murmur is the classic example of mid and late diastolic murmur best heard over the apex and the patient is in left lateral decubitus. Middiastolic murmur is low pitch and rumbling is character and is due to first rapid inflow phase of ventricular diastole which starts with an opening snap (OS). Late diastolic or presystolic component is due to increase flow of blood across mitral valve in the last part of ventricular diastole which coinside with atrial systole when the patient is in sinus rhythm. It is absent when mitral stenosis patient is in atrial fibrillation. Middiastolic low pitch rumble (murmur) may also be heard in the following situation other than MS are

- **MR, TR, VSD** due to increased flow across mitral valve.
- **Austin flint murmur** (a low pitch middiastolic rumble) in AR is due to high frequency fluttering of anterior cusp of mitral valve in between the two jet of blood simultaneously entering left ventricle in ventricular diastole.
- **Left atrial myxoma** obstructing the flow through mitral valve.
- In **ASD** over 4th space paresternal region due to increase flow through tricuspid valve.
- **Carey Coombs** murmur due to edema of cusp in acute rheumatic mitral valvulitis.

The classic description of mitral stenosis murmur is a *low pitch middiastolic rumbling murmur which start with an opening snap and has a presystolic accentuation with a short sharp accentuated 1st heart sound, best heard with the bell of the stethoscope, patient lying left lateral position and the breath held at the end of expiration*.

The murmur **starts with an opening snap** which is due to downward depression of stiff mitral cusp from upward position to downward position at the beginning of ventricular diastole).

Low pitch middiastolic rumbling murmur (which is due to turbulence at mitral valve during the first rapid filling phase of ventricular diastole).

A presystolic accentuation which is due to last rapid filling phase of ventricular diastole and is due to atrial systole.

Short sharp accentuated first heart sound is due to stiff and fibrosed mitral cusp.

Best heard with the bell of the stethoscope (as the murmur is a low pitch sound).

Patient lying left lateral decubitus and the breath held at the end of expiration (left-sided murmur increase in expiration) provided the patient is in sinus rhythm.

But when the patient is in atrial fibrillation the description of the auscultatory finding in mitral stenosis is *middiastolic rumbling murmur with a variable intensity first heart sound best heard with the bell of the stethoscope patient lying left lateral decubitus and the breath held at the end of expiration*.

Continuous murmur are those murmur that typically begins in systole spill over (envelop) the second heart sound (S_2) and continue through some (early) portion of diastole.

The classic example of continuous murmur over precordium are

- **Patent ductus arteriosus** which is heard over 2nd and 3rd intercostal space slightly away from sternum.
- **Rupture of sinus of valsalva** aneurysm with creation of aortic-right atrial or ventricular fistula.
- **Aorticopulmonary fistula**.
- **Coronary arteriovenous fistula**.

Benign causes of continuous murmur are

- **Cervical venous hump** heard in children and adolescent.
- **Mammary souffle** of pregnancy.

DYNAMIC AUSCULTATION

- **Respiration**—Right-sided murmur and sound increases with inspiration except pulmonary ejection sound.
- **Valsalva maneuver**—Most murmur decreases in length and intensity during the initial phase of valsalva except murmur of HOCM and MVP which become louder and longer.

After release of Valsalva right-sided murmur tend to return to normal earlier than left sided murmur.

- **During the strain phase of valsalva**—The **murmur associated with MVP and HOCM increase in intensity** due to rise in systolic BP of aorta left ventricle had to pump more forcefully whereas less amount of blood is ejected during this phase so the **murmur of aortic stenosis diminishes in intensity**.
- **After VPC and atrial fibrillation**—Murmur origina- ting from normal or stenotic semilunar valve increases in intensity with increase diastolic cycle length.

Systolic murmur due to MR or MVP either donot change or diminished or shorter in length with in- crease diastolic cycle length.

- **Sudden standing** which causes diminished preload in responsible for **diminished murmur except murmur of HOCM and MVP** which become louder and longer.

With sudden squatting and passive leg rising which cause increase preload, **most murmur becomes louder except those of HOCM and MVP** which becomes softer or may disappear due to increase LV volume.

- **Exercise**—Isometric or isotonic exercise cause louder murmur due to increase blood flow in PS or MS, MR, VSD and AR. But the murmur of HOCM often decrease with hand grip exercise due to increase LV volume. Left sided S_3 and S_4 due to IHD often accentuated by exercise.

Chapter 117

Examination of Central Nervous System

INTRODUCTION

Examination of central nervous system (CNS) is subdivided under following sub-headings:

- Assessment of higher function and speech
- Examination of spine and cranium
- Examination of cranial nerves
- Examination of motor system
- Examination of sensory system
- Examination of reflexes
- Examination of plantar response
- Examination of gait
- Special examination of cerebellar function.

EXAMINATION OF HIGHER FUNCTION

Level of Consciousness (Table 117.1)

Level of consciousness (assessment of the degree of altered consciousness)—This is done by **Glassgow coma scale** or **EVM scale**. (E–eyeball movement, V—vocal response, M—motor activity). In these scales three signs are noticed. Vide Table 117.1.

- **Coma**—It is a deep sleep like state from which **arousal is not possible** whatever may be the intensity of stimulus. The deeper degree of unconsciousness are common in pontine and lower brainstem lesion which is associated with loss of pupillary, corneal and swallowing reflexes.
- **Stupor**—It is lighter form of coma from which **temporary arousal** is possible by strong stimulus and the patient can resist that painful stimulus.
- **Drowsiness**—It is a deep sleep like state from which **complete arousal** for a short period is possible during which the patient is cooperative and answer reasonably but tends to sink into sleep again if stimulation cases.

  Stupor and drowsiness is accompanied by some degrees of confusion.

  A confused patient may be alert and even co-operative but he is not correct in his comprehension and assessment of his own state or environment and this is usually tested by three parameter.

Table 117.1: glassgow coma scale/EVM scale

	Eye opening	**Score alloted**
1.	No eye opening	1
2.	Eye opening to painful stimulus	2
3.	Eye opening to vocal command	3
4.	Eye opening spontaneously	4
	Vocal response	**Score alloted**
1.	No verbal response	1
2.	Verbal response limited to comprehensible sound	2
3.	Verbal response limited to appropriate word	3
4.	Verbal response limited to confused speech	4
5.	Verbal response with oriented speech	5
	Motor response	**Score alloted**
1.	No motor response	1
2.	Motor response limited to extensor of limb to pain	2
3.	Motor response limited to flexion of limb to pain	3
4.	Motor response limited to withdrawal of limb to pain	4
5.	Motor response limited to localize pain	5
6.	Motor response to obey command	6

Orientation of time, place and person

- **Orientation for time**—Ask the patient about day, date, month, year and how long he has been in his present place.
- **Orientation for place**—Ask the patient about name of the building, town and country.
- **Orientation for person**—Ask him what is his work, age, and whether he can recognize his doctor, nurse and relative.

Position of the body

- **Neck retraction**—In children it indicate meningeal irritation (**meningitis**) or **cerebellar tonsillar pressure cone**.
- **Neck retraction with opisthotonus**—It may be seen in **meningitis and tetanus**.
- Curling of the body away from light seen in meningitis or subarachnoid hemorrhage.
- Deviation of the angle mouth to one side with dribbling of saliva from other side and with unequal nasolabial fold, upper limb is pronated and adducted and lower limb is externally rotated usually seen in acute hemiplegia.
- **Decerebrate attitude**—In the position *all four limb are extended upper limbs are pronated* and *feet are plantar flexed. It is due to lesion of midbrain between superior and inferior colliculus and pons.*
- **Decorticate attitude**—In this position the *upper limbs are flexed* and *lower limbs are in extended* position is seen in the *lesion of basal ganglia or inbetween basal ganglia and cerebral cortex*.
- **Size of pupil and light reflex in comatosed patient**:
  - **Presence of light reflex** in a comatosed patient suggest—*Toxic and metabolic disorder* as a cause of coma but its *absence suggest structural lesion of brain* as a etiology of coma.
  - **Bilateral widely dilated (7–9 mm) nonreacting pupil suggest**—A lesion is midbrain that had affected either oculomotor nucleus or 3rd nerve.
  - **Bilateral medium size (4–7 mm) nonreacting pupil**—Suggest a *central compressive lesion of midbrain usually due to tentorial herniation* as a result of tumor or hematoma in the supratentorial compartment which has involved both oculomotor. Complex and sympathetic fiber in the midbrain.
  - **Unilateral pupillary dilatation** with deteriorating level consciousness suggest *unilateral tentorial herniation* and if no surgical intervention done promptly both pupil will be dilated due to secondary hemorrhage in the brainstem.
  - **Very small pupil (0.5–1 mm)** are seen in pontine lesion and in morphine like narcotic poisoning.

Examination of Memory

Memory is divided into recent and past memory.

Recent memory is tested by asking the patient about significant events of the day or previous week, months or years. Ask about how he has come to this building or about the significant events of the newspaper or TV or local important sporting news or readout clearly and slowly a series of numbers to him to repeat. Start with three digit then gradually increase by one at each time. Asking him to repeat them in forward order or reverse order. Many people can repeat seven to eight digit in forward order and four to five digit in reverse order correctly.

For past memory—Ask literate patient about date of national importance or personality of national importance. For illiterate patient ask about number of child he had and name of his eldest son or youngest daughter, his address, date, month and year.

Orientation of space and time—It is usually tested by asking the patient where he is and what is the approximate time at present. Whether it is morning, noon, afternoon or evening.

Emotional state

Make a note about the emotional state of the patient like anxious, excited, depressed, frightened apathetic or euphoric.

Euphoria is common in multiple sclerosis.

Aggressive euphoria commonly seen in severe head injury. Emotional excess like sudden laughing or crying commonly occurs in pseudobulbar Palsy due to bilateral cerebrovascular disease.

Delusion and Hallucinations

Illusion is misinterpretation of sensory stimulus. A string may be taken as snake in the semi-dark area.

Delusions are false idea or belief which cannot be erased from mind.

Hallucinations is perception of a sensory impulse although these is actually no sensory stimulus.

Temporal lobe lesion can produce well organized auditory hallucination sometime terrifying whereas occipital lobe lesion of the nondominant hemisphere usually produce well-formed visual hallucination.

SPINE AND CRANIUM

EXAMINATION OF CRANIUM

Note the **size, shape** and **position** of the head.

Palpate, percuss and **auscultate** the skull when required.

Gross hydrocephalus is obvious. If the circumference of head > 50 cm at the level of forehead usually hydrocephalus is diagnosed. In lesser degree hydrocephalus head and face resemble an inverted triangle, forehead being large, bossed and bulging forward over orbit, eyeball are displaced downwards and forward (known as rising sun sign).

- **In microcephaly**—Head appears triangular forehead sloping backward, occiput forward and the cranium coming to a rounded point.
- **In craniosynostosis**—The deformity of the head varies according to which suture are prematurely fused which is felt as hard ridges. Fontanelles are closed, orbits are flattened and the eyes are protruded sometime associated with webbing of finger.

- **In acromegaly**—Size of the head is increased by enlargement of the jaw, ear and nose while the incisor teeths are separated. Skin of the face are coarese and excessively folded around eyes.
- **In advanced Paget's disease**—Head appears enlarged and unnaturally rounded, scalp being red, warm, covered with dilated vessel.
- **In basilar invagination** (craniovertebral anomaly) head appears to lie in extension on a shortened neck, hairline is low and movement of neck is restricted.
- **Palpation of skull** to detect **depressed fracture** and **closer of fontanelles**.

  Fontanelles are normally concave and pulsating but when convex and tense is due to **raised intracranial pressure** in very young child. Anterior fontanelle usually close within 18 months of age. It is prematurely closed in craniosynostosis.

  Localized **bony lump** may lie over **exostosing meningioma** or may be a evidence of a **sarcoma**.

AUSCULTATION

Systolic bruit present over skull in:

- *In young children.*
  - ***Arteriovenous fistula***.
  - ***Caroticocavernous fistula***.
  - ***Tumors of glomus jugulare***.
  - ***Advanced Paget's disease***.
- *Enlarged external vessel supplying vascular meningioma.*
- *Conducted from **carotid stenosis** or **aortic stenosis**.*

EXAMINATION OF SPINE

- **Neck rigidity**—It is examined by placing both hand under the occiput when the patient is in supine posture and by flexing the wrist gently to raise the head forward until the chin touches sternum or by gentle rolling of head over pillow by placing hand over forehead. Neck rigidily is found in meningeal irritation of any cause:
  - **Meningitis**.
  - **Meningoencephalitis**.
  - **Meningism** (seen in enteric fever).
  - **Inflammatory** or **destructive disease** of cervical spine like cervical spondylosis.
  - **Parkinsonism**.
  - In raised **intracranial pressure** and **posterior fossa tumors**, it is a danger sign of **tonsillar herniation**.
  - **Tetanus** (due to spasm of neck muscle).
- **"Kernig's sign"**—Flex each hip in turn to bring thigh over abdomen then try to extend the knee in this position of thigh which can be easily done beyond 90° in normal person but greatly limited in meningeal irritation (**meningitis**) but not affected in other conditions of neck rigidity.
- **"Brudzinski's neck sign and leg sign"**—If the neck is flexed to make the chin to touch the sternum there will be bilateral active flexon of hip and knee known as **"Brudzinski 's neck sign"**.

  Brudzinski leg sign If one hip is flexed to bring thigh over abdomen there will be passive flexion of the other hip is called **"Brudzinski's leg sign"** seen in meningeal irritation (meningitis).
- **Straight leg raising**—In suspected lumbar disk prolapse the ability to raise the extended leg is limited on the side of disk prolapse.

  Lasegue sign raising the normal leg may produce root pain on the affected side.
- ***Kyphosis, scoliosis and kyphoscoliosis**—Usually develops following **caries spine, Friedreich's ataxia, Parkinsonism, muscular dystrophies, syringomyelia, von Recklinghausen's disease, ankylosing spondylities**.*
- **Meningocele and meningomyelocele**—It is a congenital defect in vertebral lamella produce **meningocele** or **meningomyelocele** causing neurodeficit.
- **Excessive lordosis**—It is seen in **muscular dystrophies**. Some cases of generalized **myasthenia gravis** and **congenital hip disease**.
- **Rigid spine**—On forward flexion of lumbar spine, spine remain straight when there is paravertebral muscle spasm seen in **seronegative spondyloarthritis (Schober test)**.
- **Tender spine**—Local bony tumors and infection due to **tuberculosis or pyogenic organism** cause localized tenderness on palpation.

DISORDERS OF SPEECH

Aphonia is disorder of phonation (presenting as hoarseness of voice) is due to diseases of **larynx or recurrent laryngeal nerve**.

Dysarthria—Disorder of articulation (presenting as scanned speech) is due to diseases of **cerebellum**.

Aphasia is a language problem characteristic by defect or deficit in the formal aspect of language such as naming, word choice, comprehension, spelling and syntax is called **aphasia**.

Speech is a mean through which we communicate our thoughts and experiences by linking it to an arbitary symbol known as words.

The neural network of speech language is composed of a network of neucles with interconnecting fiber distributed over the **perisylvian region of the left hemisphere**.

The posterior pole of this network is located at the temporoparietal convolution known as **"Wernicke's areas"**. The main function of Wernicke's area is to transform sensory input into their neural (symbol) word representation (neural signal). In this way every sensory input whether written language or spoken language is kept in the memory loop as neural signal.

The sensory input of written language is coming from calcarine sulcus and that of spoken language is coming from posterior temporal gyrus.

Broca's area is the anterior pole of the language network and is located in the posterior part of inferior frontal gyrus known as **"Broca's area"**. The essential function of this area is the opposite of the Wernicke's area that is it transform neural signal (word) into their articulatory sequences so that the word can be expressed in the form of spoken language or written speech. Wernicke's and Broca's area are interconnected with each other and also with additional perisylvian, temporal, prefrontal and posterior parietal region that subserve various aspect of language function. Damage to any one of these component or their interconnection can give rise to language problem known as **"Aphasia"**.

Wernicke's aphasia—In Wernicke's aphasia **comprehension is impaired** for spoken and written language. In this type of aphasia patient **language output is fluent** but is highly paraphasic and circumlocutious. Use of many word to say something which could be said in a single or few words.

Broca's aphasia—Broca's speech is nonfluent, labored interrupted by word finding pause and full of meaning appropriate nouns and verbs, e.g. I see ... doctor. Doctor send me. .... go to hospital Doctor .... kept me beside. Two .... tee days. Doctor send – me home. Even when the spontaneous speech is severly dysarthric, the patient may be able to display a relatively normal articulation of words while singing. This dissociation has been used to develop specific therapeutic approach **"known as melodic intonation therapy for Broca's aphasia"**. The speech output may be reduced to single word (yes or no). When the cause of Broca's aphasia is stroke, recovery of language function generally takes 2–6 months.

Global aphasia—It represents a combind dysfunction of Broca's and Wernicke's area. *Speech output in non fluent and comprehension of spoken language is also severely impaired. Naming, repetition, reading aloud and writing are also impaired*. It is usually due to strokes that involve the entire middle cerebral artery distribution in left hemisphere with right sided hemiplegia, hemisensory loss and homonymous hemianopia.

Conduction aphasia—Speech output is fluent but paraphasic, comprehension of spoken language is intact. Repetition, naming and writing is severely impaired. Reading aloud is impaired but reading comprehension is preserved.

The lesion spare Broca's area and Wernicke's area but causes a functional disconnection between the two so that neural symbol formed in the Wernicke's area cannot be conveyed to Broca's area for expression.

EXAMINATION OF CRANIAL NERVES

FIRST CRANIAL NERVE (OLFACTORY)

Patient is asked to sniff through each nostril separately bottle containing **coffee**, **almond**, **chocolate**, **oil of lemon**, **pippermint** and asked to name the odors. Common cause of anosmia are:

- Local acute or chronic inflammatory nasal disease (commonest cause).
- Heavy smoking.
- Head injury.
- Intracranial tumors of inferior frontal region compressing olfactory bulb or tract.
- Chronic meningitis (syphilis) and sarcoidosis.
- Parkinson's disease.

SECOND CRANIAL NERVE (OPTIC NERVE)

Second cranial nerve is examined under the following heading:

- Acquity of vision
- Field of vision
- Color vision
- Light reflex
- Ophthalmoscopic examination.
- **Acquity of vision is tested by—PL/PR, hand movement, finger counting, Snellen's type chart or Jaegar type** card depending on the level of vision of the patient.
- **Field of vision**—In clinical medicine it is tested by confrontation perimetry. The common site of lesion of the visual pathway and corresponding visual field defect are as follows:
  - **Total unilateral loss of vision** is due to lesion of the **optic nerve**. Common causes are **optic neuritis**, (demyelinating), Compression and head injury.
  - **Bitemporal hemianopia (tubular vision)**—Loss of temporal field in both eye only central vision persist. Due to lesion at optic chiasma. Common causes are **Pituitary tumors**, **craniopharyngiomas**, **suprasellar meningioma**, **Hypothalamic tumor**, **gross hydrocephalus**.
  - **Bitemporal upper quadrantic defect**—Early stage of chiasmal compression from below, common cause **pituitary tumor**.
  - **Bitemporal lower quadrantic defect**—Early stage of chiasmal compression from above common causes—**Tumors of hypothalamus, suprasellar cyst or meningoma** (not very common).
  - **Altitudinous hemianopia**—Partial lesion of blood supply to the optic nerve.
    Common causes—**Trauma and vascular occlusion**.
  - **Homonymous hemianopia**—It is the most common major field defect caused by lesion anywhere from optic tract to occipital cortex of the opposite side.

- **Lesion in the opposite optic tract** causes *complete but incongruous defect without macular sparing*.
- **Lesion in the opposite optic radiation** causes *incomplete but congruous defect with macular sparing*.
- **Lesion in the opposite calcarine cortex causes** *complete, congruous defect with macular sparing*.
  Common causes—**CVA cerebral tumor, vascular malformation and head injury**.
- **Upper quadrantic homonymous defect**—Opposite temporal lobe lesion involving lower part of the optic radiation where it sweep round the temporal horn of the lateral ventricle or lower calcarine cortex lesion. Common causes—**Cerebral tumor, CVA, cerebral abscesses and head injury**.
- **Lower quadrantic homonymous defect**—Opposite parietal lobe lesion involving upper fiber of the optic radiation where they sweep round the occipital horn of the lateral ventricle and opposite upper calcarine cortex lesion.
  Common causes—**Cerebral tumor, CVA, cerebral abscesses and head injury**.
- **Enlarged blind spot**—Enlargement of the optic nerve head.
  Common causes—**Papilledema** due to increased intracranial pressure.
- **Central and centrocecal scotoma**—It is due to intrinsic lesion of the optic nerve between chiasma and nerve head.
  Common causes—Demyelinating lesion of the optic nerve and optic nerve glioma.

Color vision—It is ideally to be examined by **Ishihara chart** but for practical purpose it is examined by asking the patient to identify the color of common object present in the examination hall.

Common color blindness seen in **red and green color**. Common drug causing color blindness is ethambutol.

Light reflex—Both direct and consensual light reflex are to be tested. The affarent path of light reflex is formed by IInd cranial nerve (from retina to midbrain) and the efferent path is formed by IIIrd cranial nerve (from Edinger-West phal nucleus of midbrain via IIIrd cranial nerve to ciliary ganglion from there via short ciliary nerve to constrictor pupillae).

Loss of direct light reflex—Lesion of the afferent visual path (prechiasmal-portion of the IInd cranial nerve) causes an absent direct but preserved consensual light reflex. The *affected eye is blind but consensual light reflex is preserved*.

Loss of consensual light reflex—It is due to the lesion of IIIrd cranial nerve. This disrupt the efferent path of the light reflex so as to produce *loss of both direct and consensual light reflex* and the *pupil remain dilated* but the *vision is preserved* on the side of lesion.

OPHTHALMOSCOPIC EXAMINATION

In clinical medicine retinal examination is needed for the presence of the following abnormalities.

Retinal Hemorrhage

It is of the following types:

1. **Small/long linear streak or flame-shaped** hemorrhage near vessel.
2. **Larger ecchymoses** capable of obscuring local vessel and retina with irregular outer margin. These two types of hemorrhage usually seen in:
   - Hypertension.
   - Raised intracranial tension.
   - Venous engorgement due to any cause (superior vena caval obstruction).
   - Systemic vasculitis.
   - Hemorrhagic disorder (in this condition it may extend to the retinal periphery).
3. **Small dot/rounded/pinhead hemorrhage**—These are **microaneurysm** of the retinal vessel seen in relation to small blood vessel in the peripheral retina diagnostic **of diabetes**.
4. **Subhyaloid hemorrhage** seen in **subarachnoid hemorrhage**. They appear as large effusion of blood related to or often below disk with cresentic lower and clear cut upper border extending forward towards the lens.

Retinal Exudate

Cotton wool retinal patches (so called because of their fluffy appearance). Causes of retinal exudates are:

- Papilledema
- Renal failure
- Hypertension
- Polyarteritis nodosa (PAN)
- SLE
- Retinal embolism
- Severe anemia.

These are actually **focal ischemic reaction (micro-infarct) of injured axon**. Exudates are not itself diagnostic.

Retinal Vasculitis

They appear as focal or extensive sheathing of vessel or occlusion of retinal vessel and hemorrhage with cells in the vitreous and abnormal leakage of fluorescein in angiography. Cause of retinal vasculitis are

- CMV infection in AIDS
- Tuberculosis

- Syphilis
- Multiple sclerosis
- Systemic vasculitis.

Tubercles

Choroid tubercles are about half the size of the disk, appear as rounded, yellowish at the center with ill-defined raised pink edges surrounded by pigmentation.

Phakomata

It appear as large white or bluish-white plaque that have almost translucent edge and about half to two-thirds of the size of the optic disk and is due to collection of neuroglial cell. It is diagnostic of tuberous scleosis.

DISK

- **Primary optic atrophy**—In this condition, the whole disk is quite white standing out dramatically like a full moon against a dark red sky due to local lesion of the optic nerve, retina or chiasma by **compression, injuries, optic neurities** or Ischemia and familial disorder like "**Leber's disease**".
- **Consecutive optic atrophy**—In this condition the whole disk appear pale, with a greenish tinge and blurred edge. This condition develops following severe swelling of the disk in **papilledema** due to raised **intracranial tension**.
- **Temporal pallor**—In this condition the retina appear pale on the temporal side in a crescentic or quadrantic manner which is usually seen in multiple sclerosis but not diagnostic of it.
- **Papilledema**—The optic disk appear swollen. The cup become less evident the disk appear more uniform color. The area covered by the disk enlarges, the margin cannot be defined and irregular radiant streaks appear. The venis are swollen and engorged and the hump of the vessel entering and leaving the disk becomes very prominent. Small hemorrhage and irregular ecchymoses appear near vein.

  White streakes and patches of exudate appear near the disk margin and spread outward towards macula to produce *macular fan*.

  The papilledema develops due to increased intracranial pressure from any cause. Despite the swelling of the disk, vision may be well-preserved with enlargement of blind spot.
- **Papillitis**—If the swelling of the disk is due to local lesion of the nerve (anterior positioned optic neuritis) the degree of swelling (although variable) is slight and unilateral. Veins are not engorged, the humping is only slight and the disk area is not greatly enlarged. There are peripapillary hemorrhage and vascular sheathing, vision is grossly disturbed due to large central or centrocecal scotoma.

  The papillitis may look more alarming when accompanied by a macular star of exudates.

  The profund visual loss distinguishes papillitis from papilledema of raised ICT.
- **Foster-Kennedy syndrome**—A tumor of the posterior interior frontal lobe can cause optic atrophy by direct compression on the optic nerve of the same side and papilledema on the opposite disk is due to obstruction of the venous return or causing raised intracranial pressure.

THIRD, FOURTH AND SIXTH CRANIAL NERVE

The action of these three cranial nerves are closely linked that is why they are examined together.

Examination of eyelids:

a. **Exophthalmos**—To assess the protrusion of the eye ball, examiner must stand behind the patient and look down on the eye from above to assess whether the eye- ball protrude beyond the level of forehead.
   - Bilateral exophthalmos occurs in **thyroid eye disease, craniosynostosis** and may be associated with downward displacement of the eyeball in **hydrocephalus** and downward and medial displacement in **lacrimal gland tumor**.
   - Unilateral exophthalmos (proptosis)—Most commonly seen in **thyroid eye diseases, retroorbital neoplasm, cavernous sinus thrombosis** (last two condition is usually associated with ptosis and oculomotor palsy).

     In **caroticocavernous fistual**—The eyeball pulsate and there is audible bruit over the eyeball.

b. **Enophthalmos**—Most commonly seen as a part of **Horner syndrome**. Rarely due to maldeveloped eye or misinterpreted in well-fitted prosthesis.

c. **Ptosis**—
   - **True ptosis** occurs in levator palpebrae superioris palsy and is usually associated with paralysis of the extraocular muscle except superior oblique and lateral rectus.
   - **Pseudoptosis**—"Occurs as a part of Horner's syndrome". It occurs due to paralysis of retroorbital muscle of Müller which is supplied by cervical sympthetic.

     Cervical sympathetic comes out from spinal cord through T_1, T_2 root and form superior cervical ganglion from which postganglionic fiber ascend up along the wall of the carotid artery and reenter cranium subsequently it form cavernous plexus from where sympathetic fiber via ophthalmic division of the trigeminal nerve reaches eye and causes pupillary dilatation and static elevation of the upper eyelid due to contraction of Müller's muscle.

Interruption of the sympathetic fiber usually occurs around the carotid artery by chronic meningitis (tuberculosis and syphilis) when the carotid artery enters the cranial cavity.

Component's of Horner's syndrome

- **Pseudoptosis**—Due to paralysis of retroorbital muscle of Müller.
- **Miosis** due to—Paralysis of dilator pupillae.
- **Hemianhydrosis**—Due to paralysis of cervical sympathetic.
- **Enophthalmos**—Due to atrophy of retroorbital Müller's muscle.
- **Loss of ciliospinal reflexes**—Loss of pupillary dilatation when nociceptive stimulus is applied over T_1 and T_2 dermatome.

CONJUNCTIVA AND SCLEROCORNEAL JUNCTION

- **Subconjunctival hemorrhage** develops following scalp injury.
- **Telangiectasia**—It is associated with skin telangiectasia and cerebellar ataxia in the syndrome called **ataxia–telangiectasia**.
- **Retro-orbital tumors** may grow forward and may be visible as red-gray felting on extreme deviation of the eyeball.
- **A yellowish tint** (jaundice) of the upper sclera may be the only sign of liver diseases visible over the bulbar sclera through transparent conjunctiva.
- **An intense inflammation** (redness) of the conjunctiva seen in viral conjunctivitis and **leptospira canicola** infection which is associated with acute meningitis.

  This type of conjunctival reaction is also seen during the migration of a filaria (Loa-Loa) which can cause encephalitis.
- **Conjunctival ulcer** form the triad of **Behçet's Syndrome**.

SCLEROCORNEAL JUNCTION

- **Arcus Senilis**—A grayish white complete or incomplete ring at sclerocorneal junction seen in elderly people some times in younger man is a nonspecific sign of premature atherosclerosis.
- **Kayser-Fleischer ring**—It is seen as golden brown ring lying just inside the limbus of the cornea may be complete or incomplete crescent at the upper and lower margin. It is readily detected by slit lamp examination, some time by ordinary torch light. It is almost diagnostic of heptolenticular degeneration (Wilson's disease due to congenital ceruloplasmin deficiency).

IRIS AND PUPIL

Argyll Robertson pupil—Seen in neurosyphilis. Important features of AR pupil are

- The pupil is small and irregular due to tearing of the margin of the iris as result of posterior synechia (adhesion of iris with the anterior capsule of the lens). as the iris become sticky due to iritis.
- React briskly to accommodation but does not react to light either directly or consensually.
- This lesion is typically bilateral but more marked on one side.
- There is usually patchy depigmentation and radial tearing of the iris (due to iritis and posterior synechia).
- Pupil dilates slowly and irregularly to conjunctival atropine installation which blocks the postsynaptic parasympathetic receptors in the pupillary muscle but there is no constriction with 2% methacholine.
- The lesion is thought to be located in the dorsal part of midbrain (pretectal region).

ADIE-HOLMES PUPIL (MYOTONIC PUPIL)

- This is usually unilateral.
- Characterized by absent or delayed pupillary constriction to light or accommodation.
- Pupillary dilatation also occurs very slowly in the dark.
- The pupil may appear small or large (more commonly large). If small, may be confused with Argyll Robertson syndrome. For differentiation conjunctival installation of 2% Methacholine causes constriction of pupil in Adie–Holmes Pupil but no response in Argyll Robertson pupil.

RELATIVE AFFERENT PUPILLARY DEFECT (MARCUS GUNN PUPIL)

When light falls alternatively on both normal eyes one per second. The pupil of both the eyes should remain constricted due to direct and consensual light reflex. In partial lesion of one optic nerve (in optic neuritis) the pupil on the affected side dilates (instead of constriction) a little or oscillates between dilatation and constriction because in that condition direct light reflex is a weaker stimulus than consensual response. This response is known as **"Marcus Gunn Pupil"**. This is a feature of ipsilateral optic neuritis but usually not seen in bilateral optic neuritis.

Light–Near dissociation—Constriction response of the pupil to accommodation is better than light reflex. This is noted in most partial IIIrd cranial nerve lesion because accommodation is in general a more robust stimulus than light. In extremely rare patient opposite response have been noted in midbrain syndrome like encephalitis lethargica where accommodatory fiber from pyramidal tract to the Edinger–Westphal nucleus are selectively involved.

EYEBALL MOVEMENT IN IIIRD, IVTH AND VITH NERVE LESION

- **VIth cranial nerve palsy** causes failure of abduction of the ipsilateral eye and as a result diplopia develop on lateral gaze to the side of lesion.
- In **complete IIIrd cranial narve palsy** eye is deviated "down and out" owing to unopposed action of the lateral rectus (6th nerve) and superior oblique (4th nerve). In addition to that there will be *complete ptosis* (due to paralysis of levator palpabrae superioris) and *dilated unreactive pupil* due to interruption of parasympathetic fiber accompanying IIIrd craninal nerve.
- In **IVth nerve palsy** patient will complain of diplopia during reading books or walking downstair as the superior oblique muscle depress the eye when it is adducted.

EYEBALL MOVEMENT IN NUCLEAR AND SUPRA-NUCLEAR LESION

The IIIrd, IVth and the VIth cranial nerve nuclei are co-ordinated via medial longitudinal fasciculus (MLF) in the brainstem to convert supranuclear command for desired ocular movement into appropriate signal to the two eye so that they move synchronously.

characteristic pattern of Gaze abnormality are encountered in brainstem lesion.

Parinaud syndrome—It is due to lesion of dorsal midbrain which result in failure of upward gaze with convergence retraction nystagmus (on attempted upward gaze due to adduction saccades and cocontraction of all rectus muscle both eye retract jerkily into the orbit. The lesion is near the colliculi of the midbrain.

- **Lesion of the VIth nerve** causes failure of abduction to the same side.
- **Lesion of the VIth nerve nucleus** causes failure of conjugate movement to the side of lesion that is abduction of the same eye and adduction of the opposite eye due to involvement of the relaying fiber of MLF to the opposite IIIrd cranial nerve nucleus.
- **Internuclear ophthalmoplegia (INO)**—In lesion of **Medial longitudinal fasciculus** (MLF) (which carries interconnecting fiber from 6th nerve nucleus to the opposite IIIrd cranial nerve nucleus) there is ***failure of the internal movement of the addneting during horizontal gauge*** *to opposite side*.

  Most patients have incomplete lesion as a result Instead of complete paralysis of adduction, there is ***slow adduction of the eye with reduced range and nystagmus in the abducting eye***. The nystagmus in the abducting eye results from involvement of the vestibular path which runs very close to MLF.
- A **larger MLF lesion (lesion of MLF and abducens nucleus) cause "one and a half" syndrome**. It results in complete paralysis of horizontal gaze (both adduction and abduction on the side of lesion) and paralysis of adduction is the opposite eye (opposite to the side of lesion). The only horizontal movement possible is the abduction of the opposite eye opposite to the side of lesion. That is why it is called **one and a half syndrome**. Vertical movements are intact.

NYSTAGMUS

It is a defect in ocular posture *characterized by involuntary movement of the eyeball*.

- **Pendular nystagmus**—usually due to defective macular fixation seen in **macular degeneration, choroido-retinitis and albinism, high infantile myopia, opacities of media** characterized by rapid horizonal oscillation to either side of midline present on forward gaze increased by fixation but often looses its pendular character on lateral deviation.
- **Jerky nystagmus**—usually due to **cerebellar disease or vestibular and labyrinthine disorder**.

  Jerky nystagmus—It is characterized by slow drift in one direction and a fast correcting movement in the opposite direction. It may be present at rest or on ocular deviation.
  - It is usually seen in disturbances of the vestibular system
    - **Peripherally in the labyrinth**.
    - **Centrally at the vestibular nucleus** and the connection in between two vestibular nerve.
    - Connection between vestibular nucleus and ocular muscle.
    - **Medial longitudinal fasciculus**.
    - **The upper most cervical segment**.
- *In more peripheral lesion the* ***quick phase is away from the side of lesion and amplitude is greatest in the direction of quick phase****.*
- In more peripheral lesion there are some additional features like **vertigo, tinnitus** and **deafness** as in **acoustic neuroma, Ménière's disease**.
- *In* ***cerebellar lesion*** *or involvements of its* ***brainstem connection*** *the* ***quick phase and the greatest amplitude is towards the side of lesion****.*
- In cerebellopontine angle lesion there are both central and peripheral effect but **amplitude is greatest towards the side of lesion**.
- In central vestibular lesions nystagmus tend to be more chronic and may cause no tinnitus, deafness and vertigo.
- Diseases produce central lesion are—
  - **Multiple sclerosis**
  - **Cerebrovascular lesion**
  - **Tumors of the cerebellum**
  - **Fourth ventricle tumor and C-P angle lesion**.

VERTICAL NYSTAGMUS

It is of the following types:

- **Upbeat nystagmus**—In this form of nystagmus the oscillation is in up and down direction. The quick phase is most often upward. It is due to intrinsic disorder of brainstem such as **vascular accident, encephalitis, multiple sclerosis, syringobulbia** and secondary to compression from **cerebellar tumor, basilar invagination with tonsillar descent and Arnold-Chiari syndrome** and drugs like **benzodiazepine, barbiturates** and **phenytoin**. Upbeat nystagmus is never of labyrinthine in origin.
- **Down beat nystagmus**—It is also a vertical nystagmus with fast phase is directed downward and is provoked by lateral gaze and is associated with oscillopsia. It is characteristic of lesion at foramen magnum usually Chiari malformation.
- **Sea-saw nystagmus**—It is a spontaneous nystagmus in which one eye moves up while the other moves down and is usually associated with conjugate rotation.

  The sea-saw nystagmus is usually due to lesion in the **suprasellar region anterior to IIIrd ventricle**.
- **Convergence-retraction nystagmus**—On looking upward which is usually defective provokes jerky nystagmus with the fast phase inward in a convergent direction.

  It is due to **compression of the upper midbrain by pineal gland tumor**.
- **Nystagmus of dissociated rhythm (ataxic nystagmus)**—This is called ataxic nystagmus seen in internuclear ophthalmoplegia (INO) in which the defective inward movement of the adducting eye is associated with fine nystagmus and coarse irregular and dramatic nystagms of the abducting eye of dissociated rate and rhythm. This is also called **"ataxic nystagmus"** also seen in myasthenia gravis due to asymmetrical weakness of extraocular muscle.

TRIGEMINAL NERVE

It has three branches of which ophthalmic and maxillary division carry only sensory fiber but mandibular division has both sensory and motor component.

FUNCTIONS OF THE VTH CRANIAL NERVE

- To carry all forms of sensation from the face, anterior part of the scalp (up to little posterior to the vertex) and the eyes.
- Carry all forms of sensation from the teeth, gum and general sensation from anterior two-thirds of the tongue, mucous membrane of the cheeks, anterior part of the palate, nasopharynx and nasal passage and sinuses.
- Supply motor connection to the muscles of mastication.

  The distribution of the three sensory divisions of the Vth cranial nerve is given in the picture.

  All forms of sensation pass through gasserian ganglion then via sensory root of Vth nerve to brain-stem.

  Fiber serving touch **sensation enter principal sensory nucleus in the pons**, efferent fiber cross the midline and ascend to the thalamus.

  Pain and temperature fibers *pass* ***downward up to second cervical segment*** *and gradually enter the* ***descending nucleus of the V nerve, ophthalmic division fibre descends to the lowest level****. The efferent fiber from the nucleus cross the midline and ascend to the thalamus via quintothalamic tract.*

ABNORMALITIES

- Total loss of sensation over one half of whole face-indicate lesion of sensory root or ganglion or extensive lesion anterior to the ganglion. Causes are
  - Tumor eroding the base of the skull
  - Large neurofibroma of the IV th or VIII cranial nerve
  - Epidermoid
  - Syphilitic meningitis
  - Fracture base of the skull
  - Sarcoidosis.
- If this sensory abnormality is associated with total loss of sensation over the same side of the body—then the lesion is near the opposite thalamus.
- Total sensory loss over one division—This is found in partial lesion of the ganglion in herpes zoster or acoustic neuroma and in the cavernous sinus by carotid aneurysm and tumors of orbital fissure. The tumor of the base of the brain can involve mandibular division usually both sensory and motor root.
- Touch sensation is only lost over whole face—due to the lesion of principal sensory nucleus is pons by CVA multiple selerosis, pontine tumors.
- **Pain and temperature is only lost but touch is preserved** in the lesion of the desending root in medula in—condition like:
  - **Syringobulbia**
  - **Foramen magnum anomalies**
  - **Thrombosis of posterior inferior cerebellar artery** (PICA).

  The last one is *associated with loss of pain and temperature on the ipsilateral face and contralateral side of whole body (lateral medullary syndrome)*.
- Hyperesthesia over the distribution of Vth nerve is seen in vascular lesion and herpes zoster.

  In **trigeminal neuralgia** light touch of the corner of upper lip, ala nassi, in front of jaw point or below lower lip will produce an intense spasm of pain in the relation

to the division of the Vth nerve and is seen in multiple sclerosis.

MOTOR FUNCTION OF THE VTH NERVE

The main motor supply of the Vth cranial nerve are to the temporalis, masseters and pterygoid muscle. The power of these muscle are tested by standing on the back of the patient and palpate the muscle while the patient clinches his teeth, and does side to side movement of the jaw and mouth opening.

Loss of power and wasting of temporalis muscles and flattening of the angle of jaw are seen in motor neuron disease, muscular dystrophy and compression of the motor root.

Weakness of pterygoid cause jaw to deviate to the normal side on opening the mouth. If the mouth remains open after chewing but closes satisfactorily after rest specially in the evening hours indicate **myasthenia gravis or paraneoplastic syndrome** in malignancy.

There are two reflexs in relation to Vth cranial nerve.

Jaw jerk—The patient opens his jaw slightly and loosely. Examiner places one finger below lower lip and taps it downward with hammer.

In normal person no response or a slight upward jerk is palpable. A brisk jaw jerk amounting to jaw clonus may be seen in bilateral upper motor neuron lesion above pons, e.g. pseudobulbar palsy, motor neuron disease and multiple sclerosis. It is a deep tendon reflex and afferent and efferent path both are formed by mandibular division of Vth cranial nerve.

Corneal reflex—A light touch of cornea with a whisp of cotton near the sclerocorneal junction at the lateral fornix causes bilateral blinking of the eyelid. The whisp of cotton to be brought from the side not from the front to prevent Mèniére's reflex. The affarent path is formed by the ophthalmic division of Vth nerve and the efferent path (closer of eyelid) is formed by VIIth cranial nerve.

- If there is no response on one side—This may be due to defect of the motor or sensory root of the reflex path, i.e. **facial** or **ophthalmic division** of the trigeminal nerve.
- Lesion of the Vth cranial nerve leads to no response from either lid when the defective side is stimulated and normal response from both lid when the normal side is stimulated.
- In VIIth cranial nerve lesion there will be no response from the side of facial paralysis no matter which side is stimulated but if Vth nerve is intact there will be a blink on the normal side even when the side in which VIIth cranial nerve is paralyzed and both eyeball are seen to turn upward.

  Loss of corneal reflex is the earliest sign of Vth cranial nerve lesion and usually seen in **CP angle tumor and aneurysm and tumors in the cavernous sinus and orbital fissure**.

VIITH CRANIAL NERVE (FIG. 117.1)

This nerve give motor innervation to muscles of facial experssion including platysma and stapedius.

The **intermediate nerve (nervous intermedius)** carries secretory fiber to the lachrymal gland and gland of nasal epithelium through the greater superficial petrosal nerve and to salivary gland through chorda tympani which also carries taste sensation from the anterior two-third of the tongue.

- **For frontal belly of the occipitofrontalis**—The patient is asked to wrinkle the forehead and raise the eye-brows and watch for *symmetry of forehead creases on each side*.
- For **corrugator supercilii, proserus and nasalis**—Ask the patient to frown. The **vertical ridges** inbetween the eyebrows are *due to corrugator. Transverse ridge across the bridge of nose is due to proserus* and *creases over the ala of the nose are due to nasalis fiber.*
- Then ask the patient to close the eye if he can do so then the patient does not have lower motor neuron (LMN) facial palsy. If the patient have LMN facial palsy the eye on the paralyzed side will remain open and *"in order to pull a black curtain infront of the eye the patient will roll the eyeball upward which is known as Bell's phenomenon."*

  If the patient can close both eyes then ask him to screw them up tightly and to resist examiners attmepts to open them up.

  If the patient *cannot screw the eyelid tightly on one side although he can close the eye on that side and the examiner can easily open it, then it is a UMN lesion* while in normal person both eyelid will be screwed up equally and equal resistance will be offered from both side.

  These maneuver differentiate UMN from LMN facial palsy very quickly.
- The **lower facial muscles** are tested by two manuver:
  a. Ask the patient to **show his teeth with slightly open mouth**. Note the symmetry of the nasolabial fold and movement of the angle of mouth on two side, and the prominence of platysma below jaw by the side of neck.

     This maneuver is for testing of **levator anguli oris, Depressor anguli oris**. **Levator anguli oris alaeque nasi, zygomaticus major and minor** of both side, **risorius**. **Levator labii superioris, depressor labii inferioris**.
  b. Second movement is **blowing out the checks as whistling or pursing the lips tightly against resistance** is used for testing the power of orbicularis oris and buccinator.

     Secretory function—The flow of tears on the sides can be compared by giving the patient ammonia to inhale. The actual amount of tear production can

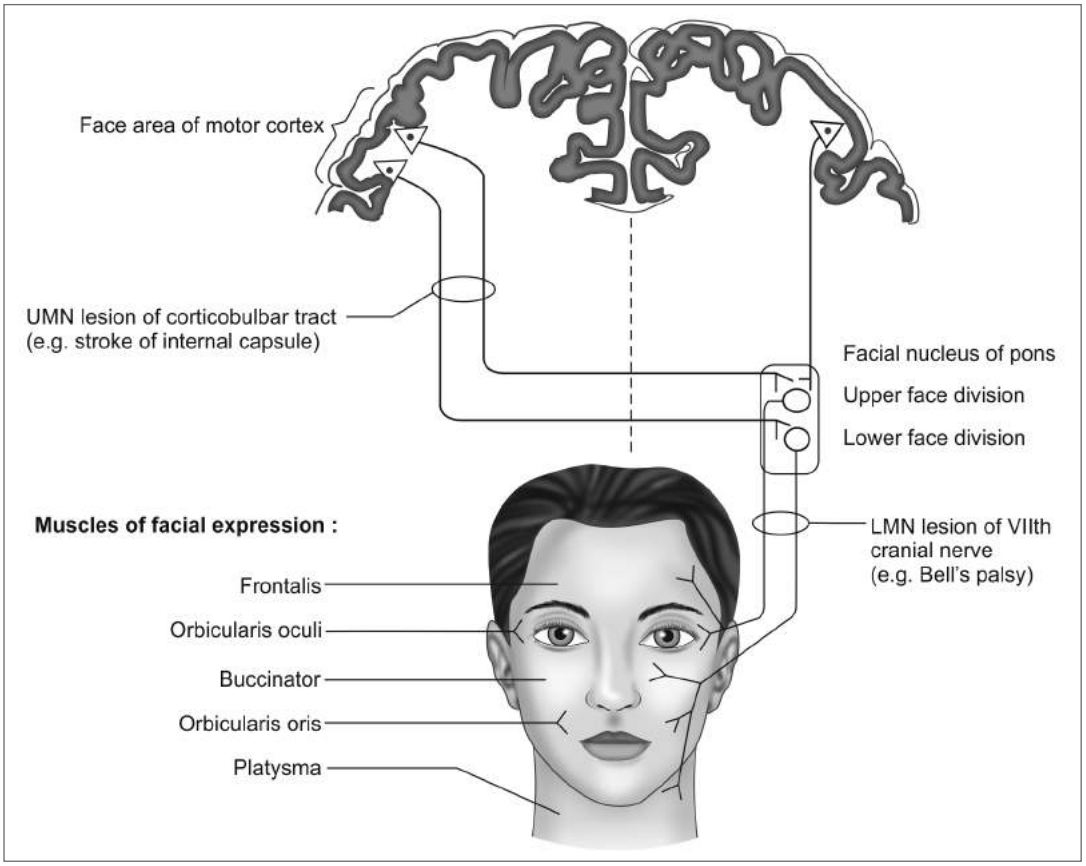


Fig. 117.1: Schematic diagram of facial nerve, nucleus and its connection

be shown by hanging a strip of filter or litmus paper from the lower eyelid and measuring the length of moistening on each side (**Schirmer test**).

UNILATERAL FACIAL WEAKNESS

- In **upper motor neuron (UMN)** type of facial paralysis the power of upper facial muscle, i.e. frontal belly of occipitofrontalis corrugator supercilii, proserus, nasalis and upper fiber of orbicularis oculi will be intact. Creases over the forehead appear on upward gaze, frawning, and simple closer of eye can be done on the paralyzed side but there will be drooping of the angle of mouth with droling of saliva from the angle of the weaker side and the nasolabial fold will be more prominent on the normal side. There will be deviation of the angle of mouth to the healthy side on voluntary action.

  The eye can be closed voluntarily but **tight screwing of eyelid is not possible** and the orbicularis oculi is much weak on the paralyzed side.

  During blowing and whistling and spitting there will be leakage of air and water from the weaker angle of mouth. This is due to lesion at some point between opposite precentral cortex and the facial nerve nucleus in pons. The upper facial muscle, i.e. frontal belly of occipitofrontalis, corrugator supercilii, procerus, nasalis and upper fiber of orbicularis on each side are controlled by both pyramidal tract and if supra-nuclear path on one side is damaged the supranuclear path of other side in capable of taking up the control of the damaged side. An associated hemianopia indicate an hemispheric lesion and hemiplegia usually present on the same side of facial palsy.
- In **lower motor neuron (LMN)** type of facial paralysis there will be absence of wrinkle over one half of the forehead, on voluntary action and the patient will be **unable to close the eye** on the paralyzed side and in an **attempt to close the eye, the eyeball will roll upward known as Bell's phenomenon**. This will be accompanied by paralysis of the lower half of the face which in usually seen in UMN palsy.

  This LML weakness is due to the damage of final common pathway from facial nerve nucleus to the facial muscle on the same side of paralysis.

  To point out the exact site of lesion of the final common path we have to consider associated anomalies.
  - If the VIth cranial nerve is also involved with the LMN facial palsy the lesion is in the pons and the hemiplegia will be on the opposite side (known as crossed hemiplegia or nuclear hemiplegia).

Fig. 117.2: Facial palsy (Bell's palsy) obliterated nasolabial furrow on the left side with paralyzed orbicularis oculi

Causes are **CVA**, **demyelinating lesion**.

– If the V th and VIII cranial is involved with the LMN facial palsy the lesion is in the cerebellopontine angle and causes are **CP angle lesion, auditory meningioma, cholesteatoma, glioma, meningioma**.
– If taste sensation, salivation and tear production is affected along with hyperacusis and LMN facial palsy the lesion is inbetween brainstem and the external genu of facial nerve from where the greater superficial petrosal nerve emerges from facial nerve.

The causes are **CSOM and fracture base of the skull involving petrous part of temporal bone**.

– If only loss of taste sensation and hyperacusis is present along with the LMN facial palsy then the lesion is inbetween the emergence of greater superficial petrosal nerve and nerve to stapedius.
– If only taste and salivation are involved the location of facial nerve lesion is after the departure of the nerve to stapedius and before the departure of the chorda tympani.
– If the taste sensation is normal and only weakness of facial muscle is present the lesion is either in the terminal part of facial nerve in the stylomastoid foramen or within the parotid gland. To differentiate between these two condition we have to examine and palpate parotid gland to exclude parotid gland pathology.

  The most common lesion is the *edema of the facial nerve or edema of the periosteum of the bony canal through which the nerve passes, i.e the terminal part of facial canal*, causing only LMN type of facial palsy commonly known as "Bell's Palsy" (Fig. 117.2).
– If only some of the facial muscles are paralyzed particularly the upper facial muscles, the lesion is either in the parotid gland or in the muscle themselves. Perineural spread of certain skin malignancy and infratemporal fossa tumor produce a gradually extending lower motor neuron type of weakness.

  Causes of unilateral emotional paralysis—Tumor and CVA affecting thalamus and thalamofrontal connection of the opposite side.

  Causes of bilateral emotional facial paralysis—Parkinsonism and pseudobulbar palsy.

  Causes of bilateral UMN facial paralysis—CVA, ICSOL, multiple sclerosis, pseudobulbar palsy, MND.

  Causes of unilateral lower motor neuron (LMN) paralysis—Bell's palsy, pontine CVA or tumor, CP angle lesion, petrous epidermoid, CSOM, neoplasm in the middle ear, fracture base of the skull involving petrous bone. Trauma to parotid and jaw. Parotid tumors and sarcoidosis.

  Causes of bilateral LMN paralysis—Myasthenia, myopathy, motor neuron disease. Encephalitis, forcep delivery, leprosy, sarcoidosis (uvoparotid fever) Lyme's disease.

VIIITH CRANIAL NERVE

TESTING OF THE COCHLEAR DIVISION

- **Clinical testing** is done by asking the patient a question in whispering voice in one ear and tell him to give the reply in loud voice while placing one finger in the patients opposite external auditory meatus and constantly rotating it to make a masking noice. So that he cannot hear anything by the opposite ear.
- **Rinne's test**—Strike tunning fork gently and hold the vibrating blade near external meatus. Ask the patient to signal when he ceases to hear the vibration of the turning fork. Immediately place the base of the fork over the mastoid process. The reverse is also done.

  In **normal person and in neuronal deafness AC > BC**.

  In conductive deafness BC > AC.

  (AC—Air conduction, BC—Bone conduction).
- **Weber's test**—Place the base of a vibrating tunning fork over the center of forehead. Normal person will hear equally in both the ear.

  In **neuronal deafness** the patient will hear more on the normal ear.

  In **conductive deafness** the patient will hear more in the defective ear *due to hypersensitiveness of the cochlea on the defective side*.

TESTING OF THE VESTIBULAR DIVISION

The patient lie supine with the head flexed at 30°. Now both the external ear are irrigated or blown with hot and cold water/air at 44°C and 30°C alternately.

The irrigation is done for 30 sec with 250 mL water. The duration of nystagmus is recorded by a stop watch. The hot water/air causes nystagmus whose fast component is directed to the same side of irrigation and cold water/ air causes nystagmus whose fast component is directed to the opposite side.

Abnormalities of the caloric testing:

- **Directional preponderance**—The duration of nystagmus to a particular side (left or right) is more for irrigation of both ear (the duration of nystagmus to right is more after irrigation with hot in right ear and cold in the left ear. The duration of nystagmus is more to the left after irrigation of hot in left or cold in right ear).
  This occurs in diseases of **vestibular nucleus, cerebellum or its connection and temporal lobe lesion**.
- **Canal paresis**—In this condition there is absent or diminished response to warm or cold water from one particular ear. This occurs in disease of Labyrinth or vestibular nerve on that side.

IXTH, XTH AND XITH CRANIAL NERVE

For examination IX, X and XI cranial nerve note for the presence of

- Nasal intonation
- Nasal regurgitation
- Dysphagia
- Hoarseness of voice.

1. The hoarseness of voice is due to vagus palsy as it supply all the muscle of larynx via superior and recurrent laryngeal nerve but examination of the interior of larynx should not be undertaken by medical specialist (by ENT expert only).
2. The nasal intonation of voice, nasal regargitation of liquid and dysphagia is due to lesion of cranial root of accessory nerve which is distributed via vagus nerve.
   For more objective examination ask the patient to open the mouth and look for the symmetry of the arch of the palate and position of uvula at rest and then ask the patient to say "Ah" and note the movement of the arch of palate and uvula and the movement of the wall of pharynx which should be symmetrical in normal person but sag downward on the side in LMN **cranial accessory palsy**.
3. The testing of the motor division of glossopharyngeal nerve is not possible as it supply the only muscle *stylopharyngeus which cannot be tested separately*. *The integrity of IXth nerve is tested by gag/pharyngeal reflex* in which posterior pharyngeal wall is touched by sterile swab stick and look for increased salivation and contraction of pharynx and palate with a sense of intense nausea and impending vomiting.

   The afferent path of gag reflex is formed by sensory fiber of 9th cranial nerve as it carry all sensory fiber from posterior one-third of tongue, pharynx, tonsil and palate.

   By the presence of intact gag reflex one can comment that the IXth cranial nerve is intact.

EXAMINATION ON SPINAL ACCESSORY NERVE

Spinal root of accessory nerve supply motor fiber to upper part of two neck muscle, trapezius and sternomastoid. Involvement of spinal accessory nerve is suspected when there is weakness of trapezius and sternomastoid.

- **Trapezius**—Severe trapezius weakness may be suspected if the unsupported **head falls forward**. For examination of trapezius go behind the patient. Make the patient sitting or standing erect and hands are symmetrically hanging by the side of the trunk. Now compare the line of curvature of trapezius of both side of neck, the height of the tip of shoulder and dropping of shoulder. Then ask the patient to raise both shoulder upward towards his ear or shrug the shoulders. Now try to depress the shoulder forcibly standing behind the patient and compare the power of trapezius on both side.

  As trapizius in partly supplied by cervical nerve power of the muscle and shrugging will be partially weak. There will be dropping of shoulder and scapula will be displaced downward and laterally giving steeper gradient to the contour of the neck.
- **Sternomastoid**—Sternomastoid weakness may be suspected if the unsupported **head spontaneously falls backward**.

  Place one hand firmly on the right side of the patient's face and ask him to turn or rotate the face to right side. In this maneuver left sternomastoid will stand out clearly. Repeat this test on the opposite direction and right sternomastoid will be prominent, and compare the power of the muscle on both side.

  Then place the hand on the forehead of the patient and ask him to push your hand forward by the forehead. Both the sternomastoid will standout clearly and compare the bulk.

Causes of Bilateral Sternomastoid Paralysis

Motor neuron disease (MND), spinal muscular atrophy (SMA), poliomyelitis, polyneuropathy, oculopharyngeal myopathy and myotonic disorder.

Causes of Bilateral Trapezius Paralysis

Motor neuron disorders (MND), polyneuropathy and poliomyelitis.

Causes of Unilateral Lesion

Trauma to base of the skull and neck, **tumors at jugular foramen** developmental anomaly associated with the base of the skull, **poliomyelitis and syringomyelia**.

XIITH CRANIAL NERVE

The main function of 12th nerve is to control all movement of tongue and certain movements of the hyoid bone and larynx during deglutitions.

METHODS OF EXAMINATION

In neurology examination of tongue is done to detect:

- Wasting
- Coating and corrugation
- Weakness
- Involuntary movement
- Voluntary power
- Myotonia
  - First inspect the surface of the tongue while it is resting on the floor of the mouth for unilateral **coating**, **corrugation, pigmentation** and **position of the midline raphe** whether it is on midline or **deviated to one side near the tip**. Ipsilateral coating, corrugation and loss of muscle bulk with deviation of the tip and midline raphe to one side on protrusion is due to unopposed action of the opposite genioglossus, suggest **LMN XIIth nerve palsy** on that side.
  - If there is gross bilateral wasting of the muscle bulk making tongue paper like thin which is sitting idly on the floor of the mouth and cannot be protruded beyond incisor teeth suggest-**bilateral LMN palsy of XIIth nerve**.
  - On the contrary in case of **bilateral UMN palsy** the tongue appears as a small tight mushroom shaped muscle bulk sitting idly on the posterior aspect of the mouth cavity near the pharyngeal inlet below uvula infront of epiglottis and almost incapable of protrusion with gross disturbances of speech.
  - **Bilateral fasciculation** on the surface of the tongue suggest slow degeneration of the XIIth cranial nerve nucleus in **motor neuron disease (MND)**.
  - A coarse from of tremor on protrusion may be seen in **parkinsonism and neurosyphilis**.
  - An alternate protrusion and retraction mixed with up and down flapping movement of tongue is common in **chorea**.
  - Dystonic movement of tongue seen in over dose of **metoclopramide and chlorpromazine** group of drugs.
  - A bulky tongue with dental indentation is seen in **Down syndrome, infantile hypothyroidism, gigantism and acromegaly**.
  - In prolong vitamin B-complex and iron deficiency the tongue will be small and there will be loss/atrophy of papilla which makes the surface of the tongue shiny and smooth with pigmentation (bald-tongue).
  - **Percussion of the tongue** is done by keeping it on the canine teeth. In normal person a small dimple will appear on the surface of the tongue which disappear almost immediately. In myotonic disorder the dimple will persist and may enlarge for a few second in a linear manner.

COMMON CAUSES OF XIITH NERVE PALSY

- **Unilateral lower motor neuron lesion**—Syringomyelia, poliomyelitis, tumor at jugular foramen, tumor or glandular enlargement high in the neck MND and CVA.
- **Bilateral lower motor neuron lesion**—Progressive bulbar palsy. Syringomyelia, foramen magnum anomalies.
- **Unilateral upper motor neuron lesion**—In profound hemiplegia due to CVA or deep seated brainstem tumor.
- **Bilateral upper motor neuron lesion**—In pseudobulbar palsy, amyotrophic lateral sclerosis.

EXAMINATION OF THE MOTOR SYSTEM

Motor system is examined under five subheadings.

- **Nutrition/atrophy**
- **Tone**
- **Power**
- **Coordination**
- **Involuntary movement.**

NUTRITION OR ATROPHY OF MUSCLE

Nutrition or atrophy of muscle is assessed by comparing the muscle bulk of the two limbs. For this purpose patient to be in lying, sitting and standing position and placing the limb in symmetrical position. Any apparent difference in muscle bulk during inspection must be confirmed by careful comperative measurement of the girth of the limb of both side (a fixed distance away from a bony land mark, i.e. comparing the girth of the thigh 15 cm above tibial tuberosity on both side or comparing girth of arm 10 cm above olecranon process on both side).

Hypertrophy of Muscle

- **Physiological hypertrophy**—Usually bilaterally symmetrical hypertrophy with strong muscle power.
- **Pathological hypertrophy**—Seen in pseudohypertrophy of Duchenne and Becker muscular dystrophy. Hypertrophy specially noticed in the cuff muscle but the muscle is weaker than normal muscle. Other diseases where pathological hypertorphy seen are myotonia

congenita, Kugelberg Welander type of spinal muscular atrophy.

Wasting of Muscle

- **Causes of generalized wasting of muscle**—***Type–I diabetes, thyrotoxicosis, malignancy, malnutrition, AIDS, motor neuron disease and myopathies (Table 117.2:)***.
- **UMN lesion**—It shows disuse atrophy of muscle bulk in one half of the body in hemiplegia, or both lower limb in **UMN paraplegia**. There is **no gross wasting**.
- **LMN lesion**—It shows **gross atrophy** of a selected group of muscle bulk. LMN lesion may be located at:
  - Anterior horn cell.
  - Anterior root.
  - Plexus injury (cervical plexus in case of upper limb and lumbar and sacral plexus in case of lower limb).
  - Nerve trunk.
  - Myoneural junction.
  - Muscle itself.

Table 117.2: Causes of muscle wasting

Causes of proximal muscle wasting	Causes of distal muscle wasting
1. Facioscapulohumeral dystrophy Limb girdle myopathy	1. Anterior horn cell diseases—Polio, MND, syringomyelia, cervical cord tumor
2. MND (motor neuron disease)	2. Anterior horn and root—Cervical spondylosis, cervical tumor
3. Myasthenia	3. Brachial and lumber plexus lesion
4. Inflammatory myopathies like polymyositis and dermatomyositis and postpolio	4. Lesion of median, ulnar and radial nerve and sciatic nerve
5. Inclusion body myositis compressive cervical radiculopathy/axillary neuropathy/brachial plexopathy	

- **Lesion of anterior horn cell**—Poliomyelitis, syringomyelia, motor neuron disease and tumor of spinal cord.
- **Lesion in the anterior root**—Cervical spondylosis, GB syndrome, lumbar disk prolapse.
- **Lesion of brachial or lumbar plexus**—Cervical rib injury, pancost tumor of lung, cervical glandular enlargement. Psoas abscess (in case of lumbar plexus).
- **Lesion of nerve trunk**—Leprosy, surgical or traumatic, carpal tunnel syndrome and tarsal tunnel syndrome.
- **Lesion at myoneural junction**—Myasthenia gravis, Eaton Lambart syndrome but in this disorder atrophy is not so prominent.
- **Diseases of muscle**—Myopathy.

In the myopathic disorder, wasting initially involve a specific group of muscles later they may spread and become symmetrical on both side.

In spinal muscular atrophy (SMA) selective pattern of individual muscle involvement is seen.

MUSCLE TONE

Muscle tone is the partially contracted state of the muscle which keeps the muscle ready for contraction.

The gamma motor neuron in the anterior horn cell sends impulse to intrafusal fiber in the muscle spindle which causes contraction of intrafusal fiber and there is rise in tension in the muscle spindle. This rise in tension is perceived by proprioceptive fiber which through posterior root stimulate the α-motor neuron in the anterior horn cell and cause contraction of the extrafusal fiber and thereby maintain the tone of the muscle. Gamma motor neuron in the anterior horn cell get the initial impulse through reticulospinal, tectospinal, rubrospinal, vestibulospinal and cerebellospinal spinal tract from supraspinal center (called extrapyramidal pathway).

Examination of Tone

It is done by rolling the limb on the bed with the palm or allow the limb to free fall on the bed during which note the absence of checking movement in hypotonic state.

Causes of Hypotonia

1. **Lesion of motor side of the reflex arch**
   a. Anterior horn cell disease
   b. Neuropathies
   c. Peripheral nerve injury.
2. **Lesions of the sensory side of the reflex arch**
   a. Neuropathies
   b. Herpes zoster
   c. Tabes dorsalis.
3. **Combined motor and sensory lesion**
   a. Syringomyelia
   b. Cord or root compression.
4. **Lesions of the muscle**
   a. Myopathies
   b. Spinal muscular atrophies
   c. Myasthenia gravis
   d. Periodic paralysis.
5. **Stage of neurological shock**—In CVA or trauma to brain or spinal cord.
6. **Cerebellar lesion**—In cerebellar lesion ipsilateral hypotonia is common and DTR are prolonged and pendular.
7. **Chorea**—In Sydenham's chorea involuntary movements are associated with marked hypotonia.
8. **Miscellaneous**
   a. Alcohol
   b. General anesthesia
   c. After GTCS
   d. Deep sleep and coma.

Causes of Increase Tone

- Anxiety
- Thyrotoxicosis
- Upper motor lesion after recovery from shock stage
- Tetanus
- Strychnine poisoning
- Meningitis.

There are three main type of hypertonia in UMN lesion:

1. **Spastic type (Clasp-kinfe type spasticity)**—In spasticity, increased resistance is usually noticed at the beginning of the passive movement of a large joint (commonly knee and elbow) but after some time the resistance suddenly passes away giving the **"clasp-knife"** like effect. That is why it is called **"clasp knief type spasticity"**. During supination and pronation of the forearm there may be a supinator catch.

   This is a sign of lesion of the pyramidal pathway (UMN). The hypertonicity is more evident in the (anti-gravity group of muscle) **flexor** and **pronator group** of the upper limb whereas **extensor and adductor group** of muscle in the lower limb. Immediately after a profound pyramidal lesion **tone may be lost in the neurological shock stage, only to reappear after few weeks after recovery from shock stage**.
2. **Rigidity (plastic/lead pipe type rigidity)**—In this condition same degree of resistance is felt during all through passive flexion and extension specially of elbow or knee. It is due to the equal increase in tone of both antagonist and agonist of the joint and is called **lead pipe//plastic type** rigidity and is due to the lesion of the **extrapyramidal system** rarely in basal **ganglia lesion** and in **catatonia**. This lead pipe type of hypertonicity may be seen in very elderly person. If this rigidity is very much increased it can make the limb almost immobile, seen in **parkinsonism**.
3. **Cog-Wheel rigidity**—In this type of hypertonicity the agonist and antagonist around a joints contract alternatively, rapidly and regularly during passive movement of the joint producing so called **cog-wheel rigidity**. This is usually present only during initial movement and usually at the wrist joint when the opposite wrist is actively moved. It is a valuable sign of extrapyramidal disease and may be felt in the absence of tremor, although it is much increased when tremor in present.

   It may be also seen in **reserpine, chlorpromazine** (and its derivatives), **metoclopramide** and **carbon monoxide** poisoning.

- **Clonus**—Sudden stretching of a hypertonic muscle produce reflex contraction of the muscle and if the stretch is maintained during subsequent relaxation further reflex contraction occurs. Theoretically this alternate contraction and relaxation can go on almost indefinitely so long the stretch stimulus is maintained at least six contraction in a row. It is called "**Clonus**". It is usually demonstrated by **sudden dorsiflexion** of foot or **suddenly moving the patella downward** with maintained stretch.

  It is usually present in hyperreflexive condition like **pyramidal tract lesion** and during severe **anxiety or frightened state**.
- **Myotonia**—In this condition muscle remain contracted beyond the required period for a particular movement.

  This can be demonstrated by asking the patient to tightly screw up his eyes or show his teeth or tightly grip the examiners finger and then asked to suddenly release it, which the patient is unable to carryout. There will be a long lag period between the examiner's command and the patient's relaxation.

  In myotonia, percussion of the tongue after placing it over canine teeth produce a dimple. Percussion over the thenar eminence results in slow adduction of the thumb and dimpling of the muscle.

MUSCLE POWER

Muscle power is graded from grade '0' to grade '5'

Grade 0/5 power = Total paralysis, no flickers of muscle contraction, no joint movement present.

Grade 1/5 power = Visible flickers of muscle contraction present but no resultant joint movement possible.

Grade 2/5 power = The muscle can move the joint when gravity is eliminated.

Grade 3/5 power = The muscle can move the joint against gravity but not against additional resistance.

Grade 4/5 power = The muscle can move the joint against gravity and against resistance but by examiner assessment it is not his full power.

Grade 5/5 power = Normal full power.

Assessment of Power of the Distal Group of Hand Muscle

- **Palmar interosseous** are adductor's of finger and the power of these muscles is tested by so-called "card test". It is demonstrated by placing the patient's palm flat on a table and a card is placed in between the fingers of the hand which the patient tries to hold in between then against the examiner's pull.
  (root C_8T_1, 1st and 2nd by Median nerve 3rd and 4th by ulnar nerve).
- **Dorsal interosseous**—Patient is asked to keep the fingers abducted against resistance.
  (root C_8T_1, 1st and 2nd by median, 3rd and 4th by ulnar nerve).
- **Lumbricals**—Power of lumbricals is tested by flexing the extended fingers at metacarpophalangeal joint against resistance.
  (root C_8T_1, 1st and 2nd by median nerve 3rd and 4th by ulnar nerve).
- **Adductor pollicis**—The patient tries to hold a card in between thumb and palm (ulnar nerve—T_1).

- **Abductor pollicis brevis**—Place an object inbetween the thumb and the base of the index finger to prevent full adduction then the patient is asked to raise the thumb vertical to the plain of the palm against resistance given at the terminal phalanx. This muscle is supplied by median nerve and first to show weakness in carpal tunnel syndrome (median nerve—T_1).
- **Flexor pollicis**—Examiner tries to extend the distal phalanx of the thumb against patient's resistance after steading the proximal phalanx by other hand (median nerve—C_8).
- **Extensor pollicis longus**—The patient tries to extend the thumb while the examiner tries to flex it at inter phalangeal joint (radial nerve—C_8).

Testing of power of the shoulder girdle muscle

- **Abduction of shoulder**—
  First 35° of abduction of shoulder is done by supraspinatus.
  From 35°–135° it is done by deltoid.
  Terminally **from 135°–180°** it is done by **rotator cuff** of shoulder girdle (supraspinatus infraspinatus, subscapularis teres major and minor).
- **Pectoralis major**—Place the hand on the hip and press it inward. The sternocostal part of muscle felt to contract. Then raising the arm forward above 90° and attempting to adduct it against resistance. This brings the clavicular part into action.
  (lateral and medial pectoral nerve root—C_6–C_8)
- **Latissimus dorsi**—Resist the patient's attempt to adduct the arm when raised above 90° (nerve to latissimus dorsi root—C_7).

Type of Weakness

Weakness due to pyramidal tract lesion—In this disorder weakness is more in the distal group of muscle than proximal group and specially **extensor** and **abductors of lower limb** and **flexor and adductor in the upper limb**, i.e. the **antigravity** group of muscle.

The weakness is incomplete except in acute severe lesion and affect particular movement than particular muscle. It is **associated with clasp knife type spasticity, exaggerated DTR, extensor plantar response and loss of superficial reflexes**.

Characteristic of weakness due to extrapyramidal lesion

In this type of disorder
- Weakness of muscle is generalized in all group.
- It is due to increased tone of the antagonist and agonist group of muscle.
- There is no true loss of muscle power.
- It is associated with lead pipe type of rigidity.
- DTR are suppressed.

Characteristic of weakness due to lower motor neuron lesion

In this type of disorder:
- Weakness is very marked.
- It is localized to muscle having that segmental supply.
- It is associated with marked wasting and hypotonia.
- Loss of DTR of that segment.
- A slow degeneration of the anterior horn cell can produce fasciculation (e.g. motor neuron disease).

Usually all muscle have supply from multiple spinal segment, so lesion of one segment produce partial weakness of the muscle whereas lesion of a peripheral nerve produce weakness of all muscle supplied by that nerve.

In peripheral neuropathy weakness is maximal in the distal group of muscle of arm and leg and is bilateral symmetrical in distribution.

Weakness due to muscular lesion

- Weakness of one single muscle is usually due to injury.
- Weakness of a group of muscle occurs in polymyositis.
- Weakness due to muscular lesion is associated with wasting of that group of muscle except pseudohypertrophy in Duchenne and Backer's type myopathy.
- It is associated with variable suppression of DTR of that group of muscle.

Weakness due to myasthenia gravis

In this condition degree of weakness of a group of muscle varies from hour to hour and weakness increases after repeated use, even to the extent of total paralysis but recover to its previous state of power after a short period of rest.

This type of weakness may affect any muscle of the body but commonly involve **eyelid, extraocular muscle, facial muscle, tongue, throat, larynx, shoulder girdle** and **hand muscle**.

This is clinically tested by
- Asking the patient to look upward for a considerable period for extraocular muscle.
- Counting successively upto 100 for bulbar muscle.
- Repeatedly sitting up and lying down for back muscle.
- Combing of hairs for shoulder girdle muscle.

The disease is confirmed by repetitive nerve stimulation or low dose Tensilon injection and by estimation of antiacetylcholine receptor antibody.

A similar condition called *Lambert Eaton syndrome* which is seen as a paraneoplastic syndrome in which muscle strength temporarily increases with repetitive movement and involve the lower limb muscle in contrast to myasthenia where ocular and bulbar muscle are commonly involve. There is no respone to Tensilon.

COORDINATION

1. **Coordination of upper limb is tested by finger nose test or finger-nose-finger test with eyes open and eyes closed**.

   For testing finger-nose test each arm is drawn out to full abduction and the patient is asked to place the tip of index finger over the tip of nose and hold over there for 5 seconds. Note the **smoothness of the movement, accuracy of placing the finger** on the tip of the nose and **steadiness** with which the finger is held on the nose for 5 seconds. Minor abnormalities can be exaggerated by asking the patient to touch his own nose and the examiner's outstretched moving finger quickly and repeatedly.

   a. **In cerebellar lesion** the arm on the side of the lesion may first be flung wildly outward then the finger move towards the nose in weavy fashion either side to side or up and down fashion but at last brought on to the tip of nose fairly accurately. This clumsiness increases with closer of the eye.

      In milder lesion this clamsiness diminishes and a wave-like movement on either side of a horizontal plane seen with a tendency to over shoot the object towards the side of lesion.

      This wavy movement should not be confused with intention tremor which is a side-to-side oscillatory movement and appears as the finger approach the target.

      This intention tremor may be very wild so that one cannot finish the movement or may be so mild that only two or three oscillation can be seen after the finger touches the nose.

   b. In **sensory ataxia** the movement of finger is a smooth one from beginning to the end, only a minimal hesitation is seen just at the finishing point but when the eyes are closed the finger will be unable to find out the target and land somewhere on the face then with help of touch sensation the finger will be ultimately dragged over the skin of the face to the target.

2. **Coordination of lower limb is tested by heel-knee Test**—The patient is asked to place the heel of one leg on the opposite knee then order him to run the heel down over the shin bone to the ankle.

   The whole test is repeated on the other side and finally it is carried out with eyes closed.

   a. **In cerebellar ataxia**—The heel over shoot the knee side ways and develop a rotary oscillation as it approaches the knee which is parallel to intention tremor of the upper limb. As the heel run down the shin bone it oscillates side-to-side and fall repeatedly from the shin and then finally over shoots the opposite ankle. In mild degree cerebellar ataxia, mild side-to-side oscillation of ankles over shin may be the only defect.

   b. **In sensory ataxia**—The heel is lifted too high initially and the patient raises his head to see the relationship between ankle and knee. In the rest of the movement the heel may fall on either side of the shin during its run towards the ankle but the movement is not rhythmical.

      During performing the test with closed eye the heel will be lifted too high and will land over the thigh or bed and then dragged towards the knee.

Dysdiadochokinesia

In this disorder the patient will be unable to perform rapidly alternating movement.

The patient sit on a chair with a table infront and place his arm on it with flexed elbow so that forearm looks vertically upward with both the palm facing inward. He is then asked to rotate his hand and forearm rapidly in clockwise and anticlockwise direction alternatively.

- **In cerebellar disorder**—The movement will be coarse, irregular and slow with the hand doriflexed and fingers extended. If this is repeated with clenched fist, a jerky flexion, extension of wrist will superimpose on rotation of forearm.
- **In motor weakness**—Due to pyramidal lesion the movement will be slow and clamsy on the affected side.

Past-pointing Test

Past-pointing is positive both in labyrinthine and cerebellar disorder.

The patient and examiner stand facing each other and holding their arm outstretched forward, horizontally and parallel so that one's finger touches with the others. The examiner then elevate his arm vertically up and depress it vertically down and immediately bring it back to the original resting condition and ask the patient to repeat the same as the examiner. This is done with eyes open and close and the test is repeated several times on each side.

- In cerebellar disorder the arm on the affected side of the cerebellum will deviate outwards, laterally instead of regaining its original position in the midline during the movement.
- In unilateral labyrinthine diseases both arm will deviate towards the side of lesion. This will be in the same direction as the slow component of the nystagmus.

Additional test—These tests are helpfull is differentiating cerebellar, pyramidal and extrapyramidal disease.

Rapid Hand Tapping

In this test back of one hand is tapped rapidly with the fingers of the other hand. This test is a good method to detect unilateral pyramidal weakness.

In cerebellar disorder the tap becomes a rotary stroking movement. The test can be reenforced by asking the patient

to rapidly supinate and pronate his forearm while tapping so that alternate tap are carried out by palmar and dorsal surface of the finger.

Tapping within a circle—A circle of 1 cm diameter is drawn and the patient is asked to put a fixed number of dot within the circle with a pencil.

In both cerebellar and sensory ataxia the dots will be spread over wide area both inside as well as outside the circle. In unilateral cerebellar disease more number of dots found to be placed *outside the circle on the side of lesion*.

Spiral drawing—Ask the patient to draw a spiral. This is almost impossible for patient of with ataxia, tremor or chorea. This last two test "tapping within a circle" and "spiral drawing" can be used for keeping a record of clinical assessment of improvement or deterioration of ataxia.

Initial observation

- Ask the patient to hold both his arm outstretched and paralled to each other and ask him to maintain the posture with eyes open and closed while examiner is observing how well the posture is maintained.

  In cerebellar disorder frequent correction of the position has to be made so that the arm appear to bounce and deviate to one side.
- In the next step the patient is asked to maintain the forward paralled posture of the hands in the above mentioned position steadily while the examiner tap each arm downward suddenly and briskly. Observe the displacement and the mode of return to the original position.

  In cerebellar disorder the arm on the affected side fly upward and overshoot the original position after each tapping and after several bounce the arm will come back to the original posture (paralled to the other arm) and is associated with hyperextension at the metacarpophalangeal joint with partial flexion of the wrist.
- The arms are then pressed downward alternatively while maintaining the forward paralleled position and release then suddenly. Very little displacement is observed in normal person.

  In cerebellar disorder the arm on the affected side fly-high up and return to parallel position with other arm after several bounce. These abnormalities will increase when the eyes are closed. In sensory ataxia during the above test the arm will drift upward and outward and grossly displaced without realizing it and maintain this position without any bounce. In Muscular weakness the arm will be only depressed further after each tapping. There will be no bounce back or abnormal positioning.
- The patient is then ask to tap his thumb of one hand with the middle finger of the other hand note the speed and rhythm and ask him to tap the thumb by each finger in sequence from thumb to little forward and in reverse order. The speed will be swifter in the dominant side.

  Finger tapping is slowed is pyramidal and extrapyramidal disorder and weakness of muscle like myopathy. The rhythm is disturbed in cerebellar disease and chorea.

INVOLUNTARY MOVEMENT

Common involuntary movements are as follows:

1. **Tremor**
2. **Dystonia**
3. **Chorea**
4. **Ballismus**
5. **Facial tics**
6. **Spasmodic torticollis**
7. **Athetosis**.

TREMOR

Tremor is due to alternate rhythmic contraction and relaxation of antagonist and protagonist around a joint. It is classified as follows:

Depending on frequency:

- Fine tremor frequency >10 Hz, e.g. anxiety and thyrotoxicosis.
- Coarse tremor frequency <10 Hz, e.g. parkinsonism.

Flapping tremor seen in metabolic disorder like *uremia, hepatic encephalopathy* and *CO_2 narcosis*.

Tremors are also classified on the basis of the circumstances they are seen under:

- *Rest tremor*—When the body part is fully supported against gravity (Parkinson's disease).
- *Action tremor*—When voluntary muscles contract (essential tremor)
- *Postural tremor*—When the arms are outstretched against gravity in front of the body (essential tremor)
- *Re-emergent tremor*—Appears in the outstretched hand after a few seconds latent period.
- *Kinetic tremor or intention tremor*—When moving finger or limb is attempted to reach a target (tip of nose)
- *Task-specific tremor*—It appears on performing a particular task such as handwriting.

Coarse Tremor

In coarse tremor, the frequency is less <10 Hz usually seen in:

a. Parkinsonism
b. Wilson's disease
c. Red nucleus tremor

Parkinsonian tremor is initially confined to thumb and index finger producing "pill rolling" movement later all the finger move as a whole producing "drumbeating" like movement and the finger are permanently flexed.

This tremor is absent during sleep and total relaxation and increased by emotion and present at rest and suppressed by initiation of voluntary activity and will

returns as long the movement continues or a new position is taken up. It is usually accompanied by cog-wheel rigidity at wrist and finger and slowing of each movement patient may show an exaggeration of the tremor with movement which is seen in essential tremor.

Essential Tremor (ET)

It is the most common movement disorder seen in general population. 50% patients with ET has positive family history.

A physiologic tremor is present whenever a muscle contract due to subtetanic contraction of the motor unit which is not visible but when enhanced by β-adrenergic stimulation of the segmental stretch reflex it become evident. The best way to demonstrate is to balance a piece of paper on the patient's outstretched fingers. This enhanced physiologic tremor is seen with anxiety, fatigue, hyperthyroidism, valproate, lithium and alcohol toxicity. This is the most common type of tremor encountered in clinical practice.

Essential tremor can be of two types:

a. Action tremor
   - Fine tremor associated with muscle contraction.
   - Mostly bilateral. Present in hand and forearm without dystonic movement.
   - Benifits from alcohol.

b. Postural tremor
   - Seen in finger and arms when arms are outstretched against gravity.
   - Usually progressive and long-lasting.

Treatment

- If anxiety, thyrotoxicosis or fatigue is presumably the underlying etiology then treatment should direct to the cause.
- β-blocker (propranolol 20–80 mg), Primidone (effective in 50% of patients) conld be used.

DYSTONIA

It is a form of hyperkinetic movement disorder characterized by sustained or repetitive involuntary muscle contraction. It is can be brought about by voluntary movement (action dystonia) or aggravated by stress and fatigue and suppressed by relaxation or touching the affected part.

Dystonia can be classified variously:

- Childhood/adult dystonia
- Focal/multifocal/segmental/generalized dystonia
- Primary/secondary dystonia.

Childhood Dystonia

Childhood dystonia is also called idiopatnhic torsion dystonia (ITD) or Oppenheims dystonia. It is an autosomal dominant disorder confined to Ashkenazi white Jews families.

This type of dystonia typically begins in upper or lower extremity gradually progress to involve head and neck and in severe cases interfere with mobility and is due to deletion of a trinucleotide GAG in 9q34 with loss of one pair of glutamic acid residue in protein torsion with variable penetration.

Dopamine responsive dystonia is also a autosomal dominant childhood dystonia due to defective synthesis of tyrosine hydroxylase leading to diminished synthesis of dopamine. This type dystonia is absent during sleep and starts in the morning and worses in the evening. Some patient present with parkinsonian feature and excellent improvement with small dose of levodopa but have normal striatal function as evidenced by normal flurodopa uptake on PET scan.

A third form of childhood onset dystonia primarily involve cervical and brachial muscle which later become generalized and is associated with impaired speech and is due to mutation in Dy T6 gene on chromosome 8P21Q found in Amish families responsible for 25% non-DyT11 young onset primary torsion dystonia.

Myoclonic dystonia results from mutation DyT11 in Epsilon Sarcoglycan gene on chromosome 7q21. This type of disorder manifest as a combination of dystonia, myoclonic jerks and psychiatric abnormalities.

Focal Dystonia

These are the most common form of dystonia present during 4th to 6th decade of life. Major types are:

- **Blepharospasm**—Dystonic contraction of eyelid manifest as increased blinking.
- **Oromandibular dystonia**—Dystonic contraction of muscle of lower face, lip, tongue and jaw opening.
- **Spasmodic dystonia**—Dystonic contraction of adductor of vocal cord which interfere with speech leading to chocking or when affect abductor of vocal cord leading to whispering voice.
- **Cervical dystonia**—Dystolic contraction of cervical muscle on one side leading to torticollis, anterocollis, retrocollis.
- **Limb dystonia**—That are present in work-specific activities like writers cramp (during hand writing) musician's cramps (during playing musical instrument jips) (during putting).

Cause of limb dystonia is unknown but is often associated with high frequencey tremor like ET (essential tremor) and the tremor disappear with disappearance of dystonic movement.

Secondary Dystonia

These dystonia can develop as a sequela of chronic levodopa and neuroleptic drug treatment or manganese

and carbon monoxide poisoning. Secondary dystonia can also develop as a sequence of lesion of striatum, pallidum, thalamus, cortex or brainstem by infarction, tumor, trauma, demyelination.

Dystonia plus syndrome—Dystonia may be associated with Huntington disease, Parkinson disease, Wilson's disease, progressive supranuclear palsy CBGD. These type of dystonia is always associated with dominant neurological features of those associated neuro degenesative disorder.

Pathophysiology of dystonia

Dystonia is due to simultaneous contraction of antagonist and agonist muscle group around a joint. The lesion is probably located in basal ganglia in some form of dystonia as evidenced by increased blood flow and metabolism in basal ganglia. Ablation and stimulation of globus pallidus can induce and ameliorate some form of dystonia Striatonigral pathway has also been implicated in some of dystonia as dopamine can both induce or treat some form of dystonia.

Treatment of dystonia

Treatment of dystonia is primarily directed toward the primary condition that leads to dystonia.

- Wilson's disease—By penicillamine (250 mg 6 hourly).
- Levodopa should be tried in all cases of childhood dystonia.
- High dose trihexyphenidyl 20–120 mg/day may be beneficial.
- Baclofen—Oral or intrathecal is helpful in leg and trunk dystonia. Side effect of oral Baclofen is sedation, weakness and memory loss. Side effect of intrathecal infusion—Meningitis, seizure and coma.
- Tetrabenzine 25–75 mg/day is helpful in some patient. Side effects are sedation and parkinsonian features.
- Neuroleptics—Can improve or induce dystonia.
- Clonazepam and diazepam are rarely effective.
- Botulinum (Both A and B) has become the *treatment of choice* for focal dystonia where involvement is limited to small muscle group, e.g. blepharospasm, torticollis or spasmodic dystonia. It acts by blocking the release of acetylcholine at neuromuscular junction leading to weakness of the muscle but the benefit is transient and repeated injections are required at 2–5 months interval.
- Surgical therapy is required for severe dystonia not responding to medical treatment. Rhizotomy or myotomy was used to treat cervical dystonia. But now DBS of palladium can provide dramatic benefit in primary DYTI. In focal and secondary dystonia stimulation is done with low frequency current and therapeutic effect is obtained after weeks latency.

There is a condition called dystonic storm which develops as a sequela of stressful situation like surgery characterized by acute onset persistent and generalized dystonia including laryngeal and pharyngeal muscle. Patient develop rhabdomyolysis and acute renal failure. These patients are managed in intensive coronary care unit (ICCU) by combination of anticholinergics diphenhydramine, baclofen benzodiazepines, dopamines agonist and antagonist.

CHOREA

Chorea is defined as a rapid *nonrepetitive, quasiperposesive involuntary movement involving both distal or proximal group of muscle*.

Causes of Chorea

- Sydenham's chorea (Saint vitus dance).
- Huntington's chorea.
- Chorea gravidarum or sex hormone chorea and chorea acanthocytosis (neuroacanthocytosis).
- Vascular chorea.
- Hypo- and hyperglycemia.
- SLE.
- Sjögren's syndrome.
- Hyperthyroidism.
- HIV.
- Polycythemia rubra vera.
- Following open heart surgery in childhood.
- Anticonvulsant, cocaine, CNS stimulant and lithium.
- Paraneoplastic disorder associated with anti-CMRP-5 or antihuantibody

Chorea is characterized by *rapid, nonpatterned, semipurposeful involuntary movement*. Initially it is *focal or segmental later it involve multiple body* segment and associated with dystonia, rigidity, spasticity, bradykinesia and myoclonus.

Huntington's disease (HD) can present with akinetic rigidity or parkinsonian syndrome (Westphal variant) gradually develop behavioral and cognitive disturbances which progress to dementia and depression.

Some HD usually have a strong family history and develop T_2DM. Site of lesion of HD is striatum with progressive atrophy of **caudate nucleus and putamen** with diffuse cortical atrophy. Histopathology shows aggregates of ubiquitin and mutant proteins Huntington in the affected neuron. HD is prevalent among white population and rare in Black and Asian. Chromosomal study shows increase number of CAG repeat in the coding sequence of huntingtion gene located in the short arm of chromosome 4.

For treatment of HD, *tetrabenazin*e is the drug of choice, anxiety and depression is treated by antidepressant and anxiolytic, psychosis is treated by atypical neuroleptics, e.g. clozapine quetiapine and resperidone.

Sydenham's chorea is more common is female and develop as a consequence of an autoinmune response to hemolytic streptococcal infection. The disease in characterized by acute onset choreiform movement with behavioral disturbances after a latent period of about six months following streptococcal infection.

This is usually a self-limiting disorder and require no drug therapy only require reassurance and prevention of self-injury. Severe cases may be treated by dopamine blocking agent, valproic acid and carbamazepine.

Among other chorea "Chorea-acanthocytosis" is a fatal autosomal recessive disorder characterized by chorea dystonia, seizure, polyneuropathy and self-mutilating behavior with acanthocyte in the peripheral blood.

Almost similiar manifestation is seen in patient who have reactivity with kell blood group antigen which is a 'X' linked form of disorder.

HEMIBALLISMUS

It is a violent form of chorea characterized by large amplitude wild flinging movement involving the proximal limb muscle and confined to one half of body. The movement is so severe that the patient may be exhausted and it is due to partial lesion of *subthalamic nucleus* but in rare cases may be due to lesion of putamen. It is associated with increased tone and reflexes of the affected limb and the movement is absent during sleep.

ATHETOSIS

Athetosis is also an involuntary movement usually involving arm, forearm and hand characterized by slow, distal, writhing movement, i.e. alternate supination and pronation of arm, forearm and hand.

TICS

Tics is an involuntary movement characterized by purposeless recurrent brief, rapid motor contraction of an individual muscle group (resulting in movement like blinking, twitching of nose, jerking of neck). It may involve multiple muscle group in a coordinated fashion resulting in jumping, sniffing, head banging, echopraxia (mimicking movement). These may be simple vocal tics like grunting or complex vocal tics like echolalia (repeating others word) palilalia (repeating own word) or coprolalia (expression of obscene words).

"Tourette's syndrome" is characterized by multiple motor tics often accompanied by vocalization (Phonic tics) sensory tics may involve face, head or neck.

Tics is usually present in between 5–15 years of age and disappear in adulthood. Patient can voluntarily suppress tics for brief period and associated with anxiety, depression, attention deficit hyperactivity disorder or obsessive compulsive disorder when it is present in adult it is usually associated with Parkinson's disease (PD), Huntington's disease (HD), dystonia, drugs like levodopa, neuroleptics.

TARDIVE DYSKINESIA (TD)

Tardive dyskinesa is a drug induced movement disorder that develop after prolong exposure to traditional antipsychotic agent. It is characterized by choreiform movement involving mouth, lip, tongue. In severe cases it may involve limb, trunk and respiratory muscle. It remits approximately 3 mouths after stopping these drugs on the contrary it may develop after stopping these agents. Atypical antipsychotics like clozapine, resperidone, olanzapine, quetiapine, ziprasidone, aripriprazole are associated with significant lower risk of TD.

Treatment

- Withdrawal of traditional antipsychotics and replace it by atypical antipsychotic.
- Valproic acid 750–3000 mg/day.
- Anticholinergics, (trihexyphenidyl hydrochloride).
- Botulinum toxin.
- Tetrabenazine, baclofen, clonazepam are also used.

RESTLESS LEG SYNDROME

Restless leg syndrome (RLS) is a neurologic disorder that usually affect 10% of white population and is characterized by the following symptoms:

- Urge to move the leg (usually due to an unplesant sensation in the leg, described as paresthesia, buring, creepy-crawly feeling).
- Symptom begins or worsen with rest.
- Partial or complete relief by movement.
- Worsening during evening or night.

It is an autosomal dominant disorder with variable penetration with average age of onset is 30 years. Secondary RLS may develop with peripheral neuropathy, Renal failure and ferritin deficiency. It is probably due to dopaminergic dysfunction associated with abnormal iron metabolism.

Most RLS have mild symptom and does not require specific treatment. Specific measures are

- Improve sleep hygiene and good quality of sleep.
- Dopamine agonist pramipexole (0.25–0.5 mg) or ropinirole (1– 2 mg) 1–2 hours before sleep.
- Anticonvulsant, analgesics and opiates can be tried in resistant cases.
- Seconday RLS—Require iron replacement for anemia.

MALIGNANT NEUROLEPTIC SYNDROME

Exposure to traditional antipsychotic may be associated with malignant neuroleptic syndrome. It is clinically

characterized by muscle rigidity elevated temperature, altered mental status, tachycardia, hyperthermia, renal failure and maked by elevated creatinine kinase level. Symptom usually appear days to weeks after initiation of the traditional antipsychotics but sometime due to abrupt withdrawal of antiparkinsonian medication.

Treatment

- Immediate cessation of the offending antipsychotic drug.
- Several measures like—Control of body temperature by antipyretics, cooling blanket, hydration, electrolyte replacement, control of BP and renal function.
- Introduction of levodopa, dantrolene, benzodiazepine.

EXAMINATION OF SENSORY SYSTEM

Somatic sensation is classified in various ways:

- **Superficial and deep sense**—Superfical senses are fine touch, tactile localization and two point discremination. Deep senses are muscle sense, joint sense, ligament sense, vibration sense, pressure sense.
- **Thalamic sense and cortical sense**—Thalamic senses are pain and temperature (<30° and 44°>). Cortical senses are all other senses including graphesthesia and stereognosis except pain and crude temperature.
- **Long fiber sensation (postcolumn) and small fiber sensation (anterior and lateral column or spinothalamic tract)**—Large fiber (tract of Goll and Budack) subserve tactile sense, muscle sense, joint sense, ligament sense, vibration sense, position sense. These fibers from the posterior root directly enter posterior column on the same side without relay and ascend up to medula where they relay in the nucleus gracilis and cuneate nucleus and the second order of neuron crosses the midline and ascend through medial lemniscus ultimately relay in the ventral posterolateral nucleus of thalamus and from there fibers ultimately project to the postcentral gyrus located in the parietal cortex.

  Small fiber (mostly nonmyelinated and small myelinated fiber) which subserve mainly nociception and temperature and touch sensation. There fiber enter the spinal cord through the posterior root after relay in the posterior column crosses the midline and ascend through anterior and lateral spinothalamic tract of spinal cord then through the brainstem to the ventral posterolateral nucleus of thalamus and ultimately project to the postcentral gyrus of the parietal cortex.

  Many other fiber particularly associated with touch, pressure and position sense ascend in a diffusely distributed pattern both on the same side and on the contralateral side in the anterior lateral quadrant of the spinal cord. That is why in complete lesion of posterior column of spinal cord is associated with little sensory deficit on examination.

METHODS OF EXAMINATION OF PRIMARY SENSATION

Pain sensation is tested with the help of a pin while patient is asked to locate the pricking point with closed eye.

- **Temperature sensation**—To both hot and cold is tested with the help of a containers (test tube) containing warm and cold water at desired temperature. Both warm and cold should be tested because different receptor is responsible for cold/warm sensation.
- **Touch sensation**—Touch sensation is tested with a whisp of cotton or fine camel hair brush on non-hairy skin because of plenty nerve ending are located surrounding each hair follicle.
- **Joint and position sense (measure of proprioception)**—It is tested by the patient's recognization of the position of the distal interphalangeal joint of great toe or finger during passive movement by the examiner while the patient's eye remain closed.

  To test the proximal joint position sense specially at shoulder is performed by asking the patient to bring the two index finger together with arm extended and eye closed. Normal individual can do so accurately with an error of 1 cm or less.
- **Vibration sense**—It is tested with help of turning fork which vibrates at 128 Hz. It is tested over bony prominence starting from dorsal aspect of distal interphalangeal joint of great toe then over malleolar prominence around the ankle. If abnormalities are noticed then more proximal joint can be examined.

  Quantitative electronic sensory testing devices are now commercially available which are useful for serial evaluation of cutaneous sensation in clinical trial.

SUMMARY OF TESTING PRIMARY SENSATION

- Pain is tested by pinprick.
- Temperature
  - Warm is tested by warm-metal/water
  - Cold is tested by cold metal/water.
- Touch is tested by wisp of cotton/fine camel hair brush.
- Vibration is tested by tunning fork of 128 Hz.
- Joint position by passive movement of distal most joint.

METHODS OF EXAMINATION OF CORTICAL SENSES

- **Two point discrimination**—It is tested by the divider of the geometry box which may be set apart starting from 2 mm to several centimeter. Pulp of the thumb and index finger and back are commonly tested. Over the pulp of

the thumb normal individual can distinguish about 3 mm separation while over back it is about 5 cm.

- **Touch localization**—It is tested by a wisp of cotton wool and the patient is asked to identify the site of touch with the fingertip while the patient's eye remain closed.
  - **"Extinction or hemineglect"** *is tested by bilateral simultaneous stimulation* of the analogous site of the dorsum of both hand.
  - **Graphesthesia**—It is tested by the capacity to recognize the number drawn over the palm or back of the patient by examiner's fingertip while the patient's eye remain closed.
  - **Stereognosis**—It is tested by the ability of the patient to identify common object (e.g. key, coin) by palpation while placed on one's palm. Both arm are tested separately.

EXAMINATION OF POSTERIOR COLUMN

Disorder of posterior column involve deep sensation arising from muscle spindle, tendons and joints and affect proprioception (position sense). Loss of which is manifested as imbalance particularly when the eye is closed or in the dark leading to clumsiness of fine movement and unsteadiness of gait which are collectively called "sensory ataxia". There is also reduced or absent joint sense, vibration sense and absent deep tendon reflexes.

Romber sign—When positive patients topples when he is aked to stand on narrow base (feet close together) with eye closed.

Pseudoathetosis a continuous involuntary movement of the outstretched hand and finger occur when eye is closed and is also present in posterior column lesion.

REFLEXES

All reflex action requires the following things:

- A stimulus
- An afferent sensory nerve
- A link with the motor neuron
- A motor neuron
- An efferent nerve
- Contractile muscle or effector element. Any breach in this path causes absent reflexes. Most reflexes are influenced by higher center.

TENDON REFLEX

All muscle will contract reflexly when suddenly stretched. For this reason tendon of a muscle in suddenly tapped with a percussion hammer.

DEEP TENDON REFLEX IN RELATION TO CRANIAL NERVE

Jaw jerk—Described under 5th cranial nerve.

Deep Tendon Reflex of Upper Limb

- **The biceps jerk**
  - **Method**—Press the forefinger gently on bicep tendon in the antecubital fossa and strike the finger with hammer while the elbow partially flexed and the hand lying loosely across the abdomen.
  - **Result**—Flexion of elbow with visible contraction of biceps. Spinal segment – **C_5, musculocutaneous nerve**.
- **The supinator jerk**
  - **Method**—Strike the lower end of the radius 5 cm above the wrist while the elbow is slightly flexed.
  - **Result**—Contraction of brachioradialis and flexion of elbow. There may be slight contraction of biceps and finger-spinal segment– **C_5 radial nerve**.
  - **Inversion of supinator jerk**—Lesion of C_5 spinal segment causes loss of contraction of Brachioradialis during demonstration of supinator jerk but there is brisk flexion of finger. This is called **inversion of supinator jerk**. Loss of contraction of brachioradialis is due to lesion of C_5 spinal segment which have an UMN effect on C_6 and C_7 spinal segment causing brisk finger flexion jerk.
  - Spinal segment **C_5–C_6. Radial nerve**.
- **Tricep jerk**
  - **Method**—Patient rest his arm across abdomen loosely and strike the tricep tendon about 2" above elbow over the back of arm.
  - **Result**—Extension of elbow with contraction of triceps. Spinal segment C_6–C_7. **Radial nerve**.
- **Finger flexion reflex**
  - **Method**—Examiner interlocks his finger with the patient's finger and strike them with the hammer.
  - **Result**—Slight flexion of all finger including thumb. Spinal segment C_6 to T_1. **Median nerve**.
- **Hoffmann reflex**
  - **Method**—Terminal phalanx of the patient's middle finger is flicked downward by the examiner's finger.
  - **Result**—In hyperreflexic state (UMN lesion) there will be flexion of all finger with adduction of thumb. Spinal segment C_6 to T_1.
- **Wartenberg sign**
  - **Technique**—Patient supinate his hand with slightly flexing his finger and the examiner pronates his hand and gently interlock his finger with patient finger and then both examiner and patient further flexes their finger against each other.
  - **Result**—Normally thumb extends though its terminal phalanx may flex slightly.
    In UMN lesion thumb adduct and flexes strongly. This is not a constant sign but if present indicate early pyramidal tract lesion.

7. **Pectoral reflex**
   - **Method**—Place the finger on the pectoral muscle infront of the anterior margin of axilla and strike the finger.

- **Result**—Adduction of the arm and visible contraction of the pectoralis major. Spinal segment **C_5 to T_1. Lateral and medial pectoral nerve**.

Deep Tendon Reflexes of the Lower Limb

- **Knee jerk**
  - **Method**—Patient lie on the bed. Examiner put his left arm in between the patient's knee and bed and lift the knee gently so that the knee flexes approximately 30°–45° and the heels rest on the bed. The patella, ligamentum patella and tibial tuberosity are palpated and the patellar tendon is struck downward lightly on each side.
  - **Alternative methods**
    - Place the finger just above the patella while the knee is in extended position. Strike your finger with hammer in downward direction.
    - Make the patient to seat on the edge of the bed so that the legs are hanging. Now strike the patellar tendon with hammer. This is the best *method for demonstration of pendular knee jerk in cerebellar disorder and hungup knee jerk in hypothyroid state*. In pendular knee jerk the number of oscillation must be more than five in number.
  - **Result**—Extension of knee and visible contraction of quadriceps. Spinal segment – L_3L_4. **Femoral nerve**.
- **Ankle jerk**—
  - **Method**—Patient's one thigh and knee is slightly flexed and externally rotated. The leg may be kept on the bed or put over other leg then the tendoachilles is struck by hammer while the examiner slightly dorsiflex the foot by the other hand.
  - **Result**—Plantar flexion of the foot and contraction of the gastrocnemius. Spinal segment –S_1. **Medial popliteal nerve**.
  - **Alternative method**—Those patients who are physically fit kneel up on the margin of the bed so that the feet are projecting from the edge of the bed. Achilles tendon is then struck downward with the hammer from above on the two side.
    This is the best method for comparison between two sides and demonstration of hang up ankle jerk seen in hypothyroid state.
    Spinal segment **S_1. Medial popliteal nerve**.
- **Rossolimo's reflex**—Patient lies supine with the leg extended and the foot partially dorsiflexed. The ball of the great toe is struck with a hammer and in UMN lesion and in hypertonic state there is a brisk contraction of all the toes. The same response is obtained by flicking the finger in the upward direction and it is similar to finger flexion jerk of hand.

Failure of relaxation is the major difficulty in eliciting DTR. If a tendon reflexes appears reduced or absent it may not have any clinical significance. The patient is asked to relax as much as possible. Then reinforcement technique is applied to facilitate the deep tendon reflex.

- *For upper limb—Clenching of teeth tightly or clenching the fist of the other side.*
- *For lower limb—Jendrassik maneuver* is more reliable method in which *patient interlocks the flexed finger of the two hand and pull against each othere while the examiner tries to elicit the reflex.*

If there is asymmetry of deep tendon reflex as occurs in compressive or degenerative lesion midline deep tendon reflex are helpful to reveal the asymmetry.

Midline deep tendon reflexes are

- **Sternal reflex**—To demonstrate the reflex patient lying on the bed places his both forearm relaxly over abdomen. Place your index finger over manubrium sterni and tap with hammer. Normally there is no response or symmetrical flexion movement of both forearm any asymmetry in clearly evident.
- **Symphysis pubis reflex**—Patient lying quitely on bed with relaxed abdominal muscle and partially flexed hip with abducted and externally rotated thigh. In this position tap over symphysis pubis. When there is spasticity due to UMN lesion there will be abduction of leg. Any symmetry will be clearly evident.
  - **Deep tendon reflexes are absent or suppressed** in the following conditions:
    - Lower motor neuron lesion (total absent).
      - » Polyneuropathy
      - » Lesion of the sensory and motor nerve
      - » Lesion of anterior horn cell
      - » Myopathies
      - » Periodic paralysis.
    - Even in upper motor neuron lesion in cerebral or spinal shock stage.
    - Deep coma.
    - After GTCS.
    - During anesthesia.
  - **Deep tendon—Reflexs are brisk** in the following situation.
    - **Upper motor neuron lesion** (after recovery from shock stage).
    - **Anxiety state**.
    - **Thyrotoxicosis**.
  - Deep tendon reflexes may be **pendular in cerebellar lesion** (more than five oscillations) very clearly demonstrated in pendular knee jerk.
  - Deep tendon reflexes may be **hang up or prolong in hypothyroid state**.

Features of conus medullaries lesion:

(Ideally ankle jerk should be lost, but as the lesion extend from higher segment into the conus the following features are seen).

- *Loss of ankle jerk*
- *Loss of knee jerk* (usually)

- *Extensor plantar response*
- *Loss of bladder bowel control*
- *Symmetrical dissociated saddle back anesthesia.*
- *Spontaneous segmental sweating in the sacral segment.*

Similiar combined upper and lower motor neuron lesion featurs is seen in subacute combined degeneration of spinal cord and in taboparesis a similar reflex changes may be seen but there is no loss of sphinteric control and no segmental sensory loss.

SUPERFICIAL REFLEX

ABDOMINAL REFLEX

Method

Patient lie flat on bed. First palpate the abdomen gently. Then draw three lines on each side of abdomen with the pointed end of hammer starting from each flank.

- Upper lines parallel to subcostal margin.
- Middle line toward the umbilicus.
- Lowest line parallel to and above the inguinal ligament.

Result

The oblique muscle of the quadrant contract and umbilicus moves in that direction. All three reflex on one side will be absent in case of unilateral UMN lesion.

In case of paraplegia with a upper level at T_9–T_{11} segment, during elicitation of this reflex the upper abdominal muscle contract pulling the umbilicus upward known as **"Beevor's sign"**.

Spinal Segment

- **Upper abdominal reflex**—T_6–T_9 spinal segment.
- **Middle abdominal reflex**—T_{10}, T_{11} spinal segment.
- **Lower abdominal reflex**—T_{11} and T_{12}, sometimes L_1 spinal segment. All fiber comes via intercostal nerve.

CREMASTERIC REFLEX

Method

Upper and inner aspect of the thigh is stroked downward and inward direction while the patient lying flat on the bed. Watch the movement of scrotum and testicle on the side of examination.

Result

Contraction of the cremasteric muscle pulls up scrotum and testis on that side. **Spinal segment L_1–L_2**.

ABSENT REFLEX

May be due to

- Defective technique.
- Failure of relaxation.
- Breach in the reflex arc due to lesion of the peripheral nerve, surgical operation.
- Pyramidal tract lesion in shock stage.

ANAL REFLEX

Method

Lightly scratch the perianal skin.

Result

Contraction of the external anal sphincter. **Spinal segment S_4 – S_5**.

PLANTAR REFLEX

This is the most important reflex and considered separately (not as deep tendon reflex or as superficial reflex).

Method

Before demonstration of actual reflex watch for the *sensitivity and thickness of the sole* and *movement of toe* specially great toe.

Patient lie flat on the bed with the hip slightly flexed and externally rotated and knee is also slightly flexed. So that lateral margin of the foot should touch the bed. Ask the patient to relax as much as possible.

Now scratch the sole slowly with a blunt point such as key or the pointed end of the hammer starting from the lateral aspect heel proceed along the lateral border of the foot upto the ball of little finger (European method), then curve medially as a hocky stick like fashion towards middle metatarsophalangeal joint (American method).

In case of no response the test is repeated with the knee in full extension and pressed downward toward the bed.

This two methods are used as counter checking technique.

Normal Response

Flexion of metatarsophalangeal joint of the great toe although interphalangeal may extend with flexion of other toes. Spinal sgment S_1.

Babinski Response

Extension of great toe at the metatarsophalangeal joint (which is most important) with fanning of other toes in a dorsiflexed manner.

In advanced case whole foot dorsiflexes with flexion of hip and knee and the contraction of the muscle can be felt. If only the foot dorsiflexes it is usually a voluntary movement also called withdrawal response.

In case where there is bony ankylosis of great toe or the great toe has been amputated or complete paralysis of extensor of toes, visible and palpable *contraction of tensor fascia lata can be observed*. Babinski responsed indicate functional disturbance of pyramidal system.

Lesion Responsible for Presence of Babinski Response

1. UMN lesion (anatomical).
2. Child below the age of 6–12 months (pyramidal tract is not myelinated).
3. Coma from any cause.
4. After GTCS.
5. Anesthesia.
6. Deep sleep.
7. Alcohol.

The true reflex movements normally starts when the stimulator instrument is about to complete one third of its journey on the sole and sometime almost at the end of stimulation.

Those patient whose sole is very thick or insensitive or hypersensitive in those condition—*Stimulation of the hairless zone of the extreme lateral aspect of the dorsum of the foot will elicit the plantar response very clearly*.

In deformities like pes cavus or surgically corrected hallux valgus the movement of the 1st metatarsophalangeal joint and movement of the other toes must be observed.

Several other methods are used for elicitation of plantar reflex of which three most commonly used methods are as follows:

1. **The Oppenheim reflex**—In this method firm pressure by index and thumb is applied over the shin bone starting from tibial tuberosity gradually downward upto the malleolus. Greater pressure is applied over the medial boarder of the tibia.
2. **The Gordon reflex**—A hard squeeze of the cuff muscle, specially near the origin of the tendoachilles.
3. **The Chaddock reflex**—A light stroke below the external malleolus in a semicircular manner on the later aspect of foot. Starting from the back of lateral malleotus.

It is said that the receptive field of the affarent path of plantar reflex is S_1 dermatome in normal person but in some patient it may extend from L_4 dermatome to S_2 dermatome.

In Oppenheim reflex, we actually stimulate L_4–L_5 dermatome.

In Gordon reflex by squeezing cuff muscle, we actually stimulate S_1 S_2 dermatome.

In Chaddock reflex, we actually stimulate L_5 dermatome.

Each has the same significance as Babinski response but each is less reliable. These methods are applied in the following conditions:

- If profound lesion of pyramidal tract is suspected
- Patient with hypersensitive sole
- Noncooperative patient
- In case of children.

SOME OTHER IMPORTANT REFLEXES AND SIGNS IN CNS EXAMINATION

- **The grasp reflex**—Place one pen or pencil in between the patients thumb and index finger and try to withdraw it out or move it towards tip of the patient's finger. If grasp reflex is present the patient' finger will flex strongly and try to hold the object tightly.
  This is present in the following conditions:
  - Physiologically infant below 6 months of age.
  - Persist in mental deficiency, birth injury.
  - CVA or SOL involving frontal lobe particularly medial surface of brain.
  - Cortical or subcortical atrophy of frontal lobe.
  - Lesions of corpus callosum (probably due to involvement of fiber arising from frontal lobe.
  - Neurodegenerative disorder.
  - Alzheimer's disease.
  - Parkinsonism and multiinfarct dementia.
  - Old age.
- **Forced grouping reflex**—In forced grouping reflex, repeated light touch of the side of the patients' palm results in attempting to grasp it or hand will follow the stimulus.
  This reflex is seen in
  - Lowered consciousness (Drowsy state/stuporous state).
  - Severe mental defect due to widespread cerebral lesion but does not indicate lesion of any specific area of brain.
- **Sucking reflex**—The reflex is normally present in infant and is characterized by sucking movement of the lip and deviation of the angle of mouth following light touch of the corner of mouth.
  In adult it may be present in
  - Cerebral atropic lesion
  - Widespread cerebral trauma or encephalitis.
- **Glabellar tap**—It is elicited by repeated tapping on the bridge or root of the nose standing at the head end of the patient which results in synchronous blinking of both eye and persist for maximum 4–5 tap in normal person

but in Parkinson's disease it will continue indefinitely and help in early diagnosis.

CLASSICAL SIGN

- **Chvostek's sign**—Direct tapping of the facial nerve in the parotid gland in front of tragus produces marked twitching and contraction of the corner of the mouth. This type of hyperexcitability is seen—
  - Tetany.
  - Other electrolyte and acid-base disorder.
  - Regeneration of damaged facial nerve.
- **Trousseau's sign**—If the arm is compressed by inflated blood pressure (BP) cuff for not more than 4 minutes the hand with finger goes into spasmodic contraction like main d'accoucheur position (policeman taking tips). This is seen in tetany or gross alkalosis.
- **Lhermitte's phenomenon**—In this sign when the neck is forcibly flexed forward a electric shock like sensation shoots down the spine and back radiating to all four limb is felt by the patient. Sometime the sensation may be unilateral.
  This sign is felt in the following conditions—
  - Multiple sclerosis (once considered diagnostic)
  - High cervical compression from spondylosis.
  - Cerebellar ectopia.
  - Early stages of radiation myelopathy.
  - Subacute combined degeneration of spinal cord.

EXAMINATION OF GAIT

Four special types of gait are usually seen.

- **Hemiplegic/circumduction gait**—This type of gait are seen in hemiplegic patient after recovery. The special features of the gait is the affected upper limb is flexed at elbow, shoulder is adducted so that arm is by the side of trunk, forearm is semipronated with the closed fist.

  The lowe limb on the affected side is extended at hip, knee and plantar flexed at ankle so that the affected lower limb appears longer than the healthy limb and during walking to clear the affected limb from ground the patient will lean on the healthy side or sometime take the help of a walking stick to maintain the balance and patient will bring the affected lower limb in a semicircular manner from back to the front with the help of pelvic girdle muscle.
- **Scissor gait**—This gait is seen in spastic paraplegia. In this gait both heel is off the around, i.e. ankle is plantar flexed. The knee joint is either fully extended or partially flexed depending whether it is paraplegia in extension or paraplegia in flexion and during walking the leg crosses midline and to maintain body balance, the patient usually take help of a walking stick in the midline with both hand.
- **Waddling gait**—This type of gait is seen in weakness of extensor the pelvic girdle muscle. The hip is partially flexed and usually during walking the patient lurches from one side to the other.
- **Parkinsonian gait**—In this gait the patient have knee and hip partially flexed with increased dorsal kyphosis and hands are by the side of trunk (simian posture). At the beginning of walking the patient usually lean forward to take the center of gravity in infront of the body and to catch the center of gravity the patient take few short steps forward. This is called propulsion and there is marked loss of associated movement of hand, during turning the patient connot turn the body as a whole, he will break the movement in short steps.

Chapter 118

Examination of Upper Gastrointestinal Tract

INTRODUCTION

Examination of upper GI tract starts with examination of lips. Pathology found in lips are as follows—

- **Herpes labialis**—Found in common cold, influenza, lobar pneumonia, meningococcal meningitis, malaria.
  It gives clue to the side and stage of lobar pneu-monia. Right-sided vesicles indicate right-sided lobar pneumonia. Vesicular stage of herpes indicates gray hepatization and denuded herpes suggests stage of resolution.
- **Cheilosis**—Fissure at the corners of lip. Usually due to deficiency of iron, niacin, riboflavin, pyridoxine.
- **Angular stomatitis**—Superficial and reddish brown linear ulcer radiating from the angle of the mouth. Causes—Ill fitted denture, deficiency of riboflavin, iron, etc.
- **Color of lip**—Blue—Cyanosis, meth or sulph hemoglobinemia.
- Examination of mucosal surface of lips for aphthous ulcers, secondary syphilitic ulcer.

CHEEK

Abormalities seen in cheek are as follows:

- Pigmentation seen in Addison's diseases, hemochromatosis, polyposis of the colon (Peutz-Jeghers syndrome), chronic arsenical poisoning.
- **Koplik's spot in measles**—Found in the vestibule of mouth near molar and premolar teeth.
- **Hemorrhagic spot** seen in thrombocytopenia, VWD, hereditary hemorrhagic telangicetasia (Rendu-Osler-Weber disease).

GUM

Common abnormalities of the gum are

- **Gingivitis**—Swollen gums, bleed easily on touch.
- **Blue line in the gum**—Seen in lead posioning.
- **Dark line along gingival margins**—Seen in mercury and arsenic poisoning.
- **Pyorrhea alveolaris**—This is due to accumulation of food debris between gum and teeth leading to growth of organisms, which causses infective endocarditis, septicemia, aspiration pneumonia and rheumatic fever.
- **Ulcers of gum seen in**
  - Aphthous ulcers.
  - Vincent's angina (acute necrotizing gingivitis, caused by fusiform bacilli and spirochetes— *Borrelia vincenti*) in neutropenic patient.
  - Big ragged ulcer with or without sloughing—acute leukemias, agranulocytosis.
- **Gum hypertrophy**—Seen in association with
  - Drug—Phenytoin
  - Pregnancy
  - Acute monocytic leukemia (M_4).
- Palpate for any tumor of gum, apical root abscess and stone in the salivary duct.

TEETH

Common abnormalities of teeth are

- **Delayed dentition**—Found in hypoparathyroidism and rickets.
- **Fluorosis**—Teeth are yellow and mottled.
- **Hutchinson's teeth**—Congenital symphilis (inverted peg-shaped teeth).
- **Tetracycline**—It causes malformed yellow colored teeth if consumed by expected mother or child up to 8 years of age.

BREATH

- **Foul smelling**—Gangrene of lung, lung abscess, bronchiectasis, pyorrhea alveolaris.
- **Sweetish or fruity smell**—Diabetic ketoacidosis due to acetone.
- **Garlic odor**—Bismuth toxicity.
- **Mousy odor**—Hepatic failure (fetor hepaticus).
- **Ammonical odor**—Uremia.

TONGUE

Detailed examination is done in 12th nerve palsy.

1. **Tongue tie**—Due to short frenum.
2. **Hydration**
   a. *Dry tongue*—Dehydration, shock, atropine and mor- phine, poisoning, uveoparotid fever, Sjögren's syndrome.
   b. *Moist tongue*—Heavy metal poisoning like arsenic.
3. **Tremor**
   a. *Fine tremor*—Anxiety neurosis, thyrotoxicosis, chronic alcoholism.
   b. *Coarse tremor (trombone)*—Parkinsonism (dementia paralytica).
4. **Deviation of tongue**
   a. In LMN lesion (lower motor neuron lesion)— Twelve nerve palsy tongue is deviated to same side.
   b. In unilateral seven nerve palsy tongue may apparently appear to be deviated.
5. **Spasticity of tongue**—Pseudobulbar palsy.
6. **Lingual hemiatrophy**—Seen in
   a. Lesions of XIIth cranial nerve or its nucleus
   b. Progressive bulbar palsy
   c. Amyotrophic lateral sclerosis.
7. **Color of the tongue**
   a. *Pale*—Anemia (at the margin of tongue).
   b. *Blue*—Cyanosis, meth/sulph hemoglobinemia (at the tip of tongue).
   c. *Yellow*—Jaundice (on the under surface of tongue).
8. **Coating on the surface of the tongue** seen in
   a. Candidiasis
   b. Enteric fever
   c. Poor hygine.
9. **Condition of papillae**
   a. *Smooth bald tongue*—Iron deficiency anemia, sprue, pellagra, pernicious anemia.
10. **Ulcer on tongue**
    a. *Snail tract ulcer over dorsum*—Secondary syphilis.
    b. *Fissured tongue*—Congenital, chronic superficial glossitis.
11. **Size of tongue**
    a. Macroglossia—Acromegaly, myxedema in creatine and primary amyloidosis.
    b. Microglossia—Cerebral diplegia, pseudobulbar palsy, bilateral hypoglossal nuclear lesion and amyotrophic lateral sclerosis.
12. **Taste sensation**.

PALATE

Detailed examination is done in 9th, 10th, 11th cranial nerve palsy.

1. **Color of the palate**
   a. *Pale*—Anemia
   b. *Blue*—Cyanosis
   c. *Yellow*—Jaundice.
2. **Movement**—Movement of arch of soft palate is noted by asking the patient to speak 'Ah'—Detailed exami- nation is done in cranial nerve section of neurology. Palatine palsy is seen in involvement of cranial root of accessory nerve found in diphtheria, GB syndrome and bulbar palsy.
3. **High arch palate** seen in—Marfan's syndrome. Mongolism or in association with congenital heart disease.
4. **Cleft palate**—Congenital anomali.
5. **Petechial hemorrhage** found in ITP and leukemia.

TONSILS

To be inspected after depressing the tongue with tongue spatula.

- Condition of the tonsil (hypertrophic/atrophic)
- Whether pus coming out from the crypts
- Presence of membrane on the surface or pillar
- Presence of congestion.

FAUCES

Examine with a torch after depressing tongue with a tongue spatula.

Gag reflex—Detailed examination is done in IXth, Xth, XIth cranial nerve palsy. When a sterile swab stick is touched to the posterior wall of the pharynx, patient will uttar 'Ah' with a sense of vomiting and increased salvation. Afferent path of the reflex is formed by IXth and the efferent path by cranial root of accessory nerve and Xth-cranial nerve.

EXERCISE

Write short notes on

1. Procedure for examination of upper GI tract.

Chapter 119

Examination of Lower Gastrointestinal Tract

INTRODUCTION

It is classically subdivided into four parts:
1. Inspection
2. Palpation
3. Percussion
4. Auscultation.

INSPECTION

During inspection, patient should lie supine over the bed, hand by the side of trunk and mouth is rotated to left and the examiner should stand on the right side of the patient. Patient should be screened all round for female patient. A female attendent must be present in case of male examiner.

Exposer—Ideally from nipple to midthigh should be exposed but usually for social reason we examine after exposer of limited part of abdomen.

Shape of the Abdomen

It is scaphoid shaped, i.e. xiphoid process and symphysis pubis are at higher plane than the central part of abdomen. The umbilical region is at a lower plane.

If the umbilical region and hypogastrium is bulged, it is probably due to
- Omental cyst
- Mesenteric cyst
- Pseudopancreatic cyst
- Ovarian cyst
- Gravid uterus
- Distended bladder
- Gaseous distension of gut
- Ascites.
  - If the bulging is localized in the right or left hypochondrium then it is possibly due to hepatomegaly and splenomegaly respectively.
  - If the two flanks are bulged symmetrically but not the umbilical region then it is possibly due to ascites (free fluid in the peritoneal cavity).
  - Bulging over hypogastrimn in either due to distended bladder or in cases of female gravid uterus.
  - If the bulging is localize to one iliac fossa then possibly it is due to ovarian cyst of that side in female patient.

Umbilicus

If the umbilicus is deeply inverted its probably due to obesity.

If the umbilicus is everted or flushed with the skin then it suggest presence of ascites or umbilical hernia.

If the umbilical slit is transverse it suggest ascites.

If the umbilical opening is dragged to one quadrant, it suggest organomegaly in that quadrant, e.g. splenomegaly will drag the umbilical opening to the left upper quadrant.

Hepatomegaly will drag umbilical opening to the right upper quadrant.

Ovarian cyst will drag the umbilical opening to the right or left lower quadrant.

Venous Prominence

Look for venous prominence after a bout of cough over the epigastrium and around the umbilicus and making the patient seated over the bed which makes the abdominal vein more prominent. If the epigastric veins are prominent, it suggest portal hypertension. Rarely a circular vein around umbilicus is prominent in portal hypertension which is called 'Caput Medusa', from which veins radiate like the legs of spider.

Pulsation Over the Epigastrium seen in the Following Situation

- Right ventricular hypertrophy (RVH)
- Tricuspid regurgitation (TR)
- Congestive cardiac failure (CCF)
- Mass arising from left lobe of liver
- Mass arising from stomach
- Mass arising from pancreas (pseudopancreatic cyst)
- Aneurysm of the abdominal aorta.

Except aneurysm of the aorta all other conditions give rise to transmitted pulsation in which if the two pointer when placed on either side of midline it will move up and down whereas in aneurysm of abdominal aorta there will be expansile pulsation where the two pointer placed on either side of midline separate from each other during pulsation.

Visible Peristalsis

In very lean and thin individual and in neonates peristaltic wave is visible over the abdomen in physiological condition.

- Visible peristaltic wave (3–5/min) starting from left hypochondrium going towards right hypochondrium touching umbilical region is suggestive of gastric outlet obstruction (GOO) in pyloric stenosis/gastric carcinoma.
- Another peristaltic wave starting from left iliac fossa moving towards right iliac fossa across the hypogastrium is suggestive of obstruction at the ileocecal valve region.
- A third type of peristaltic wave which starts from right hypochondrium moves toward the left hypochondrium in suggestive of obstruction in the splenic flexure or in the descending colon.

Examination of Inguinal Orifices and Genitalia will be Discussed in Detail in Surgical Clinical Class

Prior to palpation the following steps to be followed:

- Take verbal consent for examination from the patient.
- Ask the patient to evacuate bladder and bowel.
- Surround the bed by screen.
- In case of female patient and male examiner, one lady attendent must be there.
- Patient lie supine straight on the bed with hip and knee partially flexed with the idea that the inguinal ligament will relax as a result the tension of the oblique muscle of abdomen will minimize to some extent. The head is rotated to the left and examiner stand on the right side of the bed.
- Ask the patient to take deep breath with open mouth during palpation.
- Exposure—Ideally for examination of abdomen, from nipple line to midthigh should be exposed but usually for social reason we examine after exposure of a limited area of abdomen.

PALPATION ABDOMEN

Palpation is subdivided into superficial palpation and deep palpation.

Superficial Palpation

- For demonstration of the direction of venous flow first select a segment of vein which has no branch or tributary preferably over epigastrium. Then compress or milk the vein with the help of finger of both hand to make it blood less and release pressure from one side to identify the speed of refilling. Over the epigastrium in normal person and in portal hypertension veins will flow from below upward against gravity but in superior vena caval obstruction it will flow from above downward.

  In normal person if we imagine a horizontal plane across the umbilicus it in considered the watershed line of the abdomen. Above that plane all vein flow upward against gravity and tributary of superior vena cava and below that plane all veins flow downward and tributary of inferior vena cava.

  This direction of venous flow will remain normal in portal hypertension, only vein over epigastric region will be dilated and tortuous and very rarely a circular vein encircle the umbilicus from which veins radiates in different direction like legs of spider. It is called **caput medusa**.
  - In case of inferior vena cava obstruction, veins of hypogastrium will flow from below upward in stead of from above downward (in normal condition).
- Assess any temperature difference over the different quadrant of abdomen by the dorsum of the hand.

  The temperature difference is noted over pyogenic lesions of the skin and over severe localized peritonitis as occur in acute appendicitis, pericholecystic abscess or peptic perforation.
- Assessment of muscle guard and rigidity—for assessment of muscle guard gently rotate the palm. Over the skin of abdomen with slight pressure to the resistance offered by the muscle. This is done to assess whether any localized peritonitis present in any Quadrant like acute appendicitis, peptic perforation, acute cholecystitis or detection of any overt lump or organomegaly.

Deep Palpation/Visceral Palpation

Deep palpation of abdomen in done for liver and spleen standing on the right side of patient.

- The inital steps of the palpation of spleen is same as that of the liver.

Palpation of Liver

Palpation of liver to be started from right iliac fossa on midclavicular line by right hand. The radial boarder of index finger should be parallel with right subcostal margin. The pressure over the abdomen to be directed tangentially towards the back and towards the head end of the patient and ask to patient to take deep breath. At the height of inspiration the pressure over the abdomen to be released to some extent so that if there is organomegaly the organ will slip beneath the finger during deep inspiration and during expiration it will move up. In this way liver can be better palpated.

This is repeated for 3–4 respiration and if the organ is not palpable then withdraw the hand and move upward by 2 cm along the midclavicular line and repeat the same procedure.

If the tone of rectus abdominis is very high move up along the lateral rectal boarder. If liver is palpable then make a note of the following points:

- **Extent of the hepatomegaly** (in centimeter) from right subcostal margin along midclavicular line.
- **Surface of the liver whether**:
  - Smooth.
  - Granular (postalcoholic cirrhosis).
  - Nodular (posthepatitic cirrhosis/secondary deposit).
  - Nodule with umbilication (secondary deposit).
- **Margin**
  - Rounded
  - Well defined
  - Sharp.
- **Consistency**
  - Soft
  - Firm
  - Hard.
- **Tender or nontender**.
- **Pulsatile or nonpulsatile**.
- Span of liver is measured from lower boarder of 4th rib to the lower boarder of liver on MCL (which is 14 cm in normal person).
- For *assessment of pulsality* of liver, patient had to sit over the bed. Left hand of the examiner to be placed over lower ribs on the back and the right hand below the right subcostal margin and the patient is asked to hold the breath at the height of deep inspiration and the examiner will try to approximate his hands by giving pressure over the anterior abdominal wall.

  The liver is pulsatile in *tricuspid regurgitation* and in *big arteriovenous malformation* within liver and *congestive cardiac failure*.

Palpation of the left lobe of liver

Left lobe of the liver can be palpated by two methods:

- After palpation of the right lobe follow the lower boarder of right lobe toward the midline.
- Start palpation for left lobe of liver from umbilicus proceed toward xiphoid process along the midline.

  All person have left lobe 4 cm below xiphoid process but it is not palpable due to tonicity of rectus abdominis muscle. It is only palpable in those person whose tone of rectus is diminished, e.g. multigravida lady or whose ascites have subsided.

Causes of palpable liver

- **Liver drops down but not enlarged**
  - Pleural effusion
  - Pneumothorax
  - Emphysema
  - Subdiaphragmatic collection
  - Visceroptosis.
- **Congestive hepatomegaly**
  - Congestive cardiac failure (CCF)
  - Tricuspid regurgitation (TR)
  - Constrictive pericarditis
  - Hepatic vein thrombosis (Budd-Chiari syndrome).
- **Malignancy causing hepatomegaly**
  - **Primary malignancy**—(20%)
    - Hepatoma (90%)
    - Cholangiocarcinoma (10%).
  - **Secondary deposit**—(80%)
    - **Intraabdominal**—Malignancy
      - **Gut malignancy**
        - **Foregut**—Carcinoma arising from stomach, head of pancreas and gallbladder.
        - **Midgut**—(very rare) carcinoma of duodenum and Jejunum.
        - **Hindgut**—Carcinoma arising from appendix, cecum, colon and rectum.
        - **Malignancy of other intraabdominal organ** like kidney, prostate, ovary and testis.
    - **Extraabdominal malignancy**—Carcinoma-arising from breast, bones, lung, thyroid and malignant melanoma.

      Lymphoma and granulomatous sarcoma in CML and leukemia can also give rise to hepatomegaly.
- **Infective disorder causing hepatomegaly**
  - **Virus**—Viral hepatitis.
  - **Gram-negative septicemia**—Salmonella, Shigella and *Escherichia coli*.
  - **Parasite, protozoa**—Malaria, kala-azar and *Entamoeba histolytica*.
- **Storage and infiltrative disorder responsible for hepatomegaly**
  - **Congenital**—Wilson disease, Gaucher, Niemann-Pick, glycogen storage disorder.
  - **Acquird**—Fatty liver in alcoholic and hemochromatosis due to repeated blood transfusion (thalassemia).

Palpation of spleen

- The palpation for spleen is to be started from right iliac foss and proceed along the **spinoumbilical line** (the line joining anterior superior iliac spine and umbilicus is extended toward left subcostal margin) which correspond to the axis of 10th rib. If a mass is palpable along that line, one has to ascertain whether it is a splenic mass or a kidney mass by the following points:
  - Extent of mobility and the direction of movement—Splenic mass is more mobile with respiration and

move obliquely towards right iliac fossa, whereas movement of kidney mass is restricted and moves up and down with respiration.
- If the palpating finger follow the upper border of the mass a notch is palpated in case of spleen which is called splenic notch (nothing but embriologically incomplete fusion line between the first and the second splenic lobule).
- It is impossible to insinuate finger in between the splenic mass and the costal margin but finger can be insinuated easily in between kidney mass and costal margin.
- If percussion in done over the mass. It is all through dull in case of splenic mass but there in a band of colonic resonance over the kidney mass.
- Renal angle (angle between the lower boarder of the 12th rib and erector spinae group of muscle) will be full in case of kidney mass but empty in case of splenic mass.
- Kidney mass is bimanually palpable, i.e. it can be gripped in between two palpating hand one placed over left renal angle and the other over the left side of abdomen.
- Ballottement test is positive for kidney mass, i.e. if pressure is applied over the mass through abdominal wall it will be felt over the renal angle and vice versa but ballottement test is negative in case of splenic mass. (Kidney is usually enlarged in PCKD).

Causes of palpable spleen

Huge splenomegaly—When enlargement of spleen is more than 8 cm from tip of 10th rib, or spleen is has crossed the midline or spleen has reached left iliac fossa, specially in case of child whose gastrosplenic ligament or fold of peritoneum has not well- developed is called huge splenomegaly.

- **Causes of huge splenomegaly**
  - β-thalassemia major
  - Chronic malaria
  - Chronic kala-azar
  - Chronic myeloid leukemia
  - Myelofibrosis/myoproliferative disorder
  - Tropical splenomegaly
  - Tumor and cyst of spleen.

Moderate splenomegaly—When (enlargement of spleen is more that 5 cm but less than 8 cm or has not crossed the midline)

- **Causes of moderate splenomegaly**
  - All other thalassemia except β-thalassemia major
  - All other leukemia except CML
  - Lymphoma
  - Portal hypertension
  - Amyloidosis and sarcoidosis.

All causes of huge splenomegaly in early stage may persent as moderate splenomegaly.

Mild splenomegaly—When enlargement of spleen is less than 5 cm from the tip of 10th rib.

Causes of mild splenomegaly—

- **Infective disorder**—Infectious mononucleosis, hepatitis-B, miliary (disseminated) tuberculosis, subacute bacterial endocarditis, enteric fever (2nd weeks onward).
- **Immunological disorders**—SLE, rheumatoid arthritis (Felty's syndrome), Graves disease.
- **Hematological disorder**—Hereditary spherocytosis, (rarely sickle cell disorder, iron deficiency anemia and ITP).
- **Glycogen storage disease** and other storage disorder, amyloidosis and sarcoidosis.

Other methods for palpation of spleen

- **Right lateral method**—If spleen is not palpable by the above classical method the patient is rotated to right lateral decubitus and the same procedure is repeated as that of classical method for palpation of spleen.
- **Hooking method**—In this method, the finger of either left or right hand is hooked below left subcostal margin standing on the left side of the patient making the patient right lateral decubitus.

  To get mild splenomegaly this method is very helpful as because to become palpable **spleen must enlarge more than 2½ to 3 times of its normal size**. So mild splenomegaly also has great significane.
- **Dipping method of palpation**—This method is practiced. Where there is ascites along with organomegaly. In this method usually finger of right-hand in placed over the left- hand. For palpation of liver fingers are placed over right hypochondrium. For palpation of spleen fingers are placed over left-hypochondrium. Now a sharp tap is given over the abdominal wall, it will, displace the water of ascites and examiner can feel the surface of the organ. By this method we can just say hepatomegaly or splenomegaly is present but it is not possible to ascertain the extent of organomegaly.

PERCUSSION OF ABDOMEN

Percussion of abdomen is done to demonstrate:

- Shifting dullness.
- Fluid thrill.
- Extent of liver dullness (to know the span of liver normally which is 14 cm).
- Percussion of spleen for splenomegaly

Shifting Dullness

This is the surest test for demonstration of ascites or frce fluid inperitoneal cavity:

- Before starting percussion patient must evacuate his bladder and bowel.
- For demonstration of shifting dullness patient must lie supine and straight over the bed, hands are by the side of the trunk there is no necessity of flexing hip and knee.
- Then palpate for liver and spleen. If hepatomegaly is present then demonstration of shifting dull should not be attempted on right side of abdomen and if huge splenomegaly is present, demonstration of shifting dullness should not be attempted on left side of abdomen.
- For actual demonstration of shifting dullness percuss down from xiphoid process along midline towards symphisis pubic. Usually just below xiphoid process there is tympanicity for fundic gas of stomach but below that level and above umbilicus there is intestinal resonance due coils of intestine containing gas bubble which float over the ascitic fluid. If the percussion is continued further down along midline dullness gradually increases towards symphysis pubis.

  Now from the point of maximum resonance just above the umbilicus percuss towards each flank along a straight line. **In presence of ascites** after percussion for some distance dullness will start. Mark the point of starting of dullness on both side of midline over abdomen with a skin pencil but the percussion to be continued up to deep flank to demonstrate that the dullness is continuous and it is not a localized dullness due to fecal matter or a mass.

  Then turn the patient 90° so that one flank now become the highest point of the abdomen, and wait for 20–30 second to allow times to the ascitic fluid to gravitate down and the coils of gut to float up.

  Now start percussion from flank, (now it is the height point of abdomen) which will now turn resonant and the percussion is continued towards midline. Some distance from flank dullness will restart which is to be marked with pencil and the dullness will continue upto the touching point abdomen with the bed crossing midline.
  - If both hepatomegaly and splenomegaly is present then the shifting dullness could not be demonstrated by the above method. In this situation shifting dullness is demonstrated by '**puddle sign**'. By this method percuss the central abdomen for resonance in supine posture then make the patient genu-elbow position (like that of Quadruped animal) and percuss the periumbilical region from below which will turn dull.
  - In patient with short mesentery (in tuberculosis of intestine called tabes mesentericus) shifting dullness could not be demonstrated although there may be huge amount of fluid.
  - Each paravertebral gutter can accommodate at least 250 mL of fluid which could not be demonstrated clinically. So to demonstrate shifting dullness at least more than half liter of fluid must be present in the peritoneal cavity. If the amout of fluid is less than half liter it can be demonstrated by the ultrasonography but not climically.

Fluid Thrill

For demonstration of fluid thrill, fluid in the abdomen must be under tension. Patient must press his ulnar border of hand over the midline of abdomen and examiner tap over one flank and try to palpate the thrill by palm of the other hand over the opposite flank.

Patient's own hand over the midline will cut down the web travelling through parietes. Fluid thrill could be demonstrated in case of tense ascites, ovarian cyst, pseudopancreatic cyst, mesenteric cyst and omental cyst.

Percussion for Liver Dullness

Percussion for liver dullness to be started over chest wall on right side down the midclavicular line. Liver dullness usually starts from 5th rib downward and is continued upto the lower border of liver. Span of liver dullness is usually 14 cm.

Percussion for Spleen

Splenic percussion is done by three methods:

- **Castle's method**
- **Traube's space percussion**
- **Nixon method**.

Castle's method

In this method extent the left anterior axillary fold downward towards the subcostal margin. Mark the point where it cut the subcostal margin usually over 8th or 9th ICS. Directly percuss over that point. *If that point is dull splenomegaly is said to present.*

Traube's space percussion

Traube space is bounded above by the lower boarder of 6th rib, below and medially by the subcostal margin and posteriorly by midaxillary line.

Normally this space resonant. This space is dull in case *pneumonia, pleural effusion, pericardial effusion, mass arising from either left lobe of liver, tail of pancreas* or *greater curvature of stomach* and *splenomegaly*. If all other causes of dullness could be excluded but Traube's is dull then the dullness is due to splenomegaly.

Nixon method

In this method start percussion down the posterior axillary line on the left side. Mark the point of starting of dullness. Now find out the midpoint of the subcostal margin with the help of a measuring tape (from xiphoid process to midaxillary line). Join this two point with a line and percuss along that line from the posterior end. Posterior seven centimeter of that line is normally dull due to spleen. If *the dullness is more than seven centimeter from the posterior end then splenomegaly is present*.

AUSCULTATION OF ABDOMEN

- **Intestinal peristaltic sound**—Normally present 3–5/min over abdomen.

  Peristaltic sound is absent in **paralytic ileus**. Increased peristaltic sound is heard during **diarrhea subacute intestinal obstruction** and carcinoid syndrome.
- Bruit over abdomen is present in coarctation of aorta and narrowing of the origin of renal artery. In both this condition it is present over midline of abdomen but in renal artery stenosis it can also be heard over one renal angle but not in case of coarctation of aorta.
- Splenic rub—A rubbing sound can be heard over left hypochondrium in both phases of respiration (expiration and inspiration) in case of perisplenitis in sickle cell disorder.
- Hepatic suffle—A soft shuffling sound can be heard over right hypochondrium in case of hepatic arteriovenous malformation.

Chapter 120

Approach to a patient of Lymphadenopathy

CAUSES OF LYMPHADENOPATHY

- **Viral**
  - EBV (Epstein-Barr virus)
  - CMV (Cytomegalovirus)
  - HBV
  - HIV
  - Herpes
  - Measles
  - Rubella.
- **Bacterial**
  - *Streptococcus*
  - *Staphylococcus*
  - TB, syphilis, chancroid, leprosy
  - Diphtheria
  - Plague
  - Brucellosis.
- **Fungal**
  - Histoplasmosis
  - Coccidioidomycosis
  - Paracoccidioidomycosis.
- **Chlamydial**
  - Trachoma
  - LGV (lymphogranuloma venereum).
- **Parasitic**
  - Filariasis
  - Toxoplasmosis
  - Kala-azar (African)
  - Trypanosomiasis.
- **Rickettsial**
  - Scrub typhus
  - Rickettsialpox.

IMMUNOLOGIC CAUSES OF LYMPHADENOPATHY

- Rheumatoid arthritis (RA), juvenile rheumatoid arthritis (JRA), systemic lupus erythematosus (SLE), mixed connective tissue diseases (MCTD).
- Sjögren's, graft versus host disease (GVHD), Biliary cirrhosis, dermatomyositis.
- Serum sickness.
- Drug hypersensitivity.

  Phenytoin, hydralazine, allopurinol, primidone, gold and carbamazepine.

NEOPLASTIC CAUSES OF LYMPHADENOPATHY

- Primary non-Hodgkin lymphoma (NHL), Hodgkin's diseases (HD), acute lymphoblastic leukemia (ALL), chronic lymphatic leukemia (CLL). Malignant histiocytosis, hairy cell leukemia, amyloidosis.
- Secondary—From different sources.

LIPID STORAGE DISORDER IN LYMPHADENOPATHY

- Gaucher's
- Niemann-Pick
- Fabry.

ENDOCRINE CAUSE OF LYMPHADENOPATHY

Hyperthyroid (Graves disease).

OTHERS

- Reactive.
- Castleman's diseases (giant lymph node hyperplasia).
- Kikuchi's disease (histiocytic necrotizing lymphadenitis).
- Kawasaki disease—Mucocutaneous lymph node syndrome.
- Sarcoid.
- Histiocytosis X.
- Familial mediterranean fever.
- Severe hypertriglyceridemia.

MEDICAL HISTORY

- Age
  - Elderly age—Malignancy is more common.
  - Middle age—Immunological.
  - Young age—Infection and storage disorders.
- Sex— Female—SLE, RA, dermatomyositis.
- Region—Tubercular lymphadenitis is common in India.
- Kala-azar causing lymphadenitis common in Africa.

- Occupation
  - Exposure to chemical.
  - Exposure to pets (cat) causing toxoplasma lymphadenitis.
- **Use of drugs**—Phenytoin causes lymphadenitis.
- **Sexual (multiple sexual partner suggest)**—HIV, chlamydia, HSV-2, syphilis chancroid.
- **IV drug abuse**—*Streptococcus*, *Staphylococcus*, HIV.
- **Radiation**—Malignancy (primary or secondary).

SYMPTOMS

- Fever associated with viral or bacterial infection.
- Sore throat present in viral or bacterial infection.
- Weight loss associated with TB and malignancy.
- Night sweat associated with TB, Hodgkin's diseases and NHL.
- Fatigue seen in malignancy and leukemia.
- Prolong cough associated with tuberculosis and lung cancer.
- Similar episode in past—Common in infective disorder.
- Bleeding tendency seen in leukemia (ALL, CLL and hairy cell leukemia).
- Pallor and palpitation is due to anemia in leukemia.
- Skin rash is associated with measles, rubella and rickettsialpox.
- History of blood transfusion suggest HIV and hepatitis.

NODE (LOCAL EXAMINATION)

A lymph node is considered to be pathological when its size:

- In neck >1 cm^2
- In axilla >1.5 cm^2
- In inguinal region >2 cm^2.

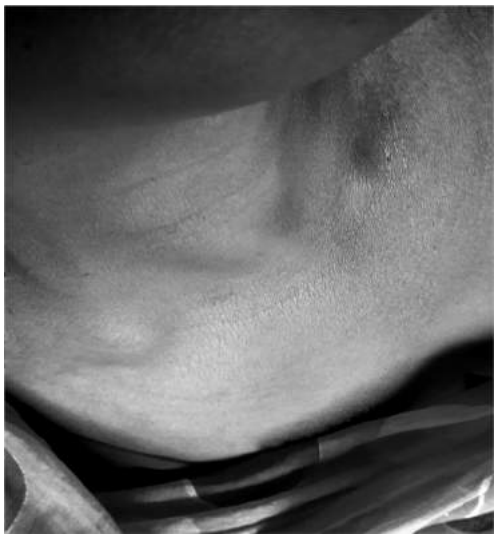


Fig. 120.1: Virchow's gland (left medial supraclavicular group)

- **Extent**
  - Localized lymphadenopathy (when a single node group is involved).
  - Generalized lymphadenopathy (more than 2 non-contageous group enlarged) mostly associated with nonmalignant cause though ALL, CLL and lymphoma can cause generalized lymphadenopathy.
- **Size**
  - <1 cm^2 suggest benign, nonspecific, reactive cause.
  - >2.25 cm^2 suggest malignant or granulomatous cause.
- **Texture/consistency**
  - Soft consistency suggest infection.
  - Firm consistency suggest chronic granulomatous disease and storage disease.
  - Rubbery consistency suggest Hodgkin's disease and NHL.
  - Hard consistency suggest malignancy.
- **Tenderness** of this gland present in infective cause or in acute leukemia due to `acute stretching of capsule.
- **Shape**
  - Oblong shape, long axis > short axis indicate non-malignant cause (ratio of long : short axis >1.5).
  - Rounded gland long axis = Short axis (ratio <1.5) indicate malignancy.
- **Signs of inflammation**—Usually present in bacterial infection-like *Streptococcus*, *Staphylococcus*, diphtheria and plague.
- **Skin lesion** with discharging sinus present in tuberculosis.
- **Splenomegaly** is associated with EBV, lymphoma, ALL, CLL, SLE sarcoid, toxoplasma, cat scratch fever and hematological disorder.
- **Site of lymphadenopathy**
  - **Occipital adenopathy** present in scalp infection.
  - **Periauricular adenopathy** present in conjunctivitis and cat scratch diseases.
  - **Cervical adenopathy** present in URTI, dental infection, EBV viral infection and thyroid, lung, breast, upper GI and nasopharyngeal malignancy.
  - **Enlargement of supraclavicular and scalene node** are always abnormal because these nodes drain lung and retroperitoneal space and they are associated with either lymphoma, cancer or infectious process arising in those areas.
    - » Supraclavicular adenopathy present in TB, sarcoid, lymphoma carcinoma of lung toxoplasma and other causes.
  - **Axillary adenopathy present in**
    - » Nonmalignant cause like infection of ipsilateral upper limb.
    - » Malignant etiology like melanoma, lymphoma and breast carcinoma.

  - **Inguinal lymphadenopathy present in**
    - » Nonmalignant cause like infection, injury, trauma to lower extremity and LGV, primary syphilis, HSV.
    - » Malignant etiology like melanoma, lymphoma or secondary from rectum, uterus and genitalia.
  - Discreat gland seen in malignancy.
  - Matted gland seen in TB
  - Mobile gland suggested infective, storage and inflammatory disorder.
  - Fixed to deeper structure suggest carcinoma.

OTHER SYMPTOMS

- **Cough and wheeze** if present is due to trachea or bronchial compression.
- **Hoarseness of voice** if present is due to recurrent laryngeal nerve compression.
- **Dysphagia** if present is due to pharyngeal and esophageal compression.
- **Swelling of neck, face, arm is due to**
  - Superior venacaval syndrome (SVC syndrome)
  - Subclavian vein compression
  - Lymphatic channel obstruction.

INVESTIGATIONS

- CBC and antibody titer against viral and other infections.
- Connective tissue disease marker (RF, Anti-CCP ANA Anti-dsDNA).
- Throat swab culture for *Streptococcus*, diphtheria, *Staphylococcus* and plague.
- Chest X-ray for TB and malignancy.
- Lymph node biopsy.
- ENT checkup for histopathological diagnosis of nasopharyngeal and laryngeal carcinoma.
- USG/CT/MRI of chest, abdomen and pelvis.

Blood examination gives clue to the

- Hematological malignancy—ALL, CLL, lymphoma.
- Serological study for EBV, CMV, HIV, toxoplasma, brucella and other viral diseases.
- Pyogenic infection like *Streptococcus*, *Staphylococcus*, infectious mononucleosis, diphtheria and plague.
- Immunological disorders—
  - Positive rheumatoid factor and anticcp suggest RA
  - Positive ANF and Anti-ds DNA suggest SLE.

CHEST X-RAY

- Pulmonary infiltrate and mediastinal lymphadenopathy present suggest—TB, sarcoid, histoplasma, EBV and lymphoma primary or secondary carcinoma of lung.

USG/CT/MRI

It helps to differentiate benign from malignant disorder.

- **USG** of lymph gland long axis-short axis ratio >1.5 suggest benign disorder in neck gland (specificity of 95%). Long axis = Short axis suggest malignant disorder.
  - CT/MRI—For hilar, abdominal, mesenteric and retroperitoneal gland measurement and CT guided FNAC.
- **Biopsy**
  - Early biopsy (before 2 weeks) done if physical finding suggest malignancy.
  - Late biopsy (after 2 weeks) done if the patient's history and finding suggest storage disease or immunological disease.
  - If any primary source or mucosal site is diagnosed—do biopsy from that site first.
  - In case of lymphnode biopsy—FNAC is the initial diagnostic procedure later confirmed by tissue biopsy.
  - <5% of the patient with lymphadenopathy require biopsy.

MANAGEMENT

Benign causes—Antibiotic for bacterial infection.

- Wait and watch for 2–4 weeks.
- Reevaluate the node after 4 weeks.
- Antibiotics are not indicated unless strong evidence of bacterial infection is present.
- Glucocorticoid should not be used to treat lymphadenopathy because of their lympholytic effect obscures some diagnosis like lymphoma, leukemia and Castleman's disease and contribute to delayed healing and activation of underlying infection.

EXERCISE

Write short notes on

1. Write notes on approach to a patient lymphadenopathy.

Chapter 121

Jaundice

INTRODUCTION

Jaundice is a yellowish discoloration of skin and mucous membrane resulting from the deposition of bilirubin. Tissue deposition of bilirubin occurs only in the presence of serum hyperbilirubinemia and is either due to liver disease or hemolytic disorder or obstruction of the common bile duct.

Slight increase in serum bilirubin are best detected by examining the sclera which have high affinity for bilirubin due to its high elastin content. The presence of scleral icterus indicates a serum bilirubin > 3.0 mg/dL. Fluorescent light makes it more difficult to detect scleral jaundice. So jaundice should be examined in broad-day light. other places to examine for jaundice are under surface of tongue, soft palate, palm and sole, and general skin. As bilirubin level rises skin will turn yellow, in light skined person if the jaundice is long-standing skin may appear green due to oxidation of **bilirubin to biliverdin**.

DIFFERENTIAL DIAGNOSIS OF JAUNDICE (YELLOW COLOR OF SKIN)

- **Carotenoderma**.
- Drugs—**Quinacrine**, or excessive exposure to **phenol**. In carotenoderma the yellowish discoloration of skin is more prominent on palm, sole, forehead and nasolabial fold, but sparing sclera. In carotenoderma the yellowish color in due to the presence of carotene which comes from carrots, leafy vegetables, squash, orange and fruits. Quinacrine can cause discoloration of sclera.

PRODUCTION AND METABOLISM OF BILIRUBIN

Bilirubin a tetrapyrrole pigment is a breakdown product of heme. About 75% of 250–300 mg bilirubin produced each day is derived from the breakdown of hemoglobin in the dying RBC. The remainder comes from the prematurely destroyed cells of erythroid series in bone marrow, myoglobin and cytochromes.

The bilirubin in produced in the cells of liver and RE system.

- **Breakdown of Heme**—The first step in the production of bilirubin from the pigment heme is the opening up of the heme ring by oxidative clevage of α-**bridge of the porphyrin group** by the enzyme **heme oxygenase** with the production of biliverdin, carbon monoxide and iron.
- **Production of bilirubin**—The second step is catalyzed by cytosolic enzyme **biliverdin reductase** (reduces the **central methylene bridge of biliverdin)** and convert it to bilirubin.
- **Transportation**—The bilirubin formed in the RE cells of spleen and liver is insoluble in water. To make it soluble for transportation via blood, it must combine with albumin. This unconjugated bilirubin bound to albumin is transported to hepatocyte where the bilirubin portion is taken up by the hepatocyte via a carrier mediated membrane transport. No specific bilirubin transporter has yet been identified.
- **Intracellular binding**—Within the hepatocyte bilirubin is kept in solution by binding as a nonsubstrate ligand to several of the **glutathione-S-transferase** formerly called ligandins.
- **Conjugation**—Bilirubin is conjugated with one or two glucuronic acid moieties by UDP-glucuronosyl transferase to form bilirubin mono and diglucuronide respectively, conjugation disrupts the internal hydrogen bonding that limits aqueous solubility of bilirubins and the resulting glucuronide conjugate is highly soluble in water. Conjugation is obligatory for excretion of bilirubin across the bile canalicular membrane into bile.
- **Bile excretion**—Bilirubin mono and diglucuronide are excreted across the canalicular plasma membrane into the bile canaliculus by an ATP-dependent transport process mediated by canalicular membrane protein called ''**Multidrug resistance-associated protein 2**'' (MRP-2). Mutation of MRP2 results in **Dubin Johnson syndrome and Rotor syndrome**.

EXTRAHEPATIC ASPECT OF BILIRUBIN DISPOSITION

Bilirubin in the gut—Following secretion into bile conjugated bilirubin reaches the duodenum and passes down the GI tract without absorption.

A portion is converted by bacterial metabolism in the gut to water-soluble colorless compound urobilinogen

which undergo enterohepatic cycling. Part of this absorbed urobilinogen is cleared by-kidney.

Unconjugated bilirubin usually does not reaches the gut except very high unconjugated hyperbilirubinenia in Crigler-Najjar type-I syndrome.

RENAL EXCRETION OF BILIRUBIN

Unconjugated bilirubin is not excreted in the urine as it is very tightly bounded to albumin whereas conjugated bilirubin are water-soluble and readily filtered by the glomerulus and excreted in the urine.

CAUSES OF UNCONJUGATED HYPERBILIRUBINEMIA IN ADULT

- **Hemolysis**
  - Congenital
    - Spherocytosis, eliptocytosis.
    - G6PD and pyruvate kinase deficiency.
    - Sickle cell anemia. Thalassemia.
  - Acquired
    - Microangiopathic hemolytic anemia
    - PNH
    - Immune hemolysis
    - Hematoma
    - Polycythemia.
- **Ineffective erythropoiesis**
  - Cobalamine, folate and severe iron deficiency.
  - Thalassemia.
- Drugs—Rifampicin, probenacid and ribavirin.
- Inherited conditions
  - Crigler-Najjar type-I and type-II (Table 121.1).
  - Gilbert syndrome (defect in both uptake and conjugation).

SOME CAUSES OF UNCONJUGATED HYPERBILIRUBINEMIA IN CHILDREN (PEDIATRIC AGE GROUP)

- **Increased production of bilirubin (unconjugated)**
  - Hemolytic disease
    - Congenital
    - Acquired.
  - Ineffective erythropoiesis
  - Drugs
  - Sepsis
  - Polycythemia.
- **Decrease bilirubin uptake**
  - Transporter deficiency—Gilbert disease
  - Competitive inhibition
    - Breast milk jaundice
    - Lucey-Driscoll syndrome.
    - Drug inhibition (radiocontrast material).
  - Miscellaneous—Hypothyroid, hypoxia, acidosis.
- **Decreased conjugation**
  - Physiological jaundice.
  - Hereditary
    - Crigler-Najjar type-I
    - Crigler-Najjar type-II.
    - Gilbert disease.
  - Hepatocellular dysfunction.
- **Enterohepatic recirculation**
  - Intestinal obstruction
    - Ileal atresia
    - Hirschsprung
    - Cystic fibrosis
    - Pyloric stenosis.
  - Antibiotic administration.

Table 121.1: Differential diagnosis of Crigler-Najjar syndrome and Gilbert's syndrome

		CN-I	CN-II	GS
1.	Total serum bilirubin	>20 mg/dL	6–20 mg dL	<4 mg/dL in the absence of fasting or hemolysis
2.	Response to phenobarbitone	None	Partial decrease of bilirubin by 25%	Decrease bilirubin to normal
3.	Kernicterus	Usual	Rare	No
4.	Bile characteristic	Pale, colorless	Pigmented	Normal dark color
5.	Bilirubin fraction	>90% unconjugated	Largest fraction Monoconjugates 57%	Mainly diconjugates Monoconjugate increase to 23%
6.	Bilirubin UDP-glucuronosyltransferases activity	Absent	Markedly reduced (0–10% of normal)	Reduced 10–33% of normal

CAUSES OF MIXED OR PREDOMINATLY CONJUGATED HYPERBILIRUBINEMIA

- Dubin-Johnson syndrome
- Rotor syndrom
- Benign recurrent intrahepatic cholestasis
- Progressive familial intrahepatic cholestasis
- Hepatocellular cause
- Cholestatic cause.

Hepatocellular Causes of Jaundice

- Viral hepatitis—HAV, HBV, HCV, HDV, HEV, EBV, CMV, herpes simplex.
- Alcohol.
- **Drugs**
  Dose-dependent—acetaminophen.
  Idiosyncratic.
- Toxin—Vinyl chloride, Jamica bush tea, kava kava, wild mushroom, amanita phalloides.
- Wilson's disease.
- Autoimmune hepatitis. } See below

Cholestatic Cause of Jaundice

- **Intrahepatic**
  - Viral hepatitis
    - Fibrozing cholestatic hepatitis, HBV and HCV
    - HAV, EBV and CMV.
  - Alcoholic hepatitis—Alcoholic hepatitis.
  - Drug toxicity—
    - Pure cholestatic—Anabolic and contraceptive steroid.
    - Cholestatic hepatitis—Chlorpromazine and erythromycin.
    - Chronic cholestasis—Chlorpromazine and prochlorperazine.
  - Primary biliary cirrhosis.
  - Primary sclerozing cholangitis.
  - Vanishing bile duct syndrome
    - Chronic rejection of liver transplant
    - Sarcoidosis
    - Drugs
    - Inherited—benign recurrent cholestasis.
  - Cholestasis of pregnancy.
  - Total parenteral nutrition
  - Nonhepatobiliary sepsis
  - Benign postoperative cholestasis
  - Paraneoplastic syndrome
  - Veno-occlusive disease
  - Graft versus host disease.
- **Extrahepatic causes of cholestasis**
  - Benign causes
    - Choledocholithiasis
    - Roundworm
    - Primary sclerozing cholangitis
    - Chronic pancreatitis
    - AIDS
    - Cholangiography.
  - Malignant causes
    - Cholangiocarcinoma
    - Pancreatic cancer
    - Ampullary cancer
    - Gallbladder cancer
    - Enlarged lymph node at porta hepatis.

EXERCISE

Write short notes on

1. Intrahepatic causes of obstructive jaundice.
2. Gilbert disease, Dubin-Johnson syndrome, Rotor syndrome and cholestatic jaundice.

Chapter 122

Cyanosis

INTRODUCTION

Cyanosis refers to bluish discoloration of skin and mucous membrane due to increased amount of reduced hemoglobin >4 g/dL or hemoglobin derivatives in the small blood vessel.

- In general cyanosis become apparent when the mean capillary concentration of reduced hemoglobin exceeds 4 g/dL.
- It is the absolute quantity rather than relative percentage of reduced hemoglobin that is important in producing cyanosis.
- Thus patient with severe anemia and with marked arterial unsaturation may not display cyanosis. Patient with marked polycythemia tend to be cyanotic at higher level of arterial O_2 saturation than patient with normal hematocrit values.
- The degree of cyanosis is modified by the color of the cutaneous pigment and the thickness of the skin and by the status of cutaneous capillary. In dark skined person the examination of mucous membrane in oral cavity and conjunctiva are more helpful in detecting cyanosis rather than the examination of skin.

Differential Diagnosis

- **Methemoglobinemia**
  - Hereditary
  - Acquired.
- Sulfhemoglobinemia.
- Carboxyhemoglobinemia (not true cyanosis but cherry red flush rather than cyanosis)—specially in smokers.

Types of Cyanosis

- **Central cyanosis**—It is due to reduced arterial oxygen saturation or due to abnormal hemoglobin derivative.
- **Peripheral cyanosis**—It is due to slowing of blood flow and abnormally great extraction of O_2 from normally saturated arterial blood.
- **Differential cyanosis**—Patient with patent ductus arterious and pulmonary HTN and right to left shunt, cyanosis occurs in lower not upper extremity. Similarly in coarctation of aorta with TGA (transposition of great aorta/vessels) cyanosis is seen in upper extremity but not in lower extremity, this is called **reverse differential cyanosis**.

Causes of Central Cyanosis

- **Decreased arterial O_2 saturation**
  - *Decreased atmospheric pressure*—High altitude.
  - *Impaired pulmonary function*
    - Alveolar hypoventilation—Pneumonia, ARDS pulmonary edema.
    - Pulmonary ventilation perfusion mismatch—Pulmonary embolism.
    - Impaired O_2 diffusion—COPD.
- **Anatomic shunt**
  - Congenital heart disease—Tetralogy of Fallot, VSD with Eisenmenger.
  - Pulmonary arteriovenous fistula—Hereditary hemorrhagic telangiectasia.
  - Multiple small intrapulmonary shunt.
- **Hemoglobin with low O_2 affinity**—Hb-Kansas
- **Hemoglobin abnormalities**
  - Methemoglobin
    - Hereditary
    - Acquired.
  - Sulfhemoglobin.
  - Carboxyhemoglobin.

Causes of Peripheral Cyanosis

- **Reduced cardiac output**—Shock, congestive heart failure—Causes cutaneous vasoconstriction and diversion of blood from skin to vital organ like brain, kidney, CNS.
- **Coldexposure**—Causing cutaneous vasoconstriction.
- Redistribution of blood flow from extremities.
- **Arterial obstruction**—Seen in peripheral vascular disease—Raynaud's phenomenon.
- **Venous obstruction**—Clinical differentiation between central and peripheral cyanosis may not always be simple and in condition such as cardiogenic shock with pulmonary edema there may be mixture of both type of cyanosis.

Sites for Examination of Cyanosis

- **Central cyanosis**
  - Warm mucous membrane of oral cavity
  - Conjunctiva
  - General body skin and nailbed.
- **Peripheral cyanosis**
  - Lips
  - Nailbeds
  - Ear lobule
  - Malar eminences.

Causes of central cyanosis

1. Decrease arterial O_2 saturation (SaO_2) results from marked reduction in alveolar partial pressure of oxygens (PaO_2) which may be brought about by a decline in partial pressure of O_2 in free air (FiO_2)

   At an altitude 8000 ft there is no cyanosis but at an altitude of 16000 ft there is marked cyanosis. The reason for the difference becomes clear if we study 'S' shaped Hb—O_2 dissociation curve.

   At 8000 ft altitude FiO_2 is 120 mm Hg PO_2 is 80 mm Hg and SaO_2 is nearly normal.

   However 16000 ft altitude FiO_2 is 85 mm Hg. and PaO_2 is 50 mm Hg and SaO_2 is about 75% which leaves 25% of Hb in reduced form in the arterial blood responsible for cyanosis.

   Mutant hemoglobin which has low affinity for O_2 and may produce central cyanosis, e.g. **Hb kansas**.
2. Impaired pulmonary function can cause cyanosis
   1. Alveolar hypoventilation
   2. Ventilation perfusion mismatch

   These two condition can be due to in acute condition like
   a. Pneumonia
   b. Pulmonary edema
   c. Pulmonary embolism

   Chronically by
   a. Chronic obstructive pulmonary diseases
3. Shunting of systemic venous blood into arterial circuit—can occur if septal defect (ASD, VSD) in combined with obstructive lesion in the downstream (pulmonary stenosis) or with elevated pulmonary vascular resistance.The most common congenital cardiac lesion associated with cyanosis is Tetralogy of Fallot (VSD with pulmonary outflow tract obstruction)

Contd...

Contd...

4. Pulmonary arteriovenous fistulae may be
   - Congenital or acquired
   - Solitary or multiple
   - Microscopic or massive

   The severity of cyanosis depends on the size and number of fistula. These fistula are seen in
   a. Hereditary hemorrhagic telangiectasia
   b. Cirrhosis of liver—Due to pulmonary arteriovenous fistulas or portal vein—pulmonary vein anastomosis through the bare area of liver.

   In patient with cardiac and pulmonary right to left shunt there is intensification of cyanosis during exercise due to two reason.
   a. Fall in systemic vascular resistance during exercise causes augmentation of right to left shunt.
   b. Exercising muscle extract more amount of O_2 from blood thereby lowers the O_2 saturation of venous blood.
5. Secondary polycythemia due to low O_2 saturation in arterial blood also perpetuates cyanosis.
6. Cyanosis can be caused by
   a. Small amount of circulating methemoglobin
   b. Smaller amount of sulfhemoglobin

Digital clubbing is absent in these two condition: These two conditions can be diagnosed by spectroscopic examination of hemoglobin when cyanosis is not readily explained by malfunctioning of heart and lung. Methemoglobinemia can be suspected if the patients blood remain brown after being mixed in a test tube and exposed to air.

Polycythemia and cyanosis is simultaneously found in:

- CCF
- COPD.

EXERCISE

Write short notes on

1. Definition and classification of cyanosis.
2. Cause of central and peripheral cyanosis.

Chapter 123

Clubbing

INTRODUCTION

The selective bulbus enlargement of the distal segments of the fingers and toes due to proliferation of the connective tissue underneath the base of the nail is called clubbing. Mechanism of clubbing is unclear but it is probably secondary to humoral substances that causes dilatation and opening of arteriovenous anastomosis causing increased blood flow in the nailbed.

Causes of Clubbing

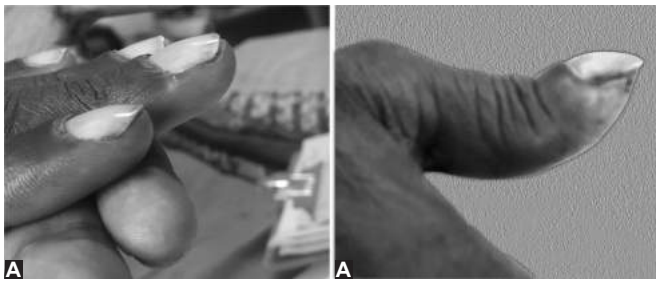
- Hereditary
- Indiopathic
- Acquired.

Acquired

- **Cardiac causes**
  - Congenital cyanotic heart disease—Tetralogy of Fallot, common trunkus, anomalous pulmonary venous drainage.
  - Subacute bacterial endocarditis.
- **Pulmonary causes**
  - Infective causes—Empyema, lung abscess and bronchiectasis.
  - Malignancy— Primary and metastatic lung cancer and mesothelioma.
  - Cystic fibrosis.
- **GI causes**
  - Inflammatory bowel diseases (IBD)—Ulcerative colitis and Crohn's disease.
  - Cirrhosis of liver.
  - Malabsorption syndrome.
- **CNS cause**
  - Peripheral neuropathy.
- **Endocrine cause:** Graves disease.

Clubbing in Clinically Classified into Four Grade

- **Grade I (Fig. 123.1A)**—Increase fluctation of base of finger nail and toe nail due to proliferation and edema of sublingual tissue.



Figs 123.1A and B: Obliterated onychodermal angle in clubbing

- **Grade II (Fig. 123.1B)**—Increased curvature of nail both antero-posterior and side-to-side and the onychodermal angle become obtuse.
- **Grade III**—The terminal portion of the finger become bulbous giving the finger drumstick appearance due to proliferation of subungual tissue.
- **Grade IV**—Grade III clubbing with Hypertrophic osteoarthopathy.

There is subperiosteal new bone formation in the distal diaphyses of the long bone of extremities. It causes pain and symmetric arthritis like changes in the shoulder, knee, ankle wrist and elbow. The diagnosis of hypertrophic osteoarthropathy is confirmed by X-ray of ankle, elbow, wrist and knee.

Grade IV clubbing is usually seen in

1. Primary and metastatic lung cancer
2. Pleural mesothelioma
3. Bronchiectasis
4. Hepatic cirrhosis.

Some Important Features of Cyanosis and Clubbing

- Cyanosis since birth or infancy is usually due to congenital heart disease.
- Massage or gentle warming of a cyanotic extremity will increase peripheral blood flow and abolish peripheral but not central cyanosis.

- Clubbing without cyanosis is frequent in patient with infective endocarditis, IBD, and occasionally in healthy person and occupational (e.g. Jack hammer operator).
- Clubbing with cyanosis is seen in congenital heart disease with right to left shunt, big lung abscess and pulmonary arteriovenous fistula.
- Cyanosis without clubbing—It is seen in peripheral cyanosis and acutely developing central cyanosis.

EXERCISE

Write short notes on

1. Clubbing.

Chapter 124

Arterial Pulse

Arterial pulse is a good indicator of some cardiovascular condition. Though arterial pulse is not singly sufficient to diagnose a disease but it helps in clinical evaluation in addition to some diagnostic aid.

It is most commonly recorded from radial artery but other arteries like brachial, carotid femoral, dorsalis pedis, popliteal artery may be palpated.

The points to be noted during examination of arterial pulse are

1. **Rate**
2. **Rhythms**
3. **Volume**
4. **Condition of arterial wall**
5. **Whether palpable at all the peripheral sites**
6. **Whether there is radioradial or radiofemoral delay**
7. **Special character of the pulse.**

Volume and contour of the arterial pulse are determined by a combination of factor including—

1. LV stroke volume.
2. Ejection velocity.
3. Relative compliance and capacity of arterial system.
4. Pressure wave resulting from antegrade flow of blood and its reflection from peripheral circulation.

Carotid pulse provide the most accurate representation of central aortic pulse but brachial artery is the vessel most suitable for appreciating the rate of rise of pulse, contour, volume, etc.

NORMAL PULSE (FIG. 124.1)

Pulse in the ascending aorta rapidly rises to a rounded dome reflecting the peak velocity of blood ejected from the left ventricle. Slight anacrotic notch may be felt on the ascending limb occasionally.

The descending limb is less stiffer and is interrupted by incisura, a sharp downward deflection related to closer of aortic valve. Immediately after that the pulse wave rises slightly and then declines gradually throughout diastole.

When the pulse wave is transmitted to periphery the following changes are seen—

- Its upstroke becomes stiffer
- Systolic peak becomes higher

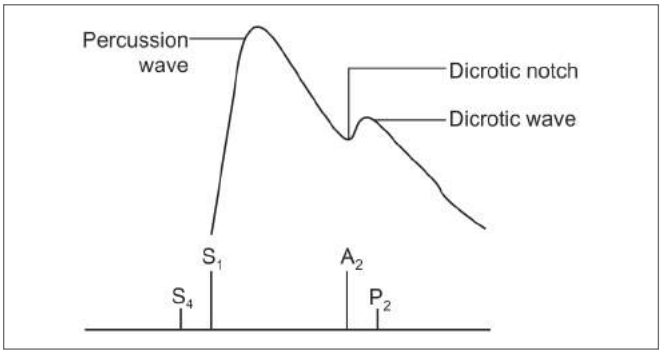


Fig. 124.1: Pulse seen in normal patient

- Anacrotic shoulder disappear
- Sharp incisura replaced by smooth diacrotic notch
- Followed by a diacrotic wave.

In the central arterial pulse, the rapidly transmitted impact of LV ejection results in a peak in early systole referred to as **percussion wave** and a second, smaller peak the **tidal wave** represent a reflected wave from the periphery that is not ordinarily palpable. But in patient with increased peripheral resistance (older subject as well as in atherosclerotic and diabetics), the tidal wave is some what higher than percussion wave, i.e. the pulse wave reaches its peak in late systole.

In peripheral artery the pulse wave normally has single sharp peak.

ABNORMAL PULSE

When the peripheral vascular resistance or arterial stiffness increases there is an elevation in pulse wave velocity and pulse contour has a more rapid upstroke and greater amplitude.

Inequality of Pulse Volume

- Reduced or unequal carotid arterial pulsation occurs in carotid atherosclerosis, disease of aortic arch—aortic dissection, aneurysm and Takayasu disease.
- The pulse of upper extremity may be reduced or unequal **in supravalvular aortic stenosis, arterial embolism,**

thrombosis, anomalous origin or aberrant path of major vessels, cervical rib or scalenous anticus syndrome.

- Asymmetry of right or left popliteal pulse is characteristic of **iliofemoral obstruction**.
- Weakness or absence of radial, posterior tibial or dorsalis pedis on one side suggest **arterial insufficiency or blockage**.
- In case of coarctation of aorta, carotid and brachial pulses are bounding and rise rapidly, have larger volume whereas in lower extremity systolic and pulse pressure is reduced and the rate of rise is slow and there is a late peak.

Special Character

- Pulsus pervus et tardus (Fig. 124.2)—Pulse of low volume with slow rise of pressure with later systolic peak.
  Cause—Occurs mostly in
  - Fixed obstruction of LV outflow—**Valvular aortic stenosis**, congenital fibrous **subaortic stenosis**.
  - Anacrotic notch is prominent and may be so distinct that two separate wave can be palpated in carotid artery known as **anacrotic pulse**.
  - The upstroke may be characterized by a thrill — known as carotid shudder in aortic stenosis.
- **Pulsus pervus**—Low volume pulse (reduced pulse amplitude) may only be present without any delay in upstroke.
  Cause—Heart failure with aortic stenosis. However in elderly patient with inelastic peripheral artery pulse may rise normally despite severe aortic stenosis.
- **Exaggerated or bounding pulse**—May be found in—
  - Patient with atherosclerosis.
  - Bradycardia.
  - Mitral regurgitation, VSD—elevated stroke volume.
  - Sympathetic hyperactivity.
    But in all of the above condition the rate of rise is increased but the pulse pressure remain normal.

WATER HAMMER OR CORRIGAN PULSE

It is characterized by abrupt upstroke followed by a rapid collapse later in systole without any dicrotic notch.

It reflects a low resistance in the reservoir into which LV rapidly discharges an abnormally elevated stroke volume.

Causes

1. Aortic regurgitation
2. Patent ductus arteriosus
3. Pregnancy
4. Severe anemia
5. Thyrotoxicosis
6. Berry-Berry
7. Padget disease of bone
8. Severe bradycardia.

Water hammer pulse is assessed by exaggering the pulse pressure by rapidly raising the patients arm above the head and palpating pulse wave with the ball of the fingers.

BISFERIENS PULSE (FIGS 124.3 AND 124.4)

A pulse with two systolic peak, the percussion and tidal wave separated by a distance—midsystolic dip. The peak may be equal or either one may be taller.

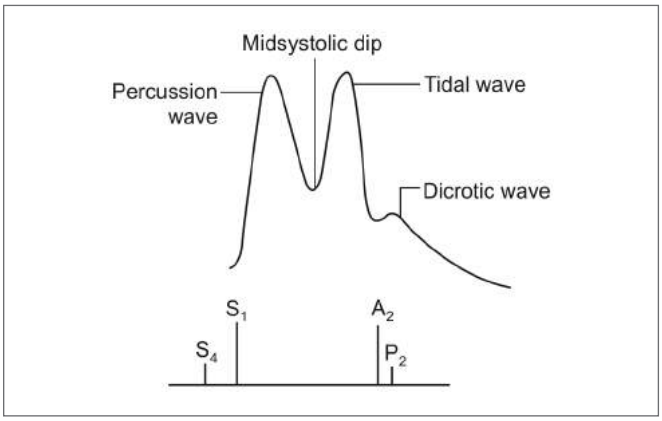


Fig. 124.3: Pulse seen in normal patient of AR

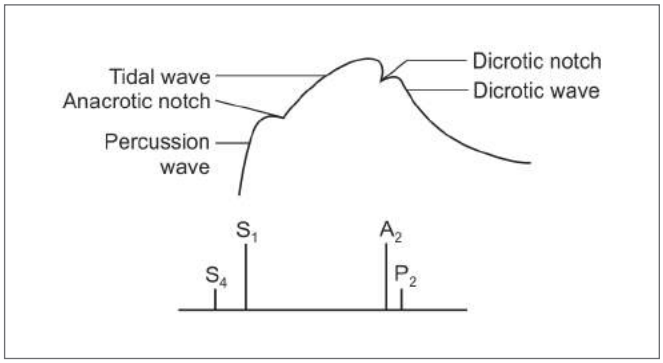


Fig. 124.2: Pulse seen in normal patient of pulsus parvus et tardus

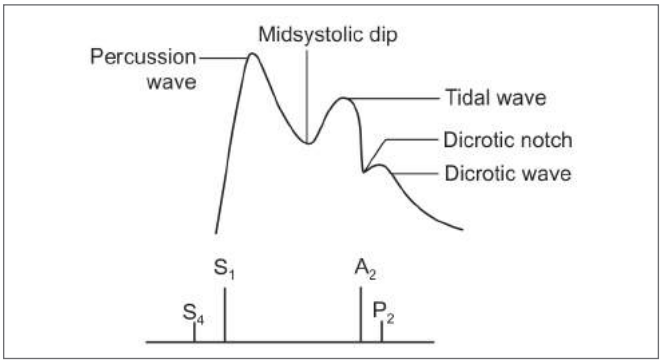


Fig. 124.4: Pulse seen in normal patient with HOCM

Causes

- Occurs when a large stroke volume ejected rapidly as in AR, AR with AS with dominant AR.
- In hypertrophic cardiomyopathy (HCM).
  Bifid nature may be recorded but not palpated. This can be elicited by Valsalva maneuver or inhalation of amyl nitrate.
- Occasionally in hyperkinetic circulatory state.
- Very rarely in normal individual.

DICROTIC PULSE (FIG. 124.5)

Two beating or double beat pulse produced by a combination of percussion wave followed by a exaggerated dicrotic notch and wave.

Causes—

- Normal hypotensive subject with reduced peripheral resistance (fever, etc.).
- Rarely in healthy adolescent and young adult.
- Cardiac tamponade.
- Hypovolemic shock.
- Severe heart failure.

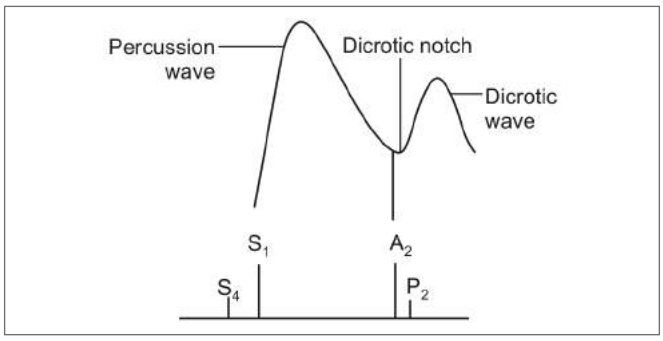


Fig. 124.5: Dicrotic pulses

PULSUS ALTERNANS

Pulse beats occur at constant interval but with a regular alteration with a peak of pressure pulse and /or rate of rise of ascending limb (alternate high and low volume pulse).

- More readily recognized by sphygmomanometry, where the SBP fluctuate more than 20 mmHg.
- Most readily found in peripheral femoral or brachial pulse than central pulse with patients breath held in midexpiration to avoid respiratory variation of pulse amplitude.

  Causes
  1. Severe heart failure.
  2. AR, systemic hypertension, vesodialators, standing posture exaggerate pulsus alternans.

PULSUS BIGEMINUS

- Caused by regular occurrence of premature contraction, (usually ventricular extrasystole) after every (other) beat resulting in alteration of the strength of the pulse with irregular rhythm.
- Regular coupling of two beats with interval between a pair of beat greater than the couple beats themselve.
- Weak beat always follows a shorter interval followed by a compensatory long pause and a stronger than normal pulse.

  Causes
  1. Premature ectopic beat.
  2. AV block—2nd degree.

PULSUS PARADOXUS (TABLE 124.1)

It is an exaggerated reduction of the strength of the arterial pulse during normal inspiration due to exaggerated inspiratory fall in SBP (greater than 10 mm Hg during quite breathing) when marked >20 mm. The paradoxical pulse can be detected by palpation of brachial artery.

- **Reverse pulsus paradoxus**—An inspiratory rise may occur in HOCM.

EXERCISE

Write short note on

1. Special character of pulse.

Table 124.1: Mechanism of inspiratory fall of SBP in pulsus paradoxus

			Causes of pulsus paradoxus
1.	Negative intrathoracic suction causes more pulling of blood in the lung	1.	Cardiac tamponade
2.	Transmission of negative intrathoracic pressure within the aorta	2.	Chronic obstruction pericarditis
3.	More negative intrathoracic pressure → more venous return → right ventricular overload → shifting of intraventricular septum to left → decrease LV volume → decrease SBP	3.	Emphysema
		4.	Bronchial asthma
		5.	Hypovolemic shock
		6.	Pulmonary embolism
		7.	Pregnancy
		8.	Extreme obesity

Chapter 125

Neck Vein

INTRODUCTION

Neck vein gives us information about the dynamics of right side of heart.

Right internal jugular vein is usually examined.

(Because—right innominate and right jugular veins extend almost straight line cephalad to superior vena cava) [Left innominate vein not in straight line may be kinked or compressed by a variety of normal structures (dialated aorta or aortic aneurysm)—so not to examined.]

The head should not be at a sharp angle with the trunk.

Most patients with heart disease are examined most effectively in the 45° position but in whom venous pressure is high a greater inclination 60° or 90° is required to obtain a visible pulsation whereas in those jugular venous pressure is low a less incline 30° is desirable.

Table 125.1: Comparison between neck arterial and venous pulse wave

Arterial pulse	Venous pulse
1. Better palpated	1. Better observed
2. Single upstroke	2. Double/triple upstroke
3. Arterial pulse remain unchanged with change of posture	3. Venous wave change with change in posture
4. Arterial pulse does not changed with respiration	4. Venous wave change with phases of respiration
5. Compression at the root of neck does not obliterate arterial pulse	5. Compression at the root of neck causes obliteration of venous pulsation

- Two principal observation
  - Hight of pulsating venous column
  - Types of venous wave pattern.
    - Central venous pressure—Height of the pulsating neck vein from sternal angle + 5 cm.
    - When the neck veins collapse in a subject breathing normally in horizontal position it is likely that central venous pressure is subnormal.
- When obstruction of veins of lower extremities is the causes for lower extremity edema— pressure in the neck vein is not elevated and abdominojugular reflex is negative.

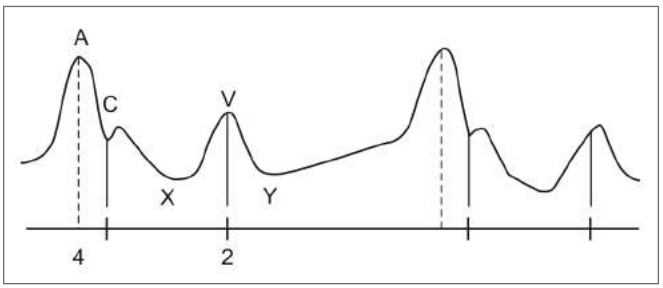


Fig. 125.1: Abdominojugular reflex

ABDOMINOJUGULAR REFLEX (FIG. 125.1)

Pressure over the periumbilical region for 10–30 seconds while the patient is breathing quitely.

In normal person jugular venous pressure rises <3 cm H_2O and only transiently, while pressure is continued.

Rise of pressure is more and persistent in *tricuspid regurgitation/right heart failure*.

Increased pulmonary wedge pressure or due to increased central venus pressure.

NORMAL WAVES

- **a-wave**—Due to venous distension during right atrial systole.
- **X-descent**—Due to atrial relaxation (denotes right atrial wall elasticity).
- **C**—Doming of atrioventricular valve towards atria during ventricular systole and impact of carotid artery adjacent to jugular vein.
- **X´**—Is due to descent of tricuspid valve and continuing atrial relaxation during late phase of right ventricular systole.
- **V-wave**—Rise of right atrial pressure when blood flows into right atrium during ventricular systole and the tricuspid is still closed.
- **Y-descent**—Decline of right atrial pressure when the tricuspid valve reopens during ventircular diastole due to passive flow of blood from right atrium to right ventricle.

- **H-wave**—Which reflects the diastasis. Height of H- wave reflects the stiffness.
- **Descents**—Downward collapsing movements of the jungular vein is (1) more rapid, (2) produce larger excursions and are therefore more prominent on eye than ascends.
- **X´$_1$**—Just before S_2
- **Y-wave**—Ends after S_2.
- **a-wave**—Just before S_1—has a sharp rise and fall.
- **U-wave**—Just after arterial pulse has a slower undulating pattern.

ALTERATION IN JUGULAR VENOUS PULSE WAVE

Elevation of JVP reflects increasing right atrial pressure which occurs in

- Heart failure.
- Reduced compliance of right ventricle–restrictive cardiomyopathy.
- Pericardial disease—Constrictive pericarditis and pericardial effusion.
- Hypervolemia.
- Tricuspid stenosis and tricuspid regurgitation.
- Superior vena caval syndrome.

KUSSMAUL'S SIGN

Paradoxical rise in height of jugular venous pressure during inspiration.

Causes

- Chronic constrictive pericarditis
- Congestive cardiac failure
- Tricuspid stenosis.

Prominent a wave (Figs 125.2 to 125.6) found in condition where increase resistance to right atrial contraction is encountered, e.g.

- Right ventricular hypertrophy and right ventricular failure.
- Pulmonary hypertension and pulmonary stenosis.
- Tricuspid stenosis.
- Also in some cases of left ventricular hypertrophy where thickened intraventricular septum (IVS) interfares with right ventricular filling.
- In mitral stenosis with pulmonary hypertension—prominent a-wave results from diminished complians of right ventricle associated with pulmonary hypertension.

Peaked a-wave represent brief period of retrograde flow from RA to SVC in tricuspid stenosis pulmonary hypertension.

Cannon-wave (amplified a-wave) found in AV-dissociation with where right atrium contracts against closed tricuspid valve.

- Regular cannon wave—Nodal tachycardia and junctional rhythm.
- Irregular cannon wave— AV-dissociation, ventricular tachycardia and right ventricular pacemaker.

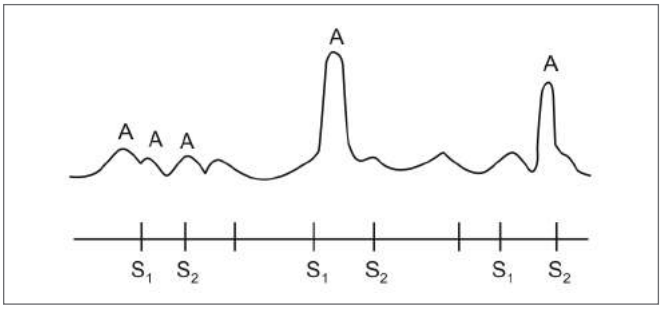


Fig. 125.2: Prominent a-wave

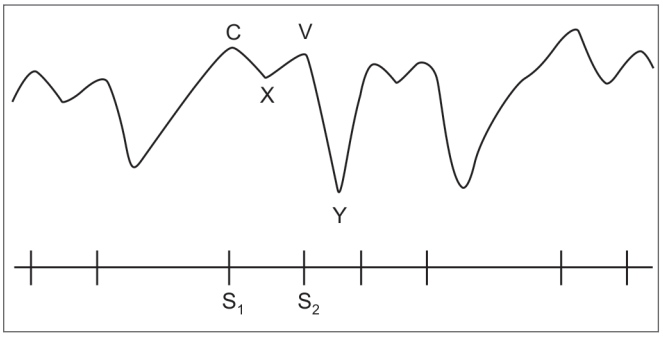


Fig. 125.3: Atrial fibrillation—absent a-wave

- **a-wave absent** in—Atrial fibrillation (Fig. 125.3).
- **Variable a-wave** in—Multifocal atrial tachycardia.
- **X´ descent in prominent** in constrictive pericarditis and atrial fibrillation.
- **X´ wave in absent** in TR (tricuspid regurgitation), where a C-V pattern is found (Fig. 125.4).

Prominent V-wave found in

- Tricuspid regurgitation (TR)
- Atrial septal defect (ASD)
- Right ventricular failure (RVF).

Steep Y-descent found in (Fig. 125.5)

- Constrictive pericarditis (Friedreich sign).
- ASD.
- Any condition of myocardial dysfunction ventricular dilatation, increased CVP.
- Severe TR.

Gradual Y-descent found in

- Tricuspid stenosis (TS)
- Right atrial myxoma.

Steeply rising H-wave

- Restrictive cardiomyopathy
- Constrictive pericarditis
- Right ventricular infarction.

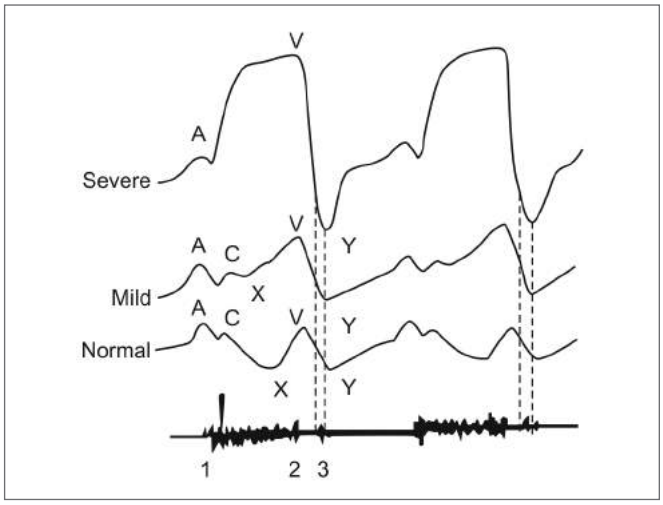


Fig. 125.4: CV pattern found in TR

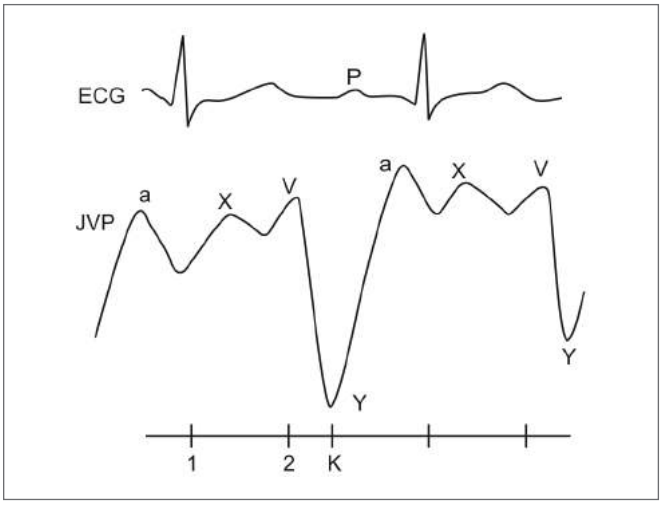


Fig. 125.5: Steep Y-descent found in constrictive pericarditis

JVP IN CONSTRICTIVE PERICARDITIS (FIG. 125.5)

- X-descent become very shallow.
- Rapid and deep Y-descent in the principal features indicating antegrade flow from venous system to right heart is now limited only in early diastole.
- A pericardial knock is seen in phonocardiography at approximately in the nadir of Y-descent.
- X-wave may be prominent due to almost absent of a-wave—giving the curve a ''W'' pattern.
- The rapid deep 'Y' descent is followed by a rapid rise to diastolic pattern (H-wave) without prominent a-wave.

JVP IN TRICUSPID REGURGITATION (FIG. 125.4)

- CV pattern.
- Regurgitant systolic wave (S-wave) blends with normal filling v wave.
- Resultant RA pressure wave form resembles RV-pressure recording (ventricularization).

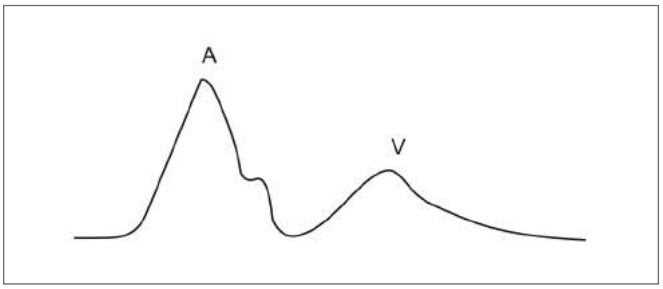


Fig. 125.6: Giant a wave

- Sometimes systolic movement of ear lobule.
- Right to left head movement with each ventricular systole.

EXERCISE

Write short note on

1. Neck vein wave.

Chapter 126

General Examination/Survey

After completion of history taking every patient is subjected to clinical examination.
Clinical examination is subdivided into two parts:

- General examination
- Systemic examination.

GENERAL EXAMINATION

The following points are given special emphasis is general examination:

- Level of consciousness
- Apparent age
- Built
- Nutrition
- Facies
- Decubitus
- Anemia/Pallor
- Cyanosis
- Jaundice
- Clubbing
- Koilonychia
- Pulse
- Respiration
- Blood pressure
- Temperature
- Edema
- Neck vein
- Neck gland.

Level of Consciousness (Table 126.1)

In clinical medicine level of consciousness assessed by Glasgow Coma Scale (GCS) or EVM scale (Eye movement, Vocal response, Motor activity). In these scales three signs are noticed.

Table 126.1: EVM scale II Glasgow Coma Scale

	Eye opening	Score alloted
1.	Eye opening spontaneously	4
2.	Eye opening to vocal command	3
3.	Eye opening to painful stimulus	2
4.	No eye opening	1
	Vocal response	**Score alloted**
1.	Vocal response with oriented speech	5
2.	Vocal response limited to confused speech	4
3.	Vocal response limited to appropriated word	3
4.	Vocal response limited to comprehensible sound	2
5.	No vocal response	1
	Motor response	**Score alloted**
1.	Motor response to obey command	6
2.	Motor response limited to localize pain	5
3.	Motor response limited to withdrawal to pain	4
4.	Motor response limited to flexor to pain	3
5.	Motor response limited to extensor to pain	2
6.	No motor response	1

Maximum score in this scale is (15) and minimum score is (3). If by consecutive examination 6–12 hours apart the score improve in this scale then the patient's condition is gradually improving while if the score decline it indicate the patient's condition is deteriorating.

Apparent Age

Apparent age of a patient usually correspond to stated age but sometime there may be discrepancy in between apparent age and stated age.

Patient apparently looks younger in *cretinism* and *Down's syndrome* where as patient apparently looks older in *progeria*.

Built

Built of a person indicate the skeletal frame of the person. For assessment of built measure the height (crown to ground) and breakup of height (crown to symphysis pubis and symphysis pubis to ground).

Measure the span length (distance between the tip of outstretch middle finger of hands).

Height = Span length—In normal person.

Height >span length—In gigantism, Marfan syndrome and hypogonadism.

Height <span length—In acromegaly.

Crown to symphysis pubis <symphysis pubis to ground —In gigantism and Marfan syndrome and hypogonadism.

Nutrition

Nutrition can be assessed by various method. The most convenient and practiced method is the measurement of body mass index.

$$\text{BMI} : \frac{\text{Weight of the person in kilogram}}{(\text{Height in meter})^2}$$

BMI from 18.5–24.99 is considered normal

BMI from 15–18.5 is considered under weight

BMI below 15 is considered malnourished

BMI from 25–29.99 is considered overweight

BMI from 30–39.9 is considered obese

BMI above 40 is considered morbidly obese.

There are many older method that are obsolete now these are as follows—

1. Measurement of midarm girth (cross sectional area) on the nondominant arm which is in normal male 48^2 cm and female is 44^2 cm.
2. The circumference of the arm at the midpoint between acromion and olecranon process in measured (MUAC). Mid upper arm circumference.
   MUAC ≥25 cm then BMI is likely ≥20
   MUAC ≥23.5 and <25 cm then BMI likely >18.5 <20. If MUAC <23.5 then BMI <18.5.
3. Waist circumference for risk of obesity associated metabolic complications.

	Increased health risk	Substantially increased health risk
Men	>94 cm	>102 cm
Women	>80 cm	>88 cm

Waist hip ratio is strongly related to coronary artery disease. waist hip ratio ≤0.8 in female or <0.9 male have a good prognosis and higher waist hip ratio has increased risk of coronary artery disease, diabetes and metabolic syndrome.

4. Measurement of thickness of subcutaneous fat over triceps on the nondominant arm by Harpenden caliper.
   - Normal skin fold thickness over triceps is male is 12.5 mm.
   - Normal skin fold thickness over triceps in female is 16.5 mm.

   Below 80% of normal skin fold thickness (in male –10 mm in female –13 mm) is called undernourished and below 60% of normal skin fold thickness, i.e. >7.5 mm in male and 10 mm in female is called malnourished.
5. Carbohydrate, protein, fat, vitamin and minerals are the essential nutrient of the body. Deficiency sign of any one of these essential nutrient is considered malnutrition, i.e. anemia, Bitot's spot in eyes are considered sings of malnutrition.
6. Weight in proportion to height.
   Normal male of 150 cm height should have 49.5 kg weight.
   Normal female of 150 cm height should have 48.0 kg weight. For 1 cm rise in height in male person add 1.1 kg and for female person add 0.8 kg.
   From this calculate the ideal weight of a person in proportionate to height.
   From 80–120% of ideal weight is considered normal.
   From 70–80% of ideal weight is considered under nourished. Below 70% of ideal weight is considered malnourished. 120–130% of ideal weight is considered overweight, above 130% of ideal weight is considered obesity.

Facies

Diagnosis of many disease can be made provisionally by observing the facial features. These are as followes:

Endocrine diseases

1. **Hyperthyroid—**Anxious looking with bilateral exposer of upper sclera above cornea.
2. **Hypothyroid**—Puffy and dull appearance.
3. **Cretinism**—Dull idiotic facies and protruded tongue.
4. **Acromegaly**—Prognathism with coarse facial feature like deep nasolabial fold, deep forehead creases with hypertrophy of nose.
5. **Cushing**—Moon facies with pimple.

Connective tissue disorder

1. **SLE**— Erythematous rash over the butterfly area of face across the bridge of nose.
2. **Progressive systemic sclerosis**—Chipmunk facies with radiating furrow from the margin of oral cavity with pinched up nose.

Neurological disorder

1. In **Hemiplegia** drupping of one angle of mouth with saliva dribbling and less prominent nasolabial fold on that side and angle of mouth is deviated to opposite side.
2. In **Bell's palsy**: There is paralysis of one half of whole pace with drupping of one angle of month and dribbling and saliva from the same side and Bell's phenomenon on the same sided eye (patient not able to close the eye is an attempt to close the eye, eyeball will roll up ward with incomplete closer of the eyelid.
3. **Parkinsonism**—Masked expressionsless facies.
4. **Myasthenia gravis**—Bilateral dropping of upper eyelid with partially open mouth and dribbling of saliva with ophthalmoplegia.
5. **Myopathy**—Gross wasting of facial muscle.
6. **Dermatomyositis**—Heliotropic (bluish) rash around eyes.

Miscellaneous

1. **Thalassemia** shows frontal bossing, zygomatic prominence malocclusion of teeth, depressed bridge of nose with pale yellowish hue.
2. **Sarcoidosis**—Lupus pernio (chronic inflammatory lesion around eyes, nose, checks).
3. **Lepromatous leprosy**—Leonine facies.
4. **Down's syndrome** has small oral aperture with protruded tongue, upward slanting of eyes, low set ear and dull idiotic look epicanthic fold small poorly developed bridge of nose short stature with a small head and flat-occiput.

Decubitus

Normal person have decubitus of no choice.

Orthopneic decubitus is prefered by patient of left heart failure and also in COPD and bronchial asthma to get more help from diaphragm in respiration.

Sitting posture with stupping forward position is prefered by patient of acute left ventricular failure with left atrial enlargement to get rid of the pressure on the left main bronchus by enlarged left atrium.

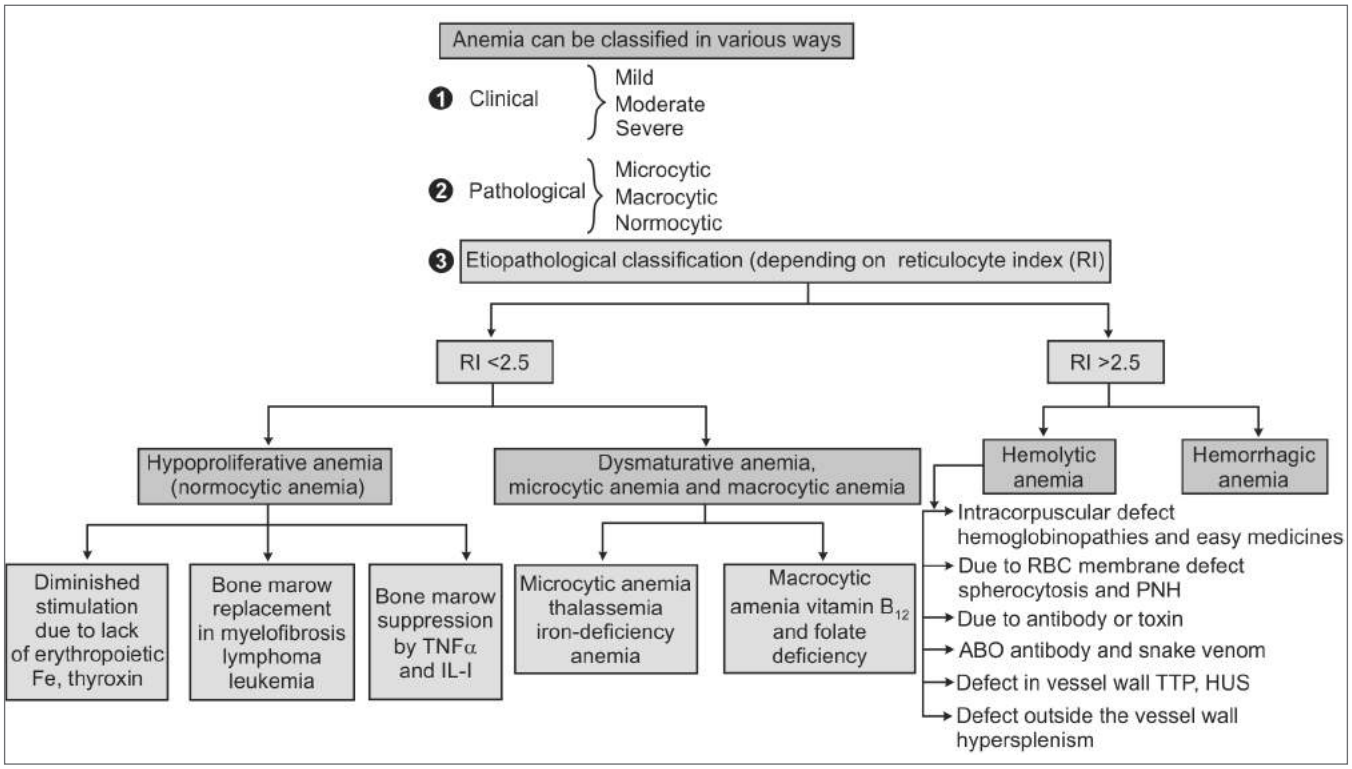
Lateral decubitus is prefered by person having disease in one hemithorax, i.e. *pleural effusion, pneumothorax* and the patient prefer to lie on the diseased side.

Anemia/Pallor (Flowchart 126.1)

Site for examination for pallor.

1. **Lower palpebral conjunctiva**—Here we can actually visualise blood in the capillary through nonkeratinized single layer mucous membrane and there-by try to assess the concentration of hemoglobin in blood.

Flowchart 126.1: Etiopathological classification of anemia



2. **Dorsum and margin of tongue and buccal mucous membrane**—Here also we try to assess the amount of hemoglobin present in blood, through nonkeratinized mucous membrance.
3. **Nail plate**—Return of reddish hue of the nail plate after release of pressure occurs within 2 seconds in normal person. If it requires more than 3 seconds patient is considered to be anemic.
4. If the palmar crease appears paler than surrounding skin in hyperextended palm then hemoglobin concentration is said to be below 8 g%.

Clubbing

In clubbing there is increase in pulp tissue (see Chapter-123).

Clubbing is subdivided into four grade:

A. **Grade I clubbing**—There is increase fluctuation of nail plate.
B. **Grade II clubbing**—Increase curvature of nail plate both and anteroposteriorly and transversely with obliteration of onychodermal angle which is (normally 160° to 170°).
C. **Grade III clubbing**—Bulbus deformity of terminal phalanx due to proliferation of subungual tissue under the influence of PDGF (platelet derived growth factor).
D. **Grade IV clubbing**—Clubbing with hypertrophic osteoarthropathy due to subperiosteal new bone formation, usually detected in the forearm above wrist and in leg above ankle joint which become tender on palpation.

Clubbing in associated with diseases of cardiac recpitratory GI and other system and the etiologies are remembered by the nemonic CLUBBING.

Causes of clubbing is remembered by the mnemonic CLUBBING.

C—Cardiac cause
Congenital cyanotic heart disease—Tetralogy of Fallot common truncus, anomalous pulmonary venous drainage. Subacute bacterial endocardities.
L—Lung cause
Infective cause: empyema, lung abscess, bronchiectasis, *malignancy*—Primary and matastatic lung cancer, mesothelioma, cystic fibrosis.
U—Ulcerative colitis
B—Bowel related cause
Crohn's disease, malabsorption syndrome.
B—Biliary cirrhosis.
I— Idiopathic.
N—Neurological cause
Peripheral neuropathy.
G—Grave's disease.

Koilonychia

It is a spoon-shaped deformity of finger nail plate and is a signs of tissue iron deficiency and is usually associated with chronic iron deficiency anemia. This type of nail deformity can also occurs due to trauma.

The other features associated with these abnormality is dysphagia due to weblike proliferation of the mucous membrane at pharyngoesophageal junction.

Combination of koilonychia, chronic iron deficiency anemia and dysphagia is called *Plummer-Vinson syndrome or Keely-Paterson syndrome.*

As chronic iron deficiency anemia is becoming rarer with improved living standard koilonychia has also becoming rarer entity.

Temperature

Body temperature is controlled by hypothalamus. The maximum normal oral temperature is 98.9°F at 4 AM.

Maximum normal oral temperature is 99.9° F at 4 PM.

So an AM temperature of >98.9°F or a PM temperature of >99.9°F defined as fever.

Rectal temperature is 0.4°C or 0.7°F higher than oral temperature.

So the normal diurnal variation is typically 0.5°C or 0.9°F but in some individual recovering from febrile illness this daily variation may be as high as 1°C.

In female AM temperature is 1°F lower for 2 weeks before ovulation and 1°F higher after ovulation and remains at that level for 2 weeks until menses occur.

Body temperature can be elevated in postprandial state, pregnancy and endocrinologic dysfunction (thyrotoxicosis and Cushing's).

Fever is an elevation of body temperature that exceeds the normal daily variation and occurs in conjunction with an increase in hypothalamic set point from 98.9°F–102.2°F.

This shift is the set point from normothermic to febrile level activate two mechanism:

1. Cutaneous vasoconstriction resulting in less heat loss from skin and helps to raise the core temperature.
   If this mechanism is not sufficient enough then second mechanism comes forward.
2. Shivering which increase heat production from muscle.
3. A third mechanism is the increase heat production by liver which can contribute to increase core temperature.

A fever >41.5°C/106.7°F is called hyperpyrexia. Hyperthermia is characterized by an uncontrolled increase in body temperature that exceeds the body's ability to heat loss and usually does not involve pyrogenic molecule of infection.

a. Exogenous heat exposer
b. Endogenous heat production. There are two mechanism by which hyperthermia can result in dangerously high core temperature.

Causes of hyperthermic syndrome

I. **Heat stroke**
a. *Exertional*—Exercise in sun
b. *Nonexertional* due to drugs like anticholinergics, antihistaminiec antiparkinsonian, diuretics, phenothiazines
II. **Drug-induced hyperthermia**—Amphetamine, cocaine LSD, salicylates, lithium anticholinergic, sympathomimetics
III. **Neuroleptic malignant syndrome**—Phenothiazine, butyrophenones (haloperidol) fluoxetine, metoclopramide, domperidone, thiothixene, withdrawal of dopaminergic agent
IV. **Serotonin syndrome** due to SSRI, MAO-inhibitor, TCAD
V. **Malignant hyperthermia**—Inhalational anesthetics and succinylcholine
VI. **Endocrinopathy**—Thyrotoxicosis and pheochromocytoma
VII. **CNS damage**—Cerebral hemorrhage, status epilepticus and hypothalamic injury

Autoinflammatory disease causing fever

1. Adult and juvenile Still's disease
2. Cryopyrin associated periodic syndrome (CAPS)
3. Familial mediterranean fever
4. Hyper IgD syndrome
5. Behçet's syndrome
6. Macrophage activation syndrome
7. Normocomplementemic urticarial vasculitis
8. Antisynthetase myositis
9. Pyogenic arthritis, pyoderma gangrenosum and acne (PAPA syndrome)
10. Blau syndrome
11. Gouty arthritis

Treatment of hyperthermia

a. Physical cooling with ice sponging, ice bath, cooling blanket
b. Gastric or peritoneal lavage with ice-cold saline
c. In severe cases hemodialysis or cardiopulmonary by-pass with cooling of blood may be done

For malignant hyperthermia
a. Cessation of anesthesia, injection dantrolene 1–2.5 gm/kg/6 hourly IV for 1–2 days then switch over to oral dantrolene
   - For neuroleptic malignant syndrome, drug-induced hyperthermia, hyperthermia of serotonin syndrome and thyrotoxicosis—Can also be treated with dantrolene with the same dose
   - Neuroleptic malignant syndrome can also be treated by bromocriptine, levodopa amantadine, nifedipine and induction of muscle paralysis by curare of pancuronium.
   - Tricyclic antidepressant overdose may be treated with physostigmine

Hypothermia

- Drop of body's core temperature below 35°C (95°F) is called hypothermia
- Primary hypothermia is the result of direct exposer of a previous healthy individual to cold
- Secondary hypothermia develop as a complication of a systemic disorder

Risk factor for hypothermia

1. Extremes of age
2. Environmental exposure
3. Malnutrition, marasmus, Kwashiorkor or hypothyroid, adrenal insufficiency, hypopituitarism
4. Hypoglycemia and diabetes
5. CVA hypothalamic disorder and Parkinson's disease, spinal cord injury
6. Trauma, sepsis, shock. Hepatic or renal failure

Different types of fever

1. Intermittent pyrexia
2. Quotidian fever
3. Tertian fever
4. Quartan fever
5. Continued pyrexia
6. Remittent pyrexia
7. Pel-Ebstein type of pyrexia.

Intermittent pyrexia—It is that type of fever in which the temperature touches the base line at least once in 24 hours.

Quotodian fever—If there is daily rise and daily fall of body temperature, it is called quotidian fever, which usually occurs due to infection.

Tertian fever—If the fever comes on every third day then this type of fever is called tertian fever, e.g. BT malaria, MT malaria.

Quartan fever—If the fever comes on every fourth day then this type of fever is called quartan fever, e.g. quartan malaria.

Continued pyrexia—If the body temperature does not touches the base line and the daily fluctuation is within 1.5°F then it is called continued pyrexia.

Remittent pyrexia—If the body temperature does not touches the base line but the daily fluctuation is more than 1.5°F then it is called remittent pyrexia.

Pel-Ebstein type of pyrexia—It is a type of periodic fever where the fever persist 10–15 days followed by a period of apyrexia for another 10–15 days. After 6–8 cycle of pyrexia/apyrexia lymphnode enlargement gradually appear.

This type of periodic pyrexia/apyrexia is seen as 'B' symptom of lymphoma. Previously it is called Pel-Ebstein type of pyrexia.

Edema

It means execss interstitial fluid in tissue. Normally there is tissue fluid in each tissue which carries oxygen and nutrition from blood to the cells.

This tissue fluid comes out from the blood from the arterial end of capillary where hydrostatic pressure is much higher than osmotic (oncotic) pressure and majority of this fluid (approx 98–99%) is reabsorbed by the venom end of the capillary where the osmotic pressure in capillary is higher than hydrostatic pressure the remaining 1–2% of tissue fluid is drained by lymphatics.

The etiology of edema are the followings:

1. *Diminished osmotic pressure* which causes excess water to comes out of intravascular compartment from the arterial end of capillary and diminished absorption of tissue fluid by the venous end of the capillary.

   Albumin is the main plasma protein that exert the osmotic pressure.

   Causes of diminished osmotic pressure (or low serum albumin):
   a. Malnutrition.
   b. Malabsorption.
   c. Cirrhosis of liver.
   d. Nephrotic syndrome.
   e. Protein lossing enteropathy (crohn's disease) causing hypoalbuminemia.

   Diminished osmotic pressure causes bilateral pedal edema.
2. *Increased hydrostatic pressure* at the venous end of the capillary also causes diminished absorption of tissue fluid by the venous end of the capillary.

   Causes of increased hydrostatic pressure:
   a. Congestive cardiac failure
   b. Inferior vena cava thrombosis

   } This two causes bilateral pedal edema

   c. Deep vein thrombosis of leg—Cause unilateral pedal edema.
   d. Obstruction to lymphatic drainage by filaria or malignant deposit in the lymphnode, may cause unilateral or bilateral pedal edema.
3. A third cause of edema is increased capillary permeability (or vasodilatation) due to effect of cytokines as occurs in (pyogenic, allergic or traumatic) inflammation.

How to examine for edema

In ambulatory person inspect for apparent swelling of the dorsum of foot and lower part of leg. Watch whether extensor tendon and venous arches are visible over the dorsum of foot. It visible then probably edema is absent. If they are not visible and on apparent inspection foot and lower legs are swollen or puffy then give a firm pressure by thumb over seen bone a few centemeter above medial malleolus for 15–30 seconds and watch for pit formation.

If pit formation appear then pitting edema is said to be present and if pit formation does not occur but the leg appear swollen then nonpitting edema is present.

Causes of nonpitting edema

a. Hypothyroid
b. Obesity
c. Storage disorder.

In case of nonambulatory bedridden patient the same procedure is done over sacrum as it is the most dependent part of the body in supine posture.

Neck Gland

Neck glands are classified according to their location:

A. Horizontal chain
   1. Upper horizontal chain
   2. Lower horizontal chain (or supraclavicular chain).
B. Vertical chain
   1. Anterior to sternomastoid.
   2. Posterior to sternomastoid (glands of posterior triangle).
C. Thyroid gland.
D. Selena group of gland—Located near the insertion of selena group of muscle at 1st rib behind clavicle and of sternomastoid muscle.

Members of upper horizontal group

1. Submental
2. Submandibular
3. Jugulodigastric and juguloomohyoid
4. Preauricular
5. Postauricular
6. Suboccipital.

For palpation of neck gland examiner must stand behind the patient and flex the neck of the patient forward and tilt it to the side of examination. This maneuver relaxes the deep cervical fascia and the finger can be easily insinuated behind the mandible for palpation of submental and submandibular gland.

Members of lower horizontal group is supraclavicular group of glands which is subdivided into (a) medial, (b) intermediate and (c) lateral supraclavicular group.

The medial supraclavicular group on left side which lies in between two heads of sternomastoid has a special name called **Virchow's gland**. This gland lies in relation to termination of thorasic duct into the junction of sub-clavian and internal jugular vein and enlarges in intra-abdominal, thoracic and mediastinal and even in testicular malignancy.

The members of the vertical chain anterior to sternomastoid are:

1. Jugulodigastric
2. Juguloomohyoid
3. Prelaryngeal
4. Pretracheal
5. Thyroid
6. Suprasternal.

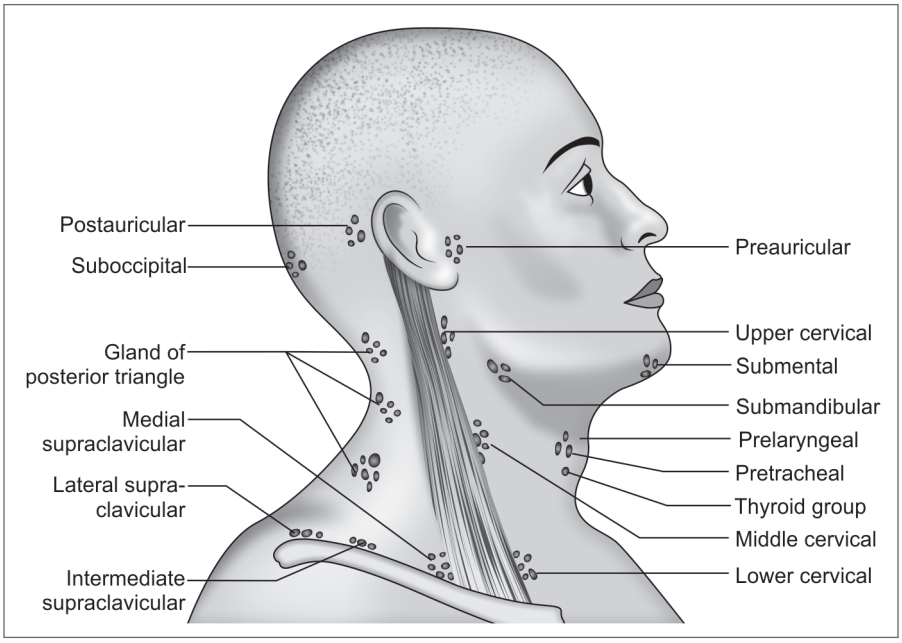


Fig. 126.1: Location of different groups of cervical lymph node

Vertical chain is behind sternomastoid are called glands of the posterior traingle and has no subdivision.

Respiration

Respiration rate of a newborn is about 60/min and with increasing age it gradually comes down to 14–15/min in adult.

Respiration rate is more slow during deep sleep and medullary compression.

Special types of breathing

Cheyne-Stoke type of breathing (Fig. 126.2)—It is characterized by alternate cyclical apnea and hyperapnea. This type of breathing is seen in *heart failure narcotic poisoning, deep sleep, neurological disorders* and *elderly person*. When there is apnea CO_2 accumulate in blood and this increased CO_2-containing blood when reaches medula it stimulate respiratory center and causes hyperapnea. During the phase of hyperapnea CO_2-concentration in blood diminishes and this blood when reaches medula it suppress the rate of respiration. By this mechanism alternate apnea and hyperapnea is produced.

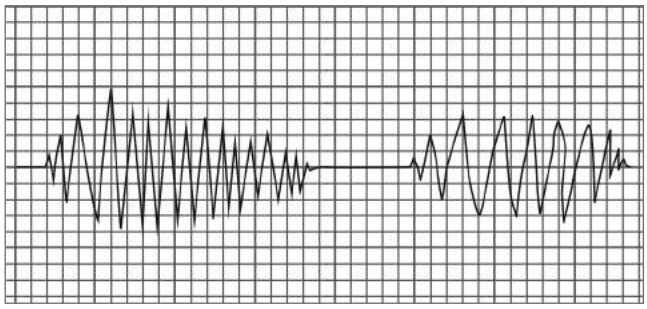


Fig. 126.2: Graphical representation of Cheyne-Stokes respiration

Acidotic breathing—When there is metabolic acidosis it stimulate respiratory center and there will be continued hyperapnea. This type of breathing is seen in uremia and diabetic ketoacidosis.

1. Cyanosis—see Chapter–122
2. Jaundice—see Chapter–121
3. Blood pressure—see Chapter–6
4. Pulse—see Chapter–116, 124
5. Neck vein—see Chapter–116, 125

Other point of general survey are discussed in details in chapter I and II and Miscellaneous Chapter.

Chapter 127

Examination of Respiratory System

Examination of respiratory system is subdivided in four parts:

1. Inspection
2. Palpation
3. Percussion
4. Ausculation.

INSPECTION

Shape of the Chest

Inspection to be done after proper exposure of the chest and the patient lying supine on the bed (Fig. 127.1).

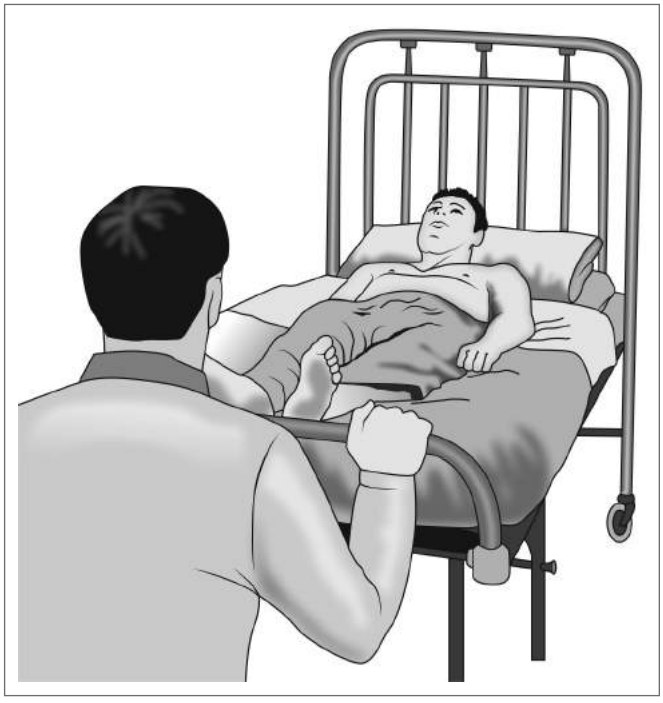


Fig. 127.1: Patient lying in supine position after proper exposure of the chest

The shape of chest is best examined by lowering the eye of the examiner and making it parallel with the plane of the

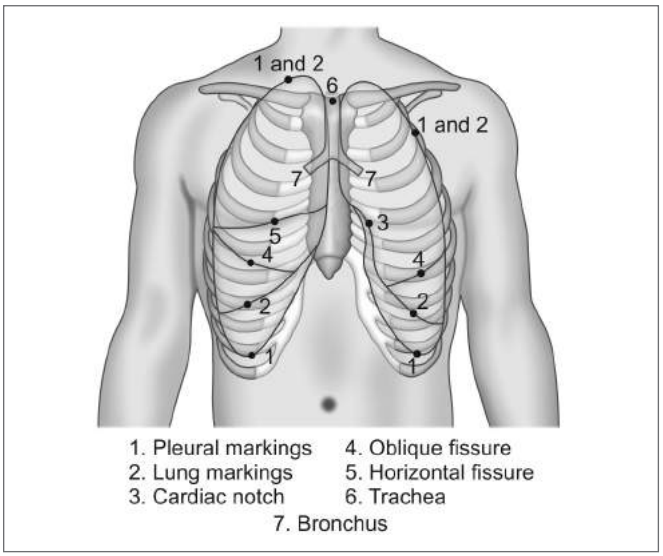


Fig. 127.2: Schematic diagram of chest with demarcation of different lobes (AP view)

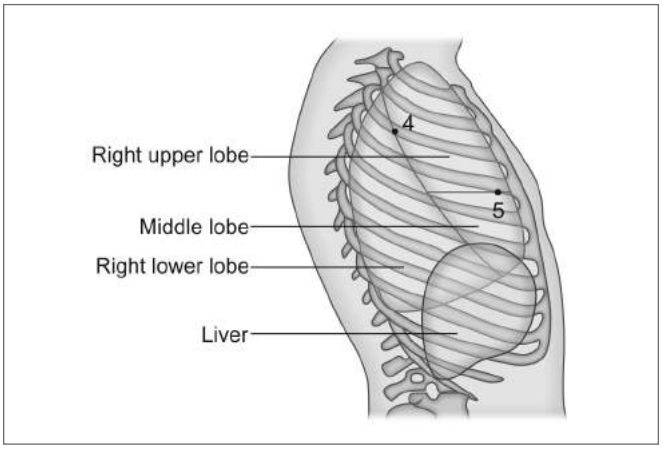


Fig. 127.3: Schematic diagram of chest with demarcation of different lobes (Right lateral view)

chest wall and standing at the foot end and alternativety on both side of the patient.

In normal person shape of the chest in bilaterally symmetrical and elliptical in cross section. The ratio of transverse diameter : Anteroposterior diameter is 7 : 5.

The abnormality of the shape of the chest are:

- Barrel-shaped chest.
- Pectus carinatum (pigeon chest)—There is localized prominence of sternum and costal cartilage and associated with symmetrical indrawing of the ribs to form horizonital groove known as Harrison's sulci above the costal margin this due to hyperinflation of lung with repeated vigorous contraction of diaphargm when ribs are not calcified and soft as in severe childhood asthma with osteomalacia and ricket.
- Pectus excavatum (funnel-shaped chest)—These is localized depression of the lower end of the sternum due to developmental deformity. In severe cases the heart in displaced to the left with compromised ventilatory capacity of lung.
- Flattening of chest due to pulmonary fibrosis in tuberculosis of lung.
- Kyphosis due to deformity thoracic vertebrae.
- Scoliosis due to deformity thoracic vertebrae.

Severe chronic airway obstruction (COPD) specially emphysema in the long-term produce over inflatted lung and the chest is called *barrel-shaped chest* where the transverse diameter: Anteroposterior diameter is 1 : 1.

Due to fibrosis of lung one hemithorax may appear depress than normal side or *flattening of chest wall* on the affected side.

Kyphosis signify forward bending and *scoliosis* signify lateral bending of the vertebral column and cause asymmetry of chest which restrict lung movement (cause restrictive lung disease).

Movement of the chest wall

Movement of the chest should be examined after the examiner flexes his knee and making the eye parallel with chest well.

Diminished chest wall movement full hemithrox. Ser

If diminished respiratory movement is noted on one side then probably that side is pathological whether chest wall of that side appear full or depressed.

In drawing of intercostal spaces or intercostal suction is seen in severe upper airway obstruction (obstruction of larynx or trachea).

Diminished chest wall movement with full hemithorax. Seen in pleural effusion and pheumothorax.

Diminished chest wall movement with depressed hemithorax. Seen in pulmonary fibrosis and absorbtion callapse.

In COPD lower rib may move inward with inspiration instead of normal outward movement.

Paradoxical inward movement of abdomen during inspiration is seen in diaphargmatic paralysis or severe COPD. Double fracture of a series of rib or sternum allow the chest wall between the fracture to become mobile or 'flail'. Paradoxical respiratory movement, i.e. sucked in with each inspiration and moves out with each expiration is seen over that portion of flail chest.

Venous prominence

If present over the neck-less region of anterior chest wall indicate superior venacaval obstruction due to malignancy of upper mediastinum.

Respiratory rate and rhythm

Respiration rate in about 14–15 breath/min respiration rate > 15 is called tachypnea.

Respiration > 30 is an important prognostic sign associated with death of the patient in community acquired pneumonia.

Abnormality of rhythm are:

a. Cheyne-Stokes respiration
b. Acidotic breathing

} Disscussed under general survey

Note for any obvious scar mark or lump over chest wall.

Pulsation below the inferior angle of scapula suggest coarctation of aorta with colateral anastomosis.

Note for spider angioma over the chest which suggest cirrhosis liver and red spot which suggest Rendu-Osler-Weber syndrome.

PALPATION

1. **Palpate for position of trachea**—Trachea should be on the midline and it is assessed by placing the terminal phalynx of the index finger in between the tracheal cartilage and sternomastoid muscle in the suprasternal notch to assess the space in between them on both side.

Causes of tracheal shifting

- Towards the side of lung pathology
  - Collapse of the whole lung or upper lobe
  - Fibrosis of uppper lobe
  - Pneumonectomy.
- Away from the side of lung pathology
  - Massive pneumothorax.
  - Massive pleural effusion. Lower mediastinal shift is assessed by the position of apex beat provided there is no ventriculomegaly or scoliosis or funnel-shaped depression of sternum.
- **Movement of the chest** (Fig. 127.4)— Corroborate the inspectory finding by placing the hand firmly on chest wall symmetrically on both side of midline and extend the thumb so that they almost touch each other in the midline.

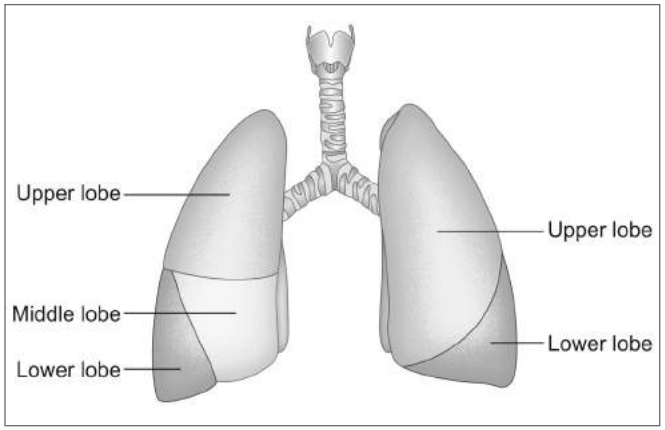


Fig. 127.4: Schematic diagram of chest with demarcation of different lobes (AP view)

Now ask the patient to take deep breath, so that the thumb move symmetrically laterally at least 5 cm apart. If one thumb remain close to midline this suggest diminished expansion of chest on that side.

- **Expansion of upper lobe**—It is asessed by seeing the movement of clavicle standing on the back of the patient during normal respiration, or it can be assessed by placing the palm firmly over the anterior chest in the infraclavicular fossa. The radial border of index finger is below and parallel with the clavicle.

  Reduced expansion on oneside indicate abnormality on that side, for example, pleural effusion or collapse of a lobe or whole lung, pneumothorax or unilateral fibrosis. Bilateral diminution of chest wall movement occur is sever COPD and diffuse pulmonary fibrosis.
- Tactile vocal fremitus is detected by palpation with palm on the chest wall when the patient asked to repeate a phrase like "99" ninetynine and symmetrical area over both side of chest are palpated and compaired.

  Vocal fremitus is increased over consolidation as the vibration produced in the larynx is easily transmitted to chest wall through the solidified lung tissue.
- Subcutaneous emphysema produce a characteristic cracking sensation during palpation over the gas containing chest wall and there may be diffuse swelling chest wall, neck and face. It may be seen as a complication of severe asthma, pneumothorax, rupture esophagus and intercostal drainage.

PERCUSSION

The middle finger of the left hand is placed firmly over the region tobe percussed and the back of middle phalanx is struk by the tip of the middle finger of the right hand. The movement should come frojm wrist not from elbow (Figs 127.7 and 127.8).

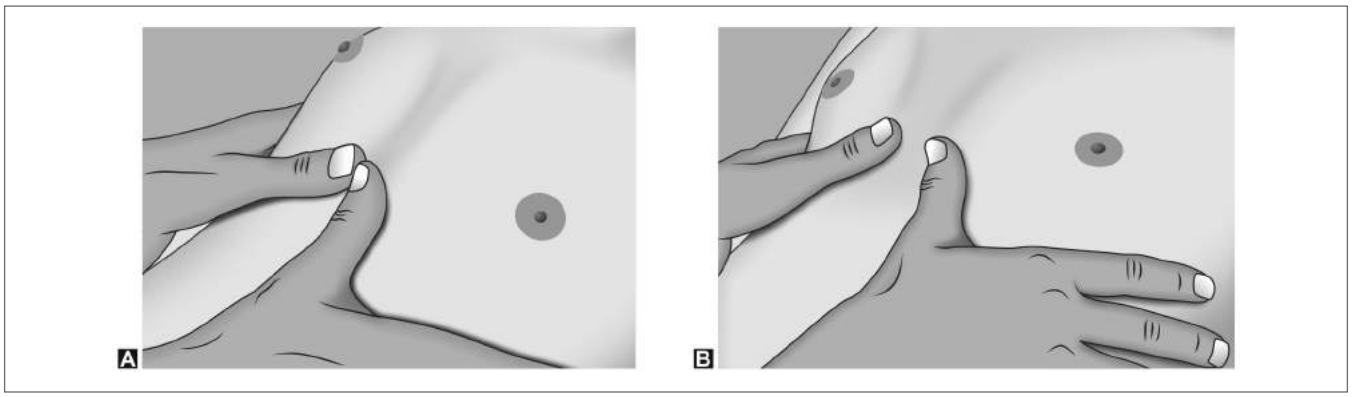
Percussion is done over the symmetrical area of chest wall on both side and compair the sound emitted by chest wall of both side.

Percussion is first done on the anterior chest wall either sitting or in supine posture. Starting from clavicle then gradually downward over 2nd, 3rd, 4th and 5th intercostal space along the midclavicular line alternatively over bothside of the sternum. Clavicle is usually directely percussed but finger may be placed over the clavicle. In adult upper boarder of liver dullness starts from right 5th rib on midclavicular line but if the heart is at its normal position then percussion along the midclavicular line on the left side will be all through resonant up to the intersection of midclavicular line with subcostal margin.

Percussion over axillary region is done in sitting posture, hands of the patient placed over the head to get easy access to the axilla and percussion is done down the midaxillary line starting from 4th ICS. As the upper intercostal spaces are blocked by the head of the humerus. On the right side 4th, 5th and 6th space will be resonant, liver dullness will start from 7th rib.

While on the left side 4th, 5th, 6th, 7th and 8th space will be resonant and splenic dull ness will start from 9th rib. On percussion down midaxillary line on rightside 3 space will be resonant (4th, 5th and 6th space) while on left side 5 space will be resonant (4th, 5th, 6th, 7th and 8th space).

During purcussion of the back, patient is in sitting posture. Examiner stand on the back of the patient.



Figs 127.5A and B: Assessing chest expansion from the front: (A) Expiration; (B) Inspiration

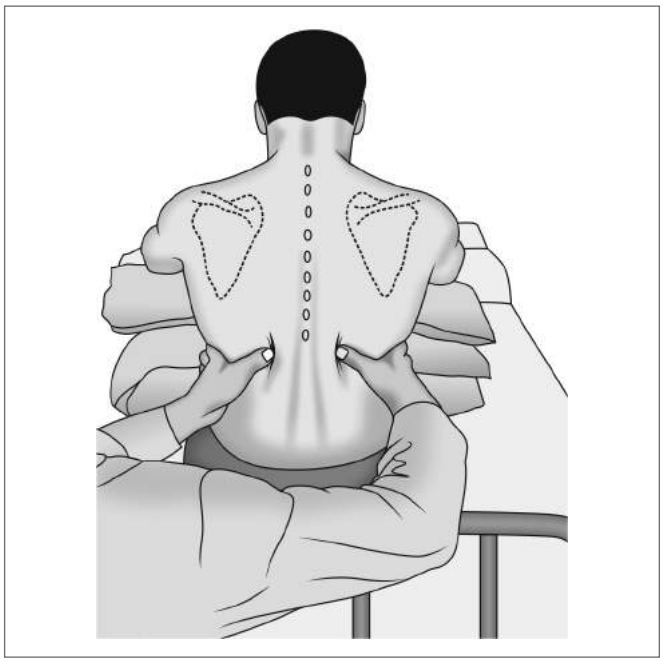


Fig. 127.6: Enpansion of chest from the back

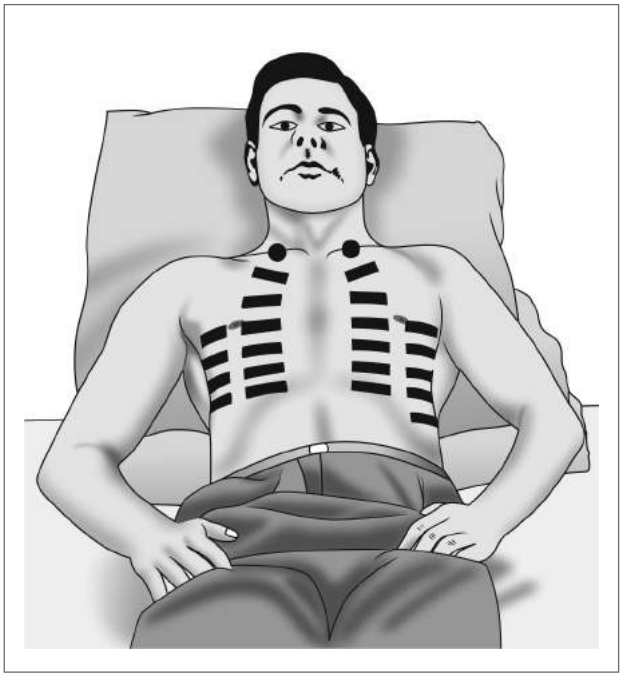
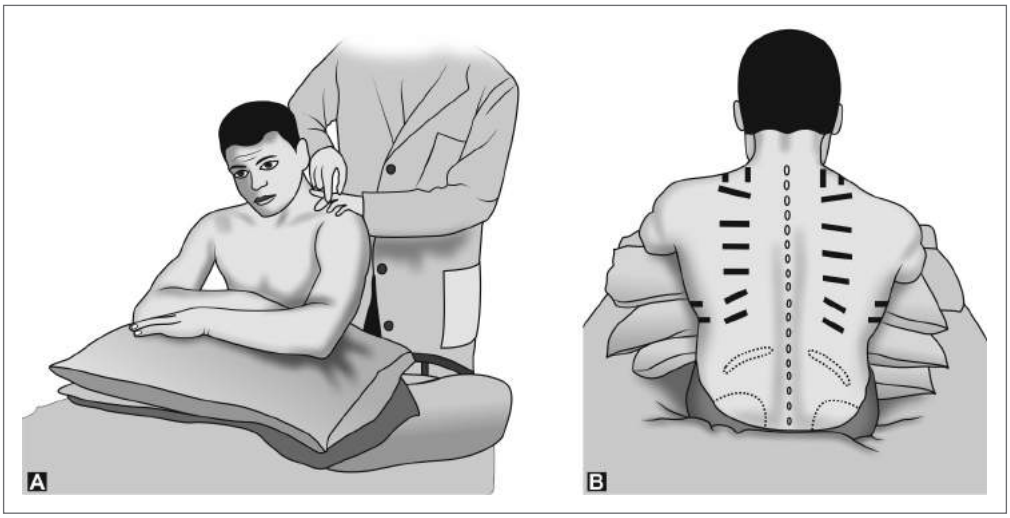


Fig. 127.7: Placement of finger during percussion on the anterior chest wall and axillary region



Figs 127.8A and B: Placement of finger during percussions over back of chest and apex of lung

First percussion is done over apex placing the finger across the trapizius from back by the side of the neck over the supraclavicular fossa. Second time fingers are placed 2 cm laterally and compair with opposite side.

Then start percussion over the back. Above the scapula fingers are palaced on either side of midline directed upward.

For percussion of the interscapular region patient is asked to cross forearm accross the chest anteriorly so that the scapula moves laterally and the interscapular space gets widen.

During percussing of the interscapular region fingers are placed horizontally by the side of midline approxmiately 4 cm apart.

Below the inferior angle of scapula fingers are placed gradually more laterally like fishbone pattern and always compare sound between two sides.

Percussion note	Detected over
Resonant note	Normal lung
Hyperresonant note	Pneumothorax
Dull (woody dull) note	Consolidation of lung, collapse of lung, severe pulmonary fibrosis, Pleural thickening
Stony dull note	Pleural effusion

AUSCULTATION

Principles of auscultation—

- Auscultating should be done with the bell of the stethoscope except higher pitch sound like pleural rub as most of the breath sound are low frequency sound, stretching of skin and hair under diaphragm during deep breathing can produce misleading sound like crackle and in thin patient it is different to get full contact between diaphragm and skin of chest wall.
- Patient is asked to take deep breath with open mouth.
- Auscultate both side alternately and compairing finding over equivalent position of both side.
- Start auscultation in front, from the clavicle along MCL down to 6 ICS, in the axilla from axilla to the 8 ICS posteriorly down to the level of 11 ICS.
- Assess the quality and amplitude of the breath sound.
- Try to identify the gap between inspiration and expiration to differentiate between bronchial and vesicular breathing.
- Normally, we get vesicular breath sound over whole lung except over manubrium sterni and over back above T_4spine.
- Avoid auscultation within 3 cm of midline above sternal angle in the front and above T_4 spine over back as there may be bronchial breathing which is directly transmitted from the trachea and main bronchi to chest wall.
- Try to identify added sound if present.

Machanism of production of breath sound—Terbulant flow of air in the large airway creates normal bronchial breath sound heard over chest when this bronchial breath sound passes through spongy lung it get modulated and is converted to vesicular breath sound. That is why bronchial breath sound is heard over a lung cavity with a patent bronchus and consolidated lung where there is no spongy lung tissue, and the bronchial breath sound is directly transmitted to the chest wall without modulation by spongy lung.

Character of Bronchial Breath Sound

- It is hollow and tubular in nature and is of high-pitched character.
- There is a gap between inspiratory and expiratory phase.
- Inspiratory phase and expiratory phase are of equal length.

Causes of Bronchial Breath Sound

- Consolidation of lung
- Cavity or collapse with a patent bronchus
- At the top of pleural effusion (rarely)
- Pulmonary fibrosis (rarely).

Character of Vesicular Breath Sounds

- It is rustling in character.
- Inspiratory phase is much more prolonged than expiratory phase.
- There is no gap between expiratory and inspiratory phase.

Causes of Diminished Vesicular Breath Sound

Due to reduced conduction

- Obesity
- Pleural effusion
- Pleural thickening
- Pneumothorax.

Due to reduced airflow

- COPD
- Collapse of lung.

Added Sound

- **Crackles' are** interrupted nonmusical sound. It is due to explosive reopening of the collapsed alveoli and sticky airway during inspiration we can have an idea about the etiology of crackle from its timing in respiratory cycle.
  - Early inspiratory crackle suggest small airway disease, e.g. bronchiolitis.
  - Midinspiratory crackle suggest pulmonary edema.
  - Fine late inspiratory crackle occurs in pulmonary fibrosis.
  - Mid inspiratory and late inspiratory crackle occurs in pulmonary edema.
  - Coarse late inspiratory crackle occurs in COPD, pneumonia, lung abscess and tubercular lung cavities. Both inspiratory and expiratory (biphasic) coarse crackles having a bubbling character heard is bronchiectasis/Coarse crackles occurs when air bubbles through accumulated secretion within dilated or large bronchi or lung cavity.
    This type of crackle has a bubbling quality and the character changes if the secretion are coughed out.
- **Wheeze**—It is a adventitious sound with musicial quality and is produced due to oscillation of the wall of airway, when the airway in narrowed due to any cause. (a) Spasm of circular smooth muscle of bronchi, (b)

edema of the bronchial mucosa and (c) accumulated secretion with in the lumen of bronchus.

It is usually heard during expiration as the airway get further narrowed during expiration. This high-pitched expiratory wheeze has a whistling quality and is usually heard in asthma, COPD. The wheeze in asthma is polyphonic in nature as it is due to simultaneous narrowing multiple air way in both lung.

In severe asthma *wheeze may be altogether absent because of reduced airflow through the airway* due to obstruction producing 'silent chest'. A wheeze at a fixed place is due to narrowing of airway by a lung cancer.

- **Pleural friction rub**—It is produced due to rubbing inflamed parietal pleura with the visceral pleura and is heard at the height of deep inspiration and beginning of expiration with the diaphragm of the stethoscope. Normally there is rubbing between parietal and visceral pleura at the height of inspiration but it does not produce any sound due to the smooth surface of the pleura and presence of lubricant fluid but when pleura get inflamed, fibrin is deposited over the visceral pleura and makes visceral pleura rough and creates the friction sound and is usually associated with pleuritic chest pain. Pleural friction rub mimics the sound of rubbing of dry hair in between fingers.

  It is usually heard at early stage of pneumonia and pulmonary embolism.
- **Stridor**—It is an inspiratory sound produced due to narrowing of large airway like trachea or bronchus, either due to growth or due to inspiratory collapse of the airway due to softeing of its cartilaginous ring.

EGOPHONY

It is the nasal intonation of vocal resonance heard at the upper level of a pleural effusion. It is due to enhanced transmission of high frequency sound across abnormal lung, the lower frequencies are not connected.

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