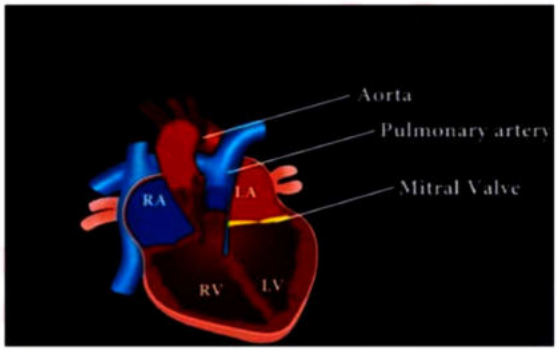
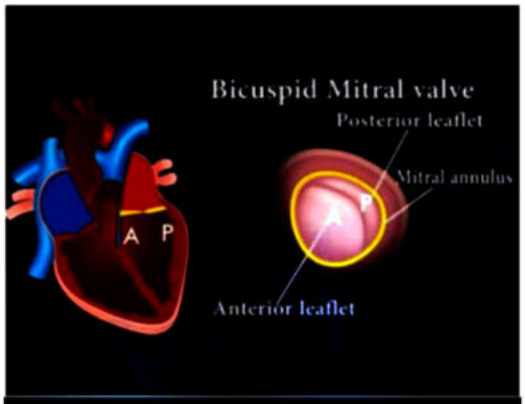
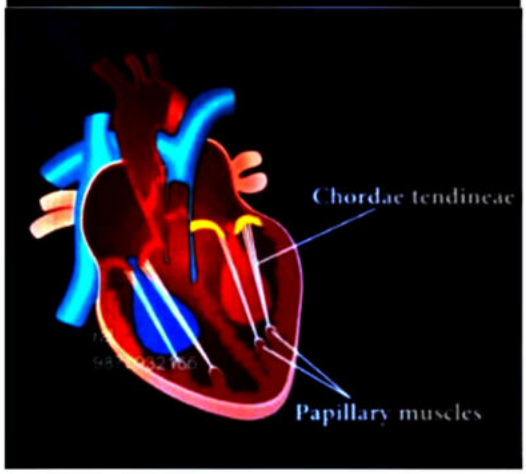
1 MITRAL VALVE PROLAPSE WITH ANIMATION

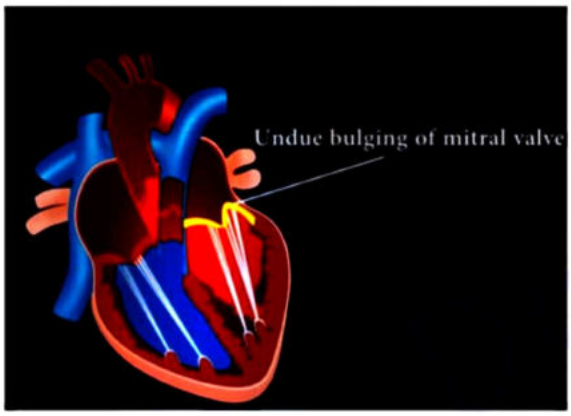
- Also known as floppy valve syndrome / Barlow syndrome
- During phase of systole, LV generates tremendous amount of pressure that push blood into aorta.



- Bicuspid mitral valve is able to retain its position due to:
  - Chordae tendineae
  - Papillary muscles







Important Information

Ejection click

- Normal finding during ventricular systolic
- Represents aortic & pulmonic valve opening

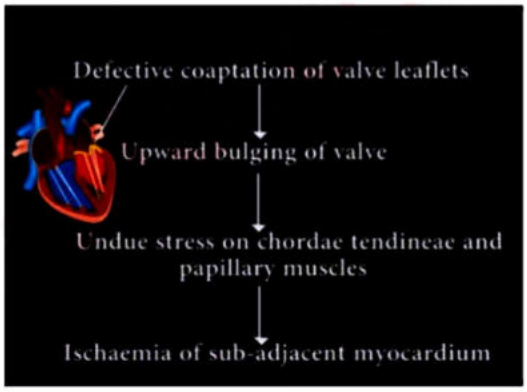
Mid Systolic Click

- Abnormal finding due to extra tension generated in the chordae tendineae during exercise bulging up of mitral valve

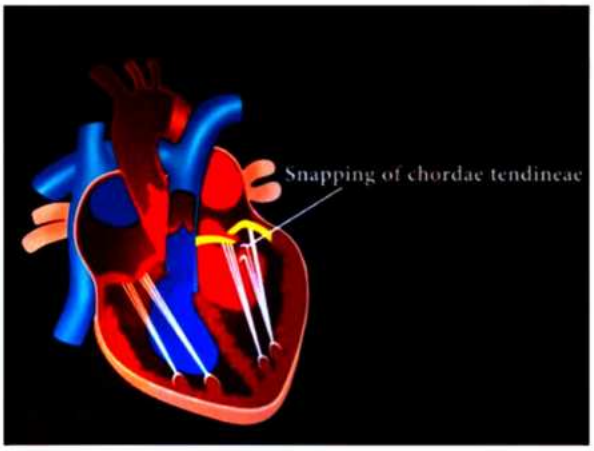
MVP

Two problems

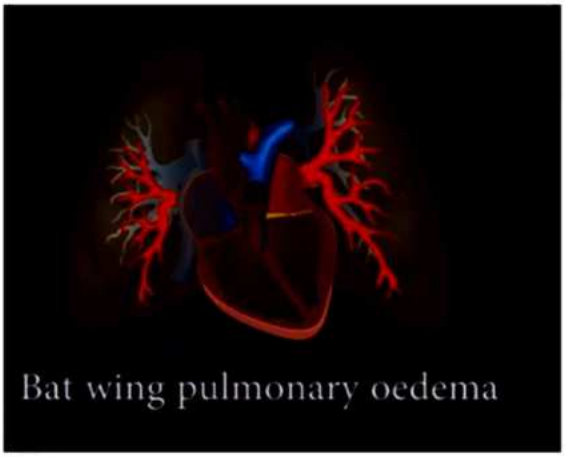
1. Defective coaptation of valve leaflets
- Upward bulging of valve
- Undue stress on chordae tendineae and papillary muscles
- Ischemia of sub adjacent myocardium
- It causes chest pain, arrythmia



2. Snapping of chordae tendineae
- Incompetent valve
- Mitral regurgitation



In Case of Incompetent Valve
- 10-30 ml of blood leakage from LV to LA
- Structural damage to left atrium
- Pulmonary venous hypertension
- Left ventricular failure (pulmonary oedema)
- Bat wing pulmonary oedema



Causes of MVP:

00:03:18

1. Idiopathic
2. Connective tissue disorders like Marfan syndrome, Osteogenesis imperfecta, Ehler Danlos syndrome
3. ADPKD
4. Straight back syndrome
5. Ostium secundum ASD

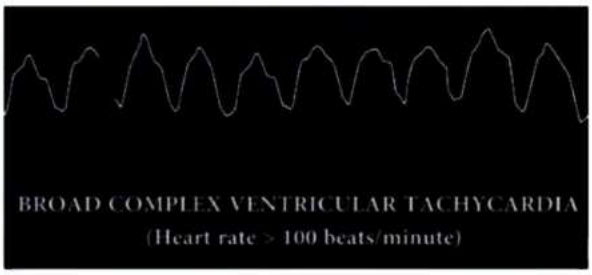
Clinical Presentation

1. Asymptomatic (M/C)
2. Chest pain
3. Palpitations
4. Orthopnea
5. Paroxysmal nocturnal dyspnea (PND)

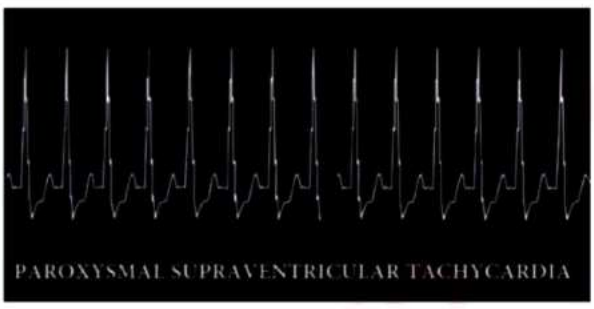
Rhythm Disorder seen due to MVP:

1. Premature ventricular contraction

2. Ventricular Tachycardia
- HR> 100 bpm



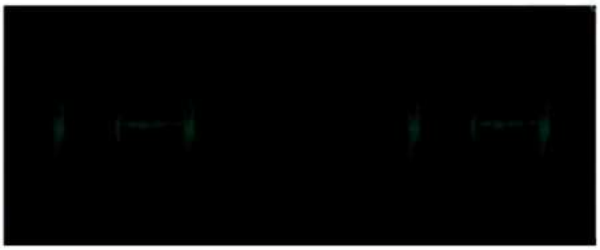
3. PSVT



4. Atrial fibrillation

Examination Findings

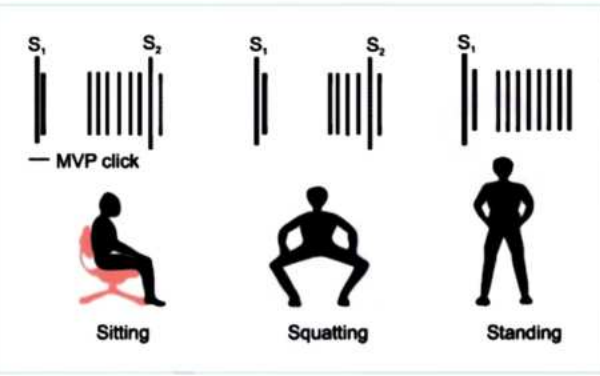
1. Mid systolic clicks
2. Late systolic murmur (due to leakage of blood into left atrium)



Important Information

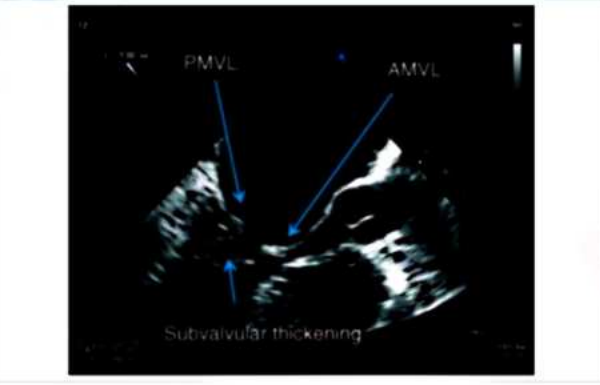
- Ejection systolic murmur heard in aortic stenosis (crescendo-decrescendo murmur)
- Late systolic murmur: Mitral valve prolapse
- Ejection systolic murmur: Aortic / Pulmonary stenosis

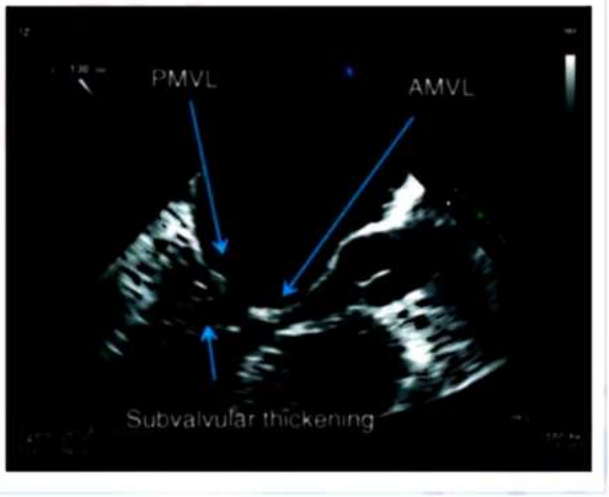
3. Murmur on Squatting & Standing
- Squatting: Shorter
- Standing: Longer



IOC

1. Echocardiogram





- Post leaflet defect
  - Jet of blood moves anteriorly
  - Murmur radiates to base of heart
- Ant. Leaflet defect
  - Jet of blood moves posteriorly
  - Murmur radiates to axilla /back

Treatment

1. β blockers
- To control heart rate
2. Mitral valve repair
- To prevent mitral regurgitation

2 PERCUTANEOUS CORONARY INTERVENTION

- Golden Period of MI: 1st hour
- Causes of Sudden Cardiac Death in Post MI patients
  - Tachyarrhythmias – Ventricular Fibrillation
    → TOC: Defibrillation
  - Bradyarrhythmia: Mobitz II heart block
    → Rx: Atropine, TCP (Transcutaneous Pacer)
    ↓
    To accelerate heart rate

Refer Graph 2.1

- Patient with ST elevation MI
  Significant ST elevation in Leads II, III, avF (Inferior leads)
  ↓
  Helps in identifying Inferior wall MI

Troponin I values show increasing trend

Refer Graph 2.2

Important Information

- Troponin I rises by approx. 3 hours so if a person reaches hospital early, Troponin values can be Normal. That's why we are taking serial evaluation of Troponin I

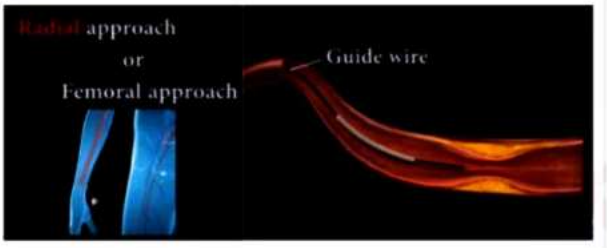
- Troponin I Values usually start doubling by 3-4 hours.
- Depending on the severity of illness: it can be tripled or become 5 times than normal.

PCI (Balloon Angioplasty)

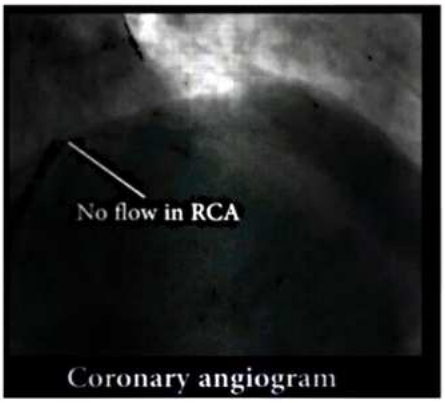
- Ideally done within 90 minutes of patient arriving in hospital
- Door to balloon time: within 90 minutes

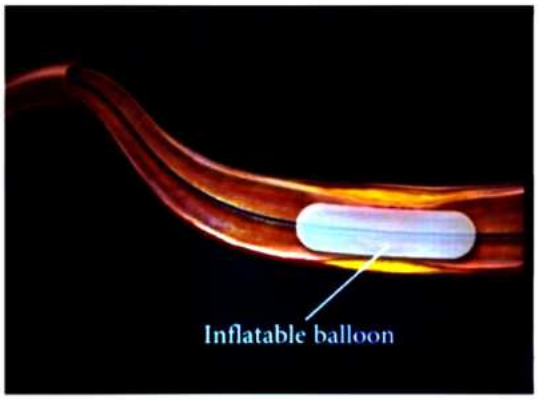
Procedure

- Preferred approach: Transradial approach



- Guidewire will navigate up From Radial artery to the subclavian artery root of Aorta right coronary artery guidewire is steered through thrombus Inflate the balloon The Force of the balloon will destroy the clot Revascularization has been obtained.

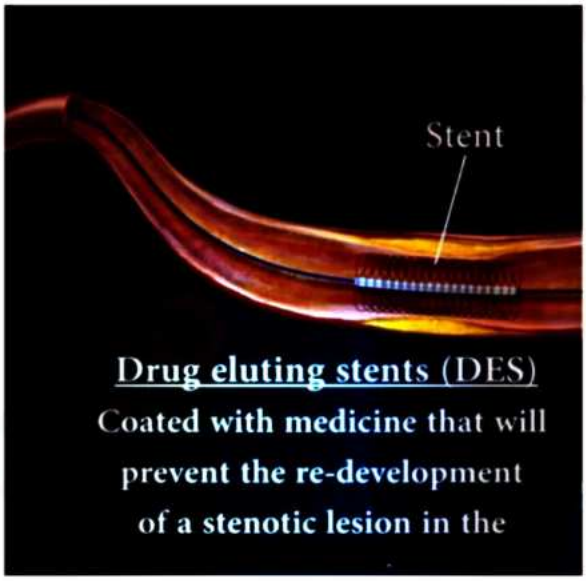




Drug Eluting Stents (DES)

- Coated with drug that will prevent the re-development of a stenotic lesion in the coronary artery.
- It can be coated with any two of the following drugs.

1. Everolimus
2. Zotarolimus



Advantages of DES

- Modify the atherosclerotic process
- Prevent re-development of acute coronary syndrome.

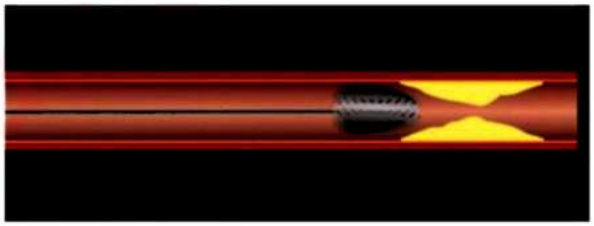
Biodegradable Stents

- Get incorporated into the wall of blood vessels
- Modify atherosclerotic process

Rotablator Atherectory

- Device used for patients having chronic stable angina
- To facilitate opening of the narrowed artery, so that stent can be deployed

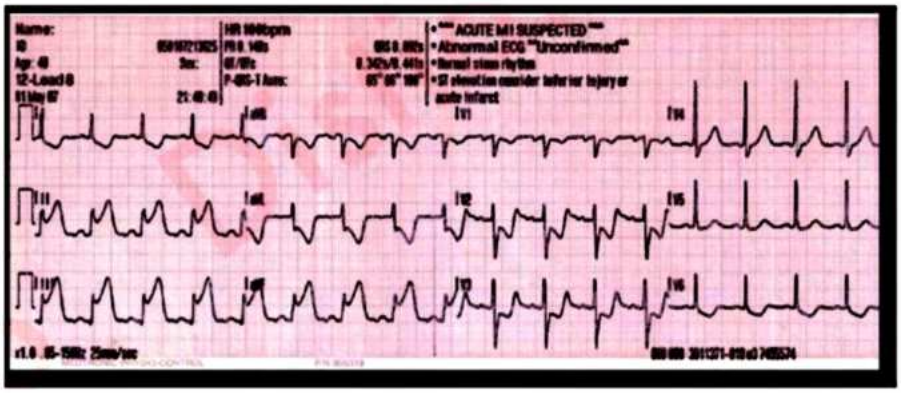
Balloon Angioplasty: If occlusion of artery by thrombus
Rotablaltor Antherectomy: If atherosclerotic plaque cause fixed obstruction



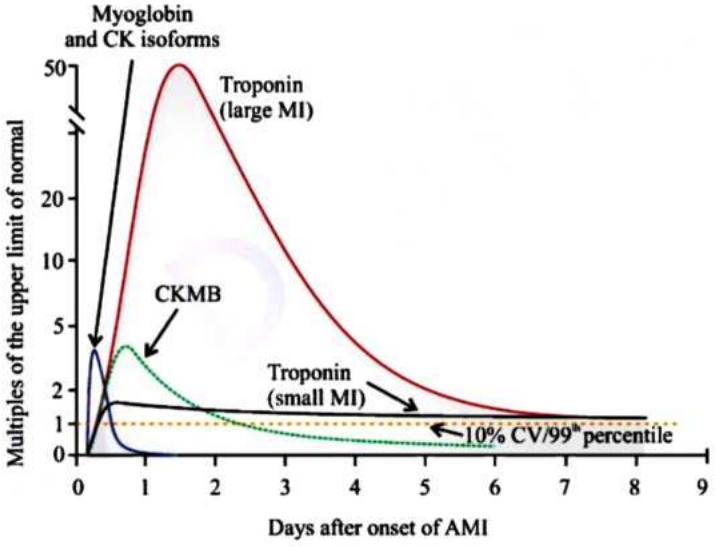
Summary

1. PCI stenting is a procedure that is done in ST elevation MI and should be done in within 90 minutes
2. Rotablator atherectomy: Helps in overcoming obstruction in chronic stable Angina, where patient having fibrous calcification plaque resulting in narrowing of the blood vessels.

Graph 2.1

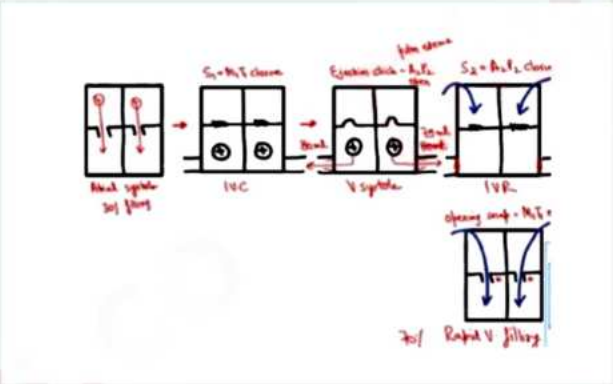


Graph 2.2



3 HEART SOUNDS -1

00:00:51



Atrial systole contributes to 30% of ventricular filling.

S_1

- Heard due to closure of mitral and tricuspid valves (M_1T_1)
  - Occurs at the end of atrial systole.

Isovolumetric contraction (IVC)

- Ventricles contracts and pressure starts building up.

Ejection Click

- Occurs due to Opening of aortic and pulmonary valves(A_2P_2) during ventricular systole.

Important Information

- Loud Ejection click - Valvular aortic stenosis
- Only Loud ejection click sound can be heard through stethoscope.

S_2

- Aortic and pulmonary (A_2P_2) valve closure at the end of systole generates sound S_2.

Isovolumetric Relaxation (IVR)

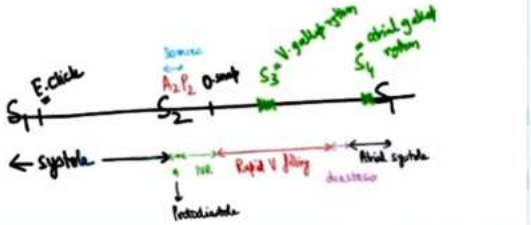
- All valves (mitral/tricuspid and aortic/pulmonary) are closed, heart relaxes at this moment, known as isovolumetric relaxation.
- Venous filling of atria starts during this phase.

Opening Snap

- Occurs due to opening of mitral and tricuspid (M_1T_1) valves at the end of isovolumetric relaxation.
- 70% filling of ventricles occurs during rapid ventricular filling when M_1T_1 opens.

Important Information

- Loud opening snap heard by stethoscope in mitral valve stenosis.



Important Information

- S_1 & S_2 are also known as lub & dub heart sounds respectively.
- Duration of systole is less than diastole (heart needs some time to get filled with blood).
- Systole is the period between S_1 & S_2.
- Ejection click comes just after S_1.
- Aortic valve closes prior to pulmonary valve.
- Time gap is 30 milliseconds.

Proto Diastole

00:10:55

- Short period between the end of systole and closure of aortic valve is known as Proto Diastole.
- Period between aortic valve closure and opening snap is known as isovolumetric relaxation.
- Momentary period of least cardiac motion after rapid ventricular filling known as Diastasis.

Important Information

- Least cardiac motion is present during the phase of diastasis

Divided diastole in 5 components

1. Proto diastole
2. Isovolumetric relaxation
3. Rapid ventricular filling
4. Diastasis
5. Atrial systole

Abnormal Heart Sounds

00:13:48

- S_3 also known as ventricular gallop rhythm.
- S_4 also known as atrial gallop rhythm.

Important Information

- Heart sound present right before S_1 is S_4

S_4

- Seen in long standing hypertension.
- In long standing hypertension there will be left ventricular hypertrophy which eventually cause left atrial hypertrophy.
- Atrial will generate more power, creates turbulence which produce S_4 sound.

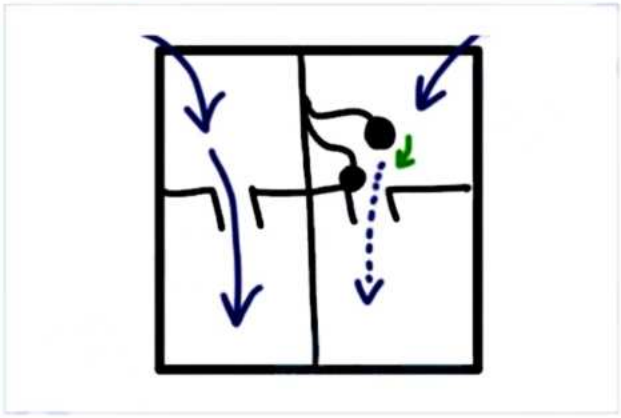
S_3

- Heard in the phase of rapid ventricular filling.
- Normal in children, pregnancy and adults upto 35 years.

Important Information

- High pitch heart sounds heard through diaphragm side of stethoscope (bigger side).
- Low pitch heart sounds heard through bell (smaller side)
  - S_3
  - S_4
  - Tumor plop sound
  - Murmur of mitral stenosis

Tumor Plop Sound 00:17:27



- Low pitched heart sound heard in Atrial Myxoma.
- It is a Diastolic finding.
- Here tumor hits an already open mitral valve, so the sound occurs after opening snap.

Atrial Myxoma

- Originates from inter atrial septum.
  - When blood enters in left atrium, it hits the tumor.
  - Then tumor impact the mitral valve leaflet and produces a sound called tumor plop sound.
  - This decreases the amount of blood entering in Left Ventricle.
  - Amount of blood entering in the left ventricle depend upon the size of the tumor.
  - If size of tumor is increasing ,this lesion can cause obstruction like in mitral stenosis and in late stages can cause physical damage to valve cusps to lead to mitral regurgitation.

Clinical Scenario

Young female presented with

C/O:

1. Effort intolerance,
2. Dyspnea on exertion,
3. Platypnea (she feels more breathless while sitting and breathlessness resolves on lying down).
4. Transient ischemic attack.

On examination:

- No pallor
- Tumor plop sound (low pitched sound so can be missed)
- Mid or late diastolic murmur

IOC:

- Transthoracic Echocardiography

Treatment:

- Refer to cardio thoracic vascular surgery & surgical resection of tumor will be done.

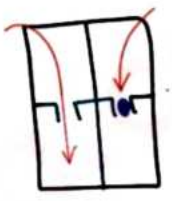
Important Information

PLATYPNEA seen in:-

- Atrial myxoma
- Hepatopulmonary syndrome

Tumor originating from heart valve.

Papillary Elastoma 00:27:42



- Shows embolic manifestations leading to Transient Ischemic Attack.

Treatment:

- Deploy Prosthetic valve.

Differential Diagnosis

- Atrial myxoma
  - Tumor plop sound and platypnea present.

Important Information

- Most common secondary heart tumors:-
  - Oat cell lung carcinoma
  - Carcinoma breast
  - Malignant melanoma
- Most common primary malignant tumor of the heart is Angiosarcoma.
  - Rhabdomyosarcoma in case of children.
- Benign tumor of the heart is Atrial Myxoma

Tubercular Pericarditis 00:31:39

- Tubercular pericarditis, form of extra pulmonary tuberculosis.

Important Information

- Most common form of extra pulmonary tuberculosis is Cervical lymphadenopathy (gohn focus - Tonsil).

- There is Serofibrous exudate outside the heart which causes inflammation and irritation to phrenic nerve.

Patient having tubercular pericarditis, Complains of:

1. Chest pain at rest (due to phrenic nerve involvement).
2. Night sweats
3. Low grade fever
4. Involuntary weight loss (5% or 10 lbs over 6 months)
5. Pain radiating to left shoulder

On examination:

- Pericardial friction rub (scratchy sound on auscultation)

Pericardial friction rub	Pleural rub
Will be present even when patient holds his breath	Heard in the phase of deep inspiration

Work Up:

- ECG
  - ST elevation

	Pericarditis:	MI:
	• ST elevation has concave shape. • Present in upward direction, in all leads except (aVR).	• (Pardee sign) ST elevation has convex shape in upward direction. • T wave inversion

- Echo
  - Presence of pericardial fluid ++.

Investigation of choice:

- CBNAAT or GENE EXPERT testing of pericardial fluid
- ECHO guided cardiac paracentesis.

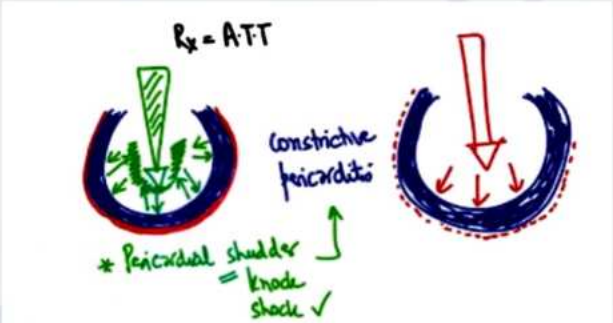
Treatment:

- ATT for 6 months.

Post treatment complication 00:40:42

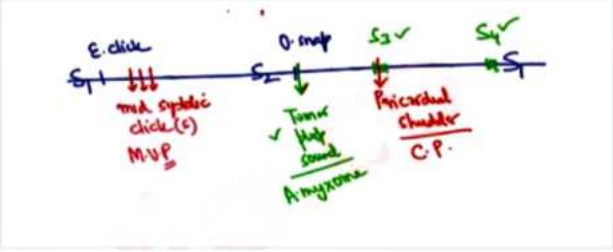
After treatment there might be development of calcification which can lead to:

Constrictive pericarditis



- It develops after ATT course
- This produces another cardiac auscultatory finding known as:
- Pericardial shudder is a diastolic phenomenon.
  - Also known as pericardial shock/knock
  - This sound is heard after the opening snap and can mimic the 3rd heart sound.

Summary 00:45:57



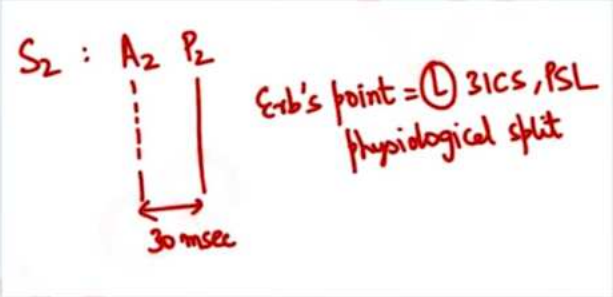
Important Information

- S4 is also known as Presystolic heart sound.
- Mid systolic click is seen in Mitral valve prolapse.
- Tumor plop sound is seen in Atrial Myxoma.
- Pericardial shudder is heard in constrictive pericarditis.

4 HEART SOUNDS PART 2

S_2

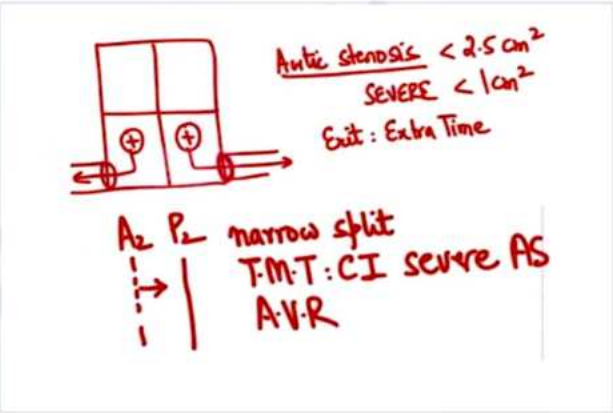
- Heard by the closure of the aortic & pulmonic valves
- S_2: A_2 P_2



- Time lag between closing of Aortic & pulmonic valve is 30msec which is called as splitting.
- Erb's point- is the point where splitting is best heard
  - It is on left side 3rd intercostal space on the parasternal line
  - Splitting is best heard in the phase of inspiration
  - It is referred as physiological splitting and it varies with respiration
  - If duration is <30msec: Narrow split heart sound
  - If duration is >30msec: Wide split heart sound

Aortic Stenosis

- Aortic stenosis < 2.5 cm^2
- Severe < 1 cm^2 or 0.6 cm^2 / m^2 of body surface area
- Blood exit will take extra time
- Normal size of aortic valve: 2.5-4cm^2



- Narrow split S2 is heard in Aortic stenosis
- Blood will take extra time to go out
- Exercise is not recommended in these patients
- Treadmill test is contraindicated

Treatment

- Aortic valve replacement
  - If Aortic valve replacement is not done the orifice will become narrower and narrower, and at one point if treatment is not done the aortic and pulmonic valve will close at the same time
  - If both valves will start closing at the same time, it is called single S_2.
  - If aortic valve closure occurs after the pulmonic valve closure, then it is called reverse splitting of second heart sound or paradoxical split.
  - $P_2 \rightarrow A_2$.

Important Information

- Reverse splitting of S_2 represents maximum severity of valvular aortic stenosis.
- Mitral stenosis severe <1.5 cm^2

Causes of Aortic Stenosis

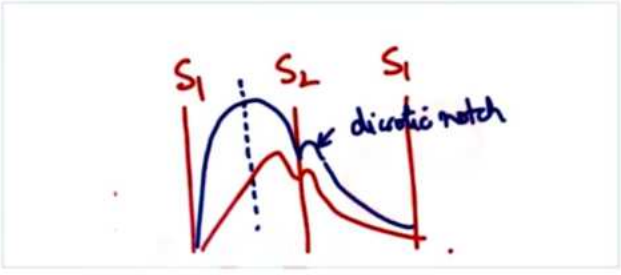
00:08:15

- Infants: Bicuspid aortic valve
- Children: Rheumatic fever
- >65 years: Degenerative senile calcification

Clinical Findings

- **S** - Syncope on exertion
- **A** - Angina: Subendocardial Ischemia compensatory left ventricular hypertrophy
- **D** - Dyspnea: Left ventricular end diastolic pressure

Examination findings



- Red line (case of aortic stenosis)
  - Slow rise pulse
  - Because of physical obstruction, peak is also delayed
  - Less Amplitude

This is called pulses parvus et Tardus also known as Anacrotic pulse

Important Information

Dicrotic pulse is seen with Dilated cardiomyopathy
Anacrotic pulse is seen with Valvular aortic stenosis and is also called as Pulses Parvus et Tardus

- Pulse pressure will be less because systolic blood pressure will be reduced
- Heaving apex beat (due to compensatory Left Ventricular Hypertrophy)
- Double apical impulse
- Presence of Carotid thrill

Important Information

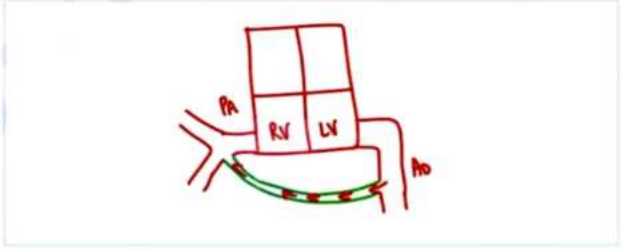
- Dancing carotids: Aortic Regurgitation
- Carotid thrill: Aortic stenosis

- Ejection systolic murmur intensity peak in the middle and then downfall.
- Also known as Crescendo-decrescendo murmur
- S_2: Narrow /single/ paradoxical
- S_4 present

Investigation of Choice

- TTE (Transthoracic echocardiography)
  - Shows the size of the reduced orifice
  - Ejection velocity >4m/sec
  - Transvalvular gradient (LV_P-AO_P) >40mmHg

PDA (Patent Ductus Arteriosus) 00:21:02



Causes

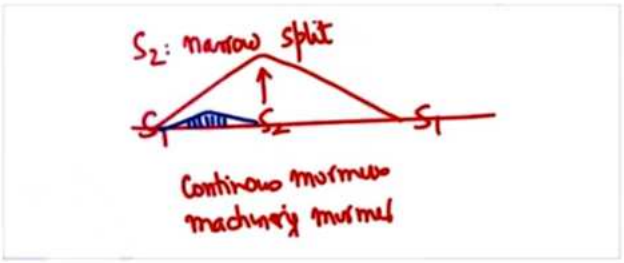
- Preterm baby
  - Hypoxia produces PGE_2 which causes patent ductus arteriosus
- Term baby
  - Congenital Rubella syndrome

Clinical presentation in orange colour

- Left to Right Shunt
- Left Ventricular Failure
- Exit of blood take extra time than normal
- Aortic valve will close later
- Narrow split S_2 second heart sound
- Preterm: symptomatic at birth
- Term: at 6-8 weeks
- Efforts intolerance (breathlessness on feeding)
  - Sweating on forehead
  - Irritable

O/E

- S_2: Narrow split



- Increased risk of Necrotizing enterocolitis

IOC

- Transthoracic Echocardiography

Treatment

- Indomethacin / Ibuprofen
- Term: Surgical ligation
- 1/year old with PDA
  - Surgical Ligation

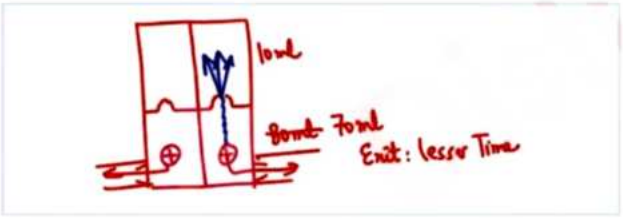
Conditions with narrow split S2 heart sound 00:30:16

- Aortic Stenosis
- Hypertrophic Obstructive Cardiomyopathy / Sub valvular AS
- Left Ventricular Failure:
  - Ant wall MI
  - Coxsackie B myocarditis
  - Wet Beri Beri
  - Severe anemia
  - PD

Mitral valve regurgitation 00:32:30

- Blood shunting from left ventricle To Left atrium
- Less blood will go from heart

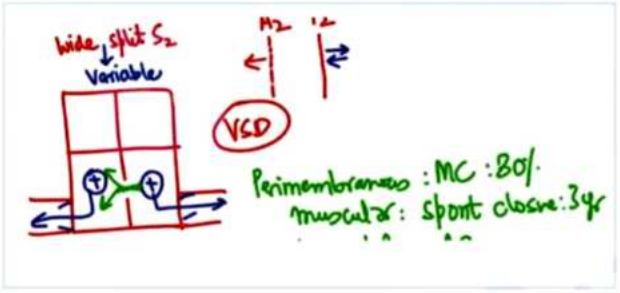
- Exit of blood will take lesser time
- A_2 will move to left, gap will be increased, Wide split sound S2



- Duration between A_2 & P_2 > 30msec

VSD (Ventricular Septal Defect) 00:34:46

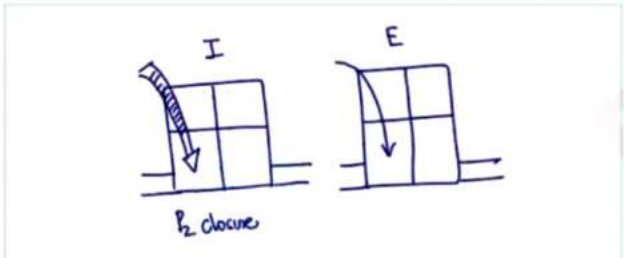
- Shunt from Left Ventricle to Right ventricle
- Less blood will go from heart
- Exit of blood will take lesser time
- Wide split sound



VSD Types

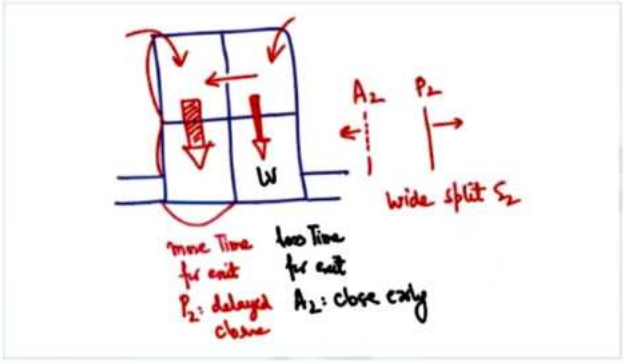
3 Types: 00:36:08

- **Peri membranous**
  - Most common (80%)
- **Muscular**
  - Spontaneous closure by 3 years
- **Supracristal**
  - Worst prognosis, associated with Aortic regurgitation
  - Normally P2 closure varies with inspiration & expiration
  - So wheather its Ventricular septal defect or mitral regurgitation
    → A2 will be early
    → P2 will oscillating with respiration (wide variable split S2 sound)



Atrial Septal Defect 00:40:05

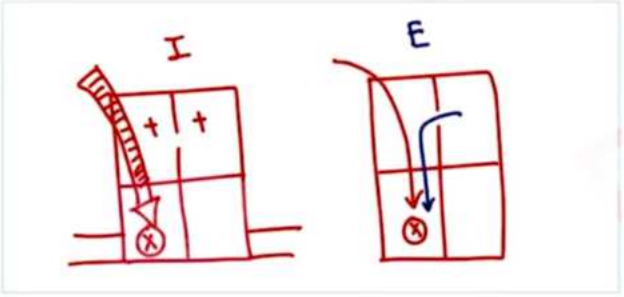
- Low pressure shunt
- Right Ventricle will have volume overloading
- More blood will take more time to exit
- P_2 will be delayed
- A_2 will close early
- Wide fixed split S_2 sound



During Inspiration

- More blood will be coming because during inspiration negative pressure will be created and send more blood into the chest cavity.
- No pressure difference.
- No shunting during inspiration

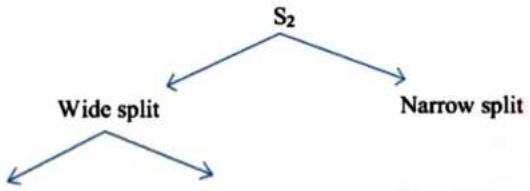
Shunting will occur only during expiration.



- Amount of blood coming will be lesser during Shunting

Important Information

- Normal person: Amount of blood coming in expiration & inspiration is differential
- Atrial Septal Defect: amount of blood coming in expiration & inspiration is same
- In normal person
  - P_2- delayed in phase of inspiration
  - P_2- earlier during expiration
- Atrial Septal Defect patient - fixed

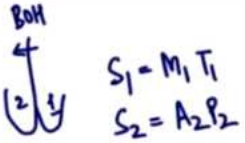


Types of ASD

1. **Ostium secundum** most common
2. **Ostium Primum / AV canal defect / endocardial cushion defect**
3. **Sinus venosus**

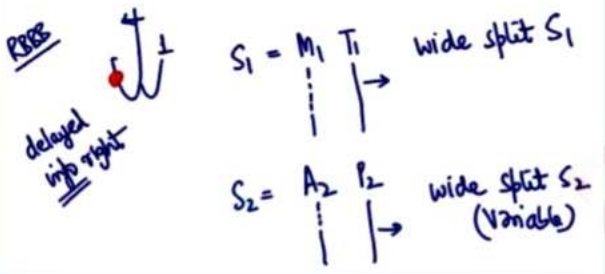
Bundle of His

00:49:24



- Refractive period of both fasicles are totally different
- Current first goes to left vesicle and then right fasicle
- So mitral valve will close first in S_1
  $S_1 = M_1 T_1$
- Similarly, Aortic valve will close first
  $S_2 = A_2 P_2$

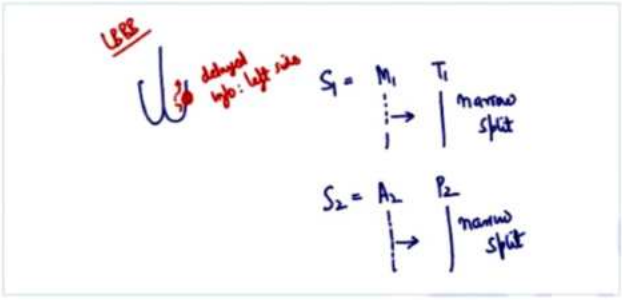
Right Bundle Branch Block



- Delayed information to the right-side valves
- Wide split S_1
- Wide split S_2 (variable)

Left Bundle Branch Block

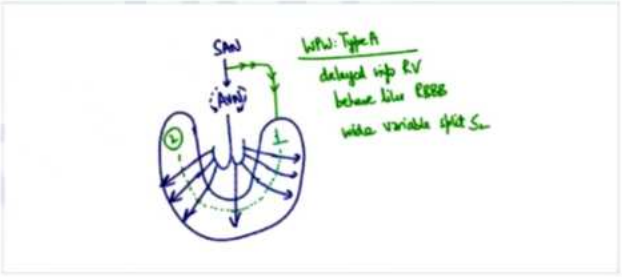
00:53:05



- Delayed information to left side
- Mitral valve closing late
- Less gap
- Narrow split S1 and S2

Wolf Parkinson White Syndrome WPW Type A

00:55:10



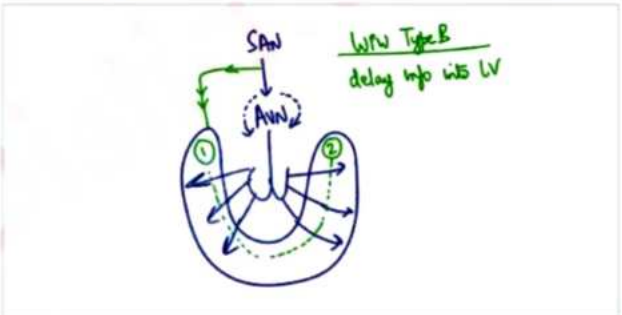
- Bundle of Kent is bypass conduction tract
- Current bypasses AV node

WPW: Type A

- Delayed information to Right Ventricle
- Condition will behave like Right Bundle Branch Block
- Left Ventricle will activate first, and Right Ventricle will activate later
- Wide variable split S2

WPW: Type B

00:57:28



- RV will activate first
- Current will not enter purkinje fibers
- Delayed information into Left Ventricle
- Behaves like Left Bundle Branch Block
- Narrow split S_2

5 HEART SOUND 3

00:00:20

- FIRST HEART SOUND S_1 = MITRAL AND TRICUSPID VALVE ($M_1 T_1$) CLOSURE
- Intensity ∝ speed of closure valve.

Loud S1

- Loud S_1 denotes Tachycardia
- PR ∝ 1/HR

Causes:

1. Short P-R interval
2. Congestive Heart Failure
3. Pheochromocytoma
4. Thyrotoxicosis
5. Severe anemia

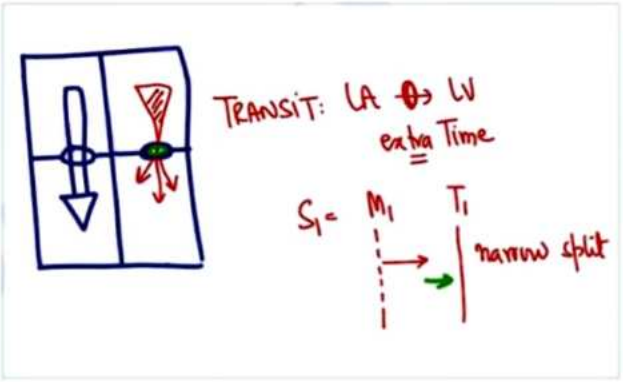
Physiological

6. Children / pregnancy

Mitral Stenosis 00:03:20

- There is a physical obstruction that leads to increase in left atrial pressure. This leads to
- Transvalvular gradient ↑
- Faster opening of mitral valve
- Faster elastic recoil of mitral valve
- Mitral Stenosis & Tricuspid Stenosis → Loud S_1

Calcified Mitral stenosis/tricuspid stenosis → Elastic recoil decreases → Soft S_1



Variations in S1 with respect to Mitral Stenosis

- Narrow split S_1
- Single S_1
- Reverse Split S_1
- Loud S_1
- Soft S_1 (due to calcification of valve)

Soft S1

Causes

1. Prolonged P-R interval
2. Hypothyroidism
3. SAN #: Sick sinus syndrome / sinus exit block
4. AVN #: 3rd degree Heart block
5. BOH #: Mobitz II Heart block
6. Inferior Wall MI

- Morbid obesity (Fat in chest wall) / emphysema (Air trapping), reduced transmission through stethoscope
- Calcified Mitral Stenosis / Tricuspid Stenosis (Due to reduced elastic recoil)
- Mitral Regurgitation / Tricuspid Regurgitation

00:13:50

S3 Ventricular Gallop Rhythm	S4 Atrial Gallop Rhythm
Early diastolic sound	Late diastolic sound
Rapid Ventricular filling in dilated ventricles	Outflow tract obstruction [LVH / LAH]
1. Congestive heart failure, myocarditis	1. AORTIC STENOSIS: Left sided S_4
2. DCM	2. HOCM: Left sided S_4
3. COPD: Cor pulmonale	3. HTN (Long standing): Left sided S_4
4. Pulmonary embolism - Acute cor pulmonale	4. Pulmonic stenosis: Right sided S4
5. Chronic M.R (severe)	
Cor pulmonale means RVF due to Non- Cardiogenic causes	5. PAH: Right sided S_4

Important Information

Atrial fibrillation

- P wave absent (ECG)
- a wave absent (JVP)
- S_4 Absent

JVP

00:25:42

- Jugular venous pressure: Preferably checked in Internal jugular vein.
- 5-8 cm H_2O from angle of Louis. Pulsations seen, JVP frequency → 2x carotid frequency

- Indicates the status of right sided heart
- JVP raised in Right ventricular failure.
- On deep Inspiration, JVP falls, and it is normal
- In constrictive pericarditis, on deep inspiration JVP rises and compliance of heart decreases.
- If JVP rises on deep inspiration it is called Kussmaul sign

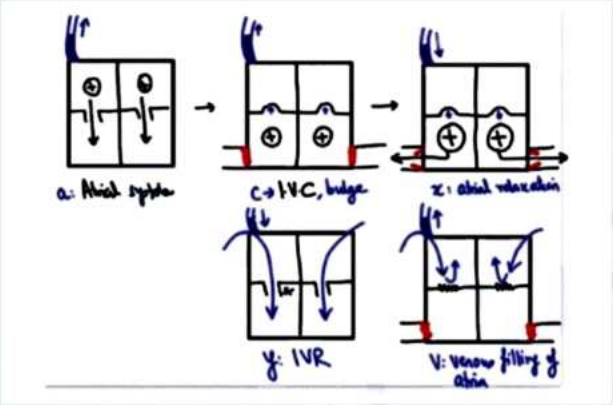
Causes of Kussmaul sign (CRR)

1. Constrictive Pericarditis (Calcification)
2. Restrictive Cardiomyopathy (Fibrosis)
3. Right Congestive Heart Failure (Inferior Wall MI / Pulmonary Embolism / COPD)

Extra Mile:
Non pulsatile elevated JVP seen in cardiac tamponade and Superior Vena Cava thrombosis

JVP Waves

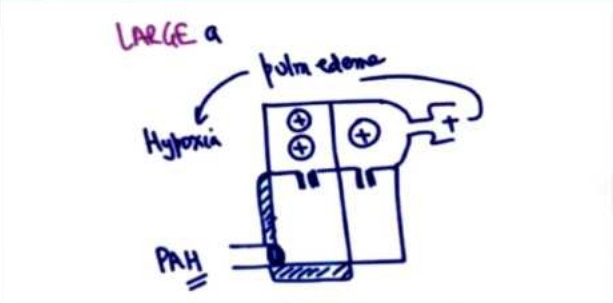
00:33:05



- A: Atrial systole
- C: Isovolumetric contraction, bulge
- X: Atrial relaxation, ventricular systole
- V: Venous atrial filling
- Y: Isovolumetric relaxation

Large 'A' Wave in JVP

00:47:55



1. Tricuspid Stenosis
2. Pulmonic Stenosis
3. Mitral Stenosis (Long standing)
4. Pulmonary artery hypertension → **Seen in:**
   - Scleroderma
   - Fenfluramines
   - Eisenmenger syndrome/ complex
5. Tetralogy of Fallot (Subpulmonic stenosis)
6. Ebstein Anomaly

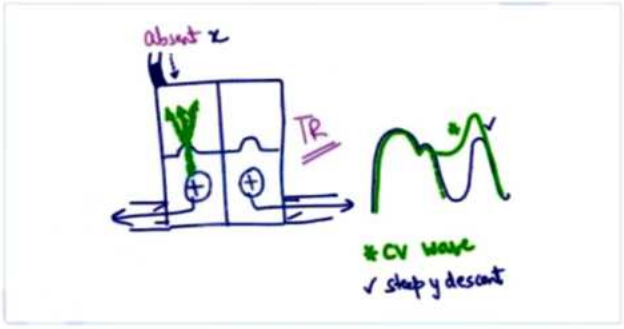
- Absent 'a' wave seen in Atrial fibrillation (Twitching)

Giant 'A' / Canon 'A' Wave

00:53:30

Seen in Atrio-ventricular Dissociation

1. Ventricular tachycardia
2. Complete Heart block (3rd degree Heart block)
3. Junctional Tachycardia (Retrograde P wave)



- Absent X descent
  - Seen in Tricuspid regurgitation
- CV wave
  - Seen in severe tricuspid regurgitation
  - Steep 'y' descent
- Absent Y descent
  - Seen in absent ventricular filling due to cardiac Tamponade

Cardiac Tamponade

01:00:00

During Obstructive Shock

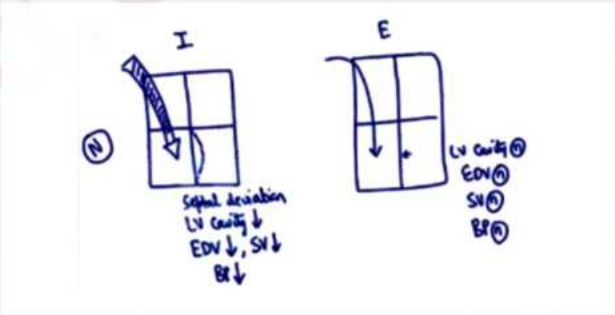
- Reduced ventricular filling, systolic volume reduces

- Cardiac output decreases
- BP decreases
- TREATMENT-Echocardiographic guided pericardiocentesis.
- Pulse will disappear during phase of inspiration
  - Called as pulsus paradoxus

Low Pressure Cardiac Tamponade

- Pulse will be weak but will not be absent
- Only atria are getting affected and they can not contribute to ventricular filling.
  - Input to heart reduced
  - BP will fall (approximately 30%)

Normally



- BP falls on inspiration because of physiological septal deviation
- During expiration BP becomes normal as septal deviation revert back
- Difference between inspiratory and expiratory BP will be <10mm/hg

In Cardiac Tamponade

- There will be exaggerated septal deviation and left ventricular cavity decreases
- End diastolic volume Systolic volume decreases
- And then BP decreases

- Difference between inspiratory and expiratory BP will be >12mm/Hg called as pulsus paradoxus
- $S_1 S_2$ muffled
- JVP, absent 'y' descent, non-pulsatile

Important aspects related to JVP 01:15:42

- Large 'a' wave seen in pulmonary artery hypertension, tricuspid stenosis
- a' wave absent in atrial fibrillation
- Canon 'a' wave seen in ventricular tachycardia/ junctional tachycardia/ complete heart block or atrio ventricular dissociation
- Absent 'x descent' is seen in tricuspid regurgitation
- cv' wave seen in exaggerated tricuspid regurgitation
- Steep 'y' descent seen in tricuspid regurgitation
- Absent 'y' descent seen in cardiac tamponade
- Steep 'x' and steep 'y' seen in constrictive pericarditis (pericardial shudder)
- Steep 'x', absent 'y' - Cardiac tamponade.
- Non pulsatile elevated JVP: seen in superior vena cava pathology and hemo pericardium (cardiac tamponade).

Important Information

- Pulses Paradoxus absent in low pressure cardiac tamponade

6 MITRAL VALVE PROLAPSE

Mitral Valve Prolapse (MVP) 00:00:16

Also called Floppy valve syndrome or Barlow syndrome

- Valve will be bulging in upward direction

- During this exaggerated bluge there is a possibility that between these defective valve leaflets, there might be leakage of blood from Left Ventricle to Left Atrium.
- This will contribute to development of murmur called Late systolic murmur

Highlight of disorder

- Slack or Loose Chordae tendineae
  - The papillary muscles must do extra work to keep infrastructure intact to prevent leakage of all the Left Ventricular cavity blood going into Left Atrium
- Defective coaptation of valve leaflets
  - Valve leaflets gets separated, variable amount of blood leaks
- In the later stages of the same disease, dilation of mitral valve annulus occurs
- This can get converted into frank mitral regurgitation

Important Information

- Most Common Cause of Mitral Regurgitation is Mitral valve prolapse

Causes 00:02:55

1. **Myxomatous degeneration of Mitral Valve apparatus**
2. **Marfan syndrome**
   - Chromosome 15 defect
   - Fibrillin-1 protein defect
3. **Ehler Danlos Syndrome**
   - Hyper extended joints
4. **Osteogenesis imperfecta**
5. **Antero posterior diameter decrease**
   - Thoracic kyphosis reduced: term used: pancaking of the heart (heart is compressed between the sternum and the vertebra)
   - Called straight back syndrome

Important Information

- Straight back syndrome – space available for the heart between the sternum and vertebra is substantially reduced, Antero-Posterior diameter becomes lesser.
- Barrel Chest in Emphysema where the AP diameter is symmetrically or disproportionally increased as compared to normal individual.

6. **Rheumatic fever** : Aschoff nodules
7. Subacute bacterial endocarditis (SABE), infective damage to chordae tendineae
8. Dilated cardiomyopathy: in this mitral annulus will be dilated
9. **Ostium Secondum (Atrial Septal Defect)**
   - If patient having loose chordae tendineae, papillary muscle will be working more than normal
   - Then in Long term it will cause subendocardial ischemia
   - Which causes substernal chest pain and palpitations

00:11:10

Pathophysiology

A. **Defective Coaptation of mitral valve leaflets**
B. **Lax chordae tendineae**

Clinical features 00:13:33

- More in females 15-30 years
- Males 50 years
- Severity is more in men as compared to women

1. Asymptomatic initially - Most Common
   - No leakage of blood from high pressure chamber to low pressure chamber.
2. Palpitations due to (Premature Ventricular Contraction) most commonly seen on ECG
3. Recurrent Syncopal attacks due to PVC

Important Information

- Most Common rhythm disorder in ECG of MVP patients is PVC (premature ventricular contraction)

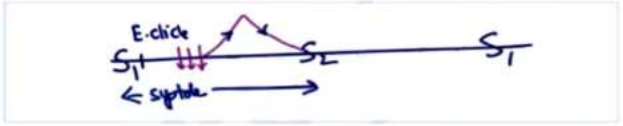
- Ventricular tachycardia (≥3 Premature ventricular contractions and heart rate > 100 bpm)

- Structural damage to Left atrium can trigger (Atrial fibrillation, that cause variable R-R interval & absent P waves.

4. Substernal chest pain without exertion (due to subendocardial ischemia).
5. Transient Ischemic attack events
   - Valvular endothelium damage
   - Miniature platelet plugs on the valve can go the circulation and can cause Transient ischemic attack
6. Increased risk of Infective endocarditis
7. Sudden cardiac death risk increase
8. Mitral regurgitation causing acute decongestive heart failure
   - Frank Pulmonary edema develops

Examination Finding 00:20:30

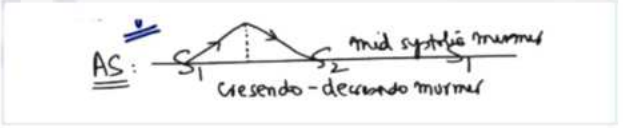
1. **Mid systolic clicks**
   - Tension in slack chordae tendineae due to



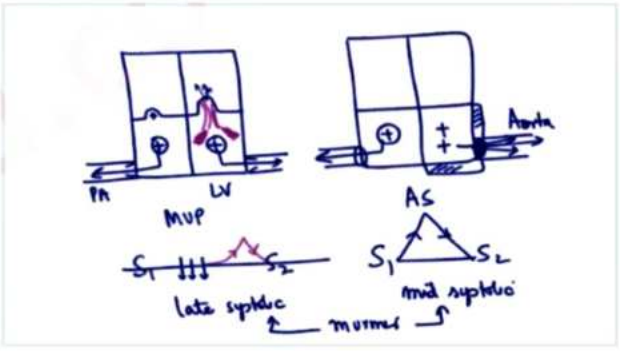
2. **Late systolic murmur**

or

Late systolic crescendo-decrescendo murmur



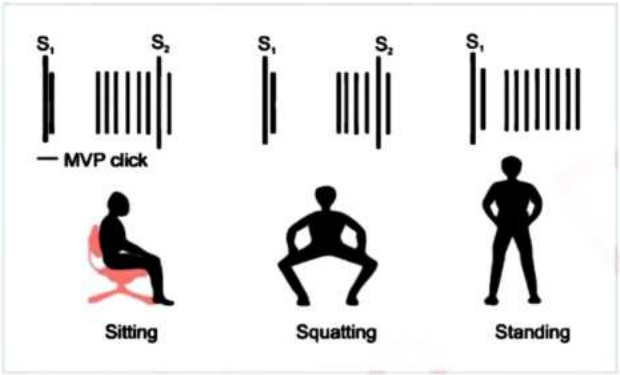
MITRAL VALVE PROLAPSE	AORTIC STENOSIS
• Murmur starts after mid systolic clicks	• Turbulence will be felt during the phase of systole
Late systolic murmur	Mid systolic murmur



- Posterior leaflet invovement more incidence than Anterior leaflet
- If posterior leaflet affected Jet of blood moves anteriorly and Murmur radiation to base of heart
- If anterior leaflet affected Jet of blood moves posteriorly and Murmur radiation to axilla (Mitral regurgitation murmur also radiates to axilla but the murmur heard is pan systolic murmur)

Position

- On standing Venous return to heart decreases, prolapse increases and Duration of murmur increases
- On squat Duration of murmur decreases
- Prolapse $\alpha \frac{1}{\text{Volume of blood in ventricle cavity}}$

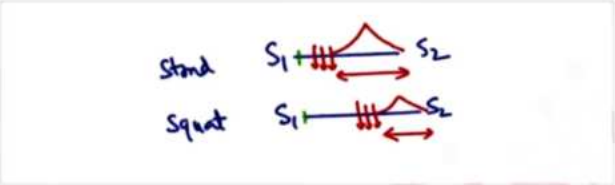


- On standing, venous return decreases, cavity size decreases, prolapse increases and the mid systolic click will occur early.
- On squatting venous return increases, so the cavity size increases, prolapse decreases and mid systolic click will occur late.

Important Information

All murmurs decrease with Valsalva & standing except

- Hypertrophic Obstructive Cardiomyopathy: Louder
- Mitral Valve Prolapse: Longer



Investigation of choice 00:37:06

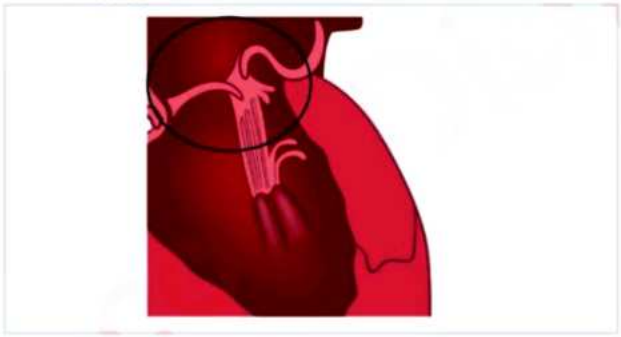
- TTE (Transthoracic echocardiography)
  - Bulge >2mm above mitral annulus
- TEE (Transesophageal echocardiography)
  - Provides more detailed anatomical information
  - Beneficial in Planning repair
- ECG
  - T wave inversion (lead II, III, aV_F)
  - Premature Ventricular Contraction: Most common abnormal rhythm
  - Cardiac MRI and Invasive left ventriculography can be done in case of Mitral Valve Prolapse.

Treatment 00:40:14

1. β-Blockers
   - Palpitation / chest pain
2. Atrial Fibrillation: $CHADS_2$ VASC score
   - Need for oral anticoagulation depends on these score values
3. Transient Ischemic Attacks-mild severity
   - Low dose aspirin
4. Mitral Valve repair > replacement
   - Transcatheter repair
5. Prophylaxis for infected endocarditis
   - If previous episode documented

7 MITRAL REGURGITATION

Mitral regurgitation



Causes of acute mitral regurgitation 00:00:40

1. Infective endocarditis/subacute bacterial endocarditis
2. Papillary muscle damage due to Myocardial Infarction
   - Most commonly involved leaflet is posterior leaflet > anterior leaflet.
3. Chordal rupture/ Flail leaflets (Myxomatous degeneration)
4. Blunt trauma to chest this can also cause Commotio cordis (leading to Ventricular fibrillation) causing "sudden cardiac death"

Causes of chronic mitral regurgitation 00:05:14

Primary:

- Intrinsic damage to valve
- Leaflets or chordae tendineae are diseased, structural damage

Causes

1. Mitral Valve Prolapse (myxomatous degeneration)
2. Aschoff nodules of rhematic fever
3. Infective endocarditis (healed variety)
4. Congenital cause: Cleft mitral valve due to ostium primum (Atrial Septal Defect)

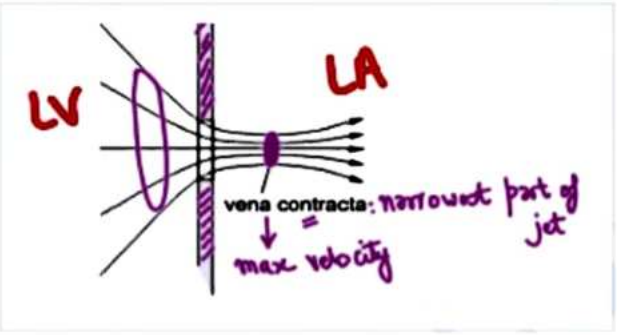
Secondary:

- Due to Annular dilatation of mitral valve (also known as functional dilatation).

Causes

1. Ischemic cardiomyopathy
2. Dilated Cardiomyopathy: Alcohol
3. Hypertrophic Obstructive Cardiomyopathy with (Systolic anterior movement of mitral valve)
4. In chronic atrial fibrillation, there is left atrial enlargement, and mitral valve annulus gets affected
   - Most Common characteristic finding occurring in secondary varieties: Mitral annular dilatation

Mechanism: 00:10:42



- Vena contracta – narrowest part of jet of blood is with highest velocity.
- Leakage of blood will be from Left ventricle to left atrium.

Criteria For Severe Mitral regurgitation 00:12:36

- Vena contracta: >0.7 cm
- Regurgitant volume: >60 ml / beat
- Regurgitant fraction: >0.5

Important Information

- Mitral valve prolapse has late systolic murmur
- Chronic mitral regurgitation has Pan systolic murmur
- Acute mitral regurgitation has early systolic murmur

Clinical Features 00:15:45

- Mild to moderate Mitral Regurgitation is well tolerated

In severe cases:

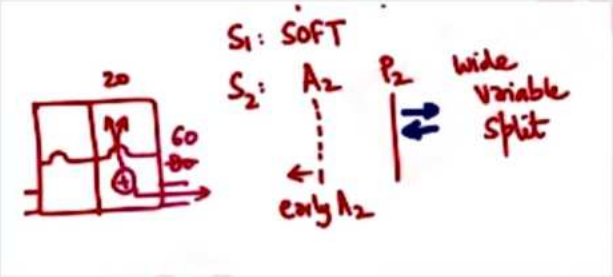
1. Exertional fatigue
2. PND (Paroxysmal nocturnal dyspnoea)
3. Orthopnoea
4. Ankle edema

On Examination 00:16:40

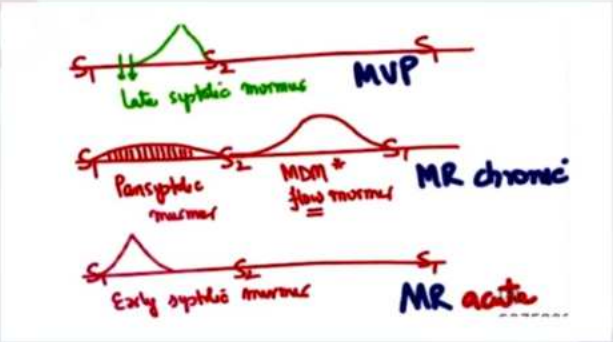
1. Blood Pressure Normal or decreased
2. JVP increased
3. Hepatomegaly due to CHF
4. Thrill present at apex on palpation(left ventricular failure, turbulence)
5. Hyperdynamic apex
6. Displacement of apex beat

Auscultation 00:18:30

- S_1 is Soft
- $S_2 = A_2 P_2$ (A_2 appears early)
  - Wide variable split S_2



- S_3 is present in chronic MR :-DCM, ICM , diastolic murmur heard – Mid Diastolic Murmur



- Chronic mitral regurgitation radiates to axilla
- Ejection systolic murmur is seen with Aortic stenosis (also known as Crescendo-decrescendo Murmur)
- Aortic stenosis murmur best appreciated at right upper sternal border and radiates to carotids.
- But vibration of cusps may radiate to axilla.
- It can mimic murmur of mitral regurgitation
- This is known as Gallaverdin phenomenon

Work Up 00:29:17

ECG

- P- Mitrale: >120msec (current will take more time, enlarged left atrium)

Chest X Ray

- Left Atrium enlargement leads to pushing of right atria leading to double atrial shadow/contour
- **Cardiothoracic** ratio increased leading to cardiomegaly (>0.5- adults, >0.6- children)
- Walking man sign on lateral view (Enlarged left atrium causing increase of carinal angle)

Transthoracic Echocardiography:

- Regurgitant jet going from left ventricle to left atrium

Treatment of Acute Mitral Regurgitation 00:32:15

It causes acute decompensated heart failure, which contribute to pulmonary edema

- Furosemide
- Sodium Nitroprusside

Treatment of Chronic Mitral Regurgitation 00:33:35

In severe variety:

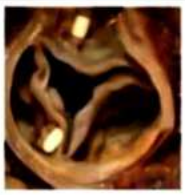
- Mitral valve repair (MVRp) is done
- **New technique is Mitra clip:** Applied with transcatheter approach
- Mitral valve repair is better than mitral valve replacement (MVR), (Prosthetic valve), as replacement requires lifelong anticoagulant therapy.
- These patients will have atrial fibrillation (due to structural damage)
  - Warfarin is used
- Majority of cases of rhematic heart disease will have mitral regurgitation, especially children
  - **Novel Oral Anticoagulants (NOAC) are contraindicated with rheumatic etiology.**

Extra Mile:

NOAC are contraindicated in:

1. Atrial fibrillation/ Mitral Stenosis/ Mitral regurgitation of rheumatic etiology
2. Mechanical metallic prosthetic heart valve

8 AORTIC STENOSIS




- Commonly seen in paediatric and senile age group

- There is difficulty in opening of aortic valve thus left ventricle develops concentric hypertrophy
- Pathology behind Aortic Stenosis:
  - Fibrosis
  - Calcification of valve
  - Congenital
- Most common congenital heart disease is Perimembranous variety of VSD
- Overall, most common Congenital heart Valvular lesion is Aortic Stenosis.

Causes 00:02:03

Paediatric presentation

1. **Bicuspid Aortic valve/ Unicuspid aortic valve**

- Unicuspid Aortic valve causes more severe disease and substantial left ventricular hypertrophy.

Old age/senile presentation

2. **Degenerative calcification**

- Associated with atherosclerosis
- Triple vessel disease can be present
- Fixed obstruction in multiple coronary arteries
- Episodes of chest pain.

3. **Rheumatic Fever**

- Combination of aortic valve lesion and mitral valve lesion usually seen.
- Presence of commissural fusion
- Development of aschoff nodules and concomitant fibrosis.

4. **Mediastinal irradiation**

- Chest radiotherapy given to a patient of Hodgkin's lymphoma for hilar lymphadenopathy
- Primarily it subsides lymphadenopathy but patient later develops aortic stenosis.

5. **Shone complex**

- Associated with Paediatric Aortic stenosis

Components of Shone complex

- Parachute mitral valve
- Supra valvular mitral membrane
- Sub valvular aortic stenosis
- Coarctation of aorta

Important Information

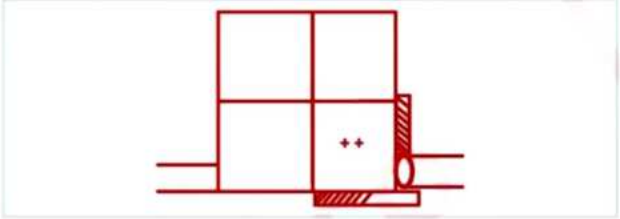
- Common heart lesion seen in patient of Turner syndrome → Bicuspid aortic valve (MC)> Coarctation of aorta
- HOCM is associated with SAM (Systolic Anterior Displacement of mitral valve)

Clinical Features of Aortic Stenosis 00:08:34

- Male and Female ratio is 2-4: 1
- Bicuspid aortic valve has Autosomal Dominant pattern of inheritance
- NOTCH 1 gene is associated with bicuspid aortic valve
  - Notch 3 gene is associated with small vessel stroke → Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
- In old age/ geriatric population Hypertension may lead to AS

Symptoms

- **Triad of Aortic Stenosis**
  - **S** - Syncope (On exertion)
  - **A** - Angina subendocardial ischemia (Secondary to Left Ventricular Hypertrophy)
  - **D** - Dyspnea (Secondary to increased left ventricular end diastolic pressure)
- Severe aortic stenosis is $< 1\ cm^2$
- $< 0.6\ cm^2/m^2$ BSA (Body Surface Area)



- Left ventricle end diastolic pressure (LVEDP) increases as a result of hypertrophy of left ventricle.
  - This leads to increased left atrial pressure
  - Congestion in lungs & pulmonary edema
  - Dyspnoea
  - Long standing pulmonary edema will cause pulmonary artery hypertension (PAH) and Hepatomegaly
  - Exercise intolerance worsened due to PAH.
  - PAH will cause right ventricle dilatation and functional tricuspid regurgitation (TR) can occur.
  - TR may produce pan systolic murmur

- Ejection systolic murmur (also known as crescendo decrescendo murmur)
  - Due to turbulence at level of aorta when blood goes out. This murmur may radiate to carotid artery and generates carotid thrill.

On Examination 00:19:38

1. Hypertension: Concomitant
2. Pulse pressure is low, Pulse Tardus et Paruus / Anacrotic pulse.
3. Apex Beat
   - heaving in nature
   - Is always displaced, Displacement to left side
   - Double apical impulse due to forceful non compliant left atrium contraction (Secondary to hypertrophy of Left Ventricle)
4. The murmur of Aortic Stenosis radiates to Carotid artery
   - known as Carotid Thrill
5. S2: Narrow split single S2 (Narrow, as gap between A2 & P2 is < 30 millisecond)
   - Reverse split/Paradoxical split P2 comes before A2 [Means pulmonary valve has closed on time but aortic valve is closing late, after the pulmonary valve]
6. S4: Present
7. Patient of Atrial Stenosis also have compensatory left atrial hypertrophy
   - Left atria generate more pressure to push blood into left ventricle.
8. Murmur: Ejection systolic murmur
   - Present at right upper sternal border
   - Radiate to carotid artery
   - Also Known as Crescendo - decrescendo murmur

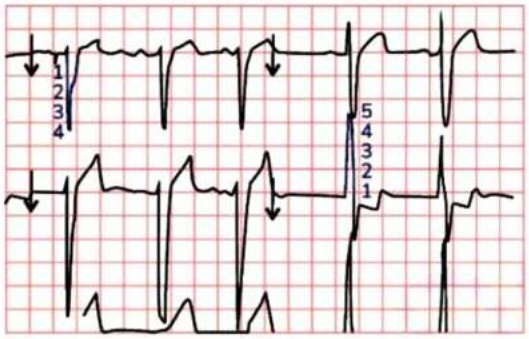
- Vibrations of valvular cusps, when blood passes from aortic annulus (narrowed opening), produces murmur, which radiates to the Axilla (mimics murmur of mitral regurgitation). This is known as Gallaverdin Phenomenon)
- This radiation into axilla can lead to confuse aortic stenosis with mitral regurgitation as murmur of mitral regurgitation also radiates to axilla

Important Information

- DANCING CAROTID seen in aortic regurgitation.

Work-Up 00:29:33

1. **ECG**
- LVH [(Sv1 + RV5/6)] ≥ 35 mm is the criteria to call it Left Ventricular Hypertrophy



2. **Chest X Ray**
- Cardio – Thoracic ratio in increased (↑ CT ratio)
3. **Transthoracic Echocardiography**
- Used to see valvular morphology

Valve size	Grade Of AS
< 1.5 – 2 cm^2	Mild AS
< 1.0-1.5 cm^2	Moderate AS
< 1.0 cm^2	Severe AS

- Treadmill test and stress ECHO are contraindicated with severe aortic stenosis
4. **Coronary Angiography**
- to check fixed obstruction in coronary arteries.
5. **CT Chest**
- Helps in anatomical reconstruction of valve, checks calcification.
6. **Cardiac MRI**

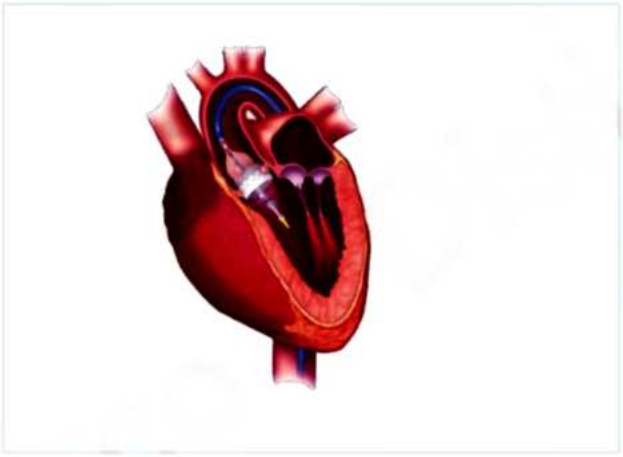
Death In Patients of Aortic Stenosis 00:35:42

- If syncope/angina is present as a symptom, death within 3 years
- If dyspnea is present as a symptom, death within 2 years
- If Congestive Heart Failure (CHF) Present, death in 1.5-2 years

Important Information

- Highest chances of death seen in patients with Congestive Heart Failure (CHF)

Treatment of Valvular Aortic Stenosis 00:37:34



- Hypertension:
  - ACE inhibitors
  - Beta blocker

Severe aortic stenosis

- Avoid competitive sports
- Avoid dehydration

Statins

- Statins are given to prevent further progression of Atherosclerosis & thus Triple Vessel Disease

Stages of Aortic Stenosis

Stage A

- Risk factors present
- No narrowing of valve

Stage B

- Mild to moderate aortic stenosis but patient is Asymptomatic.

Stage C

- Severe aortic stenosis but patient is asymptomatic

Stage D

- Severe aortic stenosis & patient is symptomatic

Treatment For stage D: Trans catheter aortic valve replacement (TAVR)

For stage C

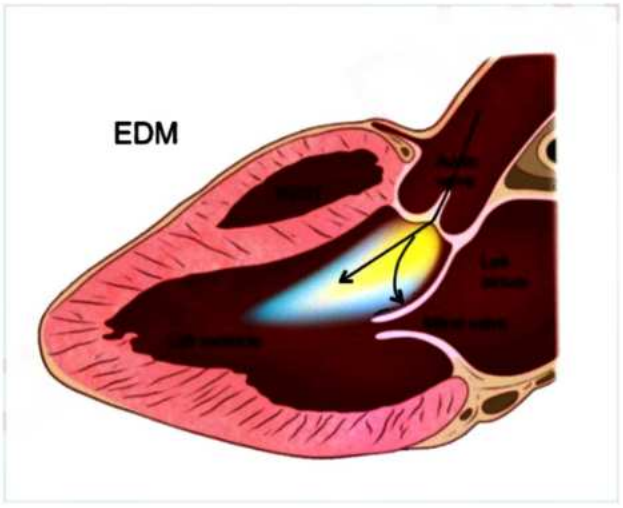
- If patient has concomitant risk factors like
  - Concomitant Triple Vessel Disease (TVD)
  - Left ventricular ejection fraction < 50%
  - Ejection velocity >5m/sec.
  - Transvalvular gradient (LV-AORTA) >60mmHg.
- Treatment is Trans catheter aortic valve replacement (TAVR)

Important Information

- Statins are given to prevent further progression of Atherosclerosis & thus Triple Vessel Disease
- Statins donot prevent further progression of calcification.

9 AORTIC REGURGITATION

00:00:10



- Incompetent aortic valve
- Early Diastolic murmur due to Turbulence
- Blood hit the anterior leaflet of mitral valve and vibrations are produced
- This produce Mid diastolic murmur called as Austin Flint murmur

Causes Of Aortic Regurgitation (AR)

00:01:32

1. Bicuspid aortic valve: Defective coaptation
2. Infective Endocarditis: Perforation in valve cusps
3. RHD (Rheumatic Heart Disease), thickening and shortening of valve of cusps
4. Myxomatous degeneration of valve
5. Syphilis: scarring of valve.
6. Ankylosing spondylitis, HLAB27 positive
7. Aortic root dilation
   - Aortitis Takayasu
8. Aortic dissection
   - HTN
9. Cystic medial necrosis
10. Marfan syndrome

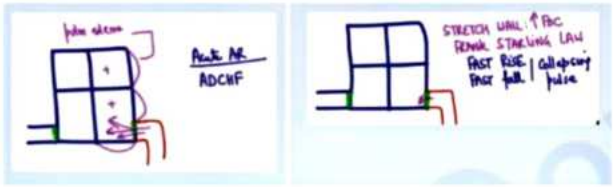
Echocardiographic Criteria To Identify

Severe aortic regurgitation (AR)

- When regurgitant volume > 60 mL/beat
- Or regurgitant fraction >50%
- Diastolic flow reversal in descending part of thoracic aorta

Progressive AR

- Left Ventricle Ejection Fraction < 50%
- Left Ventricle End systolic dimension LVESD > 50 mm
- Left Ventricle End diastolic dimension LVEDD > 65 mm



Acute presentation	Chronic presentation
(Infective Endocarditis)	Pulse → Corrigan's pulse / water hammer pulse

In Aortic Regurgitation, both Pre-load & After-load are increased

- Increased Oxygen consumption

Angina

- Mismatch between demand & supply of oxygen
- Nitrates response will be limited

Eccentric hypertrophy develops

- Left ventricular Cavity size increases

Clinical Features

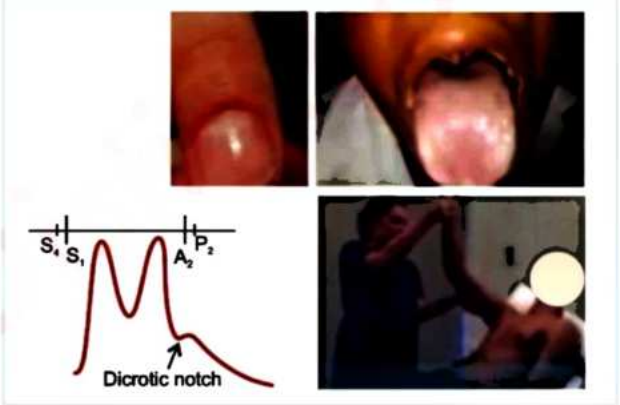
00:18:26

Latency period is 10-15 years

1. Uncomfortable sensation in supine position
2. Head pounding sensation
3. Development of exertional dyspnea
4. Paroxysmal nocturnal dyspnea
5. Orthopnea
6. Angina may be present at rest or on exertion
7. Ankle edema is seen with right heart involvement

Examination Findings

00:22:00



- De-Musset Sign: Head bobbing, to and fro
- Muller sign: Pulsation of uvula
- Ankylosing spondylitis HLA B27 positive, Modified Schober's test is used
- Corrigan's pulse / Water hammer pulse/Collapsing pulse
  - According to Frank Starling law, as end diastolic volume of LV increases, the force of contraction of LV increases. Seen on arm elevation above level of head.
- Marfan's syndrome: Arachnodactyly (Thumb Sign)
- Traube Sign: Pistol shot sounds heard at femoral artery
- Duroziez Sign: Gently press the femoral artery using stethoscope
- Quincke's sign: Flushing and blanching at root of nail
- Systolic blood pressure increased because Stroke Volume increased
- Diastolic Blood Pressure decreases and aortic recoil decreases.

Pulse Pressure

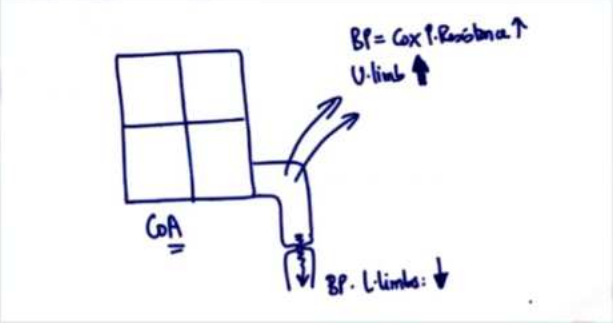
160/0, diastolic blood pressure is not 0 but the Korotkoff sound is perceived till the end, so in these patients do not wait for Korotkoff sound to disappear but check when they become muffled.

Extra Mile:

Low DBP Because of Persistent Korotkoff Sound Might Be Seen With Following

- Atrio Ventricular malformation
- Aortic regurgitation
- Atrio Ventricular fistula

- BP difference between Upper limb (UL) and lower limb (LL) < 20 mm of Hg (N)
- BP difference > 20 mm of Hg is abnormal and is called as Hill sign
- In coarctation of aorta, BP of UL is increased & BP of LL is decreased

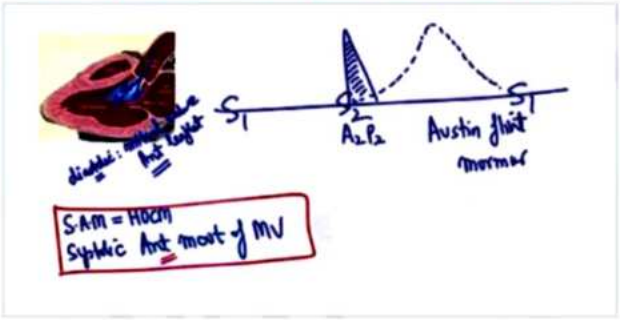


- Apex beat of Heaving character, displaced (6th intercoastal space)
- Thrill (Auscultation) felt in phase of diastole, perceived at left lower sternal border
- Systolic thrill heard at Suprasternal notch.
- In S2, A2 component is soft.
- Ejection click is present if bicuspid aortic valve is present
- S4: present: Left atrial hypertrophy

Murmurs of Aortic Regurgitation 00:36:52

- Diastolic anterior movement of mitral valve
  - Contribute to mid diastolic murmur

- Austin Flint murmur → Mid Diastolic Murmur (MDM)



- Early Diastolic murmur: Main murmur
- Mid Diastolic murmur: Austin Flint murmur (RHD), due to vibrations in anterior leaflet of mitral valve
- Ejection systolic murmur: Frank starling law, eccentric hypertrophy.
- Gerhardt's sign: Pulsation in spleen
- Rosenbach sign: Pulsation in liver
- Landolphi sign: Pulsations in pupil

Important Information

- ECHOCARDIOGRAPHIC CRITERIA OF HOCM:-
  - S.A.M(systolic anterior movement of mitral valve).
- PULSATION IN LIVER :- seen in Tricuspid stenosis
  - Tricuspid regurgitation
  - Aortic regurgitation
- TRAUBE SPACE - Spleen ++
- ROSENBACH SIGN :- GRAVE'S DISEASE :- Eyelid tremors.

Work Up 00:43:48

ECG

- Left axis deviation
- Left ventricle enlargement
- SV1 + RV5/6 > 35mm

Chest x ray

- CT Ratio > 0.5
- Left ventricular apex: Inferolateral displacement

Echocardiography

Investigation of choice

Severe AR

- **Criteria**
  - Regurgitant volume > 60/ beat
  - Regurgitant Fraction > 50%

Treatment 00:45:05

Acute AR

- Acute AR with acute decompensated congestive heart failure (ADCHF)
  - Loop diuretics : Furosemide
  - Vasodilator: Sodium Nitroprusside
- IABP: Intra-Aortic Balloon pump is Contraindicated, it worsens AR
- Beta blockers are contraindicated in ADCHF and Surgery should be done <24 hours.

Chronic AR 00:47:26

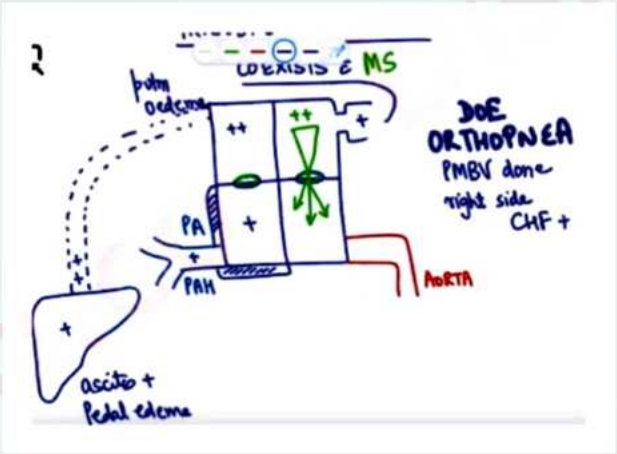
- Keep SBP < 140 mm of Hg
- Nitrates: To treat angina
- Benzathine penicillin → 2.4 MU IM x 3 shots @ 1 week gap
  - Used For cardiovascular syphilis
- Beta blockers may be used in Chronic AR
- Sx:- AORTIC VALVE REPLACEMENT
  - In severe AR, If patient is symptomatic.
  - In progressive AR, If patient is asymptomatic.

Important Information

- β-blockers → absolutely contraindicated in acute AR
- β-blockers can be given in chronic AR
- Early diastolic murmur of AR heard better on Sitting up/ leaning forward.
- In Mitral stenosis murmur is heard better on left lateral decubitus position.

10 TRICUSPID STENOSIS

Tricuspid Stenosis 00:00:10



- Tricuspid stenosis occurs with Mitral stenosis
- Coexistence is due same etiology of Rheumatic fever.
  - So, the amount of blood entering Left Ventricle is reduced.
  - Symptom of effort intolerance occurs
- Most patients would have structural damage to Left Atrium

This will lead to:

  - Development of pulmonary artery hypertension
- Pulmonary edema, dyspnea on exertion
  - Compensatory right ventricle hypertrophy
  - Diastolic pressure of right ventricle is increased
- Tricuspid stenosis prevents the transmission of pressure changes in backward direction because the orifice is relatively narrow.
  - Tricuspid stenosis acts like barrier

Chief complaints:- 00:02:10

- Dyspnea on exertion
- Orthopnea (due to pulmonary edema)

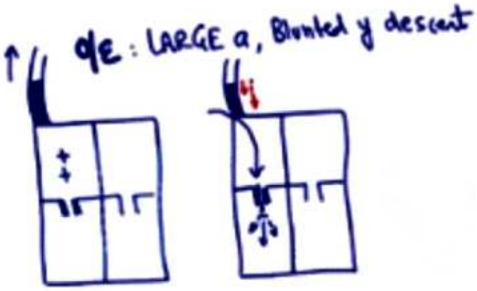
Percutaneous mitral balloon valvotomy was done .Later patient develops right sided congestive heart failure, congestion of superior vena cava, Inferior vena cava. As a result, hepatomegaly develops

- Persistent abdominal fullness
- Pain in right upper quadrant
- Ascites
- Pedal edema

If not treated cardiac cirrhosis can occur.

On Examination 00:04:51

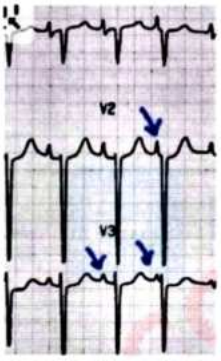
1. Large a waves



2. Presystolic Pulsations of liver
3. Mid diastolic Murmur louder on inspiration
   - Heard on Left lower sternal border
4. Isolated tricuspid stenosis results in large a wave and blunted y descent

Work Up 00:11:14

1. ECG



- Large P wave: P- pulmonale (Peaked P-wave)
  - Limb leads >2.5mm
  - Chest leads >1.5mm
- Right axis deviation

2. ECHO

- Thickened tricuspid valve. Severe if $<1\ cm^2$
- Transit Time >190 msec.
- Mitral Stenosis, severe if $< 1.5\ cm^2$

3. **Chest X Ray**
- Right Atrial enlargement
- Superior Vena Cava prominent
- Shadow of Azygous vein enlarged

Treatment 00:14:00
- Salt restricted diet
- Diuretics
- Valve repair (Main treatment)
- Prosthetic valve

Tips for effective learning and controlling back your life:
1. Keep adding points and bits to notes from what I say, MCQ Bank and make them super - potent for last month revision.
2. Adding them will activate your neo cortex and aid retention.
3. Stop notifications in device used for study. Keep other device away > 10 feet from study corner

11 TRICUSPID REGURGITATION AND PULMONIC STENOSIS

TR (Tricuspid Regurgitation) 00:00:15

Characteristic findings

- CV wave and pulsatile liver (systolic)

Causes

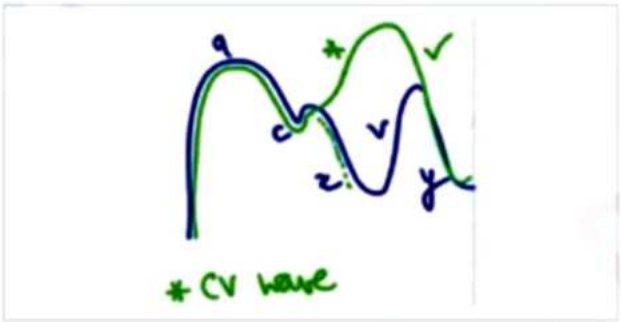
1. Most of cases are of Functional Tricuspid Regurgitation
   - Due to tricuspid annulus dilation, pressure, and volume overload
2. Severe Pulmonary Arterial Hypertension (Severe PAH > 55mmHg)
   - Normal Pulmonary Arterial Pressure = 15mmHg
3. Right ventricular dilatation
   - Dilatation of tricuspid valve annulus will contribute to
4. Right Ventricular Pacemaker
   - Wire may cause damage to heart valve
5. Rheumatic heart disease
6. Carcinoid syndrome
   - Tricuspid Insufficiency
   - Pulmonic Stenosis
7. Endomyocardial fibroelastosis
8. Radiation to chest, in Hodgkin lymphoma, post treatment Tricuspid Regurgitation
9. Infective Endocarditis
10. Ebstein anomaly
11. Wolf parkinson white syndrome
12. Pregnant female on Lithium

Clinical feature 00:07:55

- Low cardiac output (Effort intolerance)
- Visible neck pulsations, cv wave
- Abdominal fullness
- Decreased appetite

On examination 00:09:32

- **JVP findings:**
  - Absent 'x' wave
  - Cv' wave (LANCISI SIGN)



  - Steep y descent
- Hepatomegaly
- Pulsatile liver
- Pansystolic murmur also known as blowing holosystolic murmur (NEET PG 2023)

Pan systolic murmur louder on inspiration (Caravallo Sign)

Work Up

- **ECG**
  - Right axis deviation, right ventricular hypertrophy
  - Delta wave-wolf parkinson white syndrome
- **Chest X-ray:**
  - Right atrial and ventricle enlargement
- **Echocardiography: Investigation of choice**
  - Defective coaptation of leaflets
- **Doppler:leakage of blood from right ventricle to right atrium.**
  - reverse systolic flow in liver

Treatment 00:18:06

- Salt restricted diet
- Diuretics
- Surgery
  - TVRp Tricuspid valve repair
  - TVR Tricuspid valve replacement

Murmurs:

- Mild form of PULMONARY artery hypertension causes early diastolic murmur
- Severe form of PULMONARY artery hypertension causes pansystolic murmur
- Intensity of pan systolic murmur
  - Increases with inspiration
  - Decreases with Valsalva/standing

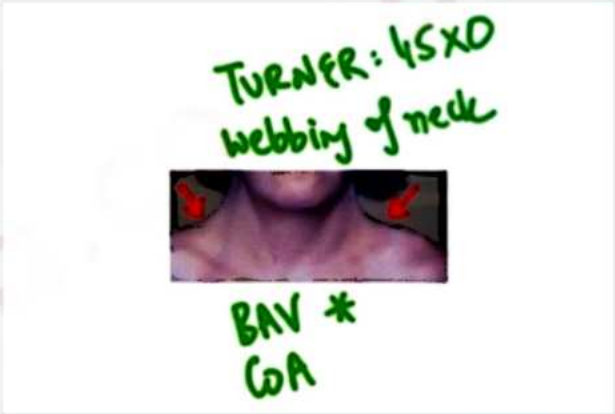
Pulmonic Stenosis 00:22:37

- Common in pediatric age group

Causes

1. Congenital
2. Dysplastic pulmonary valve (Noonan Syndrome)
   - Noonan Syndrome looks like Turner syndrome except

Noonan is chromosome 12 defect, PTPN1 gene. and Turner is aneuploidy (45XO)
  - Turner Syndrome (Most Common heart lesion) = Bicuspid aortic valve
    → 2nd Most Common is Coarctation of Aorta
  - Webbing of neck seen in both.
3. Carcinoid Syndrome {Tricuspid insufficiency, Pulmonary stenosis (T.I.P.S)}
4. Rheumatic Heart Disease (Rare)

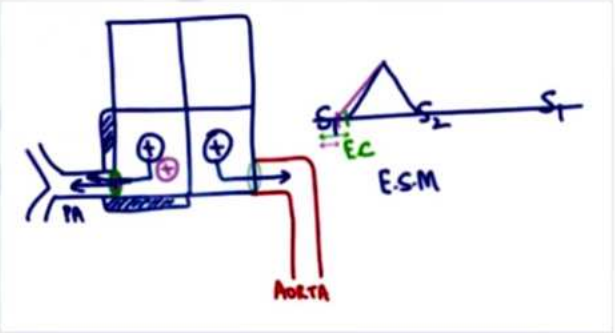


Severe Pulmonary Stenosis (> 50 mm Hg)
- Based on pressure gradient between right ventricle & pulmonary artery.

Mild Pulmonary Stenosis / Moderate Pulmonary stenosis
- Mostly asymptomatic

Clinical features
1. Effort intolerance
2. Fatigue
3. Angina

On examination
- Ejection systolic murmur present

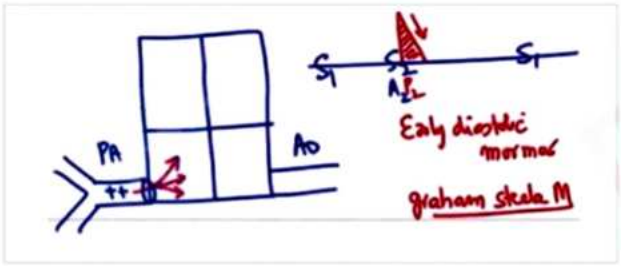


- Severity of Pulmonary Stenosis is $\alpha \frac{1}{\text{S1 - Ejection click gap}}$
- Ejection click absent
- Ejection click is less prominent with inspiration in pulmonic stenosis
  All right sided events tend to become louder with inspiration except pulmonary ejection click.
- S2 heart sound, soft S2sound/single S2 .
  - A2 heard normally
  - P2 soft
- S4 right sided heart sound present (Right atrial hypertrophy)

Work Up of Patient 00:35:38
Chest X-ray: Right ventricular enlargement, superolateral displacement of apex of heart
- **ECG:** Right axis deviation, right ventricular hypertrophy
- **Transthoracic Echocardiography:** Investigation of choice
  - Tells gradient between right ventricle and pulmonary artery > 50 mm Hg.
  - Right ventricle hypertrophy (Eccentric)

Treatment
Percutaneous Pulmonic Valvotomy (Dysplastic valve)

Pulmonary Regurgitation 00:38:20
Causes of pulmonary regurgitation
1. Annular dilatation of pulmonic valve
2. Pulmonary Artery Hypertension: annular dilatation of pulmonary valve, leaking of blood
3. Post Tetralogy of Fallot (TOF) repair
4. Post balloon valvotomy
5. Marfan syndrome



- Early diastolic murmur also known as graham steel murmur
  - seen in pulmonary artery hypertension due to annular dilatation of pulmonary valve

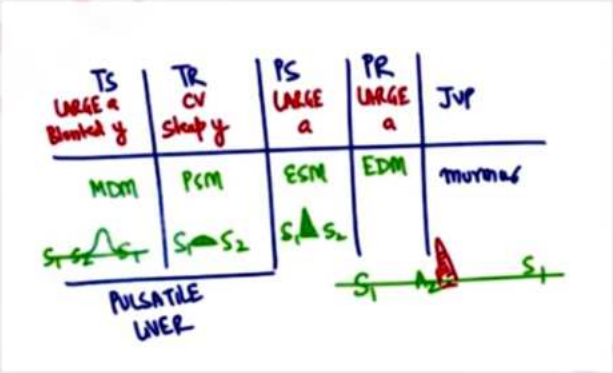
Clinical feature
- Fatigue
- Dyspnea
- Abdominal fullness
- Pedal edema

Investigation of Choice 00:42:58
Cardiac MRI > Echocardiography

Treatment

- Diuretics
- Transcatheter pulmonic valve replacement

Summary

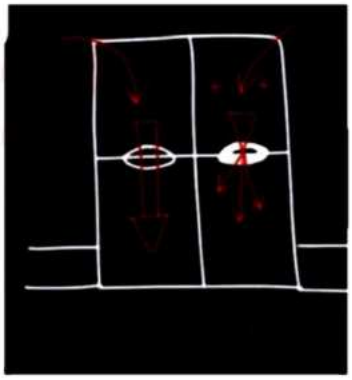


12 MURMURS

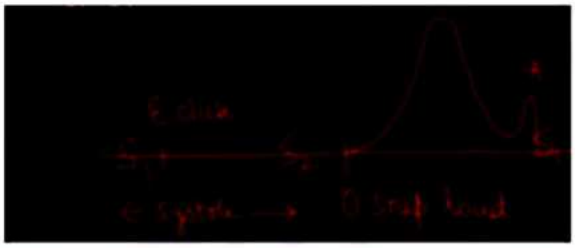
Mitral Stenosis

00:00:14

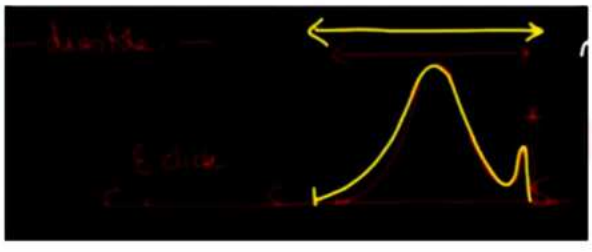
- Normal surface area of Mitral valve = 4-6cm²
- Severe Mitral stenosis surface area = <1.5cm²
- Turbulence/noise is created due to the narrow orifice
- Heard after the opening snap which is loud because of the high pressure generated in the left atria



- Turbulence peaks in the middle of the diastole with a spike creating mid-diastolic murmur



- The small secondary spike is atrial systole called pre-systolic accentuation.
- Mitral stenosis with atrial fibrillation only mid-diastolic murmur is heard without pre-systolic accentuation.
- With progressive narrower opening higher pressure leads to louder opening snap causing early opening snap and increased duration of the murmur



Important Information

- Severity of Mitral stenosis is determined by the duration of the murmur
- Severity of Mitral stenosis is inversely proportional to S_2 – Opening Snap gap

- Over time, mitral stenosis → left atrial dilatation → pulmonary venous hypertension → pulmonary edema → hypoxia → vasoconstriction of pulmonary artery → pulmonary artery hypertension → right ventricular hypertrophy.

Complaints

1. Dyspnea on exertion
2. Orthopnea
3. Paroxysmal Nocturnal Dyspnea
4. Left atria dilatation: Hoarseness of voice (Ortner syndrome)
5. Left atria dilatation: Atrial fibrillation
   - Clots: Embolic stroke
6. Pulmonary Artery Hypertension: Exercise intolerance
   - Ankle edema

On examination

1. Tapping apex beat
2. S1 loud: Transvalvular gradient ↑ (elastic recoil)
3. Soft S1: Calcified mitral stenosis
4. Narrow split S1
5. Single S1
6. Reverse split S1
7. S2 = A2P2 : Normal
8. If PAH, Loud P2. Therefore, loud S2
9. S3 = Absent
10. Murmur = Mid-diastolic murmur with pre-systolic accentuation (better heard in left lateral decubitus position)

Important Information

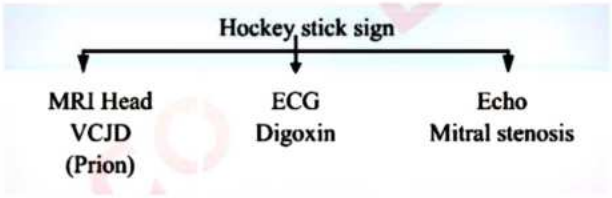
- Leading cause of embolic stroke is Non-Rheumatic atrial fibrillation

Work up

- ECG:
  - Increased duration of P wave: P-mitrale

- Increased height of P wave: P-Pulmonale
- Pseudo P-pulmonale is a feature seen in hypokalemia

- Chest X-Ray:
  - Straightening of left heart border
  - Double atrial shadow/ Double atrial contour
  - Widening of carinal angle (Tracheal bifurcation)
- Transthoracic Echocardiography (TTE): IOC
  - Candle flame jet
  - Hockey stick sign



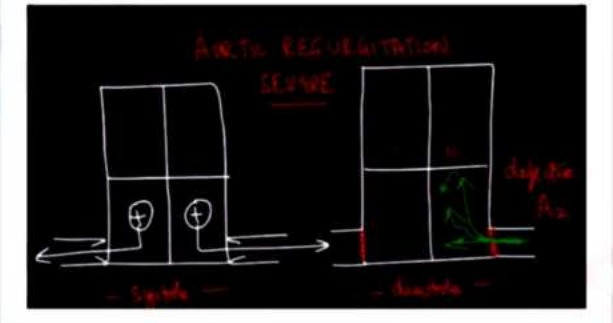
Management

- Severe MS: PMBV (Percutaneous mitral balloon valvotomy)
  - Basilic vein → SVC → RA → IAS → LA → LV
- Calcified mitral stenosis: PMBV → Contraindicated
- Severe MS with mitral regurgitation: PMBV → Contraindicated
- Severe MS with Left atrial appendix clots: PMBV → Contraindicated
- Mild to moderate MS is managed medically with drugs
  - Digoxin
  - Spironolactone
  - Thiazide

- PAH:
  - Ambrisentan: DOC

Severe Aortic Regurgitation 00:38:07

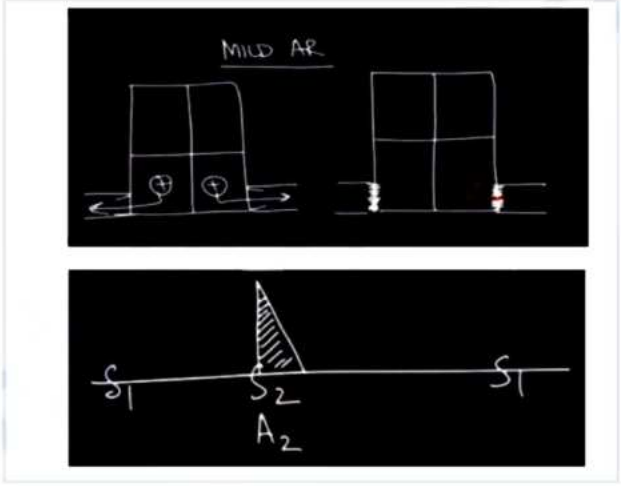
- In severe aortic regurgitation, jets of blood hits the mitral valve causing a mid-diastolic murmur. This murmur is called Austin Flint Murmur.



- The murmur starts from $S_2(A_2)$, and Not opening snap

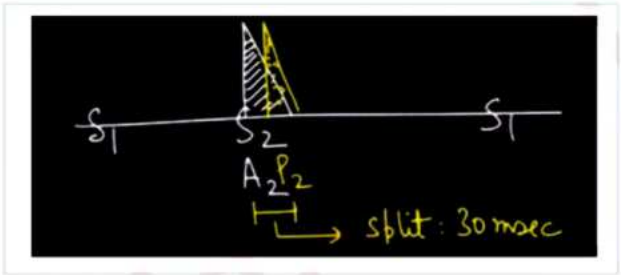
Mild Aortic Regurgitation 00:42:38

- There is minimal blood leaking back to the left ventricle gives rise to short duration murmur called as Early diastolic murmur.
- The murmur arises from $S_2(A_2)$.
- Seagull murmur
- Decrescendo murmur



Mild Pulmonic Regurgitation 00:45:25

- Minimal blood leaking back to the Right ventricle leading to a short duration early diastolic murmur.
- The murmur arises from $S_2(P_2)$



Types of Diastolic Murmur 00:46:35

- Early diastolic murmur: G.A.P
  - Graham Steele murmur (Pulmonary artery hypertension leading to mild pulmonic regurgitation)
  - Aortic regurgitation (mild)
  - Pulmonic regurgitation (mild)
- Mid-diastolic murmur: C.A.M
  - Carey Coombs murmur (Rheumatic heart disease)*

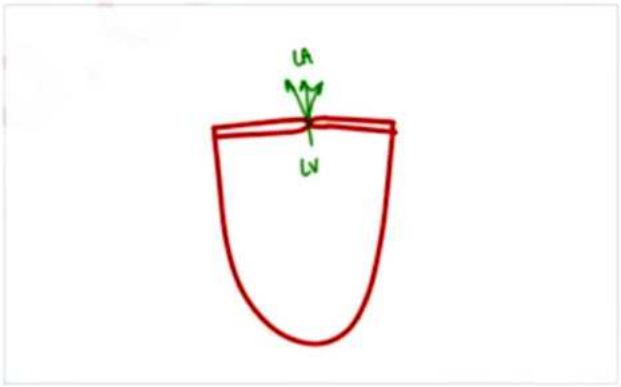
- Austin flint murmur
- Mitral stenosis
- Flow murmur

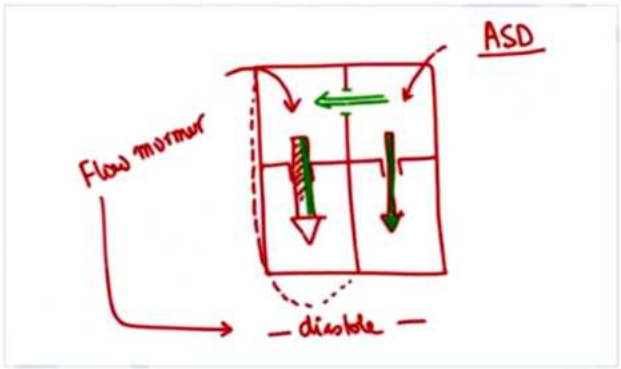
- Late diastolic murmur
  - Carey Coombs murmur (Rheumatic heart disease)

* Consider it as mid-diastolic only if choice selection is betweeen between early and mid diastolic murmurs. If there is early, mid and late diastolic murmurs, consider it in late diastolic murmurs

Carey Coombs murmur

- Cause: Valvulitis
- It is a flow murmur heard in diastole because of extra blood that came in from left ventricle due to valvulitis





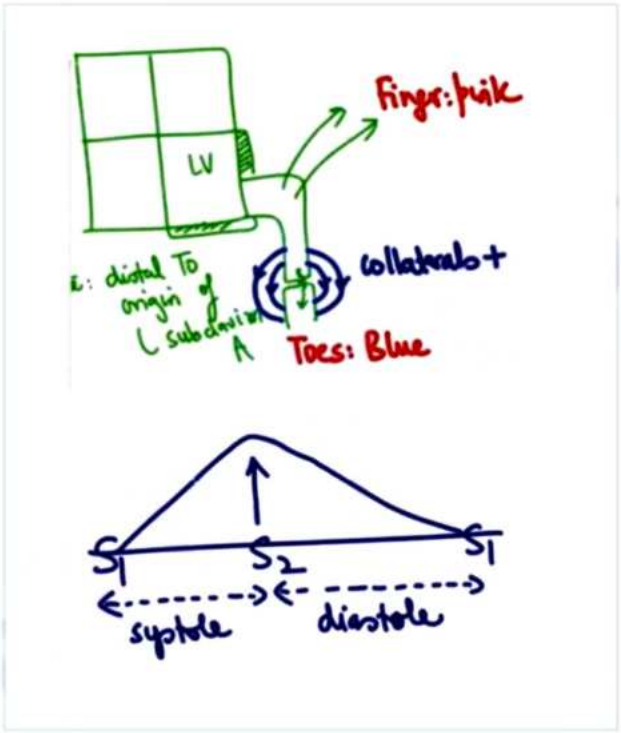
Important Information

- Most common murmur in children: Innocent murmur (systolic murmur)

Coarctation of aorta

00:58:08

- Turner syndrome (45XO): Bicuspid aortic valve > Coarctation of aorta
- Site: Distal to origin of subclavian artery
- LV hypertrophy
- Ejection systolic murmur (early phase of disease)
- Toes: Blue
- Fingers: Pink
- Continuous murmur (heard as collaterals develop)
- Peaks at S_2



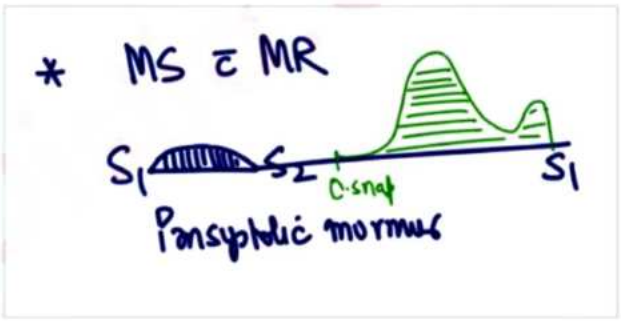
Continuous Murmur

01:03:15

1. Coarctation of aorta
2. PDA
3. Mammary souffle: ↑ Blood flow in internal mammary artery in pregnancy (Normal)
4. Venous hum
5. Rupture of sinus if valsova
6. Peripheral pulmonary stenosis

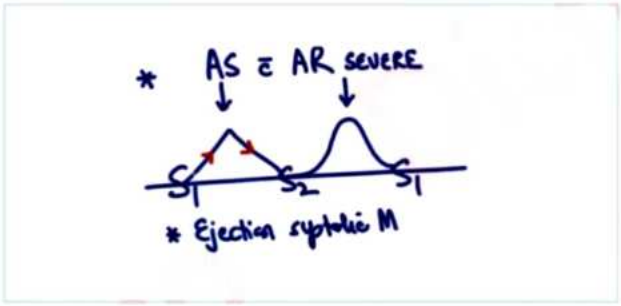
Mitral stenosis with mitral regurgitation

- Pansystolic murmur



Aortic stenosis with aortic regurgitation

- Ejection Systolic murmur
- Crescendo-decrescendo murmur



Systolic Murmurs

01:09:38

Ejection systolic murmur

- Mnemonic: PASS
- Pulmonic stenosis:
  - Carcinoid syndrome: TIPS
  - Noonan syndrome
- Aortic stenosis
- Hypertrophic obstructive cardiomyopathy (HOCM)

Pansystolic murmur

- Ventricular septal defect
- Mitral regurgitation

Mid-systolic clicks followed by late systolic murmur

- Mitral valve prolapse
  - Myxomatous degeneration of mitral valve prolapse
- Barlow syndrome

Important Information

- All murmurs decrease in intensity with:

1. Valsalva
2. Standing
3. Amylnitrate

   Except: Hypertrophic obstructive cardiomyopathy (louder) and mitral valve prolapse (longer)

- All murmurs increase in intensity with

1. Hand gripping
2. Squatting

   Except: Hypertrophic obstructive cardiomyopathy (softer) and mitral valve prolapse (shorter)

Hypertrophic obstructive cardiomyopathy

- ECG: Systolic anterior movement of the mitral valve (SAM)
- Left ventricular outflow tract obstruction (LVOTO)

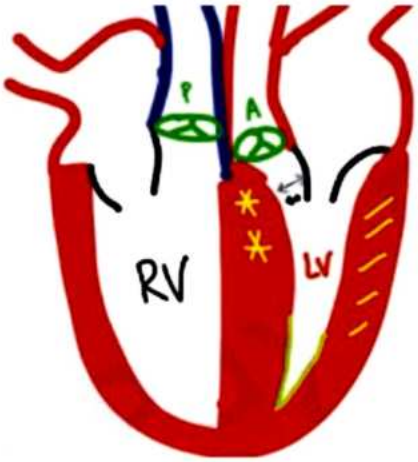
28 CARDIOMYOPATHY

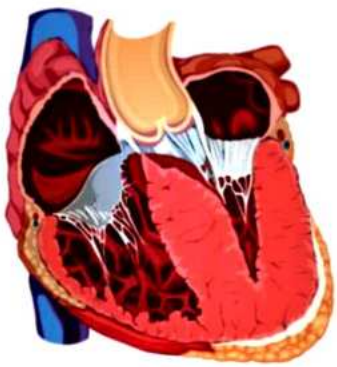
Hypertrophic Cardiomyopathy/Hypertrophic Obstructive Cardiomyopathy

- Commonest form of Cardiomyopathy
- Autosomal dominant
- MyH7 gene is affected, Chromosome 14 abnormality

Pathophysiology 00:01:20

- Asymmetrical septal hypertrophy (main cause of subendocardial ischemia)
- Left ventricular wall thickening (> 30 mm, higher risk of sudden death)
- Left ventricular outflow tract obstruction caused by sub valvular stenosis (funneling caused just below the aortic valve) causing systolic anterior movement of mitral valve.
- Banana shaped cavity of left ventricle
- Diastolic malfunction.
- Systolic Anterior movement of mitral valve.





Clinical Features 00:06:10

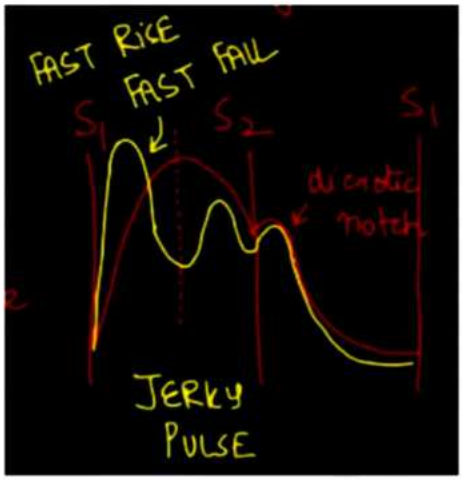
- 20 years male
- History of sudden cardiac death in a sibling
- Dyspnea
  - Diastolic malfunction>pulmonary edema
- Chest pain on exertion
- Effort intolerance/ syncope
- Sudden cardiac death on running/exercising
  - Due to Ischemic ventricular fibrillation
  - Pulseless ventricular tachycardia

Important Information

- Most common sustained Tachyarrhythmia in Hypertrophic cardiomyopathy is Atrial fibrillation

Examination 00:16:30

- Pulsus bisferiens "Jerky pulse"



- Double apical impulse
- Heaving apical Beat
- Narrow split S2/single S2/Reverse splitting S2
  - Pulmonic valve closure occurs before aortic valve closure
- S4 is heard due to left atrial hypertrophy
- Ejection systolic murmur
  - Crescendo-decrescendo murmur
  - All murmurs have decreased intensity with Valsalva, standing, amyl nitrate
  - But here a louder murmur is heard with Valsalva, standing, amyl nitrate

- Volume of blood in left ventricle is inversely proportional to the left ventricular outflow tract obstruction

Investigations 00:31:15

- Trans-Thoracic Echocardiography (T.T.E)
  - Left ventricle free wall thickness >15 mm
  - Systolic anterior movement of mitral valve
  - Asymmetrical septal hypertrophy
- ECG
  - Suggests Left ventricular hypertrophy
  - Sum of depth of 'S' wave in Lead V1 and height of 'R' wave in Lead V5/V6 is more than 35 mm
- Cardiac catheterization
  - Brockenbrough Braunwald Morrow sign
  - Square root wave sign (Constrictive pericarditis/ Restrictive cardiomyopathy)

Treatment 00:36:15

- Drug of choice: PROPRANOLOL
  - Reduces heart rate
  - Reduces Oxygen consumption
- Verapamil (Give if Propranolol cannot be given like in asthma, chronic obstructive pulmonary disorder)
- Disopyramide reduces the Left ventricular outflow tract obstruction

Clinical Scenario 00:38:00

- A 20 year male presents with chest pain at rest. An on-duty intern gives him Nitroglycerin thinking the patient will get better, but the patient gets worse.
  - This scenario is seen in Hypertrophic obstructive cardiomyopathy
  - Since Nitroglycerin is powerful vasodilator there is a reduced Right ventricular inflow > reduced left ventricular inflow > reduced stroke volume due to small left ventricular cavity > reduced cardiac output > reduced coronary perfusion

Important Information

- Nitroglycerin, Furosemide, Angiotensin converting enzymes 1, Angiotensin receptor blockers, Digoxin, Amlodipine (Calcium channel blockers) are contraindicated in Hypertrophic cardiomyopathy

Interventional Treatments 00:44:10

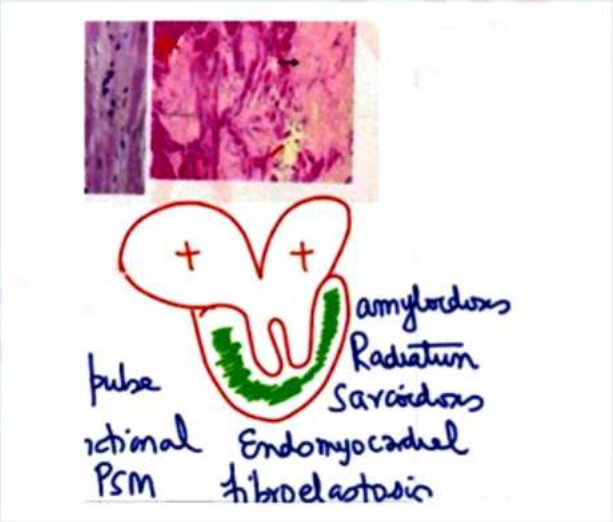
- Treatment of choice: Implantable cardioverter defibrillator
  - Detect abnormal rhythms and terminate the arrhythmia by DC shock
- Indications
  - Family history of sudden cardiac death
  - Unexplained syncope
  - Left ventricular free wall thickness is more 30 mm
- Surgical interventions
  - Alcohol based septal ablation
  - Myomectomy

Sudden Cardiac Death 00:48:00

- Athlete's heart: Kinking of coronary artery results in myocardial infarction
- Commotio cordis: Blunt trauma to chest causes Ventricular fibrillation
- Arrhythmogenic right ventricular dysplasia-
  - Fibrofatty deposition in wall of the right ventricle leads to Torsades de Pointes
  - ECG feature is Epsilon wave
- If all of the above is ruled out then the cause of sudden cardiac death is Hypertrophic obstructive cardiomyopathy

Restrictive Cardiomyopathy

- Rarest form of cardiomyopathy
- STIFF HEART: Normal size ventricle but atria is dilated to work against stiff ventricles
- Pink Hyaline deposits (amyloid protein) in the myocardium causing the stiffness of the ventricles which is shown in the below image



Important Information

Myocyte disarray on histopathological examination is a feature of Hypertrophic cardiomyopathy

Causes

00:53:35

1. Amyloidosis
2. Radiation
3. Sarcoidosis
4. Hemochromatosis
5. Storage disorders: Gaucher disease and Fabry disease
6. Scleroderma
7. Endomyocardial fibro elastosis

Clinical Features

01:02:44

- Decreased Right ventricular compliance
  - Pitting pedal edema/Ankle edema
  - Ascites
  - Hepatomegaly/ RUQ (Right upper quadrant) discomfort
  - Kussmaul sign: Jugular venous pressure rises with Inspiration
- Decreased Left ventricular compliance
  - Pulmonary edema due to pooling of blood in the lungs, Dyspnea on exertion, Orthopnea, Paroxysmal nocturnal dyspnea
  - Fibrosis triggers clots in Left atria and ventricle leading to increased chances of embolic stroke
  - Effort intolerance

Investigations

01:07:02

1. ECG- Low voltage leads due to
   - Pericardial effusion
   - Constrictive pericarditis
   - Myxedema
   - Fibrosis in heart.
2. Chest x-ray
   - To rule out Constrictive pericarditis (forms calcification around the heart)
   - To demonstrate Pulmonary edema
3. Trans thoracic echocardiography/ Trans esophageal echocardiography
   - Thickness of the Left ventricular and right ventricular wall is normal
   - Left ventricular end diastolic pressure is increased
4. Cardiac catheterization
   - The blood hits the ventricular wall, but it bounces of the wall instead of stretching of the wall due to fibrosis of the ventricular wall
   - This is called Square root wave sign due to non-compliant ventricular wall

- **Gold standard tool:** Endomyocardial Biopsy
- Cardiac MRI- preferred imaging modality

Treatment

01:13:40

- Implantable cardioverter defibrillator- To increase the chances of survival
- **Warfarin**: given to reduce the risk of cerebral thrombosis
- Diuretics- Lowest possible dose is given due to low blood pressure
- Cardiac transplant

Dilated Cardio Myopathy

01:15:50

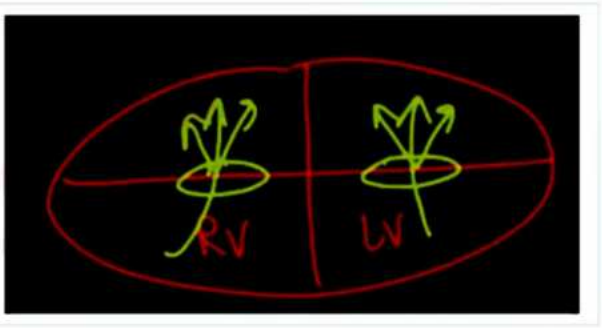
- Globular enlarged flabby heart is seen in dilated cardiomyopathy
- The histopathology shows multinucleated myocytes
- Dicrotic pulse is a important sign of dilated cardiomyopathy

Causes

- Familial causes 35%
- Idiopathic causes 20%

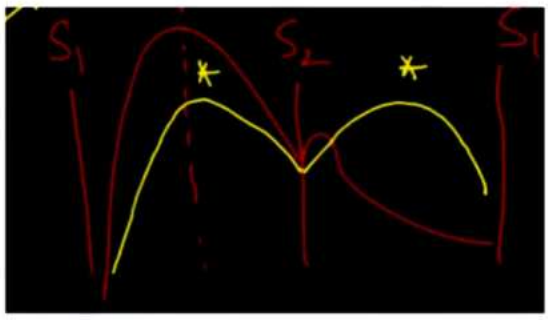
- Sequalae to Viral myocarditis
  - Parvovirus B19
  - HHV6
  - Coxsackie B
  - Covid-19
- Toxins- Alcohol
- Sarcoidosis
- Duchenne's muscular dystrophy

Functional mitral regurgitation, tricuspid regurgitation occurs due to annulus dilatation of mitral and tricuspid valves leading to non coarctation of the leaflets of the valves



Clinical Scenario 01:22:10

- An alcoholic patient presents with pitting ankle/ pedal edema, Right upper quadrant discomfort, Orthopnea.
- On examination
  - Dicrotic pulse
    → Twice beating pulse palpable in both systole and diastole.



  - Loud S1/ soft S1
  - Pan systolic murmur
  - Bilateral crepitations
  - Hypokinetic diffuse point of maximal impulse

Investigations 01:26:22

- Trans thoracic echocardiography
- Cardiac MRI
- Chest x-ray- increased cardio thoracic ratio and pulmonary edema

Treatment 01:26:53

- Implantable cardioverter defibrillator
- Cardiac resynchronization therapy

Important Information

- Leading cause of cardiac transplantation is Dilated cardiomyopathy
- Cardiomyopathy with the worst prognosis is Ischemic cardiomyopathy

Peripartum Cardiomyopathy 01:30:30

- Features of cardiomyopathy from the last month of pregnancy up to 5 months of post-partum
- Rule out Pregnancy induced hypertension, valvular diseases
- Recovery possible

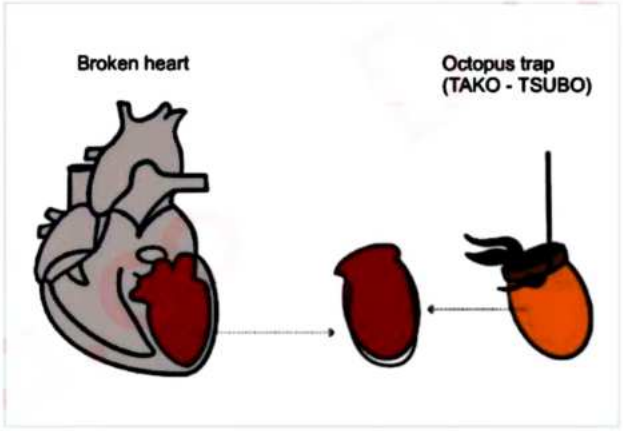
Takotsubo Cardiomyopathy 01:32:28

- Due to catecholamine surge
- Recovery possible and is also called Broken heart syndrome

13 TAKOTSUBO CARDIOMYOPATHY & BRUGADA SYNDROME

Takotsubo Cardiomyopathy

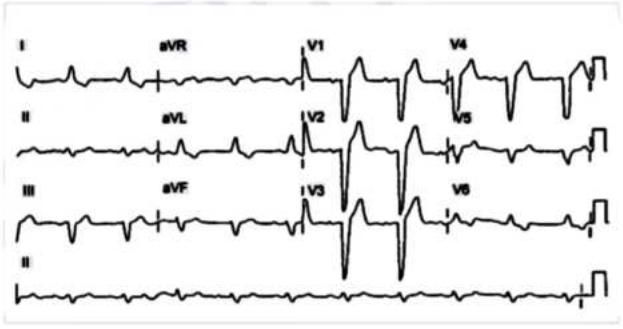
00:00:12



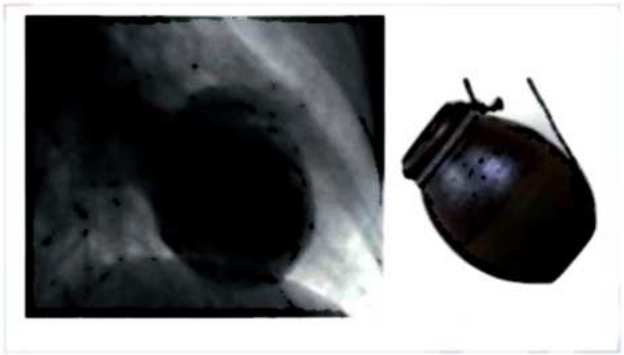
- TTCM is also called Broken Heart Syndrome
- Occurs due to catecholamine toxicity following intense emotional trauma

1. **Case based discussion:** 60 yrs ♀ trapped in a elevator during an earthquake, emergency crew rescued her, she was rushed to hospital. She complained of chest pain at rest / diffuse in character & diaphoresis HR=120/min, BP=90/60mmHg, ECG: V1 -V 6 : ST elevation, Trop I : double, Coronary angiography normal, Primary PCI: Abandoned.

- **ECG**



- "TOMB STONE PATTERN" / Pardee sign: Seen in V2-V6 leads (suggestive of extensive anterior wall MI, due to thrombus in left main coronary artery.



- Trop I:: 0.08 mg / dl
- Cath. lab - Coronary angiography normal Primary PCI: Abandoned
- ECHO: Alteration of LV shape with Hypokinesia

Treatment

- Treat as case of cardiogenic shock → Use impella device or IABP
- ACEIs, beta blockers
- Since this condition already has Catecholamine excess therefore dopamine, dobutamine should not be given

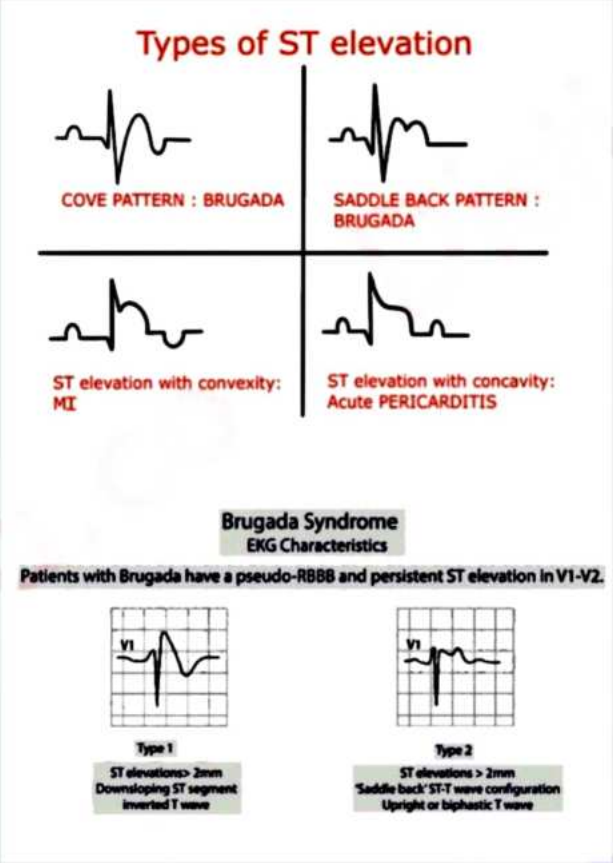
Important Information

- Acute onset cardiomyopathy
- Improvement can occur gradually.
- Mimics STEMI
- Cath Lab: Normal angiography
- It is an differential diagnosis of STEMI and diagnosis is made in cath lab due to normal coronary angiogram.

BRUGADA SYNDROME

00:14:03

- SCN5A# → defective Na+ influx
- Due to sodium channel defect, voltage gradient is created between RV epicardium & normal heart and will trigger, arrythmias.
- V. Fib/VT/TDP (Torsades de pointes)
- Patient will become pulseless, and BP will crash.
- Family H/O syncopal attacks
  - Sudden death in sibling
  - It is the leading cause of sudden nocturnal death in SE Asian males.
- ECG → ST elevation in V1 - V2 (Right chest leads)



Treatment

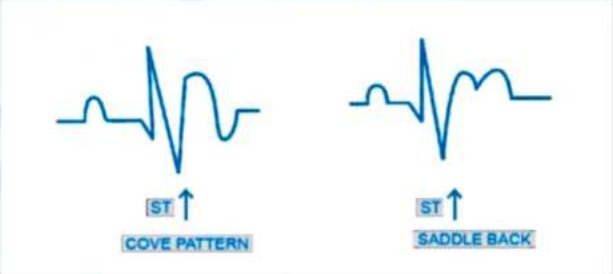
00:20:33

- I.C.D (Implantable cardio defibrillator)

Indications I.C.D

A

- LV **A**neurysm,
- **A**rrythrogenic RV dysplasia (fibro fatty deposition in RV)
  - Family H/o sudden death
  - Epsilon wave



  - T wave inversion $V_1 - V_4$

B

- **B**rugada Syndrome

C

- **C**ardiomyopathy

Causes of sudden cardiac death

00:27:44

- HOCM: V. Fib/ VT
- Holiday Heart Syndrome: A. Fib
- DM: Silent MI
- Brugada: TDP
- Long QT syndrome: TDP
- WPW: A. Fib degenerating into V. Fib

Important Information

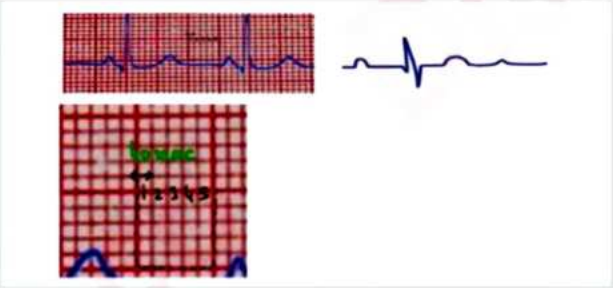
Brugada syndrome shows two different patterns of ST elevation

1. Cove pattern
2. Saddle back pattern

14 ECG AND ARRYTHMIAS 1

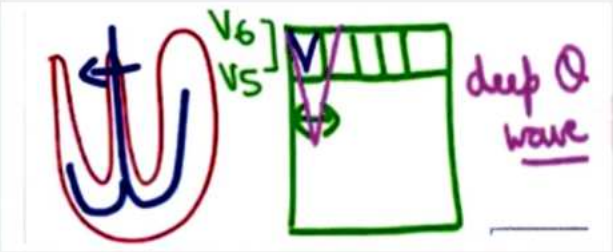
NORMAL ECG

- Duration of a small square is 40 milliseconds

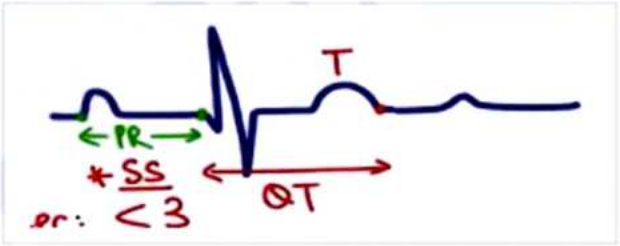


- **P WAVE**
  - Represents Atrial depolarization
  - Normal duration is <120 milliseconds (within 3 small square)
  - Vertical height is <2.5 mm in limb lead and < 1.5mm in chest leads
  - In P. pulmonale vertical height of P wave is >2.5mm
- **PR interval**
  - Start of P wave to start of Q wave
  - Signifies AV nodal conduction
  - Normal duration is 120-200 milliseconds (within 3-5 small square)
  - Inversely related to heart rate
  - Tachycardia/Tachyarrhythmias the PR interval will be short whereas in Bradyarrhythmia PR interval will be prolonged

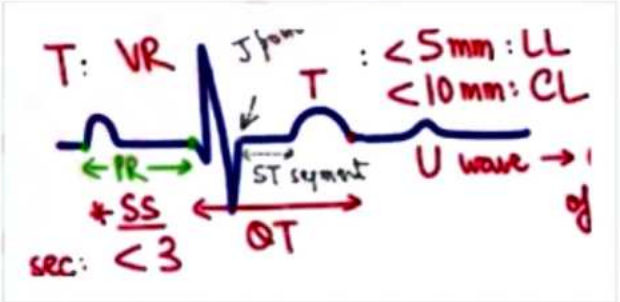
- **Q wave**
  - Signifies Septal activation
  - Normal duration is <40 milliseconds (within 1 small square, both duration and height will be in 1 small square limit)
  - Looked in leads V5 and V6 since it is a negative wave
  - Deep Q wave is seen in Myocardial infarction (Wave goes beyond 1 small square)



- **QRS complex**
  - Signifies Ventricular depolarization
  - Normal duration is 80-100 milliseconds (within 2-2.5 small square)
  - Narrow QRS complex- < 2 small squares
  - Wide QRS complex- >3 small squares
- **QT interval**
  - Signifies Ventricular depolarization and ventricular repolarization
  - Starting of Q wave to end of the T wave
  - Normal duration is 360-440 milliseconds (within 9-11 small square)
  - QT interval is inversely related to the electrolytes. E.g. In Hypokalaemia QT is prolonged and in Hyperkalaemia QT interval is short



- **ST segment**
  - It is called segment because it starts from the end of S wave and ends at start of T wave
  - J' point also called as isoelectric point is the end of S wave
  - No duration, it changes its height on various conditions
- **T wave**
  - Signifies Ventricular repolarization
  - T wave follows ST segment, changes its height
  - Normal vertical height - <5mm in limb leads and < 10mm in chest leads
- **U wave**
  - Normal finding
  - Signifies delayed repolarization of papillary muscles

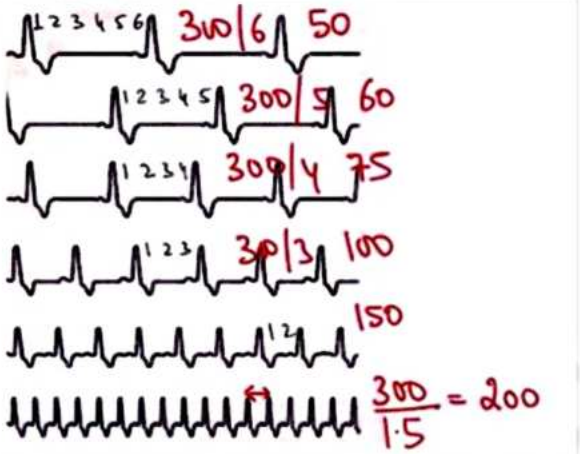


SUMMARY

- P: 3 small squares
- PR-: 3-5small squares
- Q: <1 small square
- QRS: 2-2.5 small squares
- QT: 9-11 small squares

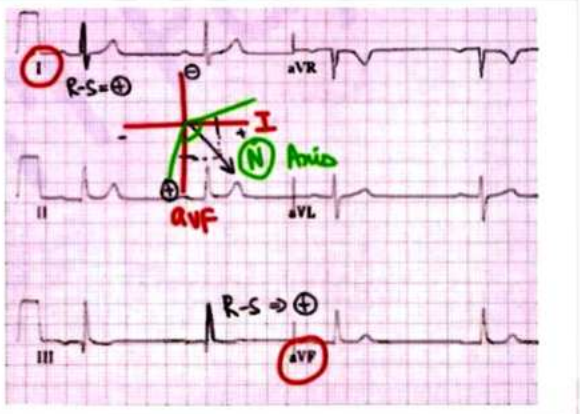
Calculation Of Heart Rate

- Count the number of large squares between the R waves. R-R interval
- Heart rate is always calculated in LEAD II: Rhythm strip
- Formula: 300/ number of large squares in the R-R interval
- Lesser the number of large squares the higher the heart rate
- <3 large squares: Tachycardia (>100/min)
- >5 large squares: Bradycardia (< 60/min)

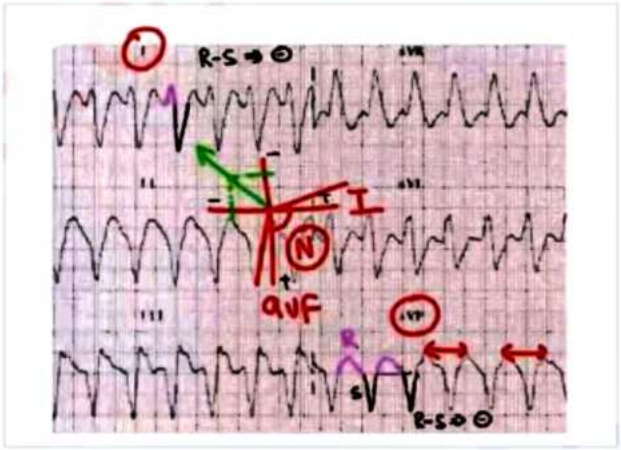


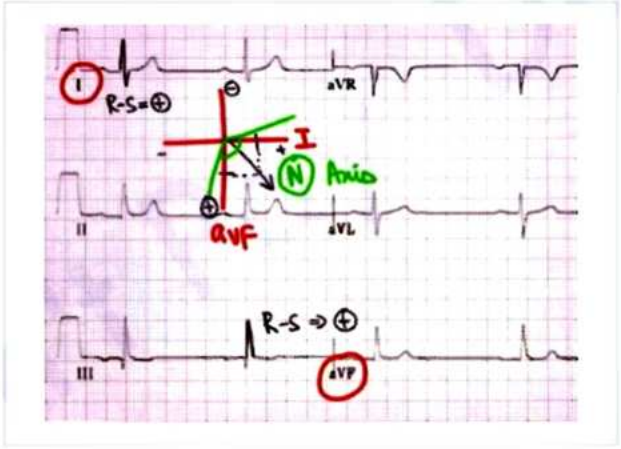
Axis Calculation

- Normal Axis: -30° to +110°
- Normal axis- The height of the R wave is more than the depth of S wave both in Lead 1 and aVF. (R-S= +ve)

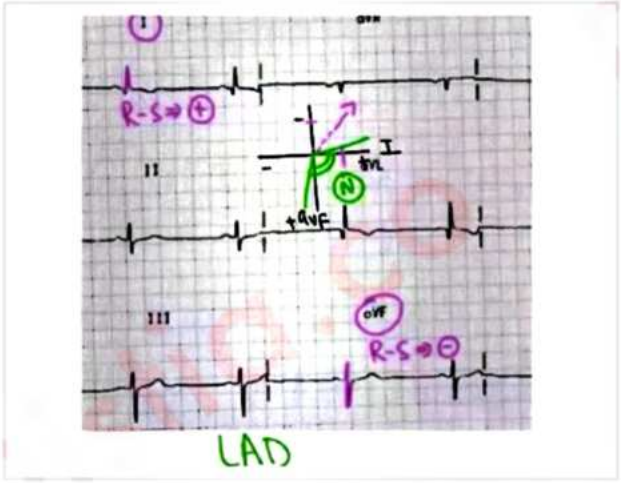


- Extreme axis deviation(Ventricular tachycardia)- The height of R wave is less than the depth of of S wave both in Lead 1 and aVF (R-S= -ve)

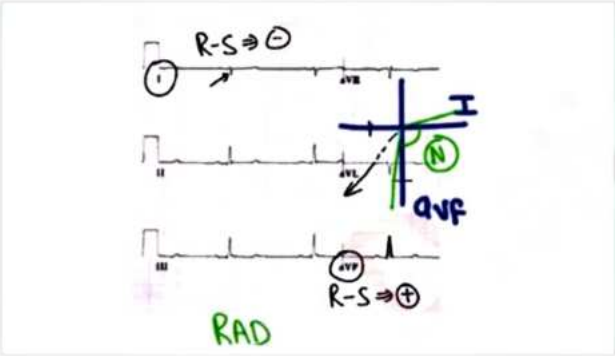




- Left axis deviation: The height of R wave in Lead1 is more then the depth of S wave (R-S= +ve)whereas the depth of S wave is more than the height of the R wave aVF (R-S= -ve)



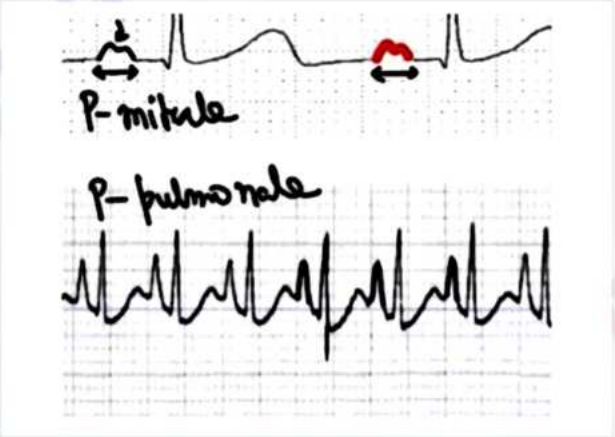
- Right axis deviation: The height of R wave in Lead1 is less than the depth of S wave (R-S= -ve) whereas the height of R wave is more than the depth of S wave in aVF (R-S= +ve)



P Wave Abnormalties

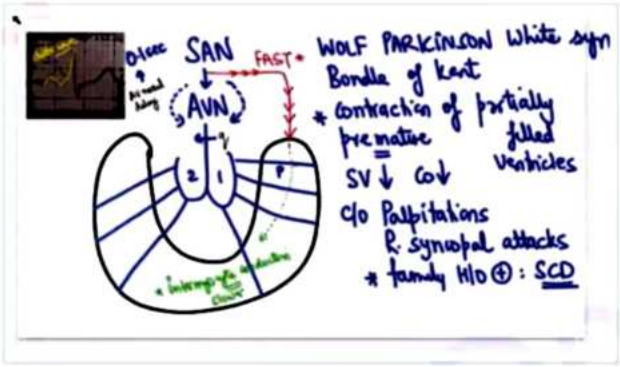
- Normal P wave is upright (positve) in all leads except in aVR it negative (Normal finding)
- In Lead V1 the P wave is biphasic where the positive part signifies Right atrial depolarizatio and the negative part signifies the Left atrial depolarization
- Normal duration is <120 milliseconds
- Normal height is <2.5mm
- **Abnormalities**:
  - P- mitrale-duration more than 120 milliseconds, signifies Left atrial enlargement.

  - P- pulmonale-Vertical height more than 2.5mm, signifies Right atrial enlargement, seen in pulmonary artery hypertension patient.



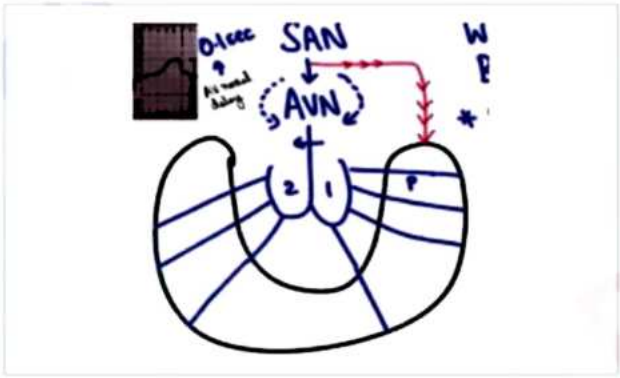
Normal Electrical Conduction

- SA node> AV node (AV nodal delay of 0.1 sec)> Bundle of His (Septal activation) > Left and right Fascicle> Purkinje fibres



PR Interval Abnormalities

- **Pathophysiology:**
  - The normal electrical conduction bypasses the AV node through the Bundle of Kent and causes early depolarization of the ventricles
  - Wolf Parkinson White syndrome/ Preexcitation syndrome
  - Premature contraction of the partially filled ventricles



- **Clinical scenario**

A patient comes with complaints of Palpitations, recurrent syncopal attacks and family history of sudden cardiac death

- **ECG:**
  - PJ interval is combination of PR interval and QRS complex
  - The PR interval is short due to the fast conduction through the bundle of kent
  - Absent Q waves due to absent septal activation
  - Instead Delta waves are seen
  - RS complex (absent Q wave) is broad due to Intermyocyte conduction
  - PJ interval is normal- Short PR interval+ Absent Q wave+ Prolonged RS complex

- **Treatment:**
  - Accessory pathway mediated tachycardia-Emergency drug- I.V Procainamide
  - Drug for prevention- Oral Flecainide
  - Treatment of choice- Radio frequency ablation

Lown-Ganong Levine Syndrome

- The current from the SA node bypasses the AV node through the James fibres directly to Bundle of His leading early contraction of partially filled ventricles causing reduced cardiac output
- Preexcitation syndrome CO ↓ SV ↓
- C/O Palpitations, recurrent syncopal attacks and Family history of sudden cardiac death

- **ECG:**
  - PR interval is short
  - QRS is normal
  - PJ interval is short
  - Patient can be denied medical fitness based on these findings while recruitment into army, police and jobs requiring medical fitness.
- **Treatment:**
  - Accessory pathway mediated tachycardia-Emergency drug- I.V Procainamide
  - Drug for prevention- Oral Flecainide
  - Treatment of choice- Radio frequency ablation

Summary:

Wolf Parkinson White syndrome	Lown-ganong Levine Syndrome
Bundle of Kent	James Fibres/ Mahaim fibres
Shot PR interval	Short PR interval
Delta wave present	Delta wave absent
PJ interval is normal	PJ interval is short

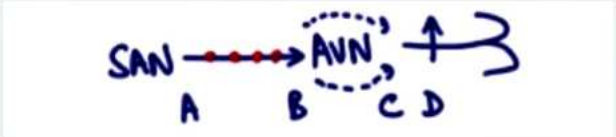
Important Information

- Delta wave in EEG seen in NREM stage III.
- Pseudo P-pulmonale seen in hypokalemia.(P wave vertical height >2.5mm in absence of PAH).

Prologed PR Interval

1. 1st DEGREE HEART BLOCK

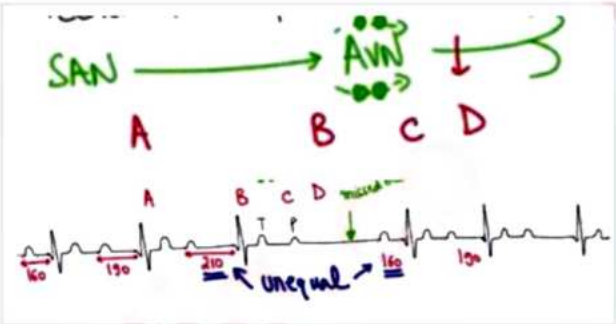
- The problem in conduction lies between the connection between the SA node and AV node



- **Causes:**
  1. Physiologic- Athletes/Marathon runner. (High vagal tone)
  2. Rheumatic- Aschoff
  3. Sarcoidosis
  4. Hemochromatosis
  5. Endomyocardial fibro elastosis
- In a Normal person the PR interval is between 120-200 milliseconds. PR interval is 160 msec, upon mild exercising like 5 sit-ups the PR interval is 140 milliseconds due to increased heart rate
- This variability of PR interval is lost in 1st degree heart block
- The patients presents with exercise intolerance/fatigue.
- **ECG:**
  - The PR interval is prolonged more than 200 milliseconds with exercising
- Treatment: No specific treatment

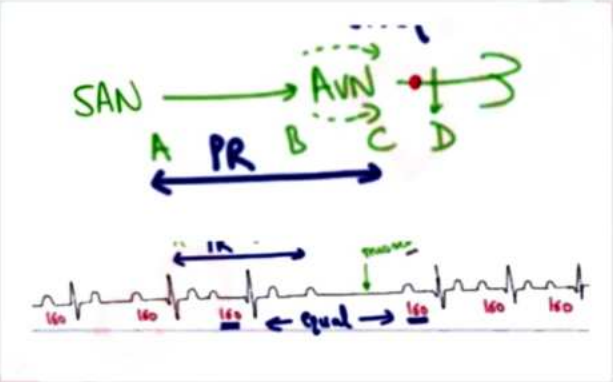
2. 2ND DEGREE HEART BLOCK

- **Mobitz 1/ Wenckebach phenomenon/ Infra nodal Heart block**
  - The AV node leading to a slower AV nodal conduction
  - Progressive increase in PR interval with each beat and there is missed beat and the process starts again
  - Characteristic feature- The PR interval before and after the missed beat are UNEQUAL



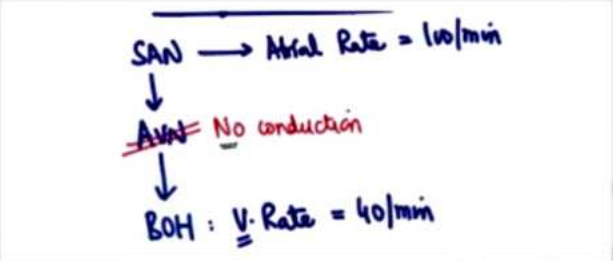
- **Mobitz 2/ Infra nodal heart block**
  - The problem lies just below the AV node and the lesion is in the Bundle of His
  - PR interval conduction is from SA node to the exit of AV node. So no change.
  - PR interval is normal with a sudden missed beat and the process continues

- Characteristic feature- The PR interval before and after the missed beat are equal
- The sudden death can occur
- Most common Bradyarrhythmia causing death after Myocardial infarction

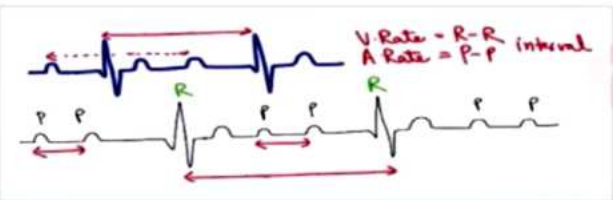


3. 3rd DEGREE HEART BLOCK

- The problem lies in the AV node itself. NO AV NODAL CONDUCTION



- SA node- Atrial Rate= 100 beats/minute
- Bundle of His- Ventricular rate= 40 beats/min
- Lack of coordination between the atria and the ventricles is called AV dissociation
- Leads to reduced cardiac output
- Bradycardia, Recurrent syncopal attacks when a patient suddenly stands (Postural hypotension)
- AV dissociation causes super large 'a' waves called Canon 'a' waves
- **ECG**
  - Prolonged PR interval
  - Broad QRS complex
  - Number of P waves will not be equal to the number of R waves. (more number of P wave).
  - P-P interval will not match the R-R interval



- **Treatment:** Permanent pacemaker (Dual pacing)

Important Information

- Absent P wave is in Hyperkalaemia, Atrial fibrillation and Sick sinus syndrome
- 1st line treatment for Symptomatic bradycardia- ATROPINE 1MG

Pacemakers

Refer Table 14.1

Sites For Pacemaker Placement

- Left side of the chest infra clavicular area, below skin

- **Placement of pacing leads:**
  - Single lead pacemaker- Right ventricle
  - Dual lead pacemaker- Right atria and Right ventricle
  - Triple lead pacemaker- Right atria, Right ventricle and left ventricle

- **IMPLANTABLE CARDIOVERTER DEFIBRILLATOR**
  - **Functions:**
    - → Read ECG
    - → Analyse ECG
    - → Abnormal rhythm detection
    - → DC shock delivery
  - **Indications: A,B,C**
    - → Tendency of Tachyarrhythmias
    - → **A**-LV Aneurysm, Arrhythmogenic right ventricular dysplasia(Fibrofatty deposition in right ventricle, epsilon wave seen)

- → **B**-Brugada syndrome, Sodium Channel defect - SCN5A, Cove pattern/ saddle back pattern seen in ECG

- → **C**- Cardiomyopathy of any etiology
  - **Clinical scenario:**

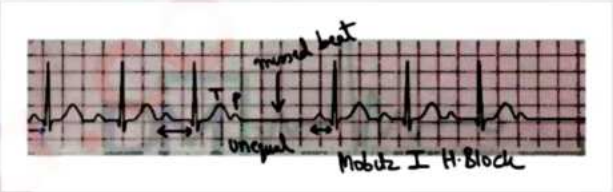
A patient on ICD, c/o electric shocks to the chest. Investigation to be done?

→ Chest x-ray : To evaluate lead malposition / lead fracture and SVC thrombosis- Extreme facial plethora

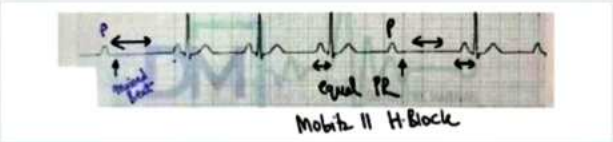
Echocardiographs

- **1st degree heart block**

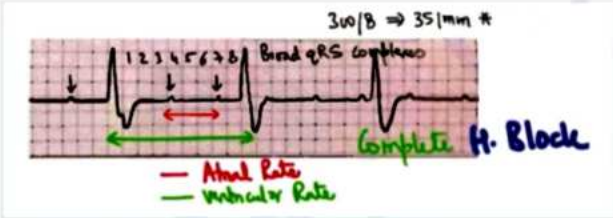
- **Mobitz 1 heart block**



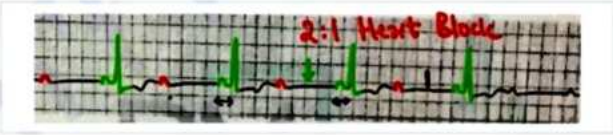
- **Mobitz 2 heart block**



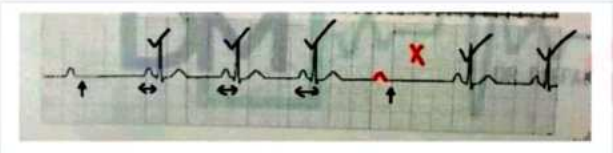
- **Complete heart block**



- **2:1 heart block**
  - Alternative conducted and non conducted P waves.



- This ECG could be confused with Mobitz II H . Block
- Multiple conduction followed by drop beat -MOBITZ II HEART BLOCK.

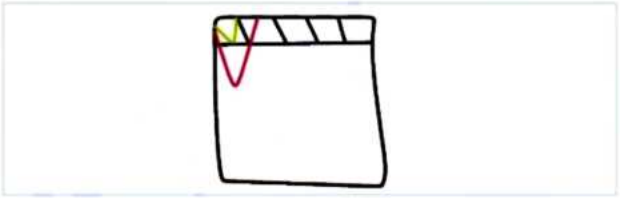


PR Interval

Short PR interval	Prolonged PR interval
Wolf Parkinson White syndrome	1st degree heart block
LOWN-GANONG LEVINE SYNDROME	Mobitz I heart block
	Complete heart block

Q WAVE

- Septal activation
- Deep Q wave
  - Myocardial infarction
  - Hypertrophic obstructive cardiomyopathy
  - S1Q3T3- RV strain seen in Acute cor pulmonale
    - → Deep S- Lead 1
    - → Deep Q- Lead 3
    - → Inverted T- Lead 3



QRS Complex Tachycardia

- Narrow QRS complex tachycardia- Supra ventricular tachycardia
- Wide QRS complex tachycardia- Ventricular tachycardia

ATRIAL FIBRILLATION

- Most common cause of embolic stroke: Non-Rheumatic atrial fibrillation
- Most common sustained arrhythmia in hypertension and patients >65 years
- **Pathophysiology**
  - The problem in atrial fibrillation is the multiple ectopic foci arise from the heart, at a rate of 300-600/min.
  - These multiple ectopic foci fire at variable rate therefor AV nodal block is variable which leads to IRREGULARLY IRREGULAR PULSE.
  - P wave is absent in atrial fibrillation

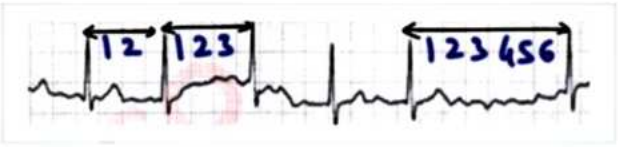
AV nodal block	Ventricular rate
2:1	100 beats/min
3:1	133 beats/min
4:1	100 beats/min

  - Atrial fibrillation is a tachyarrhythmia where heart rate can be normal
  - Atrial twitching→stasis of blood in LA→ CLOT→ STROKE. (embolic stroke)

- **Clinical scenario:**

A 40 year old alcoholic, binge drinking develops sudden onset of palpitations, dizziness and syncope

  - On examination
    - Pulse: Rate-fast, Rhythm- irregularly irregular
    - Blood pressure: 70/50 mmHg
- **ECG:**
  - R-R interval is never constant
  - Absent P waves



Important Information

- Irregular R-R interval in a alcoholic indicates Atrial fibrillation
- Irregular R-R interval in Chronic obstructive pulmonary disorder indicates Multifocal atrial tachycardia

- **Treatment: R.A.C.E**
  - Rate control: I.V Esmolol/ Verapamil
  - Anticoagulation: Novel oral anticoagulants- Oral Rivoroxaban (Factor IX inhibitor) and Dabigatron (Thrombin inhibitor)

    WARFARIN to be answered in case of Rheumatic etiology
  - Rhythm Control: Chemical cardioversion- I.V Amiodarone/Ibutilide
  - Electrical cardioversion: Synchronised DC shock of 200J

Important Information

- Warfarin toxicity With Intracranial haemorrhage and INR >20 : Prothrombin complex concentrate is given

- **NO need of anticoagulants in recent onset of atrial fibrillation.**
- **Need for anticoagulants in atrial fibrillation decided by?**
  - Trans esophageal echocardiography
  - CHA2D S2 VA Sc

CHA_2DS_2-VASc	
Risk Factor	**Score**
Congestive HF (CHF)	1
Hypertension	1
Age ≥ 75	2
Diabetes mellitus	1
Stroke, TIA, or TE	2
Vascular disease (prior MI, PAD, or CABG)	1
Age 65–74	1
Sex category (Female)	1

Important Information

- Atrial fibrillation can degenerate to ventricular fibrillation in presence of Bundle of Kent/ Accessory pathways with no decremental response only Wolf Parkinson White syndrome

Atrial Flutter

- Macro re-entrant circuit in right atrium

Atrial Flutter	Atrial Fibrillation
Macro re-entrant circuit in Cavo tricuspid isthmus of right atrium	Multiple ectopic foci on the Left atrium
Firing rate: 240-350 beats/min	Firing rate: 300-600 beats/ min
2:1 Block leading to Heart rate: 175 beats/min	4:1 Block leading to Heart rate: 150 beats/min
COPD	Alcoholic
Palpitations, loss of consciousness , reduced systolic blood pressure, fast pulse	Palpitations, loss of consciousness, reduced systolic blood pressure, fast pulse
ECG: Right sided leads I, II , aVF, saw tooth waves	ECG: All leads, irregular R-R intervals

Important Information

- Saw tooth wave in EEG- REM
- Delta wave in EEG- NREM stage 3

- **Treatment: <u>R.A.C.E</u>**
  - **Rate control: I.V Esmolol/ Verapamil**
  - **Anticoagulation: 1° pulmonary embolism**
  - **Rhythm Control: Chemical cardioversion- I.V Amiodarone/ Ibutilide**
  - **Electrical cardioversion: DC shock of 25- 50J biphasic**

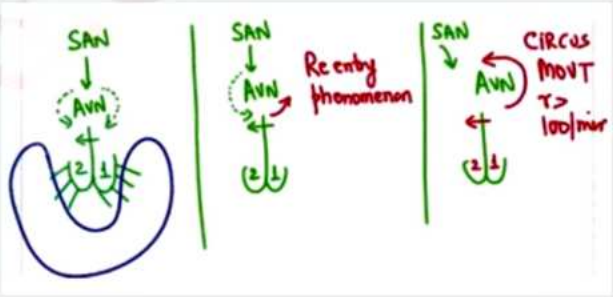
Table 14.1

Pacemaker	Normal heart rate	Disease	Abnormal heart rate	Pathology	ECG pattern
SA node	60-100 beats/min	Sick sinus syndrome	45-60 beats/min	Absent P wave	
AV node	45-60 beat/min	Complete heart block (Stokes Adem/ Ro antibodies- neonatal lupes).	~40 beats/min	AV dissociation	
Bundle of His	<40 beats/min	Mobitz 2 heart block	15-20 beats/min	Sudden cardiac death.	

15 ECG AND ARRHYTHMIAS - 2

Paroxysmal Supraventricular Tachycardia 00:00:13

- **Pathophysiology**
  - Difference in refractory period across in both sides of AV node leads to retrograde conduction called Reentry phenomenon
  - The reentry phenomenon is also called Circuit movement
  - The circuit movement competes with the normal current flow, finally taking over the activation of the ventricles leading activation of ventricles causing Narrow QRS tachycardia.
  - Also called AV nodal re-entrant tachycardia.



Clinical scenario 00:06:06

- A 25-year-old presents with recurrent episodes of palpitations, recurrent syncopal attacks and dizziness.
  - ECG:- Normal findings. Advised for placement of HOLTER device (Records ECG for 24 hrs)

- **ECG findings**
  1. Narrow QRS complex
  2. ST segment depression
  3. R-R interval decrease
  4. Hidden P waves

- **Treatment**
  - **Prevention**
    → Oral Verapamil
  - **Acute episode**
    → Systolic blood pressure < 90 mmHg /unrecordable- DC shock
    → Systolic blood pressure ≥ 90 mmHg - Carotid sinus massage
  - Carotid sinus massage: Activation of Carotid sinus nerve, a branch of Glossopharyngeal nerve and
    → EFFERENT arc is Vagus nerve.
    → Site- Perpendicular to the angle of jaw
    → Contraindication-Arthrosclerosis of Internal carotid artery (Check for carotid bruit)
    → Disadvantage: can lead to stroke
    → Carotid sinus massage Contraindicated in carotid artery bruit.
  - Paediatric case of PSVT
    → Face ice pack
    → Valsalva maneuver
    → Occulocardiac massage (Not recommended)
    → Carotid sinus massage NOT recommended due to short neck
  - **Chemical Cardioversion**
    → IV Adenosine
    → 6mg/12mg
  - **Electrical cardioversion**
    → Synchronised DC shock
    → 120-200J

Important Information

- Synchronised DC shock- Cardioversion
- Non- synchronised DC shock- Defibrillation

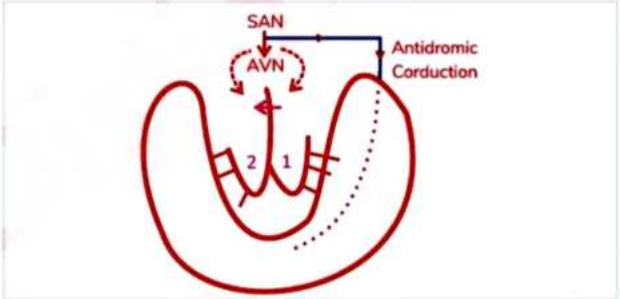
Roadmap to treat Paroxysmal supraventricular tachycardia

Acute	Crashing patient	Prevention
• Carotid sinus massage • IV Adenosine • Synchronised DC shock	• Direct Synchronised DC shock • 120-200J biphasic	• Electro physiological studies • Ablation of circuit • Oral verapamil

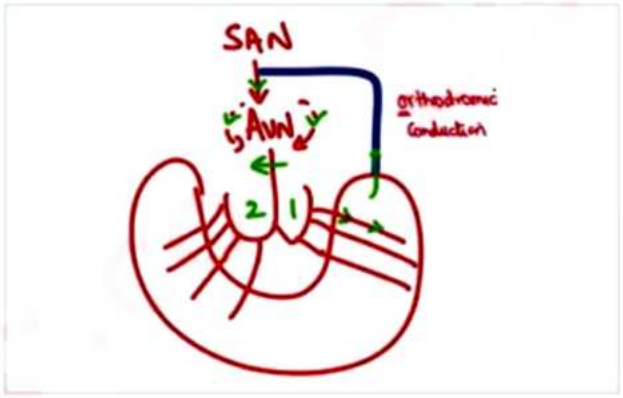
Atrioventricular Reentrant Tachycardia (AVRT)

00:28:20

- **Antidromic Conduction**
  - The conduction from SA node goes through the Bundle of Kent to the ventricle in antegrade direction activating them.
  - Current can reenter via AV node.
  - Intermyocyte conduction.
  - Broad QRS complex



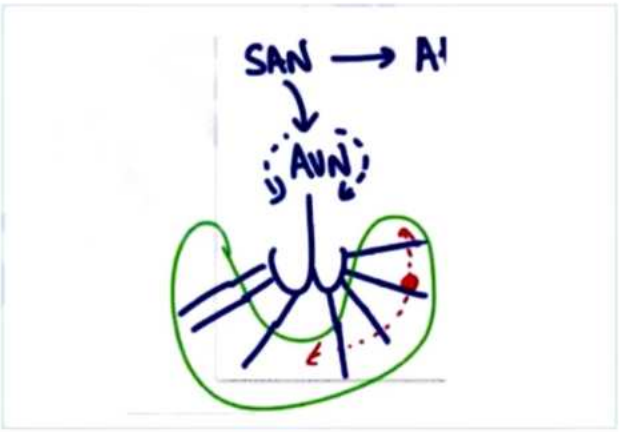
- **Orthodromic Conduction**
  - The conduction from SA node goes through a normal pathway, but a minor current leaks from Purkinje fibres and goes back to SA node through Bundle of Kent in retrograde direction
  - Narrow QRS complex



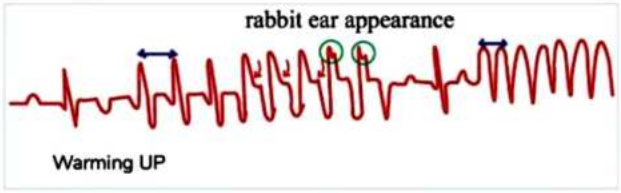
- This can occur in Wolf Parkinson White syndrome

Ventricular Tachycardia 00:34:50

- Terms used in MCQ are Pulseless ventricular tachycardia/ Monomorphic ventricular tachycardia.
- Ectopic foci in the ventricles will fire at a rate of 200 beats/min resulting in intermyocyte conduction
- Broad QRS complex
- AV dissociation: Canon a wave.
  - Atrial rate: 100 beats/min
  - Ventricular rate: 200 beats/min
  - Lack of coordination leads to reduced cardiac output
- Pathological tachycardia



- **ECG**
  - Premature ventricular complexes,>3 consecutive complexes
  - Heart rate >100 beats/min
  - Broad QRS complex tachycardia
  - Asymmetric Rabbit ear appearance
  - Josephson's sign- notch in down slope of S wave
  - CAPTURE BEATS
  - Sinusoidal appearance
  - Extreme axis deviation



- **Treatment**
  - **Pulseless ventricular tachycardia**
    → Non-synchronised DC shock (defibrillation)- 200J biphasic
  - **Stable ventricular tachycardia**
    → Systolic blood pressure >90mmHg
    → IV Amiodarone
  - Post Myocardial infarction ventricular tachycardia
    → IV Lignocaine (only for pharma MCQ if amiodarone is not given in options)

Polymorphic Ventricular Tachycardia 00:50:55

- Also called TORSADES DE POINTES
- **Causes**
  1. Hypokalaemia
  2. Hypomagnesemia
  3. Hypocalcaemia
  4. Erythromycin and Hydroxychloroquine
  5. Cisapride
  6. Astemizole
  7. Ketoconazole
  8. Class IA, IC, class III anti arrhythmics
- **ECG**
  - QTc prolongation (QTc= QT/√R-R)
  - Broad QRS complex tachycardia
  - Variable amplitude of qRS complexes

Important Information

- Tetany: QT prolongation
- Torsades de Pointes: QTc prolongation

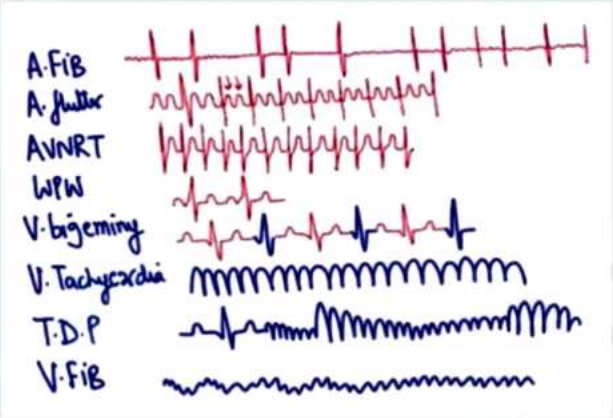
- **Treatment**
  - IV Magnesium sulphate
  - Non-synchronised DC shock in low systolic blood pressure < 90 mmHg

Important Information

- Magnesium sulphate is used to treat Eclampsia, Impending respiratory failure in asthma and Torsades de Pointes

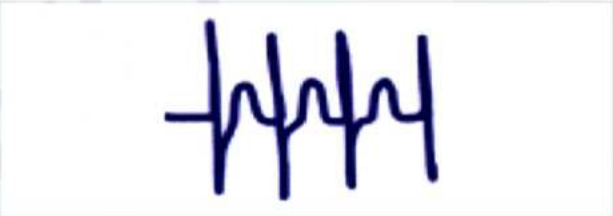
Tachyarrhythmias 01:00:00

Condition	Treatment
Atrial fibrillation	• Esmolol
Arial flutter	• Esmolol
AV nodal re-entrant tachycardia/ PSVT	• Prevention: Verapamil • Acute episode: Adenosine
Wolf Parkinson White syndrome	• Prevention: Flecainide • Acute episode: Procainamide
Ventricular bigeminy	• Lignocaine
Ventricular tachycardia	• Post MI: Lignocaine • Stable VT: Amiodarone
Torsades de Pointes	• Magnesium sulphate



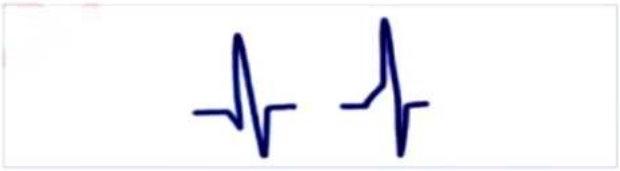
Abnormalities of QRS Complex 01:09:20

- **Narrow QRS complex Tachycardia**
  - AV nodal re-entrant tachycardia/ AV reentrant tachycardia (Orthodromic)



- **Broad QRS complex**
  - Ventricular tachycardia, Torsades de Pointes

- **Delta Wave**
  - Wolf Parkinson White syndrome



- **J wave/Osbourne wave**
  - Hypothermia

- **Epsilon wave**
  - Arrhythmogenic right ventricular dysplasia

Important Information

Ventricular fibrillation

- Treatment :-Non-synchronised DCshock 200J
- Adrenaline Increase coronary perfusion & improves response to DC shock. .

Abnormalities of ST Segment 01:14:56

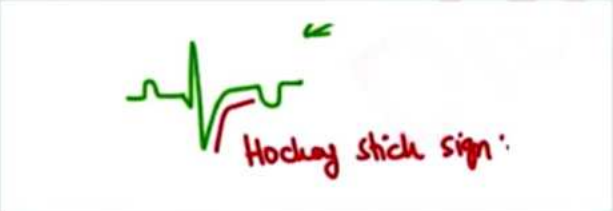
Mnemonic: ELEVATION AB

- **E**lectrolyte imbalance- Hyperkalemia
- **L**eft bundle branch block
- **E**arly repolariztion variant
- **V**entricular Aneurysm
- **T**rauma- Pericardiocentesis
- **I**schemia- Myocardial infarction- ST convex upward, Pardee sign/Tombstone
- **O**sbourne wave: J wave
- **N** occlusive Vasospasm- Prinzmetal angina
- **A**cute pericarditis:- Concave upwards
- **B**rugada syndrome, SCN5A defect- Cove pattern/saddle back pattern of ST elevation.

ST Segement Depression 01:20:25

- **Causes**
  1. Hypokalaemia
  2. Chronic stable angina chest pain on exertion (>70% block in coronary artery)

3. Cocaine overdose
4. Digoxin
   → Reduced heart rate, prolonged PR, ST depression, Short QT.
   → Characteristic feature- Hockey stick sign in ECG



Important Information

- **DIGOXIN TOXICITY**
  - Most characteristic: Non-paroxysmal atrial tachycardia with AV block (variable)
  - Most common: Ventricular bigeminy (treated with lignocaine)
  - Hockey stick sign:ECG:- digoxin
  - Hockey stick sign:ECHO:-MS

T Wave abnormalities 01:26:44

- Height <5 mm in limb leads and <10 mm in chest leads
- **Hyper acute T waves**
  - Myocardial infarction
- **Tall tented T waves**
  - Hyperkalaemia

- **T wave inversion**
  - Hypokalaemia
  - Myocardial infarction
  - Subarachnoid haemorrhage/ cerebro vascular accident
  - S1Q3T3- Acute cor Pulmonale

QT Interval Abnormalities 01:31:00

- Inversely related to calcium and magnesium
- Normal duration: 360-440 milliseconds (9-11 small squares)
- Starting of Q wave to end of the T wave
- Tetany- QT is prolonged
- HYPERCALCEMIC CRISIS
  - **Causes**
    1. Carcinoma Breast
    2. Squamous cell - Lung cancer
    3. Parathyroid adenoma
    4. Sarcoidosis
    5. Vitamin D3 intoxication
  - **Investigations**
    1. ECG- QT shortening
    2. Increased serum calcium
    3. Normal serum albumin
    4. Increased Ionized calcium
  - **Treatment**
    1. Correct dehydration with Normal saline
    2. Furosemide drip- MOA calcium loss in urine
    3. Drug of choice- IV Ibandronate
    4. Calcitonin nasal spray

ECG analysis 01:38:03

- Evaluate Heart rate: Lead II, <3 Large squares(tachycardia), >5 large squares (bradycardia), R-R interval.
- Axis calculation: Lead I/aVF
- P wave abnormalities- P pulmonale and P mitrale
- PR interval:
  - Short- Lown ganong levine syndrome, Wolf Parkinson White syndrome
  - Prolonged Heart block (except Mobitz 2)
- QRS Complex
  - Narrow QRS complex tachycardia: S.V.T
  - Wide QRS complex tachycardia: VT/TDP
- ST segment elevation/depression
- QT interval

PREVIOUS YEAR QUESTIONS

Q. Which of the following results in broad complex tachycardia?

A. Antidromic conduction, Accessory pathway mediated

B. Orthodromic conduction , Accessory pathway mediated

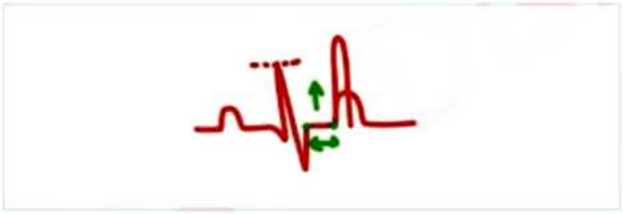
C. AV nodal re-cntrant tachycardia

D. Atrial fibrillation

16 ECG CHANGES IN HYPERKALEMIA AND HYPOKALEMIA

T Wave Abnormality (Hyperkalemia) 00:00:20

- T wave amplitude is directly proportional to potassium value



1. Tall tented T wave
2. ST elevation
3. P wave: Amplitude/ duration decreases and absent, PR prolonged
4. QRS complex broad
5. Sine wave pattern seen when values exceed> 8meq/L

Important Information

- Reason for death of the patient with hyperkalemia is due to Diastolic arrest
- Inverted T wave:-Hypokalemia,NSTEMI,Unstable Angina.

Treatment of Acute Hyperkalemia 00:05:10

- 1st line drug:- IV calcium gluconate /chloride (Drug of Choice)
  - Do not asnwer Calcium Carbonate
- Insulin Drip:- Send potassium inside cells @ 0.5-1 meq/hour
- Salbutamol Nebulization
- IV furosemide: Kaliuria
- Hemodialysis: Most effective method to lower elevated serum potassium.

CKD/ chronic hyperkalemia

- Patiromer
- Hyperkalemia with hypertension: continue ACE inhibitors and give patiromer if potassium still elevated, stop ACEI and start CCB.

Hypokalaemia 00:10:05

Death occurs due to diaphragmatic paralysis

- T wave decrease, absent or inverted

- ST segment depression
- P wave amplitude increase (Pseudo P- pulmonale)
- Prominent U wave
- Prolonged QU & PR interval (QU because T wave is absent)

Treatment

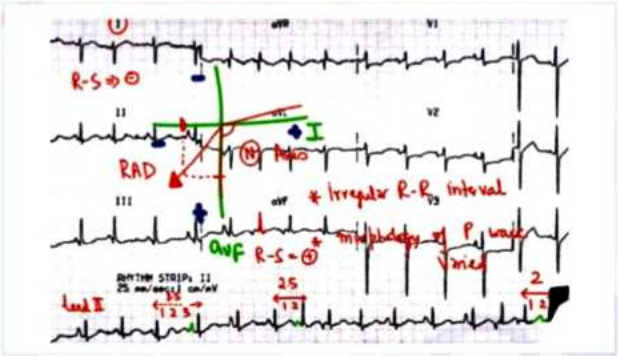
- KCl added to IV Fluids and given as infusion
- Peripheral line, at 20-40 meq/hour

Summary 00:17:49

Hyperkalemia	Hypokalemia
Tall tented T wave	T wave inverted
ST elevation	ST depression
P wave absent	Pseudo pulmonale: Prominent U wave
Calcium gluconate	Kcl+IV fluids

29 MULTIFOCAL ATRIAL TACHYCARDIA

- Overall, atrial fibrillation is the most common sustained tachyarrhythmia or hypertension or >65 years or hypertrophic cardiomyopathy or dilated cardiomyopathy.
- Sudden death in Hypertrophic cardiomyopathy is due to ischemic ventricular fibrillation.
- In atrial fibrillation on ECG, there is an:
  - Irregular R-R interval
  - Absent P- wave.
- In multifocal atrial tachycardia on ECG there are
  - P- waves present of varying morphology.



Cause

1. COPD
2. Theophylline toxicity (In PHC the puffers are not available, so these are prescribed in COPD patients)
3. Sepsis
4. Acute illness in lungs: In the past, the patient may have suffered from the covid-19, and later fibrosis in the lungs developed.

Clinical Scenario

A 70-year-old male patient has a known case of COPD. He is on theophylline or puffers. Today morning, he complained of palpitation, dizziness, and a syncopal attack.

- On ECG, there is an irregular R-R interval.
  - More or equals to 3 varied morphology of P-wave present.
  - Some of the p-wave might be peaked or amplitude or duration may be longer.
- Usual heart rate is 100-150/min.
- In old age the heart rate of 150/ minute decreases the cardiac output.
- There is a right axis deviation.
- In the case of COPD there is pulmonary hypertension leads to the dilation of the right atrium causing the right axis deviation.

Management

00:10:10

- D-C shock: ineffective
  - Usually not recommended in this patient.
  - Heart is in a hypoxic state and there is an amount of theophylline or cytokine present.
  - So, when we give DC shock the rhythm gets normal but after some time it gets abnormal.
  - So, we don't give DC shock frequently.
- Verapamil:
  - Verapamil acts on the AV node it slows down the conduction and causes stabilization of the heart.
  - The dizziness and palpitation component is managed.
- Metoprolol (Beta blocker)
- Amiodarone: it has a membrane-stabilizing effect.
  - It has its own toxicity.
  - So, it cannot be prescribed for a long time.
- Treatment of the cause:
  - Treatment of COPD with the
    - → Low-flow oxygen supplementation
    - → Increased the dose of LAMA.
    - → Add inhaled corticosteroids.
    - → Management of the COPD to prevent the recurrence of MAT.

17 ISCHEMIC HEART DISEASE PART- I

Acute Coronary Syndrome

- In India and the USA, leading cause of mortality is Coronary artery disease (CAD)

Atherosclerosis 00:01:25

- Rupture of Atherosclerotic plaque followed by clot formation in Coronary arteries leads to necrosis of myocardium, in MI.

- Accelerated atherosclerosis
  - May develop as early as 40 years of age
  - Seen not only in obese patients but also in Diabetic as macrovascular complication.
  - Also seen in patients with Hypothyroidism, SLE, Rheumatoid arthritis.
- Main arteries involved are
  - **Abdominal aorta**
    → Leads to abdominal aorta aneurysm leading to rupture if size of aneurysm is >5.5cm.
  - **Coronary arteries**
    → If the blockage caused by Atherosclerotic plaque is 70% and more, symptoms of stable angina develop.
    → Case scenario: If a patient is performing physical exertion and emotion (angry), he may experience severe chest pain which relieves once the patient rests.
    → Due to plaque fissure, it will cause Myocardial Infarction (MI).
    - STEMI (STEMI)
    - NSTEMI (NSTEMI).

    → May also lead to Unstable angina.
    → The three-differentials of acute coronary syndrome are STEMI, NSTEMI and Unstable angina.
  - **Popliteal arteries**
    → As it is a peripheral artery disease, Claudication can be seen.
  - **Circle of Willis**
    → May contribute to TIA (Transient ischemic attack) or stroke.

Important Information

- Order of prevalence of atherosclerosis, Abdominal aorta > Coronary arteries > Popliteal arteries > Circle of Willis.
- **Prinzmetal angina/Variant angina:** It is due to spasm of coronary arteries and it is the only angina with ST elevation.
- Intermittent Claudication is seen in Berger's disease which is common in patients less than 45 years of age and non-smokers.
- **Acute chest syndrome:** Seen in sickle cell anemia patients where the sticky nature of RBC contributes to block.

Markers of Atherosclerosis 00:12:10

1. High sensitivity CRP (hs CRP)
   - If the test is positive, it is a predictor of future coronary events.
   - It is the single best test to detect CAD.
2. Elevated Total cholesterol
   - **Risk factor for CAD:** Total cholesterol/HDL ratio: >3.5 - 5.5.
3. High Lipoprotein a/Apolipoprotein B ratio.
4. **Homocysteinemia**
   - It is an autosomal recessive condition.
   - Homocysteine levels are increased.
   - Premature atherosclerosis is observed.
   - Can be treated with vitamin $B_{6,9,12}$ but not Vitamin E.

Important Information

- Apolipoprotein A is related to HDL and it is cardio protective.
- Vitamin E worsens Coronary artery disease
- Framingham criteria is used in diagnosis of Congestive heart failure (CHF)

5. **High LDL and Low HDL**
   - Low HDL is comparatively a more likely risk factor than High LDL.

- **Framingham Score** 00:22:00
  - It is a 10-year mortality rate calculator
  - If the calculator shows estimated risk of more than 10% mortality, then the patient requires statin therapy.
    → Currently, LDL cutoff for low-moderate risk individuals is <115 mg/dl.
    → For high risk patients LDL cutoff is <100 mg/dl.
    → For very high-risk patients (diabetics, CKD and hemodialysis patients) is <70 mg/dl.

Important Information

- If the patient is on statin therapy, the patient should be asked for any muscle pain and followed up with a CPK-MM test to identify muscle damage.

Possible scenarios in patients with Atherosclerosis

00:27:40

- **Scenario-01: Plaque fissure/Vulnerable plaque**

  - Atherosclerotic plaque will have two layers
    → Yellow color Indicates the foam cells which are modified macrophages as a result of oxidation of LDL.
    → Blue color part is a fibrous cap.
  - If a fissure/ tear develops in the plaque it attracts platelets leading to thrombus formation ultimately causing complete occlusion of of lumen of coronary artery.
  - Thus, Patient is develops MI
- **Scenario- 2: Non-vulnerable plaque**

  - In this there will be reduction in the blood flow as a result of luminal obstruction due to plaque.
  - If the blockade is more than 70%, then there will be symptoms of stable angina (Chest pain on exertion and emotion).

Radiological Investigations in patients with Atherosclerosis

- **Coronary angiography**
  - Invasive
  - Done either by trans-radial or trans-femoral approach.
- **M.D.C.T scan (Multidetector CT scan)**
  - Non-invasive
  - Can differentiate between Vulnerable and Non-vulnerable plaques
- **Intravascular ultrasound**
  - Invasive.

Important Information

- In both vulnerable plaque and non-vulnerable plaque patient's, calcification of coronary arteries occurs on a long run.
- MDCT scan can quantify calcification.
- To determine the severity of calcification in coronary arteries, Agatson score is used.

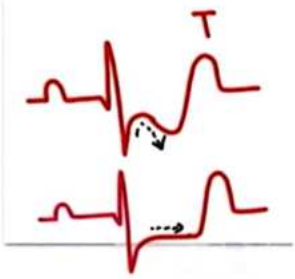
Chronic Stable Angina/ Reversible Ischemia 00:35:45

Case Scenario

Example:60 years old man with 25 year history of smoking says .Whenever he walks fast he has symptoms of chest pain. He also has hypertension but doesn't take medication. The combination of exertion and emotion will increase the chest pain. Usual duration of chest pain will be 5-10 mins. once he will sit down, the chest pain will reduce and symptoms will reverse. Hence, it is called reversible Ischemia.

- Sometimes we might get some interesting hints from patients.
- **Postprandial Angina:** The previous night he might have felt heaviness in his chest while eating. But we will definitely get this history on a retrospective basis in the individual.
- **Abdominal angina:** The patient might get post prandial abdominal pain. It occurs because of Atherosclerotic narrowing of the superior mesenteric artery.

- **ECG findings are normal if patient reaches clinic after relief of symptoms**
- **ECG shows ST depression if patient is symptomatic**
  - At this instant advised to give sublingual nitroglycerin.
  - We repeat the ECG after 10 minutes, he is feeling relatively better. Now the ST segment will become normal.
- If a person claims that he had chest pain yesterday, then advise Treadmill Test
  - Modified Bruce protocol is used in T.M.T
  - Gradually increase the speed and inclination of the treadmill every 3 mins.
  - Increase speed- 1.6 to 6 mph gradually.
  - ECG will show downsloping ST depression.
  - Target heart rate to be achieved is (220-age) x 85%.
- If the patient is 60 years old, the target heart rate is 140. The display shows heart rate above 140 and a normal ECG, we need to look for other reasons for chest pain.
- If the target heart rate is not attained, and ECG is showing ST depression $\geq$ 1 mm and persisting for at least 2 small squares in the ECG or $\geq$ 80 msec in at least 2 contiguous leads it implies blockage in coronary artery.
  - Sensitivity of this test is 75%
  - Non-invasive test



- Contraindications for TMT
  1. Paraplegia.
  2. Buerger disease/ Thromboangiitis obliterans
  3. Diabetic with a non-healing ulcer on the sole of the foot.
  4. Diabetic with charcot joints (neglected HbA1C values).
  5. Severe osteoporosis, with Bone pain
  6. Severe aortic stenosis (<1 cm^2) - absolute contraindication
  7. Morbid obesity
  8. Unstable angina
  9. MI: in previous 48 hrs

Duke Score 00:59:30

- Used to evaluate the severity of chronic stable angina
- Determine the best modality of the treatment
- Determines prognosis of the patient
- Formula:
  - No of mins walked on treadmill-[5 x ST depression]-[4 x angina grade]
- Scoring:
  - **Low risk:** A score of more than 5. Chances of a patient dying in the next 10 years are very negligible. Advise medical treatment for chronic stable angina.
  - **Intermediate risk:** A score of +4 to -10. PCI drug eluting stent is advised.
  - **High risk:** A score of -11. Treated with a CABG.

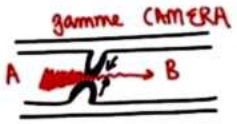
Morbid Obesity and CSA investigation

- Stress Echocardiography
  - Dobutamine activates the βeta1 receptors resulting in increased heart rate.
  - If the coronary arteries are of normal caliber then it will not cause any changes in the ECG as the supply of oxygen will be normal.
  - But, in a person with more than 70% blockage in any of the coronary arteries, after this drip you will see that the ECG of the person will show ST depression
- Echo- Regional Hypokinesia.
- If you compare the sensitivity of stress echocardiography with a treadmill test, the sensitivity is relatively better, it goes up to 80%.

Hibernating Myocardium

- Gradual decrease in the myocardial activity due to blockages in the coronary arteries leading to reduced oxygen supply.

Myocardial Perfusion Imaging 01:10:25



- In a patient with a fixed stenotic obstruction caused by atherosclerotic plaque, the amount of blood going across the physical obstruction will be limited.
- The magnitude of blood flow between point A and B will have differentials.
- A gamma camera is used to pick up these differentials.
- A radioactive agent either Thallium 201 or Tc99 is used along with stress.
- Alternate names- Thallium scan, Sestamibi scan.

Important Information

- Stunned myocardium- Sudden decrease in myocardial contractility seen MI.
- Sestamibi scan is used to identify Parathyroid adenoma.

Hibernating Myocardium vs SCAR – Dead tissue 01:12:50

- If there is a scar anywhere in the heart, it will exhibit less contractility.
- Common thing between the two is if some part of the heart has less contractility there can be two reasons:
  - Less supply of oxygen
  - Scar
- How do you differentiate between a scar and Hibernating Myocardium?
  - PET Scan
- How to pick up blockages in the coronary artery?
  - Treadmill Test
  - Stress Echocardiography
  - Sestamibi Scan
  - PET Scan - Hibernating Myocardium/ Reversible Ischemia

Q. What is the gold standard test for Chronic stable angina?
Ans. Coronary angiography

Treatment: Chronic stable angina 01:16:35

- Tablet Aspirin (Enteric Coated) - 75 mg - Continued on a life-long basis
- The major mortality reducing drug for Chronic stable angina- Beta blockers- Metoprolol. [DOC]
- Sublingual nitroglycerin (or a Buccal spray) - For emergency usage
- Long acting nitrates - Isosorbide mononitrate: For postprandial chest pain.
- Metoprolol/Carvedilol - Contraindications: Sick Sinus Syndrome /high grade Heart Blocks
- Amlodipine is used in cases where Metoprolol/ Carvedilol cannot be used.
- Atorvastatin.
- Stop Smoking.
- Vitamin B6/9/12.
- New Drugs - Ranolazine , Ivabradine , Trimetazidine.

Important Information

- Sildenafil and NTG should not be used together since they both can increase nitrous oxide in the blood leading to hypotension.

Q. All of the drugs reduce mortality for a person with chronic stable angina except?
Ans. NTG/Nitrates

- Nitrates have no mortality benefits when it comes to patients with chronic stable angina but give symptomatic relief.

Clinical Scenario 01:29:45

- The patient with chronic stable angina did not responded to the medical therapy, It could be due to the fact that the number of blockages might be more or percentage might be more.
- If there is a failure of therapy then schedule
- Why is Coronary Angiography advantageous?
  - It is because it gives real time evidence of number and severity of blockages in CSA.
- Approach that will be used will be either transradial or transfemoral.
- Technique of the puncture of the artery is called the Seldinger Technique.

Triple Vessel Disease 01:33:40

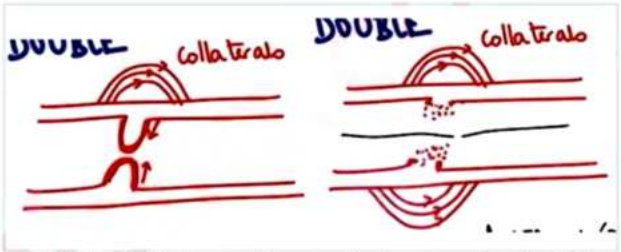
- Medical therapy will continue
- As per the current guidelines of the American Heart Association, continue 75 mg Aspirin tablet, if patient is scheduled for any other surgery.
- **What is the preferred bypass graft?**
  - The performance of an arterial graft will always be superior to a venous graft.
- Internal Mammary artery grafts or Radial artery grafts will be superior as compared to saphenous vein.

Q. What is the preferred Revascularization procedure required for Triple Vessel Disease?
Ans. Coronary Artery Bypass Grafting

Q. What is the preferred Revascularization procedure required for Single Vessel Disease?
Ans. Percutaneous Coronary Intervention with Stenting.

Single Vessel Disease 01:39:35

- When it comes to single vessel disease occurring in a person Chronic stable angina it is said to have a good prognosis. The reasons are:
  - It is a slow progressing disease.
  - Collateral will be formed which ensures at least some blood flow.



- If during the PCI procedure somebody were to develop MI on the table due to platelet plug formation, then it would be called Type 4 A Myocardial Infarction.
- Troponin I values elevate substantially in this case. There is a

5 times elevation of the value of Troponin I over the baseline value.

- **What are the drugs that are used during or before the procedure to prevent the onset of Myocardial infarction?**
  - Pre Operation - Antiplatelet drugs
    - → Ticlopidine
    - → Ticagrelor
    - → Prasugrel
  - Intra Op gp IIb/IIIa platelet inhibitors
    - → Enoxaparin
    - → Abciximab
    - → Eptifibatide
    - → Tirofiban
- Atherosclerosis has a tendency to recur at the same site and again contribute to a blockage.
- In this case a stent is deployed to prevent the re-blockage from reoccurring.
- The stents used are drug eluting stents. The coating over the stent is Everolimus/ Sirolimus (Immunomodulatory in nature).

Double Vessel Disease 01:50:21

- Treatment of choice for Double vessel disease with multi-site grafting is CABG - Coronary artery bypass grafting.

Q. LAD blockage and EF <40%

Ans. LAD is too precious a blood vessel to be handled by PCI and stenting. The treatment approach here will be CABG.

Important Aspects of Chronic Stable Angina 01:53:45

- Alternative name for CSA - Hibernating Myocardium/ reversible ischemia.
- This condition will be having at least more than 70% blockage to cause symptoms to occur in a person.
- When it comes to bio markers, they will always be normal.
- First Investigation - A treadmill test (TMT) showing ST 80 positivity.
- If a scenario is formulated that the person is unable to walk, then the investigation of choice will be Stress Echo cardiography
- To differentiate between scar and Hibernating Myocardium the best investigation is a PET scan because the scar will not have any metabolic uptake whereas Hibernating Myocardium will have some kind of uptake.
- Nuclear Scan - Sestamibi Scan
- **Which is the major mortality reducing drug for CSA?**
  - Metoprolol
- **Revascularization procedures**
  - CABG
  - PCI + Stenting
- **Gold Standard investigation - Coronary angiography bypass grafting**

Unstable Angina/ Accelerating Angina 01:58:45

Trigger for Unstable Angina

- Plaque Fissure
- Platelet Plug
- Thrombus
- Disintegration of thrombus by Protein C/S/AT 3

Atheroembolism of clot fragments into downstream perforators

- These perforators will be blocked by the thrombus fragments leading to chest pain.
- If thrombolysis is performed in this patient, it will further break down these small fragments and worsen the condition.
- Unstable angina is a condition where thrombolysis is **absolutely contraindicated.**

Case Study 02:04:35

- A 60 Year old Hypertensive male who smokes 2 packs of cigarettes every day is suffering from diffuse chest pain since morning. When the pain became intolerable he called up his son to help him travel to the hospital. He may have been suffering from the past 3-4 hours.

- You have to look at the ECG findings in this case and compare it with NSTEMI.
- In unstable angina ST is normal in 50% of the cases. 25% causes have ST depression and 25% cases have T wave inversions.
- Biomarkers values were normal in the patient

Treatment of unstable angina

- TBE-MOAN
  - T: Tirofiban/ Eptifibatide
  - B: Beta-Blocker
  - E: Enoxaparin
  - M: Morphine
  - O: Oxygen
  - A: Aspirin 300 mg chewable
  - N: Nitroglycerin drip

[2022 update on treatment of unstable angina / NST - ACS is given in next video of Ischemic heart disease part 2]

- If the high risk patient's Spo2 is not increasing, the blood pressure is not picking up and the crepitations in the chest that were earlier not present or scattered in the lung basis are now more extensively present in both the lungs then you will opt for a Percutaneous Coronary Intervention.
- This process of Percutaneous Coronary Intervention is implemented in all such high risk cases.

Prinzmetal Angina 02:12:15

- It is called Variant Angina because it is the only angina with ST elevation.
- Arginine causes the production of Nitric Oxide in the coronary arteries with help of NO synthase type 3 in coronary endothelium.
- When it comes to normal coronary endothelium, there is a release of Acetylcholine (acts via NO) contributing to coronary vasodilation.
- Injecting Acetylcholine into the coronary artery in Prinzmetal angina patients causes vasoconstriction, since NO production is less
- Provocative test
  - Intra coronary Acetylcholine in a Prinzmetal angina patient leads to Coronary spasm and this spasm is relieved by injecting nitro-glycerine.

Clinical Case Presentation

- A 60 year old female with recurrent attacks of early morning chest pain, she says as the day progresses chest pain tends to reduce and disappear.
- All coronary events are more common in the left coronary artery but in case of Prinzmetal angina, an exception to the rule is that the right coronary artery exhibits spasm.
- Continuing the case the lady tells you when she was around 30 years of age, she visited a lot of doctors because whenever she put hands in cold water, she noticed a change in the color of her fingertips. Vasospastic disorder, Raynaud's phenomenon is usually present in the past medical history of the patient.
- ECG in this patient will show ST elevation, but the cardiac biomarkers will be normal. Serial troponin values will also be normal.

Treatment

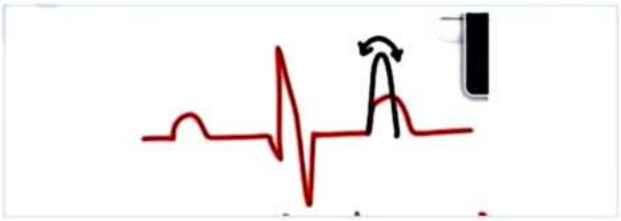
- NTG Drip: In acute setting
- Tablet Isosorbide Mononitrate
- Amlodipine: DOC for prevention of recurrent episodes in Prinzmetal angina.

Follow up

- Many of these patients may suffer from Chronic stable angina i.e, multiple blockages in the artery.
- Chronic stable angina can co-exist with any variety of angina. It may exist with unstable angina or even Prinzmetal angina.

Myocardial Infarction 02:25:00

- Earliest ECG finding in MI- Hyperacute T waves



ECG findings

1. Hyperacute T waves
   - Occurs within a few seconds of blocking anyone of the coronary arteries.
2. ST elevation with convexity upwards

   - It is also called Pardee sign or Tombstone pattern .
   - Males- $\geq$ 2mm in V_2, V_3
   - Females- $\geq$ 1.5mm in V_2, V_3
3. T wave inversions can also be seen.

4. Deep Q waves
   - Persists for life
   - Suggestive of Old MI / Previous MI
5. Non progression of the R wave

- Inferior wall MI is best evaluated in lead II, lead III and lead aVF

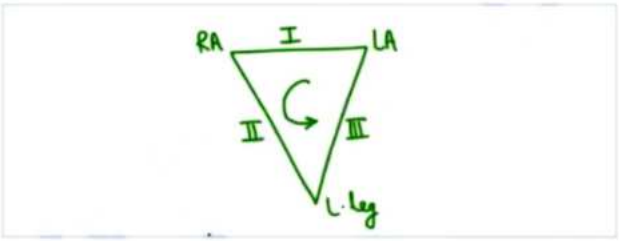
Important Information

- ECG finding seen with myocardial ischemia- Hyperacute T waves, which later are replaced by T - wave inversion.
- ECG Finding seen in myocardial injury- ST elevation.
- The current of injury in MI- ST elevation

Chest Leads 02:40:10

- V1: 4th ics (on right hand side; Line is PSL)
- V2: Same as V1 (but on left hand; PSL)
- V3: Between V2-V4
- V4: 5th ics (on left-hand side; Line is MCL)
- V5: 5th ics (on left-hand side; Line is AAL)
- V6: 5th ics (on left-hand side; Line is MAL)
- V7: 5th ics (on left-hand side; Line is PAL)
- V8: 5th ics (on left-hand side; Line is Scapular)
- V9: 5th ics (on left-hand side; Line is Paravertebral)

Eithoven Triangle:

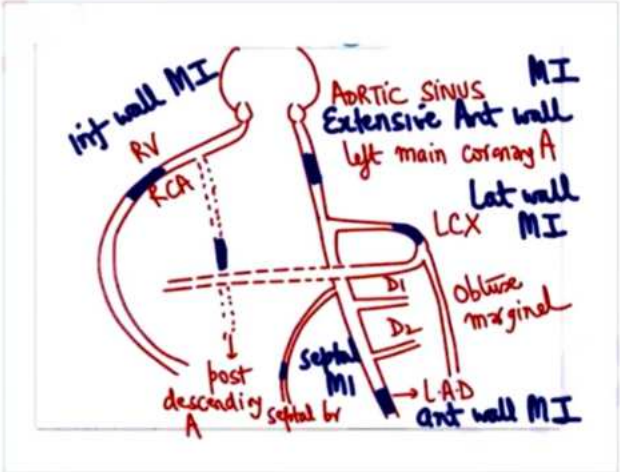


- Lead I is connection between left and right arm
- Lead II is connection between Right arm and left leg
- Lead III is connection between left arm and left leg

Augmented Leads 02:44:35

- Called Augmented because voltage output is better (1.5 times higher than limb lead)
- Lead aVL studies left surface of heart
- Lead aVR studies right surface of the heart
  - It reads all the data inverse of the data in the routine leads.
- Lead aVF is like a camera on the foot and it scans the RV that is facing the diaphragm.

- Einthoven Law
  - Voltage in lead II = lead I+III



- Coronary arteries originate from the root of the aorta.
- First branch of the aorta is the coronary artery.
- Aortic sinus is the site of origin of the coronary artery
  - The 1st blood vessel is the left main coronary artery (if blocked, a person can die before reaching hospital).
  - Then, the branch of the coronary artery is the LCX and supplies the posterior and lateral surface of the heart.
  - Then the branch of LCX which is obtuse marginal (involves lateral heart)
  - LAD is the blood vessel responsible for anterior wall MI and 50% cases are of this.
  - There is also a Septal branch which supplies the interventricular septum (involves septal myocardial infarction).
  - The other is the right Coronary artery supplying the right ventricle.
  - There is a branch running Posteriorly which is the posterior descending artery.

- If a Thrombus occurs in the left main coronary artery, then the type of MI will be Extensive anterior wall MI.
- If a Thrombus occurs in the LCX, then the type of MI will be Lateral wall MI.
- If a Thrombus occurs in the LAD, the type of MI will be Anterior wall MI.
- If a Thrombus occurs in the septal branch, MI is septal MI.
- If a Thrombus occurs in the right Coronary artery, there is inferior wall MI.
- If a Thrombus occurs in the posterior descending artery, the MI is posterior wall MI.

Cardiac Biomarkers 02:53:25

- Troponin I / T: Normal- <0.04ng
  - For identifying at least the value should be double from the normal value.
  - Upto 5 times value can be seen in Type 4A MI.
  - Upto 10 times the value can be seen in Type 5 MI.
- Elevated biomarker is >99th centile URL
- An important test done is CPK-MB:
  - Whenever there is reinfarction >72 hrs.
  - If reinfarction occurs before then, Troponin I test is to be done (Trop I >20% hike over baseline admission value (already elevated value))

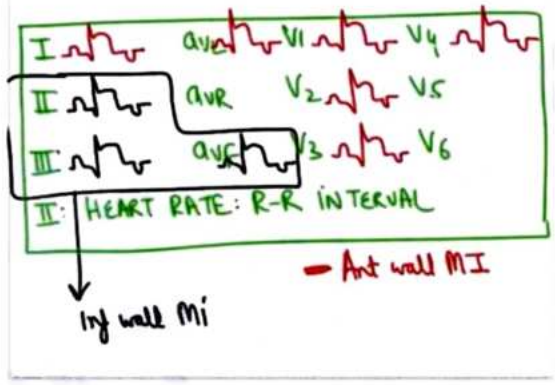
	Rise	Peak	Fall
CPK-MB	4-6 hrs	24hrs	48-72 hrs
Trop I	3 hrs	24hrs	10-14 days
Trop T	3 hrs	24hrs	7-10 days

- Overall best Test for Reinfarction is Troponin I
- Serial Troponin I → on admission, 6 hrs (later values will be elevated)
- Trop I is a highly sensitive Test (quantitative)
- 1st marker to identify MI is H-FABP (Heart fatty acid binding protein) within 1 hr of onset of MI. Another up coming is ischemic modified albumin.

- **Limitations of ECG**
  - Assume a thrombus in the curvature of the LCX.
  - V5 and V6 are acting like cameras but all have the blind spot and here for V5 and V6 it is Curvature of the artery.
  - The findings may be missed by the electrodes.
  - LCX ischemia is poorly localized by ECG.
  - RV ischemia is relatively poorly localized, hence V4 chest lead is used and it is used routinely.
- Best test / most specific test / IOC is Serial Troponin I

Infarct Localization 03:06:47

MI	Blood vessel	Leads
Lateral	LCX	V5,V6, I, avL
Septal	Septal branch	V1,V2, I, avL
Anterior	LAD	V1-V4, I, avL
Extensive Anterior wall	Left main coronary artery	V1-V6, I, avL
Posterior wall	PDA	V1-V4 → ST depression V7,8,9 → ST elevation
NSTEMI anterior wall	LAD	V1-V4 → ST depression
Inferior wall	RCA	Lead II, III, avF



Important Information

First to rise in MI
- HFABP.
- Myoglobin (can also be elevated due to other problems).

Last to rise in MI
- LDH 1 / LDH 2 (Flipping effect / flipping of value).

Levine Sign 03:16:55

- Implies diffuse chest pain persisting in anybody for > 20 min, MI is suspected.

1. ECG: ST elevation or ST depression (STEMI vs NSTEMI).
   - New onset LBBB (if the left ventricle doesn't contract on time causing pulmonary edema).
2. Troponin I: Should exhibit doubling/ Rise above 99th centile of upper reference limit.
3. For the person undergoing a surgery and suffering MI, the test is Transoesophageal echocardiography → Stunned Myocardium.

Types of MI 03:21:22

- Type 1: Atherosclerosis is the main cause; coronary Artery thrombosis; Coronary Artery Dissection
  - Thrombolysis would be of no use.
- Type 2: Cocaine overdose; Severe anemia; CO Poisoning

- Type 3: Sudden cardiac death; two reasons-
  - V. Fib / V.T
  - Mobitz II Heart block
- Type 4:
  - A: Can occur during PCI; Elevation of Troponin 1 x5 times
  - B: Latent stent thrombosis
- Type 5: during CABG, MI can develop because of-
  - Clamp on blood vessel mistakenly by surgeon due to sudden bleeding.
  - Elevation of Troponin I x10 times

19 SYMPTOMATIC BRADYCARDIA WITH A PULSE

- Bradycardia means the heart rate less than 60/minute.
- On ECG strip, count the large square between the R-R interval

- Asymptomatic bradycardia requires no treatment.
- People who are into endurance sports have a high vagal tone.
  - Because it is the physiological response of the body to conserve oxygen so heart works for a long duration.
  - So, no need for treatment.
- In hypothyroidism, bradycardia is seen.
- Only symptomatic bradycardia has to be treated.

Chemical Pacing 00:02:35

- We want to increase the heart rate with the drugs like atropine, epinephrine, and dopamine.
- It is useful in patients with symptomatic bradycardia.

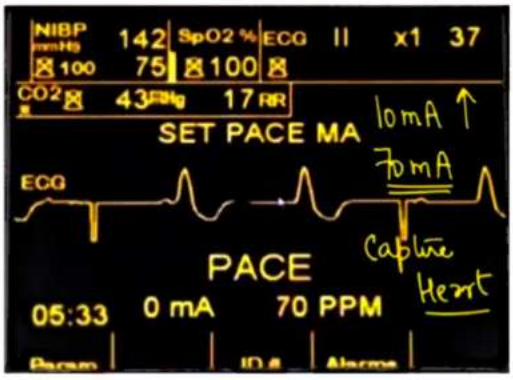
Clinical Features 00:03:50

1. Dizziness
2. Altered mental status.
3. Chest pain: The heart beating slowly leads to a decrease in cardiac output causing a decrease in systolic blood pressure and diastolic blood pressure causing a decrease in coronary blood flow.
4. Dyspnea, pulmonary oedema: Pooling of blood into the lungs as well as in peripheral circulation.
5. Inferior wall MI
   - Right ventricular failure occurs because the right coronary artery is occluded.
   - Kussmaul sign is positive.
   - Raised JVP
   - Full neck veins
- On ECG, the R-R interval is having more than 5 large squares.
- If there is a Heart block P-R interval increased.

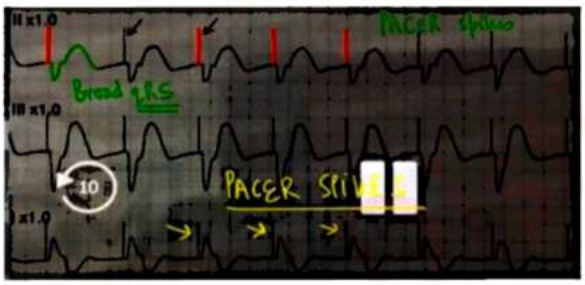
Treatment 00:05:32

1. Patent airway
2. Monitor SpO_2
3. Assisted ventilation: Using NIV.
   - In unconscious patients to prevent aspiration, we do endotracheal intubation.
4. Secure the IV access: Atropine is given.
   - Dosage of atropine: 1 mg, repeat after 3-5 mins.
   - Maximum dosage that can be given is 3 mg.
   - In spite of atropine, no change in HR, or HR is still dropping
   - Immediately move to TCP
   - Adrenaline: 2-10 µg/kg/min
   - Dopamine: 5-20 mcg/kg/min

Transcutaneous Pacing 00:12:25



- Delivery of current in an incremental fashion.
- We start with the 10 mA and till we attain the 70 mA we capture the heart.
- On ECG, the vertical lines are pacer spikes.
- We put pedals as same as used in the automated defibrillator.
  - One on the right side of the chest below the right clavicle
  - 2nd on the apex of the heart on the nipple near the axilla.



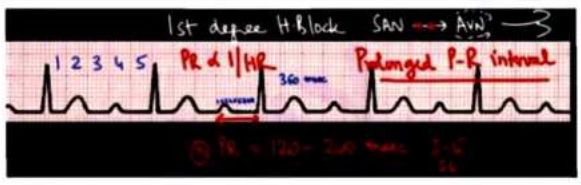
- On ECG, the broad QRS complex is followed by a small T.
  - No P wave because of the SA node working at the moment.
- In a person having a heart rate of 40/minute if we are able to attain a target heart rate of 70-80/minute is very commendable.
- So, TCP improves the perfusion of the heart and the brain.
- First-line management on the failure of chemical pacing.

Trans Venous Pacing

- Indication: if TCP fails or worsening of hemodynamics.
- Giving electrical stimulation to the heart via the muscle of the chest wall creates fluttering in the chest muscle as well as in the neck muscle itself.
- Normally to check the adequacy of perfusion we feel the carotid pulse but, in this case, we use the femoral pulse.

1st Degree Heart Block

00:17:18



- In sinus sick syndrome, there is an SA node malfunctioning so no P wave.
- Because there is the presence of a P wave so sinus sick syndrome is ruled out.
- Example is Rheumatic fever where Aschoff nodule is present in between SA node and AV node slowdowns the conduction.
- PR interval is outrageously increased.
  - Normal PR interval is 120-200 msec.
- Prolonged PR interval and Presence of P wave.
- There are no dropped beats.
- Exercise tolerance will be the primary complaint.

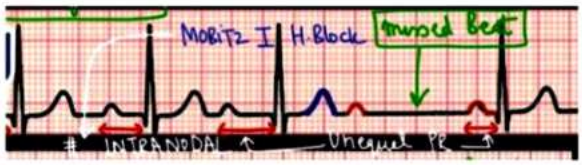
Important Information

- PR interval is inversely proportional to Heart rate.

2nd Degree Heart Block

00:19:16

Mobitz I heart block



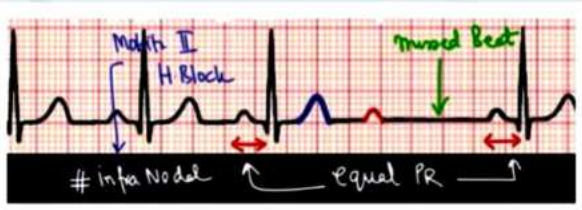
- In ECG, there is substantial increase in duration of PR interval and a P wave is present but as there is no QRS wave, a dropped beat is present.
- The problem lies in the AV node also known as the intranodal block.
- The PR interval after and before the missed beat is unequal.
- Serial prolongation of the PR interval.
- It doesn't occur at regular intervals.

Important Information

- Vertical height of P wave is 2.5 mm.
- Vertical height of T wave is 5 mm in limb lead and 10 mm in chest lead.

Mobitz II heart block

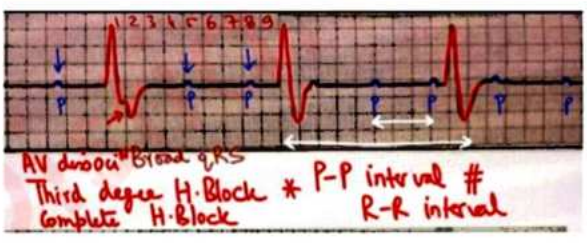
00:21:29



- PR interval before and after the missed beat is equal.
- Defect is in the bundle of his also known as an infranodal defect.
- PR interval remains constant.

3rd Degree Heart Block

00:24:19



- On ECG, a broad QRS complex is seen.

- Slurring in S wave
- More P waves as compared to a number of R waves.
- P-P interval is not equal to R-R interval
- As, AV node is not working, bundle of his decides the ventricular firing rate.
- Maximum ventricular firing rate is 40/min.
- So, there is AV dissociation.
- Bardycardia with the AV dissociation is feature of complete heart block.

2:1 Block

- On ECG, there is an inverted T wave.
- Alternatively conducted impulse and non-conducted impulse i.e., for every one conducted P wave, there is one non-conducted P wave
- Dropped beat is present alternatively unlike in Mobitz II where multiple impulses are conducted followed by a drop.

20 CONGENITAL HEART DISEASE

NADAS Criteria

00:00:30

Major

- Congestive Heart Failure (Left to Right shunt)
- Cyanosis (Right to Left shunt)
- Diastolic murmur
- Systolic murmur more than grade 3

Minor

- Systolic murmur grade I/grade II
- Abnormal S2
- Abnormal ECG
- Abnormal Chest X ray
- Abnormal Blood Pressure values

Important Information

- 1 Major or 2 Minor Criteria are required for diagnosis of congenital heart diseases.

Acyanotic Congenital Heart Diseases

00:07:30

	Ventricular septal defect(VSD)	Patent ductus arteriosus (PDA)	Atrial septal defect (ASD)
Age	6 weeks	Birth/6 weeks	5 year/ 25 year
Congestive heart failure + Recurrent Pneumonia Episodes			
S_2	Wide split (variable)	Narrow split	Wide split (fixed)
Shunt murmur	Pan systolic murmur	Continuous murmur	Flow murmur (Mid Diastolic Murmur/ Ejection systolic Murmur)
Treatment	Dacron patch	Preterm: indomethacin Term child: surgery	Occlusion device used

Atrial Septal Defect /Ventricle Septal Defect

00:10:42

ASD	VSD
• Ostium secundum (most common) right axis deviation • Ostium primum, Atrio Ventricular canal defect, endocardial cushion defect o Left Atrium size increased: Left Axis Deviation • Sinus venosus: PAPVC (Partial) o Scimitar Sign	• Peri membranous (most common) • Muscular variety o Spontaneous closure • Supracristal variety with Atrial Regurgitation

Cyanotic Heart Diseases

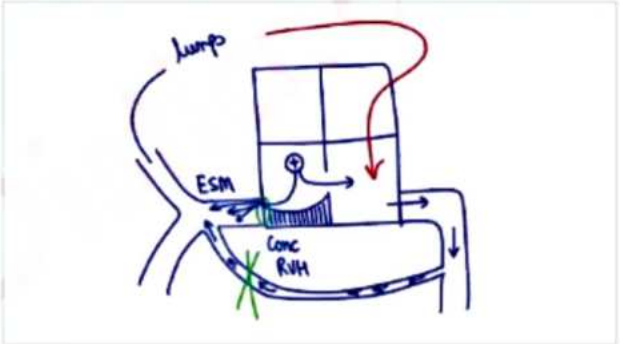
00:18:00

Tetralogy of Fallot

1. Subpulmonic stenosis (hallmark)
2. Concentric Right Ventricular Hypertrophy
3. Ventricle Septal Defect (Right to Left Shunt)
4. Overriding aorta

Tetralogy of Fallot	Triology of Fallot	Pentalogy of Fallot
• Subpulmonic stenosis • Concentric Right ventricular Hypertrophy • Ventricle Septal Defect (Right to Left shunt) • Overriding aorta	• Subpulmonic stenosis • Concentric right ventricular hypertrophy • Atrial Septal Defect	• Tetralogy Of Fallot + Atrial Septal Defect

- Major determinant of central cyanosis is Subpulmonic stenosis



- Central cyanosis in a baby on day 0 is seen in Transposition of Great Arteries
- Central cyanosis in Tetralogy of Fallot develops on/after day 7

Treatment

- **Drug of choice** – Alprostadil (Maintain Ductal Patency)
- **Palliative surgery** – Blalock Taussig shunt
  - Connects subclavian Artery with Pulmonary Artery)
- Tetralogy of Fallot is Ductal dependent pulmonary circulation

Tet Spells / Hyper Cyanotic Spells 00:27:15

- Right to Left shunt: increased
- Lips: Blueness increases to a level that they look black
- In Tet spells intensity of Ejection Systolic murmur become less, murmur will become softer
- **Complication**:
  - Brain infarction
  - Contralateral hemiplegia
- Decreased Po_2 leads to increased production of Erythropoietin, which increases RBC count.
- Secondary polycythemia: Sluggish circulation
- **Management of Tet spells**
  - Knee- chest position
  - Increased peripheral resistance (due to compression of femoral artery)
    → Right to Left shunting decreases
  - IV Morphine
  - IV Soda bicarbonate
  - IV Methoxamine
    → It increases Systolic Blood Pressure: to counterbalance shunting by increasing left ventricular pressure
  - IV propranolol

Important Information

- Calcium gluconate is not useful in the management of Tet spells

Tetralogy of Fallot Clinical Features

- Most common congenital heart disease (Cyanotic)
- Central cyanosis day 7
- Tet spells / F.T.T failure to thrive

On examination

- Clubbing, cyanosis
- S_2: A_2 P_2 (single S_2)
- Flow murmur: Ejection Systolic Murmur, intensity low, Tet spells
- Ejection systolic murmur: Intensity of murmur will reduce during Tet spell

Work Up 00:39:30

Chest X-ray

1. Right Ventricular hypertrophy (Boot shaped heart)
2. But CT ratio is normal
3. Apex displaced superolateral: Right ventricle enlargement
4. Pulmonary oligemia
5. Right sided Aortic arch
6. Appearance also called as COER EN SABOT

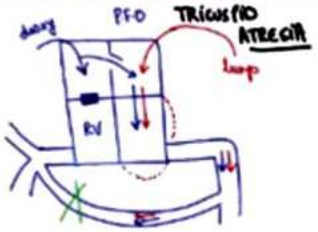
Investigation of choice:

- Transthoracic Echo (TTE)

Treatment

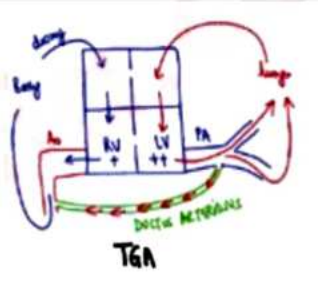
- Alprostadil IV and Blalock- Taussig shunt (palliative Surgery)

Tricuspid Atresia 00:44:20



- Central cyanosis on day 0
- Death on day 7
- Central cyanosis, Left sided enlargement of heart
- Preferred drug to maintain ductal patency: alprostadil
- Chest X-ray: CT ratio increased (Left sided enlargement)
- S_1: M_1 louder (Single loud S_1, T_1 absent)
- S_2: A_2 normal (Single S_2)

TGA (Transposition of Great Arteries) 00:53:40



- Drug used: Alprostadil IV

- Ductal Patency maintained by: Alprostadil
- Atrial septostomy
- Central cyanosis on day 0

Chest X Ray

Egg on side appearance

Important Information

- Egg shell calcification: Sarcoidosis, Silicosis
- Egg in a cup: Constrictive pericarditis

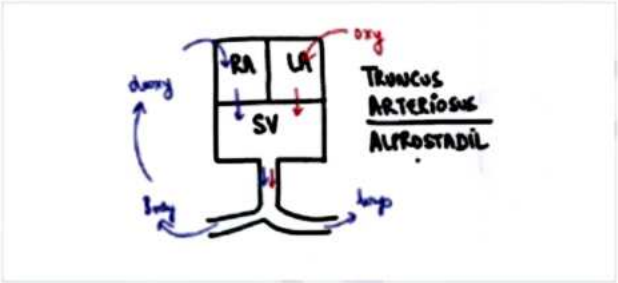
Important Information

Ductal dependent pulmonary circulation

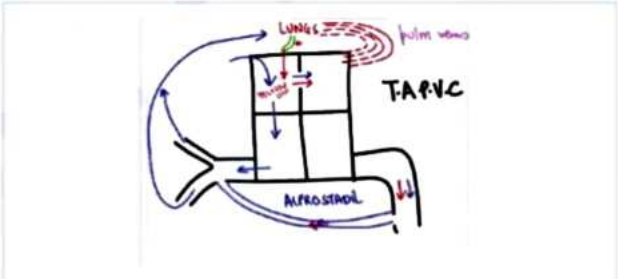
1. Tetralogy Of Fallot
2. Tricuspid Atresia
3. Pulmonary atresia with ulnar intact Ventricular Septum.

Truncus Arteriosus 00:59:50

- Also known as Co - Truncal abnormality
- Alprostadil is contraindicated
- Ductal independent circulation



Total Anomalous Pulmonary Venous Connection 01:02:12



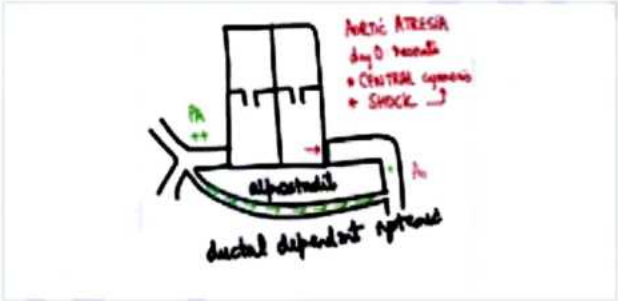
- If Abnormal Vein enters Superior Vena Cava, then it is Supracardiac type
  - Most common type and Figure of 8 or snowman heart appearance on Chest X Ray
- Abnormal vein Right Atrium: Cardiac type
- Abnormal vein Inferior Vena Cava: Infracardiac type
- ALPROSTADIL is contraindicated as it lead to overloading of stressed out RA.

Important Information

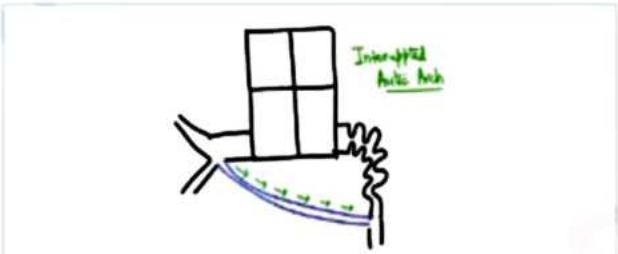
- Total Anomalous Pulmonary Venous Connection with Atrial Septal Defect → **Wide fixed split S_2**

Aortic Atresia 01:09:00

- Symptomatic on day 0 (central cyanosis)
- Neonate: Shock cyanosis
- Ductal dependence systemic circulation
- Ductal patency maintained by alprostadil IV



Ductal Dependent Systemic Circulation 01:13:35



- **Interrupted aortic arch**
- Neonate:Shock with cyanosis
  - Alprostadil IV used

Pulmonary	Systemic
1. Tetralogy Of Fallot	1. Mitral atresia
2. Tricuspid atresia	2. Hypoplastic left heart syndrome
	3. Aortic atresia
	4. Interrupted aortic arch.

Ductal independent circulation

- Total Anomalous Pulmonary Venous Connection
- Truncus arteriosus (Co - Truncal abnormality)
- Kawasaki disease

Ebstein Anomaly 01:17:09

- History of lithium intake by the mother
- Due to inferior displacement of tricuspid valve
- Tricuspid regurgitation
- Association of WPW syndrome
- Right ventricle small

Summary 01:21:07

Left to Right shunt (CHF + Recurrent Pneumonia)	R → L shunt (Cyanosis, Failure to Thrive) single S2	Mixed combo (Cyanosis + CHF)
• VSD (wide variable S_2) • ASD (wide fixed S_2) • PDA (Narrow split)	• TOF • Tricuspid Atresia • Ebstein anomaly	• TGA (Egg on side appearance) • TAPVC (Figure of 8 appearance)

Coarctation of Aorta

- Obstructive defect
- Left ventricular hypertrophy
- Low Blood pressure in lower limb
- Comparatively higher blood pressure in Upper limb due to obstruction in aorta that is increasing total peripheral resistance.

21 METABOLIC-SYNDROME-X AND SYNDROME-Z

00:00:30

Metabolic syndrome/Syndrome X

Diagnostic features 00:01:58

- Centripetal obesity:- Abdominal circumference
  - (Globally) Males >102cm
  - (Globally) Females: >80cm
  - (Indian male) >90 cm
  - (Indian Females) >80cm
- Impaired glucose tolerance test/ insulin resistance
  - FBS = 100-125 mg/dl
  - 2 hours = 140-199 mg/dl
  - Or the patient is on oral hypoglycaemic drugs
- Hypertension with BP value >130/85 mmhg
- Increased Triglycerides >150 mg%
- HDL decreased

3 out 5 features must be present for syndrome X or metabolic syndrome

Syndrome Z 00:06:00

- Obstructive sleep apnea + with syndrome X
- Apneic episode lasting for >10 secs, >5 episode/hour

Coronary syndrome X/Microvascular angina 00:07:22

- Narrowing of perforators leading to coronary ischemia

Presentation

- Recurrent episodes Chest pain on exertion/ emotion
- Treadmill test: ST depression of ≥1mm for ≥80msecs in two contagious limb leads
- Coronary angiography: Normal as it is only identify large vessel ischemia.

Treatment

- Isosorbide mononitrate + Aspirin 75 mg

22 HYPERTENSION

Introduction 00:00:15

- Normally BP values show a nocturnal dip around 4-6 am with approximately 10% fall in blood pressure from baseline.
- ABPM of HTN patient:- Early feature: Loss of nocturnal dip
- Elevated Systolic blood pressure leads to an increase in Cardiovascular mortality.

Important Information

- Antihypertensive medication should be taken either in early morning or late at night, so that morning increase in BP due to increased vasomotor tone in morning can be prevented.

- In patient with good control of HTN, incidence of:
  - Acute coronary syndrome is reduced by 25%
  - Stroke is reduced by 30%
  - Heart failure is reduced by by 50%

Blood Pressure 00:04:50

- Values vary with Race.

- If Systolic blood pressure (SBP) rises more than 20 mm, diastolic blood pressure (DBP) by 10 mmHg above baseline BP. Then the cardiovascular mortality risk increases
- Due to more vasoconstriction in morning hours incidence of MI or stroke is more in early morning.

Classification 00:06:40

	AHA guidelines
Elevated	120-129/ < 80 mm of Hg
Stage I	130-139/ 80-89 mm of Hg
Stage II	> 140/90 mm of Hg

- AHA guidelines cut offs are to be answered in exam.

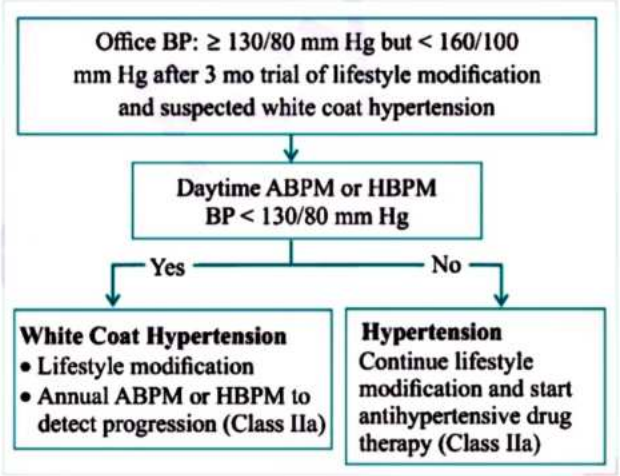
Automated office Blood Pressure	Ambulatory Blood Pressure monitoring
• 3 readings • Discard 1 • 2 reading = average •> 135/85 mm Hg	• Average awake BP= > 135/85 mm of Hg • Average sleep BP= > 120/75 mm of Hg

Home based BP monitoring (HBPM)

- >135/85mm Hg
- 7 days: Morning / Evening
- Discard 1st day value
- 6 days: average
- Cuff size: 80% of arm circumference
- Width: >40%
- Reading to be taken after Rest: 5 min
- After smoking / coffee consumed: Wait 30 min

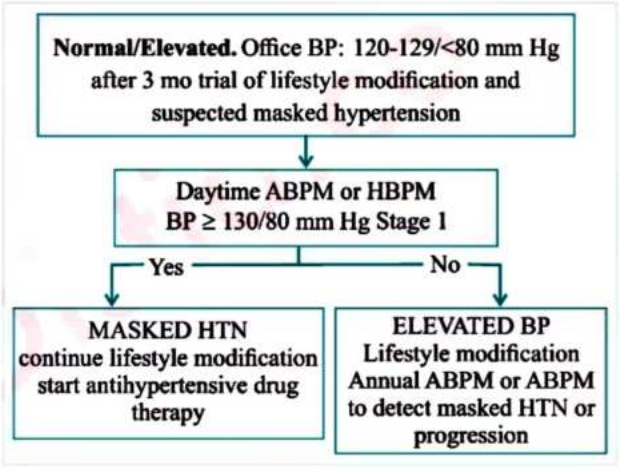
White coat HTN

- BP normal at home but increases in clinic
- Can develop HTN in future



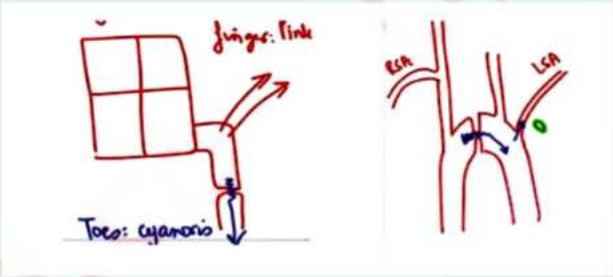
Masked HTN

- BP normal in clinic but elevated at home (stage1)
- Need anti-hypertensive medicine



Causes Of Hypertension (HTN) 00:21:50

- Most common cause of HTN: Essential HTN/ idiopathic
- Most common cause of secondary HTN: Renal Parenchymal disease
- Most common congenital cause of HTN is Coarctation of Aorta
- In Coarctation of Aorta, BP in upper limb is higher and BP in lower limbs is lower



Important Information

- Normally BP in upper limb = < 120/80, & BP in lower limb <140/80, difference range b/w U.limb and L.limb <20mmhg.
- Reverse scenario is seen in coarctation of aorta, where BP in legs is lower and Upper limb has higher.
- Isolated systolic HTN -In old age (↓compliance of blood vessels)

Unequal Blood Pressure in left/right arm is seen in 00:27:25

1. Takayasu's arteritis (Important cause of renal artery stenosis in India)
2. Supravalvular Aortic Stenosis: William syndrome (Due to Conda Effect)
3. Coarctation of Aorta (Pre ductal variety)
4. Aortic Dissection

Secondary Causes of HTN 00:30:25

1. **Renal parenchymal disorder**
   - Chronic Kidney disease
   - Chronic glomerulonephritis
2. **Renovascular HTN**
   - Fibromuscular dysplasia in young age
   - Atherosclerotic renal artery stenosis in smoker, old age
3. **Metabolic syndrome/ syndrome X**

   5 components of metabolic syndrome:
   - Centripetal obesity
   - Insulin resistance
   - Hypertriglyceridemia
   - Low HDL
   - HTN

   3 out of 5 should be present for diagnosis
4. **Obstructive Sleep Apnea (OSA)**
   - Fluctuation of heart rate during sleep increases the stress on the heart and that manifests into HTN
   - During apneic episode there is bradycardia due to Hypoxia, and it leads to peripheral vasoconstriction
5. **Endocrinological causes:**
   - Hypothyroidism: Myxedema (Isolated diastolic HTN)
   - Thyrotoxicosis
   - Pheochromocytoma: Episodic HTN
   - Bilateral Adrenal Hyperplasia,CONN syndrome :-ARR↑
   - OCP: due to Secondary Aldosteronism
   - Acromegaly: Increased Growth hormone
   - Neurogenic: Spinal cord transection (At T_6 level above due to: unopposed sympathomimetic outflow to heart)
   - Cushing reflex: decreased HR and increased BP
6. **Mendelian causes** 00:41:54

- **Liddle syndrome (Autosomal Dominant)**
  - Overactivity of ENac – causes more salt/H_2O to retain in the body
  - HTN with loss of K+/H+ causing hypokalemic alkalosis
  - Low aldosterone, Low renin, and High blood pressure
  - Treatment: Amiloride (ENac blocker)
- **Gordan syndrome**
  - Autosomal Dominant
  - Mutations are WNK-1/ WNK-4: gain of function
  - Na/Cl cotransport in Distal Convoluted Tubule
  - HTN due to more Na/Cl retaining in the body
- **Polycystic kidneys**
  - Autosomal Dominant in adults, Autosomal Recessive in pediatrics

USG criteria:
- Should have 2 or more cyst in per kidney
- **Adults:** Hepatic cyst is leading extra renal finding in polycystic kidney
- **Pediatric:** Hepatic fibrosis

- **Pheochromocytoma**
  - Autosomal Dominant
  - Associated with MEN-2A (Sipple Syndrome), MEN-2B, Von hippel lindau, Neurofibromatosis-1

- **Congenital adrenal hyperplasia (CAH)**
  - 17-α hydroxylase deficiency (Autosomal Recessive), causes increase in Aldosterone and thus HTN
  - 11 – Beta hydroxylase deficiency (Autosomal Recessive) causes increase in 11 deoxycortisol which stimulates ENaC and cause HTN

Work up for newly diagnosed HTN patients 00:50:25

1. Echocardiography: Left ventricular hypertrophy
2. Fasting blood sugar,
3. lipids
4. High sensitive CRP.
5. TSH
6. Urine microscopy, Albumin Excretion Rate (AER) $\frac{\text{Urine albumin}}{\text{Urine creatinine}}$ = (30-300 mg/gm)
7. BUN, Serum creatinine Na+/K+, Uric acid values

Target Organ Damage 00:55:25

- Eyes
- Brain
- Kidneys
- Aorta
- Heart

Heart damage

- 1st organ to be to damaged:
  - Left ventricular hypertrophy
  - Increased Oxygen demand
  - Subendocardial Ischemia
  - ST segment depression

Eyes

- Hypertensive Retinopathy
  - Earliest Fundus findings
    - → Stage I: Focal attenuation of arterioles (earliest)
    - → Stage II: I+A-V Nipping (Salu sign)
    - → Stage III: I+II+Flame shaped hemorrhage, Cotton wool spots
    - → Stage IV: I+II+III+Papilledema

Brain

- Hemorrhagic stroke
- Most common site: putamen

Kidneys

- GFR reduces progressively leading to Hypertensive nephropathy

Aorta

- Aortic dissection
  - Tearing chest pain in interscapular area
  - Antegrade progression of dissection can manifest neurological features like Horner syndrome
  - **Diagnosis:**
    - → Trans Esophageal Echocardiography: In Unstable patients
    - → CT angiography: Tennis ball appearance
  - **Treatment:**
    - → Type A (Tear in Ascending Aorta) → surgery
    - → Type B (Tear Descending Aorta)
    - → ↓↓ BP → Surgery
    - → Crashing BP normal to low → Esmolol (to reduce the progression of tear)
    - → In case of HTN crisis: Labetalol

When to treat HTN as per ACC/AHA 01:06:30

- ASCVD risk increased: <130/80
- ASCVD risk not increased: > 140/90
- Age > 65 year: > 130/80

Treatment

- **Lifestyle modification**
  - D.A.S.H (Dietary approaches to Stop Hypertension): reduced intake of sodium and increased of potassium
  - Physical activity
- If the patient is Hypertensive despite 3-6 months of lifestyle modifications, then switch to drugs

Important Information

- Allow 2 weeks to reach full effect of each drug.
- Beta-blockers can be used at any stage if specifically indicated, e.g., Heart failure or Angina.

- **<55 years**
  - ACE inhibitor, in case of dry cough, angioedema then switch to "ARB"
  - ACEI/CCB
  - ACEI + CCB + Thiazides
- **>55 years**
  - CCB
  - CCB + ACEI + Thiazides

Resistant HTN 01:15:45

- Elevated Blood pressure inspite at least 3 classes of anti HTN concurrently used in patient
- Must include Thiazide (at least 2 weeks)
- Improper BP measurement should be first ruled out
- Cox-I inhibitor cocaine, Steroids, Erythropoietin
- Excess salt intake, Obesity
- Alcohol intake
- Noncompliance of patient

Uses Of Anti-Hypertensive 01:20:37

ACE/ARB inhibitors

- Acute coronary syndrome -post MI
- Diabetic nephropathy

- Ischemic nephropathy (Unilateral RAS)
- Heart failure with reduced ejection fraction
- Chronic hyperkalemia
  - Patiromer
  - K^+ biding Resin (SPS): Sodium Polystrene Sulphonate
  - Sodium Zirconate

Important Information

- Contraindicated in Bilateral RAS and can cause AKI

β- Blockers (Cardio selective)

- Carvedilol
- Metoprolol
  - HTN + Chronic stable angina, Congestive heart failure

Aldosterone antagonist

- Used in patients of heart failure with preserved ejection fraction

α- Blockers

- HTN in patients having BPH use Prazosin
- HTN in Pheochromocytoma use Phenoxybenzamine
- End stage renal disease (diabetic nephropathy) use α- blocker

Hypertensive Urgency 01:29:00

- If BP > 220/130 mm Hg but life-threatening end-organ damage is absent. In Harrison 21st edition page 2086 cut off is > 180/120 mm Hg.

Hypertensive Emergency/ Crisis

- If BP > 220/130 mm of Hg + Target organ damage is present In Harrison 21st edition , cut off is > 180/120 mm Hg.

Goal/ Objective:

- In patients with Encephalopathy reduce MAP by 25% within 2 hours (Mean Arterial Pressure) or maintain BP 160 / 100 mmHg
- Presence or absence of target organ damage defines the urgency or emergency than recorded numerical values.

Malignant HTN 01:31:40

- Fibrinoid necrosis occurs in the vessels supplying various parts in the body and the mortality rate increases by 50% in 6-12 months. It is a hypertensive emergency with an abrupt rise of BP in patient with pre-existing Hypertension with features of

1. Retinopathy: hemorrhage
2. Encephalopathy: putamen bleed intra parenchymal bleed
3. Kidney: Proteinuria
4. Blood vessel: Microangiopathic hemolytic anemia

- Malignant HTN: Drugs used are Labetalol, Nicardipine, Nitroprusside.
- Hypertensive encephalopathy, sodium nitroprusside is used

Stroke + HTN

- Thrombolysis (Window period < 4.5 hours)

Ischemic stroke

- Thrombolytic candidate
  → To initiate thrombolysis first bring BP <185/110 mmHg with Nicardipine
- Not a thrombolytic candidate
  → If BP is 220/130 mmHg (first lower BP)

Intracerebral Hemorrhage

- Target BP 130-140mmHg

* **(Postoperative HTN / MI/ Unstable Angina/ Acute decompensated CHF) IV Nitroglycerin**
* (In patients of "Adrenergic Crisis" in pheochromocytoma surgery): Nitroprusside is used

Pheochromocytoma

- Pre op: Oral phenoxybenzamine
- Intra op + HTN crisis: Nitroprusside
- Heart failure: IV Nitroglycerin

Target Blood Pressure 01:42:05

- Target BP/ Goal to be maintained in patients with HTN: 135-140/ 85-90 mm of Hg
- Target HTN along with Diabetic nephropathy = < 130/80 mm of Hg
- CKD grade I-III: ACEI/ARB + Thiazide + CCB
- eGFR< 30ml/min: Preferred Diuretic is Metazolone
- ESRD
  - CCB
  - Alpha blocker

23 DISEASES OF PERICARDIUM

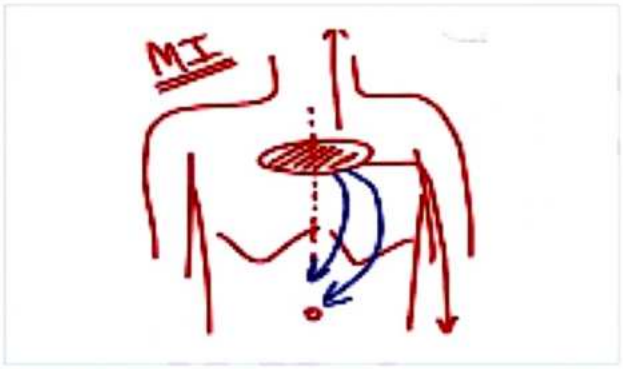
Acute Pericarditis 00:00:18

Etiology

1. Idiopathic (Most common)
2. Viral
3. Tuberculosis
4. Dressler Syndrome: Autoimmune pericarditis seen post MI [3-6 weeks later], Treatment: Aspirin
5. Malignancies: Oat cell carcinoma lung, Carcinoma Breast
6. Uremic pericarditis [CKD, Diabetic Nephropathy] with GFR <15 ml/min/1.73m^2

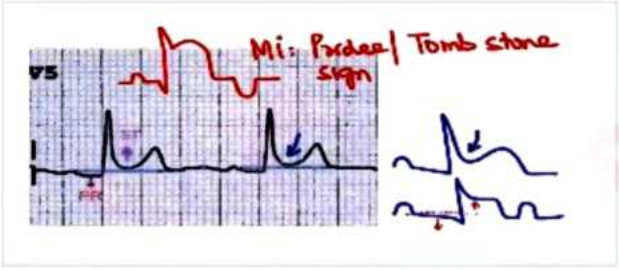
Clinical Features 00:04:51

1. Patient presents with diffuse chest pain at rest
   - Relief on sitting
   - Radiation to left shoulder (Phrenic nerve involvement)
2. Pericardial friction rub heard on auscultation (scratchy sound)
   - S1 S2 are heard normal
   - Sound persists on breath holding



Investigations 00:09:50

1. **ECG:**
   - ST elevation, concave upwards in all leads except aVR: ST depression
   - PR segment depression, all leads except aVR



2. **Echocardiography:**
   - Check for presence or absence of effusion

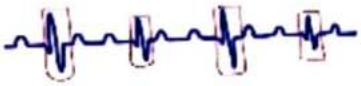
3. **HRCT chest:**
   - Rule out metastasis to chest

Treatment 00:14:55

- Viral Pericarditis = NSAIDS
- TB Pericarditis = ATT + short course of steroids
- Dressler Syndrome = Aspirin
- Malignancy = Chemotherapy
- Uremia = Hemodialysis

Pericardial Effusion

- Normal fluid in pericardial space= 20-50 ml
- Pericardial effusion- fluid accumulation in pericardial space >50ml.
- ECG low voltage ECG (R + S < 5 mm in Limb leads, < 10 mm in Chest leads)



ELECTRICAL ALTERANS

Important Information

Causes of law Voltage ECG:

1. Restrictive cardiomyopathy (Fibrosis)
2. Myxedema heart
3. Constrictive pericarditis (Calcification)
4. Pericardial effusion

Electrical Alternans

- Duration will not change but amplitude of QRS will change. It occurs due to swinging motion of heart in a bag of fluid.

Chest X Ray

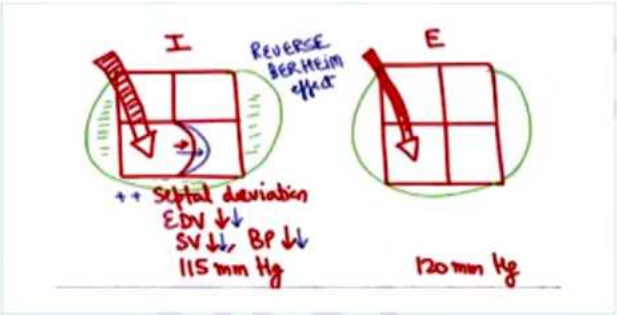
- Narrow vascular pedicle, Money bag appearance / Water bottle appearance with increased CT ratio.

Low Pressure Cardiac Tamponade 00:24:47

- External pressure enough to crush atria but not ventricles: low pressure cardiac tamponade
- Atrial collapse, 30% reduced filling of ventricles 30% fall in Systolic blood pressure, pulse: Weak pulsus paradoxus is absent in Low pressure cardiac tamponade.

Cardiac Tamponade

- Atrial + ventricular collapse
- Pulse: disappears in inspiration
- Heart is beating but pulse is disappeared is called Pulsus paradoxus
- Pulsus paradoxus is a finding of cardiac tamponade and is not seen in Low pressure cardiac tamponade.



- Normal SBP falls < 10 mm Hg on deep inspiration, if it falls > 10 mmHg (in case of cardiac tamponade) this is known as Pulsus paradoxus
- In cardiac tamponade, there is an exaggerated septal deviation leading to reduction in Left Ventricle cavity size.
- This reduces EDV, stroke volume and leads to crashing blood pressure.
- This is called reverse Bernheim effect
- Normally inspiratory expiratory variation of blood pressure, fall is <10 mm Hg
- If inspiratory fall of systolic blood pressure >10 mmHg, then it is called Pulsus Paradoxus

Causes of Pulsus Paradoxus

1. Cardiac tamponade
2. Status asthmaticus
3. Acute cor pulmonale: Massive Pulmonary Embolism
4. Pregnancy
5. Constrictive pericarditis

Massive Pericardial Effusion 00:36:25

- Seen in Hypothyroidism: Myxedema heart
- Lymphedema, leading to 400ml (20 ml / year x 20 years), fluid accumulation in Pericardial space
- This is very slow accumulation of fluid in pericardial space. Hence ventricles adjust to this gradual rise of intrapericardial space pressure.
- So pulsus paradoxus is absent

Case: 25-year male has a car crash while driving under influence of alcohol and was not using seat belt. Ambulance crew: Patient is breathing, Heart rate 130/min, BP: 80 mmHg, IV Fluids started, Transport to hospital in few minutes, Patient died on arrival to emergency room. Cause of death?

1. Hemopericardium
2. Hemothorax
3. Hemoperitoneum
4. Vertebral artery dissection

Answer: Hemopericardium led to obstructive shock, No role of IV fluids in this condition.

- If driver was using seatbelt during car crash
  - Mesenteric tear can develop and is called seat belt syndrome.
  - Superior mesenteric artery, inferior mesenteric artery will bleed.
  - It will cause hemoperitoneum, and expiry of patient.

Cardiac Tamponade Summary 00:46:55

1. Pulsus paradoxus: present
2. Beck's Triad
   - BP fall: Obstructive shock (IV fluid contraindicated)
   - JVP: Elevated, non-pulsatile, Kussmaul sign is absent
   - S1S2 muffled/distant

Chest X Ray

- Water bottle heart

ECG

- Electrical alternans positive

Treatment of choice

- Echocardiography guided Pericardiocentesis

Pulsus Paradoxus + Electrical Alternans = Cardiac Tamponade

Important Information

- If electrical Alternans is given alone in a MCQ then answer as Pericardial Effusion

Car crash:

- Obstructive shock
  - Muffled S1 S2, JVP elevated, BP low
  - Echo guided pericardiocentesis
- Hypovolemic shock
  - Loud S1, BP low, abdominal bruising, distention (trauma to abdomen)
  - CT abdomen, exploratory laparotomy

Constrictive Pericarditis 00:53:40

- Sequelae:
  - Pyopericardium
  - TB Pericarditis
- Compliance of ventricles is decreased

Right Ventricle ↓	Left Ventricle ↓
1. Pedal Oedema	1. Pooling of blood in the lungs
2. Hepatomegaly, abdominal fullness (RUQ discomfort)	2. Pulmonary edema
3. Ascites	3. Dyspnea on exertion/rest
	4. Orthopnea, PND
	5. Effort intolerance

- Pericardial shudder / knock/ shock
- JVP:
  - Kussmual sign (+)
  - Rise of JVP on inspiration.
  - steep x, steepy
- S4 present
- Bilateral fine crepitations present: pulmonary edema

Work up 00:59:40

- **CXR:** Egg in a cup appearance
- **ECG:** Low voltage ECG
- **Echo/doppler/ cardiac catheterization:** Square root wave sign
- **CT chest/ Cardiac MRI:** Calcification around the heart
- **Endomyocardial Biopsy:** Gold Standard investigation to differentiate RCM from Constrictive pericarditis

Treatment 01:02:28

- Pericardial stripping procedure

	Acute pericarditis	Pericardial effusion	Cardiac tamponade	Constrictive pericarditis
ECG	ST elevation Concave upwards	Electrical alternans	Electrical alternans + Pulsus paradoxus Beck's triad	Low voltage ECG + Pulsus paradoxus, Steep y Steep x Egg in a cup appearance, Pericardial shock, Square root wave sign

24 CONGESTIVE HEART FAILURE (CHF)

Clinical features 00:00:40

1. Palpitations
2. Diaphoresis
3. Dyspnea on exertion/rest, pink frothy sputum
4. Nocturnal cough, Paroxysmal nocturnal dyspnea, Orthopnea
5. Nocturia
6. Effort intolerance

On examination

- Tachycardia

Left ventricular failure	Right ventricular failure
• Reduced SBP • Oliguria • S3 present: Ventricular gallop rhythm • Bilateral fine crackles/crepts • Bilateral reduced air entry due to pleural effussion • Reduced vital capacity	Most common cause of Right Ventricular Failure is Left Ventricle Failure • JVP elevated • Kussmual sign: JVP elevation on inspiration • Abdomino- jugular reflux positive • Tender hepatomegaly • Pitting pedal edema [Chronic CHF]

Framingham Criteria for Diagnosis of CHF 00:14:07

Minor Criteria

1. Tender hepatomegaly
2. Pitting pedal edema
3. Pleural effusion
4. Tachycardia
5. Oliguria

Major Criteria = B/L Crackles/Crepts positive
Abdominojugular reflex

For Diagnosis

- 2 major criteria should be present or
- 1 major + 2 minor

Framingham heart risk calculator

- To determine risk of coronary events in next 10 years

Stages of CHF 00:17:22

Stage A: No structural damage, high risk of developing symptoms (risk factors present)

Stage B: Structural heart disease + No signs and symptoms of CHF

Stage C: Structural heart disease + Signs and Symptoms of CHF

Stage D: Refractory heart failure

Work Up 00:20:28

BNP levels / N-terminal Pro BNP

- Released from ventricles of heart
- If > 100 pg/ ml – It helps to differentiate from non-cardiogenic pulmonary edema

Chest X-ray/radiological findings:

- Earliest radiological finding: Prominent upper lobe veins / Antler sign or Reverse moustache sign
- CT ratio increased > 0.5
- Bat wing pulmonary edema
- Costo – phrenic angle blunting
- Bilateral pleural effusion
- Kerley B lines: Located perpendicular to pleural surface. Also seen in lymphangitis carcinomatosis
  Kerley A lines: Present in the perihilar area
  Kerley C lines: Reticular opacities at lung base

Important Information

- Reverse Bat Wing Edema- Chronic Eosinophilic Pneumonia
- Moustache sign – Pneumoperitoneum (gas under diaphragm)

Echocardiography

- Ejection fraction = $\frac{\text{Stroke volume}}{\text{End diatolic volume}}$ 80ml/130ml = 65%
- In systolic malfunction = SV ↓/EDV = ↓

In HTN patient

- In diastolic malfunction, there is Left ventricular hypertrophy
  - Left ventricular end diastolic pressure increase
  - EDV decreased, SV decreased. If both decreased then ejection fraction can be falsely normal.
  - Pulmonary edema due to Pooling of blood in lungs

Cardiac MRI

- Preferred modality to evaluate cardiac function and structure
- Type of malfunction: Systolic Vs Diastolic
- Etiology: Fibrosis / Ischemic Cardiomyopathy/ DCM

BORG scale - Tells functional assessment of the patients

Treatment

00:33:57

Heart failure with preserved EF (HFpEF)

- Preserved EF ~ 50%

Seen in:

- HTN, RCM, Radiation
- Connective Tissue Disorder, Aging
- Endomyocardial fibroelastosis
- Hemochromatosis

Treatment:

- Aldosterone antagonist
- ARNI: Valsartan (ARB) + sacubitril (nephrilysin inhibitor: inhibit degradation of BNP)
- Aldosterone antagonist, ARNI - may decrease mortality
- Digoxin
  - Ineffective
  - It increases oxygen demand of heart
  - Can be detrimental

Heart failure with reduced EF (HFrEF)

Seen in:

- CAD: Ischemic cardio myopathy
- HTN: recent onset
- Valvular Lesion
- Left to Right shunt
- Cor Pulmonale
- Chagas diseases / Chronic Arrhythmias

Management

Treatment of acute pulmonary edema

L → Lasix (Furosemide) IV
M → Morphine (↓Pulmonary edema)
N → Nitroglycerine drip
O → Oxygen (NIV)
P → Positioning of patient

Vasodilators

- Nitroglycerine
- Nesiritide
- Nitroprusside

Diuretics

- Furosemide

Nesiritide

- BNP Analogue
- Lead to Natriuresis

Treatment of Acute decompensation with cardiogenic shock

Vasopressors

- Nor-epinephrine : Increase DBP and improves coronary perfusion
- Dopamine: Improves GFR
- Dobutamine: β_1 stimulation → ↑HR → ↑ O_2 consumption

Inodilators: Milrinone & Amrinone

Levosimendan

Omecamtiv: Production of stronger actin-myosin complex

Medically Refractory Cardiogenic Shock

- Impella Device
- IABP

Chronic CHF

- ACEI + βblockers (Major mortality reducing drugs)
- Spironolactone. Keep watch on KFT and S. Potassium.
- SGLT-2 inhibitors in diabetes reduce CV mortality

Refractory congestive heart failure

- LVAD: LV assist device
- CRT: Cardiac resynchronization Therapy
- Cardiac transplantation

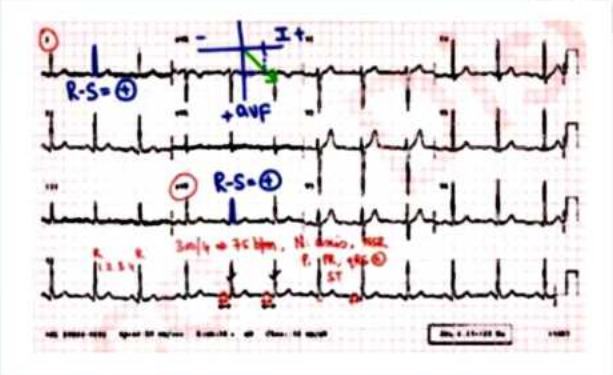
Acute CHF / HFrEF: <40% of EF	
Cardiogenic Shock	**Volume overload**
• Vasopressors	**L** → Lasix (Furosemide) **M** → Morphine (↓Pulmonary edema) **N** → Nitroglycerine **O** → Oxygen (NIV) **P** → Positioning

Heart failure	
HF with preserved ejection fraction EF ≥ 50%	**HF with reduced ejection fraction EF < 40%**
Causes	Causes
• Long standing HTN • ARNI • Aldosterone antagonist	• Acute pulmonary edema • S. anemia with CHF • T3 pregnancy • Treatment: o LMNOP o ACEI+ β blockers • Cardiogenic shock o Vasopressors

Digoxin toxicity can cause

- Ventricular Bigeminy (most common arrythmia)
  - **Treatment:** Lignocaine
- Non paroxysmal atrial Tachycardia with: Variable

25 BUNDLE BRANCH BLOCK



Normal ECG

00:00:13

- Check HR - Calculate R-R interval on lead II

$$\frac{300}{\text{No.of large squares}} = \text{No. of beats / min}$$

- Calculate Axis, normal axis in given ECG
- Check if every P wave followed by QRS (Normal P wave = < 120 msec)
- Height of Pwave -1.5 -2small squares, P-R interval 3-5small squares)
- Duration of QRS complex
- Check Q wave in lead V5,V6. for bundle branch block, for ST segment changes like ST – elevation, depression, coving
- Height of T wave in precordial lead should be < 10 mm
- Height of T wave in limb leads = < 5 mm and in chest leads = < 10 mm
- Check for QT interval, and look for 'q' wave in V_5 & V_6
- Look for progression of R & S wave in V_1 to V_3 leads from V1 to $V_3 \rightarrow$ R & S become equal in amplitude in lead V_3 and from $V_3 \rightarrow V_6$, R becomes bigger than S (progression of R wave)

LBBB

00:09:05

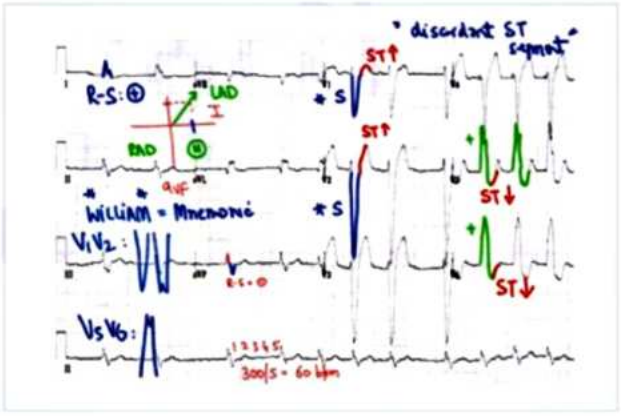
- Intermyocyte conduction: Broad QRS
- Damage in left fascicle so refractory period of left side is more than right
- Normally refractory period of right fascicle is relatively higher than left sided fascicle, as current moves from left to right.
  - Sequential contraction of ventricles (instead of simultaneous contraction which occurs normally)
- Current will go to right side first, delay conduction on left side.
- Vector changes with respect to change in septal activation (towards right side)
- Absent 'q' wave in lead V_5 and V_6
- Tall & Broad R wave in V_5 and V_6 (lateral leads)
- ventricles contract independent of each other, results in pooling of blood in lungs cause pulmonary edema
- LBBB is lethal
- WILLIAM- "Rabbit ear" pattern in dominant S & peak of R, W is seen at V_1 and V_2, M is seen at V_5 and V_6
- Deep & Broad S V1 lead

Important Information

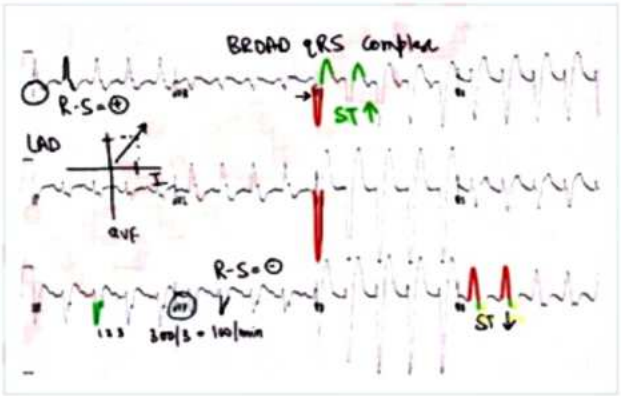
- A new onset LBBB is suggestive of MI as anterior wall MI damage conduction system of heart
- Septal activation is responsible for generation of 'q' wave

ECG

00:13:44



- Axis: Left axis deviation
- Discordant ST segment changes (due to abnormal repolarization & depolarization)
- In ECG having Broad qRS –due to conduction delay, HR= Normal
- Absent Q wave



- HR = 100/ min
- Lead I = +ve, aVF = -ve so there is Left Axis Deviation
- Deep 'S' in V_1& V_2 as the abnormal current is going away from V_1 & V_2
- Predominant broad S waves present in lead V_1 & V_2
- Broad QRS complex
- Dominant 'S' lead V1& V2
- Failure of progression of R wave
- Broad dominant R wave in V5 & V6
- Absent 'q' wave narrow split S1 and S2.

Sgarbossa Criteria

00:24:53

- To diagnose an MI when LBBB is present

Important Information

- New onset LBBB could be present in MI & MI diagnosis can be missed in the patient having LBBB
- The patient can have MI as a cause of LBBB

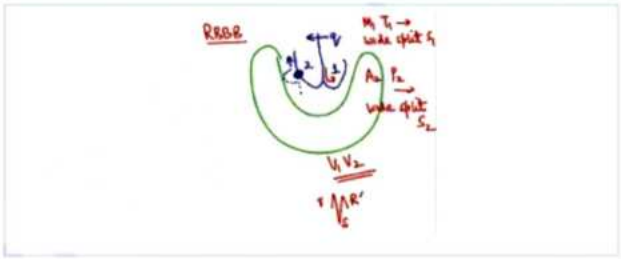
Causes of LBBB (A2H2D2)

- **A** - Aortic Stenosis
- **A** - Ant wall MI
- **H** – HTN
- **H** – Hyperkalemia
- **D** - Digoxin Toxicity (most common – Ventricular bigeminy)
- **D** - Dilated cardiomyopathy

Right Bundle Branch Block (RBBB)

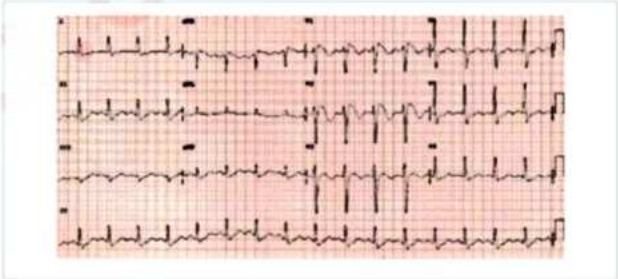
00:26:23

- Defect in Right bundle branch
- Left ventricle activated normally



- rSR pattern in V_1& V_2. It is also looking like a rabbit ear appearance
- V5/V6 W pattern and M pattern in V_1/ V_2
- Dominant & Broad S in V5/V6

ECG



- Broad QRS
- M_1 T_1 shifted laterally → Wide split S_1
- P_2 shifted → Wide split S_2
- rSR pattern in V_1&V_2- due to intermyocyte conduction

Cause of RBBB

1. Physiological
2. Right Ventricular Hypertrophy
3. Pulmonary embolism
4. Cor pulmonale
5. Ischemic Heart Disease
6. Rheumatic Heart Disease
7. Cardiomyopathy.

LBBB Vs RBBB

00:31:53

LBBB	RBBB	
V_1 V_2	Dominant S	rSR pattern or M pattern
V_5 V_6	Tall & Broad R wave absent q wave	Dominant S
	WILLIAM	MARROW

26 RHEUMATIC HEART DISEASE

Acute rheumatic fever 00:00:02

- Acute rheumatic fever is also known as a disease of absolute poverty.
- It is generally seen in a patient of 5 to 15 years of age having recurrent sore throats caused by group A Beta-hemolytic Streptococci.
  - Antibodies which are formed, cross react with human connective tissue and damage the heart valves and cause joint manifestations or cause chorea.

Secondary prophylaxis

- In secondary prophylaxis, Injection of Benzathine penicillin is given three to four weekly.
- 10 year child with rheumatic fever has developed Mitral regurgitation.
  - This is demonstrable clinically by auscultation of Pansystolic murmur
  - → On echocardiography a jet of blood leaking from LV to LA is seen
  - In this case, the duration of antibiotic prophylaxis is till 40 years of age or 10 years after the last documented attacks.
- If there is an evidence of carditis but there is no valvular disease present, then:
  - Injections are given up to at least 21 years of age or a minimum of 10 years after the last attack.
- If the patient has penicillin allergy, then macrolides or erythromycin are used.
  - Allergy can lead to anaphylactic shock.
- If there is plain rheumatic fever, then the injection are given till 21 years of age or 5 years after the last attack.
- Whichever is longer duration should be given to the patient.

Pathogenesis 00:08:00

- If ARF is left untreated:
  - Course of disease - 12 weeks
- If treated:
  - Course of disease - 1-2 weeks
- It is important to diagnose ARF for Cutting short the morbidity component.
- ARF is an Autoimmune disorder caused by Type 2 hypersensitivity reaction.
  - Alternative term is molecular mimicry i.e., Immune system is attacking self.
- Causative agent is Group A Beta-hemolytic Streptococci that leads to recurrent sore throat.
  - Common antigen between cell wall of the bacteria and the human connective tissue is N acetylglucosamine due to which the antibodies cross react.
- The Most common acquired heart disease in developing countries is Rheumatic fever
- Rheumatic Heart Disease is more common in females.
- But Acute rheumatic fever incidence is gender neutral.

Course of disease

- It Spans over a course of 12 weeks occurring in a child with recurrent sore throat.
- Child will have difficulty in walking (limping) due to Arthritis which is an early manifestation of disease.
- Child may also be suffering from:
  - Pericarditis
  - Endocarditis
  - Myocarditis
- Many patients may remain asymptomatic from carditis as the heart can compensate so, the features of congestive heart failure are absent.
- Late features include:
  - Sydenham's chorea – occurring 6 months after the onset of a sore throat leading to involuntary movements in extremities.
- Chorea develops in about 2-30% of the case.
- Subcutaneous nodules and erythema marginatum have very low incidence of less than 5%.
  - Arthritis occurs in about 60-75% cases and is mostly the Migratory polyarthritis involving the large joints like knee joint and will jump from one joint to another.
- Carditis can also occur in 50-75% cases.
- If the case is not managed aggressively
  - Subsequent damage to heart valves leading to congestive heart failure.
  - Arrythmias may also occur due to structural damage to the heart.
  - In Mitral Stenosis there is Left atrial dilatation occurs leading to clot formation in left lateral appendage due to atrial fibrillation which can go in systemic circulation in the brain leading to stroke.
- Primary prevention is starting of oral penicillin or amoxicillin to a child for sore throat within 9 days so that the chance of rheumatic fever is curtailed.
- Secondary prevention is administration of Injection of Benzathine penicillin on recurrent basis, but test dose should be given before injectable parenteral penicillin is started.

Carditis 00:25:29

- Any of the three layers of heart can get involved leading to - pericarditis, endocarditis or myocarditis.

- Aschoff nodules can be present in the outermost layer of the heart causing inflammation leading to chest pain.
- ECG finding of ST elevation can help identify the disease where clinical signs like pericardial friction rub can't be elicited.
- In case of myocarditis congestive heart failure, LMNOP is done.
- Hallmark feature seen in these patients is endocarditis.
  - The Heart valves involved are:
    → Mitral > Aortic
  - Valvular lesions seen are:-
    → Mitral regurgitation or Aortic regurgitation when carditis (Active) occurs.
    → If the age > 18 years, mitral stenosis (MS) is more common.
  - Endocarditis:
    → Leads to Commissural end involvement, and causes valvulitis.
    → If echocardiography in this patient is done even in the early phase of disease, it will show the presence of inflammation in the tip of the valve.
    → Due to Commissural end involvement, the characteristic murmur of the rheumatic etiology is the Carey Coombs murmur, which is a mid-diastolic murmur.
  - Earlier, only clinical findings such as commissural murmurs were taken into consideration. But now, echocardiography is considered a major diagnostic criteria for rheumatic etiology for early diagnosis.
- Heart valve which is least likely to be involved is the pulmonic valve.
- If the left side of heart will suffer, pulmonary venous congestion occurs and ultimately the pressure is transmitted to the right side of the heart also.
- The involvement of Tricuspid & Pulmonic valve is secondary to left sided valve involvement.
- At later stages of involvement, there may be a subsequent dilation of the annulus of the tricuspid valve even leading to tricuspid regurgitation.
- Most common valve involved -
  - Mitral valve
  - Aortic valve

Arthritis (Rheumatic Arthritis) 00:40:10

- It involves large joints of the body like knee joints, ankle joints, elbow joints.
- Rheumatic Arthritis tends to jump from one large joint to another and cause pain and severity. So, it is called migratory polyarthritis.
- If a child with history of recurrent sore throats is not able to walk because of the swelling of even one joint i.e., even if it is mono-arthritis, it is sufficient to diagnose it is a case of rheumatic arthritis.
- The population is termed as **low risk population** when involvement is:
  - <2/100,000 school age children
  - <1/1000 entire population
- Sometimes, there may not be any redness of joint or any inflammation, but there is pain in standing or walking of a child - Polyarthralgia.
- So, as per Indian perspective which is a high risk population doctor should not wait for migratory polyarthritis to develop and monoarthritis is sufficient for diagnosis to occur.

Treatment

- Naproxen
- Aspirin

Sydenham Chorea 00:46:00

- CHOREA is defined as a fast distal involuntary movement due to Antibody induced damage in the caudate nucleus.
- It can be found in hands and the feet, and the person might be described as a fidgety or restless person.
- In contrast, Athetosis is the slower distal involuntary movement.

Incidence: Females >> Males.

- Chorea may not develop immediately after a sore throat, but due to Prolonged latent period after the person has suffered from group A beta hemolytic streptococcus.

Clinical Features:

a. Darting tongue
b. Pronator sign
c. Emotional lability
d. Obsessive compulsive behavior.

- 50% cases of chorea will have carditis as well which may not be identified in the early period.
- Children may feel tired easily, or parents start noticing that their child is not active as before.
- Chorea has a self-limiting course.

Skin features

- SC (Subcutaneous) Nodules:
  - Extensor in distribution.
  - May happen on the bony prominences - Hands, olecranon, or occiput.
  - The lumps are mobile in nature.
- Erythema marginatum.
  - They may have serpiginous margins. (May not be found in Indian patients)
  - They look like a pink macule having a central clearing.

- Rash tends to appear when child becomes or disappear (when fever resolves).
- Erythema marginatum can be seen only on patients who have fair skin.

Modified Jones Criteria 2015 update 00:54:51

Initial Acute rheumatic fever:

- Presence of 2 major criteria is required.
- Clinical manifestations that cannot co-exist in RF patients simultaneously are arthritis and chorea.
  - Because Arthritis is early and chorea is later, so we can have sequential involvement but not simultaneous involvement.
- When 2 major criteria are not present, 1 major + 2 minor criteria are needed.

Recurrence Acute rheumatic fever:

- Presence of 2 major criteria is required.
- When 2 major criteria are not present, 1 major + 2 minor criteria are needed.
- When none of the major criteria is present, 3 minor criteria will be needed.

Major Criteria

Refer Table 26.1

Minor criteria

- These include Laboratory parameters and Clinical Findings.

1. Fever
   - It occurs due to inflammatory condition.
   - Cut off of fever is 38.5 degree Celsius for low risk whereas for high-risk population the cut of is 38 degrees Celsius
2. Elevated ESR
   - The cut off of ESR for low risk population is 60 mm fall in first hour
   - For Indian population, cut off is more than 30 mm fall
3. CRP positive
   - More than 3.0 mg/dL
4. Aschoff nodules damage the conduction system of the heart.
   - Due to this the P-R interval has a prolongation. (Normal P-R interval is 120 to 200 millisecond).
   - P-R interval prolongation is also known as 1st degree heart block and can be demonstrated on ECG because of slowing of conduction between SA and AV nodes.
5. **Polyarthralgia:**
   - It is a major diagnostic criterion for high risk population because the incidence of disease is higher.
   - But is minor criteria for low-risk population

Diagnosis of the disease 01:06:29

Tests to confirm the Diagnosis

1. ECG
   - Showing P-R interval prolongation
2. Echocardiography
   - Shows MR or AR (two most common lesions)
   - Mitral Stenosis can also be present in older patients
3. Complete blood count check
   - Shows raised TLC
4. Streptococcal serology
   - To prove causation by bacteria which leads to this condition.
   - Two tests available are:
     → Antistreptolysin test
     → Anti DNAse B

Tests to exclude alternate Diagnosis

- Autoimmune profile
- Double stranded DNA test
- Anti CCP (cyclic citrulline peptide) antibody
  - More accurate as compared to RA factor because RA factor can also be biologically false positive.
- Urine Analysis to rule out the possibility of reactive arthritis.
  - Patient maybe exposed to chlamydia trachomatis which can result in reactive arthritis.
  - Therefore, molecular test is done
    → Nucleic acid amplification technology can be done to detect the presence of the causative organism.

Management of the disease 01:10:20

Primary prevention with antibiotics

- Amoxicillin
- Ampicillin
- Phenoxymethylpenicillin
- These are oral penicillin that are administered to the patient with sore throat.
- It should be started as early as possible
  - If it started within 9 days of sore throat, then the chances of development of rheumatic fever and the cross-reactive antibodies almost becomes zero.

Aspirin

- It is mainly used for management of arthritis or polyarthralgia
- The Side Effects include GI irritation or the development of the erosive gastritis
  - Therefore, the patient is observed for the possibility of a GI bleed.
- Side effects also include Salicylate toxicity which can be a development of metabolic acidosis due to salicylic acid leading to compensatory respiratory alkalosis.
- Another problem is the multiple dosing will be required per day to get sufficient amount of analgesia and thus Naproxen is preferred.

Steroid

- The use of steroids remains controversial in the treatment of the condition.
- 2 meta-analyses have failed to demonstrate the benefit of steroids in improving either a short- or long-term outcome of the carditis component.

- Carditis may contribute to congestive heart failure so the steroids are being used but if there is acute congestive heart failure then steroids alone will not mitigate the short term mortality or the pulmonary edema component.
- For myocarditis component or if there is a valvular lesion then the standard LMNOP is used.
  - Lasix, Morphine, NTG, Oxygen, Positioning (head end of the patient will be kept at high position to reduce the chances of orthopnea)

Role of bedrest

- Earlier strict bed rest was advised.
- Minimal amount of mobility should be allowed in patients as the arthritis component will subside due to usage of Naproxen or Aspirin.

Chorea

- If it is mild and not debilitating, then most of the time providing a calm environment will help as it will have a self-limiting course.
  - So, no treatment is required.
- Moderate to severe condition: If it is interfering with day-to-day activity including the feeding of children then Drugs like Carbamazepine or Valproate can be used.
- Haloperidol was the initial approach for management of chorea but it carries the risk of drug induced Parkinsonism.
- Many chorea patients can also have concomitant carditis as well.
- If Steroids are used in patients having Chorea, it can lead to faster resolution
- For medically refractory chorea Intravenous immunoglobulins can be used

AHA Guidelines for Secondary Prophylaxis 01:17:17

- A Long Acting Benzathine penicillin should be administered to the patient.
- Range at which injection of Benzathine penicillin should be administered is between a gap of 3 to 4 weeks, after test dose administration is done.
  - It is Intramuscularly administered.
  - For High-risk cases, penicillin is given in the gap of as early as 2 weeks.
- Anaphylaxis may occur causing the lips of the patient to turn blue and then leading to death. So, test dose is to be given before every dose of Penicillin.
  - In these cases, laryngeal edema can be the cause of death.
  - Anaphylaxis is mediated by Basophils.
  - Cytokine involved is Interleukin 4.
  - Management is done by giving undiluted Inj. Adrenaline (1:1000) IM.
    → Anaphylaxis is the only case where adrenaline is given undiluted.
  - IV Inj. Adr is not given as Histamine release will cause Vasodilation.
- **Duration of Antibiotics:**
  - RHD with MR – till 40 years of age / total of 10 years since last attack - whichever is longer.
  - RF with carditis -till 21 years of age / total 10 years since last attack- whichever is longer.
  - RF without carditis – till 21 years of age / total 5 years since last attack- whichever is longer.

Echocardiographic evidence of Rheumatic carditis 01:21:42

- **Pathological MR**
  - Occurs when the blood leaks from LV to LA.
  - Jet length > 2 cm.
  - Blood leaking from a high-pressure chamber to low pressure chamber.
  - Peak velocity >3 m per second
  - It is Pan systolic as jet blood will be moving during the phase of systole.
- **Pathological AR**
  - Occurs when the blood leaks from the aorta back into the left ventricle (LV)
  - The jet length> 1 cm
  - Peak velocity > 3 m/sec
- **MS (Mitral Stenosis)**
  - The mathematical gradient between LA - LV should be > 4 mm Hg.

Important Information

- For Sub-clinical carditis, Echocardiographic evidence will be Valvulitis. But later MR and AR might develop in these patients.
- In older patients, there will be a chance of developing Mitral Stenosis.

Table 26.1

Low risk population	Moderate - High risk population
MAJOR	**MAJOR**
Carditis components: clinically detectable, echocardiographic events (presence of echogenic murmur or valvulitis)	
Arthritis components: migratory polyarthritis is a must for diagnosis.	Arthritis: mono-arthritis/poly-arthritis is sufficient for diagnosis. Polyarthralgia
Chorea	Chorea
Subcutaneous Nodules/ erythema marginatum	Subcutaneous Nodules/Erythema marginatum

* Polyarthralgia is major criteria for High Risk population but minor criteria for low risk population.

27 INFECTIVE ENDOCARDITIS

Causative Organisms

1. For Native valve endocarditis:

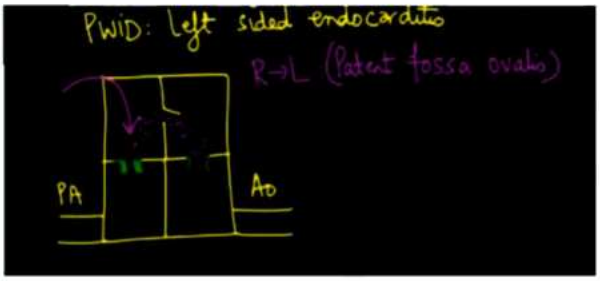
- Community acquired: Streptococcus.
- Hospital acquired: Staphylococcus aureus.

2. For Prosthetic valve endocarditis:

- Within 2 months
  - Coagulase negative staphylococcus (CONS)
- Between 2 - 12 months
  - CONS
- After 12 months
  - Streptococcus
- It is caused due to intro operative contamination of the operating field, or it can be post operative.

Valvular lesions:

- One of the most common valvular lesions found in an western population is aortic stenosis due to Senile calcification of aortic valve.
  - TREATMENT-**Trans catheter aortic valve replacement** procedure **(TAVR)**
- After the new valve is introduced in TAVR and Infective Endocarditis occurs, it is called PVE (prosthetic valve endocarditis)
  - Enterococcus > Staphylococcus aureus
- In a patient of heart disease CIED-IE (cardiovascular implantable electronic device) may be implanted.
  - Implantable cardioverter-defibrillator (ICD) is used in patients who have a tendency of development of tachyarrhythmias.
  - Cardiac resynchronization therapy device is implanted in patient of Dilated cardiomyopathy.
  - Pacemaker is implanted in the patients suffering from bradyarrhythmias.
  - Incidence of infective endocarditis in devices like ICD and CRT is higher than pacemaker.
  - Staphylococcus aureus is the leading organism associated with Infective Endocarditis in patients with implantable devices.
- In case of People who would inject drugs (PWID)/ IV Drug user (IVDU):
  - Infection will go in the right side of the heart causing Right sided endocarditis damaging Tricuspid valve
  - Methicillin-resistant Staphylococcus aureus is causative organism involved.
- Rarely PWID there is Left sided endocarditis then:
  - Congenital heart disease associated is Patent fossa ovalis (PFO)
  - The organisms responsible are:
    - → Enterococcus
    - → Pseudomonous
    - → Candida



Incidence of Infective Endocarditis 00:12:20

- Incidence is directly related to pressure gradient that might be present in a valvular lesion or congenital heart disease
- Highest chances of development of infective endocarditis is with Mitral regurgitation.
- Least chances of development of infective endocarditis is atrial septal defect
- Infective endocarditis Vegetations Developing on the heart valve, that can embolize to systemic circulation.
- Whenever there is a valvular lesion in the heart, there is a jet of blood that can cause damage to the endocardium and the bacteria can adhere to damaged endocardium and lead to:
  - Acute bacterial endocarditis
    - → Progression is faster (within weeks)
    - → High chances of death
      - Due to sepsis and vegetation embolising in the distal circulation
    - → Hectic febrile illness (high grade fever with chills and rigors)
    - → Caused by Staphylococcus aureus
  - Subacute bacterial endocarditis
    - → Pre-existing valvular lesion can worsen can lead to MI.
    - → Mycotic aneurysm (via middle cerebral artery,anterior cerebral artery) may rupture and lead to Subarachnoid hemorrhage ,death of the patient.
    - → Slow progression (weeks to months)
    - → Streptococcus Viridans is the leading cause.
    - → It has a Gradual Indolent course.
- Major Embolic event such as stroke can occur.

Infective Endarteritis 00:22:40

- It is an analogous process to endocarditis.
- Infection is not in heart valve, but it causes damage to arterio-venous fistula or arterio-arterial fistula or arterio-arterial shunt.
  - Arterio-arterial shunt is seen in congenital rubella syndrome.
  - In PDA, infection of ductus arteriosus is termed Infective Endarteritis.
- It may also occur in patients with Intracardiac devices like CRT and pacemaker.
- In Infective Endarteritis, it is the blood vessels that are getting involved.

Prosthetic Valve Endocarditis (PVE) 00:25:08

- Risk of PVE is maximum in the first year of implantation.
- Bioprosthetic valves have a greater incidence of infective endocarditis than the metallic valves.
- TAVR - PVE
  - Old aortic valve is not removed, and the new valve is deployed over and above the calcified valve.
- Risk of post TAVR PVE is equal to that of PVE after surgical implantation of bioprosthetic valve (open heart surgery)
- In CIED implanted, there is a increased risk of development of endocarditis.
  - Risk with ICD> Pacemaker

Culture Negative Endocarditis 00:31:02

Cause

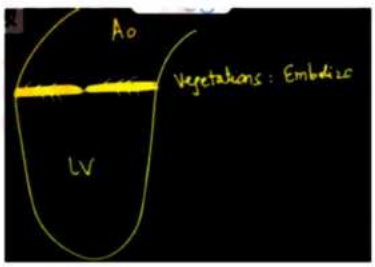
- Prior antibiotic exposure
- Fastidious organisms.
  - They are not detected by routine culture medium.
  - Some species of Streptococcus.
  - Granulicatella
  - Abiotrophia species
  - HACEK group of organisms
    - → Haemophilus species
    - → Aggregatibacter species
    - → Cardiobacterium
    - → Eikenella
    - → Kingella
  - Bartonella
  - Tropheryma whipplei (causes Whipple disease)
    - → It can have CNS manifestations, cardiovascular implications and can also be incriminated in causing infective endocarditis.
    - → Other species- Corynebacterium, Propionibacterium.
  - Mycobacterium chimaera
    - → It has been responsible for the outbreak of prosthetic valve endocarditis in certain hospitals.
      - Attributed to patients who are exposed to cardiopulmonary bypass machines with imperfect sterilisation techniques followed in hospitals.
- SHOT metagenomics- to identify causative organism.
  - It is a next generation sequencing, i.e sequencing of DNA of pathogens in serum of the patient.

Portals of entry 00:37:28

- Oral cavity
  - Occurs in case of Person with heart disease undergoing a dental procedure.
- Skin
- Upper Respiratory Tract
  - Causative agent-Streptococcus,Staphylococcus aureus.
- GIT
  - Incidence is higher in patients with pre-existing Polyps or tumour.
  - Causative agent- Streptococcus gallolyticus.
- GU (genitourinary)
  - Causative agent- Enterococcus.
- Patient with pre-existing heart disease, the GU infection should be treated aggressively.
- Patient with cardiac valvular lesion with H/O episode of infective endocarditis- advised to maintain Dental hygiene.
  - Patients are given antibiotic prophylaxis before any dental procedure or extraction to prevent further damage to the heart.

Pathogenesis 00:40:55

- Bacteria (causative organism)
- Endothelial injury
- Endothelial injury is caused by a high velocity of jet of blood.
  - Valvular Mitral regurgitation
- Ventricular septal defect (VSD) or Patent ductus arteriosus (Low-pressure side of congenital heart disease).
- Lead to formation of Platelet fibrin thrombus called as Nonbacterial thrombotic endocarditis (NBTE)
- NBTE non-infectious causes:-
  - Acute promyelocytic leukaemia
  - Malignancy
  - Antiphospholipid antibody syndrome
- In the pathogenesis of infective endocarditis, initially a lesion devoid of infection is developed called NBTE.
- Over this lesion the bacteria can seed which have:-
  - MSCRAM (microbial surface components recognizing adhesive matrix molecules)
  - Infective vegetation can break and embolise to distal circulation.



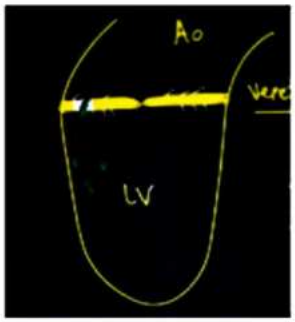
Complications related to Embolization

1. Bacteraemia
   - o High grade fever
   - o Abscess formation
2. Infraction
3. Abdominal pain
   - o Left hypochondrium pain
   - o Pain in flank region
     - → Renal or splenic artery occlusion
     - → Septic emboli formation
   - o IV drug user - Pulmonary septic infarcts.
4. Tissue injury due to circulating immune complexes leading to Glomerulonephritis.

Case Study:

A patient suffering from fever with chills and rigors had his routine investigations done, but cause of fever was not detected. The patient has a pre-existing heart disease.

- The infection will increase in magnitude.
- Formation of Valve abscess with pus spreading in the tissue of the valve.
- Perforation developing in the valve leaflet leading the aortic blood to leak into the left ventricle causing new onset murmur.



Manifestations 00:53:55

Cardiac manifestations

- Valve perforation that is visualised on echocardiography.
  - o Also called Paravalvular or ring abscess
- Heart blocks (brady arrhythmias)
  - o Syncopal episodes or even death
- Damaged heart valves, Mitral regurgitation with infection (pulmonary oedema) can cause ADCHF (Acutely Decompensated Congestive Heart Failure)
- Intracardiac fistula.
- Coronary embolism of vegetation can cause Myocardial infarction.

Non cardiac manifestations

Peripheral manifestations:

- Janeway lesions
  - o Erythematous macules on palms and soles.
- Subungual haemorrhages
- Roth spots
  - o Seen on fundus examination.
  - o Roth spots also seen in leukaemia, lymphomas, anaemia)
- Osler nodes
  - o Pea shaped nodules located at tips of finger.
- Cardiovascular emboli -Stroke
- Regional or abdominal pain/ infarction.
  - o Also referred to as organ dysfunctional.
  - o Organs involved are kidney, spleen.
  - o Splenomegaly is not a diagnostic criteria of infective endocarditis.
- Meningitis (Multi focal brain abscesses)
- Mycotic aneurysm.

Modified DUKE's Criteria 01:03:08

Algorithm:

- 2 major criteria
- 1 major criteria + 3 minor criteria
- 5 minor criteria

Investigation - Blood culture:

- 3 sets of 2 culture bottles each are taken from different Venepuncture sites over a span of 1-2 hours.
  - o Out of these three sets, at least two sets should be positive for same bacteria to incorporate in major diagnostic criteria.
- Advantages:-
  - o To demonstrate the dissemination that the heart is the source of pumping these bacteria into systemic circulation.
  - o To reduce the trauma at the same site.
  - o To reduce local contamination on the same site.
- Once the blood culture result is positive, specific antibiotics can be given.
- Empirical treatment is given to the patients till the culture reports arrive.
- In prosthetic valve endocarditis-IV antibiotics X atleast 6 weeks.

Major Criteria

1. Positive blood culture
- Typical organisms positive from 2 separate blood cultures.
  - o Typical organisms include streptococcus viridans oral cavity or skin, streptococcus gallolyticus GI tract, staphylococcus aureus HACEK.
  - o Persistently positive blood culture :-
    - → Typical organisms are isolated from blood culture.
    - → And these blood cultures are done > 12 hours apart.
  - o Single positive blood culture :- Coxiella.
    - → Coxiella infection causes Q fever.
    - → It is a zoonotic infection.
    - → Phase I: IgG titre > 1:800.

2. Echocardiographic evidence
- Types of echocardiography:
  - Transesophageal echocardiography (TEE)
  - Transthoracic echocardiography (TTE)
  - TEE > TTE
- HIV does not change the organisms(bacteria) responsible for development of endocarditis.
- Vegetation or oscillating intracardiac mass.
- Vegetation < 2 mm size it might be missed on Transthoracic echocardiography.
- Partial dehiscence of the prosthetic valve or New valvular regurgitation - Bioprosthetic valve damaged by the bacteria.

3. New onset murmur in patient with pre-existing heart lesion

Minor modified criteria

1. **Predisposition:**
- Pre-existing heart disease or patient of IV drug usage.
2. **Fever > 38°C**
3. **Vascular phenomenon**
- Major embolic phenomenon
- Septic pulmonary infarction
- Mycotic aneurysm
- Intracranial haemorrhage
- Janeway lesion (palm, soles)
4. **Immunological phenomenon (Mnemonic – ROG)**
- R- Roth spots
- R- RA Factor +ve
- O- OSLER Nodes (tip of finger)
- G- Glomerulonephritis
5. **Microbiological evidence:**
- +Ve blood culture which is not satisfying the major criteria
- As per the current guidelines:
  - Moderate-high clinical suspicion
    → Perform transoesophageal echocardiography (TEE)
  - Low clinical suspicion
    → Perform transthoracic echocardiography (TTE)
  - SHOT metagenomics: Next gen sequencing.
  - Multi-slice CT angiography has comparable results in detecting infective endocarditis as compared to Transoesophageal echocardiography (TEE)
    → Multi-slice CT angiography and TEE >> Transthoracic echocardiography (TTE)
  - FDG PET-CT
    → Diagnosis of fever of unknown origin.
    → Detect occult malignancy.
    → Infective endocarditis

Treatment

01:33:36

- MRSA – NVE: Vancomycin / Daptomycin X 6 weeks.
- MRSA – PVE: Vancomycin + Gentamycin + Rifampin
  - Rifampin kills bacteria embedded in biofilm
- MSSA – PVE: Naficillin + Gentamycin + Rifampin
- Enterococci: Ampicillin + Gentamycin
- Streptococci: Ceftriaxone + Gentamycin
- Coxiella - Doxycycline + Hydroxychloroquine
- Bartonella - Doxycycline + Gentamycin
- Candida (fungal endocarditis) - IV amphotericin B + Flucytosine
  - If PVE - early surgery is the treatment of choice

High risk cardiac lesions for which endocarditis prophylaxis is advised prior to dental procedures

01:37:57

1. Prior Endocarditis
2. Prior deployment of prosthetic valve
3. Artificial left ventricle - battery powered left ventricular assist device (LVAD)
4. Unrepaired Congenital Heart Disease or a previous palliative surgery like BT Shunt (to connect the subclavian artery to pulmonary artery to establish substantial blood flow to pulmonary circulation)
5. Complete repair of Congenital heart disease
   - In the first six months, the chances for infection are high for infective endocarditis.
6. Transcatheter pulmonic valve deployment or deployment of a conduit.
7. Valvulopathy after cardiac transplantation
   - Amoxicillin should be started.
     → 2 gm X P.O. 1 hr before the procedure

30 BASIC CARDIAC LIFE SUPPORT

Introduction

- Out of the hospital care in unresponsive/ pulseless person
- In western countries, cardiac event occurring out of hospital has survival rate of 10%
- Cardiac event occurring outside with bystander CPR, survival rate= 20%

Cardiac Arrest

- Unresponsive due to lack of cerebral blood flow
- Pulseless, carotid pulse is checked since it is the closest to heart and the last pulse to go
- Apnea/gasping/Agonal rhythm

Pulseless Conditions

Shockable rhythm	Non-shockable rhythm
Ventricular fibrillation 	Asystole
Ventricular tachycardia 	Pulseless electrical activity 
Treated with cardioversion, More survival chances	Less survival chances

Important Information

- Both shockable and Non-shockable rhythms are interconvertible i.e., Ventricular fibrillation may convert into asystole and vise versa

Clinical Scenario

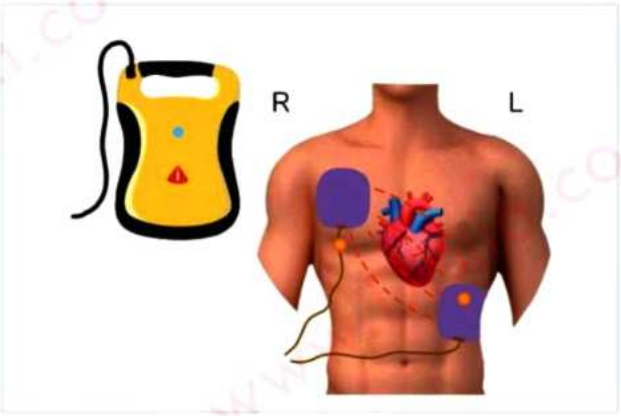
An elderly person, 60-70 years old, collapses suddenly in the airport near the boarding gate. What will the management be this patient?

- **Steps in management of the patient**
  - Check for Scene safety- move the patient to a smooth flat surface
  - Check for Responsiveness of the patient- tap on the shoulders
  - Shout for help
  - Activate the Emergency response
  - Simultaneously check for Breathing effort- Feel the breath of the patient, look for rise and fall of the chest
  - Check for Carotid pulse
- **Scenario 1**
  - Indication for cardiopulmonary resuscitation- 30:2
  - Pulse: Absent
  - Respiration: Absent
  - One cycle of cardiopulmonary resuscitation is 2 minutes
- **Scenario 2**
  - Indication for rescue breaths
  - Pulse: Present
  - Respiration: Absent
  - Should be given at 10-12 breaths/minute or 1 breath every 6 seconds
- **Scenario 3**
  - Pulse: Present
  - Respiration: Present
  - Loss of consciousness
  - Monitor the patient until the emergency services arrive

Automated External Defibrillator: A.E.D

- Once CPR is initiated attach the AED pads to the chest of the patient
- AED verbally commands whether it is a shockable/ Non-shockable rhythm
- If its shockable rhythm- DC shock of 200J is delivered
- After shock delivered, check for pulse and respiration
- All AEDs are programmed to deliver 200J DC shock

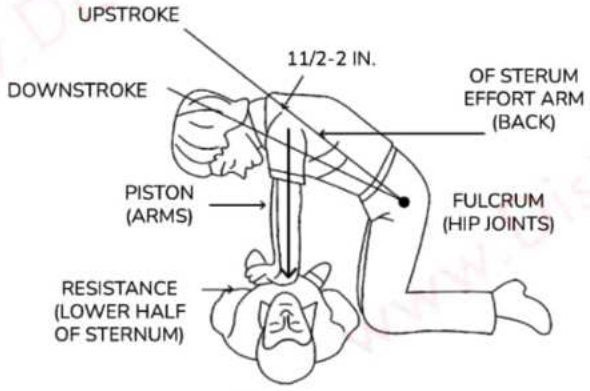
- **Positioning of the AED pads**
  - 1st pad: Below the right infra clavicular region
  - 2nd pad: Below the left nipple going into the axilla



Cardiopulmonary Resuscitation: CPR

Circulation

- Chest compressions are given at a rate of 100-120/minute with 2 rescue breaths every 30 compressions, 30:2
- Sternum should go down by 5 cm
- Allow for proper recoil of the chest between every compression
  - Allows hearts to fill blood
  - Ensures coronary blood flow
- Place the hands on the lower 1/3rd of the sternum
- Placing the hands on the Xiphisternum (pointed) can cause injury to the liver
- Lean forward on the body of the patient, weight of the head, neck and chest allows for 5cm compressions
- Fulcrum to be used is hip joint
- Elbows should be straight and locked
- Flexing of the elbows leads to use of the back muscles causing rib fractures
- Do not stop chest compressions even after rib fracture



- **Ratio of CPR administration**

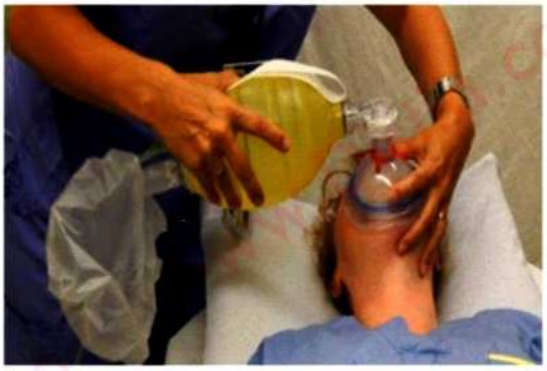
Adult	3:2	1-2 rescuers
Pediatrics (Child)	30:2 15:2	1 rescuer 2 rescuers
Neonate	3:1	2 rescuers mandatory

Important Information

- Most common injured solid organ in CPR is liver (not lungs)
- Lung is not a solid organ
- Most common ribs fractured during CPR- 4th to 6th

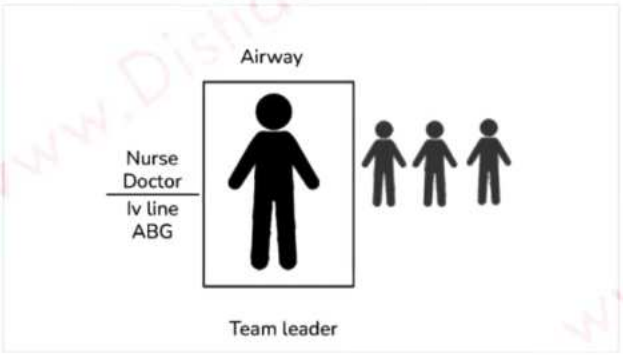
Respiration: Airway Management

- Bag and mask ventilation with AMBU BAG
- Tilt the head and lift the chin of the patient (sniffing position)
- Allows for better passage of the airway
- **How to use Ambu bag**
  - Mask is held between the thumb and index finger forming the 'C' shape, allow the mask to fit tightly to the face
  - Remaining three fingers are placed on the lower border of the mandible/ chin, allow for the chin lift



Positioning of the Rescue Team Around the Patient

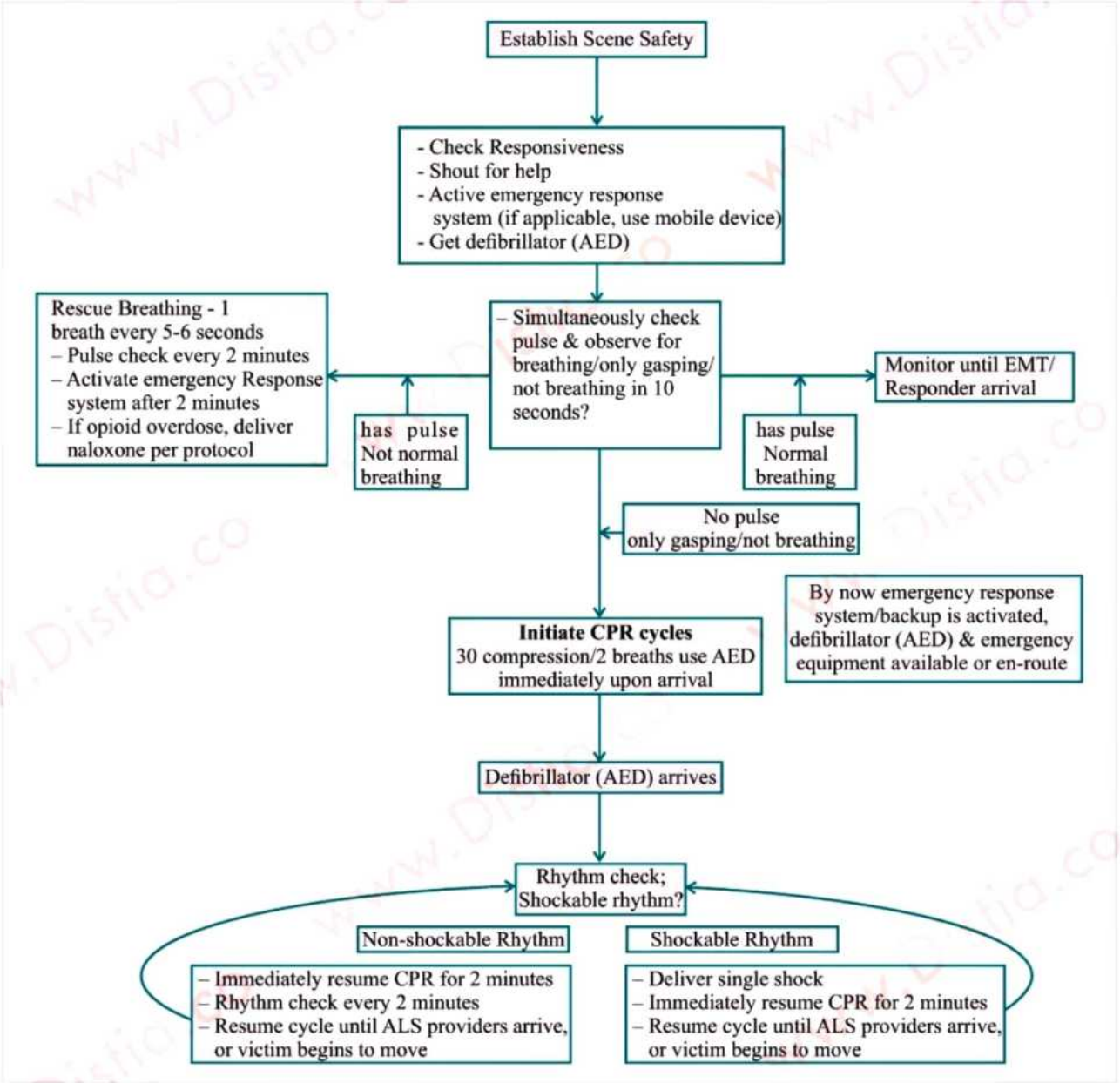
- Head end- Rescuer with the Ambu bag
- Foot end- Team leader to give clear instructions to the rescuers
- Right side- 2-3 rescuers for chest compressions
- Left side- Doctor/ nurse to gain IV access



Causes of Cardiac Arrest

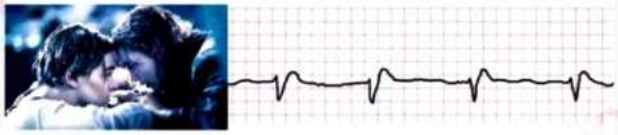
1. Coronary artery disease
2. Cardiomyopathy- Hypertrophic obstructive cardiomyopathy/ Takotsubo cardiomyopathy
3. Valvular lesions
   - Mitral stenosis/ mitral regurgitation-> Left atrial dilation->Atrial fibrillation->Stroke
4. Electrolyte imbalance- Hyperkalemia
5. Toxins- Tricyclic acid overdose
6. BBB/ Brugada syndrome- SCN5A, TDP

Refer the Adult BLS Algorithm



31 PULSELESS ELECTRICAL ACTIVITY

introduction



- Electrical activity of the heart i.e., SA node, AV node, Bundle of His and Purkinje fibers are working normally but there is no pulse
- Finding cause is important for treatment of Pulseless electrical activity

Outcomes By Diagnosis

- Shockable
- Non-shockable

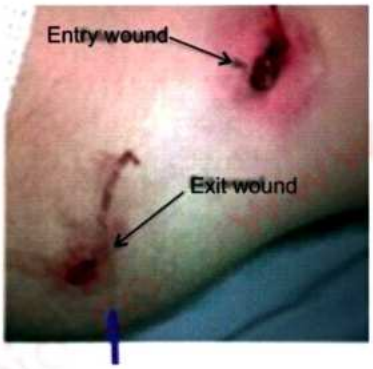
Diagnosis	Survival rate
Unstable Ventricular tachycardia	65-70%
Ventricular fibrillation	25-40%
Pulseless electrical activity	11%
Asystole	0-2%

Causes of PEA

1) EMPTY HEART

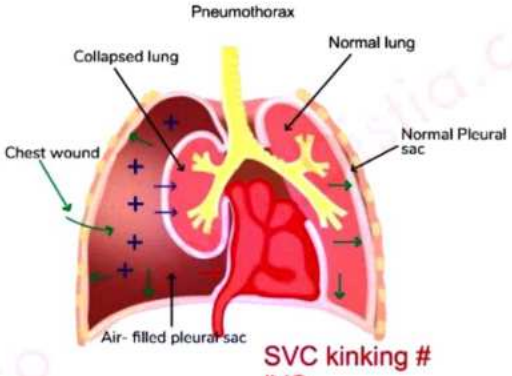
a) Hypovolemia:

- Bullet injury to the heart can rip the aorta/ superior mesenteric artery/ Inferior mesenteric artery
- Leads to hypovolemia-> decompensatory shock-> pulselessness



b) Tension Pneumothorax:

- Bullet injury to the chest->air rushes to the lungs-> increase the positive pressure-> collapse of the lung-> Kinking of the superior and inferior vena cava-> pulselessness

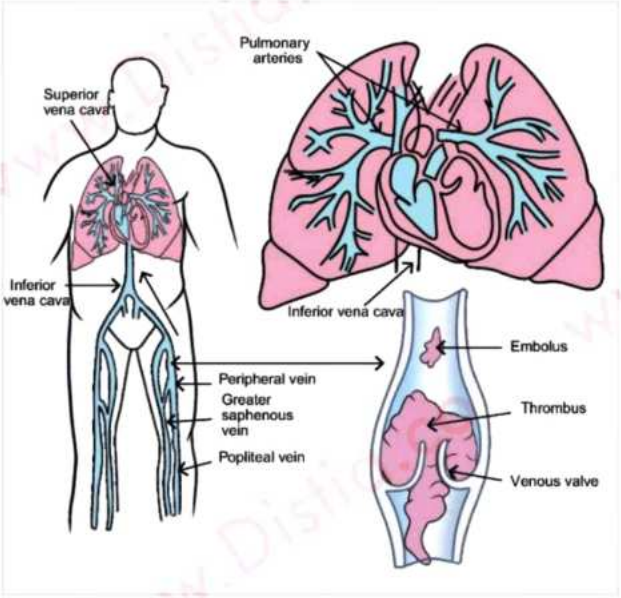


c) Cardiac Tamponade:

- Fluid in the pericardial space-> exerts pressure on the heart from outside-> Venous return to the heart is compromised-> reduced cardiac output-> pulselessness

2) ELECTROMECHANICAL DISSOCIATION

- Conduction is normal but the problem lies in the mechanics of the heart
- Myocardial infarction- Stunned myocardium due to hypoxia (Extensive anterior wall myocardial infarction)
- Pulmonary embolism:
  - Postpartum patients, orthopedic implant surgeries
  - Develops clots due to immobilization-> spreads retrogradely to the heart-> severe hypoxia and right-side heart failure-> pulselessness



Treatable Causes Of Cardiac Arrest

- 5 H's and 5 T's

5 H's	5 T's
Hypoxia- Acute myocardial infarction	Toxins- Tricyclic acid toxicity
Hypovolemia- Rupture aorta	Tamponade, cardiac
Hypo/Hyperkalemia	Tension pneumothorax
Hydrogen ion excess- acidosis	Thrombosis, pulmonary
Hypothermia- <35°C	Thrombosis, cardiac

- Easy method
- Hypokalemia- Diaphragmatic paralysis.
- Hyperkalemia- K+ >8.0 mEq/L (leads to diastolic arrest).

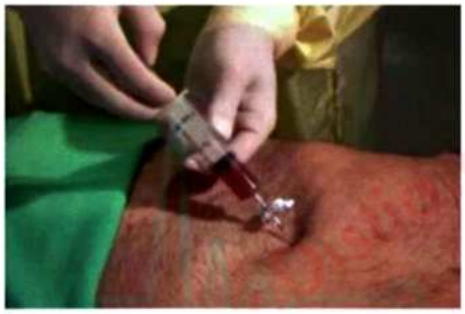
HEART	CONDITION	LUNG
Hypovolemia	**Not enough blood**	Hypoxia
Cardiac tamponade	**Squeezed**	Tension pneumothorax
Acute myocardial infarction	**Killed**	Massive pulmonary embolism

- Remaining causes of Reversible cardiac arrest: H.E.A.P
  - **H**ypothermia
  - **E**lectrolyte imbalance
  - **A**cidosis
  - **P**oisoning

Interventions

- Rapid infuser with in line warmer- Prevent hypothermia

- Echocardiographic guided Pericardiocentesis- Manage Cardiac tamponade



- Wide bore needle
  - 2nd intercostal space
  - Mange Tension pneumothorax
  - If the soldier has bullet proof vest /big pectoral muscles, 5th intercostal space is used [Preferred site]

- Air blanket- Manage Hypothermia

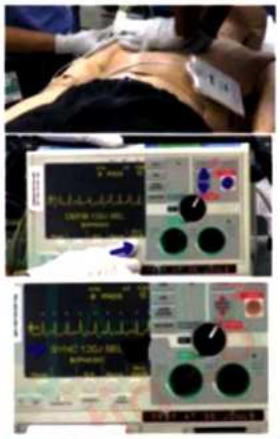
32 ADVANCED CARDIAC LIFE SUPPORT

How is ACLS different from BLS?

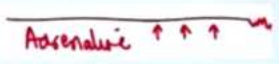
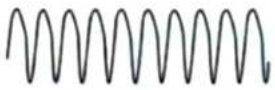
- In ACLS, the differential diagnosis of the cause of pulselessness are found and the patient is treated accordingly
- In BLS, the main aim is to maintain the brain perfusion
- **Differential diagnosis of pulselessness**
  - Ventricular tachycardia
  - Asystole
  - Pulseless electrical activity
    - → Hypovolemia
    - → Tension pneumothorax
- AED is used in BLS- the machine detects the rhythm and delivers the shock
- Defibrillator is used in ACLS- the machine detects the rhythm but the doctor decides when to give the shock
- Advanced and secured airway management in ACLS "(1 breath every 6 seconds)"

Difference between Defibrillation and Cardioversion

Cardioversion	Defibrillation
• Synchronized "DC" shock given at the peak of R wave • Peak of R wave- point at which the heart is contracting abnormally • "Shocks the" heart to relax, fill blood and SA node takes over • "Used" in Paroxysmal supraventricular tachycardia, Atrial fibrillation, Atrial flutter	• Impulse given irrespective of the peak of the R wave • "Used" in Ventricular fibrillation, Pulseless ventricular tachycardia



Shockable and Non-shockable rhythms

Shockable Rhythm	Non shockable rhythm
V. Fib	Asystole
	
Monomorphic V.T.	P.E.A
	

- Asystole: Management is to give adrenaline which helps to convert asystole to Ventricular fibrillation and DC shock can be given
- Pulseless electrical activity: Seen in Hypothermia, Tension pneumothorax, Hypovolemia

Agonal Rhythm

- Few lasts breaths of a person- efforts of brain stem
- Irregular broad QRS complex due to firing of Bundle of His, after this Asystole

Treatable causes of cardiac arrest

- Hypokalemia- Results Torsades de Pointes, Diaphragmatic paralysis
- Hyperkalemia- Bradycardia- > Diastolic arrest
- Tamponade- Identified by electrical alternans of ECG
- Tension pneumothorax- Identified by absent breaths sounds on ipsilateral side
- Coronary artery disease- ST elevation
- Massive pulmonary embolism- Have right ventricular failure, S1Q3T3 and Kussmaul's sign

H	Hypovemia	Hypoxia	Hydrogen Ion (acidosis)	Hypo/Hyperkalemia	Hypothermia
	Loss of fluid volume in the circulatory system. Look for obvious blood loss. Most important intervention is to obtain IV access and administer IV fluids. Use a fluid challenge to determine if the arrest is related to hypovolemia	Deprivation of an adequate oxygen supply can be a significant contributing cause of cardiac arrest. Ensure that the airway is open. Ensure adequate ventilation, and bilateral breath sounds. Ensure oxygen supply is connected properly.	Obtain an arterial blood gas to determine respiratory acidosis. Provide adequate ventilations. Use sodium bicarbonate to prevent metabolic acidosis if necessary.	Both a high and low k+ can cause cardiac arrest. Signs of high K+ include taller, peaked T-waves, and widening of the QRS complex. Signs of low K+ include flattened T-waves, prominent U-waves and possibly widened WRS complex.	If a patient has been exposed to the cold, warming measures should be taken. Core temp. should be raised above 86 F and 30 C as soon as possible. The patient may not respond to drug or electrical therapy while hypothermic.

T	Tioxins	Tamponade	Tension pneumothorax	Thrombosis (heart; acute, massive MI)	Thrombosis (lungs; massive PE)
	Accidental overdose: Some of the most common include: Tricyclics, digoxin, beta bbckers, and calcium channel blockers). Cocaine is the most common street drug that increases incidence of pulseless arrest. Physcal signs: include bradycardia, pupil symptoms, and other neurological changes. Poison control can be utilized to obtain information about toxins ard reversing agents.	Fluid build-up in the pericardium results in ineffective pumping of the blood which can lead to pulseless arrest. ECG symptoms: Narrow QRS complex and rapid heart rate. Physical signs: jugular vein distention (JVD), no pulse or diffculty palpating a pulse, and muffed heart sounds. Perform: pericardiocentesis to reverse.	Tension pneumothorax shifts in the intrathroacic structure and can rapidly lead to cardiovascular collapse and death. ECG sings: Narrow QRS complexes and slow heart rate Physical signs: JVD, tracheal deviation, unequal breath sounds, difficulty with ventilation, and no pulse felt with CPR. Treatment: Needle decompression.	Cause acute myocardial infarction ECG sings: 12 lead ECG with ST-segment changes, T-wave inversions, and/or Q waves. Physical sings: elevated cardiac markers on lab tests, and chest pain/pressure. Treatments: use of fibrinolytic therapy, PCI (percutaneous coronary intervention). The most common PCI procedure is coronary angioplasty with or without stent placement.	Can rapidly lead to respiratory collapse md sudden death. ECG signs of PE: narrow QRS Complex and rapid heart rate. Physical sings: No pulse felt wth CPR. Distended neck veins. positive d-dimer test, prior positive test for DVT or PE. Treatment: surgical intervention (pumonary thrombectomy) and fibrinolytic therapy.

Steps to treat Shockable and non-shockable conditions

- **Shockable Conditions**

Premature ventricular tachcardia/ Ventricular fibrillation
↓
Non synchronized DC shock given
↓
Continue CPR for 2 mins, IV/IO line is established(as close to the heart)
↓
Fails- Repeat non synchronized DC shock
↓
CPR for 2 mins, IV/IO epinephrine 1 mg in 1:10000 dilution
↓
Epinephrine increases coronary circulation as it is a vasoconstrictor
↓
Advanced airway, Capnography (Breathing 1 breath/6 seconds after endotracheal intubation)
↓
Fails- 3rd shock given
↓
CPR for 2 mins, IV Amiodrone given for shock refractory ventricular tachycardia
↓
Treat reversible cause

- **Non-Shockable Conditions**

Pulseless electrical activity/ Asystole
↓
CPR for 2 mins, IV/IO(tibia/sternum) epinephrine
↓
Advanced airway, capnigraphy
↓
Fails- CPR for 2 mins, repeat Epinephrine
↓
Treat reversible causes mainly Hypothermia
↓
Epinephrine repeated every 3-5 mins

- If Return of spontaneous circulation (R.O.S.C) is achieved-> Targeted temperature management, Therapeutic hypothermia
- **Amiodarone**
  - Three doses can be given
  - 1st dose- 300 mg
  - 2nd dose- 150 mg after 3-5 mins
  - Amiodarone is useful for stable ventricular tachycardia as well as shock refractory ventricular tachycardia
  - Amiodarone and Adrenaline have been shown to increase response to Electro-shocks.

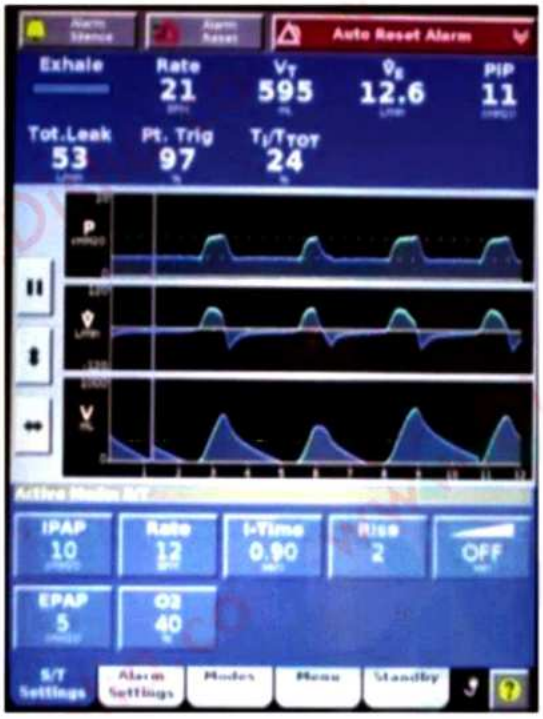
33 MECHANICAL VENTILATION

Tidal Volume (V_T)

- 12-12 ruleis followed
- V_T=12ml/ kg lean body weighti.e., fat component should be subtracted and Respiratory rate= 12/min
  E.g. In two patients with 70kg and 90kg bodyweight, the lung capacity will be the same but one of them is heavier due to higher fat content (obese). This fat content should be subtracted from the total weight.

Important Information

- 12-12 rule is not followed in Acute respiratory distress syndrome
- V_T = 6ml/ kg lean body weight is followed to minimize volutrauma in the patient
- ARDS is a condition with inflamed alveoli. Inflation and deflation with standard rule will cause Barotrauma to the alveoli.
- A patient with Guillain-Barre syndrome/ transverse myelitis with diaphragmatic paralysis, standard 12-12 rule can be followed since there is no inflammation of the alveoli



Respiratory Rate

- Have to calculate minute volume
- Minute volume = V_T x Respiratory rate

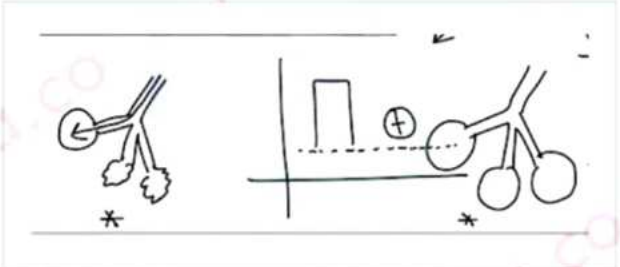
- Conditions where Respiratory rate is deliberately increased:
  - Raised intra cranial pressure
    →Elective hyperventilation in raised Intra cranial pressure contributes to vasoconstriction of capillaries responsible for production CSF (Reduced CSF= decrease in intra cranial pressure)
  - Diabetic ketoacidosis
    →Hyperventilation is a method of compensation to clear the acidosis component in Diabetic ketoacidosis

F_iO_2(Fraction Of Inspired Oxygen)

- F_iO_2 1.0 = 100% O_2, F_iO_2 0.6 = 60% O_2 F_iO_2 0.4 = 40% O_2
- F_iO_2 is started from 0.4.
- Objective is to maintain Oxygen saturation
- Partial pressure of oxygen - PaO_2>60mmHg PaO_2

Peak End Expiratory Pressure (PEEP)

- There is always a baseline pressure in the lung, whatever inflation/deflation done will always be above the baseline
- Applying PEEP will lead to recruitment of alveoli (More surface area of the alveoli for gas exchange)
- Better oxygen saturation
- PEEP of 3-5cm of water will help in the recruitment of alveoli



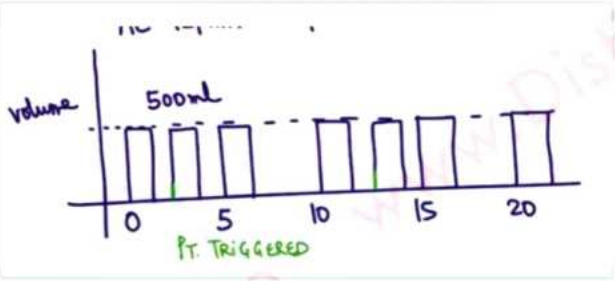
- Disadvantages:
  - Increased PEEP - > increases pressure on the great veins of the chest-> decreased venous return to the heart - > reduced blood pressure
  - High PEEP= Hypotension

Scenario With ABG Parameters

Patient A	Patient B
• pH- 7.40(Normal) • pO_2- 60 (Deficient) • pCO_2- 40 (Normal)	• pH- 7.20(Acidosis) • pO_2- 100 (Normal) • pCO_2- 60 (Increased, Respiratory acidosis)
Management: • Increase F_iO_2 • Increase PEEP • Recruitment is better • Hypoxia- F_iO_2 and PEEP should be taken care of	**Management:** • Increase the Respiratory rate • Increase the Minute volume • Corrects acidosis by CO_2 washout • Respiratory acidosis- Respiratory rate and minute volume should be taken care of.

Assisted Control Mechanical Ventilation (ASMV)

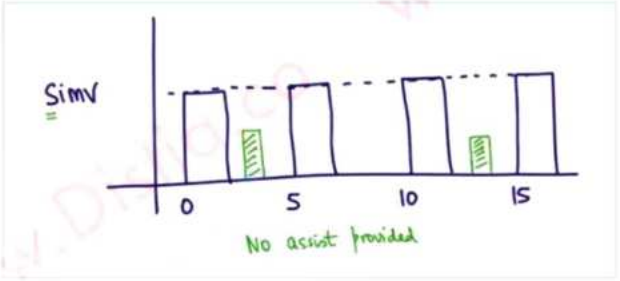
- Mechanical ventilator is set at:
  - Respiratory rate- 12/min
  - V_T=500ml
  - F_iO_2= 0.4 (40%)



- Used in patients with no spontaneous breathing
- Patient triggered breaths are also assisted
- Most common mode used in invasive mechanical ventilation
- Side effects
  - HYPERVENTILATION -> CO_2 washout-> Respiratory alkalosis-> Hypocalcaemia (Tetany) and Laryngospasm-> Hypoxia-> Seizures and myoclonus

Synchronised Intermittent Mandatory Ventialtion (SIMV)

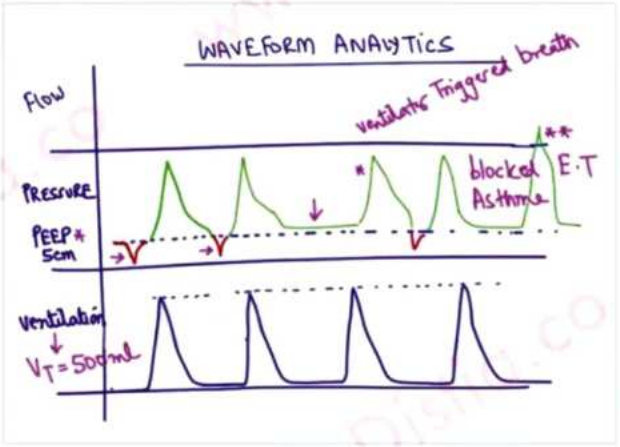
- The breathing is synchronized but not assisted by the ventilator
- Advantage
  - Support/ wean of the patient from ventilator
  - Ensures minute volume is provided
- Disadvantage
  - HYPOVENTILATION- If the patient tries to breath at the same time as the ventilator breath, it results in inhibition of ventilation leading to reduced minute volume



Important Information

- DO NOT USE SIMV if the patient has tachypnoea
- ASYNCHRONY (Lack of coordination between the patient and the ventilatory) leads to hypoventilation

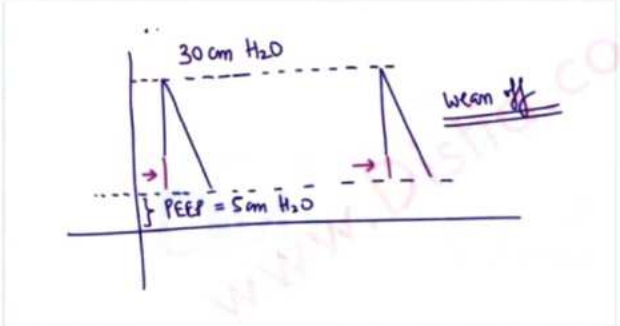
WAVEFROM Analytics



- Negative spike (red)- Inspiratory effort from the patient
- Flatline- Ventilator triggered breath
- **spike of the wave form due to blocked endotracheal tube/ asthma

Pressure Support Ventilation (PSV)

- The patient's breathing effort is supported by the pressure
- Used to wean off patients from ventilation



Important Information

- ACMV- To put patient ON ventilation
- SIMV and PSV- To wean patient OFF ventilation

Pressure Controlled Ventilation

- CONTROL here means tolimit the inflation of the lungs to a level where it may cause worsening of pre-existing barotrauma
- Indications
  1. Pre-existing barotrauma like Pneumothorax
  2. Cardiothoracic vascular surgery to reduce the shear stress over the surgical scar

Basic Rules Of Ventilation

1. Tidal volume in ARDS= 6ml/kg (6-8ml/kg) lean body weight
2. Peak pressure= 30 cm of water to limit Barotrauma component
3. F_iO_2= 0.4, initiated and then gradually upgraded
   - SaO_2 = >90%SaO_2
   - pO_2= >60mmHg
4. PEEP= 5cm of water to decrease the venous and increase the recruitment of alveoli

Non-Invasive Ventilation (NIV) Vs Continous Positive Airway Pressure (CPAP)

Refer Table 33.1

Summary

- CPAP
  - Airways kept open by splinting
  - Method of Non- invasive ventilation
  - Indications: Hyaline membrane disease, Obstructive sleep apnea
- NIV/BiPAP
  - Positive pressure varies in inspiration and expiration
  - Indication: COPD exacerbation
- ACMV
  - Most common mode of ventilation
  - Supports patient efforts
  - Side effects: HYPERVENTILATION, respiratory alkalosis, seizures, myoclonus
- SIMV, PSV
  - Used for weaning o ffpatients from ventilation
  - Side effects: HYPOVENTILATION. Respiratory acidosis
- PCV
  - Cardiothoracic vascular surgery, pre-existing barotrauma
  - Side effects: Respiratory acidosis, hypoventilation

Table 33.1

NON-INVASIVE VENTILATION (NIV)	CONTINOUS POSITIVE AIRWAY PRESSURE (CPAP)
• Positive pressure generated VARIES in the phase of inspiration (iPAP) and expiration (ePAP) • Reduces the load on accessory muscles • A type of pressure support ventilation without intubation • Indications: 1. Chronic obstruction pulmonary disorder exacerbation- Respiratory acidosis- pH = 7.25-7.35 2. Intubation is being avoided to avoid development of ventilator associated pneumonia and local trauma to the airways 3. NIV is recommended for patients with Type-2 respiratory failure • Advantages: o Reduced incidence of ventilator associated pneumonia o Reduced incidence of tracheo-laryngeal trauma • Progress monitoring: o Reduced respiratory rate, reduced use of accessory muscles of respiration • Contraindications: 1. Encephalopathy/ patients who can't protect their airways 2. Cardio-respiratory arrest 3. Gastro intestinal bleeding 4. Unstable angina/ Myocardial infarction (any acute pulmonary syndrome) 5. Facial surgery 6. Upper airway obstruction	• Positive pressure generated is CONTINOUS for both inspiration and expiration • According to Harrison CPAP is not a method of ventilation, it is just splinting of airways • Indications: 1. Hyaline membrane disease 2. Obstructive sleep apnoea (In REM sleep, tongue falls back-> narrowing of airways nocturnal awakening) 3. CPAP is initiated if there are >15 apnoeic episodes/hour (minimum) 4. Cardiogenic pulmonary edema

34 MASSIVE TRANSFUSION PROTOCOL

00:00:19

- Replacement of the entire blood volume of the patient by more than 10 Units of whole blood within 24 hours or more than 2.5 L (5 units) of whole blood given within 4 hours period
- 6 units of Packed RBC, 6 units of FFP, 6 units of PRP can be given to the patient

- 6 units of platelet-rich plasma are condensed into a single bag and are available as SDP (Single donor Platelet) which is prepared by Apheresis.
- Efficacy of SDP: 6 Units of Platelet Rich Plasma (PRP)
- Ratio of administration: PRBC: FFP: PRP is 1:1:1. If instead of PRP, single donor platelets is used then ratio is 1:1:0.25.
- In a bleeding patient, there would be hypoxia and acidosis due to blood loss.
- First thing to be administered in these patients is Packed RBC (followed by FFP and PRP) which carries oxygen and neutralizes the acidosis component.
- Acidosis impairs the ability of blood to clot, which may worsen the coagulopathy of the patient.

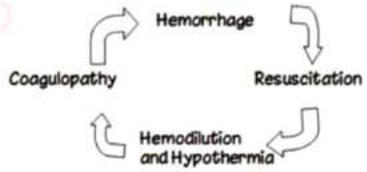
- RED COOLER BAG: Have 6 units of packed RBC
- Plasma is stored at -30° C.
- Plasma when required for transfusion is thawed and kept at room temperature.
- Platelets are not kept in cooler bags and these are stored at room temp (20-24° C)

Trauma Induced Coagulopathy

- Trauma in a patient causes blood loss, which can lead to loss of clotting factors and hypothermia (due to loss of heat) leading to trauma-induced coagulopathy
- The human coagulation system is slow and weak.
  Clotting takes time (2-10 minutes in the best circumstances)
  - Clots are physically weak.
  - There is limited clotting material to work with (even in the whole body):
    → 10 g of fibrinogen total
    → 15 ml of platelets total in normal individuals
- If we give packed RBCs which are stored at 4° C to these patients it worsens hypothermia which further results in coagulopathy.

Bloody Vicious Cycle

00:05:44



- Poor circulation results in metabolic acidosis (because cells are in anaerobic respiration)
- Giving cold blood components triggers Hypothermia and interferes with the clotting process leading to coagulopathy.
- Triad of acidosis with hypothermia and coagulation is difficult to manage.
- To minimize hypothermia, ensure in-line warmers in the Rapid Infusion Pump.
- In obstetric hemorrhage, resuscitation of a patient with massive transfusion protocol:
  - When initially crystalloid fluids followed by blood transfusion is given hemodilution occurs causing hypothermia which Interferes with the coagulation process and worsens coagulopathy.
- Ensure in-line warmers in the rapid infusion pump: components are warmed to a sufficient temperature to minimize the hypothermia component. If there is 150 ml blood loss/min in a patient within 20 minutes, there is depletion of circulating volume causing decompensated shock (↓↓ BP) leads to Death.
- So, in a bleeding patient, infused blood should be equal to output that is blood loss so as to prevent the patient from going into decompensated shock.

Triggers of Massive Transfusion Protocol 00:09:23

Assessment of Blood Component Score (ABC Score)

Components	Points
1. Penetrating Injury	1
2. FAST positive	1
3. HR > 100 / min	1
4. SBP <90 mmHg	1

- If ABC score ≥ 2 then there is 75% accuracy in the prediction of Massive Transfusion Protocol [MTP]

Setup Required For Initiating MTP in A Patient 00:11:45

- **Pressurized Rapid Transfusion (PRT)**
  - Ensures that the blood components reach the body of the patient on time
  - Ensures that infusion matches output & chances of survival increases
  - Has in-Line Warmer reduces the chances of Hypothermia. Hence, coagulation problems are taken care of and hemostasis is achieved.
- **Tranexamic Acid**
  - Antifibrinolytic agent but limited role
  - Stabilize the clot: Provide the hemodynamic stability

Adult Massive Transfusion Protocol 00:13:05

Triggers

- ABC Score (ABC > 2)
- Surgery (Trauma to the Major blood vessel)
- Hematemesis due to PUD (Peptic Ulcer Disease)
- PPH (Postpartum Hemorrhage)
- Penetrating traumatic Injury
- Presence of Low BP

Round 1:

- Call Blood Bank and inform MTP protocol to be initiated
- Assign Team Members to do specific tasks and Divide Teams into A, B, and C.
- Team A: Administer Blood Components to patients (not be responsible for drawing, labeling blood samples, or writing notes in a file about units of blood sample given)
- Team B: Record Keeping, Sampling, labeling of samples, an entry in the file of units of blood, etc, so that proper documentation is maintained.
  - Blood Sample: CBC and CMP (complete metabolic profile)
  - PT and aPTT
  - ABG (from a radial artery)
- Team C: The runner goes to the blood bank and get a cooler bag or blood units to the hospital

Team A:

- Give 1g of Tranexamic acid to patient I.V Stat, then give 8 hourly
- Connect the pressurized rapid transfuser to the patient
- Give 4 Units of PRBC (O-VE) & 2 units FFP (AB +)
- After Round 1, Reassess the patient: If NO Improvement: ROUND 2

Round 2:

- Infuse
  - 4 Units PRBC
  - 4 Units FFP
  - 1 Unit SDP (Single Donor Platelet)
- Team B: Resend blood to Lab so that we can evaluate coagulopathy and metabolic acidosis component.
- Calcium gluconate is given to prevent tetany (caused by citrate in PRBC).
- Cryoprecipitate is given: If the fibrinogen < 100 mg/L
- If No Improvement: ROUND 3

Round 3:

- Repeat Round 2 + Factor VII a

Important Information

Indications to administer Factor VIIa:

- Surgical hemostasis
- temperature-37 degree celsius (stabilized)
- pH-7.35 (stabilized) has been achieved but the patient is still bleeding

Challenges During Massive Transfusion Protocol 00:23:36

Hypovolemia

- All efforts should be made to stop the bleeding rather than replace blood loss.
- The loss of 150 ml of blood per minute results in a loss of half the blood volume in 20 Minutes

Hypothermia

- Because Erythrocytes are stored at 1°C-6°C, rapid blood product administration can lead to hypothermia which leads to coagulopathy.

- 6 Units of RBC will decrease body temperature by 1°C.

Hypo-coagulopathy

- There is a dilution effect from an infusion of crystalloid volume expanders.
- Hypothermia reduces the activity of coagulation proteins and prevents the activation of the platelet.

Complications of Massive Transfusion Protocol 00:24:50

Coagulopathy

- Minimized by Pressurized Rapid Transfusion within line warmer

TRALI (Transfusion Related Acute lung injury)

- Respiratory Distress (non-cardiogenic pulmonary edema) + BP normal + BNP normal

TACO (Transfusion Associated Circulatory Overload)

- Respiratory Distress (cardiogenic pulmonary edema) + BP ↑ + BNP ↑

Hyperkalemia

- Packed R.B.C are stored at a lower temperature, near expiry date causing Na+/ k+ pump is shut down which leads to hyperkalemia which causes Diastolic arrest (Bradycardia)

Hypocalcemia

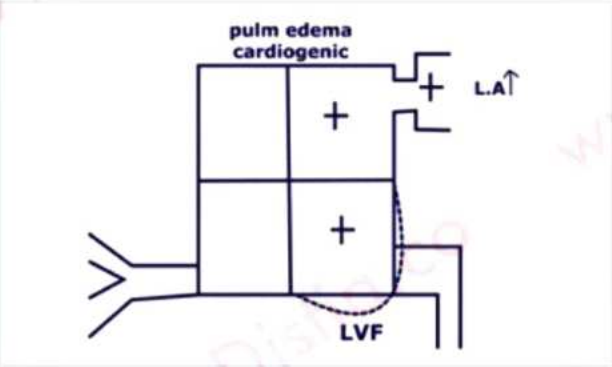
- Laryngospasm (Difficulty in breathing, stridor in clear chest)

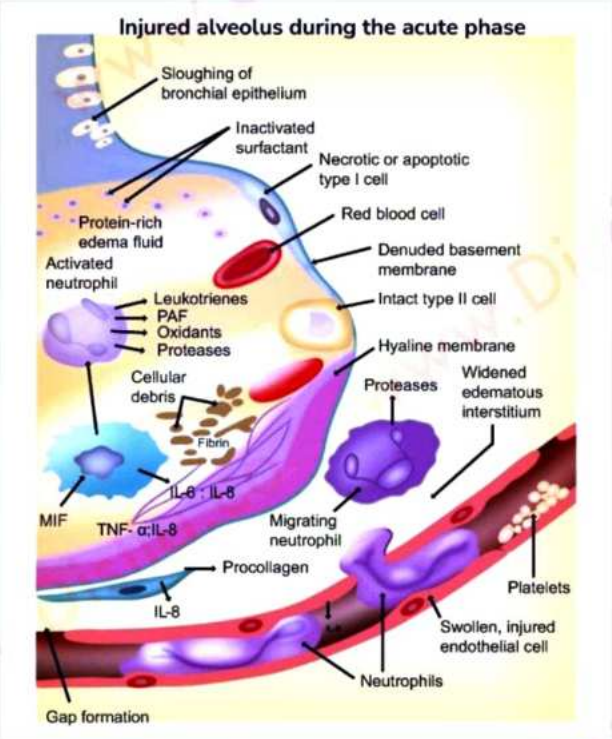
Respiratory Distress after Blood Transfusion can be due to

- TRALI: Pulmonary edema (non-cardiogenic pulmonary edema)
- TACO: Pulmonary edema (cardiogenic pulmonary edema). SBP will be evaluated
- Laryngospasm: Chest is B/L clear but adventitious sounds are heard - (adventitious sounds are the sounds from upper airway)

35 ACUTE RESPIRATORY DISTRESS SYNDROME

00:00:39





- Cardiogenic pulmonary edema: Increase in left atrial pressure secondary to LVF. The leaked fluid is a transudate
- Acute respiratory distress syndrome is due to Non-Cardiogenic Pulmonary Edema

Non-Cardiogenic Pulmonary Edema

- Example, A patient has swine flu or bird flu. As the swine flu virus damages pneumocytes without damaging heart, this will end up in ARDS.
- Collapse of alveoli leads to hypoxia and which in turn leads to damage of Endothelium (damage to gap junctions)
- Leakage of fluids from the pulmonary capillary into alveoli
- ARDS occurs in 10% of ICU patients.
- Sudden onset Respiratory distress
  1. Presence of CXR Bilateral infiltrates on Chest X-ray. (No cardiac cause found)
  2. Reduced pO_2
  3. Normal left atrial pressure

00:05:20

Triggers for ARDS

Direct (Most common)	Indirect

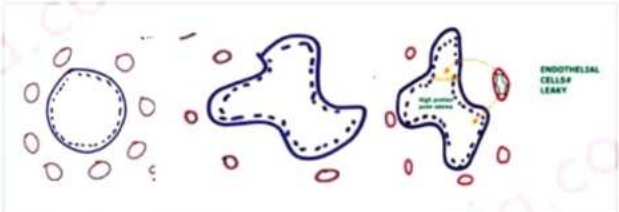
• Pneumonia (H_1N_1)
• Mendelson syndrome
• Toxic gas inhalation
• Pulmonary contusion
• Near drowning
	• Sepsis
	• Trauma
	  ○ Multiple bone fracture
	  ○ Flail chest
	  ○ Head injury
	  ○ Burns
	• Multiple blood transfusion /TRALI
	• Acute pancreatitis
	• Post cardiopulmonary bypass

- Mendelson syndrome: Aspiration of stomach acid (Chemical Pneumonitis)

Important Information

- Both Pneumonia > Sepsis are the leading causes of ARDS
- Leading cause of death after blood transfusion: TRALI
- Status asthmaticus (disease of the airway) is not ARDS (disease of alveoli)

Clinical Presentation



- Type 1 pneumocytes: cover 90% of surface area (injured during adult ARDS)
- Type 2 pneumocytes: produce surfactant (most abundant cell of alveoli)
- IN ARDS, Type 1 pneumocytes are affected, and Type 2 pneumocytes are not affected.

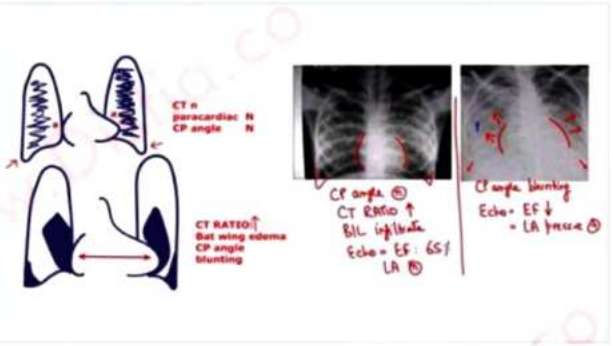
- Normal surfactant with a reduced surface area of alveoli for gas exchange
- Ventilation and perfusion imbalance (perfusion is secondary to the hypoxia component)
- Hypoxia causes dilatation of all blood vessels in the body except vessels of the pulmonary circuit
- Most vulnerable cells/most damaged cells in ARDS is endothelial cells of alveoli due to hypoxia
- Endothelial cells become leaky resulting in Exudative high-protein pulmonary edema.
- In heart failure: Low protein pulmonary edema

FEATURES: (Sudden onset Respiratory Distress) 00:19:57

EXUDATIVE PHASE	PROLIFERATIVE PHASE	FIBROTIC PHASE
• 0-7 days • Respiratory distress starts within 12-36 hours of triggers onset. • Intrapulmonary shunting (Blood is getting wasted in the lungs due to alveolar collapse or endothelial injury) • Increase in work of breathing. • ↓ pO_2, ↑ pCO_2 (Refractory hypoxia) • Dead space increased. • Type 2 Respiratory failure / Respiratory acidosis	• 7-21 days • Able to wean off the ventilator. • Proliferation of type 2 pneumocytes • Some differentiate into type-1 pneumocytes. • Recovery is possible	• >21 days • Require supplemental oxygen for the rest of their life (requirement varies from case to case) • It results in pulmonary artery hypertension. • Bulla or blebs can also be seen in ARDS

- In the initial phase of ARDS, because of tachypnoea, there will be Respiratory alkalosis (CO_2 washout)
- In acute asthma: Type-1 Respiratory Failure and respiratory alkalosis due to CO_2 washout
- In status asthamaticus: type-2 respiratory failure & Respiratory acidosis due to CO_2 overproduction in lungs
- When PCO_2 is 60mm of Hg, then the compensatory mechanisms begin to fail.

Work –Up in ARDS 00:29:44



CXR

- **In ARDS patient**: Bilateral extensive infiltrates
  - Cardiothoracic ratio is normal.
  - Para cardiac area sparing
  - CP angle is normal.
- **In cardiogenic pulmonary edema**
  - Cardiothoracic ratio is increased.
  - Bat wing edema seen.
  - CP angle is blunted.
- **Echo**:
  - In ARDS: Ejection fraction is normal, LA pressure is normal.
  - In cardiogenic pulmonary edema: Decrease ejection fraction and LA pressure increased
- **ABG in ARDS**: ↓ pO_2, ↓ pCo_2 due to Hyperventilation. If respiratory muscle fatigue occurs due to lack of ventilator support, then Co_2 levels will rise

Extra Mile

Sudden onset respiratory distress case scenarios:

- Central line insertion: Pneumothorax
- S. Aureus pneumonia: receiving I.V Vancomycin for 2 days.
  - Pneumatocele rupture resulting in Pneumothorax.
- Massive blood transfusion or Acute pancreatitis: ARDS

Keywords: Essentials of Diagnosis

ARDS: BERLIN Criteria 00:40:58

1. Sudden onset resp. distress
2. CXR: B/L pulmonary infiltrates
3. $PaO_2 / FiO_2 < 300$ (most important diagnostic criteria for ARDS)
4. Absence of left aterial Hypertension

GRADING

ARDS	PaO_2 / FiO_2
• Mild	<300
• Moderate	<200
• Severe	<100

- Volutrauma can occur in ARDS: Seen in high or normal volume ventilation resulting in Pneumothorax.

Management of ARDS

00:42:01

1. Low volume ventilation: 6 ml/kg to minimize BAROTRAUMA to the chest. (Normal tidal volume is 12 ml/kg)
   - Plateau pressure of ventilator: <30 cm H_2O
   - Respiratory rate of ventilator: <35/min
2. Prone-position ventilation
   - Risk of extubation
   - CVP line displacement
   - Orthopedic injuries
3. Extracorporeal membrane oxygenation (ECMO): Patient in whose heart and lungs are too weak for ventilation.
4. Limited fluids and diuretics: To maintain normal left atrial pressure.
5. Ensure neuromuscular paralysis: Cisatracurium (for effective ventilation)
   - Steroids, surfactant therapy and high-frequency jet ventilation (HFJV) have no role in the treatment.

- Most common cause of death in ARDS: Sepsis (non-pulmonary causes)

00:52:21

Congestive heart failure	ARDS
Transudative pulmonary edema	Exudative pulmonary edema
Hydrostatic pressure increased	Hydrostatic pressure normal
LA pressure increased	LA pressure normal
Low protein pulmonary edema	High protein pulmonary edema
BNP increased	BNP normal

36 SNAKE BITE

Common Snakes Found in India

Cobra

Krait

Russel Viper

Saw Scaled Viper

Humped Nose Viper

- Cobra and Krait contribute to Neurotoxicity.
- Russel viper and Saw scaled viper Contribute to hemotoxicity
- Humped nose viper
  - Can also cause hemotoxicity
  - Anti-snake venom available in India is ineffective
  - Bleeding manifestation can go as long as up to 3 weeks.
- Bite of a poisonous snake and non-poisonous snake becomes difficult to identify due to local edema of soft tissue.
- About 50000 deaths per year in India are due to snake bites.
- About 50 million people are exposed to the risk of getting a snake bite especially increased during monsoon or harvesting season.
- However, 70% of bites that occur are non-venomous
- Bite from a venomous snake might be a dry bite (that means the snake might bite at an angle that it is able to inject its teeth or fangs into the body of the person but may not be able the inject the poison, as the person might perceive pain and withdraw the arm away)
- 50% bites: Venomous snake bite is Dry bite. (No manifestation occurs in the patient)
  - The manifestation occur is due to fear of snake bite. (excessive catecholamine release)

Management in Case of Snake Bite We Follow The First Aid 00:05:35

- **R- R**eassure the patient. 70% snake bites – nonvenomous species. Only 50% of bites by venomous species envenomate the pt.
- **I – I**mmobilize: which prevents faster spread of venom.
  - Do not walk.
  - Do not apply a tourniquet: To avoid pressure necrosis.
- If a tourniquet is already applied then, don't cut the tourniquet, as it may cause the extensive spread of poison resulting in
  - Diaphragm paralysis

- Sudden onset hypotension due to histamine release
- So, apply the B.P. cuff proximal to the tourniquet and inflate it to a pressure almost equivalent to the tourniquet and then cut the tourniquet and Then gradually deflate the B.P. cuff.
- No cutting or electrocautery of that area and no walking as well
- Nitrogesic ointment, nitrate spray can be applied locally (but didn't show any efficacy in clinical trials)
- **GH** – **G**et to the hospital immediately.
- **T** – **T**ell the doctor of any systemic symptoms that manifest on way to hosp.

How to remember

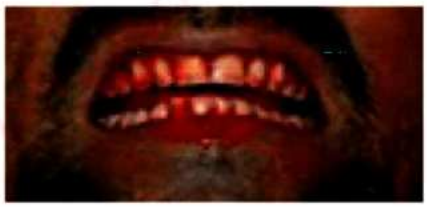
- **RIGHT**

Important Information

- Cobra bite (Neurotoxic): affects postsynaptic transmission. It hampers the action of ACh at the neuromuscular junction.
- Krait: Mainly affects presynaptic transmission that is release of ACh at the neuro-muscular junction is affected
- Russel viper and Hump nosed viper cause Acute kidney injury/ Acute tubular necrosis and Uremia
- Hump-nosed viper: can cause hemorrhagic manifestations which can persist for weeks.
- ASV should be given within 4 hours of snake bite.
- ASV: Bite to needle Time <4 hours.

Viper Envenomation Manifestations

00:12:38



Gum bleeding in Viper Bite

- Local pain, tender lymphadenopathy: Noticed with viper bite and not noticed with cobra bite, or krait bite.
- One of the earliest bleeding manifestations is Subconjunctival Hemorrhage
  - Epistaxis
  - Gum bleeding
- Severe abdominal pain (due to bleeding in the mucosa of the stomach)
- BP decreases (due to a combination of histamine release, bleeding & vomiting)
- Purpura (Palpable bleeding on the skin)
- Retro peritoneal bleeding
- Kidney: Acute tubular necrosis, flank pain or tenderness in costovertebral junction, Black/dark urine (due to hemoglobinuria)

Elapid Envenomation Manifestations (By Krait/ Cobra)

00:15:15

4P's

- **P**tosis: Paralysis of Levator Palpebrae, Diplopia, or ophthalmoplegia
- **P**aralysis of jaw/ tongue**:** inability to swallow saliva.
- **P**ooling of secretions: cause aspiration and can die due to aspirational pneumonia.
- **P**aradoxical Respiration

4D's

- **D**iplopia
- **D**ysphagia
- **D**ysarthria or **d**ysphonia
- **D**yspnea
- There is the development of descending paralysis in patients.

Work up

00:18:52

20 whole blood clotting test (WBCT)

Draw 2 mL of venous blood and transfer it directly into a lean and dry glass tube. Leave it upright, open, and undisturbed for 20 and or 30 minutes at room temperature.

- After exactly 20 minutes, pick up the tube and invert it. If a solid clot is retained, the test indicates normal coagulation.
- If the clot breaks down quickly upon inversion of the tube or fails to coagulate, the test indicates a coagulopathy.

Collection: a blood sample for 20 WBCT testing immediately after collection.

Normal: a solid clot is retained on the inversion of the tube at 20 or 30 minutes (Grade 0, no coagulopathy)

Abnormal: clot degrades rapidly (Grade 1, friable clot) or fails to coagulate whatsoever (Grade-2

- 20 minutes Whole Blood Clotting Test
  - Repeat every 30 min for the first 3 hours of the admission (then after giving ASV it can be done on a 1-hour basis).
- CBC
- LFT
- KFT (baseline serum creatinine)
- Coagulogram: To check PT or aPT

Management

1. Pain: Paracetamol
2. BP cuff (above the level of the tourniquet and then gradually deflate the B.P. cuff).
3. Polyvalent ASV: No effect against humped nose viper
   - Dose: 10 – 30 vials (same for adult or pregnant or child).
   - T½ of ASV ≈ 90hrs.
   - Re-administration of Indian ASV is not required.
   - 1 vial can neutralize 6 mg of Russel viper venom
   - Bite to needle time < 4 hours

Prevention of Anaphylaxis to ASV

- To prevent primary reaction to ASV: Administer Hydrocortisone, H_1 Blockers
- As ASV can result in anaphylactic shock so keep the adrenaline ready in the syringe
- Anaphylactic shock can be recognized by the presence of Stridor, Cyanosis, Crashing of blood pressure, etc
- Adrenaline intramuscular is the 1st line of Management of anaphylactic shock but I.M. is avoided in case of ASV because there can be muscle hematoma in case of viper bite and BP can be too less, so absorption may not occur.
- Therefore, I.V. adrenaline is given in case of anaphylaxis due to ASV.

INDICATIONS OF ASV

1. Coagulopathy
2. Neurotoxicity: 4P's
   Ask the patient.
   - To raise the neck
   - Count numbers in one single breath
   - In neurotoxicity, the patient can't do these
3. CVS abnormalities: BP decreased, tachyarrhythmia.
4. GIT: Severe vomiting with abdominal pain may be due to retroperitoneal bleeding.
   - It is diagnosed by CT or MRI abdomen.
5. Local swelling: ≥ ½ circumference of arm or leg.
6. Swelling has extended rapidly above the level of the waist (after cutting the tourniquet)

(Neostigmine is avoided as a solo drug to avoid cholinergic crisis)

- Neostigmine + Atropine is more useful in neurotoxic cases (mainly cobra poisoning)

Refer Table 36.1

Recovery Phase

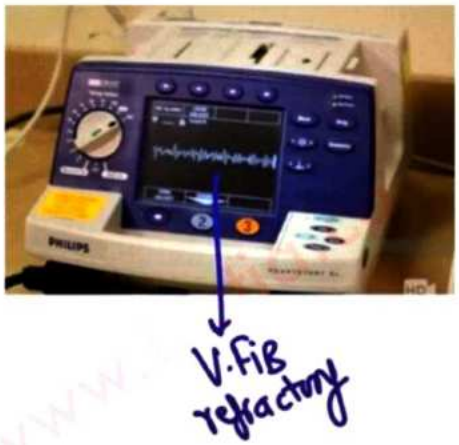
- If an adequate dose of appropriate anti-venom has been administered, the following responses may be seen:
  - Spontaneous systemic bleeding such as gum bleeding usually stops within 15-30 minutes.
  - Blood coagulability is usually restored in 6 hours. The principal test is 20 WBCT.
  - Post synaptic neurotoxic envenoming such as Cobra may begin to improve as early as 30 minutes after antivenom but can take several hours.
  - Presynaptic neurotoxic envenoming such as the Krait usually takes a considerable time to improve reflecting the need for the body to generate new acetylcholine emitters.
  - Active hemolysis and rhabdomyolysis may cease within a few hours and the urine returns to its normal color.
  - In patients who were in shock, blood pressure may increase after 30 minutes.

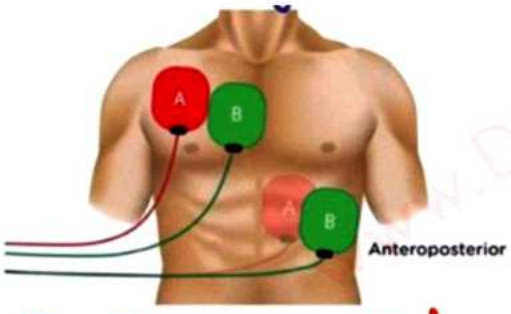
Table 36.1

Clinical features of snakebite					
Feature	**Cobra (post synaptic)**	**Krait (pre synaptic)**	**Russell viper**	**Saw scaled viper**	**Humped nose viper**
Local Pain/ Tissue damage	Yes	No	Yes	Yes	Yes
Ptosis, Neurological sign	Yes	Yes	No*	No	No
Hemostatic abnormality	No	May Occur	Yes	Yes	Yes
Renal complication	No	No	Yes	No	Yes
Response to neostigmine	Yes	+/-	No	No	No
Response to ASV	Yes	Yes	Yes	Yes	No

37 AHA 2020 UPDATE ON CPR GUIDELINES

Double Sequential Defibrillation





- A patient has been given 3 DC shocks: The patient is still in Ventricular fibrillation
  - Hook patient to 2 defibrillators

1st

- One paddle has to be placed on the Right upper sternal border.
- One paddle has to be placed on the Left Cardiac apex.

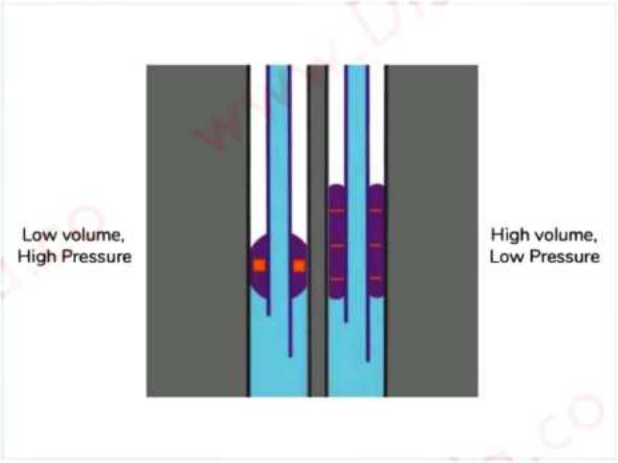
2nd

- Medial to paddles of 1
- Should not be in contact to avoid damaging circuits.
- 1 paddle can be placed posteriorly
- Double sequential defibrillation is not supported.

Epinephrine Use

- In pediatrics, within 5 minutes of CPR initiation
- Epinephrine in Ventricular fibrillation or ventricular Tachycardia Enhances coronary perfusion (decreases ischemia)
- In Non-Shockable Rhythm Give ASAP.
- In Ventricular fibrillation, Continue CPR give Epinephrine with 2nd shock, It increases Electro shock responsiveness

Pediatrics

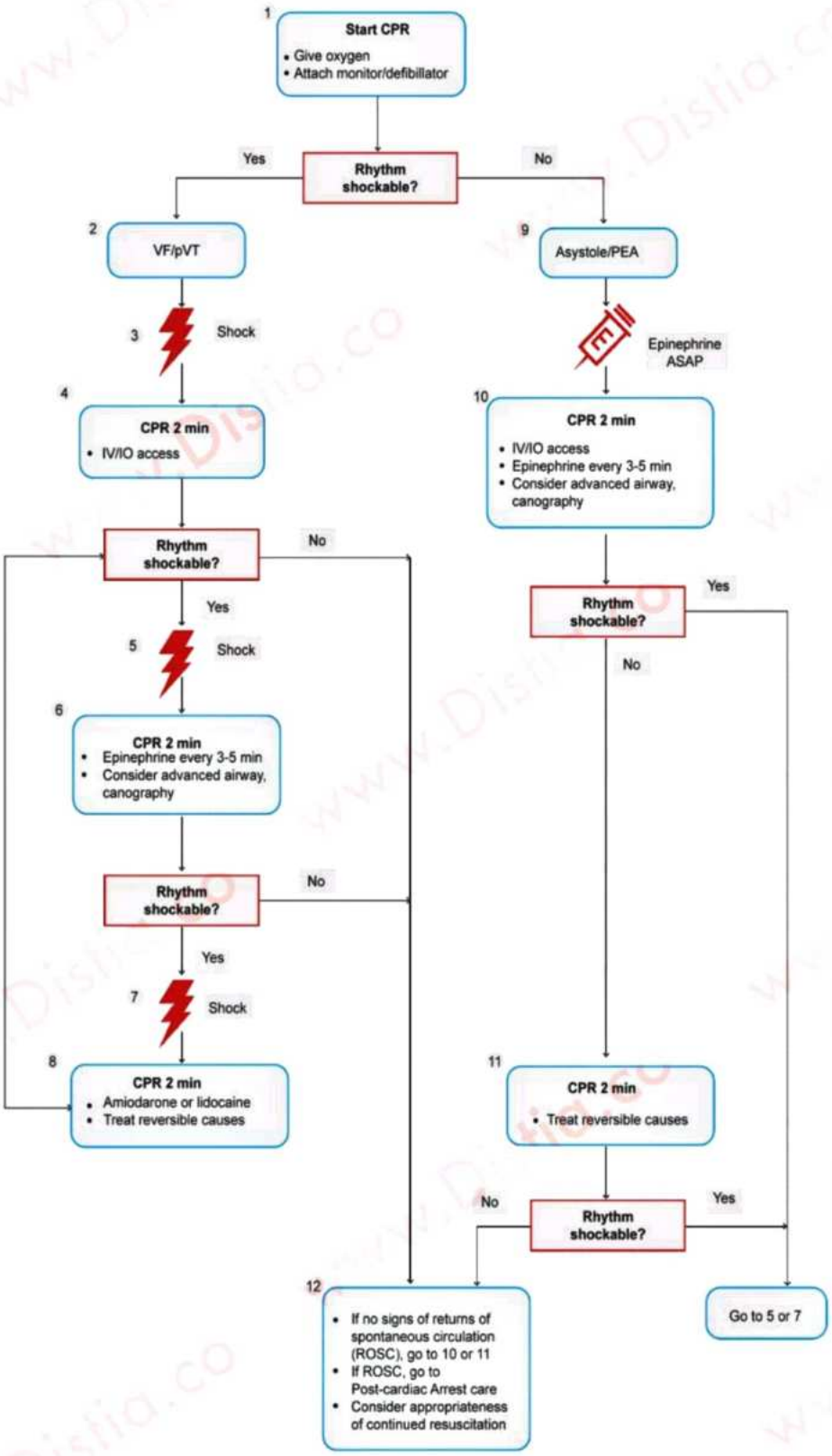


- Both in Infants and children Choose cuffed ETT over Uncuffed (Reduces chances of aspiration)
- Cuffed ETT: High Volume, Low pressure is chosen to reduce subglottic stenosis,
  - Cuff pressure < 20 cm H_2O
- Cricoid pressure is not recommended as it does not reduce the chance of aspiration
- Advanced airway (After intubation)
  - Older guidelines: 1 breath / 5-6 Sec i.e. 10-12 breaths /minute
  - New guidelines: 1 breath / 2-3 Sec i.e. 20-30 breaths/minute

Steroids

1. Used successfully in COVID-19 Pneumonia
2. Used for pediatric septic shock which is non-responsive to fluid or vasopressor.
   - Vasopressors that can be used are:
     → Epinephrine
     → Nor epinephrine: Preferred in septic shock
     → Dopamine

Adult Cardiac Arrest Algorithm



CPR Quality

- Push hard (at least 2 inches [5cm]) and fast (100-120/min) and allow complete chest recoil.
- Minimize interruption in compressions,
- Avoid excessive ventilation.
- Rotation compressor every 2 minutes, or sooner if fatigued.
- If no advanced airways, 30:2 compression-ventilation ratio.
- Quantitative waveform capnography
  If $Petco_2$ <10 mm Hg, attempt to improve CPR quality.

Shock Energy for Defibrillation

- **Biphasic:** Manufacturer recommendation (eg, initial dose of 120-200 j); if unknown, use maximum available. Second and subsequent doses should be equivalent, and higher doses may be considered.
- **Monophasic:** 360 j

Drug Therapy

- **Epinephrine IV/IO dose:** 1mg every 3-5 minutes
- **Amiodarone IV/IO dose:** First dose: 300mg bolus. Second dose: 150mg.

Advanced Airway

- Endotracheal intubation or supraglottic advanced airway
- Waveform capnography or capnometry to confirm and monitor ET tube placement
- Once advanced airways in place, give 1 breath every 6 seconds (10 breaths/min) with continuous chest compressions

Return of spontaneous circulation (ROSC)

- Pulse and blood pressure
- Abrupt susained increase in $PETCO_2$ (typically >40 mm Hg)
- Spontaneous arteries pressure waves with intra-arterial monitoring

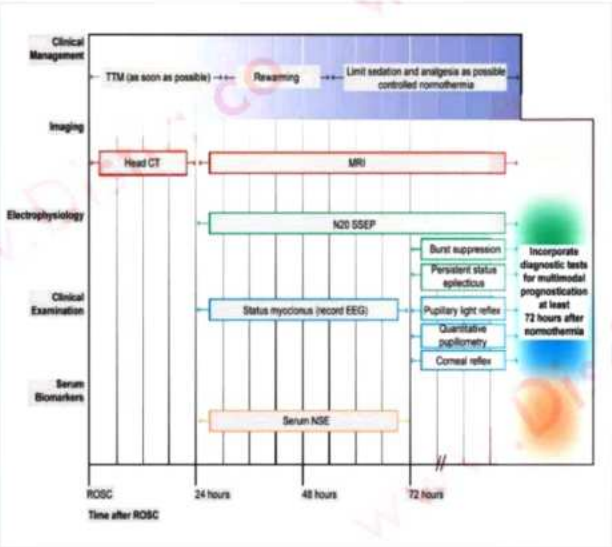
Reversible Causes

- Hypovolemia
- Hypoxia
- Hydrogen ion (acidosis)
- Hypo-/hyperkalemia
- Hypothermia
- Tension pneumothorax
- Tamponade, cardiac
- Toxins
- Thrombosis, pulmonary
- Thrombosis, coronary

6th chain added to in-hospital cardiac arrest (IHCA)

IHCA	OHCA
Early recognition & Prevention	Activation of Emergency response
Activation of Emergency response	High Quality CPR
High Quality CPR	Defibrillation
Defibrillation	Ambulance resuscitation
Post cardiac arrest care	Post cardiac arrest care
Recovery	Recovery

Neuroprognostication



In case of return of spontaneous circulation (ROSC)

- 1st 24 hours: Targeted temperature management: Therapeutic Hypothermia
  - Lower temp of brain
  - Metabolism of energy needs of neurons reduces they can survive better.
- Next 24 hours: Rewarming is done.
- And then controlled normothermia is ensured after rewarming.
- Biomarker: increase in Neuron Specific Enolase: a marker of dying neurons
- EEG: Somato Sensory Evoked Potential returns (When Heading toward Brain death, burst suppression Pattern is seen, followed by Silence)
- First 24 hours: CT is recommended
- After 24 hours: MRI is recommended.

Cardiac Arrest in Pregnancy

Etiology

- A - Anaesthesia
- B - Bleeding
- C - CVS (Pre-existing)
- D - Drugs
- E - Embolism
- F - Fever
- G - General Anaesthesia: 5H and 5T
- H - HTN

Maternal Intervention

- Airway management
- 100% O_2
- IV Line above diaphragm
- Mg So_4 stopped (Antidote is $CaCl_2$)

Fetal Intervention

- Perimortem C Section (If no return of circulation within 5 mins)
- Early CPR For Presumed Cardiac Arrest

A	B
• Elderly man, DM, Hypoglycemia, Collapsed • CPR facility available • Minimal damage	• Elderly man: Known case of Chronic Stable Angina, Ventricular Fibrillation collapsed. • CPR ⊕ • Recovery ++

- IF CPR is withheld in Outside Hospital Cardiac Arrest, the risk for damage is high.
- Use of audio: visual feedback during training for CPR to increase performance in Real time scenario.
- ROSC: ET $CO_2 \geq 20$ mm Hg there is Higher Chances of ROSC, DBP and CV O2 saturation
- I.V. access is better than IO (intraosseous).

38 HIGH ALTITUDE PULMONARY EDEMA

Some Facts

- High Altitude: > 2500m
- High altitude pulmonary edema usually develops on 2nd day and high altitude always causes hypoxia.
- If a person is staying at a high altitude for a longer time, he may feel headaches due to low partial pressure of oxygen that results in cerebral vasodilation.
- At Mount Everest inspiratory partial oxygen pressure is much less: 43mmHg.

Acute mountain sickness:

1. Nausea, vomiting, Flatulence, Abdominal pain or distension
2. Vomiting leads to Dehydration of the person and also person is having tachypnea on altitude that may worsen the dehydration by heat vaporization from the body.
3. Acute mountain sickness is Prevented by Acetazolamide

High Altitude Pulmonary Edema or Cerebral Edema

- 1 atm = 760 mm of Hg
- As Ascent increases: pO_2 decreases leading to Hypobaric hypoxia.
- Cerebral Blood vessel dilatation will stretch the Dura mater which is pain sensitive and causes Headaches.
- Pulmonary blood vessel vasoconstriction: Increase in hydraulic stress on the basement membrane of the pulmonary blood vessel. This high-pressure results in the leakage of fluids from the endothelium leading to Non-cardiogenic Pulmonary Edema.

- Treatment of choice for HAPE is Immediate descent.

Periodic Rhythm

- Most people who go to high altitudes, cannot sleep properly due to the periodic rhythm of both hyper and hypoventilation simultaneously, so oxygen saturation keeps on fluctuating, so people never feel fresh.

- **Acetazolamide:** Carbonic Anhydrase inhibitor
  - Urinary loss of HCO3-
  - Metabolic Acidosis
  - Hyperventilation
- Used to prevent Acute mountain sickness and helps to maintain body oxygen saturation by maintaining hyperventilation.
- Acetazolamide: No role in prevention of HAPE or HACE
- BAL (Bronchoalveolar Lavage): ↑ RBC/↑ Proteins: It represents the integrity of blood vessels is damaged.
- BAL in ARDS (Adult Respiratory Distress Syndrome): Neutrophils ↑↑
  - Unacclimatization is a risk factor for HAPE.

Clinical Features

1. First timers and reclimbing for 2nd time can also cause high pulmonary edema.
2. Young adult begins to deteriorate between day 2 to day 4 when he arrived at a height of 2000- 2500 m
3. Decrease in Exercise intolerance: The person feels breathlessness.
4. Non-productive cough
5. Frank Hemoptysis
6. Cyanosis
7. Increase in Heart Rate, Respiratory rate.
8. Person should drink water continuously to prevent dehydration.
9. Crackles in the chest: Mostly involved in the middle zone of lungs.

Work Up

1. CXR: Pulmonary edema on the left and right middle zone, but there is no batwing edema, no cardiomegaly.

2. ABG: Respiratory Alkalosis.
   - Marked reduction In Co_2
   - If PH is more than 7.7, then the person won't survive.
3. Echocardiography: RV strain (Working against constricted PA)
4. PCWP: Normal, because this is an example of non-cardiogenic edema.

Treatment of HAPE

- Drug of choice is Nifedipine 60 mg sustained release Tablet
  - Dilates pulmonary vessels which will decrease pulmonary artery hypertension and pulmonary edema component.
- Immediate descent should be done.
- If immediate descent is not possible, then the Gammow bag can help.
- Gammow bag: It provides simulated descent above 2000 m. There is a hyperbaric oxygen available in this bag.

- Supplemental oxygen (4-6 L/min): sPo2 > 90%
- Salmeterol or salbutamol with 40% alcohol nebulization and Tadalafil (PDF – 5 Inhibitor)

Summary

Drugs	Disease
Acetazolamide	Acute mountain sickness
Nifedipine	HAPE
Dexamethasone	HACE

39 DIABETES MELLITUS -1

Diabetes Mellitus (DM)

Classical Symptoms 00:01:00

- Polyuria
  - >3L/day or >40 ml/kg
- Polydipsia
  - >6L H_2O intake/ day
- Polyphagia
- Weight loss, muscle wasting

Important Information

- Polyphagia is not a classic symptom of diabetes mellitus as it is not measurable.

Diagnosis 00:06:00

- Classic Symptoms + RBS ≥ 200mg
- Asymptomatic Patient with FBS > 126mg
- After Giving 75gm glucose: 2hr value > 200mg
- Asymptomatic patient: HbA_1C (glycosylated Hb) ≥ 6.5% (best answer)
  - Normal HbA1C = ≤ 5.6%
  - Impaired Glucose Tolerance = 5.7-6.4%
  - DM = ≥ 6.5 %

HbA_1C test

- It is a retrospective test
- It gives average value of blood sugar level of last 3 months (8-12 weeks)
- Not effected by exercise, fasting and recent food intake
- If HbA1C value >8%, multiply by 25, it gives average blood sugar value
  - E.g.: HbA1C=10%; Average blood sugar = 250mg%
- If HbA1C value <8%, multiply by 21, it gives average blood sugar value
  - E.g.: HbA1C=7%; Average blood sugar = 147mg%
- Investigation of choice/ Most specific test/Best test for long term control/ Best test for severity in DM
  - HbA1C
  - TARGET HbA1C < 7%: Good sugar control
- Best test for short term control is Serum fructosamine (Glycated albumin)
  - Retrospective test
  - Formed by Non enzymatic glycosylation of serum proteins
  - Estimates average value of blood sugar level of last 2-3 weeks
- Best test for control in bronze diabetes is Serum fructosamine (Glycated albumin)
  - As HbA1C values are falsely low in these patients
  - Non enzymatic glycosylation of serum proteins.

To diagnose DM in PHC setting:

	Normal	Impaired Glucose tolerance	Diabetes Mellitus
Fasting	100 mg	100-125 mg	≥ 126 mg
2-hour value after 75 gm glucose	<140 mg	140-199 mg	≥ 200 mg

Important Information

- Postprandial values are not useful for diagnosing DM. It is useful for follow up & monitoring

Complications 00:26:55

Microvascular Complications

- It is directly proportional to HbA1C levels
- Best way to reduce the incidence of MICROVASCULAR complications is strict HbA1C CONTROL
- Retinopathy
  - 25 times Increased incidence of blindness
- Neuropathy
  - Increased Incidence of Silent MI
  - Overall m/c complication of DM
- Nephropathy
  - MC cause of CKD in India / USA
  - Treament- Allogenic kidney transplant/ Haemodialysis.

Macrovascular Complications

- Peripheral Artery Disease
  - 100 times increase in risk
  - increase incidence of digital gangrene
- Best way to reduce macrovascular complication is Strict BP control
- Coronary Artery Disease
  - MI, Unstable angina, prinzmetal angina etc.
  - 5 times more increase in risk than normal population
- Stroke
  - Due to accelerated Atherosclerosis

Important Information

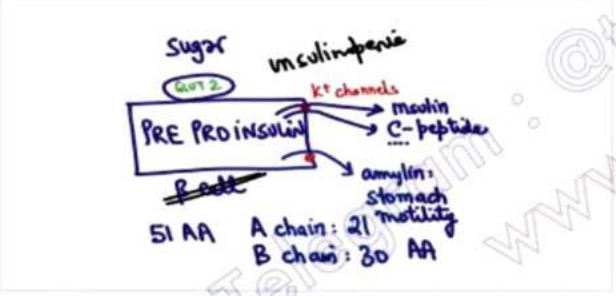
- Best way to reduce the incidence of MICROVASCULAR complications is HbA1C control and best way to reduce the incidence of MACROVASCULAR complications is Strict BP control

Management

- Depends upon type of Diabetes

Type I DM

- Beta cells are damaged
- If >80% β-cell mass is damaged, clinical features appear
- Beta cells are damaged, leads to decrease production of insulin: resulting in INSULINOPENIA
- Insulin and C - peptide are released at ratio of 1:1
  - Insulinoma: both insulin & c-peptide values increase
  - DM: both values decrease
- Apart from insulin, hormone released by β-Cell is AMYLIN
  - It regulates stomach motility
  - Regulates entry of osmotic contents into small intestine
  - >80% of Beta cell destruction will lead to clinical features of DM



Causes

- Autoimmune destruction
  - Most Common cause
  - HLA DQ2, DR 3, DR 4 genes are involved
- Viral etiology
  - Causes Fulminant Diabetes
  - Coxsackie B: MC viral cause
  - Mumps, Rubella

Age is never a cutoff for determining type of diabetes mellitus

- Bronze diabetes
  - Caused due to Iron toxicity
  - Triad of bronze DM
    1. Liver: Cirrhosis
    2. Bronzing / Hyperpigmentation of skin (increase in melanin)
    3. Beta cell mass decrease: Insulinopenia

Case scenario Type 1 DM

- 8yr child admitted with pneumonia, IV Azithromycin is given, after 48 hours of admission mother reports that child is very Drowsy and has decreased oral intake. spo2: 98% on Room Air. On ABG/VBG PH=7.2, PCO2 = 40 mm Hg, HCO3 =15 meq (22-26 meq), urine ketones: ++ and RBS = 300 mg %
  - Diagnosis: Diabetic ketoacidosis (DKA)
  - Investigation of choice: Plasma Beta hydroxy butyrate increased
  - Treatment: 1st line NS drip correct dehydration @ 10-20 ml/kg. For shock, give fluid @ 20 ml/kg
  - Treatment of choice: Regular Insulin drip
  - Mechanism of injury: Insulinopenia and increased energy requirement in pneumonia causes SC fat oxidation and formation of ketones. As ketones are acidic in nature causes damage to blood brain barrier and cerebral oedema (cause of death in DKA)

Long term management of type 1 DM 00:59:15

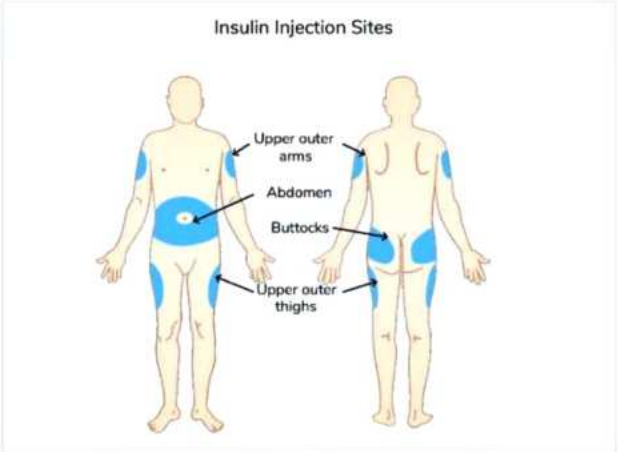
- Carbohydrate counting
  - Calculate the amount of carbohydrate based on body weight & give insulin proportionate to it
  - 1 unit of lispro is sufficient to neutralize 15g of Carbohydrates
- Insulin

Insulin 01:01:55

- Route of administration: Subcutaneous
- Sites of insulin injection
  - Anterior abdominal wall
  - Arm
  - Anterolateral aspect of thigh
  - Buttock

Important Information

- Never give insulin in Dorsum of Hand



Insulin Delivery

- Insulin Pump
  - Best method
  - Mimics artificial pancreas
  - Microprocessor device
  - Continuous SC insulin infusion
  - Continuously Releases Basal Insulin into body
  - Bolus insulin delivery at Mealtimes is also programmed proportionate to carbohydrate intake
  - High cost
- Insulin Pen
- Inhaled Insulin
- Multidose Vial with 1ml syringe
- Longest acting insulin: Degludec: Act for 42 hours
- Insulin calculated on basis of body weight and is given as: 50% Basal, 50% bolus before meals.

Complication of Insulin

Hypoglycemia

01:09:28

- Blood sugar <54mg%

Clinical features

- Features of increased Sympathetic system stimulation

1. Rage attacks
2. Emotional lability
3. Diaphoresis
4. Drowsy
5. Stupor
6. Seizures

Beta blockers are contraindicated in DM as they mask the symptoms of hypoglycemia except sweating.

Treatment

- IV 25-50% Dextrose
- In case of failed IV access use glucagon subcutaneously
- Avoid long-acting insulin

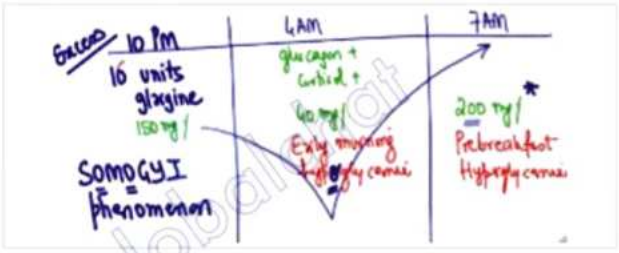
Somogyi Phenomenon

01:17:28

- Early morning hypoglycemia d/t intake of overdose of insulin at bedtime
- At 4A.M → Person wakes up with sympathetic symptoms like Palpitations, Tremors, Diaphoresis etc.
- At 7A.M → Glucagon in circulation → glycogenolysis → Blood sugar value → pre-breakfast hyperglycemia
- Thus, main manifestation of Somogyi phenomenon is early morning hypoglycemia.

Treatment

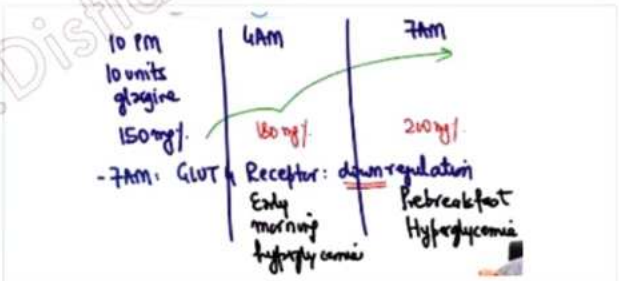
- Adjust the night dose.



Dawn Phenomenon

01:22:28

- 4 AM: Early morning hyperglycemia, due to downregulation of GLUT-4 receptors in muscle in T2DM
- 7 AM: Pre-breakfast hyperglycemia



- Insulinoma: 72-hour prolonged fasting test is done to diagnose.

40 DIABETES MELLITUS-2

Type 1.5 Diabetes Mellitus 00:00:12

- Also known as LADA Latent autoimmune Diabetes in Adults
- Variant of Type-II DM presenting in adults (Shares etiology with Type-1 DM)

Etiology

Autoimmune

- Anti-GAD: Anti-Glutamic acid decarboxylase antibody (Main Antibody)
- Anti-ICA: islet cell Antibody (2nd Antibody)
- Anti-GAD- also present in paraneoplastic manifestation of oat cell Ca of lung known as Stiff Person Syndrome this cancer causes:
  - SIADH
  - Cushing syndrome
  - Lambert Eaton syndrome
- Type 1.5 DM manifests with insulinopenia.

Treatment

- ADA 2023 update: Determine C - peptide levels. If values less than 0.3nmol/L start insulin. For values 0.3-0.7 nmol/L, give metformin with SGLT2 inhibitor for increased ASCVD risk

Insulin type	Insulin name	Onset
Rapid acting analog	LISPRO, ASPART, GLULISINE	20 minutes
Short acting	Regular SC/IV	30 minutes
Intermediate	NPH (Neutral Protamine Hagedorn)	2 hours
Basal Long acting	Glargine/Detemir	24 hours
Ultra-long acting	Degludec	42 hours

- Peakless insulin: Long and ultra-long acting.
- **ADA 2023: Now Ultra Rapid acting** Aspart is available and acts within 10 minutes.

Uses of insulin:

- Type 2 DM (β cell exhaustion): insulinopenia
- Newly diagnosed type 2 DM: HbA1c >10%
- Pregnancy
- End organ damage
- Acute illness

Type 2 DM 00:14:27

- Increased insulin, resistance of receptors

Etiology

- Polygenetic
- Insulin resistance is due to
  - Resistin
  - High levels of Adipokines → promote weight gain
  - Decreased levels of Adiponectin: Guardian angel against obesity

Treatment

- **Diet control** (1st line intervention in Type 2 DM)
  - Hypocaloric diet and Carbohydrate intake is strictly regulated.
  - Carbohydrate with low glycemic index: Oats, multigrain bread, egg white, brown rice, white meat, and multigrain Atta
  - PUFA: Safflower Oil Sunflower oil, Olive oil.
  - Trans fat: Should be avoided at all times.

- **Exercise**
  - Increases GLUT4
  - Promotes Sugar entry into muscle resulting in decreased blood sugar level
  - Jogging: 30 min X 5 DAYS / week is recommended light aerobic activity of (150 min/week)

- **Oral Hypoglycemic Drugs**
  - Controls HbA1C
  - Started in newly diagnosed Type 2 DM whose HbA1C is 8-10%.
  - Objective- Good sugar control, HbA1C: <7%.
  - If HbA_{1C} > 10% : Start insulin directly.

Oral Hypoglycaemic Drugs 00:26:49

Biguanides

- Inhibit Hepatic gluconeogenesis
- HbA1C is decreased by 2% over a period of 3-6months
- **Drugs:** Metformin
- Excreted via kidney
- Causes Lactic Acidosis if given in patient with nephropathy
- Avoided in kidney damage
- **Stop metformin when**: eGFR <30-45ml/min, increase chances of lactic acidosis

Important Information

Drug of choice for T2DM: Metformin
Drug of choice for T2DM + Nephropathy: Linagliptin / Glipizide / Tolbutamide

- These drugs are metabolized by liver
- Metformin is contraindicated in nephropathy.

- **Side effects of metformin**
  - Nausea / vomiting
  - Lactic acidosis: If there is Concomitant renal failure
  - B12 deficiency
- **Phenformin**
  - Banned as it causes Lactic acidosis
  - If ASCVD Risk is increased, then add SGLT 2 inhibitors.

Types of lactic acidosis

- Type A: Due to under perfusion of the tissues, shock: decreased perfusion: DM with septic shock
- Type B: Diabetes mellitus, drugs: Metformin/phenformin, C.K.D

Important Information

- To reduce the microvascular complication in DM- HbA1C.
- To reduce the macrovascular complication in DM- Strict Blood pressure control.

Sulfonylureas 00:36:45

- **Mechanism of action**: Insulinogenic, causes Burst of Insulin, leads to increased receptor sensitivity
- Decrease HbA1C by 1.5%
- **Side effect:** Hypoglycemia attack (mealtime Regulation)
- 1st Generation → Tolbutamide
- 2nd Generation → Glibenclamide, Glipizide, Gliclazide
- 3rd Generation → Glimepiride

Thiazolidinone

- **Mechanism of action:** Increased peripheral utilization of glucose by increasing GLUT4 Receptors on muscle/adipose tissue
- Reduces serum triglycerides
- Decrease HbA1C by 1%
- **Drugs:** Pioglitazone, Rosiglitazone. Both have good compliance, but worsens cardiovascular mortality in preexisting CAD patients, DM+CHF/CAD = contraindicated
- Increases risk of bladder cancer.

α-Glucosidase inhibitors

- These are taken with meals.
- **Mechanism of action:** They act by inhibiting sugar absorption from GIT.
- Control Post Prandial spikes
- **Side effect**: Osmotic diarrhea
- Decreases HbA1C by 0.25%
- **Drugs:** Acarbose, Voglibose, Miglitol

Meglitinide

- **Mechanism of action:** Insulinogenic action
- Improves sensitivity of receptor
- Designed for control of post prandial spike of Sugar
- **Drugs:** Repaglinide, nateglinide

Dipeptidyl peptidase-4 inhibitors 00:49:00

- **Mechanism of action:** Inhibits degradation of GLP-1 and Glucose dependant insulinotropic Peptide and Sends sugar into muscles).
- **Drugs:** Linagliptin (metabolized by Liver); Sitagliptin (metabolized by kidney)

Incretins

Mechanism of action increases GLP-1

- Terminal ileum has 'L' cells, which produce a hormone which Behaves like insulin
- Increases GLP - 1
- **Drugs**
  - **Exenatide:** Injection once a week
  - Expensive
  - Side effects: Hemorrhagic Pancreatitis
  - **Liraglutide**

SGLT – 2 Inhibitors

- **Mechanism of action**: Promotes urinary loss of sugar resulting in decrease of blood sugar level
- **Side effect**: Incidence of UTI increases
- Reduce cardiovascular mortality
- **Drugs:** Canagliflozin
- Should be started in all diabetic with increased ASCVD Risk.

Drugs Used in both Type 1 & Type 2 DM

- Pramlintide , insulin

If Hba1c is <9%, then mono therapy is recommended, lifestyle modification
If Hba1c 9-10%, dual therapy, metformin + SGL2 inhibitors
If Hba1c >10% insulin + metformin +/- SGLT 2 inhibitors

Insulin indications:

1. Type 1 DM
2. Type 1.5 DM
3. Type 2, In beta cell exhaustion, sulfonylureas will stop working. Insulinopenia will be present in all form of diabetes.
4. Acute hyperkalemia
5. Diabetic ketoacidosis
6. Non ketotic Hyperosmolar coma

MODY (Maturity Onset Diabetes in Young) 01:03:06

- Autosomal Dominant- 75% chance of expression of disease in next generation
- Peak onset 25 years of age

Case Scenario: MODY

- 25 year, Asymptomatic, FBS > 200 mg, Father DM +, Grandfather DM +
  - Expressed in every generation due to autosomal dominant pattern of inheritance.

Types

6 types → MODY 1-6

- Most common type in India/ USA – MODY 3
- Gene involved in MODY 3: HNF 1 Alpha
- Chromosome involved in MODY-3: Chromosome-12
- Insulinopenia: Beta cell mass is normal, but not functioning optimally

Case Scenario of Type II DM

- Grandson -40yrs DM+, Father – Normal, Grandfather – +
- Here generation is skipped
- But in MODY generation is not skipped, Radio Immune Assay of insulin → Normal/Low
- In type 2 DM: increased

Treatment of MODY

- Initiation of treatment by Sulfonylureas
- Diet control
- Exercise

	RiA Insulin	Beta cell mass	Why?	Treatment
T_1DM	Insulin ↓	Reduced	Autoimmune	Insulin SC
T_2DM	Insulin ↑/↓	Normal/ exhaustion	Polygenetic	Metformin
$T_{1.5}DM$	Insulin ↓	Reduced	Anti-GAD	Varies with C - peptide levels
MODY	Insulin ↓	Normal	AD, Ch12 defect – in MODY-3	Glipizide

Long Term Complications in Diabetes 01:13:36

Diabetic Retinopathy

- 25% higher chances of blindness than normal population
- DM with HbA_1C > 7% (poor sugar control) progresses to Diabetic Retinopathy / Nephropathy in
  - T_1DM = 5 years
  - T_2DM = 20 years
  - Both Progress simultaneously

Markers

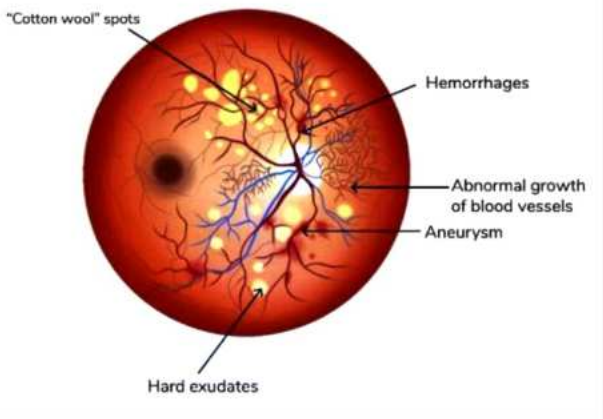
- Homocysteine levels (best method)
- Albumin Excretion Rate (30-300 mg of albumin/gm of urinary creatinine)
- Serum Creatinine/ Creatinine clearance

Fundus Examination

- Microaneurysm
  - Earliest seen in Inner nuclear layer

Non-Proliferative Retinopathy

- Macular edema: leads to visual loss



Proliferative Retinopathy

- Occur because of Neovascularization
- Leads to retinal detachment, Vitreous hemorrhage and Blindness

Treatment

- Pan Retinal photocoagulation by NdyAG → destroys pre-existing Blood vessels
- Bevacizumab (Anti-Vascular Endothelial Growth Factor) → Intravitreal injection → prevents formation of new blood vessels

Important Information

- Cause of visual loss macular edema
- Cause of blindness Retinal Detachment

Prevention of Blindness in Diabetic

- By controlling levels of HbA1C < 7%
- Pan Retinal Photocoagulation
- Bevacizumab Injection.

Diabetic Neuropathy 01:23:21

- 50% of DM Patient will develop neuropathy. MC complication
- Irreversible process
- Sequence of involvement → Sensory > motor > Autonomic
- Symmetrical sensory - motor Polyneuropathy

Sensory Involvement

- Distal sensory loss Vibration sense → First affected → tested by tuning fork of 128 Hz
- Small unmyelinated C-fibers are involved → Hence DM is called → Small fiber neuropathy
- Clinical feature: pain in soles of feet (nocturnal pain)
- Another cause of Small fiber Neuropathy → HIV
- **Treatment**
  - Duloxetine
  - Pregabalin
  - Amitriptyline

Motor Involvement

- Cranial Nerve involvement
  - Most common cranial nerve involved is 3rd Cranial Nerve
  - 3rd nerve palsy *with pupillary sparing* is seen. Manifestations include:
    → Ptosis/Squint.
    → Light reflex spared

Autonomic Involvement

- Postural hypotension (recurrent falls)
  - SBP falls > 20 mm of Hg on changing position from supine to standing
  - DBP falls > 10 mm of Hg
- Calculate B.P change from supine to standing position in a time lag of 3 mins
- Drug of choice for Postural Hypotension: Midodrine
- Silent MI → Leading cause of sudden death in Diabetics.
- Hypoglycemic Unawareness
- Diarrhea (vagal action dominating), drug used is clonidine
- Constipation (sympathetic action dominating)

Non-healing ulcer/ Neuropathic ulcer

- Affects sole, heel/metatarsal head
- **Causes:**
  - angiopathy, delayed healing
  - Neuropathy: neglection
- Increased sugar in local tissue: Presence of bacteria

3rd Nerve Palsy with Pupillary Sparing	3rd nerve Palsy with Pupillary Involvement
• Unruptured Berry aneurysm • AV Malformation • Diabetic Neuropathy	• Weber Syndrome • Claude syndrome • Benedicts syndrome • Miller Fisher syndrome

Important Information

6th Nerve Palsy, Seen in:
1. Raised ICP
2. Millard gubler syndrome
3. Wernicke's Encephalopathy → feature of Dry Beri Beri

7th Nerve Palsy
- Unilateral 7th nerve palsy: Bell's palsy
- Bilateral palsy of 7th nerve, feature of Facial diplegia, Seen in
  1. G.B.S/AIDP
  2. Sarcoidosis
  3. Lyme's disease
  4. Melkersson-rosenthal syndrome

Infections in DM 01:37:33

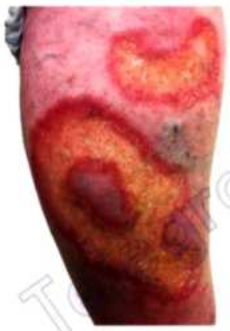
Case scenario:

- 60-year male Type 2 DM is brought with complaints of exhibiting aggressiveness, antisocial behaviour and Black nasal discharge.

- On examination: Nasal speculum; Black fungal mass seen in both nostrils, MRI head → shows Fungal mass at Cribriform plate
- Diagnosis
  - Rhinocerebral Mucormycosis
  - Anti-social behavior is due to extension of fungal mass from roof of nose to frontal lobe of brain
- Treatment
  - IV. Amphotericin B

Diabetic Dermopathy/Neuropathic Ulcer 01:40:53

- Delayed wound repair
- Acanthosis nigricans
  - Type 2 DM + hyperpigmentation (At extensor aspects like back of neck etc.)
  - Also seen in
  1. PCOD
  2. Carcinoma Pancreas/colon
  3. Metabolic syndrome
- Necrobiosis Lipoidica Diabeticorum



Acute Complications in DM (Case Based Discussion)

01:44:05

Case scenario

- Unconscious, unresponsive known case of Type 2 DM is brought to ER
- Vitals: HR 100/min, BP 140/100
- Glucometer: Capillary blood glucose: 30mg%

	LACTIC ACIDOSIS (Type – A)	DIABETIC KETO ACIDOSIS	NON-KETOTIC HYPEROSMOLAR COMA
URINE KETONES	Negative	Positive	Negative
pH (arterial blood gas analysis)	7.2	7.2	7.38
HCO3- (22-26 meq/L)	15meq/L	15meq/L	24meq/L
BLOOD SUGAR	300mg%	300mg%	600mg%

Treatment:

- IV 25-50% Dextrose IV

If Glucometer shows: 300mg%

- Arterial blood analysis: pH decreased, HCO3 decreased
- Urine ketones *absent*

Diagnosis: Lactic Acidosis

Treatment

- Fluid of choice: Normal saline along with Regular insulin infusion
- If blood sugar normal and no acidosis metabolic causes are ruled out then consider possibility of Stroke

Normal saline is given in:

1. Crashing patient
2. DKA
3. Non-ketotic hyperosmolar coma
4. Acute Hypercalcemic Crisis

Ringer lactate is given in:

1. Burns
2. Cholera
3. Metabolic Acidosis

41 DIABETIC KETOACIDOSIS AND HYPEROSMOLAR COMA

Diabetic ketoacidosis and hyperosmolar coma

- Diabetic Ketoacidosis - common in Type 1 diabetes
- Non-ketotic hyperosmolar coma - common in Type 2 diabetes

Diabetic Ketoacidosis 00:00:10

- Primary problem - Absolute insulin deficiency
- As a result sugar does not get into the cells
- The patient has intra-cellular starvation.
- Cells use an alternative source of energy which is fats.
- Because of subcutaneous fat oxidation that will be occurring, free fatty acids will be produced, which will contribute to the production of ketones.
- Ketones are acidic in nature.
- This will cause a decrease in the pH of blood.
- Average PH of blood is 7.4
- In this patient, it can decrease below 7.1
- The lowering of pH causes damage to the blood-brain barrier, which can lead to cerebral edema.
- What contributes to death in a patient with Diabetic Ketoacidosis?
  - cerebral edema
- 3 types of ketones:
  - Beta-hydroxybutyrate
  - Acetoacetate
  - Acetone
- Mortality rate can go up to 20% if the age is more than 40 years.
- This disease can be seen in type 2 diabetes but is more common in type 1 diabetes mellitus.
- Mortality rate is lesser if the age group is lesser.
- Why is there a development of absolute insulin deficiency?
  - The insulin pump being used can malfunction, or parents forget to give insulin to the child. Or maybe the child not eating anything, so insulin was not given. So there is substantial insulin deficiency.
- Triggers that are responsible for Diabetic Ketoacidosis can be the 3 'I's.
  - Insulin decrease due to insulin pump malfunction
  - Sudden jumps in the requirement of energy can be caused due to Infection. Common infection in an adult is UTIs and pneumonia in infants, like COVID-19 or pneumococcal pneumonia.
  - Infarction due to poor compliance especially due to a minor's illness. This can cause MI stroke. The minor patient should be given insulin. It should not be stopped.
- Cocaine can contribute to the triggering of diabetic Ketoacidosis and individuals undergoing surgery in a minor or a major accident.
- Sugar content will rise. Cortisol is increasing. Counter regulatory hormones like cortisol, glucagon and growth hormone decreases ketolysis. Ketones are being produced due to insulin deficiency, but they are not getting destroyed.

Clinical Features of D.K.A 00:07:57

1. Nausea, vomiting - Vomiting is due to Ketonemia which contribute to the trigger of the chemoreceptor trigger zone
2. Epigastric pain
3. Increase in plasma osmolality up to 310-320 which will result in fluid shifts across the brain
   Child will become lethargic or can have a stupor or coma
4. Osmotic diuresis - High sugar will also contribute to the development of osmotic diuresis leading to polyuria and increased thrist.

- **Examination Findings:**

1. Fruity odor in the breath patient because of acetone.
2. Heart rate will increase.
3. Blood pressure can be normal to slightly elevated - due to Sympathomimetic stimulation occurring and counterregulatory hormones being released. If there is dehydration blood pressure can be low as well.
4. Kussmaul breathing - Respiratory rate will increase, and you will have acidotic hyperventilation.
   - Why is Kussmaul's breathing occurring in this patient? This is a compensatory mechanism. The basic reaction of carbon dioxide and water forms carboxylic acid and bi-carbonates. The protons produced here are in excess. So, the protons will cause consumption of the bi-carbonate which is present in the blood. The value will always be less than 15meq.
   - The excess proton will stimulate the respiratory center, so the person has deep and fast breathing.

Work Up of Patients 00:14:31

1. Urine examination - Ketostix
2. Plasma beta butyrate is the sure-shot way to confirm diagnosis.
3. Random blood sugar of the patient will be usually less than 600 mg percent.
4. pH is always inverse to the potassium values. Acidosis will lead to a compartmental shift, leading to a rise in serum values of potassium.
5. Total body potassium will be less due to vomitting but it can be more in blood.

Q. Which ketone body can be normal in diabetic ketoacidosis?
Ans. If acetoacetate is converted into acetone and is getting lost from the body, as this is getting converted, it still might be present in the body at normal levels.

6. Sodium values -
   - Mild cases value is normal
   - Elevated blood sugar the water is removed from the cells
   - Solvent drag will draw in more water to the blood
   - It will cause a dilution component
   - Therefore, hypertonic hyponatremia will occur in the patient
- **Note:**
   - Hypervolemic Hyponatremia
     → Total body water and total body salt are more
     → Amount of water in the body is more than amount of salt in the body
     → Other causes are Ascites, CHF.
- If the blood sugar of a patient rises by 100 mg %, then the sodium value will fall by 1.6 meq
- If sugar is grossly elevated, like 400 or 500. The higher the sugar value solvent drag is also more.
- Suppose sugar is 800 mg % and it goes up to 900 mg %. The solvent drag will increase, and the sodium will decrease by 3 meq.
- If the sugar value is usually in the range of less than 400, then from 300 - 400, the fall will be 1.6 meq.

7. Phosphate
   - Phosphate value may be elevated
   - There might be total body phosphate depletion, but in the blood, it may be elevated.
8. Blood urea nitrogen and creatinine might be increased
9. Arterial blood gas analysis (ABG) / Venous blood gas analysis (VBG) - On scanning, we will observe pH is less, pCo2 is less, and Hco3 is less.
- Difference between uncompensated and partially compensated acidosis.
   - If the value of carbon dioxide is less, compensation occurs. Hyperventilation occurs due to short breathing.
   - If that is not happening it is the early part of the disease.

10. Amylase/Lipase:
   - The rise in amylase/lipase is mostly of salivary origin and not pancreatic origin. Done as patients presents with severe epigastric pain

11. Lipid profile:
   - Hyperlipidemia will be present
   - Hypertriglyceridemia is an independent risk factor for acute pancreatitis.
   - If triglycerides are more than 500, they are a risk factor for acute pancreatitis.
12. TLC count is increased.
13. Anion gap - Subtract positive sodium and a combination of chlorine and bicarbonate. Here positive charges will increase. So the term here is HAGMA (High anion gap metabolic analysis).

Treatment 00:31:40

Severity	pH	Beta OH Butyrate
Mild	7.25 - 7.30	3 - 4
Moderate	7.00 - 7.24	4 - 8
Severe	< 7.0	> 8 mmol/L

- Death in case of Diabetic Ketoacidosis of a child:
   - Cerebral edema
- Death in case of Diabetic Ketoacidosis of an adult:
   - Acute respiratory distress syndrome
   - End-Stage Renal Disease
   - Bowel infarction
- The first step to manage this is giving IV fluids.
- Normal saline is the ideal choice for fluid
- Magnitude of dehydration could be from 3 to 5 liters.
- 2 liters of fluid should be given in 2 hours
- If insulin is less, potassium will be elevated in the blood.
- After 2 hours, the rate of fluid administration is decreased. It should be 200 to 400 ml per hour.
- If greater fluid is given, the risk of ARDS increases in the patient.
- If the value of sodium is deliberately higher, then what fluid will you select? It will be N/2.
- 0.45 % normal saline will be given.
- Monitor the blood glucose of the patient
   - If it is 250 mg%, only 5 % Dextrose will be given to avoid a sudden fall in sugar.
   - Insulin - Regular insulin in 0.1 units/kg infusion
   - ISPAD 2022 guidelines state no role of insulin Bolus. However in Harrison 21st edition bolus is mentioned. If Q mention ISPAD 2022, then answer insulin infusion.
   - Amount of fall in blood sugar will be 50 mg % per hour
   - If on admission the potassium is less than 3.5 meq, then delay insulin infusion
   - Hypokalaemia can lead to torsade de pointes.
   - Another outcome is muscle paralysis or diaphragm paralysis.
- Potassium chloride will be added to normal saline.
- For the management of metabolic acidosis, there is requirement for sodium bicarbonate only if the pH is less than 7.0.

- If pneumonia or other infection is present, it needs to be controlled.
- COVID-19 pneumonia is managed with steroids and heparin. Strict sugar regulation needs to be done. Shift to SC insulin. Anytime potassium is between 3 to 3.5 meq, and the patient cannot take it orally, then IV can continue.

Hyperglycemic Hyperosmolar Coma 00:47:20

- In this condition, the plasma osmolality will be higher therefore, the fluid shifts will also be higher. The dehydration magnitude will also be higher. The mortality can be as much as 10 times more as compared to diabetes in the case of Diabetic Ketoacidosis.

Clinical Features

- Patient is unaware initially of his Type 2 diabetes mellitus status.
- Trigger could be MI, Stroke, COVID - 19 pneumonia.
- As such patients have undiagnosed diabetes mellitus, there is a relative insulin deficiency.
- Blood sugar will start rising.
- Insidious onset - can go up to days or weeks, before Coma develops.
- Urine output will decrease
- There can be the development of azotemia

Workup

1. Random blood sugar - 600 mg %
2. Do a CT head- Normal, and is done to rule out Stroke
3. ABG
   - pH - 7.40
   - pCO2 - 40mmHg
   - HCO3 - 24mEq
4. Ketostix
   - Ketostix usually negative for ketones.
   - Plasma beta-hydroxybutyrate might be elevated due to starvation
5. AG can be normal, or increased due to Lactic acidosis
6. Plasma osmolality is greater than 330 mOsm/Kg.
7. KFT value in this patient will substantially increase

Treatment

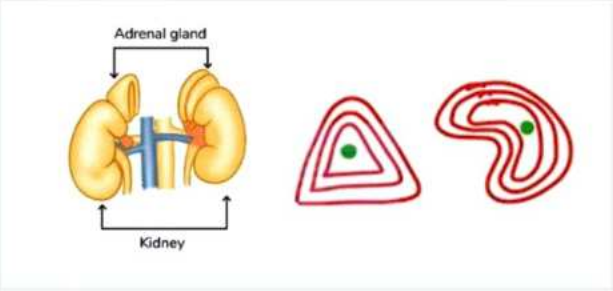
- Magnitude of normal saline is over 10 L over 1 - 2 days
- Blood sugar less than 250 mg % change to 5% dextrose
- Insulin bolus is not required
- Insulin regular - 0.05 Unit/kg/hour.
- KCL can be included with IV Fluids .
- Phosphate replacement is common in ketoacidosis

Lactic Acidosis	Diabetic Ketoacidosis	Hyperglycemic Hyperosmolar coma
Known case of diabetic nephropathy.	Child off unsulin admitted due to pneumonia	Occult type 2 DM with insidious onset
PH - 7.25	PH - 7.25	7.40
HCO3 < 15	HCO3 < 15	24
Urine Ketostix - negative	Urine Ketostix - positive	Urine Ketostix - negative
RBS - 300 mg %	RBS - 350 mg %	800 mg %
Serum lactate values	Beta OH Butyrate levels	Plasma osmolality grossly elevated

42 DISORDERS OF ADRENAL GLAND

Adrenal Gland

00:00:13



- Functioning depends on
  - CRH (from hypothalamus
    ↓
  - ACTH (from anterior pituitary)
    ↓ acts on
  - Adrenal glands

Layers of Adrenal Gland

Zona Glomerulosa

- Produce Aldosterone (under control of RAAS)
- Aldosterone
  - Receptors are in kidney (K/A ENac) Located in Collecting duct >>DCT

- Functions of Aldosterone
  - Main function Postural adjustment of Blood pressure
  - Mechanism:
    → Absorption OF SALT & WATER
    → Excretion OF POTASSIUM & HYDROGEN

Zona Fasciculata

- Produce cortisol
- Cortisol is a Stress Hormone which regulates Blood Sugar Levels
- Elevated Cortisol in Cushing syndrome leads to Impaired Glucose tolerance

Zona Reticularis

- Releases sex steroids like DHEAS
- Responsible for Secondary sexual characteristics

Medulla

- Synthesize & release catecholamines (Epinephrine, Norepinephrine, Dopamine)
- Major catecholamine– Epinephrine (60%)
- Most of pheochromocytomas produce Norepinephrine
- Amino acid involved in synthesis of catecholamines → Tyrosine (also for T4 and T3)
- Vanillylmandelic Acid (VMA) is the end product of metabolism from Epinephrine & Norepinephrine
- End product of dopamine metabolism is Homovanillic Acid
- Catecholamines are responsible for Fight or Flight Phenomenon

Important Information

- 24 hr urinary VMA is increased in Neuroblastoma.

Hyperaldosteronism

00:10:32

Primary

- **Causes**
  - Bilateral Adrenal Hyperplasia: Most common cause (90%)
  - CONN'S Syndrome: Adrenal Adenoma

Secondary

- Cirrhosis, Nephrotic syndrome, CHF, Protein losing enteropathy

↓
Ascites
↓
Decrease circulating Fluid volume
↓
Decrease in GFR
↓
Positive stimulation to RAAS ⊕ → Increase in Aldosterone
(2° hyperaldosteronism)

- Pregnancy induced HTN, Barrter/ Gitelman Syndrome also cause secondary aldosteronism

Clinical Features

00:15:34

- Increase in aldosterone stimulate E NaC
  - Increase sodium & water absorption resulting in expansion of plasma volume
  - Increased Urinary loss of potassium & sodium

1. Hypertension leading to headache
2. Urinary loss of potassium/hydrogen ions→ Hypokalemia → resulting in Muscle Cramps and weakness.

- More salt and water in the body cause increase in preload

- Right atrium dilatation
- ANF release
- Natriuresis

- Gain of water = Loss of water→ So, no Pedal edema

3. Polyuria (due to ANF)
4. Polydipsia

Work Up 00:24:08

1. Sodium levels :Serum sodium values may be normal due to simultaneous excess of water. But Total body salt is more
2. Potassium levels decrease
   - In the presence of Aldosterone → Na α 1/K
3. Unenhanced CT Abdomen
   - Shows Bilateral Adrenal Hyperplasia or Tumor
4. Aldosterone renin Ratio=Plasma Aldosterone/ Plasma Renin
   - Best screening test
   - Autonomous tumor

↓
Increase Aldosterone
↓
(-) Feedback RAAS
↓
Decrease Renin levels
↓
Aldosterone renin ratio (ARR) increases

- False positive ARR is seen with patients on β blockers.

5. Investigation of choice: Saline infusion test (best diagnostic yield) / Salt loading test.
6. Adrenal vein sampling to detect Unilateral or Bilateral autonomous Tumor.

Treatment 00:32:02

Conn's Syndrome

- Initially give Spironolactone for 4-6 weeks
  - Potassium sparing diuretic so manages both hypertension & hypokalemia
- Post PAC fitness: Surgery Unilateral Laparoscopic Adrenalectomy → definitive treatment.

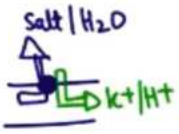
Bilateral Adrenal hyperplasia

- Drug of Choice: Life-long treatment with spironolactone
- Side effect: Gynecomastia in males
- So, Alternate drug: Eplerenone for males

Adrenal vein sampling done to localize the tumor before surgery
Incidence of osteoporosis/T2DM is higher in these patients
Concomitant Increased cortisol will cause CONNSHING syndrome.

Liddle Syndrome 00:37:14

- Autosomal dominant
- Epithelial Na+ Channel defect, exhibits gain of function



- This gain of function cause HTN, hypokalemic alkalosis

↓
(-) RAAS system
↓
Renin decreases
↓
Aldosterone decreases

- Aldosterone renin ratio: normal
- Unenhanced CT abdomen shows normal adrenal size
- Drug of choice: Amiloride (Inhibit function of overactive Epithelial Na channel)

Gordon Syndrome

- Affects DCT: Sodium chloride cotransporter, gain of function
- Sodium/water increases, causes HTN, Hyperchloremic acidosis

HTN, Hypokalemic alkalosis	CONN, Liddle
HTN, hyperchloremic acidosis	GORDON

Important Information

- In LIDDLE Syndrome Aldosterone levels are decreased due to feedback mechanism but hypertension occurs due to excess salt & water in the body secondary to excessive activity of epithelial sodium channel.

Addison's Disease 00:46:00

- Autoimmune destruction of gland

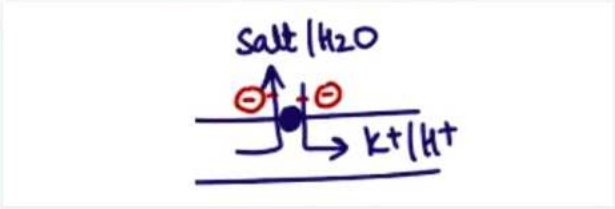
Etiology

1. Autoimmune polyglandular syndrome type 1 > isolated autoimmune adrenalitis
2. Miscellaneous causes: TB/HIV, histoplasmosis, sarcoidosis
3. Addisonian crisis: Waterhouse freidschen syndrome (n. meningitis) cause sepsis, DIC
4. Sudden stoppage of steroids
5. Adrenoleukodystrophy

Presented as decrease in Aldosterone, decrease in Cortisol, and decreased DHEAS

Clinical Features 00:51:46

- Decrease in Aldosterone results in
  1. Salt wasting, craving for salty foods
  2. Polyuria (urine output >3L/day)
  3. Postural Hypotension



  4. Weight loss, Fatigue
  5. Reduced Cortisol leads to Hypoglycemic attacks)
     - Palpitations
     - Tremors
     - Diaphoresis
     - Rage attacks
     - Emotional fragility
  6. Loss of inhibitory control over vasopressin: water gain hyponatremia
  7. Eosinophilia
  8. Increase in ACTH → leads to Partial Melanocyte Stimulating Hormone like action, resulting in
  9. Hyperpigmentation (over the areas of friction)
     - Palmar/ sole creases
     - Scars / Areola / axilla / cubital fossa
     - Groin area
     - Oral Mucosa
     - Nails
  10. Low levels of sex steroids results in
     - Loss of Libido
     - Erectile dysfunction
     - Loss of pubic hair, axillary hair

Work Up

1. Low sodium and high potassium values
   - Rule out Sampling errors as usage of thin bore needle may result in Factitious Hyperkalemia
2. CT Abdomen: Shows destruction of bilateral adrenals glands
3. Investigation of choice: ACTH Stimulation test / Cosyntropin test
   - Normally ACTH → raises Cortisol → which raises Blood Sugar
   - In this disease, there is no rise of blood sugar levels

Treatment 01:10:57

- Drug of choice for Primary Addison disease:
  - Hydrocortisone (oral)
  - In Addisonian crisis, give IV Hydrocortisone
- For management of Low BP
  - Fludrocortisone added
- For management of Decreased Sugar levels
  - Dexamethasone added

Sheehan Syndrome

- Postpartum hemorrhage causes Pituitary infarction and results in Secondary Addison's disease
- Results in ↓ ACTH → ↓ CORTISOL → Hypoglycemia, hyponatremia, Postural hypotension
- B.P is normal as aldosterone is not affected
- No hyperpigmentation as ACTH levels are low

Treatment

- Dexamethasone

Hypothalamus Damage

- AVM rupture, HTN, sickle cell crisis
- Results in → low CRH → low ACTH → low Cortisol
- Also known as Tertiary Addison's Disease
- No hyperpigmentation, & B.P is normal

Treatment

- Dexamethasone

Summary of Addison's disease

Refer Table 42.1

CONN Syndrome Vs Addison disease 01:20:51

Refer Table 42.2

Pheocromocytoma 01:24:00

- Tumor of adrenal medulla
- Also known as chromaffinoma
- Chromaffin cells are found in
  - Adrenal medulla
  - Sympathetic ganglia (paravertebrally located)
- Produce NE 80% >> Epi 20% >>> Dopamine
- Produce epinephrine if associated with MEN-2/Multiple endocrine Neoplasia (SIPPLE SYNDROME)
- Benign vs Malignant differentiated by
  - MRI Abdomen
  - Biopsy/FNAC → Contraindicated → as it may result in damage to normal layers of gland
- 15% tumor → Extra-adrenal
  - Tumors could be deep seated in medulla (85%) → MIBG scan can be done
  - Tumor could be inside sympathetic ganglia (15%) → ORGAN OF ZUCKER KANDL

Imaging

1. MRI abdomen
2. PET DOPA /M.I.B.G Methyl Iodobenzyl Guanidine scan
   - Done for Adrenal Pheochromocytoma if MRI abdomen is normal

Important Information

- Imaging modality of choice in pheochromocytoma is MRI abdomen but in case tumor size is < 1.5 cm, we have to perform the PET DOPA/ M.I.B.G scan

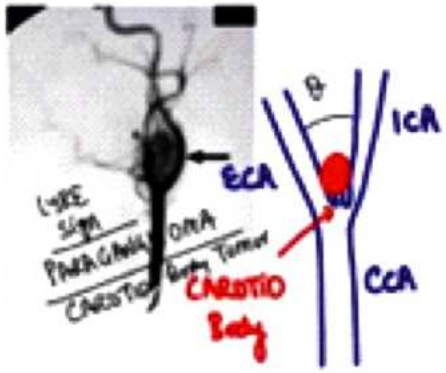
- Familial basis of Pheochromocytoma 10%
  - MEN-type 2- Multiple endocrine Neoplasia (SIPPLE SYNDROME)
    - → **P** - **P**heochromocytoma
    - → **P** - **P**arathyroid Adenoma
    - → **M** - **M**edullary Ca thyroid
  - Due to Ret gene defect in chromosome 10

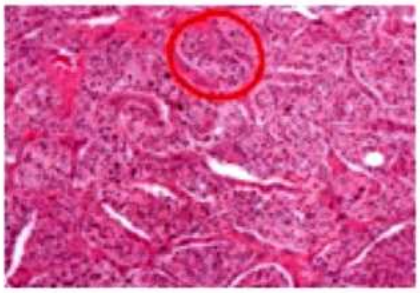
Epidemiological summary

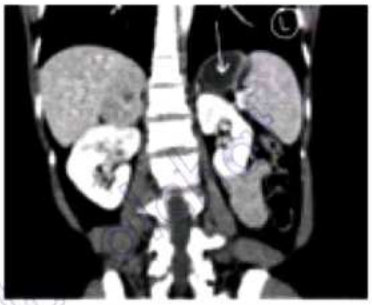
- 10% tumors are Bilateral
- 10% tumors are malignant
- 15% extra adrenal
- 10% familial

Paraganglioma

- Catecholamine producing tumor.
- Present at skull base neck, may or may not produce catecholamines
- Lyre sign: seen in paraganglioma/carotid body tumor/ chemotactoma
- Nest of zellballen appearance in Histopathology
- In Contrast Carcinoid syndrome aka Argentaffinoma causes excess production.
- Of 5HT derivatives like Serotonin, Histamine
- 24-hour urinary 5 HIAA levels







Immunohistochemistry

- Chromogranin
- Synaptophysin
- s-100

Clinical Features / Pheochromocytoma 01:46:15

Excess of catecholamines cause

- Excess activation of β 1 and β 2
  - β1: Increased heart rate and palpitations
  - β2: Fine tremors in fingers
- Diaphoresis Sweaty palms / soles
- α1 stimulation vasoconstriction:
  - Paroxysmal/episodic HTN
  - Headache
- Hypertension is episodic / Paroxysmal
  - Catecholamines have a short duration of action and hence BP can be increased for only few hours / minutes initially
  - Can be triggered by position change, pregnancy, and urination. Pheochromocytoma is called Great masquerader
- Triad (PHD) to suspect, not confirmatory

1. Palpitations
2. Headache due to Hypertension
3. Diaphoresis
4. Can be misdiagnosed as anxiety neurosis
5. Fasting Blood sugar → 100- 125 mg/dl, 2-hour blood sugar 140-199 mg/dl → Impaired Glucose Tolerance
6. Weight loss

7. Extreme vasoconstriction volume contracted state can lead to postural hypotension
8. Relative polycythemia
9. Falsely increased calcium and Increased Hematocrit (Due to volume contracted state)

Work Up 01:58:18

1. 24 hours Urinary fractionated metanephrine levels: Screening Test
2. 24 hours Urinary Catecholamines
3. Investigation of choice: Plasma free Metanephrine levels

Tumor Localization

4. MRI Abdomen → Overall best modality
5. MIBG scan
6. PET dopa scan → Useful for extra -adrenal pheochromocytoma with size < 1.5cm

Treatment 02:01:23

- Surgery is contraindicated in malignant pheochromocytoma
- Benign Pheochromocytoma partial /total adrenalectomy
  - Medically stabilize the patient & then do surgery
- Oral Phenoxybenzamine: Best drug for Pre-operative Hypertension management
- β1 - Palpitations β2 - fine tremors: Use Propranolol
- For symptomatic management give
  - Alpha- blocker → Oral phenoxybenzamine (controls B.P) → in early morning
  - β- blocker → Oral propranolol (control palpitations & tremors) → post breakfast
- Alpha- blocker should be always given before – ß blocker (i.e., α+ ß)
  - If we give ß - blockers prior to alpha-blocker, vasodilation is blocked
  - Unopposed alpha receptors stimulation causes Vasoconstriction resulting in severe Hypertension (may result in CNS Bleed / hypertensive encephalopathy)
  - Thus (ß + α) blockade is Contraindicated
- Intra-Operative HTN crisis
  - Tumor manipulation causes spikes in levels of catecholamines
- Treatment: IV NTG / Sodium nitroprusside

Carcinoid tumor	Pheochromocytoma
5HT Serotonin/histamine Pellagra can be present	Nor-Epinephrine Epinephrine Dopamine
CVS presentation: TIPS Tricuspid insufficiency (pan systolic murmur) Pulmonary stenosis (ejection systolic murmur)	
Sites: Bronchus, Ileum, Rectum, Appendix	Sites: Adrenal medulla, and organ of zucker kandl
Clinical features: Secretory diarrhea Asthma like symptoms Pruritis Gastritis Flushing episodes	Clinical features: Paroxysmal episodic Headache due to HTN, diaphoresis
Test: 24-hour urinary 5 HIAA levels, Octreoscan	Test: 24-hour urinary fractionated metanephrine levels MRI abdomen, PET scan or MIBG scan
Treatment: Octreotide	Treatment: Phenoxybenzamine Sodium Nitroprusside

Table 42.1

	Cause	ACTH	Hyper-pigmentation	DOC
1°	Autoimmune	Increased	Present	Hydrocortisone
2°	Pituitary damage Obstetric cause: SHEEHAN syndrome. Non-obstetric cause: SIMMONDS	Decreased	Absent	Dexamethasone
3°	Hypothalamus damage	Decreased	Absent	Dexamethasone
Crisis	Waterhouse-Friedrichsen Syndrome/ Sudden stoppage of Steroids	Normal	Absent	I.V. Hydrocortisone

Table 42.2

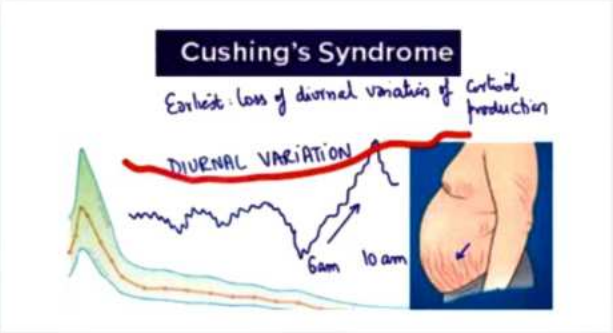
	CONN Syndrome (↑ Aldosterone)	Addison disease (↓ Aldosterone)
Cause	Tumor	Autoimmune destruction of adrenals
BP	Increased	Decreased
K+	Hypokalemic Alkalosis	Increased
Special	Pedal edema is absent	Hyper Pigmentation
IOC	Saline infusion Test/ salt loading test	ACTH stimulation test or COSYNTROPIN Test
Treatment	SPIRONOLACTONE	HYDROCORTISONE

43 CUSHING SYNDROME

Cushing Syndrome

Introduction

00:00:10



- Cortisol is lowest in the morning at 6:00 am
- 75% of daily cortisol is produced in morning hours
- Earliest presentation: Loss of diurnal variation of cortisol production.

Causes

00:02:36

1. Iatrogenic steroids (exogenous) most common cause of Cushing syndrome
   - Cortisol raised, ACTH Decreased (by feedback mechanism)
2. Ectopic production of ACTH
   - Carcinoid tumor
   - Oat cell CA lung
   - Ectopic ACTH production → increased Cortisol
   - ACTH have partial melanocyte stimulating hormone like action
   - Hyperpigmentation on creases of skin (palms and soles)
3. Pituitary Adenoma, Aka Cushing's disease
   - Increased ACTH production → increased Cortisol (Endogenous cause)
4. Adrenal adenoma involving zona Fasciculata

Clinical Features

00:11:42

1. Moon facies
2. Centripetal Obesity (lemon on stick appearance)
3. Easy bruisability
4. Proximal myopathy
5. Violet/ purple Striae, Thin skin, Purpura
6. Weight gain
- Increased Peripheral resistance → HTN
7. Insulin resistance, cortisol increases, leads to blood sugar increase
   - Secondary DM
   - FBS > 126 mg
   - 2hr > 200 mg
8. Cortisol ↑ → Activates ENaC (epithelial sodium channel)
   - Causes salt & water retention
   - Urinary loss of potassium and hydrogen
   - Hypokalemic Metabolic Alkalosis

9. Cortisol ↑ → Activates Sex steroid receptors
   - Causes Hirsutism, weight gain, oligomenorrhea, infertility in women

   Clinical presence of PCOD >> Cushing Syndrome
10. Hyperpigmentation
    - Will be present in Ectopic ACTH production
    - Not seen in Exogenous cause

Work Up

00:23:45

1. **Screening test**
   - 24-hour urinary cortisol: increased
   - Spot Salivary cortisol: increased
   - Overnight dexamethasone suppression test
2. **Investigation of choice**
   - Low dose Dexamethasone suppression test

Important Information

- High dose dexamethasone suppression test is used for etiological diagnosis. It Helps to differentiate Ectopic ACTH production vs Pituitary adenoma (2mg 6 hourly for 2 days).

- **Imaging:**
  - MRI Head for pituitary adenoma: ACTH **dependent** Cushing syndrome
  - CT Abdomen: Adrenal adenoma: ACTH **independent** Cushing syndrome
  - ACTH levels (↑ / ↓) depending on etiology

Treatment

00:32:28

- Iatrogenic steroids
  - Taper steroids
  - Start alternate steroid sparing agents like Azathioprine

- Oat cell lung cancer
  - Chemotherapy with Cisplatin + Irinotecan
- Pituitary adenoma/Cushing disease
  - Trans-sphenoidal Surgery. Post surgery transient diabetes insipidus can develop in 20% patients (page 2905: Harrison 21st edition)
- Adrenal adenoma
  - Prior to surgery
  - Medical Adrenalectomy done using to control cortisol excess in period leading to surgery
    1. Mitotane
    2. Metapyrone
    3. Aminoglutethimide
    4. Oral Ketoconazole
    5. (Harrison 21st update): Osilodrostat inhibitor of 11 β hydroxylase, etomidate infusion in Low anaesthetic dosages.

Important Information

- Sudden stopping of steroids leads to Addisonian crisis

Nelson Syndrome

- Caused due to bilateral Adrenalectomy performed to treat bilateral adrenal adenoma producing a mass effect.
- During Surgery to prevent Addisonian crisis → IV Hydrocortisone drip can be given
- Post op: Life-long Hydrocortisone supplementation
- Follow up: Due to static levels of steroids, no feed-back inhibition on ACTH → ACTH will be increased → resulting in Hyperpigmentation
  - Only Pulsatile release of cortisol can inhibit ACTH production

44 DISEASES OF THYROID

Thyroid Storm 00:00:13

Case presentation

- Patient with massive thyroid enlargement has been referred to surgery department
- Intra op: Manipulation of gland
- Persistent Sympathetic stimulation: Massive surge in T4 and T3 values
- Heart rate increase, high output congestive cardiac failure, BP crashed due to CHF. Before CHF occurs BP will Rise
- Crepts are present and SpO2 falls.
- Increased Calorigenesis: Temp increase that further worsens the condition of patient

Thyroid Storm can develop

1. Preoperative
2. Intraoperative complication of thyroid surgery
3. After Radioactive Iodine: ablation

Treatment

1. In case of pulmonary edema fluids to be stopped. If patient has dehydrations without pulmonary edema IVF need to be given.
2. Propylthiouracil (PTU)
   - By NG Tube
   - Can be given by rectal route
   - Inhibits conversion of T4 to T3
   - If not available methimazole can be given
3. Propranolol/esmolol
   - Prevents further increase of Heart Rate
4. Hydrocortisone for endocrine emergency
5. Cholestyramine
   - Sequestration of thyroid hormones
6. ICE packs / Soda Bicarbonate

- Saturated solution of potassium iodide (SSKI): used to prevent thyroid storm
  - Acts by Wolf chaikoff effect
  - Prevent further formation of thyroid hormone by downgrading iodine trapping

Prevention

- Give saturated solution of Potassium Iodide/ Lugol Iodine pre-operatively
- SSKI x 10 days → Causes shrinking of gland and decreases surge of T3 and T4
- Decreases Iodine TRAPPING → Decrease in T4 → T3 production.
- Occurs by Wolf Chaikoff effect → Downgrade process of iodine trapping which decreases T3 & T4 production

Summary for Thyroid

- Prevention: SSKI: Mechanism of action: Wolf chaikoff effect
- Death: CCF, Arrythmias, Acidosis, Hyperthermia, Dehydration
- **Clinical features of Thyroid Storm**
  1. Known case of Thyrotoxicosis
  2. Fever
  3. CNS: Delirium, coma, seizures
  4. CVS: Arrythmias
  5. GI: Nausea, vomiting, diarrhea
  6. Liver: Jaundice

Burch Wartofsky Scale

- Scale for thyroid storm
- If value is more than 45, high incidence of thyroid storm in patient
- If < 25, chances are lesser

Jod Basedow Effect 00:21:17

- Seen with intake of iodized salt for long duration: increase in iodine trapping: Increased T4-T3 production
- Leads to thyrotoxicosis
- **SSKI**: Large doses of iodine for 10 days: Decreases iodine trapping: Decrease T4, wolf chaikoff effect
- **Iodized salt**: Minute doses of iodine for years: Increase iodine trapping: increase T4: Operates via Jod basedow effect

Thyrotoxicosis Factitia (Exogenous)

- Intake of Cattle/beef meat containing thyroid gland of animal
- Leads to: Palpitations heat intolerance
- Thyrotoxicosis occurring due to cause other than high salt intake.
- **Obesity**: Consumption of Ayurvedic medicines containing Levothyroxine. Lot of these are marketed as weight loss medication
- Thyroid hormone excess: HR increase, cardiac O_2 consumption will increase which can lead to angina

Hyperthyroidism 00:29:30

- Hyperthyroidism: Increased Function of gland
- Thyrotoxicosis: Excess T4 levels

Important Information

- Causes of Thyrotoxicosis without Hyperthyroidism
  - Subacute thyroiditis
  - Silent thyroiditis
  - Thyrotoxicosis factitia
  - Radiation / Amiodarone / Infarction of Large tumor

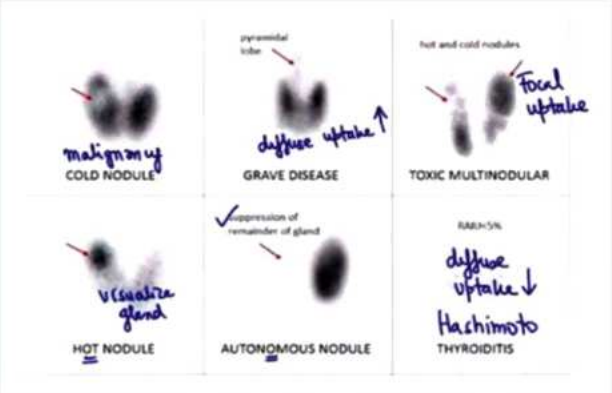
Causes of Hyperthyroidism

- **Primary Hyperthyroidism**

1. Most common cause of Primary Hyperthyroidism → Grave's Disease
   - Grave's disease → have L.A.T.S- Antibody (long-acting Thyroid stimulating Antibody)/TSI/TBII (Thyrotropin binding inhibitory immunoglobulin assay)
   - TSI will stimulate gland → T4 ↑ T3 ↑; TSH will be reduced
2. **Secondary Hyperthyroidism**
   - Due to Pituitary adenoma: Excess synthesis of TSH → leads to increase in T4 ↑ T3 ↑
3. Toxic Multinodular Goitre/Toxic adenoma/activating mutation of TSH receptor
4. Jod Basedow Effect
5. Thyrotoxicosis Factitia
6. Struma Ovarii
   - Ovarian tumor synthesising Thyroid hormones
7. Gestational Trophoblastic Neoplasia (HCG can bind to TSH receptors & stimulate them)

Thyroid Scan

- Cold nodule
  - Decreased uptake
  - Suggestive of malignancy
- Iodine used for scan: Iodine 123 (t 1/2 13.2 hours) or
- Iodine 132 (half-life 2-3 hours)



- Grave's disease: Increased diffuse uptake of radioactive iodine
- Hashimoto's thyroiditis: Decreased diffuse uptake
- Toxic multinodular goiter: Focal areas of increased uptake
- Hot nodule: Remaining gland is visualised
- Autonomous nodule: Complete suppression of gland

Clinical Features

00:46:00

1. Hyperactivity and irritability
2. Palpitations → β1 stimulation
3. Fine Tremors → β2 stimulation
4. Sweaty Palms/soles
5. Sustained HTN
6. BMR increased → Resulting in weight loss
7. Calorigenesis increased → Causes heat intolerance
8. In female patients
   - Oligomenorrhea
   - Infertility

9 Proptosis

On Examination

1. Sleeping Pulse Rate increased → Most reliable sign to diagnose thyrotoxicosis (resting tachycardia)
2. Arrhythmias: Sinus Tachycardia and Atrial fibrillation
3. CVS → Loud S1, Ejection systolic murmur, Means Lerman Scratch [due to hyperdynamic circulation]
4. Pretibial Myxoedema, orange discoloration on shin initially Myxoedema is non pitting in nature
5. Grave's ophthalmopathy
   - Lid retraction
   - Due to contraction of Muller's muscle [sympathetic overactivity]
6. Lid-lag sign/ stare sign

   - Earliest feature
   - Inability of upper eyelid to follow the object from top to bottom
   - Inadequate blinking
   - Exposure keratitis
- "Inferior Rectus" is most common extra ocular muscle involved
  - Diplopia

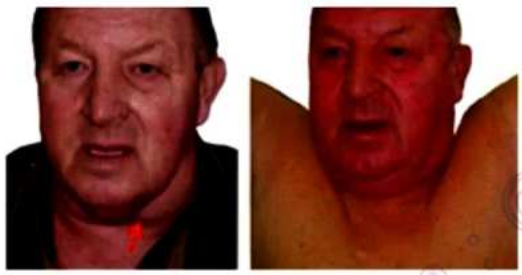
- Retrobulbar neuritis
  - Due to pressure on optic nerve

Manifestations of grave's ophthalmopathy NO SPECS scheme

- 0 = **N**o signs or symptoms
- 1 = **O**nly signs (lid retraction or lag), no symptoms
- 2 = **S**oft tissue involvement (periorbital edema)
- 3 = **P**roptosis (>22 mm)
- 4 = **E**xtraocular muscle involvement (diplopia)
- 5 = **C**orneal involvement
- 6 = **S**ight loss

7. Clubbing/Acropachy is seen in Grave's disease.
8. Pemberton Sign

- On Raising arms, there will be Facial congestion due to compression of Superior Vena Cava by retrosternal goiter.
- Seen in patients with retrosternal extension of goiter.



Work-UP

1. Thyroid Function Tests → Total T4 & T3 increased, Free T4 & T3 increased
- TSH
  - If severely reduced: Primary hyperthyroidism [Grave's disease]
    → Next investigation will be TBII/ TSI
  - If increased/ normal: Pituitary adenoma
    → Next investigation will be MRI Head
2. Thyroid scan: Increased uptake (multinodular goiter/grave's disease), decreased uptake (destructive thyroiditis)
3. USG / MRI of Neck

- Subclinical hyperthyroidism- free T4 and T3 is normal and TSH levels are increased.

Treatment of Grave's Disease

- Spontaneous relapse/ remission
  - Fluctuation of free t4 levels
- Ophthalmopathy: Methylprednisolone, initially worsens but later improvement is seen.
- **Treatment of choice for grave's disease:**
  - Radioactive iodine (isotope 131, $t_{1/2}$ =8 days)
  - Contraindicated in pregnancy/breastfeeding
- **Antithyroid Drugs**
  - PTU (Propylthiouracil)
    → Safe in pregnancy [first trimester T1] / breastfeeding
    → as it has high protein binding
    → Black box warning: Hepatotoxic on prolonged use
  - Carbimazole/ Methimazole
    → Safe in 2nd Trimester
    → Drug of choice
    → Causes Aplasia cutis, Choanal atresia
  - Total Thyroidectomy in case of Poor response to medical Therapy
  - Propranolol → for symptomatic management

Important Information

- Dose limiting side effect of Antithyroid drugs is agranulocytosis

Treatment of 2° Hyperthyroidism

- Due to pituitary adenoma
- **Treatment:** Trans-sphenoidal Surgery

Hypothyroidism 01:21:00

Primary hypothyroidism	Secondary hypothyroidism
Thyroid Gland is involved	Pituitary Gland is involved
T4 ↓ T3 ↓, TSH ↑	• T4 ↓, T3 ↓, TSH ↓ • T4 ↓, T3 ↓, TSH (N) but biological inactive
• Causes 1. INDIA most common cause →Hashimoto thyroiditis 2. Iodine deficiency disorder GLOBALLY 3. ENDEMIC CRETINISM → Baby with hypothyroidism since birth 4. Food Goitrogens → Cabbage, Cassava 5. Drug induced Hypothyroidism: Amiodarone, Lithium, T.K.I	• Causes 1. Sheehan syndrome 2. Non obstetric cause of pituitary damage called as Simmonds's disease 3. Cranial Radiation 4. Sarcoidosis 5. Hemochromatosis

Congenital hypothyroidism

- **Cause:** Thyroid dysgenesis >>Thyroid dyshormonogenesis, Endemic cretinism

Clinical Features of Hypothyroidism 01:28:50

1. Modest weight gain due to decrease of BMR

2. Decreased calorigenesis :- Cold Intolerance
3. Myxoedema
   - Alopecia
   - Puffy face
   - Hoarseness voice
   - Isolated diastolic Hypertension
   - Constipation
4. Menorrhagia & infertility
5. Hashimoto encephalopathy
   - Myoclonus
   - EEG: Slow waves
   - Steroids responsive encephalopathy

On Examination

1. Hung up ankle jerk:Most reliable sign
2. HR decrease, Isolated diastolic Hypertension
3. Coarse / Dry Skin
4. Pale yellow skin
   - Occurs due to β Carotenemia, sclera is normal
5. Galactorrhoea: (Other causes)
   - Primary hypothyroidism
   - Prolactinoma
   - Chronic renal failure

Work-Up

01:43:34

1. TFT
   - Total T4, T3- ↓
   - Free T4, T3- ↓
   - TSH can be elevated or reduced

Primary hypothyroidism	Secondary hypothyroidism
• TSH is high	• TSH is low
• Defect is in thyroid gland	• Pituitary defect [obstetric/ non-obstetric casuse of damage]
• Next best investigation • Anti-TPO [thyroid peroxidase] • Anti Thyroglobulin antibody	• MRI head

2. USG/ MRI neck
3. ECG: Low voltage ECG/ Electrical Alternans
   - Serous cavity effusions
   - Lymphedema/ myxoedema: Massive pericardial effusion
   - Gradually over long duration
   - Pulsus paradoxus absent
   - Water bottle heart/money bag appearance
   - This condition is known as Myxoedema heart
4. Lipids and Serum cholesterol Increases
5. Accelerated atherosclerosis
6. CBC:MCV increases, Macrocytic anemia

Treatment

- Levothyroxine
- Available as 25 µg / 50 µg / 88 µg / 100 µg
- If dose is >100µg, it increases O2 consumption → Resulting in Angina. so, be very careful while doing upward Titration of dose

Complications of hypothyroidism

- **Myxedema Coma** 01:54:11
  - 60 years old hypothyroid patient, non-compliant, with medication suffers from UTI: prescribed antibiotics.
  - She is found Unconscious, unresponsive HR 60/MIN, BP 100/60 mm/hg, Temp: 35°C
  - ECG shows P-R increased, R-R increased
- **Diagnosis**:Myxedema Coma
  - The Trigger is an intercurrent illness such as UTI.
- **Treatment**
  1. Space blanket [Active rewarming]
  2. Levothyroxine by NG Tube (Drug of choice)
  3. IV Liothyronine [Active T3 derivative]
  4. IV Hydrocortisone

Sick Euthyroid Syndrome

02:00:37

- Impaired conversion of T4 to T3
- Triggers
  - Illness
  - Sepsis
- Work up
  - TSH decreased
  - TSH normal or increased in: Recovery

Exta Mile:

Accelerated atherosclerosis seen in

- SLE/RA
- DM, CRF/CKD, hemodialysis
- Syndrome X
- Nephrotic syndrome

45 PANCREATIC NEUROENDOCRINE TUMORS

Two types 00:00:11

- **Functioning NET**
  - Most common is Insulinoma
- **Non-Functioning NET**
  - Most common is PP-OMA (Pancreatic polypeptide)
  - Does not cause any symptoms from hormones perspective
  - Produces Chromogranin
  - Produce mass effect (mimic features of pancreatic adenocarcinoma)
    1. Abdominal pain
    2. Obstructive jaundice
    3. Weight loss
    4. Diagnosed at later stages

Hypoglycemia 00:01:55

- If Sugar lever fall < 54 mg%– patient will have symptoms of Hypoglycemia
- Normally, When Blood sugar < 70 mg%
  - Alert value for DM patient
  - Insulin production stops
  - Counter regulatory hormone Increase
    1. Glucagon
    2. Catecholamines
    3. Growth hormone
    4. Cortisol

Levels of Hypoglycemia

- Level 1 55-70%
- Level 2 <54%
  - Ability to perform substantially decreased
  - Lethargic and sleepy
  - Neuroglycopenia starts
- Level 3
  - Requirement of assistance
  - Hypoglycemic seizures
  - Coma

Causes of Hypoglycemia

1. Chronic kidney disease
2. Severe liver disease
3. Alcoholism
4. Poor nutrition
5. Extra pancreatic tumor
6. Insulin/Sulfonylureas abuse
7. Insulinoma

Treatment

- IV Dextrose
- In case of failed IV access Injectable Glucagon

Insulinoma 00:10:52

- Overall leading functioning Pancreatic Neuroendocrine Tumor
- Usual age of presentation: 40-50 years of age
- Associated with MEN 1

Whipple Triad

1. Symptoms of hypoglycemia
   - Eccentric psychiatric behavior
   - Emotional outburst
2. Blood sugar <54 mg%
3. Immediate relief of symptoms with iv glucose

Insulinoma vs Glucagonoma

	Insulinoma	Glucagonoma
Malignancy	Majority are benign 5-15 % Malignant	Majority cases are Malignant
Size	Size at diagnosis < 2 cm difficult to diagnose at early stages with CT/MRI	5-10 cm
Location	Equal distribution in all areas: Head, neck, tail of Pancreas	Mc location at Tail of Pancreas

Insulinomatosis

- Patient has Multiple micro or macro adenomas/island of tumor in Pancreas behaving like Insulinoma.

Nesidioblastosis

- It is a pediatric precursor of Insulinoma characterized by excessive insulin (hyperinsulinism) concomitant with Hypoglycemia

Clinical features of Insulinoma

1. Frequent eating and Weight gain
2. Concentration Span decreases
3. Irritability
4. Rage attacks and emotional liability

5. Visual disturbance
6. Irrational behavior
7. Symptoms of Sympathetic Stimulation
   - Fine tremors
   - Diaphoresis
   - Palpitations

Work Up

1. 72-hour prolonged fasting test:Investigation of choice
- Low blood sugar levels < 40 mg and RIA insulin elevated > 6 µu/ml
  - In normal persons when Blood sugar reaches 40 mg
    → Insulin production stops
    → Insulin by RIA < 6 µu/ml
- C peptide elevated
  - Insulin produced by Pancreas comes into circulation along with amylin & C-peptide
  - Active Insulin has 51 amino acids
  - A chain = 21 AA
  - B chain = 30 AA
  - C-peptide = 33 AA, is a interlinking chain

2. Proinsulin elevated
3. Insulin/ glucose ratio = > 0.3
   - Normal value < 0.3
4. Low plasma β OH butyrate values
5. Check for Urine Sulfonylureas (to r/o factitious hypoglycemia as Sulfonylureas causes hypoglycemia like features)

Imaging

1. Endoscopic Ultrasound
2. Somatostatin receptor Scintigraphy/ Imaging (SRI)
   - Useful in localizing pancreatic Neuroendocrine tumor including GI endocrine tumors Except Insulinoma
   - As they are small & have low densities of Somatostatin receptors
3. PET CT -gallium 68: Best investigation if other tests are negative and minimally invasive surgical approch is planned.
4. MRI/CT abdomen :- For tumors >2cms

Treatment

- Frequent small meals
- Diazoxide (drug of choice)
  - Insulin production decreased from β cells hormone
- Octreotide/ Lanreotide
  - Somatostatin analog
  - Decreases GH and Blood sugar
- In case of malignant Insulinoma
  - mTOR inhibitors
    → Everolimus
    → Rapamycin
  - Chemoembolization
  - Radiolabeled Somatostatin

Glucagonoma 00:31:13

- Mostly located in Tail of Pancreas
- Tumor is malignant; 5-10 cm in size
- Characteristic finding in skin: necrolytic migratory erythema

Clinical features

- **D - D**iabetes Mellitus (pre) / Impaired glucose Tolerance
- **D - D**iarrhea
- **D - D**ermatological features
  - Migratory necrolytic erythema
  - Rash → Bullae → Erosions
  - Present at Intertriginous/ Peri-orofacial sites
- Weight loss

Work Up

1. Plasma glucagon > 1000 pg/ml
2. CT/MRI abdomen
   - Metastasis to liver 80%
3. SRI – to identify location of tumor (Tail)

- Prognosis is bad as it is mostly malignant

Treatment

- Debulking surgery
- Radiolabeled somatostatin analogues

Dermatological manifestations seen in various diseases

- Necrobiosis lipoidica diabeticorum
  - Characterized by erythematous lesion with central clearing in diabetics
  - Grossly red and inflamed
  - Usually on shin
- Acanthosis Nigricans
  - Diabetic patient with Hyperpigmentation
  - Present on groin, axilla or back of the neck
  - Seen in PCOD, DM, Carcinoma pancreas
- Migratory Necrolytic Erythema
  - Seen in glucagonoma, Myeloproliferative disorders

Somatostatinoma 00:37:32

- Excess of somatostatin
  - Inhibitor of other hormones
  - It is a tetra-decapeptide
- Found in CNS (in pituitary)/GIT

Clinical Features

1. **D - D**iabetes Mellitus
   - Due to inhibition of insulin

2. **D** - Secretory **D**iarrhea
   - Due to inhibition of pancreatic amylase
   - Steatorrhea
     → Due to inhibition of pancreatic amylase
3. **G** - **G**all bladder disease
   - Incidence of gallstones increases
   - Due to inhibition of CCK
4. Hypochlorhydria

Imaging

- Somatostatin receptor Scintigraphy/ Imaging (SRI)

VIPoma

00:40:42

- Excess production of vasoactive intestinal polypeptide
- It is series of 28 AA peptide
- Released by F cells of pancreas
- Present in both GIT/CNS
  - Causes vasodilation
- Mechanism
  - Causes opening of water channel in gut
    → Causing secretory diarrhea/rice water stool
    → Consistency of stool is just like stools in cholera. Therefore, also known as Pancreatic cholera
    → Non responsive to fasting.
    → Stool osmolol gap <50 mOsm
  - Other important features of VIPoma
    → Hypokalemia
    → Flushing episodes
    → Achlorhydria
    → Hyperglycemia and Hypercalcemia

Secretory Diarrhea 00:44:42

- Nonresponsive to fasting
- **Causes**
  - **D** - **D**iabetic diarrhea
  - **M** - **M**edullary carcinoma thyroid
  - **M** – **M**astocytosis
  - **C** - **C**arcinoid syndrome
  - **C** - **C**holera and Pancreatic Cholera
  - **L** - **L**axative abuse
  - **G** - **G**astrinoma
- **Stool osmolar gap**
  - Differentiate b/w secretory and osmotic diarrhea
  - Stool osmolar gap =290 – 2 [(stool Na+) + (Stool K+)]
  - If stool osmolar gap > 100 = osmotic diarrhea
  - If stool osmolar gap < 50 = secretory diarrhea
- **Treatment**
  - Octreotide

Important Terminologies

- P. NET: Primitive Neuroectodermal Tumors
  - Neuroblastoma
- ppNET: Peripheral primitive Neuroectodermal tumor
  - Medulloblastoma
  - Ewing Sarcoma

46 DISORDERS OF PARATHYROID GLAND

- Hormones secreted by the parathyroid gland are:
  - PTH (parathyroid hormone)
  - FGF (fibroblast growth factor)
  - Calcitonin

Parathyroid Hormone

- It constitutes 84 amino acids.
- Functions of PTH:
  - Cause bone resorption: if calcium is less in the blood PTH will cause enhanced bone resorption.
  - Increase in calcium reabsorption via acting on distal tubules in kidney.
  - This occurs via special sensor named CaSR in distal tubule.
  - Action on PCT kidney: Regulate Po_4 values and promote phosphate Wasting. It will cause phosphaturia. The phosphate value will be reduced.
- PTH causes calcium and phosphate to have an *inverse* relationship.
- It increases bone turnover.
  - Marker for bone turnover is serum alkaline phosphatase (SAP).
  - Osteoclast have the bone destroying action.
  - Osteoblast has the bone-forming action and is Responsible for SAP production.
  - In bone resorption, osteoclastic activity increases which results in a secondary increase in osteoblastic activity causing an increase in SAP.

Fibroblast Growth Factor 23 (FGF23)

- It regulates calcium/phosphonate metabolism.
- It causes suppression of PTH.
- It causes loss of phosphate- which results in phosphaturia.
- Increase in either calcium or phosphate contributes to nephrolithiasis.

Calcitonin

- Calcitonin is used in osteoporosis/hypercalcemia for a therapeutic purpose.
- It will act by inhibiting osteoclastic-mediated bone reabsorption.
- Calcitonin is not having a significant effect on bone density.
- It will promote renal calcium clearance.
- Tolerance against calcitonin occur very soon.
- Calcitonin is the tumor marker for medullary thyroid carcinoma.
- CaSR present in the parathyroid and kidney.

Important Information

Increased SAP
1. Rickets (in children)
2. Osteomalacia (in adults)
3. Hyperparathyroidism

Decreased SAP
- Hypophosphatasia

SAP normal
1. Hypoparathyroidism
2. Multiple myeloma
3. Osteoporosis

Disproportionate increase in SAP
- Paget's disease

Primary Hyperparathyroidism 00:12:43

- The leading cause is parathyroid adenoma (Inferior parathyroid is usually involved).
- The calcium levels are raised. (Raised up to 15mg%)
- Normal calcium levels: 9-11 mg%
- Usually occur in 3rd-5th decade.
- Either Having a solitary adenoma.
- Associated with MEN 1, MEN 2/2A.

Clinical Features

1. Bone pain: due to enhanced bone resorption.
2. Recurrent stones
3. Moans (psychosis)
4. Groans (abdominal pain): due to constipation.

Raise of calcium and its manifestations

- 11-12 mg%
  - Renal colic
  - Nephrolithiasis: it can be either calcium oxalate or calcium phosphate stones.
  - Calcium-induced ileus: due to spasms of sphincters of the gut causes constipation (abdominal pain).
  - Calcium increase causes activation of parietal cells leading to peptic ulcer disease. It may lead to perforation.
  - If associated with MEN 1: Zollinger Ellison syndrome.
- 13-15 mg%
  - Bone pain: Osteitis cystica fibrosa
  - Proximal muscle weakness
  - Depression/psychosis
- >15 mg%
  - Systolic arrest

Hypercalcaemic Crisis

1. Humoral hypercalcemia of Malignancy:
   - PTH-r-p Squamous cell Carcinoma of the lung.
   - Carcinoma Breast
2. Parathyroid Adenoma: initially, it is asymptomatic.
3. Sarcoidosis: Non caseating Granuloma leads to Synthesis of Vit D_3.
4. Vitamin D_3 Intoxication
5. Milk Alkali Syndrome: due to excessive intake of antacids.
   - Antacids have calcium carbonate.
6. Jansen disease:
   - It is an autosomal dominant condition.
   - Due to a Defect in the PTH Receptor.
   - This receptor exhibits gain of function mutation.
   - Receptor working more than normal and causing hypercalcemia.
7. Lithium: It causes nephrogenic diabetes insipidus and activation of the parathyroid gland.
   - On withdrawal of lithium, hypercalcemia regress.
8. Familial hypocalciuric hypercalcemia (FHH)
   - Autosomal dominant condition
   - Due to a defect in CaSR malfunction.
   - CaSR Located at parathyroid and kidney.
   - Under the impression of CaSR malfunctioning the parathyroid will secrete more PTH and causing the hypercalcemia.
   - More calcium reabsorption
   - Urinary calcium would be less.
9. Steroid responsive Hypercalcemia
   - Sarcoidosis
   - Vitamin D3 Intoxication

Work up

1. Serum calcium is increased.
2. Serum phosphate is decreased.
3. Serum alkaline phosphatase is elevated.
4. Serum PTH assay (2^{nd}-3^{rd} generation): tremendous increase.
5. To localize the tumor:
   - Sestamibi scan (Tc_{99} scan) is an imaging modality.
- Tc_{99} pertechnate scan used in Meckel's diverticulum.
6. X-ray hand: subperiosteal resorption of phalanges.

Treatment

- In the asymptomatic patient, we have to do only screening.
- Resection of adenoma (treatment of choice):
  - Indication of surgery:
    → Age is <50 years of patient.
    → Documented elevated calcium levels.
    → Creatinine clearance <60 ml/min
    → 24-hour urinary calcium value is elevated.
    → Dexa scan: T-score is <2.
- In Asymptomatic parathyroid adenoma annual monitoring has to be done.

- **Management of Hypercalcaemic crisis:**
  1. Hydration of the patient with Normal saline (dilutional effect)
  2. Normal saline with furosemide (forced diuresis)
     - Furosemide causes the loss of calcium in the urine.
     - Furosemide is rapid acting.
  3. Zolendronate (drug of choice) given intravenously.
     - Onset is 1-2 days.
     - The effect lasts for 3 weeks.
  4. Calcitonin nasal spray
     - Rapid onset
     - There is the development of tachyphylaxis.
  5. Denosumab (Monoclonal antibody)
     - Given subcutaneously.
     - It binds to the RANK ligand, which inhibits osteoclast differentiation.
  6. Oral phosphate
  7. Steroids: Dexamethasone can be used.
  8. Dialysis: peritoneal dialysis
     - Dialysate fluid which is used is calcium free.
     - This can immediately reverse life-threatening hypercalcemia.
     - Useful in renal failure

Secondary Hyperparathyroidism 00:56:16

- Most common cause is Chronic Renal failure.
- In India, CKD is mostly due to diabetic nephropathy.
- Kidney is the site of vitamin D_3 production.
- In PCT, there is 1α- hydroxylase which secretes the active form of vitamin D.
- In patients of CKD, synthesis of vitamin D_3 would be less.
- Decreased calcium is the trigger for the secretion of increased PTH.
- There is increase in phosphate levels due to low GFR
- PTH causes bone resorption and leads to bone weakness.
  - Have symptoms of bone pain and pathological fractures.
  - Azotemic dystrophy
  - Osteitis cystica fibrosa (brown tumor)
  - Osteitis cystica fibrosa can be seen with both primary and secondary hyperparathyroidism.

Work up

1. Calcium is decreased.
2. Phosphate is elevated because it is not getting excreted.
3. SAP is high: because bone turnover is enhanced in hyperparathyroidism.
4. PTH values would be elevated.
5. Vitamin D_3 would be relatively less.

6. eGFR: Use online calculators like the MDRD formula for estimated GFR in the patient would be Reduced.
7. Urinary albumin creatinine ratio increased: Because the kidney is damaged so, therefore, urinary albumin would be increased.
   - Informally we used the term microalbuminuria but now we just use the term Urinary albumin creatinine ratio.
   - That could be in excess of 30 milligrams to 300 milligrams per gram of urinary creatinine.
8. Serum creatinine would be elevated.

Management

- Kidney transplantation: but that may not be feasible all the time.
  - Start calcium and vitamin D supplements.
  - But the problem is that the PTH is still high and it will be causing both reabsorption and damage to bones and can even cause fractures. Hence to supress PTH, Cinacalcet is used
  - Cinacalcet:
    → Calcimimetic drug, behaves like calcium.
    → It will stimulate the calcium-sensitive receptor and will tell the parathyroid gland that calcium has come, and the parathyroid gland will shut down its excess PTH production

Hypoparathyroidism 01:01:32

- PTH Values would be lesser.

Causes

1. There is a decrease in PTH production due to autoimmunity.
2. Autoimmune polyglandular syndrome:
   - It has a combo of Addison's disease, hypoparathyroidism and candidiases.
     → Chromosome 21 AIRE gene defect.
3. Post-operative Thyroid surgery
   → The patient has papillary cancer thyroid, and he underwent a total thyroidectomy with inadvertent removal of the parathyroid glands.
   → The calcium values in this patient would be less.
   → The chances of development of this would be relatively lesser nowadays because the surgeon would be performing parathyroid reimplantation.
   → Brachioradialis is the preferred site for parathyroid Re - implantation.
   → If this procedure has been done, then the chances of manifestations of hypoparathyroidism would not be occurring in a patient.
4. DiGeorge syndrome:
   → The problem in chromosome 22 and defect related to the 3rd and the 4th branchial arches.
   → As a result of this not only the development of the thymus will be defective but the development of parathyroid in this defective
   → The child from a young age will be having repeated infections because cell-mediated immunity is reduced.
   → Values of PTH are less.
   → Hypocalcaemia will occur.
   → The height will not increase. (Short stature)

Clinical Presentation

- Acute hypocalcaemia: Tetany: Serum Calcium < 7 mg%
  - It is a life-threatening condition.
  - After Thyroid surgery usually by the 2nd or 3rd day manifestations of tetany can occur in a patient.
  - **Case scenario:** Patient has undergone a total thyroidectomy. You are the intern in a surgical unit on day 3. The patient complains that he is having a tingling sensation around his lips and around his fingertips.
  - Post - op, the earliest clinical manifestation of tetany would be perioral and periungual paraesthesia.
  - **Trousseau sign:**
    → Deploy the BP cuff and raised it to 20 mm above the systolic blood pressure.
    → keep it there for three minutes normally, it will cause discomfort. But in these patients, you will notice that you will be able to elicit nerve irritability.
    → Irritability of median nerve cause adductor spasm of the thumb, called carpopedal spasm.
    → The neuromuscular excitability is increased in hypocalcemia.
    → So, this patient there is potentially increased risk of dying because of development of laryngospasm
  - **Chvostek sign:**
    → Tapping on the anterior border of the parotid gland
    → To demonstrate the facial nerve irritability in a normal person if you tap on the order of the facial nerve it will not contribute to anything but in this person, you will be able to elicit the irritability which will contribute to the development of twitching of muscles around the lips.
  - Trousseau sign is also read in surgery causing migratory superficial thrombophlebitis due to malignancy like Stomach cancer, Lung cancer .

Work Up

1. ECG: QT prolongation.
- The calcium in the blood is inversely related to the QT interval.
2. Albumin values are normal values.
3. Serum Calcium and ionized calcium values are reduced.

Treatment

1. I.V. 10% calcium gluconate will be given in the initial crisis. (Not the permanent solution)
2. Surgically induced hypoparathyroidism can be easily prevented by doing parathyroid reimplantation but that was never done in this, case.
3. Teriparatide
   - PTH manufactured by DNA recombinant technology given for Surgically induced Hypoparathyroidism.

Chronic Hypocalcaemia 01:14:25

- In the pediatric age group: There is a rickets-like illness.
- In adults: Leads to **basal ganglia calcification**
- The phosphate will be elevated, and it is this elevated phosphate that is contributing to the development of deposition of calcium phosphate in the tissues.
- As a result of this the features of extrapyramidal involvement develop:
  1. Dystonia
  2. Oculogyric crisis (person's neck would be turned to one side, eyes deviated maybe to the contralateral side)
  3. Hemiballismus (Due to damage to the subthalamic nucleus).
  4. Ocular cataracts
  5. Abnormal dentition
  6. Dry skin mostly
  7. Features of Addison's disease may be present (Salt wasting, salt craving, postural hypertension)
  8. Candida infection due to association with autoimmune polyglandular syndrome.

Work up

1. Calcium is decreased.
2. Phosphate is increased.
3. SAP is normal.
4. Serum PTH assay is very less.

Treatment

- Teriparitide is given in surgery - induced hypo parathyroidism.
- Calcium and vitamin D supplements.

Pseudo Hypothyroidism 01:20:59

- PTH values are high. (Due to feedback mechanism)
- There is resistance to PTH receptor due to defect in GNAS gene.
- Reduced responsiveness to PTH in kidney.
- In DCT, absorption of calcium is less. so, calcium value is less.
- In PCT, less excretion of phosphate. so, phosphate value in blood is high.
- There is defect in GNAS locus on chromosome 20.
- It acts by inactivating GPCR.
- Inherited from the Maternal side.

Clinical Features:

1. The clinical features are described as Albright hereditary osteodystrophy.
2. Short stature
3. Obesity
4. Brachydactyly (short metacarpal and metatarsal bone)
5. Low I.Q
6. Having short 4th and 5th metacarpal bones leads to Knuckle-Knuckle- dimple–dimple sign also known as Archibald sign.

Work up

1. Serum Calcium is Decreased
2. Phosphate is increased.
3. SAP is Normal
4. PTH increased in pseudo-hypoparathyroidism and reduced in hypoparathyroidism.

Management

- No definitive treatment.

Pseudo Pseudo Hypoparathyroidism 01:30:30

- Inherited from paternal side.
- Tissue specific difference in action
  - Action of PTH on bones is defective and leads to features of AHO
  - Action on Kidney is Normal and phosphate levels are normal.

Work up

1. Calcium level is normal.
2. Phosphate levels are normal.
3. PTH levels are normal.

Treatment

- No definitive treatment.

Refer Table 46.1
Refer Table 46.2

Nutritional Rickets 01:39:48

- Decrease Vitamin D_3 causes decrease in serum calcium.
- It elevates the level of the PTH and leads to Phosphate wasting (urinary loss) occurs.
- Decrease in phosphate levels.

Work up

1. Calcium levels are decreased.
2. Phosphate levels are decreased.
3. Serum alkaline phosphatase is increased.

Osteoporosis

01:41:33

- Calcium and phosphate and SAP values are normal.

Work up

- DXA scan: T-score < – 2.5 SD
  - Z-score < – 2.5 SD

Treatment

- Bisphosphonates: Drug of choice for Osteoporosis
  - Side effects of bisphosphonates are osteonecrosis of jaw and atypical femur fracture.
  - Discontinue after 3-5 years.

Vitamin D Dependent Rickets

01:44:12

Type 1	Type 2
• Previously, known as pseudo vitamin D resistance rickets. • The gene that encodes for 1 α hydroxylase activity is defective. • Synthesis of active form of vitamin D is decreased. • Work up: o Calcium levels are decreased. o Phosphate levels are decreased. o SAP increased. o PTH increased.	• End-organ resistance to active form of vitamin D • Work up: o Calcium levels are decreased. o Phosphate levels are decreased. o SAP increased. o PTH increased.
Treatment Reverse by giving active form of vitamin D	Treatment • Calcium infusion • It tends to normalise the PTH of the patient. • Improves the Rickets and bone pain

Table 46.1

Disease	PTH	Causes	Phosphate	Clinical feature
Hypoparathyroidism	Decreased	Autoimmune		• Basal ganglia calcification • Cataract • Dry skin • Altered dentition
Pseudohypoparathyroidism	Increased	Maternal inheritance	Increased	AHO
Pseudo pseudo hypoparathyroidism	Normal	Paternal inheritance	normal	AHO

Table 46.2

	Primary PTH increased (adenoma)	Secondary PTH increased (chronic kidney disease)	Hypoparathyroidism (PTH decreased)	Pseudohypoparathyroidism (PTH increased)
Calcium	Increased	Decrease	Decreased	Decreased
Phosphate	decreased	Increased	Increased	Increased
SAP	Increased	Increased	Normal	Normal

47 MULTIPLE ENDOCRINE NEOPLASIA

CRITERIA for diagnosis of MEN

1. Clinical features of 2 or more than 2 endocrine tumors in an individual.
2. It has an Autosomal dominant inheritance/ Familial basis
3. Germline mutation analysis has to be done.

- For diagnosis of MEN At least, 1 out of 3 criteria should be present.

MEON (Multiple Endocrine and Other Organ Neoplasias) 00:02:04

- Von hipple- Landau syndrome (VHL)
  - It is a defect in chromosome 3.
  - Associated with the presence of Renal cell carcinoma, clear cell carcinoma, cerebellar and retinal hemangioblastoma.
- Cowden syndrome
  - It is related to the PTEN gene mutation.
  - Multiple hamartomatous lesions in the oral cavity, small intestine and colon
- McCune albright syndrome
  - Polyostotic fibrous dysplasia.

MEN I / Wermer Syndrome 00:03:35

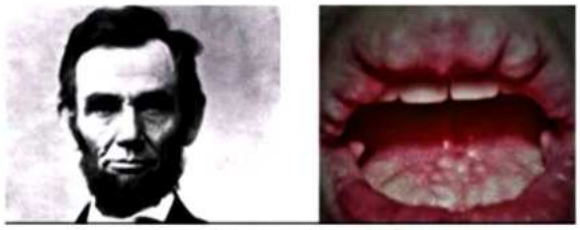
- It is due to defect in chromosome 11q13.
- Involves the MEN-1 gene mutation responsible for uncontrolled mitosis in the endocrine glands.
- It involves:
  - **P - P**arathyroid gland
  - **P – P**ancreatic tumor
  - **P – P**ituitary adenoma
- Parathyroid adenoma
  - It is most common.
  - It causes an increase in PTH and Calcium leading to damage to the tubular kidney.
  - It presents with recurrent nephrolithiasis, polyuria, polydipsia, and constipation.
- Pancreatic adenoma
  - MC seen in MEN 1 gastrinoma called Zollinger-Ellison syndrome
  - Peptic ulcer disease is the leading cause of death in MEN1
- Pituitary adenoma
  - Usually a prolactinoma.
  - Female presenting with amenorrhea and infertility
- Associated features seen are:
  - Angiofibroma
  - Collagenoma
  - Adrenocortical tumour
  - Carcinoid tumors
    → They originate from the thymus and bronchus.
  - Pheochromocytoma is present in 1% of cases.
- Management: all 4 parathyroid glands are affected so the surgeon have to perform total parathyroidectomy (1st preferred answer) or either do Subtotal parathyroidectomy.

MEN-2 / Sipple Syndrome 00:12:00

- It is due to a defect in chromosome 10.
- Due to RET gene mutation (RET mutation gene analysis)
- It includes:
  - **P – P**arathyroid adenoma
  - **P – P**heochromocytoma
  - **M – M**edullary thyroid carcinoma
- Parathyroid adenoma
  - It is the most common presentation of MEN 2
- Pheochromocytoma
  - There is a spike in catecholamines levels which results in poorly controlled hypertension.
  - Surgeries on these patients are always risky.
  - Patients can develop intraoperative complications.
  - It is the leading cause of death in MEN 2.
- Medullary thyroid carcinoma
  - There is an increase in calcitonin.
  - Calcitonin is only a tumor marker.
  - High value of calcitonin will not cause Hypocalcemia in this patient.
  - Patient presents with a lump in the neck.
  - On thyroid scan, there is the presence of cold nodules.
  - On PET scan, there is evidence of metastasis.
  - Clinical presentation:
    → Usually asymptomatic, later it can be asymptomatic.
    → Mass in the neck, dysphagia.
    → Diarrhea: due to an increase in calcitonin and serotonin. Calcitonin also contributes to secretory diarrhea.
    → Calcium value is normal in more than 50% of patients.
- Associated with Hirschsprung disease: Involves rectosigmoid junction with aganglionosis leading to delayed passage of meconium.
- Management:
  - Prophylactic thyroidectomy
    → Current studies show increase in the life span of the individual with lifelong thyroxine replacement.

MEN -3 / MEN 2B

00:19:10



Abraham Lincoln : Former US President

Abraham Lincoln was suffering from MEN-3.
It includes:

- Medullary carcinoma thyroid: it is the most common presentation.
- Pheochromocytoma: it is the leading cause of death in MEN3
- M_4 Seen:
  - **M**arfanoid habitus (when the arm span is longer than the height of the person.
  - **M**ucosal neuromas (Bumpy lips and tongue)
  - **M**edullated corneal nerve fibers.
  - **M**egacolon

MEN-4

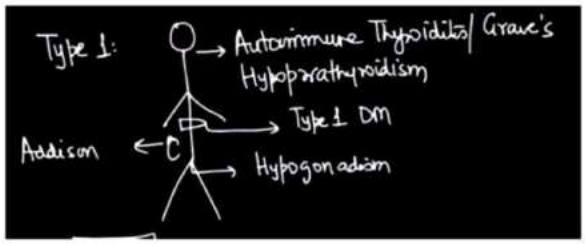
00:22:58

- It is due to a mutation in CDKN1B gene (chromosome 12 p 13)
- It involves:
  - Pituitary adenoma usually Prolactinoma.
  - Parathyroid adenoma: Hypercalcemia is the manifestation
  - Reproductive tract tumors:
    → Testicular tumors: they can be seminomatous or non-seminomatous.
    → Neuroendocrine tumor of cervix.
  - It is may or may not be associated with the Adrenal or Renal tumor.

Autoimmune Polyendocrine Syndrome

00:26:29

- Types:
  - Type-1 APS
  - Type-2 APS
- Type 1: Multiple endocrine glands are involved.



  - It is due to a defect in chromosome 21.
  - There is destruction to the endocrine gland and the gland will not perform optimally.
  - In the neck, the thyroid and parathyroid gland both can be involved, leading to Auto immune thyroiditis and hypoparathyroidism.
  - In pancreas, Autoimmune damage to the pancreas leads to type-1 DM.
  - In Kidney: Destruction of Adrenal glands leads to Addison's disease.
  - In genital: There is hypogonadism.
  - For diagnosis: Presence of 2 out of 3 findings mentioned above should be present.
    → AIRE gene (gene analysis)
  - Associated with asplenia that can explain mucocutaneous candida presentation.
- Type-2:
  - The only difference is hypoparathyroidism is not present in type2.
  - Associated with: Celiac sprue, Dermatitis herpetiformis.

48 DISORDERS OF ANTERIOR PITUITARY

Acromegaly 00:00:10

- It occurs due to excess Growth hormone after puberty.
- Somatotrophs are most abundant cells in the pituitary.

Causes

1. Somatotroph adenoma
2. Mixed Mammosomatotroph adenoma:
   - Growth hormone increases.
   - Prolactin increase leads to galactorrhoea and hypogonadism.
3. Hypothalamic hamartoma (increase in GHRH), Choristoma
4. Extra pituitary GHRH source: Carcinoid tumor
5. Extra pituitary GH source
   - Ectopic pituitary tissue (present in the nasopharynx can be presented by carcinoma)
   - Pancreatic tumor

Clinical Feature

- Leading cause of mortality is cardiovascular causes like fatal arrhythmia.

1. Acral enlargement:
   - Increase in size of Hands and Feet called spade like hands.
   - Increase in Finger thickness leading to ring gets impacted.
   - Glove size increases.
   - Shoe size increases.
2. Facial feature:
   - Frontal bossing
   - Large fleshy nose
   - Coarse facies
   - Hyperhidrosis (Increase in sweating)
   - Increased sebum excretion
   - Widened space between the lower incisors. Prominent mandible called Prognathism
3. Height remains the same.
   - Heel pad thickness increases (Radiological parameters) → More than 25 mm.
4. Arthropathy, kyphosis, carpal tunnel syndrome.
5. Cardiomyopathy: Risk of arrhythmia in the patients (common cause of mortality)
6. Macroglossia leading to obstructive sleep apnoea.
7. Colonic polyps and malignancy can develop.
8. Impaired glucose tolerance
   - Increase in growth hormone leads to increased sugar levels causing diabetes mellites.
   - Fasting blood sugar level is 100 – 125 mg % (impaired fasting glucose)
   - 2-hour value is 140-199 mg % (Impaired glucose tolerance)
9. Hypertension
10. Rare findings:
    - Galactorrhoea
    - Visual field defects: Bitemporal hemianopia.

Important Information

Important Causes of Galactorrhoea
1. Prolactinoma
2. Chronic kidney disease (CKD)
3. Drugs: Antipsychotics.
4. Primary Hypothyroidism
5. Acromegaly

Work Up 00:17:48

1. Screening test is insulin-like growth factor 1 (IGF-1) levels
2. Investigation of choice is an oral glucose intolerance test.
   - In normal individuals 75 grams of glucose suppresses the growth hormone.
   - Failure to suppress growth hormone (less than 0.4 µg/liters is seen in acromegaly).
3. Prolactin levels increased.
4. TSH is normal or may be suppressed.
5. MRI head: To localize the pituitary adenoma
6. X-ray foot (Lateral:) Heel pad thickness is increased.

Management 00:23:10

- Treatment of choice is Trans-sphenoidal surgery.
- Preoperatively to shrink the tumor and in frail patients, Somatostatin receptor ligand analogs are given:
  - Octreotide
  - Lanreotide
  - Pasireotide
  - They act on the SSTR 2 and SSTR 5 receptors which are highly expressed in Growth hormone producing tumors.
- After surgery, first improvement is reduction in soft tissue swelling.
- Transient diabetes insipidus can occur after Trans-sphenoidal surgery.
- Aggressive surgery in patients may lead to hypopituitarism.
- PEGVISOMANT
  - It is given in the recurrence of tumor and if poor response to somatostatin receptor ligand analogues.
  - It blocks the growth hormone receptors.

SHEEHAN SYNDROME 00:27:28

- Anterior pituitary damage due to P.P.H that leads to pan-hypopituitarism.
- Growth hormone is 1st to fall.
  - Results in hypoglycemia
    1. Emotional lability
    2. Mood swings
- ACTH decreases leading to a decrease in cortisol causing a decrease in blood sugar levels (last hormone to fall).
  - It worsens pre-existing hypoglycemia.
- Prolactin decreases leading to failure of lactation. (Acute presentation)
- LH hormone decreases leading to secondary amenorrhea and infertility.
- FSH hormone decreases.
- TSH decreases leading to secondary hypothyroidism leading to
  - → Weight gain
  - → Constipation
  - → Alopecia
  - → Myxedema

Imagining

- MRI head: Anterior pituitary damage is seen.

Management

- Dexamethasone is 1st to be supplemented.
  - It replaces cortisol deficiency.
  - Stabilise the blood sugar levels.
- Combined oral contraceptives: Estrogen and Progesterone.
- Levothyroxine

Simmonds Disease

- It is the cause of non-obstetric damage to the anterior pituitary.
- Can occur in Hypertension, sickle cell disease or Rupture of AV Malformation

Hypopituitarism 00:34:24

- It implies only GH deficiency.
- Seen in the pediatric population.

Clinical Features

1. Present since birth (developmental defects)
2. Short stature (height less than 3rd centile)
3. Shrill voice
4. Doll-like Facies

Work Up:

- Investigation of choice is Insulin tolerance test / Arginine challenge test.

Treatment

- GH injections made by DNA Recombinant technology till Puberty.

Summary

Endocrine disorder	Test
Acromegaly	Oral Glucose Tolerance test
Conn Syndrome	Saline infusion test / Salt loading test
Addison disease	ACTH stimulation test/cosyntropin test
Diabetes Insipidus	Water deprivation test
SIADH	Water loading test
Hypopituitarism	Insulin tolerance test
Cushing disease	Low dose dexamethasone suppression test
Pheochromocytoma	Plasma Free metanephrine levels

Prolactinoma 00:40:41

- It is the most common *Functioning* pituitary tumor
- Overall most common Pituitary Tumor is a non-functioning Tumor
  - Dopamine inhibits prolactin production.
- Prolactin has an inhibitory effect on LH and FSH

Clinical Features

- In Females,
  1. Anovulation
  2. Amenorrhoea
  3. Secondary infertility
- In males,
  4. Galactorrhoea
  5. Bitemporal hemianopia due to pressure on optic chiasma

Investigation

1. Serum Prolactin levels
2. MRI Head

Treatment

- Bromocriptine/ Cabergoline (Long acting) cause micro adenoma to shrink and prolactin levels to normalize.
- Surgery needed only for invasive macro adenoma not responding to medical therapy

49 ELECTROLYTE IMBALANCES

Dyselectrolytemia and Fluid Imbalance

Hyponatremia

00:01:00

- Hyponatremia is the most common electrolyte imbalance in hospitalized patients:
  - Mainly due to decreased intake
- Clinical Implications of hyponatremia
  - Affects plasma osmolality
  - This will result in fluid shift across brain
  - Resulting in Cerebral edema
  - And contribute to Seizure
- **Plasma osmolality**
  - Factors affecting plasma osmolality:
    - → Sodium concentration
    - → Potassium level
    - → Blood urea nitrogen
    - → Glucose levels
  - Plasma osmolality = 2 (Na^+ + K^+) + BUN/2.8 + Glucose/18
  - Normal plasma osmolality = 285-295 mOsm
  - In hyponatremia → plasma osmolality decreases
- Urine osmolality
  - Normal Urine osmolality = 100 - 900 mOsm
  - When person do not consumed water at all → the urine becomes highly concentrated → 900mOsm
  - When consumed aerated drinks → urine is extremely dilute
  - Urine osmolality fluctuation help in maintaining plasma osmolality

Hypotonic hyponatremia

- Normal Sodium - 135-145 mEq
- Severe hyponatremia - <125 mEq
- Mild hyponatremia - 130 - 135 mEq
  - Most patients will be asymptomatic.
- But when it falls below 130 mEq
  - Headache
  - Irritability
  - Loss of concentration
- Below 125 mEq
  - High risk of seizure due to fluid shift across brain
- Plasma osmolality is always < 285 mOsm
- Types of Hyponatremias is dependent on Volume status of the patient
  - Volume status can be
    - → Hypovolemic
    - → Euvolemic
    - → Hypervolemic

Hypovolemic hyponatremia

For instance, a person with Diarrhea/vomiting

- Loss of water
- TBW- Total body water ↓
- TBS- Total body salt ↓
- The technical term used for this subtype of Hypotonic Hyponatremia is Hypovolemic hyponatremia.

Treatment:

- Fluid replenishment
- Oral - ORS
- IV fluids (if ORS cannot be taken orally)

Euvolemic Hyponatremia

SIADH
↓
Excess ADH → Activate V2 receptors
↓
more reabsorption of water
↓
TBW - ↑
TBS - N
Water > salt
Dilutional hyponatremia

- Euvolemic -Total body water is more and Total body salt is normal
- SIADH - CNS Infections are important cause for development of SIADH. They cause reset of osmostat at higher level.
  1. Brain abscess
  2. Cerebral Toxoplasmosis
  3. Meningitis/Encephalitis
  4. Herpes Simplex Encephalitis
  5. Herpes zoster
- Ectopic production of ADH - Lung cancer or carcinoid tumor

Hypervolemic Hyponatremia

- Massive ascites
  - Cirrhosis
  - Nephrotic syndrome
  - Malabsorption syndrome
- Results in reduction in circulating fluid volume (fluid is redistributed in the 3rd space)
- Renal perfusion low
- GFR ↓
- Activates RAAS

- Leads to Secondary hyperaldosteronism
- Activate ENac - epithelial sodium channel
- More water and more salt reabsorbed
- Corresponding loss of K+ and H+
- Water elevated disproportionate to the amount of salt
- TBW - ↑↑
- TBS - ↑
- Hypervolemic hyponatremia - both water and salt are more and water is disproportionate compared to salt

Case

- If patient has Berry aneurysm in anterior circulation and it ruptures by itself or minimal trauma resulting in SAH producing Thunderclap headache.
- As this is extremely painful, body produces BNP, resulting in Natriuresis.
- Due to Salt loss → water lost along with it
- TBW ↓
- TBS ↓
- This is called CSWS- Cerebral salt wasting syndrome - reduction of both water and salt

Hypovolemic	Euvolemic	Hypervolemic
TBW ↓, TBS - ↓	TBW ↑, TBS - N	TBW ↑↑, TBS ↑
Diarrhea, vomiting	SIADH CNS infections Oat Cell tumor Carcinoid tumor	Ascites: CHF Cirrhosis Nephrotic syndrome CKD
CSWS	Post Op patients	
Diuretics - excess use	Endurance sports	
Addison disease: Aldosterone deficiency	Psychogenic polydipsia	
Urinary sodium: GI loss:- U. sodium - low Renal:- Urinary sodium-high	Compulsive beer drinker- beer potomania	
	Hypothyroidism: Excess ADH	
Treatment: ORS IV fluids	Treatment: SIADH - fluid restriction initially VAPTANS- block V2 receptor	Treatment: Diuretics Ascites - cirrhosis - spironolactone CHF - furosemide

Hypertonic hyponatremia

- Plasma osmolality > 295 mOsm
- Blood sugar - is one of the determinants of plasma osmolality
- If blood sugar is high as in Hyperosmolar coma
- There is Osmotic shift of water → Draw in water
- This leads to dilutional hyponatremia
- For every 100mg% rise in sugar, the value of sodium ↓ by 1.6 mEq
- Sugar and sodium have inverse relation
- **Causes**
  1. High glucose (Hyperosmolar coma)
  2. Mannitol - osmotic diuresis
  3. Radiocontrast

Isotonic hyponatremia

- Also known as Pseudohyponatremia:
  - TBS - N
  - Low sodium value due to Lab error - as other values interfere with the measurement of sodium
- Hyperlipidemia
- Hyperproteinemia
  - Multiple myeloma
  - Paraproteins - Bence Jones Proteins
- **Hypotonic hyponatremia**
  - Hypovolemic - Diarrhea, CSWS
  - Euvolemic - SIADH, Endurance sports
  - Hypervolemic - Ascites, CKD
- **Isotonic hyponatremia** - Lab error due to increased lipids or proteins
- **Hypertonic hyponatremia**
  - Hyperosmolar coma
  - Mannitol

Management of Chronic hyponatremia

- Fluid of choice - 3% saline
- Cause only gradual rise - 4-8 mEq/day
- Na^+ <125 mEq = seizure +
- Fast correction of sodium can lead to Stroke like manifestation Called Central pontine myelinolysis. Now called, Osmotic demyelination syndrome. The features are:
  - Quadriplegia
  - Demyelination of corticospinal tract
  - Babinski +

Q. A 60 Kg female athlete participated in a marathon, before finishing the race, she collapsed. When brought to the hospital, electrolyte panel showed: sodium - 120 mEq. Calculate sodium correction to be given over the next 24 hours.

Ans: Sodium correction to be given over first 24 hours = TBW × (desired sodium - actual value)

- TBW - total body water
- TBW = weight × 0.6 (for males)
- TBW = weight × 0.5 (for females)
  - Women have more fat
  - Men have more water
- Sodium correction = 60 × 0.5 (128-120) = 240 mEq/24 hours Via infusion pump
- Fluid of choice - 3 % saline
- 0.9% saline = 154 mEq of Na^+ and 154 mEq Cl^- Per 1000 ml
- 3% saline = 514 mEq Na^+ and 514 mEq Cl^- Per 1000 ml
- 1 ml of normal saline = 0.15 mEq Na^+
  1 ml of 3% saline = 0.5 mEq of Na^+
- For total correction value in this case will be 60 × 0.5 × (140-120) = 600 mEq

Important Information

Correction formula for hyponatremia = TBW x 8
Acute onset Hyponatremia with seizures can be corrected fast. Only in chronic Hyponatremia, gradual correction should be done

Hypernatremia

00:42:44

- $Na^+ > 158$ mEq
- Hypernatremia will cause fluid shift across brain and can cause seizure.
- Fluid of choice - dilute fluid - 5 % dextrose
  - N/2 in 5 % dextrose - 0.45 % saline

Causes

1. Geriatric age group
   - Extreme debilitation
     → Alzheimer's
     → Hip surgery
2. Diabetes insipidus
   - Urine Osmolality - low < 250 mOsm
   - Polydipsia - but not drinking water
   - Nephrogenic or central
3. Excessive sweating
   - Urine osmolality - > 400 mOsm
4. Lactulose - osmotic diarrhea - water loss
5. Mannitol - osmotic diuresis
6. Postoperative: If not consuming sufficient amount of water

- Asymptomatic hypernatremia
  - Treatment - Liberal water intake
- Volume of fluid correction = TBW × (Na^+ actual - 140)/140

Hypokalemia

00:52:15

Important Information

- pH and potassium are inversely proportional
- Acidosis can lead to hyperkalemia

DKA - sugar ↑
↓
Solvent drag
↓
Potassium efflux
(Draw potassium out of cells into blood)
↓
K^+↑
So in Acidosis - potassium comes out of cells

- Hyperkalemia can result in acidosis
  When potassium is high (CKD, renal failure)
  ↓
  Affects function of kidney tubules
  ↓
  Inhibit tubular excretion of ammonia
  ↓
  Excretion of hydrogen ions affected
  ↓
  Metabolic acidosis

- Similarly in Alkalosis - pH > 7.5 → potassium low → Hypokalemia
- Potassium↑ by 0.7 mEq/L for 0.1 fall in pH

- $K^+ < 2.5$ mEq/L can cause death due to respiratory muscle paralysis

Causes

1. Decreased intake
2. Alkalosis → potassium shift into cells
3. Sympathomimetic stimulation - trauma, thyrotoxic periodic paralysis
   - Thyroid hormone → sympathomimetic drive → muscle cramp → muscle paralysis
4. Salbutamol toxicity
   - In hyperkalemia - salbutamol is given 4 times higher dose than in asthma
5. Renal losses
   - Aldosterone increased
     → More salt and water to come in
     → More loss of potassium and hydrogen
       - Hypokalemic alkalosis

   A. Conn's syndrome
   B. Bilateral adrenal hyperplasia
   C. Ascites
   D. CHF

6. BARTTER/GITELMAN syndrome - defect of thick ascending limb of loop of Henle
7. Salt losing nephropathy
8. Renal tubular acidosis - TYPE 1 and 2
9. Vomiting, diarrhea due to Secondary aldosteronism

Clinical features

1. Muscle cramps and weakness
2. Ileus
   - Absent bowel sound
   - Normal: 3 bowel sounds are heard per min in RIF
3. Areflexia
4. Flaccid paralysis
5. Carbon dioxide Retention due Diaphragmatic Paralysis
6. Asterixis

Work up

1. Serum K^+
2. TTKG - trans tubular potassium gradient
   - > 4 – renal wasting of potassium
3. ECG -
   - K^+ Responsible for repolarization
   - Height of T wave proportional to K^+
   - T wave – height will be lesser/absent/inverted
     → T wave Inversion
     - Unstable angina
     - NSTEMI
     - Hypokalemia
   - ST segment depression
   - Peaked P wave - pseudo P pulmonale
     → P wave > 2.5 mm in limb lead in absence of PAH
   - Prolongation of PR interval as conduction velocity is affected
   - PR prolongation
   - Prominent U wave
     → Prolonged QU interval

Treatment

- Trigger ventricular arrhythmia - Torsades de Pointes
  - Also seen with hypomagnesemia
- K^+ 3-3.5 mEq
  - Oral potassium chloride supplementation
  - Potchlor
- K^+ < 3 mEq or can't take orally (ileus or sick)
  - IV correction
  - Potassium chloride
  - Slow in the form of infusion
- 1 mEq/L rise in the blood : 200 mEq of KCl has to be supplied as slow IV

Q. In a patient receiving amphotericin B, the patient develops extreme lethargy, muscle weakness, carbon dioxide ↑. Patient is hyperventilated. S.potassium = 2.3 mEq/L
Calculate the correction of potassium to be given to patient?

- To be corrected 2.3 → 3 mEq
- After 3 mEq → correction can be given orally
- 1 mEq/L rise in the blood : 200 mEq of KCl has to be supplied as slow IV
- 0.7 mEq rise × 200 = 140 mEq KCl/24 hour fluid

Hyperkalemia

01:13:44

- K^+ > 8 mEq - death - diastolic arrest
  - Systolic arrest - Ca > 13 mg%

Causes

1. Lab error (pseudohyperkalemia):
   - Fist clenching during drawing of blood or narrow bore of needle can cause destruction of RBCs.
   - Cooling of sample.
   - Increase in TLC, platelet, RBCs.
2. Acidosis - transcellular shift
3. CKD/AKI
4. Aldosterone deficiency
   - ENac - gain of salt and water and loss of potassium and hydrogen normally
   - If aldosterone is deficient → potassium excess
   - Addison
   - Histoplasmosis
   - HIV
   - Waterhouse Friderichsen Syndrome
5. Gordon syndrome - DCT
   - Gain of function of Na-Cl cotransporter
   - More salt and water → hypertension
     → Liddle syndrome - gain of function of Enac
     → Gitelman - loss of function of Na-Cl cotransporter

Work up

1. Serum K^+ ↑
2. ECG:
   - Tall tented T wave
   - ST elevation
   - P wave height decreases/ - (>7 mEq)
   - Broad QRS
   - Sine wave pattern (> 8 mEq)

Treatment

1. **Antagonize effects of potassium**
   - Calcium gluconate
   - Calcium chloride - superior
   - Calcium carbonate - not used
2. **Redistribute potassium**
   - Insulin drip with 50 % dextrose

- Salbutamol neb - in a dose 4 times higher than that in asthma
  → Potassium shifts into intracellular compartment

3. **Removal of potassium by GI or renal route**
   - Furosemide - Kaliuria
   - Sodium polystyrene sulfonate
     → Risk of GI necrosis
     → Resin is not safe
   - PATIROMER
   - ZS-9 - Sodium zirconate cyclosilicate

- Not routinely used for management of Hyperkalemia
  - Soda bicarbonate

Calcium

01:24:24

Calcium ↓	Calcium ↑
< 7 mg%- Tetany	> 13mg% acute hypercalcemic crisis
Death: Laryngospasm	Death - systolic arrest
Treatment: IV 10% Ca gluconate	Treatment: Normal saline Furosemide Drip - Calciuria

- Thiazides worsen hypercalcemia
- DOC - bisphosphonates
  - IBANDRONATE
- Calcitonin nasal spray
- Steroids - IV hydrocortisone, useful in
  - Vit D intoxication
  - Sarcoidosis

Hypomagnesemia

01:25:37

- 1 % extracellular, 99% intracellular
- Intracellular depletion → blood value will not reflect the decrease
  - Spuriously normal
- Normal 1.3-2.1 mEq/L
- Hypokalemia and hypomagnesemia - similar

Causes

1. Diarrhea
2. Alcoholics
3. Drugs
   - Thiazide
     → Act on DCT → TRPM6 → needed for magnesium reabsorption → magnesium wasting
   - Amphotericin - B
   - Aminoglycosides
4. Renal wasting: Gittelman syndrome

Pathophysiology

- Antagonize calcium
  - Magnesium - relaxation
  - Calcium - constriction
  - Vasoconstriction - due to decreased relaxation
- Magnesium - when value increases or decreases from normal → Inhibit Release of PTH → Decrease calcium → Neuromuscular irritability

Clinical features

Features of hypokalemia + tetany

1. Muscle cramps
2. Hypertension
3. Tachycardia
4. Torsades de pointes
5. Neuromuscular irritability
   - Tremor
   - Nystagmus
   - Athetosis

Work up

1. S. Magnesium
2. Urinary Mg - for Mg wasting
3. ECG- Prolonged QT

- Predisposes to TDP
  - Mg sulfate is treatment of Torsades De Pointes

Treatment

- Parenteral supplementation
- IM/IV mg sulfate
- Mg oxide - oral

Magnesium toxicity

- Keep a watch on urine output and reflexes to check for Mg toxicity
  - Areflexia in toxicity
- Nm excitability inversely related to magnesium concentration
- Death occurs due to asystole > 10 mEq/L

Causes

1. CKD
2. Toxicity (Eclampsia management)
3. Antacids - contain Mg
4. Laxative abuse

Pathophysiology

Magnesium - When value increases will antagonise intracellular calcium leading to vessel relaxation.

1. Hypotension
2. Nm excitability - reduced in case of high magnesium value
3. Earliest sign of magnesium toxicity - shock not responding to fluid resuscitation or vasopressors

4. Reflexes - DTR less
5. Urine output reduced
6. Respiratory rate - Reduced

Management

1. Vigorous IV hydration
2. Calcium gluconate
3. Hemodialysis
   - Ultrafiltration

Electrolyte and concentration	Results in	Management
Na^+ < 125 mEq/L	Seizure	Hypertonic saline (3% saline)
Na^+ > 158 mEq/L	Seizure	5 % dextrose
K^+ > 8 mEq/L	Diastolic arrest	Ca gluconate
K^+ < 2.5 mEq/L	Diaphragmatic paralysis	KCl drip
Ca^+ > 13 mg%	Systolic arrest	Ibandronate
Ca^+ < 7 mg%	Laryngospasm	Ca gluconate
Mg^+ > 10 mEq/L	Asystole	Ca gluconate
Mg^+ < 1 mEq/L	V. arrhythmia - TDP	MgSO4

Metabolic acidosis

01:41:52

- **KULT**
- **K - K**etoacidosis
  - Diabetes
  - Starvation
  - Alcoholic
- **U - U**remia
  - AKI/CKD/RAS/ATN
  - ATN - Rhabdomyolysis , Ethylene glycol , Ischemia, post op, Toxin induced
- **L - L**actic acidosis
  - Type A
    - → Shock
    - → CO poisoning
    - → Oxyhemoglobin less: lactic acid ↑
  - Type B
    - → DM
    - → Drugs
      1. Phenformin
      2. Vancomycin
  - Type D
    - → Short Bowel syndrome
    - → Jejunoileal bypass
    - → Carbohydrate fermentation by bacterial flora produces D-lactate
- **T - T**oxins
  - Methyl alcohol
    - → Metabolized by same enzyme that metabolizes ethyl alcohol (Alcohol dehydrogenase)
    - → Metabolizes Methyl alcohol → Formaldehyde → Formic acid
    - → Formic acid has Low pH
    - → Causes BBB damage
      - Encephalopathy
    - → When consumed in small amount of 15-30ml
    - → Also cause damage to retina
    - → Antidote - Fomepizole
      - Inhibit Alcohol dehydrogenase
  - Ethylene glycol - antifreeze agent
    - → Precipitates Calcium oxalate crystals
    - → Cause ATN
    - → Leads to Metabolic acidosis

Treatment

- Fluid of choice – Ringer Lactate
  - Lactate - metabolized by liver to bicarbonate
  - Bicarbonate helps in neutralization of Protons
- If pH < 7.2 in spite of adequate fluid resuscitation, then give Sodium bicarbonate
- Adequate fluid resuscitation:
  - CVP normalizes
  - Pulse - Rate becomes normal
  - BP - Recordable
- Correction for sodium bicarbonate = Weight × 0.5 × (24 - actual value)
  - Half given initially as bolus
  - Other half given as infusion
- Initial correction - 0.5 × weight (15 - actual value)
- Initially corrected to 15 and then to 24

Metabolic alkalosis

01:53:20

- Chronic vomiting
  1. Gastric Outlet obstruction
  2. CHPS - congenital hypertrophic pyloric stenosis
  3. Ca stomach
  4. Healed peptic ulcer disease

Excess vomiting
↓
Loss of water
Loss of hydrochloric acid
↓
Dehydration
↓
Less blood supply to kidney
↓

GFR ↓
↓
RAAS activated
↓
Aldosterone↑
↓
Salt and water reabsorbed
K^+ and H^+ loss
↓
Hypochloremic Hypokalemic Metabolic Alkalosis

- Trigger - dehydration
- Fluid of choice - NS
  - Prevent further potassium loss
  - Contain chloride - so correct hypochloremia
- Saline responsive or chloride responsive metabolic alkalosis
- If pH > 7.55 in spite of saline administration
  - Give Ammonium chloride

DKA

- Acidosis can cause potassium efflux causing hyperkalemia, though Total body potassium is low due to vomiting and poor oral intake
- RL - is a potassium rich solution
- In DKA - RL should not be given - due to risk of hyperkalemia plus cause of Acidosis i.e. Ketone production need to be shut down by giving insulin drip.
- Fluid of choice - normal saline
- Along with Insulin IV
- All other metabolic acidosis - RL is the fluid of choice

Ascitis
↓
Circulating fluid volume↓
↓
GFR ↓
↓
RAAS activated
↓
Aldosterone ↑
↓
ENac - salt and water reabsorbed
↓
Loss of K^+ and H^+
↓
Hypokalemic Metabolic Alkalosis

- Aldosterone antagonist - spironolactone is the treatment
- Saline/chloride non responsive metabolic alkalosis
  1. CHF
  2. Cirrhosis
  3. Nephrotic syndrome
  4. Protein Losing enteropathy
     → Celiac sprue
     → Ulcerative colitis
     → Crohn's disease
     → Menetrier's disease

Metabolic alkalosis	
Saline Responsive	**Saline non-responsive**
GI causes: • Gastric Outlet Obstruction • CHPS - Congenital hypertrophic pyloric stenosis • Ca stomach • Healed peptic ulcer disease	Ascites: • CHF • Cirrhosis • Nephrotic syndrome Aldosterone excess: • Conn's syndrome • Cushing's disease (Cortisol activate Enac) • Bilateral adrenal hyperplasia
Treatment - Normal Saline	Treatment - Spironolactone

Respiratory and Metabolic alkalosis can trigger tetany

- Metabolic alkalosis → Bicarbonate is more
- To neutralize bicarbonate, hydrogen ion is needed
- Hemoglobin act as a buffer
- Vacant sites are created by hydrogen ions on hemoglobin
- These vacant sites will be occupied by calcium i.e Calcium redistribution
- As a result, ionized calcium becomes low
- This results in tetany
- So, Metabolic alkalosis can trigger tetany
- Correction -IV saline

Q. A 3-week-old boy is diagnosed with CHPS and is scheduled for Ramstedt operation. Pre-operative electrolyte report shows S. Ca^{++} 6.0 mg%, What is the next best step in management of this patient?

a. Cancel surgery
b. Administer RL
c. Administer Cal gluconate
d. Administer NS

Answer - d

- If RL is given bicarbonate produced will worsen Metabolic Alkalosis and tetany will worsen.
- Hypocalcemia is due to redistribution → so Calcium gluconate not given

Q. A 20-year-old girl suffers from anxiety neurosis and also has fear of heights. She sets off to travel by airplane. She hyperventilated out of fear developing respiratory alkalosis due to carbon dioxide washout and complains of perioral paresthesia and carpopedal spasm. What is the next step?

Treatment:
Paper bag rebreathing
Exhaled air contain carbon dioxide

Respiratory acidosis 02:15:28

$$CO_2 + H_2O \leftrightharpoons H_2CO_3 \leftrightharpoons H^+ + HCO3^-$$

Causes

CO_2excess

1. Status asthmaticus/impending Resp. arrest in Asthma
2. Flail chest
3. COPD exacerbation
   - Chronic bronchitis
4. Diaphragmatic paralysis
   - Hypokalemia
   - GBS
   - Transverse myelitis
   - Poliomyelitis
   - Botulinism
   - C3, C4, C5 fracture

Respiratory alkalosis 02:17:45

- CO2 wash out
- Hyperventilation:
  1. High altitude pulmonary edema
  2. Pneumonia
  3. Pleural effusion
  4. ILD
  5. Acute asthma
  6. Acute hypoxia

Metabolic acidosis	KULT	RL, soda bicarbonate
Metabolic alkalosis	GOO, ascites, endocrinological	NS, spironolactone
Respiratory acidosis	CO_2 increased	PPV
Respiratory alkalosis Most common -as hyperventilation is a common response of our body	CO_2 wash out	Paper bag rebreathing

Normal parameters of ABG:

- pH 7.35-7.45
- pO_2 :- 60-100 mmHg
- pCO_2 :- 35-45 mmHg
- HCO_3^- :- 22-26 mEq

- Flapping Tremor:
  1. Ammonia intoxication/Liver failure
  2. Uremia
  3. CO2 narcosis
- Fine tremor
  1. Thyrotoxicosis
  2. Anxiety neurosis

50 BARTTER SYNDROME, GITELMAN SYNDROME, LIDDLE SYNDROME & COMPARISON WITH SIADH

Gitelman Syndrome

00:00:12

- Autosomal recessive
- Defect in "Na^+ - Cl^- co-transporter and TRPM6 transporter" in Distal Convoluted Tubule
- Hallmark feature: Salt wasting and Polyuria.

Features

- Failure to thrive
- Dehydration: Sunken Anterior Fontanelle/ dry oral mucosa
- Diaper change frequency increased
- RAAS activation, GFR decreased: Renin increased: Aldosterone increased (2° Aldosteronism)
- Hypokalemic metabolic alkalosis
- Sluggish MORO/Reflex poor cry: manifestation of Hypokalemia
- Mg^{2+} wasting: Release of PTH reduced → hypocalcemia (tetany)

Work Up

00:07:37

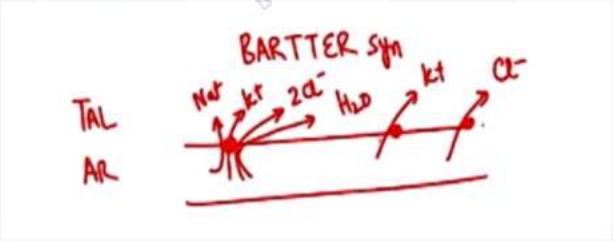
1. Serum Electrolyte: Na^+ reduced, K^+ reduced
2. Urine Osmolality: Low
3. Investigation of choice: 24-hour Urinary Chloride
4. Serum Mg^{2+}: decreased

Treatment

- No definitive treatment

Bartter Syndrome

00:11:02



- Hyper prostaglandin E syndrome
- Autosomal recessive
- Defect in "Na-K-2Cl co-transporter, Cl channel & ROMK" in loop of Henle
- These channels are responsible for voltage gradient which causes Ca++ reabsorption.
- Hence defect in these channels leads to Ca^{2+} wasting
- Cl^- Channels present in inner ear are also defective: SN deafness.
- Antenatal presentation of poly hydramnios

Manifestations

1. Failure of thrive
2. Dehydration: Sunken AF/ delayed skin pinch
3. Increased Aldosterone (2° Aldosteronism) → Hypokalemic alkalosis
   - Chloride non-responsive/ saline nonresponsive metabolic alkalosis
4. K^+ channel defect: Hypokalemia severity higher than Gitelman syndrome
5. Voltage gradient falls → Calcium resorption decreases → Hypercalciuria
   - Hypercalciuria can manifest in 2 ways
     → Kidney stones
     → Renal rickets: Delayed dentition, wide open AF, short stature

Important Information

- Calcium loss in the Bartter syndrome is sufficient to cause stone formation and renal rickets but not severe enough to cause tetany

Work Up

00:19:22

1. Serum electrolyte: Na decreased, K^+ decrease
2. 24-hour Urinary chloride: increased
3. Serum magnesium: Normal (TRPM-6 is still functional in DCT)
4. 24-hour Urinary calcium: increased

Treatment

- Indomethacin:

GITELMAN (DCT #)	BARTTER (TAL #)
• Common features: Failure to thrive, Polyuria, Dehydration, Na↓, K↓ • Common test: 24-hour urine Cl increased • BP can be Normal / decreased but never increased in both	

• TRPM6 # → Mg reduced
• Tetany
• Treatment: no definitive treatment
	• SN deafness
	• Calcium wasting
	  ○ Nephro-calcinosis
	  ○ Renal rickets
	• Treatment: indomethacin

Conditions in which Indomethacin is the DOC

1. Patent Ductus Arteriosus
2. Acute gout
3. Acute migraine
4. Bartter Syndrome

Liddle Syndrome 00:26:33

- Gain of function of epithelial Na channel (ENaC)

Features

1. HTN
2. Hypokalemic alkalosis
3. Low renin HTN (HTN → feedback RAAS →decrease in Renin → decrease in Aldosterone)

- Dehydration is absent

Treatment

- Amiloride (ENaC inhibitor)

Important Information

- Hypokalemic Metabolic alkalosis seen in
  1. BAH/CONN
  2. Cushing syndrome/disease
  3. Chronic vomiting (CHPS/ Healed PUD/ Ca stomach)
  4. Ascites: CHF/ Cirrhosis/Nephrotic syndrome
  5. BARTTER syndrome
  6. Gitelman syndrome
  7. Liddle syndrome
- For Chronic vomiting (CHPS/ Healed PUD/ Ca stomach) Normal saline is used, as all the conditions mentioned are chloride responsive alkalosis
- For other conditions except BARTTER, Gitelman and Liddle syndrome Spironolactone is used
- For BARTTER: Indomethacin
- For Liddle: Amiloride

Diabetes Insipidus 00:33:25

Features

1. Polyuria: Urine output > 3L /day
2. Polydipsia
3. Nocturia

Types

1. Central Diabetes Insipidus

2. Nephrogenic Diabetes insipidus

1. Central Diabetes Insipidus (ADH Decreased)
   - Damage to the Posterior pituitary or the Hypothalamus which can be due to:-
   - Idiopathic
   - Tumor
   - Post cranial surgery
   - Head injury
   - Granulomatous damage to the posterior pituitary
     → Sarcoidosis
     → Histiocytosis-x
   - AV Malformation
   - Sheehan syndrome
2. Nephrogenic Diabetes insipidus
   - Due to V_2 Receptor resistance
   - Cause of NDI
     1. Drugs: Lithium, Amphotericin B
     2. Hypercalcemia
     3. Sickle cell anemia
     4. Amyloidosis

Work up 00:37:31

1. Timed 24hr Urine collection
2. Urine Osmolarity (decreased), Plasma osmolarity (increased), Na concentration (Increased)
3. Plasma ADH level
4. Water deprivation test (Miller-Moses)
5. Healthy: water deprivation: 3% ↓ of weight.
6. Urine.osm>>>> Plasma.osm
7. MRI T1W -

- Normally :- Post.pituitary- Hyperintense signal
- In Central DI - Hyperintense signal ABSENT.

Treatment

- Central Diabetes Insipidus
  - Desmopressin (first line drug)
  - Carbamazepine -promote ADH release
- Nephrogenic diabetes insipidus
  - Thiazides
  - Indomethacin
  - Amiloride

SIADH 00:47:46

Causes

- CNS infection leading to Resetting of Osmostat in the Hypothalamo Pituitary Axis

Reset osmostat:- Threshold for release of ADH is reduced.

1. Cerebral Toxoplasmosis (HIV+)
2. Meningitis
3. Encephalitis
4. Brain abscess
5. Ectopic sources
   - Kulchitsky cell Tumor/ Carcinoid syndrome
   - Oat cell cancer

6. Drugs: Vincristine, Chlorpromazine, Haloperidol, Chlorpropamide
7. Multiple sclerosis

Criteria for diagnosis of SIADH

1. Plasma osmolarity <275 mosm/Kg H_2O
2. Clinical Euvolemia (TBW increased, TBS normal): no edema, no ascites, no orthostatic hypotension
3. Urine Osmolarity increased
4. Urine sodium: >40 mmol/L
5. Normal Thyroid function test, Normal adrenal function test
6. Normal KFT
7. No use of diuretics
8. No hypokalemia

Supportive evidence in diagnosis of SIADH 01:01:52

1. BUN: reduced
2. Uric acid: reduced
3. Investigation of choice: Water loading test

Treatment

1. Primary treatment: Water restriction
2. VAPTANS: V_2 defect
   - Tolvaptan: Also used for Hyponatremia in CHF

Diabetes Insipidus Versus SIADH 01:05:50

	SIADH (gain of H_2O)	DI (loss of H_2O)	Psychogenic polydipsia	Adipsic Hypernat-remia
U. osmolarity	↑	↓	↓	↑
P. osmolarity	↓	↑	↓	↑
Na^+ concentration	↓	↑	↓	↑

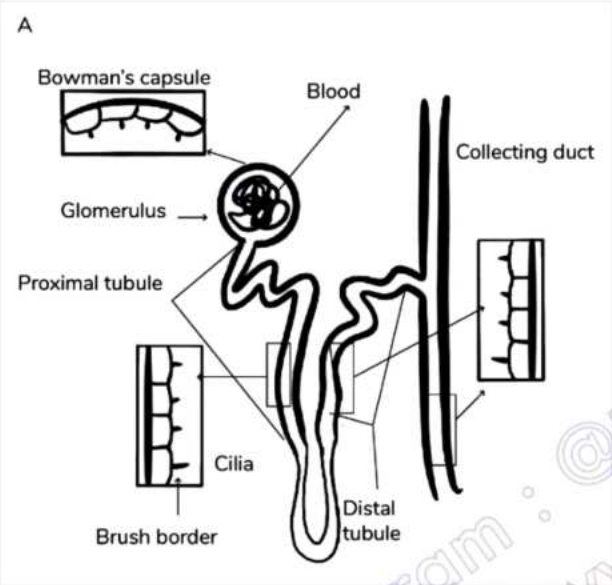
Normal values

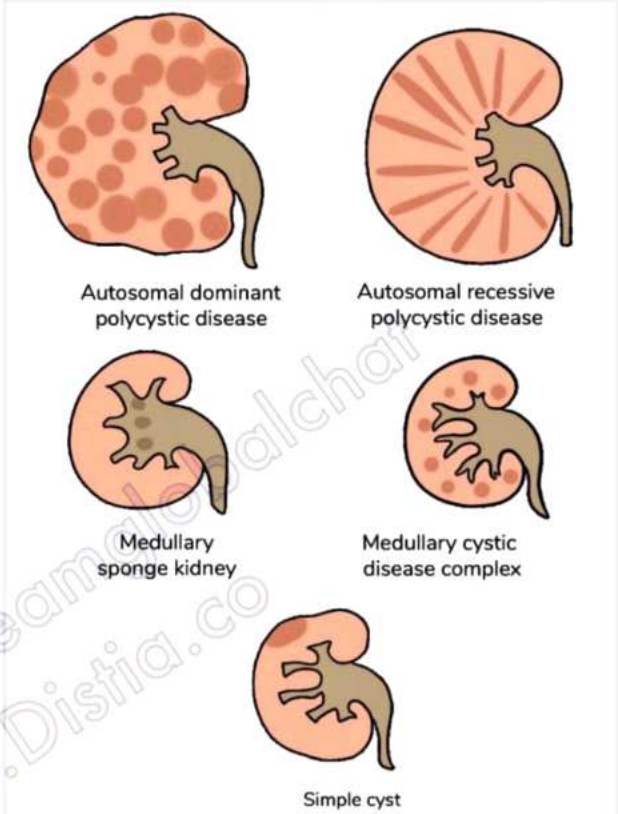
- Plasma osmolarity: 275- 295 mosm
- Urine Osmolarity: 100 – 900 mosm
- SIADH: Urinary sodium increase

51 CILIOPATHIES/CHRONIC TUBULOINTERSTITIAL DISORDERS

Ciliopathies/chronic tubulointerstitial disorders

- The Cillia of the kidney act as sensor between the tubular cells and tubules.
- Amount of electrolytes, solutes, and the amount of water travelling via kidney tubules are sensed by cilia with a basal body.





Important Information

Location of Cilia:

- It is located in the Proximal convoluted tubule, Distal Tubule, and collecting duct. (EXCEPT - loop of henle)
- Motile cilia -present in lungs , Embryonic development.
- Non-motile is present in the collecting duct, and RPE

Topics

1. ADPKD
2. ARPKD in children
3. Medullary sponge kidney
4. Autosomal dominant Tubulointerstitial kidney Disease – ADTKD
5. Medullary Cystic Kidney disease - MCKD
6. Nephronophthisis

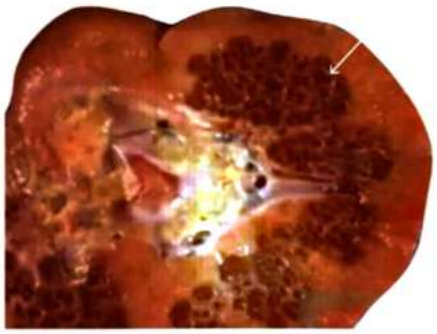
Medullary Sponge Kidney 00:06:00

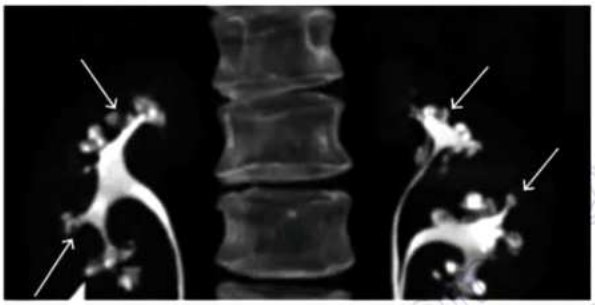
- Spongy appearance restricted to the medulla outer part of the cortex is normal
  - It is a sporadic developmental malformation related to defective cilia
  - Cystic dilatation of the collecting duct– the greater part of kidney is affected
  - Incidental diagnosis – 5th to 6th decade (50-60 years old patient) of life with following complaints:

1. Recurrent stone formation the kidney (calcium oxalate)
2. Pyelonephritis / tenderness at costovertebral junction
3. Recurrent hematuria
4. Polyuria– reabsorption of water is not happening – collecting duct is not able to function properly
5. Peritubular cells are responsible for Erythropoietin production are damaged causing anemia.
6. RTA type 1

- **Work up** - Intravenous pyelography - Paintbrush appearance or bouquet of flowers or Papillary blush
- CT scan- Papillary calcification

- Donot mix with papillary necrosis seen in analgesic nephropathy
  - Must know causes of papillary necrosis are
    - → Diabetes mellitus
    - → Sickle cell anemia
- Lifespan of the patient is normal in M.S.K.





ARPKD 00:11:55

Autosomal recessive polycystic kidney disease

- The gene is PKHD 1, related to chromosome 6
- The protein that is defectively expressed here is **fibrocystin/ polyductin**

- Gross specimen finding :-
  1. Multiple small cysts
  2. Radial appearance
  3. Loss of corticomedullary differentiation

Clinical Features

1. May be diagnosed Incidentally in antenatal **ultrasound at 24 weeks of gestation**
2. Manifestation - ultrasound shows echogenic or enlarged kidney
3. Oligohydramnios
4. Lung development is also reduced, causing pulmonary hypoplasia
   - Resulting in the neonate age group of death.
5. Late presentation at 1-year Renomegaly and Hypertension
   - ESRD and hypertension lead to death (infant or toddler)

Extrarenal Manifestation

ARPKD

- Congenital hepatic periportal fibrosis
- Portal hypertension can result in esophageal varices,
- Biliary dysgenesis
- Caroli cysts

Work-up:

- Ultrasound /CT scan showing echogenic kidneys

TREATMENT

- ACE inhibitors for hypertension
- ESRD- Allogeneic kidney transplant

Important Information

ADPKD extra renal manifestations are

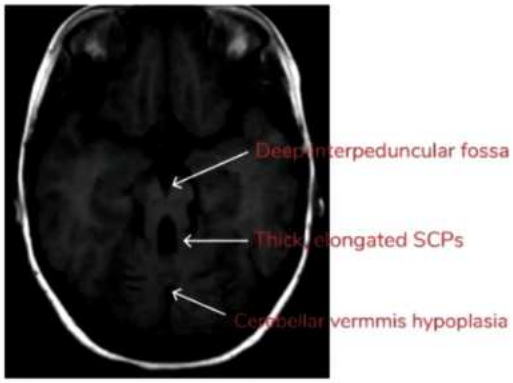
1. Hepatic cyst
2. Pancreatic cyst
3. Splenic cyst
4. Arachnoid cyst
5. M.V.P
6. Berry aneurysm in the brain
7. Colonic diverticulosis

ADTKD 00:20:15

Autosomal dominant Tubulointerstitial disease

- Formerly called medullary cystic kidney disease - MCKD
- Genes involved:
  - MCKD 1- MUCIN 1
  - MCKD 2- UMOD (Uromodulin)
  - Adult presentation
- **Nephronophthisis**- NPHP 1 gene defect on chromosome 2
- NPHP 2 gene defect on chromosome 9
- Total 11 types of Nephronophthisis

Adults	Children
Salt wasting and polyuria	Anemia Failure to thrive Stunting
Hyperuricemia	Joubert syndrome • Agenesis of vermis of cerebellum • Appearance of molar tooth sign • Bat wing appearance in CT head



52 POLYCYSTIC KIDNEY DISEASE

Autosomal dominant polycystic kidney disease

- Kidneys can be grossly enlarged, filling up the abdomen and reaching upto the pelvis.
- Peritoneal dialysis will not be possible.

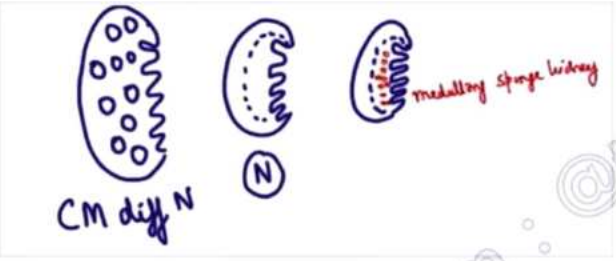
Genetics 00:00:44

PKD -1 GENE encoding for protein POLYCYSTIN-1 related to chromosome 16

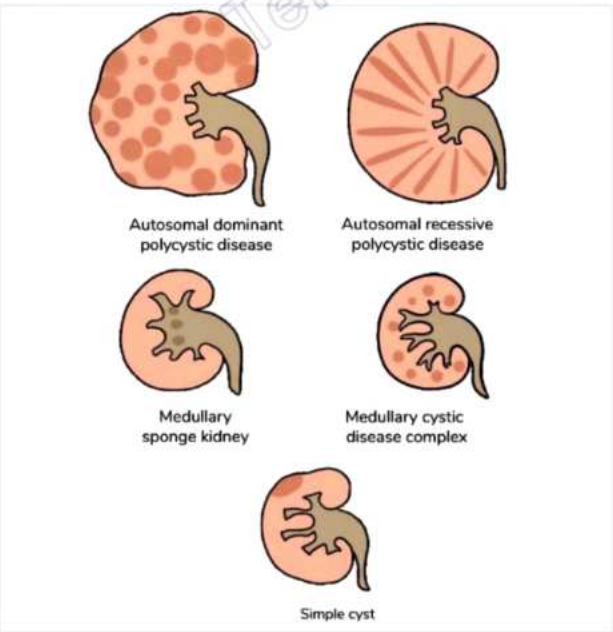
PKD -2 GENE encoding for protein POLYCYSTIN-2 related to chromosome 4

Pathological Specimen Features:

Cortex and medulla studded with large cysts with internal bleeding. Complete loss of corticomedullary differentiation in ADPKD



- Cysts in medulla like holes in a cheese seen in medullary sponge kidney.
- Radial striations in ARPKD
- ADTKD – Cysts at cortico-medullary junction



ADPKD

- High genetic penetrance with variable expression
- The usual age of presentation is 30-45 years

Clinical Features 00:01:29

1. Flank pain is MC symptom
2. UTI: pyelonephritis: Tenderness at the costovertebral junction
3. Stones formation increased in malformed kidney: Urate stones
4. Renal cell cancer: Bilateral, multicentric: More aggressive
5. GFR reduces, increasing renin leads to hypertension

Important Information

- Low renin hypertension
  - Liddle syndrome and conn's syndrome

Extrarenal Manifestations 00:09:44

1. Liver cysts
2. Pancreas cysts
3. Spleen cysts
4. Lungs cysts are unlikely to be seen
5. The Parenchyma of the brain doesn't have cysts
   CNS features are:
   - Arachnoid cysts
   - BERRY aneurysm/ AVM
   - Arterial dolichoectasia– development of stroke
6. CVS Features:
   - MVP- mid-systolic clicks
   - MR– pan systolic murmur
   - TR-pan systolic murmur
7. GI diverticulosis manifestation of constipation

MC cause of death in ADPKD is CV mortality due to hypertension

Work-Up 00:14:10

1. **K.F.T with S. electrolytes**
2. CT abdomen/ MRI-(T2W) Abdomen or Ultrasound. Ultrasound is ideal for screening family members of patients ADPKD.

Question: How many cysts per kidney would be required for diagnosis of ADPKD

≥ to 2 cysts per kidney	30-59 years
≥ 4 cysts per kidney	≥ 60 years

3. Genetic linkage studies- The best investigation to confirm diagnosis

Treatment 00:17:47

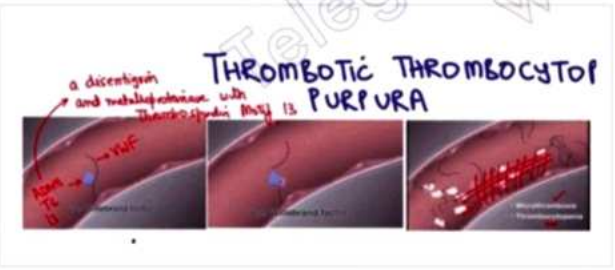
1. ACEI / ARB for Hypertension
2. Hyperkalemia - G4/G5 CKD, Chronic hyperkalemia Patiromer/SPS
3. Target BP in the patient- less than 140/90
   - Note: Target BP less than 130/80 mm Hg in C.K.D caused by Diabetic nephropathy.
4. Lipid soluble antibiotics: Cotrimoxazole/Quinolones
5. Analgesia for flank pain due to bleeding in cysts: Tramadol
6. Transcutaneous electrical nerve pacing helps in overcoming the stimulus of pain reaching the brain
7. Kidney transplant - Allogeneic kidney transplant with Pre-transplant nephrectomy
8. SIROLIMUS: it will modify the disease progression and inhibit Cell proliferation
9. TOLVAPTAN/OCTREOTIDE-slow the decline of GFR

53 THROMBOTIC THROMBOCYTOPENIC PURPURA

TTP - Thrombotic Thrombocytopenic Purpura 00:00:15

- Deficiency of ADAM TS 13 - metalloprotease

- ADAM TS 13 - Destroys Ultra large multimers of von Willebrand factor
- Absence of ADAM TS 13
- Ultra large multimers of Von Willebrand factor not destroyed
- Leads to formation of Multiple microthrombi in Brain and kidney micro vessels.
- Microthrombi in the circulation affect brain perfusion lead to Headache, Ischemic stroke.
- Red blood cells smash into microthrombi and hemolysis ensues
- This is called to MAHA- Microangiopathic Hemolytic Anemia
  - In Autoimmune hemolytic anemia - antibody destroys RBCs
  - In TTP - RBCs smash into microthrombi and gets destroyed
- Peripheral smear
  - Schistocytes /Helmet cells
    → Seen in both HUS and TTP
  - HUS- Child developing renal failure with MAHA
  - TTP - Adults- Pentad discussed subsequently
- Platelets gets consumed during clot formation causing thrombocytopenia and Purpura



- VWF - produced by endothelial cells
- Disintegrated by metalloprotease by ADAM TS 13
- A Disintegrin and metalloprotease with thrombospondin motif 13

Absence of ADAM TS 13
↓
Adhesion to VWF multimers
↓
Microthrombi formation
↓
Platelets gets consumed
↓
Consumptive coagulopathy
Thrombocytopenia

Mesh of microthrombi
↓
RBCs smash into microthrombi
↓
RBCs destroyed
↓
MAHA

Causes 00:06:52

1. **Primary/idiopathic**
   - Antibody - increases clearance of ADAM TS 13
2. **Secondary**
   - **Drugs**
     → Anticancer
     - Mitomycin C
     - Gemcitabine

     → Immunomodulators
     - Cyclosporine
     - IFN - alpha, beta, gamma
     - Sirolimus, Everolimus

     → Clopidogrel

Q. Which antiplatelet drug can cause TTP?
Ans: Clopidogrel
→ Quinine
→ Bevacizumab - anti VEGF used in Diabetic retinopathy

3. **Congenital absence of ADAM TS 13**
   - Upshaw Schulman Disease

→ Routine plasma infusions are the treatment
→ Not plasmapheresis

4. Pancreatitis
5. Malignancy
   - Neutrophils in the inflammatory state produce peptides that Inhibit ADAM TS 13 activity

Clinical features 00:11:32

- **FAT NRI: Mnemonic**
  - HUS no fever

1. **F - Fever**
2. **A - Anemia**
   - MAHA - microangiopathic hemolytic anemia
   - Hyperbilirubinemia due to destruction of RBCs
   - Elevated LDH
   - Increased reticulocyte count
   - Coombs negative hemolytic anemia
3. **T - Thrombocytopenia**
   - Thrombus formation consumes platelets
4. **N - Neurological features**
   - More characteristic in TTP than HUS
   - AIS - acute ischemic stroke
   - Aphasia
   - Hemiplegia
5. **R - Renal failure**

Pentad

- Fever
- Anemia
- Thrombocytopenia
- Neurological features
- Renal failure

Work-up 00:14:53

1. CT HEAD
2. PT ⊘/↑
   aPTT N/↑
3. Peripheral smear - Schistocytes
4. Fibrinogen - Normal in TTP
   - Reduced in DIC - consumptive coagulopathy
   - FDP - increased in both TTP and DIC
   - D- dimer - increased in both TTP and DIC
5. Reticulocyte count Increased
6. Coombs negative Hemolytic Anemia
7. LDH - ↑

- NCCT - AIS - acute ischemic stroke
  - Radiological features depend on the duration of onset of Stroke
  - Hyperdense MCA
  - Loss of gray and white matter differentiation at basal ganglia - MCA territory
  - Hypodensity

Treatment 00:19:00

1. Plasmapheresis - Treatment of choice
   - Help in the clearance of harmful antibodies that lead to clearance of ADAM TS 13
2. UPSHAW SCHULMAN disease- Pooled plasma transfusion
3. Rituximab
4. Caplacizumab
5. Hemodialysis
   - Done in Uremic pericarditis, Metabolic acidosis, and hypertension - not responding to medical treatment.

HUS 00:21:23

Causes of D⁺ HUS

1. Infection - E.coli O157:H7
2. STEC- Shiga toxin producing escherichia coli
3. EHEC - enterohemorrhagic E.Coli

Toxin

- Shiga toxin/Verocytotoxin

Mechanism

1. Complement activation
2. Red blood cells damaged
3. Microthrombi in kidney vessels
4. Neurological manifestations

Clinical features

- Usually in Children

1. Initially presents with GI symptoms
   - Nausea, vomiting, abdominal pain
   - Fever not a feature
   - Approximately 7 days after the initial presentation
2. Child develops pallor and scanty urine output

- MAHA
- AKI
- Antibiotics have to be stopped if started empirically for GI illness.
  - Antibiotics - Increases the chance of mortality

3. CNS manifestations :-

- Seizures +
- Encephalopathy
- Agraphia
  - Donot mix with HSP which has no Thrombocytopenia and is called Non- Thrombocytopenic Purpura
  - Due to IgA
  - Presents with Extensor Purpura

Treatment

1. Pneumococcus can rarely cause HUS
   - Neuraminidase - Activates complement system leading to MAHA with A.K.I.
   - Azithromycin may have to be given
2. Atypical HUS

  - Complement system dysregulation
  - Factor H deficiency
- Plasma exchange - not beneficial in STEC. Give plasma infusion
- Stop antibiotics
- Eculizumab
- Packed RBC
- Hemodialysis for Uremia

HUS	TTP
Child	Adult
H/o GI illness ↓ after 7 days ↓ MAHA AKI Thrombocytopenia	Headache ↓ weeks or months ↓ Stroke MAHA AKI Thrombocytopenia
No fever	Fever +
Incidence of neurological symptoms is low	Striking neurological feature of Stroke
Treatment • Packed RBC • Hemodialysis	• Plasmapheresis

ITP	HSP	TTP	DIC
Autoimmune Antibody → destroys platelets	Ig A → activation of complement system	ADAM TS 13 Absence	Sepsis AML -M3
BT – ↑ PT , aPTT- N	No coagulopathy BT,PT,aPTT - N	BT,PT,aPTT - N/↑ Fibrinogen - normal P.S - Schistocytes	Fibrinogen - ↓ or absent
Steroids Splenectomy No platelet transfusion			
Purpura Epistaxis Petechiae Non palpable purpura	Extensor Purpura	Headache AIS , AKI	Septic shock

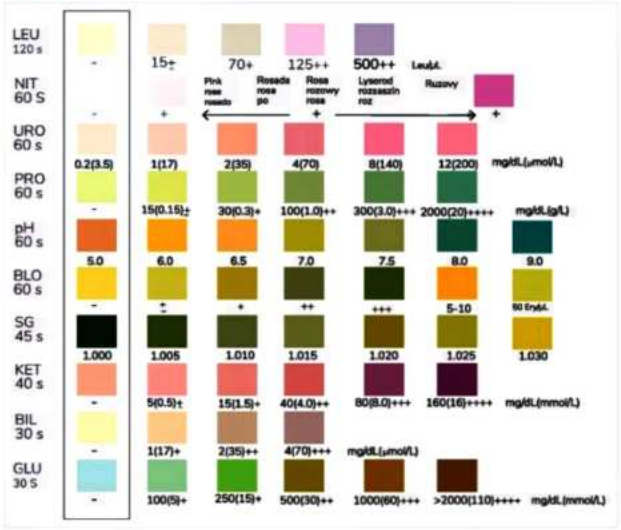
HUS	RVT - Renal Vein Thrombosis
Begin with GI symptoms	Dehydration due to GI illness
AKI USG - Normal echogenic kidneys. Bilateral kidney size is Normal	AKI USG - Unilaterally enlarged kidney
Schistocytes Platelet - ↓	

Both HUS and RVT are seen in pediatric age group.

54 KIDNEY URINE ANALYSIS

Proteinuria

00:00:22



- Dipstick test
  - Very good for negatively charge proteins (Albumin) but not good in picking up positively charged proteins aka Paraproteins
  - In multiple myeloma dipstick test - false negative.
- Proteins in urine
  - Protein present in urine of a normal individual: <150mg/day
    → Protein Glomerulus: Albumin (<30mg/day)
    → Protein Tubules: Tamm Horsfall proteins/ Uromodulin (120mg/day)
- Estimation of Albumin in spot sample
  - Albumin excretion rate = $\frac{\text{Urine albumin}}{\text{urine creatinine}}$
  - Albumin excretion rate can be expressed as
    → Milligram per gram of urinary creatinine (mg/gm of urinary creatinine)

Moderately increased Albuminuria

- Albumin excretion rate (AER) /Urinary albumin creatinine (UAC) ratio if 30-300 mg/gm = Moderately increased albuminuria (earlier known as Microalbuminuria)
- Has an increased risk for Cardiovascular mortality
- Causes for Moderately increased albuminuria
  1. Diabetic nephropathy
  2. Hypertension
  3. Glomerulonephritis

Severely increased Albuminuria

- Albumin excretion rate (AER) /Urinary albumin creatinine (UAC) ratio is 300 mg–3500 mg/gm/g of U.C = Severely increased albuminuria (earlier known as Macroalbuminuria)
- Increased cardiovascular mortality
- Causes :-
  1. Diabetes Mellitus
  2. HTN
  3. Glomerulonephritis
  4. Multiple myeloma/ Para- proteinuria
  5. Congestive Heart Failure
  6. Fever
  7. Exercise
  8. Orthostatic proteinuria

Overload proteinuria

00:11:23

Causes
1. Multiple myeloma / MGUS
2. Rhabdomyolysis
3. Haemoglobinuria

Functional proteinuria

Causes
1. Jogging
2. Exercise

Nephrotic range proteinuria

- Albumin excretion rate (AER) /Urinary albumin creatinine (UAC) ratio is >3500 mg /gm = Nephrotic Range proteinuria
- Causes for Nephrotic range proteinuria
  1. Diabetic Nephropathy
  2. Amyloidosis
  3. Minimal change disease/Lipoid nephrosis
  4. Focal segmental glomerulosclerosis (FSGS)
  5. Membrano-glomerulonephritis (MGN)

Time after micturition
15 minutes

4600 mg/24h
Proteinuria

- Urine sample
  - Foamy urine- Nephrotic range proteinuria
  - Urine turns Yellow on-air exposure (due to urochromes)
- Screening Test for Multiple myeloma: Urine Electrophoresis showing a M-Spike

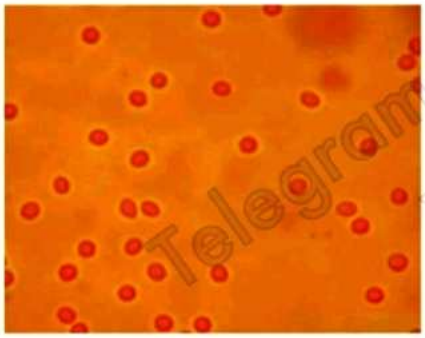
Important Information

1. CSF electrophoresis is done in: Multiple Sclerosis
2. Oligoclonal Ig G bands are present in CSF of patients of multiple sclerosis

Dipstick test	
Trace	15-30 mg/dl
1+	30-100 mg/dl
2+	100-300 mg/dl
3+	300-1000 mg/dl
4+	>1gm

Hematuria

00:20:44



- RBCs are also present in urine of normal person
- Normally <3 RBC/HPF
- Significant / Persistent haematuria
  - >5 RBC/ HPF centrifuged specimen x 3 times; at an interval of 1 week
  - > 100 RBC /HPF in single sample
- Dysmorphic RBCs: Glomerular bleed
- Causes of gross hematuria: Urological (90%) > Renal parenchymal (9%) > Hemolysis (1%)
- Causes of Microscopic hematuria: URTI: IgA nephropathy (IgA↑↑:48hours,Gross hematuria)

- **Causes of red urine**
  1. Clofazimine
  2. Porphyrins

- Red urine tested positive for dipstick test

↓

Centrifuge specimen @ 1500 rpm for 5 min

Supernatant clear	Supernatant red
↓	↓
Hematuria	Myoglobinuria / Hemoglobinuria

Keep for 3 hours

Clearing of test tube	Test tube Still Red
↓	↓
Myoglobinuria	Hemoglobinuria

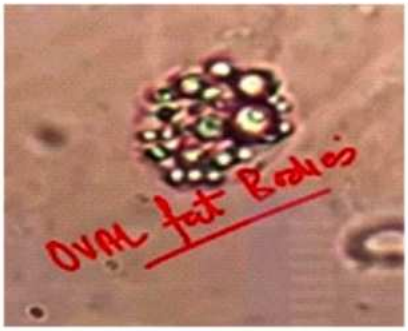
- Hematuria + Pyuria/ Bacteriuria: UTI
- Hematuria + RBC cast / dysmorphic RBC + Proteinuria: Glomerulonephritis
- Schistosomiasis haematobium
  1. Causes hematuria & fever (known as Katayama fever)
  2. Eosinophilia in blood
  3. Its egg has terminal spine

Eosinophiluria

00:34:01

Causes

1. Atheroembolic kidney disease: (Coronary Angiography → Damage to atherosclerotic plaque → Fragments embolize to Renal Artery leading to AKI) Post coronary angiography- KFT ↑↑, Purpura in toes and fingers.
2. Allergic interstitial nephritis (AKI due to antibiotic Intake)



- Stain used to evaluate Eosinophiluria = Wright and Hansel's stain

- Fat in urine / Oval fat bodies found in
  1. Nephrotic syndrome
  2. Fat embolism syndrome
  3. Chyluria
- Maltese cross appearance
  - In Urine
    → Nephrotic syndrome
    → Fabry's disease: α Galactosidase deficiency
  - In Peripheral smear: Babesia microti
  - In CSF: Cryptococcal meningitis

Specific Gravity of Urine

00:44:45

- Normal: 1.020 – 1.030
- U.Osm - 100-900mosm.
- Isosthenuria: Inability to concentrate the urine
  - Causes:
    → Chronic tubulointerstitial disease
    → Sickle cell anemia
- Special Gravity helps in differentiating Pre-renal vs. Renal cause of AKI
- Pre-renal AKI the Specific gravity increased (or normal), while in Renal AKI the specific gravity decreases (Urine cannot be concentrated due to tubular damage).

pH of Urine

- Normal pH of urine: 4.5 -8.0

If pH > 5.5	
PCT	**DCT**
• Damage to PCT causes HCO_3^- loss known as Bicarbonaturia as a result the PH will be increased k/a RTA type 2	• Damage to DCT causes Inability to acidify the urine k/a RTA type1

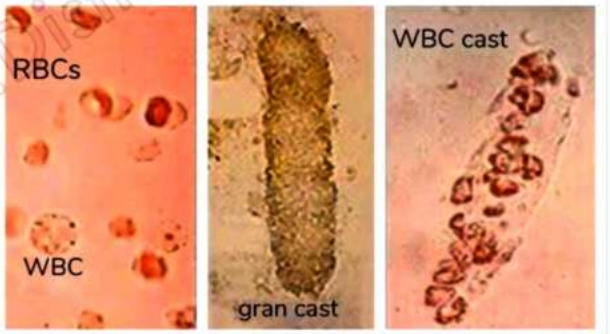
Color of Urine

- Pink urine = Deferoxamine
- Pink diaper sign = Caused by Serratia Mascarens
- Red urine = Clofazimine / Porphyria / Myoglobinuria
- Cola colour = Hematuria
- Black = Haemoglobinuria (PNH/PCH)
- Black on-air exposure = Alkaptonuria
  - Prevention by vitamin C

Casts

00:52:32

- Hyaline casts are seen normally
  - Composed of Tamm Horsfall Protein
- RBC cast
  - Acute glomerulonephritis
- WBC cast
  - Acute pyelonephritis
  - Chronic pyelonephritis
  - Acute interstitial nephritis
- Muddy brown cast
  - Acute tubular necrosis
- Broad cast
  - (D. nephropathy) CKD
- Granular waxy cast
  - Chronic glomerulonephritis



55 ACUTE KIDNEY INJURY

Classification of AKI

00:00:18

- Based on serum creatinine and urine output - acute kidney injury classified into 3 stages
- Normal urine output-1 ml/kg/hour

Stage	Serum creatinine	Urine output	Over a duration of
STAGE I	1.5 - 1.9 times normal	< 0.5 ml/kg/hour	6 hours
STAGE II	2.0 - 2.9 times	< 0.5 ml/kg/hour	12 hours
STAGE III	≥ 3 times Absolute value of S.Creatinine > 4mg%	< 0.3 ml/kg/hour	24 hours

Biomarkers of AKI

- For early identification

In Urine

- NGAL - neutrophil gelatinase associated lipocalin
- K.I.M - 1 - kidney injury molecule - 1
- IL - 18

Etiology of AKI

00:06:06

- **PRE-RENAL - Commonest**
- **RENAL**
- **POST-RENAL**

Pre-Renal AKI

- **Hypovolemia causing underperfusion of kidney**
  - Rice water stool in cholera
  - Congestive heart failure
  - Massive ascites

In alcoholic cirrhosis
↓
Massive ascites
↓
Redistribution of fluid in 3rd space
↓
Reduction in circulating fluid volume
↓
Kidney injury
↓
Hepatorenal syndrome

Hepatorenal syndrome

- Cirrhotic patient - fall in albumin and rise in creatinine
- Kidney failure sets in a cirrhotic patient

1. **HRS 1**
   - develops in 2 weeks
   - S. Cr > 2.5 mg%
   - Even after ensuring normal perfusion and stopping diuretics
2. **HRS 2**
   - In people with refractory ascites

- Afferent arteriole - works by vasodilation- by prostaglandins
- Efferent arteriole - vasoconstriction
- Both works to maintain GFR
- Drugs causing Pre-Renal AKI: NSAIDS, ACEI in bilateral Renal Artery Stenosis

1. In a patient with CHF
↓
Also having OA knee (osteoarthritis)
↓
NSAIDS given
↓
NSAIDS inhibit prostaglandin synthesis
↓
Vasodilation compromised
↓
Afferent arteriole cannot dilate
↓
Reduced blood flow to kidney
↓
Prerenal AKI

2. Bilateral renal artery stenosis
↓
Started on ACE inhibitors
↓
ACEI - blocks angiotensin II
↓
Further reduced perfusion of kidney
↓
Prerenal AKI

Cyclosporine leads to pre renal AKI

Calcineurin inhibitors like Tacrolimus leads to Renal AKI

Renal AKI

Glomerulus	Tubules SIN - mnemonic	Vascular
AGN	**S - SEPSIS** Toxins in sepsis can cause tubular damage • septic shock-pre-renal AKI	**HUS/TTP**
PSGN	**I - ISCHEMIA** • 20% of total cardiac output - kidney • Consumes 10 % of oxygen • Weight of kidney - 0.5 % of body weight • Outer medulla - most vulnerable • S3 PCT	**Malignant hypertension** • Flea bitten kidney • Fibrinoid necrosis
LUPUS	**N - NEPHROTOXINS**	**Renal vein thrombosis**
AGBM - goodpasture syndrome		**Athero-embolic kidney disease** • Eosinophiluria
ANCA		

Eosinophiluria
- **Allergic interstitial nephritis**
- **Athero-embolic kidney disease**

Postoperative renal failure
- **Athero-embolic kidney disease**

When doing coronary angiography
↓
Guidewire Scrapes against Atherosclerotic plaque
↓
Plaque fissure causes Emboli to block small blood vessels
↓
Vascular renal AKI
↓
Cause Ischemic Tubular necrosis
↓
Ischemic renal AKI

- **Prolonged anesthesia**

Prolonged anesthesia
↓
Vasodilation
↓
Reduced perfusion to kidneys
↓
Ischemia of outer medulla
↓
Postoperative renal failure

- **Cardiopulmonary bypass**

In cardiopulmonary bypass
↓
Non pulsatile flow
↓
Blood flow to both cortex and medulla - reduced
Medulla is more prone to develop necrosis

Burns

Aggressive fluid resuscitation
↓
Fluid tends to leak out of blood vessels
↓
Fluid in peritoneal cavity
↓
Abdominal compartment syndrome
Pressure of peritoneal cavity > 20 - 25 cm H_2O
↓
Compress renal vein from outside
↓
Renal AKI

- Burns if not treated→ prerenal AKI due to hypovolemic shock
- But after Aggressive fluid resuscitation in burns risk of developing Renal AKI

Nephrotoxins 00:22:32
- Exogenous causes
- Endogenous causes

Exogenous causes
- Aristolochic acid
  - In Chinese traditional herbal medicine
  - Balkan nephropathy in Europe
- Aminoglycoside toxicity
  - Gentamicin, Amikacin
  - Leads to Non - oliguric AKI
  - Urine output > 400 ml/ day
  - Aminoglycoside → Affects collecting duct
  - V2 Receptors impaired.
  - Reabsorption of water is impaired.
- Amphotericin B
- Cisplatin
- Contrast induced nephropathy
  - Radio contrast given to patient with deranged kidney function.
  - Recovers in 7 days
  - Always check Serum creatinine values when doing coronary angiography/Performing contrast based radiological investigations in patients who are Diabetic or has Kidney disease

Endogenous causes of A.T.N

1. Hemolysis
2. Rhabdomyolysis
3. Multiple myeloma
4. Crystals

Crystals

1. Ethylene glycol poisoning
   - A patient consumed antifreeze agent
   - Ethylene glycol poisoning → precipitates Calcium oxalate crystals
   - Fomepizole - Antidote

Both for methyl alcohol and Ethylene glycol poisoning

2. Tumor lysis syndrome
   - Cancer cell
     → Extensively basophilic nucleus
     → Nucleocytoplasmic ratio is distorted - Anaplasia
     → More bigger nucleus - more amount of DNA
   - DNA breaks down to form uric acid - block tubule
   - When starting cancer patients on chemotherapy - kills cancer cells
   - Leads to Hyperkalemia due to release of potassium from cells
   - Adenosine triphosphate-release phosphate - Hyperphosphatemia
   - Phosphate chelate with calcium → Hypocalcemia
   - Uric acid formed when DNA breaks down
   - Uric acid crystals block kidney tubules causing Acute Tubular Necrosis and renal shutdown
   - So, Adequate hydration has to be ensured before the starting of chemotherapy

- Management
  - Hydration
  - Furosemide
  - Allopurinol
  - Rasburicase - Drug of choice of Tumor lysis syndrome

Vascular causes of renal AKI

Renal vein thrombosis

- Occurs after diarrhea in Children or adults with MGN
- Unilaterally enlarged painful kidney
- **First Investigation** - Doppler. IOC is CT angiography.
- Thrombus can embolize leading to pulmonary embolism

Miscellaneous causes

1. **Crush injury**
   - Myoglobin blocks tubules of kidney
2. **P. falciparum malaria**
   - Extensive hemolysis → black colored urine
   - Blackwater fever - complication of falciparum malaria
   - Hemoglobin blocks tubules of kidney

Important Information

- Berger disease - Microscopic hematuria
- Red urine
  1. Porphyria
  2. Beetroot ingestion
  3. Crush injury
  4. Urological causes.
- Rifampicin - Orange discolouration of urine

Atheroembolic kidney disease

- Patient is undergoing coronary angiography and has Atherosclerosis involving abdominal aorta
- Guidewire scrapes atherosclerotic plaque leading to shower of emboli
- Emboli - Block small blood vessels of kidney

Work Up

1. Eosinophilia
2. S. creatinine - before procedure - normal
3. Post procedure - S. creatinine - doubled or tripled
4. Livedo reticularis - fishnet appearance of skin - emboli can distribute to skin
5. Retinal plaques - hollenhorst plaques

- **Contrast induced nephropathy**
  - S. creatinine before the procedure is also elevated
  - Good prognosis
  - Resolves in 7 days
  - Needs urinary alkalanization with N-acetyl cystiene

HUS/TTP

- E.coli - O157:H7
- Produces Shiga Toxin
- Activate complement system
- Complement Mediated kidney injury
- MAHA -Microangiopathic Hemolytic Anemia
- Coombs negative hemolytic anemia
- Peripheral smear: Helmet cells / schistocytes
- Uremic symptoms
  - Uremic pericarditis
  - Uremic encephalopathy
- In a patient after Diarrhea/Dysentery episode leads to severe hemolysis.
- Don't give antibiotics in HUS
  - Mortality increase by 17 times
- Also called D^- HUS
- Anticancer drugs cause similar presentation: D^- HUS

Postrenal Causes of AKI

1. Bilateral stone in pelviureteric junction
2. Bladder outlet obstruction

- BPH
- Blocked foley's catheter
- Stone
- Tumor

3. Bilateral ureteric fibrosis
   - Scleroderma -Antitopoisomerase antibody positive
   - Bleomycin

Clinical feature of AKI 00:47:55

1. Urea ↑
   - Severe vomiting
   - Hiccoughs
   - Uremic Pericarditis → Chest pain
     → Encephalopathy and Asterixis
2. GFR ↓ → renin ↑ → high blood pressure
   - Hypertensive encephalopathy
   - 220/130 + Papilloedema
3. Volume overload
   - Puffy eyes
   - Pulmonary edema → Dysnea
4. Anuria
   - Urine < 100 ml /day

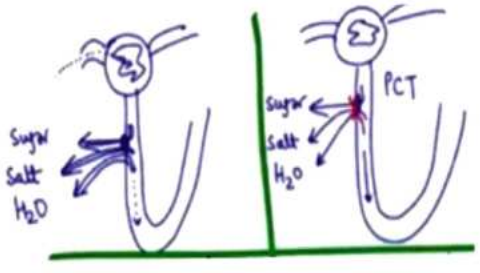
Work-up 00:51:37

1. KFT with electrolytes

- Serum creatinine Rises proportional to degree of injury
- Hyponatremia - Hypervolemic Hyponatremia
- Hyperkalemia
  - ECG - tall tented T waves and ST Elevation

2. USG - to rule out post renal causes
3. ABG - Detect Metabolic Acidosis

- PH < 7.35
- Bicarbonate < 22



To differentiate between prerenal and renal AKI

4. Urinary sodium - FeNa - fractional excretion of sodium
5. Urinary osmolality

Pre-renal AKI	Renal AKI
Example - cholera ↓ Dehydration ↓ Body tries to reabsorb sodium and water so as to compensate for reduced perfusion ↓	Example - Tubular damage ↓ Salt wasting and water loss ↓ Dilute urine ↓
• Urinary sodium - LOW • FeNa - <1% • Urine osmolality >500 mOsmol	• Urinary sodium -High • FeNa >1% • Urine osmolality <300 mOsmol

Treatment of AKI 01:00:29

1 **Maintain fluid balance**
Input = Urine output + Insensible losses
   - If urine loss is 0 in last 24 hours, then input is to replace only insensible losses
   - Insensible losses = 400 -800 ml
     → Water vapor in Breathing
     → Stool

2. **Furosemide**
   - Enhance Glomerular Filtration
3. **Hyponatremia**
   - Hyponatremia (Na+↓ <125meq) cause seizure
   - Corrected with 3 % saline
4. **Management of hyperkalemia**
   - If potassium > 6.5
   - Calcium gluconate- antagonize action of potassium
   - Insulin drip - potassium influx to cells
   - Salbutamol nebulisation - potassium influx

- Hemodialysis - most effective method to treat hyperkalemia
- Most effective drug to treat hyperkalemia - Insulin drip

5. **Metabolic acidosis**
   - Intravenous bicarbonate to stabilize the patient.
6. **Management of Hypertensive crisis /Encephalopathy**
   - IV Labetalol
   - IV Fenoldopam
   - IV Nicardipine
7. UREMIA MANIFESTATION- HEMODIALYSIS
   - Using Central access
     → subclavian double lumen catheter
     → Internal jugular vein

Recovery phase of AKI

- Polyuria
- Hypernatremia
- **Hypokalemia** - Urinary loss of potassium

Indications for dialysis/Renal Replacement Therapy in patients with A.K.I

1. Volume expansion that cannot be managed with diuretics
2. Hyperkalemia refractory to Medical Therapy
3. Correction of severe acidosis refractory to Medical Therapy
4. Severe Azotemia (BUN >100mg)
5. Uremic Pericarditis, Encephalopathy

56 CHRONIC KIDNEY DISEASE

Evaluation of CKD Patient 00:00:17

GFR Calculators:

1. CKD - EPI - Cystatin C Formula
2. Modification of Diet in renal disease formula
3. Cockroft Gault Formula
   - **Formula,** $$\frac{(140 - age) \times weight}{72 \times serum\ creatinine}$$
   - The result should be multiplied with 0.8 in case of a female patient.
4. Creatinine clearance- Dependent on muscle mass and gender of an individual.
5. Inulin clearance

- **Best method to calculate eGFR** - CKD - EPI - Cystatin C method

Cystatin C

- Produced by nucleated cells in the body.
- Achieves steady state and is excreted from the body.
- It is expected to be more accurate than Serum Creatinine.

Definition of CKD 00:07:24

Older definition:

- If a person has GFR < 60 ml/min/1.73m² surface area with proteinuria X 3 months.
  - This identifies the disease when 50% of damage has already occurred.

Current GFR Grading for C.K.D

- **Grade 1:** GFR > or = to 90 ml/ min/1.73m² surface area with proteinuria.
- **Grade 2:** GFR 60 to 89 ml /min/1.73m² surface area with proteinuria.
- **Grade 3:** GFR 30 to 59 ml/ min/1.73m² surface area with proteinuria.
- **Grade 4:** GFR 15 to 29 ml /min/1.73m² surface area with proteinuria.
- **Grade 5:** GFR < 15 ml/min/1.73m² surface area with proteinuria.
  - End stage renal disease, now called Renal failure.
  - URAEMIA occurs.
- GFR can be greater than 125 ml in patients with diabetic nephropathy initially, due to Hyperfiltration.
- Hemodialysis increases cardiovascular mortality.
- Best treatment for CKD - Allogeneic kidney transplantation.
- For evidence of Proteinuria or albuminuria spot samples of urine are collected.

- **Evaluation of albumin in urine:**
  - Urine albumin ÷ urine creatinine.
  - Measured in mg/g.
  - **Normal** - 150 mg/g among which 30mg is urine albumin.
  - **A1** - <30 mg/g.
  - **A2** - 30 to 300 mg/g.
  - **A3** - > 300 mg/g.

CKD grading table

Refer Table 56.1

Problems Associated With CKD

1. Hypertension develops in Grade 2
   - ACE inhibitors should be started.
2. Anemia develops in Grade 3
3. Metabolic acidosis and hyperkalemia develops in Grade 4
4. Careful monitoring is necessary in patients receiving ACE inhibitors with grade 4 CKD, because ACE inhibitors lead to hyperkalemia.
   - If ACEI is stopped Calcium channel blockers are added.
5. Patient requires dialysis or renal transplantation.
6. Uremia develops in Grade 5
7. PTH rises when a patient falls to G3 from G2 and leads to bone resorption.
8. Phosphate levels increase when a patient falls to G4 from G3.
   - Calcification of important blood vessels occurs.
   - Leads to increased cardiovascular morbidity.

Causes of CKD 00:20:42

1. **Diabetic nephropathy** - Most common, cause
2. Chronic Glomerulonephritis
3. Ischemic Nephropathy
4. Autosomal dominant polycystic kidney disease.
5. Chronic tubulointerstitial disorders (CTID) - also referred to as ciliopathies.
   - Tubules are damaged.
   - No reabsorption of water and important components.
   - Leading to renal failure.

Treatment for Grade 1 to 3 CKD 00:23:04

Mnemonic: ABCDEK.

Managing HbA1c

- Keeping HbA1c < 7% and stop metformin in diabetic nephropathy patients with CKD with eGFR < 30ml/min
  - It is excreted through the kidney.
  - Contraindicated in patients with serum creatinine > 1.5mg%.
  - If given, it may lead to Lactic acidosis.

- **Insulin** - excreted through kidneys.
  - Dose of insulin should be reduced.
  - **If not reduced**-won't be excreted through kidneys leading to severe hypoglycemia.
  - Dose reduction:- Only 80% of Total calculated dose should be given.

Managing High BP

- CKD patients have high renin HTN.
- **Targeted BP**-130/80 mmHg or 140/90 mmHg if not tolerated.
- **Drugs:ACEI** / ARBs - do not combine both due to risk of Hyperkalemia.
  - If needed CCB can be added. If BP is still not controlled then add Alpha Blocker.

Managing High Cholesterol

- High cholesterol in CKD patients leads to atherosclerosis.
- **Targeted LDL** - <70 mg%
- **Drugs** - Statins like atorvastatin.

Managing Low Vitamin D3 Levels

- Vitamin D3 levels are low in CKD patients.
- Because active Vitamin D3 is synthesized in the PCT of the kidney.
- **Less vitamin D3** - decreases calcium levels.
  - Activates calcium sensitive receptors.
  - Stimulates PTH, increasing its levels and causes Secondary hyperparathyroidism.
- **Increase in PTH causes**
  - Increased Bone Resorbtion.
  - Patients may present with bone pain.
    → Pathological fracture of ribs.
    → Pathological fracture of vertebra.
  - Subperiosteal resorption of phalanges.
  - Bone marrow fibrosis.
- All these in pathological terms is expressed as:
  - **Osteitis Cystica Fibrosa /Brown Tumor/ Azotemic osteodystrophy**

Treatment

Manage hyperphosphatemia

- Drugs like Sevelamer and Lanthanum carbonate are used.
- Calcium acetate.

Drugs that Inhibit PTH release

- Calcimimetic drugs like cinacalcet are used.
  - Behave like calcium in the body - Act via calcium sensitive receptors.
  - PTH release is reduced.
  - Reduces the Bone turnover.

Low Bone Turnover state in C.K.D

- As more and more calcium and Vitamin D3 supplements are given:
  - Calcium levels increase - PTH decreases.
  - Leads to low bone turnover.

- **Primary Hyperparathyroidism**- Leading cause is parathyroid adenoma.

- **Secondary hyperparathyroidism** - Leading cause is CKD.
  - Low calcium.
  - High phosphate levels.
  - Low Vitamin D3.

- **Tertiary hyperparathyroidism** - Complication of untreated secondary hyperparathyroidism.
  - The gland releases PTH autonomously.
  - Calcium levels rise.
  - Phosphate levels increase.
  - Forms chelate and may lead to atherosclerosis.
- Before giving calcium or vitamin D3 directly to the CKD patients - should be treated with phosphate binders.
  - Sevelamer and lanthanum carbonate.

Management of Erythropoietin Release

- Erythropoietin is synthesized by peritubular cells of kidneys.
- In CKD - Erythropoietin synthesis is less.
- Anemia (normocytic normochromic anemia) - 4 reasons for anemia.
  - CKD - less erythropoietin synthesis.
  - Bone marrow fibrosis.
  - Anemia of chronic disease.
  - Bleeding manifestations.

- **Drugs**
  - **Iron:** Given parenterally.
  - **Erythropoietin:** Given subcutaneous or intravenous.
    → Started once Iron levels are stable.
    → Long acting drugs used:
      - Darbepoetin
      - Epoetin beta
    → **Side effects:** Risk of heart stroke and MI.
    → Should not administer Packed RBCs (PRBCs) - makes patient transfusion dependent.
      - Endogenous erythropoietin production may decrease.

Managing HyperKalemia

- Develops between G3 and G4.
- To treat chronic hyperkalemia-Sodium polystyrene sulfonate (resin).

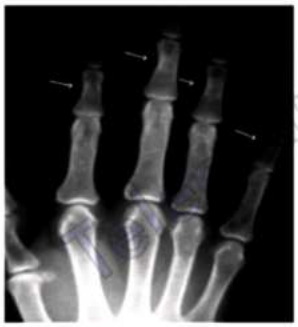
- Administered in the form of enema or tablet.
  - Helps in fecal excretion of potassium
  - The resin may cause necrosis of the gut.
- Alternatives of sodium polystyrene sulfonate:
  - Patiromer
  - Sodium zirconium cyclosilicate - ZS-9.

Summary 00:48:10

Treatment of G1 to G3 CKD

- A (HbA1c) - Low dose insulin.
- B (BP) - ACEI / ARB + CCB if needed.
  - Target BP - <130/80 mmHg
- C (cholesterol) - Statins.
  - Target - < 70 mg%.
- D (vitamin D3) - phosphate levels increase. Managed by:
  - Phosphate binders like sevelamer and lanthanum carbonate.
  - Cinacalcet is also given.
- E (Erythropoietin) - Epoetin beta to manage erythropoietin values.
- K (Hyperkalemia)-Patiromer and sodium polystyrene sulfonate.
- If a patient moves towards G4 and develops Metabolic acidosis - Soda bicarbonate given.

X-Ray



- The x-ray shows subperiosteal resorption of phalanges.
  - Feature of hyperparathyroidism.
  - Mostly the middle phalanx is affected.
- As the condition becomes worsen, TREATMENT:-
  - Renal dialysis
  - Kidney transplantation.
- **In G4 CKD** - Renal replacement is recommended.
  - Life quality of renal replacement is more than dialysis.
  - Cardiovascular mortality is higher in hemodialysis.

Treatment for G4 and G5 Patients

- **Renal replacement** - requires Allogeneic kidney donor.
  - Common infections should be ruled out.
  - Has a higher survival rate than others.
- **Hemodialysis**-Done 3 times a week.
  - Time period - 4 hours for 1 session.
- **Peritoneal dialysis** - mainly for children.
  - Has risk of peritonitis.
  - Hemodialysis is preferred over Peritoneal dialysis.

Allogeneic Kidney Transplantation

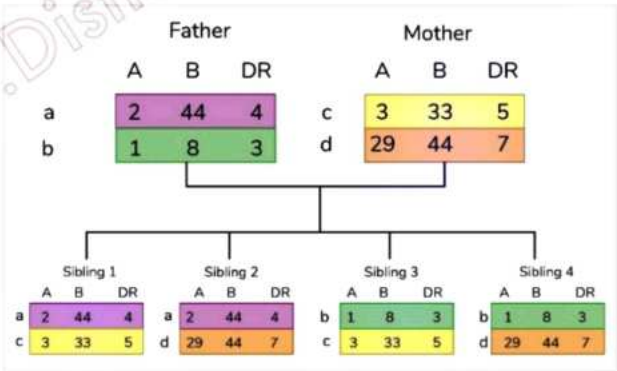
- HLA matching and blood group matching is necessary.

To Remember

HLA matching is not necessary in:

- Liver transplantation
- Cornea transplantation
- Heart transplantation
- Donor should be tested for various infections like:
  - HIV
  - Cytomegalovirus
  - Hepatitis B and C
  - Syphilis
- Doppler should be done in donors - to identify the presence of unilateral renal artery stenosis.
  - If present, no fit for donation
- If the donor kidney matches the requirements - the left kidney from the donor is removed.
- The kidney is then placed in the right iliac fossa extraperitoneally of the recipient.

HLA inheritance 00:53:04



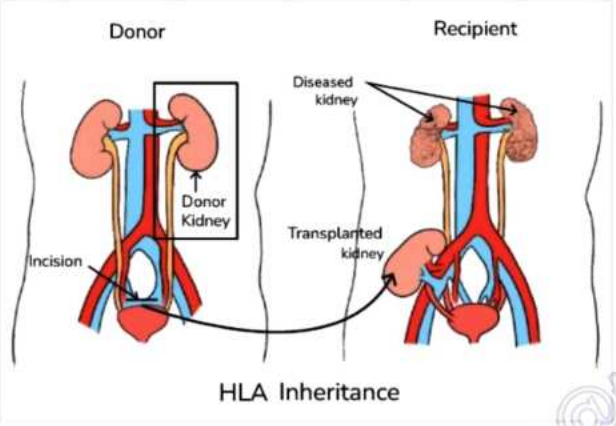
- HLA - A, B, C, DP, DQ, DR.
- In kidney transplantation the matching is done for HLA - A,B and DR.
- For Allogeneic kidney transplantation the matching can be 1 out of 6, 2/6, 3/6 or can be 6/6.
- **Ex:** HLA inheritance of donor and recipient as follows.
  - In the table below only 1 HLA gene is matching for both recipient and donor - 1/6

Donor	Recipient
• A - 2, 1	• A - 2, 3
• B - 44, 8	• B - 8, 44
• DR - 4, 3	• DR - 3, 4

- **Syngeneic transplantation / isograft Transplantation in monozygotic Twins**
- Allogeneic resemblance of HLA inheritance with parents - 3/6.

- The new kidney is placed in right iliac fossa of recipient because:
  - It is easy to remove the kidney if it is rejected by the recipient.
  - The new kidney is supplied by the iliac artery.

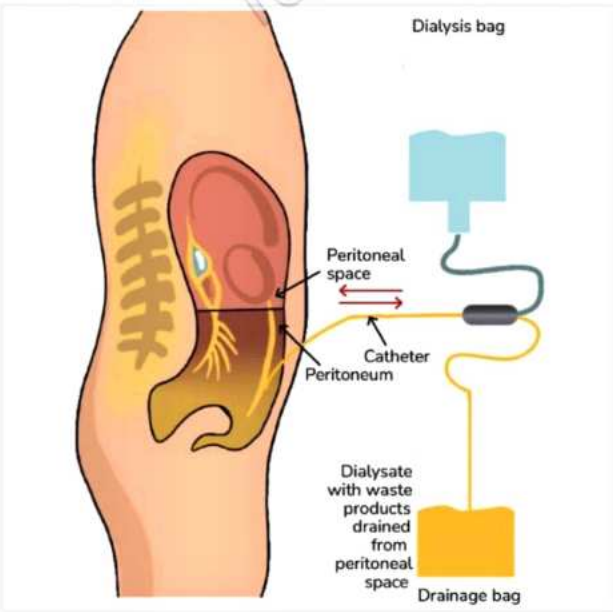
Transplanted kidney



HLA Inheritance

- Before transplantation the functioning of the iliac artery is checked.
  - If any calcification is present-high chances of graft rejection.

Peritoneal dialysis



- Takes longer to complete.
  - Good for children.
  - For adults hemodialysis is more preferred.
- **HLA inheritance**
  - **1/6 or 2/6 -** Induction with ATG (anti thymocyte globulin) should be done.
  - **3/6 -** Anti CD-25 molecule - Basiliximab is used.

Rejection

01:01:29

3 types of rejections are seen

- Hyperacute
- Acute
- Chronic

Rejection	Hypersensitivity Reaction	Occurring Time
Hyperacute	Type 2	Within minutes of transplantation
Acute	Type 4	< 6 months of transplantation
Chronic	Type 4	> 6 months

Prevention of Graft Rejection: HLA Inheritance

- **1 out of 6 or 2/6-**Induction with ATG (anti thymocyte globulin) should be done.
  - Followed by maintenance therapy.
- **3/6 -** Anti CD-25 molecule - Basiliximab is used, followed by maintenance therapy.
- **4/6, 5/6-**no Induction required, directly maintenance therapy.
- **Maintenance Drugs**
  - Steroid
  - Tacrolimus or Cyclosporine
  - Mycophenolate
  - Azathioprine
  - Sirolimus - backup drug

- The patient should be encouraged to wear a mask and stay away from those who are having infections.

Opportunistic Infections in Post kidney Transplantation

01:05:55

- Infection < 1 month of kidney transplantation - may be due to surgical infection.
  - MRSA:SSI.
- **1 to 6 months**
  - Causative organism - P. Jiroveci.
    → Identified with bronchoalveolar lavage.
    → Cotrimoxazole should be used.
  - Causative organism - Cytomegalovirus (CMV)
    → Common cause for graft failure.
  - Others - Hepatitis B and C.

- **>6 months:** Causative organisms are
  - Aspergillus
  - Nocardia
  - BK virus (polyoma virus)

To Remember

- Overall CMV is the main cause for graft rejection.
- After 6 months the virus causing graft rejection is - BK virus (polyoma virus).

Note

- **CMV**-Most common infection for graft rejection in SOT (solid organ transplantation).
- **CMV**-Most common infection for graft rejection in Hematopoietic stem cell transplantation.
- **EBV (Ebstein Barr Virus) -** Most common infection in post transplantation lymphoma.
- Most common Malignancy during post kidney transplantation maintenance therapy - Skin cancer.

Hemodialysis 01:17:35

Radial artery and cephalic vein are selected

↓

A fistula is created between the both-called Cimino Brescia fistula

↓

This is done for arterialization of the vein

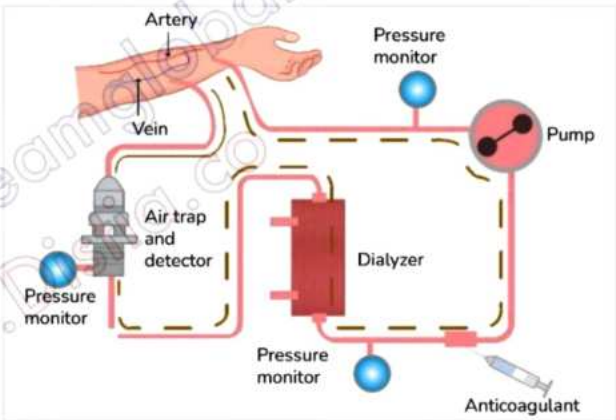
- The fistula is created so that there are less chances of thrombophlebitis and permanent access for cannulation to perform hemodialysis.
- The fistula takes 6 weeks to develop completely.
  - Its patency is checked with Bruit or Doppler - Echocardiography.
  - If the fistula is functioning properly a bruit can be heard.
- If the site gets obliterated a new fistula can be created in the cubital fossa and groin.
- **Complication of hemodialysis**-Hypotension (most common).
- **Complication of recurrent hemodialysis**-Accelerated atherosclerosis.
- Other complications of recurrent hemodialysis:
  - **Dialysis dementia-**due to beta2 microglobulin not excreted through dialysis membrane filters.
    → Deposition of A beta 2 amyloid in the brain.
- A beta amyloid deposition is seen in Alzheimer's disease.
- A beta2 amyloid deposition is seen in Dialysis dementia due to recurrent hemodialysis.
  - Also leads to Carpal tunnel syndrome.
- Dialysis disequilibrium: Aggressive dialysis in first few sessions will cause dramatic change in plasma osmolality.
  - There will be a fluid shift across the brain.
  - Cerebral edema develops and is treated with Mannitol .
  - Can cause seizures in the patient.
- Peripheral neuropathies- Due to loss of vitamins from the dialysis membrane pores.
- Myopathy - As dialysis is a catabolic process.

Principle of Hemodialysis

- **Diffusion:** Movement of molecules from higher concentration to lower concentration.
- Solvent Drag: Water moves and along with-it solutes also moves.
  - Referred to as ultra filtration.

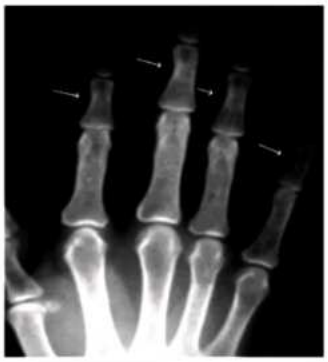
- **Main principle -** Diffusion followed by ultrafiltration.
- The principle depends on the counter current mechanism.
  - The dialysate and blood moves in opposite directions.
  - This is similar to the flow of blood in Vasa recta and ultra filtrate in renal tubules.
- Double lumen catheter is used.

Principle of dialysis 01:21:15



- Risk of cardiovascular diseases like MI, Angina increases.
- Hence transplantation is more preferable.

Important Aspect



- The x-ray shows subperiosteal resorption of phalanges.
- Feature of hyperparathyroidism.
- Mostly the middle phalanx is affected.

Table 56.1

				Albuminuria categories		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300mg/g ≥30 mg/ mmol
GFR stages	G1	Normal or high	≥90			
	G2	Mildly decreased	60-90			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

57 DIABETIC NEPHROPATHY

Diabetic nephropathy 00:00:19

Introduction

- Most common cause of C.K.D (chronic kidney disease)
- Rx- Kidney Transplantation or Haemodialysis X 3times per week.
- Occurrence depends on Duration of disease and Severity of the disease
- Type 1 DM ($HbA_1C > 7\%$) for more than 5years leads to nephropathy
- Type 2 DM more than 20 years leads to nephropathy
- Bilateral enlarged kidneys
- Other conditions where bilateral enlarged kidneys are seen
  1. HIV associated Nephropathy
  2. Amyloidosis
  3. Diabetes Mellitus
  4. Polycystic kidney disease
  5. Hydronephrosis
- Painful unilateral enlarged kidney with Acute kidney Injury: Renal vein Thrombosis

Screening

- Albumin Excretion Rate or Urine Albumin creatinine Ratio
  - In Spot urine sample we check for Urinary Albumin Creatinine Ratio

$$\text{Spot sample} = \frac{\text{Albumin (mg)}}{\text{Urinary Creatinine (gm)}}$$

  - 30-300 mg/gm (moderately increased albuminuria): increase in cardiovascular mortality
  - Serum creatinine may be Normal
    → Rises late (After 60% of kidney damaged)
    → Most specific: Kidney function test
- Low dose ACE inhibitors or ARB can reduce the progression of disease

Histopathological features of Diabetic Nephropathy 00:13:01

1. **Diffused glomerular sclerosis**: Most common histopathological finding seen in a patient of Diabetic nephropathy
2. Nodular glomerulosclerosis: Kimmelstiel Wilson Change
3. **Armani Ebstein change**: Affects PCT
4. Damage to DCT leads to development of Type 4 RTA (Renal tubular acidosis) and resultant Hyperkalemia
   - Thus ENa_c Resistance (Epithelial sodium channel) resulting in Impaired excretion of K^+/H^+

GFR in Diabetic Nephropathy

- Initial 0-5 years, GFR increased: Glomerular hyperfiltration
- 5-10 years basement membrane damage → Albuminuria → Irreversible damage.
- False positive albuminuria:
  1. Hypertension
  2. Congestive Heart Failure
  3. Pyelonephritis
- Co-existing: Complications in DM at onset of Albuminuria
  1. HTN
  2. Non healing ulcer
  3. Peripheral Vaso-occlusive disease

Treatment 00:19:22

- Stop Metformin if GFR <30ml/min /1.73m2
- Glipizide
- Linagliptin

  } Can be given in kidney disease as they are metabolized by liver

- Initiate Insulin: 80% of calculated dose (dose adjustment)

Target BP

- < 130/80 mm of Hg if Tolerated
- ACE Inhibitor / ARB
- Side effect: Hyperkalemia (due to Type IV RTA)
- If K^+ is increasing the stop ACE inhibitors and start CCB
- If Potassium is not rising and BP is not under control the combination of ACE + CCB can be given, if edema present then add thiazide
  - If eGFR <30ml then the diuretic used: Metazolone
- In ESRD patient, K+ is increasing then Alpha blockers are used

Treatment of Hyperkalemia

1. K^+ Binding Resins - Sodium Polystyrene sulfonate
2. Patiromer
3. Sodium Zirconate

Eligibility for kidney Transplant indication in CKD

- eGFR < 20 ml/min/ 1.73 m^2 + proteinuria

Practice question

Q. A chronic renal insufficiency patient present with peripheral edema and reduced urine output. Which of the following drugs will be suited in this patient for management of high renin Hypertension?

A. Aliskiren
B. Chlorthalidone
C. Prazosin
D. Beta blocker

58 KIDNEY STONES

Types of Kidney Stones 00:00:17

Calcium Oxalate Stones

- MC cause is Idiopathic Hypercalciuria.
  - Defective handling of calcium by kidney tubules.
- 24-hour urine calcium : Gross Elevations
- Urine microscopy shows Envelope shaped crystals.
- Most common type of kidney stone.
- **Treatment to prevent Recurrence:**
  1. Thiazides: Reduce calcium excretion in the tubules.
     → Less chances of precipitation.
  2. Normal calcium diet is recommended.
     → Less calcium intake may worsen the condition.
  3. Sodium reduction in diet is recommended.
  4. Furosemide is contraindicated - Increases urinary calcium excretion.

Monohydrate form of calcium crystals - These are dumb bell shaped.

Calcium Phosphate Stones

- Formed due to hyperparathyroidism, R.T.A
- Calcium × Phosphate > 55 - Chelate with each other and form calcium phosphate stones.
- **Urine microscopy shows:** Rosette shaped crystals.

Triple Phosphate Stones

- **Composition** - MgNH4PO4
  - These 3 crystallize to form a stone in alkaline pH.
  - Takes the shape of the kidney.
- These are called Struvite stone or Staghorn Calculus.
- Proteus mirabilis converts urea to ammonia.
  - Alkaline PH of urine crystallizes the 3 components - Mg, NH4, Po4.
- Alkalization of urine results in stone formation.
- **Urine microscopy shows:** Coffin lid appearance of crystals.

Important Information

- Calcium oxalate stones formation is independent of urine pH.

Urate Stones

- Softest kidney stone.
- 24-hour urinary uric acid values are measured.
  - **If over producer** - Allopurinol is given to prevent the formation of stone again.

Cystine Stones

- Hardest kidney stones.
- **Urinary microscopy shows:** hexagonal shaped crystals.
- Commonly seen with Cystinuria.
- In case of cystinosis - inborn error of metabolism.
  - Children die within 1 year.
- Sodium nitroprusside cyanide test is performed on urine sample for cystinuria.

Clinical Features 00:10:34

1. **Flank pain** - radiates to the umbilicus of the patient.
   - Sometimes the fragment of the stones can enter the ureter or junction of ureter entering the bladder.
     → Pain may radiate to genitals.
2. **Vomiting due to Renogastric reflex**
3. Gross hematuria

Investigation 00:12:26

1. Non contrast CT scan abdomen focussing on K.U.B areas.
2. Ultrasound can miss small kidney stone due to Bowel gas.

Treatment of kidney stones 00:13:08

- **If the stone is < 2 cm** - Extracorporeal Shock Wave Lithotripsy (ESWL) can be done.
  - **Contraindicated in:**
    → Bleeding diathesis
    → Pregnancy
- **If the stone is ≥ 2-** Percutaneous Nephrolithotomy can be done.

Preventing Recurrence of the Stones

- **Calcium oxalate stones** - Thiazides are given.
- **Calcium phosphate stones** - Treating the underlying cause.
  - The cause is adenoma of the parathyroid gland.
- **Triple Phosphate stones** - Antibiotics to eradicate proteus mirabilis.
  - Irrigation with Aceto-hydroxamic acid acid at the time of surgery.
  - To prevent the invasion of proteus mirabilis.

- **Urate Crystals**
  - Allopurinol is given to prevent the formation of stone again.
  - In under excretors with chronic gout- Probenecid is given.

- **Cystine Stones** - Tiopronin with urine alkalanization.
  - Previously d-penicillamine was given.

- Tiopronin > d-penicillamine
- **Xanthine Stones -** Tiopronin > d-penicillamine

X-ray KUB

- It is usually not performed.
- Chances of missing out on of radiolucent stones.
  - Urate Stones and xanthine Stones.
  - Mnemonic: LUX.
- Most kidney stones develop due to change in urine pH except the Calcium oxalate stones.

59 RENAL TUBULAR ACIDOSIS

Renal tubular acidosis

- Three types of Renal tubular acidosis – 1, 2, 4
- RTA type 4 is the most common and is associated with Diabetic Nephropathy

Important Information

α intercalated cells in DCT are responsible for hydrogen excretion from the body
β intercalated cells in DCT are responsible for bicarbonate excretion from the body

RTA 1 – Distal Convoluted Tubule 00:00:30

In RTA 1:

- α-intercalated cells are not functioning.
- Impaired hydrogen excretion from the body or inability to acidify urine – metabolic acidosis
- Impaired ammonium chloride excretion as kidney with maintain electroneutrality
- Hypokalemia leading to muscle weakness
- Metabolic acidosis will impair tubular reabsorption of calcium - Nephrocalcinosis – hypercalciuria

Causes

1. Multiple myeloma
   - The Bence Jones proteins cause damage to DCT
2. Scleroderma
3. Amphotericin B
4. Kidney stones

RTA TYPE 2 00:05:10

- Characterised by damage to the proximal tubule
- Reabsorption of bicarbonate will be reduced, serum bicarbonate will be reduced.
- The proximal tubule absorbs water and salt
- Coexist with Fanconi syndrome
- Phosphaturia and aminoaciduria
- Glucosuria
- Bicarbonaturia - metabolic alkalosis (15 -18 mEq - serum bicarbonate)
- Normal serum bicarbonate - 22-26 mEq

Causes

1. Multiple Myeloma.
2. **Wilson disease**
3. Expiry date tetracycline

Treatment

- Soda bicarbonate in all RTA
- Thiazides are used to mitigate the effect of RTA as they cause metabolic alkalosis on prolonged usage.

RTA TYPE 4 00:10:12

Causes

1. Diabetic nephropathy
2. AIDS - HIV nephropathy
3. CTID - chronic tubulointerstitial disease
4. Hypertensive Nephrosclerosis

Aldosterone deficiency/resistance in distal Tubule

The function of Aldosterone:

- Absorbs salt and water
- Excretes potassium and hydrogen
- Resistance to the effect of aldosterone leads to Hyperkalemia
- Metabolic acidosis due to the inability to excrete the hydrogen

Treatment

1. Fludrocortisone
2. Dietary potassium restriction
3. Furosemide - for a short duration to cause kaliuria and stabilize serum potassium
4. Soda bicarbonate

RTA 1	RTA 2	RTA 4
ALPHA - intercalated cells	Proximal convoluted tubule	Deficiency of aldosterone/ resistance to aldosterone - due to diabetic nephropathy Or HIV nephropathy
Calcium reabsorption - nephrocalcinosis, Hypokalemia	Bicarbonaturia Amino aciduria Glucosuria Hypokalemia	Hyperkalaemia Inability to Acidify urine

All varieties of Renal tubular acidosis will have NORMAL ANION GAP

- The anion gap is the difference between positive and negative charges
- In all these diseases, both charges are equally lost.
- Normal anion gap metabolic acidosis

High anion gap metabolic acidosis (**HAGMA**)

- **Mnemonic: KULT**
- **K**etoacidosis
- **U**raemia
- **L**actic Acidosis (drugs/shock)
- **T**oxins (methyl Alcohol poisoning)

Urinary Anion Gap

00:17:37

- Urinary anion gap is positive in renal tubular acidosis
  - In blood, anion gap is *Normal*
  - In urine, anion gap is *Positive*
- Urinary Anion Gap = $(Na^+ + K^+) - (Cl^-)$
- If hydrogen is not excreted via Tubules. Chloride is not excreted to maintain electro neutralisation
- If urine chloride ↓. so, Urinary anion gap rises.

Highlights of Renal Tubular Acidosis

00:18:46

1. NAGMA - Normal Anion Gap Metabolic Acidosis
2. RTA:
   a. RTA 1: Kidney stone
   b. RTA 2: Bicarbotonuria- Low Bicarbonate
   c. RTA 4: Potassium elevated
3. Urinary Anion Gap is positive
4. Soda Bicarbonate

60 NEPHROTIC AND NEPHRITIC SYNDROME

Nephrotic Syndrome 00:00:17

Essentials to diagnose nephrotic syndrome

1. Massive proteinuria more than 3.5 g /day
- Spot sample: urine protein more than 2g of protein/ gram of urinary creatinine
2. Hypoalbuminemia: Serum Albumin less than 2.5 gm%
3. Oncotic pressure decreased: Oedema

Others features of Nephrotic syndrome

4. Increased lipids–Accelerated atherosclerosis
   - Also Seen in
     → SLE
     → APLAS
     → Syndrome X
     → DM
     → Hypothyroidism
5. Lipiduria
   - Also seen in
     → Filariasis syndrome
     → Fat embolism syndrome
- Under microscope: oval fat bodies / maltese cross appearance
6. Hypercoagulable State
   - Urinary loss of protein C/S / Antithrombin III
   - Deficiency of ferritin
   - Ceruloplasmin loss in urine
   - Fibrinogen values are either normal or elevated

Primary Nephrotic Syndrome 00:10:40

- Focal Segmental Glomerulosclerosis (FSGS): M/C in adults
  - Primary FSGS: Idiopathic
  - Secondary FSGS: cause include
    1. HIV associated nephropathy
    2. HBV
    3. Human parvovirus B19 (Slapped cheek appearance, Erythema infectiosum, Aplastic crisis)
    4. Heroine, Pamidronate, Lithium
    5. Reflux Nephropathy
    6. Hypertensive Nephrosclerosis and Alport syndrome
    7. Sickle Cell Anemia
- Membranous Glomerulopathy (most common in > 65 years)
- Minimal Change Disease (most common in children)

2° Nephrotic Syndrome

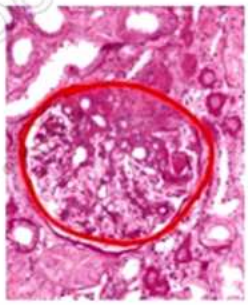
- DM (Most common)
- Amyloidosis
- Lupus nephritis
- Pregnancy Induced HTN

Clinical features

1. Hematuria / cola color urine
2. HTN – Headache
3. Nephrotic range proteinuria: Foamy urine, periorbital edema, Pedal edema, Ascites, Pleural effusion
4. Anasarca
5. Decrease GFR: Uremia 50% next 6-8 years

Work-up

1. Kidney Function Test will be deranged
2. Urine microscopy shows more than 3 RBC / HPF
   - Normal: Centrifuged specimen < 3 RBC / HPF
3. Spot sample more than 2g/gram of urinary creatinine
4. Ultrasound guided Kidney Biopsy:



- On Light Microscopy
  - Segmental obliteration of glomerulus / solidification of glomerular tuft
- On Electron microscopy
  - Podocytes foot process showing effacement of podocytes
  - Podocyte Vacuolization
  - Podocyte Detachment
5. Infection Panel
6. Urine toxicology screen
7. Autoimmune panel SLE → ANA, ds DNA
8. Ultrasound shows bilateral Enlarged Kidney (HIV Associated Nephropathy)

Management

Primary

- HTN – ACEI/ARB
  - Edema → Thiazides, For refractory edema give Metazolone + Furosemide
  - Once EDEMA reduces -Spirinolactone.
  - Proteinuria: Steroids /Cyclosporine
  - Salt restricted diet
- Secondary FSGS: Treat the cause

Membranous Glomerulopathy (MGN) 00:32:10

- Most common in Geriatric population older than 65 years old
- 1°: Antibody against PLA_2 receptor
- 2°: Causes include
  - Infection – Hepatitis B Virus / Hepatitis C Virus
  - Autoimmune disorders like Hashimoto thyroiditis / Grave's
  - Connective tissue disorder: Rheumatoid Arthritis / SLE / Scleroderma
  - Solid organ tumors: Lymphoma, Leukemia
  - Drugs: d-Penicillamine, Captopril, Mercury based compounds

Important Information

- HCV can cause MPGN.
- On kidney biopsy MPGN shows: Tram track appearance.

Clinical Features (65-year-old patient)

1. Puffy eyes
2. Pedal edema
3. Anasarca
4. HTN
5. Foamy urine

Work up

1. Kidney Function Test: creatinine increased
2. Urine microscopy shows oval fat bodies, maltase cross appearance
   - Maltase cross appearance in Peripheral smear: Babesia Microti
   - Maltase cross appearance in CSF: Cryptococcus neoformans
   - Maltase cross appearance in urine under microscope also seen with Fabry's disease
3. Urine protein > 2g/gm of Urinary creatinine
4. Urinary protein electrophoresis reveals albumin
   - If its multiple myeloma, then it shows globulin
5. Anti-PLA_2 Antibody if positive diagnostic of Primary MGN.
6. Kidney Biopsy on Electron Microscopy shows Sub epithelial deposits + spikes (trichrome stain)
7. Serum electrolytes
8. Infection panel, autoimmune panel
9. FDG-PET scan
10. Ceruloplasmin & Ferritin decreased: Nonselective proteinuria

Treatment

- HTN – ACEI / ARB
- Edema: thiazides
- For management of proteinuria: Steroids / Cyclophosphamide (Given alternate month to minimize side effected of both)

Complication of MGN

- Most important complication: Renal vein thrombosis
  - Unilateral enlarged painful kidney with AKI features
- Renal vein thrombosis in pediatric age group: Severe Diarrhea contribute to AKI + Unilateral enlarged painful kidney
- Child with dysentery (E. coli O157:H7) followed by AKI + Schistocytes: Hemolytic Uremic Syndrome

Congenital Nephrotic Syndrome (Finnish variety) 00:53:32

- NPHS1-gene: Nephrin decreased
- NPHS2 gene: Podocin decreased (Poor Prognosis)
- α1 Actinin Gene
- These proteins regulates filtration slit and defect leads to leakage of proteins in urine.

Clinical features

1. Non-immunogenic Hydrops fetalis
2. Anasarca
3. Foamy urine

Work up

1. 24-hour urinary protein Increased, value should be more than 40mg / m2 BSA
2. Spot sample: 2-3 mg albumin/mg of urinary creatinine

Treatment

- Daily IV Albumin Infusion
- Cause of Death – Infection

MCD (Minimal Change Disease) 01:00:16

- Alternate terms: NIL lesion, lipoid nephrosis
- Most common cause of nephrotic syndrome in children.
- Most common cause of MCD is Idiopathic
- Other causes include: NSAIDS usage and Hodgkins's lymphoma
- Steroid responsive nephrotic syndrome.

Clinical features

1. Puffy eyes
   - Vulvar edema / Scrotal edema
   - Pedal edema, with variation of edema
2. Weight gain (+)
3. Pleural effusion Bilateral (Transudative)-dyspnea
4. Ascites-Abdominal distention

Work up MCD

1. KFT: normal
2. BUN / creatinine – (Normal)

3. Urine M/E - Oval fat Bodies
4. 24-hour urine protein increased
5. Urine protein electrophoresis
6. C_3 levels (normal) / decreased
7. Kidney Biopsy
   - Light Microscopy (Normal), IgM deposits
   - Electron Microscopy – Podocyte effacement

Treatment

- **STEROIDS x 8weeks.**
- **Spirinolactone**

Steroids

Remission	Urine albumin nil or trace (or proteinuria <4 mg/m2/h) For 3 consecutive early morning specimens.
Relapse	Urine albumin 3+ or 4+ (or proteinuria > 40 mg/m2/h) For 3 consecutive early morning specimens, after having been in remission previously.
Frequent relapses	Two or more relapses in the initial 6-month period or more than 3 relapses in any 12 months.
Steroid dependence	Two consecutive relapses when on alternate day steroid therapy or within 14 days of its discontinuation.
Steroid resistance	Absence of remission despite therapy with daily Prednisolone at a dose of 2 mg/kg/d for 4 weeks.

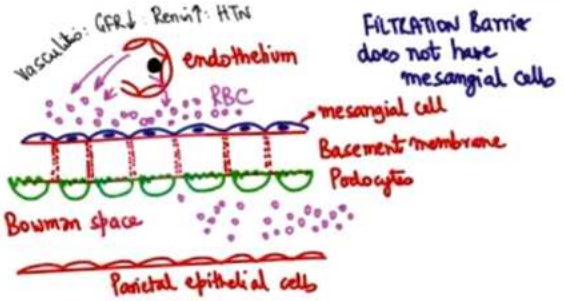
- **For Steroid dependent Nephrotic Syndrome:**
  - Steroid toxicity: cataract, hirsutism, myopathy, weight gain,↑BP.
  - Treatment: taper steroids, cyclophosphamide, levamisole
- **Steroid resistant nephrotic syndrome**
  - Absence of remission, daily
  - In Spite of steroid: 2 mg/kg for 4 weeks
  - Treatment: Tacrolimus/ cyclosporine

Quick Summary of Causes of Nephrotic Syndrome

FSGS(Adult)	Non-selective proteinuria	Foot process detachment/effacement, Hyaline deposits, vacuolization
MGN (Geriatric age)	> 65 yrs	Subepithelial deposits +spike
MCD (Child)	2-8 yrs selective proteinuria	IgM, Foot process effacement
Finnish (neonate)	Neonatal-hydrops fetalis	NPHS 2: Poor prognosis

Nephritic Syndrome

01:20:53



- Vasculitis – GFR Decreased, and Renin increased leading to
  - HTN
  - Hematuria: Cola colour urine.
  - Sub Nephrotic proteinuria (1-3gm/24hr)

Post Streptococcal Glomerulonephritis

- Type III Hypersensitivity reaction
- Immunological manifestation seen with Nephritogenic stain – Streptococcus
- Antigen – Streptococcal Pyrogenic exotoxin B (SPEP)
- Immune complex Activation
- Complement mediated vasculitis
- PSGN- begin as Impetigo or Pharyngitis

Group Aβ hemolytic streptococci

Impetigo	SP-EB	**Pharyngitis**
47 49 50	Strep	1 2 3 4
55 60	Pyrogenic	25
(2 – 6 weeks)	Exotoxin-B	(1 – 3 weeks)
	Immune complex	

1. Hematuria
   - Cola colored urine
   - Smoky urine (Freshly voided sample)

2. HTN – Headache
   - Sudden onset:

- Pulmonary edema: shortness of breath
- Hypertensive Encephalopathy → Loss of consciousness

3. Renal Insufficiency leading to features of Uremia, Oliguria.

Work Up

1. Urine m/e – more than 5 RBC / HPF or Gross Hematuria
   - RBC casts
   - Dysmorphic RBC: Indicate Glomerular bleeding.
2. $C_3 \downarrow CH_{50}$ decreased C_4 (normal)
3. KFT → increased two times
4. Potassium increased
5. Anti DNAse increased, Anti Hyaluronidase Increased, ↑ ASO titer
6. Kidney Biopsy
   - Light Microscopy – Hyper cellular glomerulus, PMN infiltration
   - Electron Microscopy → IgG / IgM / C3 deposits (sub epithelial cell deposits as humps)
7. Immuno florescence study – Starry Sky appearance

Treatment

- Acute Pulmonary Edema – Furosemide
- HTN crisis – IV Labetalol, Sodium Nitroprusside,
- Benzathine penicillin

Berger Disease / IgA Nephropathy 01:40:04

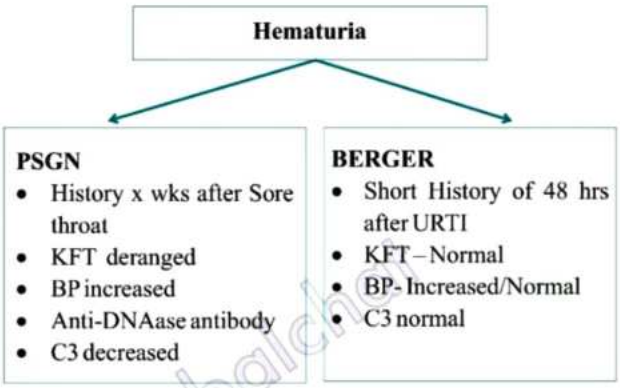
- Most common form of Glomerulonephritis worldwide
- IgA1 contributes to damage of basement membrane
- Mesangial cell proliferation
- Cytokines: Damage to podocytes, tubulointerstitial nephritis.
- In Berger disease IgA increased with diffuse mesangial deposits
  - Capillaries normal
  - GFR, RFT, Urine Output normal
  - BP normal
  - Microscopic Hematuria
- If Patient develops URTI – IgA levels rise significantly over next 48 hrs,
- Microscopic Hematuria is replaced by macroscopic/Gross hematuria.
- Some patients who have asymptomatic microscopic Hematuria and may be picked up on annual clinical medical checkup.
- On examination– BP, KFT, urine output, C3 are normal, no edema is noted

Work up

- Urine m/e ->100 RBC/HPF, microscopic hematuria
- C_3 NORMAL

Treatment

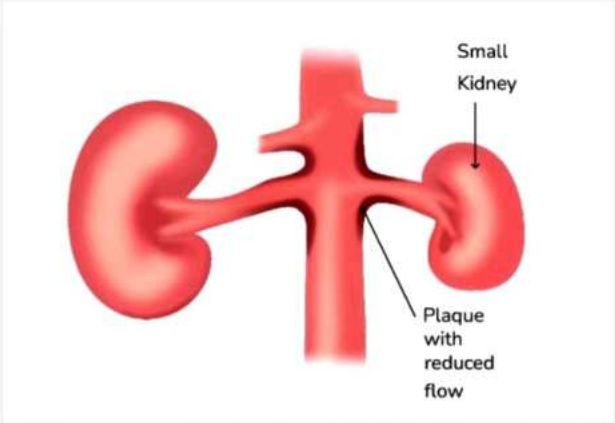
- No definitive treatment
- Steroids: only when patient is recovered from URTI
- ACE inhibitors: May be used (BP might show transient elevation.)
- Fish oil, Tonsillectomy



Q. Which of the following statement is correct about definition of steroid resistant nephrotic syndrome? (FMGE June 2021)

A. Absence of remission x 4 weeks
B. Absence of remission x 6 weeks
C. Absence of remission x 8 weeks
D. Absence of remission x 12 weeks

61 RENAL ARTERY STENOSIS



- Renal artery stenosis also known as Reno Vascular Hypertension
- On Ultrasound: Asymmetric kidneys, affected kidney will be smaller in size and contralateral kidney will be enlarged due to compensatory mechanism.

Etiology 00:00:47

1. Most common cause is Atherosclerosis/ Atherosclerotic renal artery stenosis (Ostial narrowing)
2. Fibromuscular dysplasia (FMD) seen in young females
3. Takayasu arteritis seen in Asian population also known as Pulseless disease
- Polyarteritis Nodosa is not a cause of Renal Artery stenosis

Clinical Features/ old person, smoker 00:04:57

1. Hypertension Persisting with medication
2. ACEI given in undetected Bilateral RAS can lead to AKI
3. Flash pulmonary edema (due to acute Left Ventricular Failure)
4. Presence of Abdominal Bruit (Systole + diastole) (Intensity is directly proportional to severity)
5. Peripheral pulses may be absent or feeble if etiology is Takayasu disease

Work up 00:13:21

1. Ultrasound: Asymmetric kidneys size (size variation >1.5cm)
2. Doppler –Best Screening test, obesity will reduce sensitivity
3. CT Angiography: small risk of Contrast nephropathy
4. Magnetic Resonant Angiography expensive
   - False positive results – due to turbulent flow
   - Gadolinium → cause Nephrogenic systemic fibrosis
5. Investigation of choice: Renal Angiography (Invasive test) (Gold standard)
6. Captopril Renogram: should not be done if serum creatinine is more than 2mg %
7. KFT to assess kidney function over time
8. Urine albumin excretion rate increase

Treatment 00:19:18

- Unilateral Renal Artery Stenosis (RAS): ACEI + CCB + α-Blocker
- For Bilateral RAS
  - ACE Inhibitors: Contraindicated in Bilateral RAS because it causes efferent arteriole dilatation leading to loss of filtration gradient and increasing the risk of acute kidney injury.
- Fibro Muscular Dysplasia: PTRA [Percutaneous Transluminal Renal Angioplasty] + Stenting
- Atherosclerotic renal artery stenosis ARAS: Medical therapy

Malignant Hypertension (arteriolonephrosclerosis)

- Blood Pressure rises with age
  - Disproportional rise of blood pressure causes renal malfunction and then death can occur
  - Mortality rate for 6-12 months is 50%.
- On fundus examination: Retinal hemorrhage can be seen
- Encephalopathy
- KFT deranged
- Microangiopathic hemolytic anemia: Schistocytes present on Peripheral smear
- Postmortem Kidney biopsy shows
  - Fibrinoid necrosis
  - Onion skinning appearance
- More common in Afro-Americans

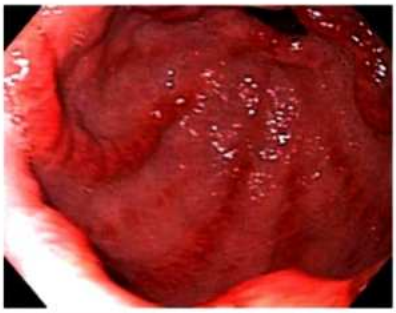
Atheroembolic Kidney Disease 00:28:37

- Post angiography: Sudden derangement of KFT (immediately or 1 to 14 days after the procedure)
- AKI
- Toe gangrene
- Fever, abdominal pain
- Eosinophiluria

Postmortem Kidney Biopsy finding:

- Micro vessel occlusion by cholesterol crystals: Cleft

62 BLEEDING FROM THE GUT



- Ligament of TREITZ [Duodenojejunal flexure]
  - Anatomical landmark to differentiate between Upper Gastrointestinal (GI) & Lower GI Bleeding:

Causes of Upper GI Bleeding / Hematemesis 00:01:05

Peptic ulcer disease

- Leading cause of hematemesis
- It can be either due to duodenal ulcer or gastric ulcer

Duodenal ulcer

- Source of bleeding is Gastroduodenal artery

Gastric ulcer

- Source of bleeding is Left gastric artery
- Most common site for Gastric Ulcer is lesser curvature
- Presentation: In both bleeding DU, GU will lead to crashing blood pressure

Management

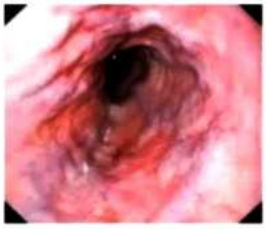
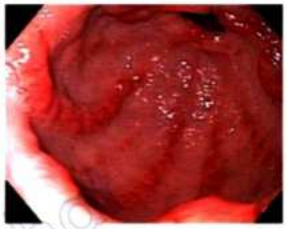
1 Grey IV cannula insertion
2 Fluid bolus
3 Massive transfusion protocol
4 Hemodynamic stability achieved
5 Upper GI Endoscopy + cautery

Drug induced gastritis

- COX-1-inhibitors (like Indomethacin, ketorolac)
- Erosive gastritis
  In contrast, H. Pylori causes Non-erosive gastritis

Portal hypertension

- Presents with Hematemesis with Splenomegaly
- Defined as hepatic venous pressure gradient more than 5mmHg
- Once the pressure is more than 12 mmHg, rupture of esophageal varices occurs
- Source of bleeding: Coronary veins/Esophageal collaterals with gastric veins.
- Leading cause of Portal Hypertension is Alcoholic Cirrhosis
- Liver damage with Negative viral markers, nonalcoholic, non-metabolic cause: Cryptogenic Cirrhosis / Non-Cirrhotic Portal Fibrosis

- Portal Hypertension in pediatric patient with splenomegaly: Extrahepatic portal vein obstruction

Management

- For non-bleeding esophageal varices – Propranolol
- Propranolol uses:
  1. Management of Non-bleeding esophageal varices
  2. Prophylaxis of migraine
  3. Hypertrophic cardiomyopathy
- Bleeding oesophageal varices - Infusion of Octreotide > Terlipressin

Treatment of choice:

- Upper GI Endoscopy + Sclerotherapy

Mallory Weiss syndrome

- Sub mucosal tear
- Alcoholic binge drinking/pregnant lady suffering from hyperemesis gravidarum: RETCHING episodes

Primary site of tear

- Lower esophageal sphincter (starts from cardia goes to lower esophageal sphincter. Non-variceal GI bleeding

Presentation

- Retching + Hematemesis ± Vasovagal Syncope

On examination

- HR increased, BP 100/70 mmHg

Treatment

- Mostly self-limiting condition
- If Bleeding reoccurs – Upper GI Endoscopy + Inj. Adrenaline / Cautery / Endoscopic Clipping

Source of bleeding

- Left gastric artery

Dieulafoy's lesion

- Aberrant sub mucosal artery bleed [Spurting or oozing from pinpoint defect]

G.A.V.E.

- Gastric Antral vascular ectasia (Watermelon stomach) - Least common/rare cause

Watermelon Stomach

Lower Gastrointestinal Bleeding

00:21:05

Hematochezia: It is defined as fresh blood in stool

Piles/ Internal hemorrhoids

- Painless bleed: post defecation
  - "Flash in the pan", and present with anemia

Source of bleed- Superior Rectal Vein

Investigation of choice: Proctoscopy

Two types according to location (clockwise)

- Primary piles: Present on 3, 7, 11 O'clock position
- Secondary piles: positions other than primary piles.

Grading of piles: According to severity

- Grade I – Visible on proctoscopy
- Grade II – Veins prolapse out, spontaneous reduction
- Grade III - Veins prolapse out, digital repositioning successful
- Grade IV - Veins prolapse out, digital repositioning fails

Treatment:

- Grade III & IV – Hemorrhoidectomy
- Grade II – Banding, Cryosurgery

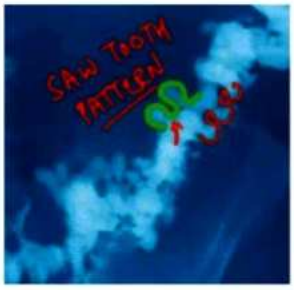
Diverticular Bleeding

- Diverticulosis is common in western population in sigmoid colon.

  ↓

  MC lower GI bleed causing hospitalization is diverticular bleeding.
- Presentation:
  - Geriatric patient with history of constipation presents with life threatening- Hematochezia

- Investigation of choice diverticulitis: CT abdomen
- Investigation of choice for Diverticulosis: Barium enema showing saw tooth pattern.



- Diverticular bleeding can be confirmed and treated with colonoscopy and electrocautery

Extra Mile

- SAW Tooth Ba enema: Diverticulosis
- SAW Tooth on ECG: Atrial flutter
- SAW Tooth EEG: REM phase of sleep
- SAW Tooth CT Abdomen: Diverticulitis

Inflammatory bowel disease

- It can manifest as Crohn's disease or Ulcerative colitis
- Crohn's disease is more common in European and American population
  - It presents with colicky abdominal pain
  - Ulcerative colitis: Severe bloody diarrhea 10-15 times/ day
  - Pallor develops, Albumin decrease protein losing enteropathy - Puffy eyes / Pedal edema
- IBD is not an autoimmune disease but still some antibodies are associated with IBD
- Antibody Crohn's disease: A.S.C.A (Anti saccharomyces cerevisiae antibody)
- Antibody for Ulcerative Colitis: p-ANCA

Malignancy colon

- Carcinoma caecum: Bleeding present
- Carcinoma rectum: Obstructive symptoms predominate
  - Presented as 65 years: progressive constipation, Progressive constipation, Tenesmus, weight loss
  - 33% of patients at diagnosis present with liver metastasis
  - Staging → Duke staging
  - Investigation: Proctoscopy + biopsy

Note:

- Duke staging = CA. RECTUM
- DUKE CRITERIA = IE (Infective Endocarditis)
- DUKE SCORE = Severity of chronic stable angina

Treatment

- Injection of Intra-Arterial [hepatic artery] – 5-FU for hepatic metastasis

Angiodysplasia of colon (Vascular malformation of colon):

Case scenario:

- 50 years male presents with multiple episodes of hematochezia. Colonoscopy was done in 2022 and 2023 with normal report. It is possible that patient is having a vascular lesion that may not bleed on the day colonoscopy was done
- Investigation of choice: CT - Angiography to identify this vascular lesion

Melena 00:47:00

- 60-80 ml blood, remain for 12-16 hours in the gut to result in Black tarry stool.

Cause

1. P. U.D (Peptic ulcer disease)
2. Erosive gastritis - Drug induced (COX 1 inhibitors)
3. Esophageal varices
4. Mallory Weiss
5. Dieulafoy's Lesion

Investigation of choice

- Upper GI Endoscopy
- In case patient presents with acute lower GI bleed with melena upper GI endoscopy should be done.

Hemobilia-(Upper GI Bleeding) 00:49:43

- Trauma (Iatrogenic) - Lap cholecystectomy [Most Common]
- Instrumentation: (like ERCP)
- Cholangiocarcinoma
- Klatskin tumor (also a type of cholangiocarcinoma)
- Parasites

Investigation of choice

- Angiography

Treatment

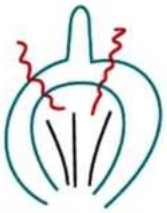
- Gel embolization of bleeder

Summary

- Hematemesis + BP ↓ → 1st step → Fluid resuscitation
- Hematemesis, Melena → Peptic ulcer Disease
- Hematemesis + Splenomegaly → Portal hypertension
- Alcoholic binge / Hyperemesis gravidarum + vomiting → Mallory Weiss syndrome
- Hematochezia → Diverticulitis

Causes of Hematochezia in Pediatric

- **Rectal polyp**
- Meckel's diverticulum (follow rule of 2)
  - Remnant of vitello intestinal duct and occurs on anti – Mesenteric Border.
  - **Rule of 2:**
    → 2% population
    → 2 inches size
    → 2 feet from ileocaecal junction



    → 2 mucosa seen: Stomach/pancreatic
  - Asymptomatic: > 98%, Maroon color stool

Investigation of Choice: Tc99 pertechnetate scan

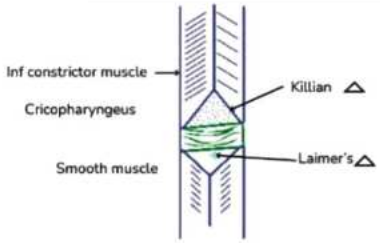
Treatment

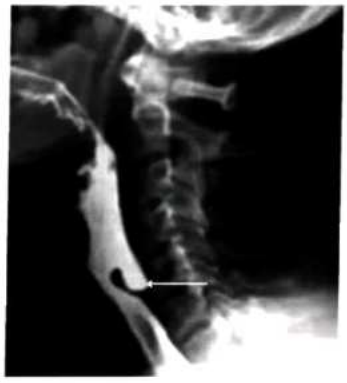
- Resection and end to end anastomosis
- **Intussusception: Infant with Hematochezia**
  - Enlargement of Peyer's patches
  - Red currant jelly stools

Neonate with Hematochezia

- Case Scenario
  - Home delivery of baby, mother expired
  - Feeding with cow's milk → blood in the stool
  - Diagnosis – NECROTIZING ENTEROCOLITIS
  - Staging used – BELL staging
  - **X-Ray Abdo: Pneumatosis Intestinalis:** Air inside the intestinal walls

Esophageal Disorders 01:05:11





Zenker diverticulum: (Location: Killian Triangle > Laimers triangle)

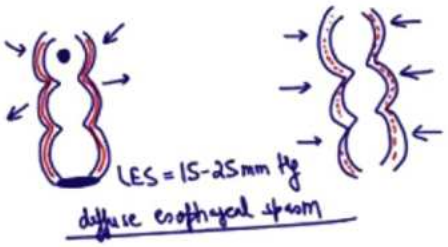
1. Geriatric patient, Non- progressive dysphagia
2. Halitosis
3. Regurgitation of yesterday food items
4. Most common site: Killian triangle

Investigation of choice: Barium swallow

Treatment

- Surgical resection

Diffuse Esophageal Spasm 01:11:25



- Also known as esophageal angina
- Average tone of LES - 25 mmHg
- Most common cause: Idiopathic

Clinical Features

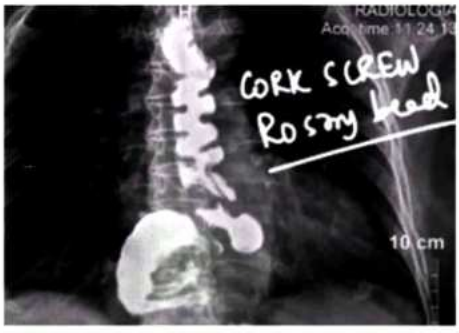
1. Intermittent Chest pain at rest, rule out CAD: TMT/Stress ECHO/ECG
2. Dysphagia

Investigation of choice: Esophageal manometry

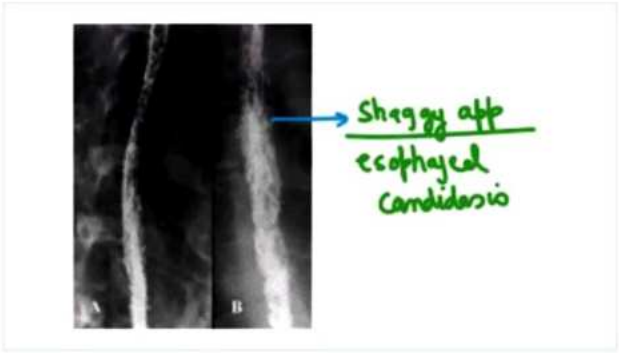
- Diffuse esophageal spasm: Luminal pressure ≥ 120 mmHg for > 3sec

Nutcracker esophagus: If pressure > 180mmHg > 6.5 sec

Barium swallow: Corkscrew appearance or Rosary bead appearance



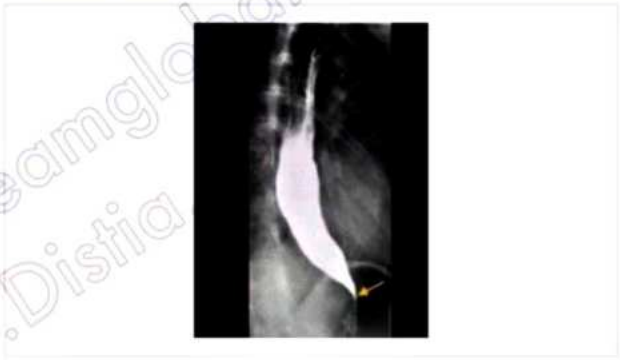
Ba swallow → irregular shaggy appearance → [esophageal candida infections]



Treatment

- Anxiolytics (Buspirone)
- Nitrates: Isosorbide mononitrate (long acting)
- Calcium channel blocker: Amlodipine

Achalasia Cardia 01:22:00



Causes

- Autoimmunity (most common)
  - Oat cell Carcinoma lung (Anti-Hu antibody)
  - Cause: SIDAH, Cushing syndrome, Lambert eaton syndrome
- Chagas disease: Trypanosoma cruzi

Pathophysiology

- Aperistalsis and increased Tone of LES due to loss of inhibitory control.

Clinical features

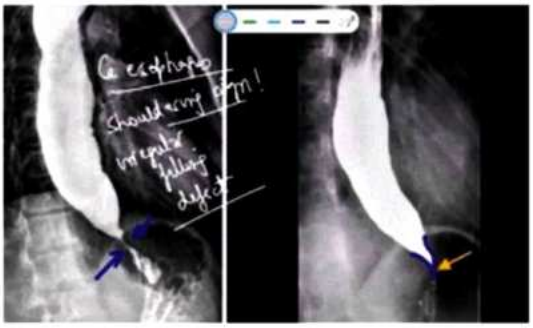
1. Young Female: progressive dysphagia
2. Halitosis
3. Liquids > solid (Dysphagia)
4. Regurgitation of previous day food items
5. Recurrent pneumonia episodes

Investigation of choice

- Esophageal manometry: (LES tone increase)
- Barium swallow: Bird beak appearance/pencil tip appearance
- Barium enema: Bird beak → Sigmoid volvulus

Treatment

1. Laparoscopic Heller's myotomy + Partial fundoplication
2. Botulinum toxin
3. CCB



Note

- Carcinoma Esophagus
- Shouldering sign – irregular filling defect – Rat tail appearance

Case scenario

- 25yr old female presents with progressive dysphagia (oropharyngeal dysphagia) but LES tone: decreased, leather like skin, Raynaud's phenomenon, HTN crisis
- Then Diagnosis is Scleroderma and not Achalasia cardia where LES tone is increased

Investigation of choice

- Anti-Topoisomerase Ab

Refer Table 62.1

Case Scenario 01:39:00

- 30 years alcoholic, binge drinking, recurrent vomiting, retching: chest pain, syncope
- On examination:
  - Subcutaneous Emphysema
  - Crepitus: below skin
  - HR= 120/min
  - BR = 90/60 mmHg
- Mackler's triad = Chest pain + Vomiting + SC emphysema

Diagnosis

Boerhaave syndrome

- Esophageal Rupture: Lower 1/3 of esophagus is involved (posteriorly)
- Chemical mediastinitis leads to chest pain
- If occurs during instrumentation of Esophagus: Cervical Esophagu is the site of rupture.

Investigation

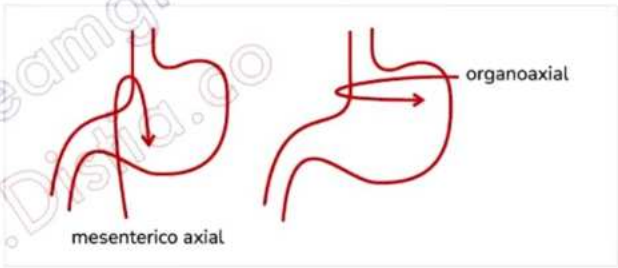
- Chest X-Ray: Continuous diaphragm sign may be seen.
- **IOC** - CT chest + Oral contrast (Gastrografin contrast)

Treatment

- Surgical repair

Case Scenario 01:45:17

- 30 years old lady, alcoholic presents with epigastric pain, nausea, no vomit but willing to vomiting. Doctor notices failure to pass NG tube Probable diagnosis?
- **Stomach Volvulus**



Borchardt Triad

- Epigastric pain, Nausea minus vomiting, Failure to pass NG tube

Investigation

1. Chest X-Ray
2. Investigation of choice: CT abdomen with oral contrast, Barium contrast

- NG Tube should be put in conscious patient in sitting position with neck partially flexed to protect the airway

Treatment

- Surgical exploration

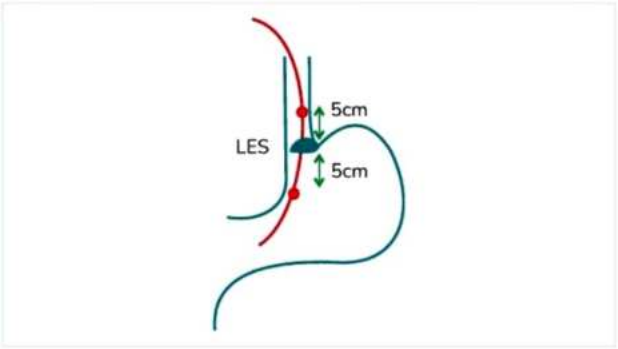
GERD/ Non-Ulcer Dyspepsia (NUD) 01:52:58

Clinical features

1. Chest pain/heartburn/LES tone decrease/retrosternal pain
2. Sour brash
3. Dental enamel damage
4. Nocturnal cough (Chemical tracheitis) - seen in asthma/ post nasal drip/GERD
5. Sore throat (multiple episodes) – Chemical laryngitis

Investigation of choice

- 24-hour pH monitoring Esophageal pH: < 4.0 for > 4 hrs/day



Treatment

- Drug of choice is PPI + Prokinetic agents (like Mosapride / Itopride) improve symptoms faster.

Note:

- Curling ulcer of burns: More common in the Duodenum
- Cushing ulcers of raised ICP: More common in the Stomach
- Cameron ulcer: Seen due to hiatus hernia

Barrett Esophagus

- Histopathology: GOBLET cells in Esophagus
- Metaplasia: Squamous to columnar
- Carcinoma in situ

Investigation

- Upper GI Endoscopy and Punch biopsy (Goblet cells)

Treatment

- Esophageal resection + Stomach mobilization

Extra Mile:

- Most common type of metaplasia
  - Columnar to squamous seen with smoking

Table 62.1

DYSPHAGIA	
OROPHARYNGEAL	**ESOPHAGEAL**
• Structural defect o Zenker's diverticulum o Neoplasm o Plummer Vinson syndrome → Esophageal web: Post cricoid dysphagia → IDA → Koilonychia • Neurogenic defects o CVA (Cerebral vascular accident) • Myogenic defects o Myasthenia gravis	• SCHATZKI RING o Lower 1/3rd o Not premalignant o Meat impaction o Aphagia

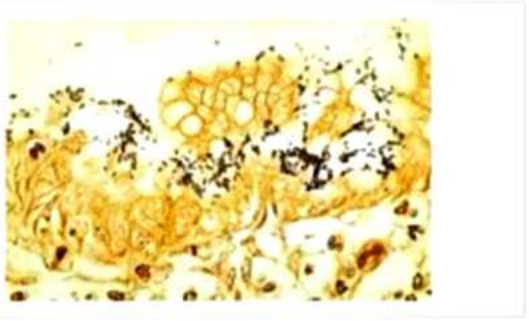
63 PEPTIC ULCER DISEASE

Type B Gastritis

00:01:00

Warthin Starry Stain

- In the following picture black dots represent presence of Helicobacter Pylori



Helicobacter pylori

- Leading cause of PUD: Type B gastritis
- Gram negative coccobacilli
- Non-Sporing: Eradication possible
- Route of spread: Feco-oral route
- Extra Cellular Bacteria / Microaerophilic
- Mechanism of action:

00:02:37

Urea —urease→ Ammonia (Alkaline)

↓

Irritation of G cells & parietal cell ⊕

↓

Excessive acid production (Hyperchlorhydria)

↓

Ulcer

Duodenal ulcer>Gastric ulcer

Work Up

00:05:09

1. Screening test → Breath urea test (Non-invasive)
   - Also best test to determine the eradication of H. pylori.
2. Urease test (Invasive) (CLO TEST- commercial name) → stomach scraping during endoscopy
3. Biopsy: Warthin starry stain

Treatment

- Antibiotics

00:07:02

  - Triple Therapy x 2 weeks
    1. Pantoprazole (PPI)
    2. Clarithromycin
    3. Amoxicillin/clavulanic acid
  - Quadruple therapy
    1. Bismuth
    2. Tetracycline
    3. Metronidazole
    4. Pantoprazole (PPI)
  - Erythromycin not used for treatment
  - Bismuth acts by reducing acid-mucosa contact time

Type A Gastritis

00:09:44

- Autoimmune disorder, premalignant condition
- Anti- IF cell antibodies, Anti-parietal cell antibodies
- Achlorhydria leads to Gastric ulcer
- Intrinsic factor deficiency, B_{12} deficiency: Pernicious anemia
- Hypergastrinemia, Achlorhydria

00:11:49

	Gastric ulcer	Duodenal ulcer
Blood group	A	O
Site	Type 1: lesser curvature (MC site)	D_1: Duodenal Cap/First part of duodenum
Pain	Epigastric pain (Immediately after food Intake) weight loss	Epigastric pain "hunger pain" Snacking by patient leads to weight gain

Important Information

- H. Pylori is an Extracellular bacterium while Tropheryma whippelii leading to Whipple's disease is intracellular bacteria found inside macrophages of gut.

Workup of P.U.D

1. Investigation of choice: Upper GI endoscopy (UGIE) + Biopsy
2. Urease test

Treatment of peptic ulcer disease

- PPI x 6 weeks

Important Information

Refractory PUD may be due to Zollinger-Ellison Syndrome

Complications of Gastric and Duodenal ulcer 00:17:21

Gastric ulcer

- Source of bleeding: Left gastric Artery
- Management:
  - Make hemodynamically stable with IV fluids
  - Upper GI Endoscopy +Cautery
- Perforation: Fluid leaks out, enter via Foramen of Winslow-Lesser sac peritonitis
- Gastric outlet obstruction (GOO): Tea pot stomach

In duodenal ulcer

- Perforation (More common): Anterior > Posterior
- Most common cause of peritonitis is DU.
- X-Ray Abdomen: Moustache sign: Gas under diaphragm
- Bleeding: Posterior > Anterior Source - Gastroduodenal artery
- Management:
  - UGiE with Adrenaline at base of ulcer and Electro-cautery

Refer Table 63.1

Sigmoid Volvulus

- Case: 60-year-old presents with left iliac fossa pain and Obstipation (Can't even pass flatus)
- X- Ray abdomen: Coffee bean sign
- Barium enema: Bird beak appearance
- Anticlockwise rotation.

Treatment

1. Intravenous Fluids
2. Flatus tube
3. Colonoscopic detorsion

Pre-Malignant Conditions of Gut 00:30:00

Oral cavity

1. Oral submucosal fibrosis: Betel Nut/Gutka
2. Leukoplakia: More common
3. Erythroplakia: More malignant
4. Syphilitic glossitis

Esophagus

1. Tylosis palmaris: Hyperkeratosis in palms and soles
2. Achalasia cardia
3. Barrett's esophagus
4. Plummer Vinson syndrome: Esophageal web (Post cricoid dysphagia) + IDA (Iron deficiency anemia) + Koilonychia (Spoon shape defect on nails)

Stomach

1. Gastric ulcer
2. Type A Gastritis
3. Menetrier's disease
   - Proliferation of foveolar cells and decrease of parietal cells: Achlorhydria/Gastric ulcer
   - UGiE shows cerebriform appearance of stomach mucosa

Treatment: Cetuximab

Small Intestine

- Crohn's disease
- Cronkhite Canada Syndrome: Polyps in duodenum
  - Sporadic hamartomatous polyps

Large Intestine

- Inflammatory bowel disease
- Familial adenomatous polyposis (FAP)
  - APC gene
  - Chromosome 5 defect
  - >100 polyps / colon
  - Primary colectomy (Prophylactic)

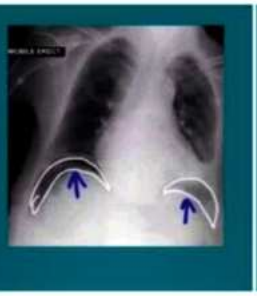
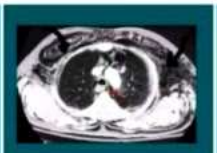
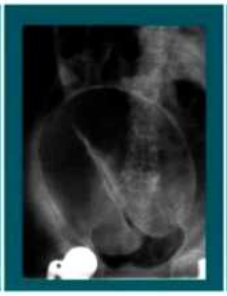
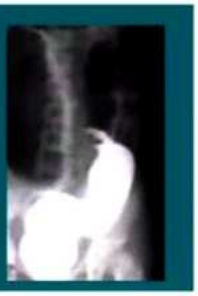
Peutz-Jegher's Syndrome 00:38:52

- Autosomal dominant
- STK 11 / LMB 1 gene
- Chromosome 19
- Hamartomatous polyps in jejunum that lead to bleeding, obstruction & intussusception

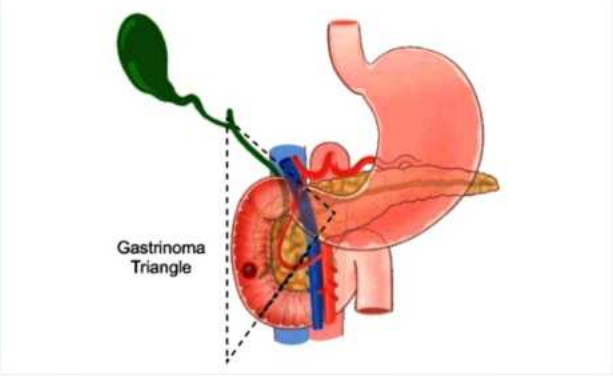
Arborizing pattern

- Most common site: Jejunum
- Increased incidence of Ca stomach / ovary / cervix/ Hepatobiliary cancer
- Polyps themselves are not premalignant but a definitive association with both intestinal, hepatobiliary, and extra intestinal malignancy.

Table 63.1

				
Gas under diaphragm: moustache sign: Pneumoperitoneum (Perforation peritonitis)	Pneumomediastinum; continuous diaphragm sign (air around the heart)	Subcutaneous emphysema	Coffee bean appearance, Sigmoid volvulus	Bird beak appearance in barium enema: Sigmoid volvulus

64 ZOLLINGER ELLISON SYNDROME



Zollinger Ellison Syndrome/ Gastrinoma 00:00:13

- Most common Site of presence of G Cells: Stomach
- Most common Site of Gastrinoma: Duodenum > Pancreas > Stomach

Clinical Scenario

- 30–50-year-old female, presents with recurrent epigastric pain for which she is taking PPI for long time with diarrhea.
- Primary reason for diarrhea:
  - Gastric hypersecretion leads to: Acidic pH in duodenum, this leads to: inactivation of pancreatic enzymes → Unabsorbed Sugar
  - Mucosal damage secondary to increased HCL from stomach in response to increased Gastrin
- Association with M.E.N. Type 1

Important Information

MEN I

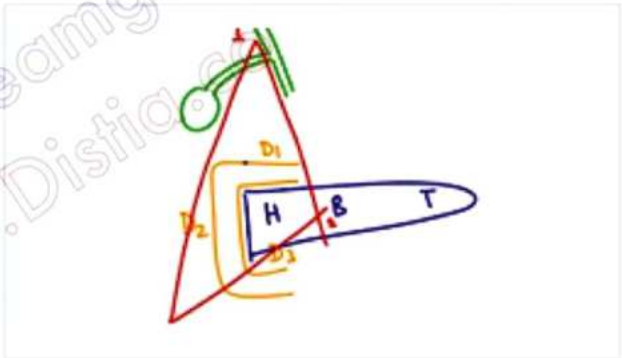
- Pituitary adenoma → Prolactinoma
- Parathyroid adenoma → ↑ Ca^{2+} → Acid secretion
- Pancreatic adenoma → Zollinger Ellison syndrome

- Family history of Kidney stones
- Past medical history of kidney stones
- Liver metastasis – Hard consistency of liver edge

Work – up 00:07:30

1. Upper GI Endoscopy: Multiple duodenal ulcer/Atypical (2^{nd} part of duodenum / Giant ulcers)
   - PUD usually seen in 1^{st} part of duodenum
2. Breath urea Test: Negative
3. UREASE: Negative

- PTH assay, Serum Calcium, Pancreatic polypeptide, Prolactin levels.
- Investigation of choice
  - Secretin Study
  - Check fasting Gastrin (x 10 times → 1000 pg/ mL)
    → Falsely elevated fasting gastrin levels are seen in: PPI, H. pylori, Gastric outlet obstruction.
  - Basal Acid Output > 15 meq/ hour
  - Basal Acid output/ Max. Acid output > 0.6
- Investigation of choice for Tumor localization – Endoscopic ultrasound
  - Duodenum > Pancreas > Stomach
  - It could also be in the mesentery, ovary or heart.
- Imaging for ZES: Endoscopic Ultrasound
- Imaging for Metastatic ZES: Somatostatin Scintigraphy
- Harrison 21st edition update: Functional imaging of choice EUS is 100% sensitive for pancreatic lesions but 43% sensitive for duodenal lesions.

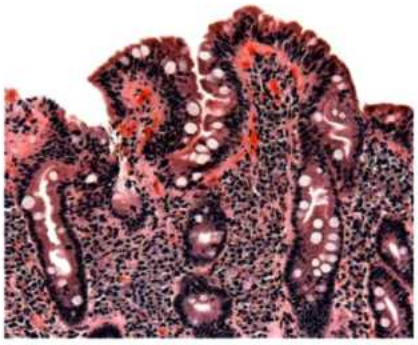


Treatment 00:16:15

- Drug of choice: PPI (to heal ulcers)
- Inj. Lanreotide. (Long-acting derivative of octreotide)
- Surgery: Resection > 1.5 – 2 cm

65 MALABSORPTION SYNDROME

Introduction 00:00:13



- Malabsorption syndrome:
  - Mucosal damage leads to osmotic diarrhea
  - Responsive to fasting
- In Pancreatic tumor Insulinoma, there is secretory diarrhea, which is Non – responsive to fasting
- Unabsorbed Carbohydrate draws out H_2O
  - Leading to osmotic diarrhea
  - Therefore, During Fasting: Decreased osmotic load, reduced diarrhea severity
- Damage to mucosa of:
  - Duodenum: Absorption of iron (Fe) decreases
    → Serum Ferritin decreases
  - Jejunum: Reduced Absorption of Folic Acid
    → RBC folate levels
    → Urinary FIGLU (formiminoglutamic acid)
  - Ileum: Reduced Absorption of Vitamin B12
    → Schillings test
    → Serum Vitamin B12 reduced
    → Serum Homocysteine increased
    → Methylmalonic Acid increased
- There is also reduction of fat-soluble Vitamins (A, D, E, K) due to steatorrhea

Carbohydrate Malabsorption 00:05:56

1. D-Xylose absorption test Screening test
2. 14C –D – Xylose Breath test
3. Stool for reducing substances
4. Breath Hydrogen test [Lactase deficiency]

- Small intestinal mucosal biopsy – Investigation of choice for mucosal disease

Fat Malabsorption 00:09:56

- Steatorrhea (Greasy, bulky, foul-smelling stools)
  - Breath triolein test
  - 24-hour fecal fat estimation/72 hrs.

Celiac Sprue/ Gluten Sensitive Enteropathy 00:12:47

- Exclusive breast feeding – 6 months
- Prelacteal feeds: contraindicated
- So, symptoms arise after 6 months when complimentary feed is initiated.

Pathophysiology

- Cereals (gluten / gliadin in BROW leads to production of antibodies- aTTG)

BROW
- B - Barley
- R - Rye
- O - Oats
- W - Wheat

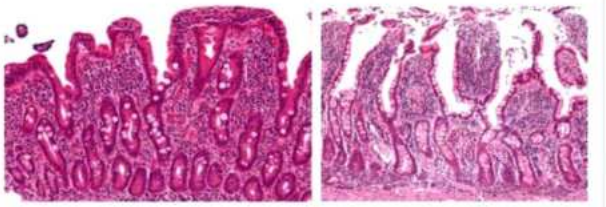
↓
Anti-tissue transglutaminase antibody
↓
Microvilli damage leads to reduction of absorptive surface area
↓
Osmotic diarrhea

Clinical features

- > 6 months child
  1. Failure to thrive (Signs of malnourishment)
  2. Persistent diarrhea
  3. Pallor present
  4. Delayed milestone
  5. Microcytic Hypochromic anemia (due to iron deficiency)
  6. Macrocytic anemia (due to folate deficiency)
- Disease affects Proximal parts of the intestine more commonly, hence, Microcytic anemia is more common

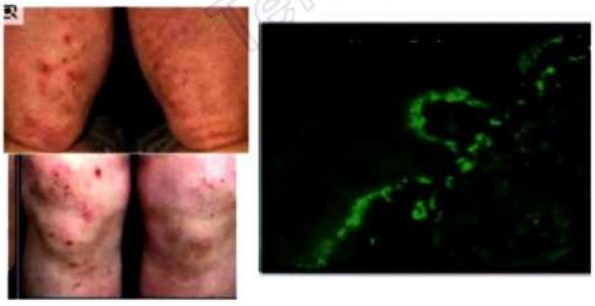
Screening
- Anti TTG antibody (screening test): IgA
- Anti endomysial antibody
- Anti-gliadin antibody

Investigation of choice
- Small Intestinal mucosal biopsy, done twice, initially and then is repeated after 4-6 weeks.
  - Shows Blunting of villi/villous atrophy
  - Gluten Elimination (4-6 weeks)
  - Repeat Biopsy: Regeneration of Villi



Treatment
- QUINOA (Cereal)
- Maize
- Iron and Folic acid suppliments.
- Strict diet restriction
- Important to continue with follow up
- Severity decreases by 10 years of age

Follow up of celiac sprue to detect complications
- Dermatitis Herpetiformis



  - Pruritic vesicles on Elbows & Knees (Gottron Papule - Seen on Knuckles – Dermatomyositis
  - Anti-Epidermal Transglutaminase Ab
  - Biopsy/Immunofluorescence shows break in basement membrane with immune complex deposition (IgA/C3).
- Type1 DM (HbA1C > 6.5)
- May develop lymphoma of gut and happens to be Most common cause death in celiac sprue.

Tropical Sprue 00:33:24

Causes
- Coliforms – E. Coli/ Giardiasis
- Recurrent infection leads to → Mucosal injury
  - Osmotic contents remain in gut for relatively longer duration due to slight decrease in the gut motility.

Clinical: Adult
1. Osmotic Diarrhea: Bloating, borborygmi
2. Weight loss
3. Steatorrhea
4. Deficiency of Vitamins
   - A → Nyctalopia
   - D → Bone Pain
   - E → Ataxia, Acanthocytes
   - K → Purpura
5. Deficiency of B complex – stomatitis, gingivitis
6. Muscle weakness due to electrolyte imbalance (K ↓).
7. Edema due to, decreased Albumin

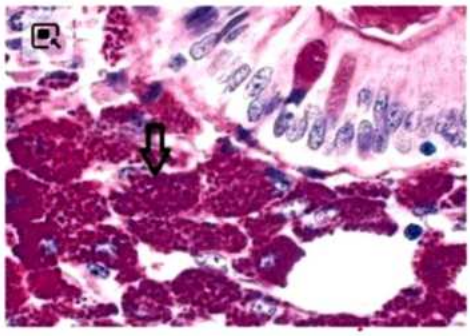
- **Investigation of choice** is Small intestinal mucosal Biopsy
- **Diagnostic criteria for tropical sprue**
  - 2 product malabsorption (carbohydrate & Fat) present with mucosal biopsy showing villous atrophy
  - History of travel to developing countries
- **Treatment:** Tetracycline + folic acid supplementation.

Whipple's Disease 00:41:36

Cause
- Tropheryma whipplei (Intra cellular bacteria in macrophages of gut)

Clinical features: Adult
- Same as tropical sprue + protein losing enteropathy leading to hypoalbuminemia
- CNS: Dementia, nystagmus, Seizures
- CVS: Aortic Valve disease

Investigation of choice
- Small intestinal mucosal biopsy

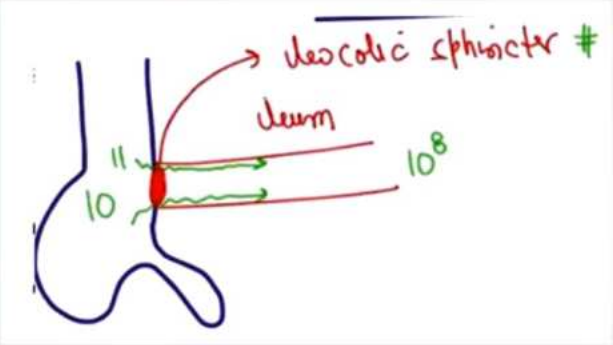


- PAS positive intracellular bacteria
- PCR

Note: PAS positive inclusion in hepatocytes are seen in α1 anti trypsin deficiency

Treatment
- IV Ceftriaxone (at least for 2 weeks)
- Oral Cotrimoxazole: 6 months

Bacterial Overgrowth Syndrome 00:48:06



- Large intestinal flora proliferation in ileum causing mucosal damage and bile acid malabsorption
  - Vit B12 deficiency
  - Increase in Folic acid (Bacterial metabolism produces folate compounds)

Clinical features
- Adult presenting with abdominal Bloating, weight loss, bile acid diarrhea

Investigation of choice
- Duodenal/Jejunal Aspiration and Culture

Treatment
Metronidazole

Schilling Test 00:56:41

- If Abnormal schilling test shows, normalization with a short course of metronidazole →SIBO (Small intestinal bacterial overgrowth)
- If Abnormal Schilling test shows normalization with pancreatic enzymes supplementation → Chronic Pancreatitis
- If Abnormal Schilling test shows normalization with supplementation with intrinsic factor → Type A gastritis

Celiac sprue	SI mucosal Biopsy
Whipple disease	SI mucosal Biopsy shows PAS positive inclusions in gut macrophages
S.I.B.O	Duodenal/Jejunal aspirate and culture showing greater 10^{11} organism / ml

- Intestinal Lymphangiectasia
  - Malformation of lymphatic channels in the gut
  - Steatorrhea
  - Schilling's test (n)
  - D-xylose test (n)
- Diagnosis: Biopsy - abnormal dilated lymphatics

Results of diagnostic Studies in different causes of Steatorrhea

	D-Xylose test Mucosa defect	Schilling Test B_{12} deficiency	Duodenal Mucosal Biopsy
Chronic pancreatitis	Normal	50% abnormal; if abnormal, normal with pancreatic enzymes	Normal
Bacterial overgrowth syndrome	Normal or only modestly abnormal	Often abnormal; if abnormal, normal after antibiotics	Usually normal
Ileal disease	Normal	Abnormal	Normal
Celiac sprue	Decreased	Normal	Abnormal: probably "flat"
Intestinal lymphangiectasia	Normal	Normal	Abnormal: "dilated lymphatics"

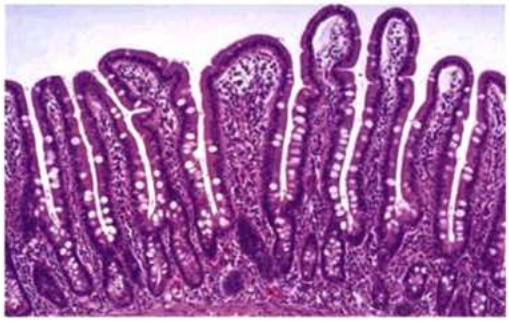
66 INFLAMMATORY BOWEL SYNDROME

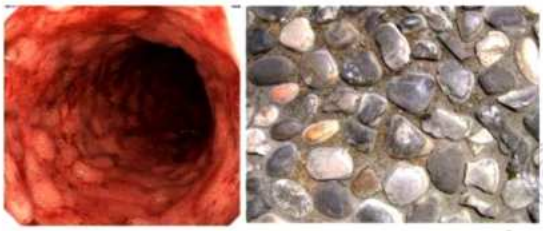
Crohn's Disease

Introduction

00:00:14

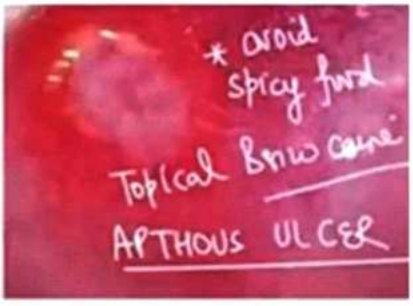
- Not an Auto immune disorder.





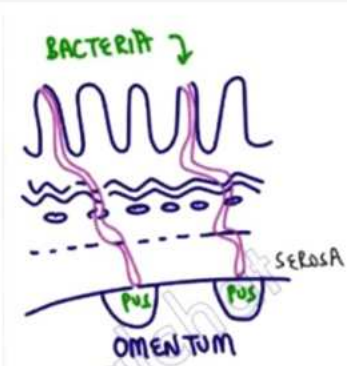
00:00:20

- Cytokines involve is TNF-α
- Most common site involved: Terminal ileum
- Sparing: Rectum
- Entire gut can be involved
- Earliest Presentation: Aphthous ulcers. They progress to cause deep serpiginous ulcers in entire gut
- Serpiginous ulcers in esophagus are a feature of CMV
- Transmural involvement and Submucosal fibrosis lead to Irregular appearance of mucosa called as cobble stone pattern of mucosa. Occasional sparing is called skip lesions.



Clinical Features

00:11:19

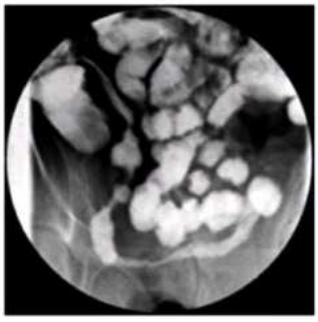


- Colicky pain due to formation of multiple structures
- Bile acid diarrhea due to damage to ileum
- Intraabdominal abscess and serosal inflammation
- Adhesions (between bowel wall and fallopian tube)
  - Infertility
- Fistula (Hallmark feature of Crohn's)
  1. Perianal fistula and sepsis
  2. Vesico colic fistula
  3. Entero cutaneous fistula

Work-up

00:19:33

1. ASCA -Anti Saccharomyces Cerevisiae Antibody
2. Imaging-Wireless capsule endoscopy / Upper GI endoscopy/ Colonoscopy
3. CT Enterography
4. Barium meal follow through (Enteroclysis)
   - "String Sign of Kantor" due to stricture formation



Treatment

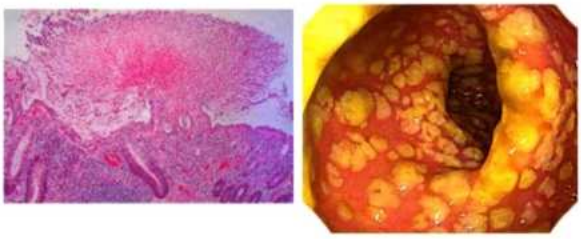
00:23:14

- Drug of choice: Steroids > Mesalamine
- Bile acid diarrhea: Cholestyramine/ Colestipol

- Azathioprine
- Infliximab
  - (TNF – α antagonist): Used for healing of enterocutaneous fistula.
  - 1st step in management of perianal fistula-maintain perineal hygiene and use antibiotics

Pseudo Membranous Colitis

00:27:44



- Suspected: When antibiotics have been taken in the last 3 weeks
- Antibiotic most commonly causing Pseudo Membranous Colitis (PMC): Cephalosporins > Clindamycin
- **Cause:** Clostridium difficile toxin leading to Alteration in gut flora
- **Clinical features:** Explosive watery diarrhea, cramps, abdominal pain

Work-up

00:30:01

1. Stool culture
2. Stool ELISA – Glutamate dehydrogenase (most sensitive)
3. **Investigation of choice**: PCR for Clostridium difficile: Toxin A, B
4. Stool ELISA for Toxin A/Toxin B
5. Colonoscopy: Colonic mucosa → exudates of 2-5 mm coalesce →Pseudo membrane.
6. **Histopathological Examination**: Mushroom cloud extruding above damaged colonic mucosa

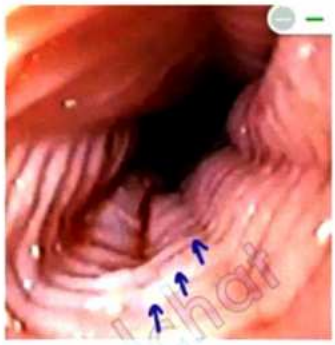
Treatment

00:34:50

- Vancomycin and Fidaxomicin
- Metronidazole
- Fidaxomicin
- Teichoplanin
- Recurrent PMC-Fecal Transplantation (fecal microbiota transplant)

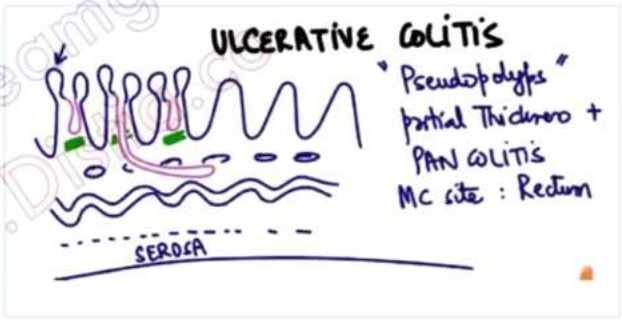
Important Information

- UGIE Esophagus
  - "Feline esophagus" seen
  - Eosinophilic esophagitis: associated with GERD
  - Biopsy > 15 eosinophils/ HPF



Ulcerative Colitis

00:38:59



- "Pseudo polyps" Partial Thickness involvement + Pan Colitis
- Most common site: Rectum

Clinical features

00:41:50

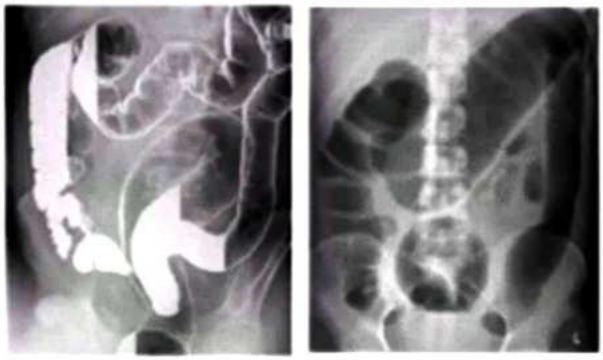
1. Bloody diarrhea 10-15 times /day
2. Anemia
3. Protein Losing enteropathy (Albumin decreased: Puffy eyes)
4. Toxic megacolon (colon loop dilation> 6cm) – [UC > CD]
5. Malignancy incidence in Ulcerative Colitis is equal to that in Crohn's disease

Work-up

00:44:30

1. p-ANCA
   - Also, in
     → Primary Sclerosing Cholangitis
     → Microscopic Polyangiitis
2. **Investigation of choice:** Colonoscopy reveals Proctitis + Biopsy (Granulomas are not seen).

3. CT Enterography
4. Barium enema: (Earliest feature is Granular appearance due to pseudo polyps)
   - Later – loss of Haustrations leading to PIPE STEM COLON appearance.



5. Fecal Calprotectin levels help to differentiate IBD vs IBS (IBS has No Blood in stool)

Treatment

- Drug of Choice of Ulcerative Colitis – Sulfasalazine
- Drug of Choice of Ulcerative Colitis exacerbation – Budesonide enema
- Infliximab infusions in case of disease progression.

Indication for surgery in Ulcerative Colitis

- Toxic megacolon
- Friable rectal mucosa that Bleeds on touch
  - Surgery of choice: Proctocolectomy + ileal pouch Anal Anastomosis (IPAA)

Extra Intestinal IBD

00:54:24

- Most common – Arthritis (Migratory Polyarthritis)
  - HLA B27 (+) – Sacroiliitis (Also in AS, PsA, JRA, Reiter's syndrome, IBD)
- Hepatobiliary – PSC (UC > CD)
  - Extrahepatic fibrosis → Intrahepatic fibrosis
  - Biliary Atresia
  - Obstructive Jaundice
- Dermatologic – Erythema Nodosum over Shin (also seen in Sarcoidosis)
  - Sweet syndrome – febrile neutropenic dermatitis (Upper back)
- Clubbing
- Osteoporosis
- Eye manifestations – Scleritis

Harrison 21st update: MC extraintestinal involvement is metabolic Bone disease: Osteoporosis

*Incidence of malignancy in both UC and CD are equal.

67 IRRITABLE BOWEL SYNDROME

Introduction 00:00:13

- Recurrent Abdominal Pain
  - >1 day/ week for min 3 months with any 2 or more of the following

Manifestations

1. Associated with defecation
   - Passage of flatus with fecal matter, relief of pain
2. Associated with change in frequency of stool
   - Diarrhea/Constipation (Varies with time/ season)
3. Associated with Change in appearance of stool

- If a patient of < 45 years age arrives with 2 out of 3 of the above mentioned for a duration > 3 months, IBS should be considered.
- It is a functional disorder.

IBD Vs IBS 00:03:40

IBD	IBS
Increased Fecal calprotectin levels	Normal range
Bleeding seen	Not seen
Sleep deprived due to colicky pain	Rare
Malnutrition seen	Rare
(-)	Pain is increased by anxiety
(-)	Exaggerated with menses in female
(-)	Nocturnal diarrhea present

- If pain occurs 2 hours post prandial at epigastrium → suspect P.U.D
- If patient complains of diffuse abdominal Pain (Post Prandial) → Suspect Abdominal angina
- Abdominal angina - Occurs due to atherosclerotic Narrowing of Superior and/or Inferior mesenteric artery

↓

decreased blood supply to bowel

↓

No relief with defecation & No changes in stool

Why IBS develops ?

- Dysbiosis 00:09:24
  - Flora of the gut is altered.
  - Firmicutes/Bacteroidetes: (F/ B Ratio) in IBS increases
- In Pseudomembranous colitis, Clostridium defficile produces enterotoxin A&B which leads to manifestation
- Genetic
- Environmental
  - Altered gut permeability

    ↓
  - Increased antigen presentation

    ↓
  - Mast cell activation

    → decreased Cytokines

    → Altered enteric Neuronal function (enhanced- Diarrhea/ reduced- constipation)

    → Smooth muscles activation (colicky/ crampy pain)
- IBS-Diarrhea 33%
- IBS-Constipation 33%
- IBS-Mixed 33%

Clinical features 00:13:53

1. Age group: < 45 yrs.
2. Constipation with Poor response to laxatives
   - Stools are Hard & Narrowed caliber.
   - Incomplete evacuation (anxious about need to use toilets)
3. Diarrhea < 200 ml/ day
   - Nocturnal Diarrhea not seen
   - Bleeding from gut is not seen.
4. Belching/ Bloating/ Borborygmi
5. Nausea/ Vomiting/ Dyspepsia
6. Post prandial pain

Investigations 00:17:56

1. CBC (Anemia present in IBD, not present in IBS)
2. Stool for parasites
3. Sigmoidoscopy with biopsy (rule out microscopic colitis)
4. Colonoscopy
5. Breath hydrogen test (can be false positive)
6. Anti – TTG Antibody titer

Treatment 00:19:34

- Diet low in FODMAPs
  - Fermentable
  - Oligosaccharides
  - Disaccharides
  - Monosaccharides
  - Polyols
- Constipation
  - Tegaserod (5 HT4 Receptor Agonist)

    → Promote Peristalsis
  - Lubiprostone

    → Cl- Channel activator

    → Passive Na+ loss & water loss to maintain soft stools.

- Linaclotide: Guanylate cyclase C agonist acting on luminal surface of enterocytes
  → Increased GI motility & decreased nociception
- Antispasmodics – Dicyclomine
- SSRI – Paroxetine, Alosetron (decreased perception of pain)
- Rifaximin, Neomycin – Bacteriostatic Antibiotics
- Prebiotics-increase activity of good bacterial
- Probiotics – Live microbes
  - Bifidobacterium
  - Lactobacillus
- Diarrhea: Loperamide, Cholestyramine
- High fiber diet: Bran, Psyllium

1 CHRONIC LYMPHOCYTIC LEUKAEMIA

Chronic lymphocytic leukaemia

- Commonest cancer in pediatric age group: Acute Lymphoblastic Leukemia
- Commonest leukemia in geriatric population: Chronic Lymphocytic Leukemia
- Commonest acute leukemia in adult population: Acute Myeloid Leukemia

Important Aspects of Chronic Lymphocytic Leukemia

00:01:00

- Majority of the Chronic lymphocytic leukemia cases are asymptomatic at time of diagnosis.
  A 70 year old retired from the army came for the annual medical checkup and his CBC report was not normal. TLC was high DLC showed predominant lymphocytosis. whenever **Absolute lymphocyte count:** More than 5×10^9 cells per ml for 3 consecutive months, then CLL must be suspected.
- Atypical lymphocytosis is caused by the Epstein Barr virus
- CD5 is expressed by B cells
- The tumor originated morphologically, immunophenotypically *mature* appearing lymphocytes. [Page 834: Harrison 21st edition]
- According to hematology, in 60% of the cases tumors are originated from the mature memory B cell
- Older books say naive B cell for the cell of origin

ZAP- 70 (Zeta associated protein)

- Intracellular tyrosine kinase
- Present inside the T cells
- Bad prognosis: If the patient is ZAP- 70 positive, early treatment is recommended
- Good prognosis: If the patient is ZAP- 70 negative, delayed treatment (8 to 11 years)
- CLL produces autoantibodies due to the proliferation of immuno-incompetent B cells
  - Antibodies damaging RBC: Coombs positive hemolytic anemia or autoimmune hemolytic anemia
  - Antibodies also damage self-platelets: Immune mediated thrombocytopenia
- Generally blood cancer causes predominant bone marrow involvement which contribute to anemia, thrombocytopenia in contrast to CLL which produces auto antibodies.
- But in this condition it is immune mediated because incompetent cells will not have the ability to fight against the infection
- Hence the leading cause of the death for Chronic lymphocytic leukemia patients is due to infections
- If the absolute lymphocyte count is less than the threshold and there is no lymph node, liver, spleen involvement and there is an absence of autoimmune hemolytic anemia or Immune mediated thrombocytopenia. This condition with absent cytopenia is precursor of CLL and is called Monoclonal B cell lymphocytosis. MBL has 1-2% chances/year to progress to CLL.

Chronic lymphocytic leukemia patients can differentiate into diffuse large B cell lymphoma (DLBCL)

- Lymph nodes will grow exponentially
- This is known as Ritcher transformation.
- Associated with Hypogammaglobulinemia:
  - Production of IgM is lesser than normal
  - More susceptible to infections and may lead to death

Why is the Disease Developing?

00:11:24

Chromosome defects

1. Deletion of chromosome 13q
2. Trisomy 12
3. Deletion of chromosome 17p short arm (Worst prognosis)

Overexpression of two components

1. ZAP 70
   - Expressed on B cell tumor
2. BCL 2
   - It inhibits apoptosis

Gene Mutations in CLL

- SF3B 1
- NOTCH 1

Extra Mile:
NOTCH 1: Valvular Aortic Stenosis
NOTCH 3: CADASIL: Small vessel Stroke

- All blood cancers are seen after radiation exposure except Chronic lymphocytic leukemia (Expresses T cell markers)
- Agent orange used in chemical bombs (Vietnam war)
- Patients with similar family history has more chances to Chronic lymphocytic leukemia. It is one of most familial associated malignancy.

Clinical Features of Chronic Lymphocytic Leukemia

- Median age group- 72 years
- Male: Female - 7:1
- 50% cases are asymptomatic (Western countries) at presentation.
- In India, patients will have the category B symptoms (Features identical to TB)

Chief complaints

1. Fatigue
2. Weight loss
   - Category B or hematological malignancy, 10% over 6 months
3. Night sweats
4. Progressive cervical lymphadenopathy
5. Splenomegaly (Early satiety)

Infections

6. Recurrent Pneumonia
7. Herpes Zoster: Painful blisters in dermatomal distribution (Appear in one single line)
8. Reactivation of chickenpox

Other complaints

9. Anemia may occur before the significant bone marrow involvement because of autoantibodies (Coombs positive hemolytic anemia)
10. Coombs negative hemolytic anemia: Bone marrow involvement (Late phase)
11. Decreased platelets may cause:
    - Petechiae
    - Purpura
    - Epistaxis
12. Hepatosplenomegaly

Extra Mile:

Splenohepatomegaly

1. Myelofibrosis
2. Thalassemia: Extramedullary hematopoiesis

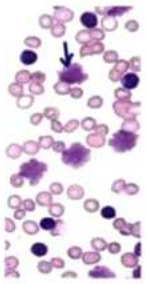
Workup of Chronic Lymphocytic Leukemia 00:22:00

Investigations

Complete blood count

- Total leukocytes count is elevated
- Decreased levels of hemoglobin
- Thrombocytopenia

Peripheral smear



1. Mature looking lymphocytes at 6° clock position
2. Presence of smudge cells (Arrow Mark)
3. Autoimmune hemolytic anemia: Spherocytes seen below smudge cell.

- To identify:
  - Normal RBC: Central pallor
  - Spherocyte RBC: Central pallor is absent

Diagnosis

- Flow cytometry on Peripheral Blood IOC
- Results will be:
  - CD 19 positive
  - CD 20 (dim) positive
  - CD 23 positive
  - CD 5 positive
    → It is a B cell tumor expressing the T cell marker

Differential diagnosis

1. Mantte cell Lymphoma

- In this case flow cytometric markers include
  - CD 19 positive
  - CD 20 (bright) positive
  - CD 5 positive
  - Cyclin D1 positivity

2. Follicular Lymphoma

Flow cytometric markers are:

- CD 10 positive
- CD 19 positive
- CD 20 (dim) positive
- CD 23 positive
- CD 5 is not present
- Cyclin D1 is not present

Other Investigations

- Immunoglobulin G levels (Hypogammaglobulinemia)
- Complete metabolic profile (Due to comorbidities in case of triple vessel disease, BPH, and diabetic)
- Excision biopsy of lymph nodes (Based on FDG-PET report)
  - To detect the Ritcher transformation: PET SCAN
  - Ritcher transformation is Chronic lymphocytic leukemia: evolving to DLBCL

Staging 00:28:44

It is done through two systems:

- Rai classification
- Binet classification

Rai Classification	Binet Classification
Low Risk: Lymphocytosis	**A:** Less than 3 areas of lymph node enlargement
Intermediate Risk: • Lymphocytosis and enlarged lymph nodes • 50% of the cases belong to intermediate risk • Hepatosplenomegaly may or may not be present	**B:** More than or equal to 3 areas of lymph node enlargement
High Risk: • Lymphocytosis + Anemia and thrombocytopenia • Anemia and thrombocytopenia occur due to bone marrow involvement • Anemia may occur due to: o Autoimmune hemolytic anemia o Clonal expansion of the immunocompetent cells	**C:** • **Hemoglobin:** Less than 10 g/dl • **Platelet count:** Less than 1 lakh per cubic mm

Need for Therapy

00:31:17

Progressive bone marrow failure	• Treatment is started with chemotherapeutic drugs • Autoimmune destruction will not cause anemia and thrombocytopenia
Massive splenomegaly	• Value: At least 6 cm below the costal margin • Symptomatic condition (Compresses the stomach)
Massive lymphadenopathy	• Progressive cervical lymphadenopathy • Lymph node size: More than 10 cm
Autoimmune hemolytic anemia	• Other Name: Coombs positive hemolytic anemia • Non-responsive to steroid therapy • Treatment needs to be started immediately
Fever for previous two weeks	• But no infection is found (Malignancy responsible for cytokines like IL-1) • Fever is more than 100°F • Significant unintentional weight loss

Treatment for Chronic lymphocytic leukemia

00:34:30

Less than 65 years age	• No comorbidities • Chemotherapeutic drugs include FCR. • In older edition it includes: PCR (Pentostatin, Cyclophosphamide, and Rituximab) o **F:** Fludarabine (DOC for Chronic lymphocytic leukemia) o **C:** Cyclophosphamide (Causes hemorrhagic cystitis) o **R:** Rituximab (Anti CD20 molecule)
More than 65 years	• Comorbidities are present (Hypertension or DM but HbA1C is well controlled) • Chemotherapeutic drugs include: o Chlorambucil o Obinutuzumab • Alternative drugs o Bendamustine with Rituximab • Antiapoptotic drug: o Venetoclax • B cell signaling inhibitors specifically affects the cells of Chronic lymphocytic leukemia but doesn't cause damage to the normal cells present in the bone marrow • Drugs include o Ibrutinib (Bruton tyrosine kinase inhibitor) o Idelalisib

Clinical Remission

00:38:08

- Absolute lymphocyte count: Less than 4000 per microlitre
- When the size of the lymph nodes is less than 1.5 cm
- Liver and spleen are Non-Palpable
- Normocellular bone marrow
- Platelet count is more than 1 lakh per cubic mm
- Hemoglobin levels are more than 11 gm%

Complications of Chronic Lymphocytic Leukemia

00:39:40

- Infection: Hypogammaglobinemia
- Secondary malignancy
  - o Increased incidence of skin and prostate cancer
  - o Incidence is 10 times more compared to older population in the patients with Chronic lymphocytic leukemia.
- Autoimmune mediated damage:
  - o Autoimmune Hemolytic anemia
  - o Autoimmune Glomerulonephritis
  - o Autoimmune Vasculitis

Autoimmune hemolytic anemia

- Warm antibody mediated
- Coombs positive hemolytic anemia
- Bilirubin values will be increased
- LDH values are increased
- Haptoglobin will bind with the hemoglobin (In case hemolysis, haptoglobin is consumed)
- Hence levels of haptoglobin is decreased
- This will respond to steroids
- Immune mediated thrombocytopenia may occur

Evan Syndrome

- Presence of concomitant autoimmune hemolytic anemia and immune mediated thrombocytopenia
- If they are not responding to steroids, then chemotherapy is recommended based on the age of the patient and comorbidities
- If ZAP 70 is positive, early treatment is recommended
- If ZAP 70 is negative, treatment can be delayed up to 10 years

Richter transformation

- CLL transformation into Diffuse Large B cell lymphoma
- Excision of Lymph node biopsy is based on the FDG-PET scan
- Treated on the lines of Non-Hodgkin Lymphoma

2 CHRONIC MYELOID LEUKAEMIA

- It occurs due to translocation of Philadelphia chromosome t(9:22)(q34.1, q11.2)
- This 9:22 translocation is also seen in Acute Lymphocytic leukemia.
- Tyrosine kinase inhibitors are used for the management of Chronic myeloid leukemia and Acute lymphocytic leukemia
- Bcr-abl-1 translocation is called balanced because there is no loss of genetic material
- **Bcr-abl-1** is a hybrid gene
- It is a translocation with respect to long arm of chromosome no. 9 to long arm of chromosome no. 22
- **Bcr:** Breakpoint cluster region
- **Abl:** Abelson leukemia
- Bcr-abL1 results in the production of novel oncoproteins (Molecular weight: 210 kilo daltons)
- **Novel oncoprotein:** $p210^{bcr\text{-}abl\text{-}1}$

Novel Oncoproteins 00:03:40

- They Inhibit Apoptosis and activate Tyrosine kinase of all the cells in myeloid lineage.
  → It results in uncontrolled mitosis
- In case of AML or ALL, multiplication of one single cell will continuously occur (Clonal arrest)
- In CML, the entire sequence of the precursor cells ranging from metamyelocytes, myelocytes, myeloblasts will increase. This is called Shift to left.

Other Novel Oncoproteins

Other Novel Oncoproteins	Description
$p190^{bcr\text{-}abl\text{-}1}$	• It is produced with respect to acute lymphocytic leukemia • Epidemiological Data: 2/3rd of Philadelphia chromosome positive in ALL patients • Hence tyrosine kinase inhibitors are used in the management of ALL • Worst Prognosis: p190
$p230^{bcr\text{-}abl\text{-}1}$	• Indolent outcome • Progression of the cancer is slow

Phase of Chronic myeloid Leukemia

- Asymptomatic
- Development of accelerated phase
- Blast crisis

Radiation exposure is responsible for the development of all blood cancers except Chronic lymphocytic leukemia

- These novel proteins are making the cell immortal

Neutrophils surviving beyond the senescent age implies that inside the neutrophils the granules are consumed
↓
As a result Neutrophil alkaline phosphatase score is decreased (Measure of the killing power of neutrophil)
↓
In CML neutrophils quantity is more but quality is poor as they passed their expiry date and don't have the capacity to fight
↓
It results in the development of Infections
↓
Total leukocyte count will be increased due to Blast crisis (Immature cells will be present in the circulation)

Prognosis with T.K.I 00:10:15

- Before the advent of tyrosine kinase inhibitors, the 10 years survival rate is 30%
- After the advent of tyrosine kinase inhibitors, the 10 years survival rate is greater than 85%

Clinical Features 00:12:10

- Age group: 55 - 65 years or older

1. Involuntary weight loss (Cut off: >5% over 6 months)
   In category B symptoms, the involuntary weight loss is 10% over 6 months (Hematological malignancy)
2. Fatigue
3. Sweating (Due to Hypercatabolic stage)
4. Pruritus (Basophil count is increased)
5. Diarrhea
6. Flushing
7. Early satiety due to Marked splenomegaly
8. Progressive constipation
9. Pallor
10. Enlarged lymph nodes
11. Thrombotic events:

A. Total cell count is elevated Viscosity of the blood is increased:
   → Priapism (Painful erection)
   → Myocardial infarction
   → Respiratory distress Supplemental oxygen is recommended even though there is no infection
   → Cardiovascular events
   → Deep vein thrombosis
   → Blindness (Retinal artery circulation)

B. Bcr-abl-1 leads to increase in the platelet count
   → Excessive production of platelets Increased chances of thrombophilia

Leukostasis: WBC count is increased to 1 lakh per cubic mm

- Causes: Acute myeloid leukemia or CML in Blast crisis
- It effects:
  - **Lungs:** Difficulty in breathing
  - **Brain:** Stroke manifestations
- Platelet count is decreased in blast crisis
  - It results in the Nasal bleed (Epistaxis)
  - Bruises
  - Hematochezia
  - Vision is affected (Retinal Hemorrhage)
- Infections:
  - Neutrophils which passed their expiry date are still living (They don't have the capacity to fight)
  - As a result, neutrophil alkaline phosphatase score will be decreased
  - Hence infections will be increased (Recurrent Pneumonia)

Work Up the Patients of Chronic Myeloid Leukemia

00:23:47

Investigations

- **Complete Blood Count**
  1. Hb ↓
  2. TLC ↑
  3. DLC: Basophilia
     → Presence of myelocytes, metamyelocytes, and promyelocytes seen in peripheral smear called shift to left
  4. Neutrophil Alkaline Phosphatase Score: Low
  5. Vitamin B12 levels are elevated (B12 is the fuel for synthesizing DNA)
  6. Platelets will be increased in chronic phase but later part of the disease they will be decreased (Blast crisis)
- Bone marrow Examination:
  - Hypercellular marrow with myeloid hyperplasia
  - Myeloid erythroid ratio: 15 to 20:1
  - Stain to determine Reticulin fibrosis is Snook silver stain
  - Karyotyping is done
- FISH (Fluorescent in situ hybridization) done on blood/ Bone marrow samples.
  - Analysis to quantify Philadelphia chromosome positive cells
  - Estimates the tumor load
- RT - PCR on blood/ Bone marrow sample
  - To quantify bcr-abl-1
  - It can be false negative or false positive
  - False negative: Early part of the disease
  - Useful in post Therapy Monitoring

Criteria for diagnosing the Accelerated Phase

1. Blast concentration in peripheral blood is greater than 15%
2. Peripheral blood shows more than 30% blasts and promyelocyte (Immature cells)
3. Peripheral blood: greater than 20% of basophil count
4. Platelet count is decreased to 1 lakh per cubic mm

10 to 19 % of blasts are demonstrated either in the peripheral blood or in bone marrow (According to older books, not followed)

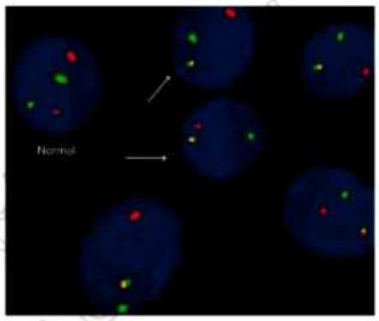
Blast Crisis in Chronic Myeloid Leukemia

00:33:23

- If the blasts are more than 30% in peripheral blood or in bone marrow
- Extramedullary blast proliferation (Blast migration to lymph nodes) gives more credibility for diagnosis

Treatment of Chronic Myeloid Leukemia

00:34:33



- Green represents: bcr
- Red represents: abl
- The technique involved is fluorescent in situ hybridization

Goals of Treatment:

Complete Cytogenetic Remission	• Start tyrosine kinase inhibitors • Absence of Philadelphia chromosome positive metaphase cells
Major molecular Remission:	• Less than 0.1% BCR-ABL-1 transcript cells are currently surviving or • 3 log reduction
Molecular Remission 4.5:	• Less than 0.0032% BCR-ABL-1 transcript cells are left behind • 4.5 log reduction of the total load of the cancer cells in the patient

Drugs for CML

Imatinib

Second generation tyrosine kinase inhibitors

- Dasatinib
- Nilotinib
- Bosutinib:
  - Most effective in case of imatinib resistant chronic myeloid leukemia

Third generation tyrosine kinase inhibitors

- Mutation: T 315 I (1st and 2nd generation drugs are not effective)
  - Gatekeeper mutation
  - In this condition, Ponatinib, Omacetaxine are recommended

Atypical Chronic Myeloid Leukemia

- Bcr-Abl-1 is negative
- Chromosome 20 mutation
- Treatment: Allogenic stem cell transplantation

Juvenile Chronic Myelomonocytic Leukemia

- Fetal hemoglobin levels are increased
- It is also increased in case of
  1. Sickle cell anemia
  2. Alpha thalassemia
  3. Hereditary Spherocytosis

Sokal Risk Score

- Online calculator for median survival of the patient (Statistical analysis)
- Mnemonic: ASPM
- Statistical determinants for patient's survival
- **A:** Age
- **S:** Spleen size (cm below costal margins)
  - It can also be measured through:
    → Ultrasonography
    → Clonal evaluation
- **P:** Platelet count
- **M:** Percentage of myeloblast in the peripheral smear

3 ACUTE MYELOBLASTIC LEUKEMIA

Acute myeloid leukaemia

- 5 year survival rate for AML is 25%
- Extremely high TLC count contributing to Leukostasis
- Secondary to the hyperviscosity, there is a possibility that.
  - Patient might develop acute coronary syndrome
  - There can be stroke like manifestations, priapism, and lungs involvement causing respiratory distress.
- DIC

Causes 00:02:20

1. **Idiopathic:** 25- 50%cases
2. **Bone marrow failure**
   A. Fanconi Anaemia
   B. Diamond black fann syndrome: can develop Aplastic Anemia
   C. **Shwachman diamond syndrome**
   → Autosomal recessive, Exocrine pancreatic insufficiency
3. **Defective DNA repair**
   A. Bloom syndrome
   B. Ataxia telangiectasia (In the sclera, leash of dilated blood vessels are seen)
   → Lymphoreticular malignancy
4. **DOWN syndrome**
   - Acute megakaryoblastic leukaemia
     → Also known as M, AML.
     → GATA 1 gene
5. **Exposure to anticancer drugs**
   - Alkylating agents
   - Usually takes 4 to 6 years to develop post exposure.
   - This happens due to monosomy 5 and monosomy 7 chromosomes.
   - It takes only 1-3 years to develop AML by exposure to other anticancer agents like Topoisomerase II inhibitors Involves chromosome 11
6. **Radiation exposure**
   - Benzene
   - Phenylbutazone
   - Chloramphenicol (causes aplastic anaemia, AML and bone marrow failure)
7. **t(15:17)**
   - Formation of PML- RARA
   - It causes differentiation blocks.
     → Promyelocytes are not going to differentiate due to differentiation block. single cell multiplies repeatedly
   - For treatment of these patients, cytarabine is not used as DIC risk is increased. ATRA is used
8. **t(8:21):** Myeloid sarcoma
   - Chromosomal swap in this case results in a fusion product
     → RUNX1- RUNX1T1
9. Inversion of chromosome 16 and t(16:16)
10. FLT3-ITD activation mutation
    - 30% cases of AML

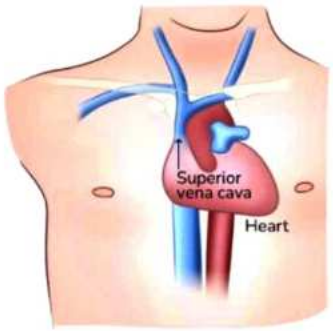
Favourable Prognosis

- FLT3-ITD
  - ITD stands for internal tandem duplication
- CEBPA
- NPM1
- t(8:21)
- Inversion of chromosome 16
- t(16:16)

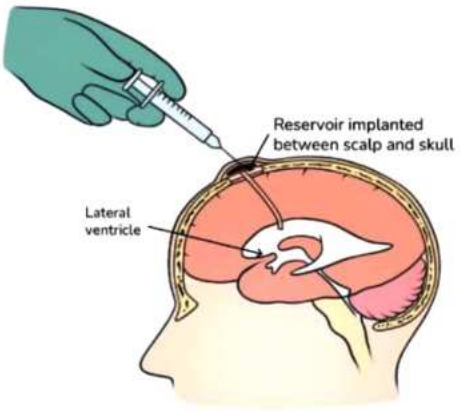
Clinical Features 00:17:10

Important Information

- FLT3-ITD^High- POOR PROGNOSIS.



- Chemoport is deployed in the superior vena cava of the patient.
- Injection is given directly through the chemoport.
- The drug will go directly toward the heart bypassing the risk of superficial thrombophlebitis.



- If a patient is having craniospinal axis involvement or leptomeningeal metastasis.
- The injection is given into CSF directly via Ommaya reservoir

Clinical manifestations

Age group > 65 years,

1. Fatigue
2. Weight loss
3. Fever
   - Manifestation of a catabolic process.
4. TLC is very high Contribute to leukostasis
   - Organs involved in Leucostasis are:
     → Lung
     → Brain
     → Priapism
     → Blindness
5. Thrombocytopenia
   - Petechiae (develops initially on the ankle), Epistaxis, Purpura
6. Lymphadenopathy and Hepatosplenomegaly
   - Hilar lymphadenopathy contributing to cough.
7. Gingiva Involvement
   - Commonly seen in M_5AML
8. Development of chloroma
   - Also called Granulocytic sarcoma
   - Common with t(8:21)
   - Unilateral proptosis
   - Can cause paraplegia.
9. DIC is more common in t(15:17)
   - M_3APML- Acute Promyelocytic Leukaemia.

Work Up

00:25:34

- Bone marrow aspiration at posterior superior iliac spine (recommended site)
  - Percentage of myeloblasts >20%
  - If chromosomal abnormalities are present then diagnosis can be made Even if the blast concentration is <20%.
  - Cut off is <20% in cases of:
    1. t(15:17)
    2. t(8:21)
    3. Inv 16
    4. t16:16)

Salah needle

Klima needle

Bone marrow biopsy needle

  - Thrombocytopenia is not the contraindication to perform bone marrow biopsy.

Lab Investigations

1. Hb ↓
2. TLC ↓
3. Platelets ↓
4. Bone marrow aspiration
   - Morphological analysis of cells must be done
     → Auer rods are seen
   - Cytogenetics
   - Flow cytometry analysis on BMA(IOC)
     → CD13, CD117 are the flow cytometry markers for AML.
     → For M_7 variety: Megakaryoblastic leukaemia: CD41, CD61 are the markers.
5. Molecular study for genetic mutations
   - FLT3
   - CEBPA
   - NPM1
6. Chest X-ray
7. Echocardiography
8. HLA typing
   - In future planning of allogeneic stem cell transplantation.

9. Baseline KFT
   - **Tumour lysis syndrome.**
     A. Excess uric acid production, blocking kidney tubules
     B. Elevated Po4
     C. Elevated Potassium
     D. Low Calcium
- Treatment
  - Adequate hydration.
  - Allopurinol
  - Rasburicase

WHO 2016 Classification 00:34:55

- **AML with recurrent genetic abnormalities**
  - t(8:21)
  - inv 16
- **APML** with PML-RARA
  - RARA stands for retinoic acid receptor alpha
  - It is related to the development of DIC.
- AML with MDS changes
- AML with NOS
- Myeloid sarcoma
- Myeloproliferative with Down syndrome
  - Transient abnormal myelopoiesis

AML Not otherwise specified

- AML with minimal differentiation: M_0
- AML without maturation: M_1
- AML with maturation: M_2
- Acute myelomonocytic Leukaemia: M_4
- Acute monoblastic leukaemia : M_5
- Pure erythroid leukaemia : M_6
- Acute megakaryoblastic leukaemia : M_7
  - Related to Down syndrome
- Acute basophilic leukaemia
- Panmyelinosis with myelofibrosis

Treatment 00:39:45

1. Cytarabine + Anthracyclines
   - Daunorubicin
   - Idarubicin
   - Alkylating agents can trigger AML. So, treat with anthracyclines.
   - They both can cause cardiac toxicity.
2. For M_3AML; ATRA is used
   - All trans retinoic acid
   - It causes differentiation of neoplastic cells.
   - Senescence is achieved and Cells will die
   - Cells adhere to the pulmonary endothelium
     → Releases cytokines
     → Causes damage to the pulmonary endothelium
     → Fluid leakage into alveoli
     → Respiratory distress
     → This is differentiation syndrome which is a side effect of ATRA
     → It is managed with Supplemental oxygen and steroids.

3. Arsenic Trioxide is effective in management of APML, both as single Agent and in Combination with ATRA

- Most common acute leukaemia in paediatrics is Acute lymphoblastic leukaemia
- Most common acute leukaemia in adults is Acute myeloid leukaemia
- Allogeneic stem cell transplantation is done after proper candidate selection.
  - It is mainly relapse prevention strategy.

4 ACUTE LYMPHOBLASTIC LEUKAEMIA

- Commonest tumour in children
- Commonest leukaemia in children.
- This tumour can cross BBB, to form CNS leukaemia and features of meningismus and raised ICP.
- It is a haematological malignancy that can lead to the development of testicular lump, by crossing the blood testis barrier.

Pathogenesis: 00:01:02

- Majority of the acute lymphoblastic leukaemia is of B cell origin - 76%.
- Most common subtype of B type ALL: Common ALL
- **Marker** - CD 10 (CALLA), associated with Philadelphia chromosome - t(9:22).
  - ALL associated with the Philadelphia chromosome can become a high risk tumour.
  - Use tyrosine kinase inhibitors for management of ALL.
  - Philadelphia chromosome is also seen in CML.
- 24% are T cell tumours:
  - Mediastinal mass.
  - Testis lump.

Etiology 00:03:07

- **A:** Ataxia Telangiectasia (Neurocutaneous disorder).
  - It involves spinocerebellar pathways leading to ataxia.
- **B:** Bloom syndrome, Benzene exposure.
- **C:** Chemotherapy.
  - Nitrosoureas and epipodophyllotoxins
- **D:** Down syndrome.
  - ALL is common in children with Down syndrome.
  - Most common subtype of AML seen is Acute Megakaryoblastic Leukaemia.
- **I:** Ionising radiation and Infection - HTLV-1.
- **F:** Fanconi's anaemia.
- **K:** Klinefelter syndrome.
- **N:** NF-1.
  - It is associated with pheochromocytoma.
- **P:** Philadelphia chromosome
  - t(8:14)
    → Should be remembered in both Burkitt's lymphoma and ALL.
  - t(4:11)
  - t(1:19)

HTLV-1 can contribute to:

- Adult T cell leukaemia
  - Peripheral smear shows lymphocytes with a nucleus which is shaped like a flower or clover leaf. (Flower cells)
- Neurological feature - Tropical spastic Paraparesis.

CNS Leukaemia 00:11:04

- Prevalence - ALL > AML.
- Raised ICP/Meningismus.
- While performing lumbar puncture, if a blood vessel (Present in epidural venous plexus) got ruptured, there is a chance that the blood cells might enter the intrathecal space or CSF space, there is a chance that the patient may develop CNS leukaemia. Hence while taking sample for CSF
- Cytology, patient should be given intrathecal methotrexate in the same sitting to prevent iatrogenic CNS leukaemia.
- Cell count - >5 cells/cumm.
- Investigational scan - CT scan - Leptomeningeal metastasis.
  - Breast cancer is one of the major reasons for leptomeningeal metastasis in adults.
  - In the paediatric age group, leptomeningeal metastasis is associated with CNS leukaemia.

Clinical Presentation 00:14:38

Paediatrics: 2-8 years (Fast progression of disease).
Adults: > 50 years.

1. Pallor, anaemia.
2. Bleeding: Epistaxis
3. Infection: Recurrent pneumonia
4. Bone pain, Sternal Tenderness
5. Hepatosplenomegaly
6. Lymphadenopathy
   - In hilar lymphadenopathy for T cell leukaemia with mediastinal mass can include;
     - Superior vena cava syndrome.
     - Facial congestion.
     - Collateral development.
7. CNS leukaemia
   - Raised ICP.
   - Development of repeated episodes of vomiting.
   - 6th nerve palsy.
8. Testis lump

Work Up 00:19:23

1. **CBC**
   - Hb ↓
     → The anaemia would be normocytic normochromic.
   - TLC can be normal/↓/↑↑.
     → Higher risk patient - Grossly elevated levels, Leukostasis (Incidence - AML>ALL).
     → Hyperleukocytosis – 1 Lakh/cumm.
     → It can cause sluggish circulation.

2. **Bone marrow aspiration**
   - Salah and Klima needles are used.
   - Site: Posterior superior iliac spine.
   - Bone marrow aspiration: Blasts >20%.

   A. Morphological perspective classifies the ALL into three subtypes;
   → **L1:** Most common type.
   → **L2**
   → **L3:**
   - Also referred to as Burkitt's leukaemia.
   - It is a mature B cell ALL.
   - Flow cytometric marker - CD10+ with S Ig+ (Surface immunoglobulin).

   B. Immunophenotyping
   - **Cytogenetics**
     → FISH - t(9:22), t(8:14 - Associated With Burkitt's leukaemia), t(4:11), t(1:19).
   - **Cytochemistry**
     → TdT+ (Terminal Deoxynucleotidal Transferase).
     - The cancer cells have over activity of DNA Polymerase, the multiplication of cells is at a higher rate.
     - High cell turnover.

     Note: ↑ Cell turnover is directly proportional to ↑ Chances of getting Tumor Lysis Syndrome.

3. Tumor Lysis syndrome investigations:
   - Phosphate ↑, Calcium ↓, Potassium ↑, Uric acid ↑.
4. LP
   - CSF should be checked for leukaemia cells.
   - After centrifugation, the cancer cells can be identified with normal microscopy.
   - The patient should be given intrathecal methotrexate in the same sitting to prevent iatrogenic CNS leukaemia.
5. HLA Matching
   - Allogeneic stem cell transplantation - Ultimate choice for high risk ALL.

High Risk ALL
- Age group: <1 and >10 years.
- Higher WBC count: >50000 per microlitre
- Organomegaly
  - Lymphadenopathy or Hepatosplenomegaly or Mediastinal mass (Manifestations like stridor, superior vena syndrome, cholecystitis).
- Mature-B Cells are more dangerous.
- Hypoploidy
- Chromosomal swaps:
  - t(9:22), t(8:14 - For Burkitt's leukaemia), t(4:11), t(1:19).
  - They increase the need for bone marrow transplantation.
- Blasts:
  - >1,000/cumm in the peripheral smear after 14 days of chemotherapy.
  - The chemotherapy can risk TLS of the kidney by clogging the tubules.
- Absence of Cd10.
- MLL (Mixed lineage leukaemias).
- **Recommended management** - Allogeneic stem cell transplantation in the 1st remission with chemotherapy, and later on bone marrow transplantation from a healthy person.

Low Risk ALL
- Age group: 1-9 years.
- Higher WBC count: <50000 per microlitre
- Pre-B cell ALL.
- Hyperploidy.

Standard Risk ALL
- Same as high risk
- Cytogenetics are normal, no chromosomal swaps are present.
- Chemotherapy is the treatment both in low and standard risk patients.

Very-High Risk ALL
- Induction in combination with chemotherapeutic agents is given to the patient. But there is an induction failure, especially in Philadelphia chromosomes.
- Treatment in High and Very-High patients for ALL - Allogeneic stem cell transplantation.

Treatment 00:34:23
Goals of the treatment - Complete Molecular Remission.
- Achieved in 6-16 weeks of start of chemotherapy.
- Success rate:
  - High risk patient - 80%.
  - Low risk patient - 90%.
- <0.01% or <1 leukaemia blasts/10,000 for normal cells - PCR technique is used.
- <5% Blast in bone marrow - Light microscopy is used for it.

Chemotherapy Drugs for Patients with High Risk ALL and Philadelphia chromosomes positive
- Tyrosine kinase inhibitors:
  - Dasatinib (2nd generation).
  - Ponatinib.
  - Both can cross the BBB (Even treat CNS leukaemia).
- CART-19 (New approach).
  - Chimeric antigen receptor target approach.
  - Selectively Destroy the abnormal cells in the bone marrow rather than all the cells.
  - Drug - Blinatumomab.

Chemotherapy Drugs for Patients with Low Risk ALL

- **Induction**
  - Induction 01: Vincristine (Side effect - Peripheral neuropathy), daunorubicin (Side effect of cardiac issues - Cardiomyopathy), L-asparaginase, prednisolone are used.
    → Iatrogenic introduction of cancer cells into the CSF - Intrathecal Methotrexate is given. It is also given in patients with CNS leukaemia.
  - Induction 02: 6-Mercaptopurine, methotrexate, cyclophosphamide (Alkylating agent - Contribute to hemorrhagic cystitis), cranial irradiation are used.

Note: In paediatric wards, many patients are bald because of cranial irradiation, so encourage their mother or father to shave off their heads.

- Cranial irradiation generally contributes to hair loss in the patients.
- 18 - 24 Gy are required and are delivered as 12 fractions as a fractioned cranial irradiation.
  - Side effect - Meningioma.
- It is given in childhood and in later ages, the patient may develop meningioma

- **Consolidation**
  - Duration: 14 - 28 weeks.
  - Cyclophosphamide, vincristine, daunorubicin, cytosine arabinoside are used.
- **Maintenance**
  - Duration: 2-2.5 years.
  - VDAP + 6-Mercaptopurine is used.
    → V - Vincristine
    → D - Daunorubicin
    → A - L-asparaginase
    → P - Prednisolone

Relapse

- >5% leukaemia cells in bone marrow under light microscopy.

5 MULTIPLE MYELOMA

- Also referred to as "Plasma Cell Dyscrasia."
- Wide spectrum of presentations ranging from
  1. Smouldering myeloma
  2. Monoclonal gammopathy of unknown significance
  3. Plasma cell leukaemia
  4. Multiple Myeloma

Pathogenesis 00:00:56

- Antibodies have:
  - **Heavy chain isotypes:** Ig - G, A, M, D, E.
    → The 1st line of defence in the body is by IgA.
  - **Light chain isotypes:** K/λ.
    → Multiple Myeloma has Overproduction of light chain Component of antibodies. The defective antibody formation leads to increased incidence of acquiring infections of Pneumococcal pneumonia and or Pyelonephritis
    - Excess light chains excerted in urine can lead to tubular damage and result in Renal failure. Hyperviscosity will also contribute by causing organ infraction.
    → The major reason for death in MM is infections.
- When the light chain protiens appear in the urine, then they're referred to as Bence Jones proteins.

Important Information

- If the urine of a patient with MM is analysed with a dipstick method (Designed to recognize urine protein - Albumin), it will be false negative for Bence Jones proteins (Positively charged antibodies).

- The plasma cells produce cytokines to form lytic lesions in:
  - Spine
  - Ribs
  - Pelvis
  - Skull (Raindrop Configuration)

- Imaging modality used to identify lytic lesions in Multiple Myeloma is PET-CT

Important Information

- Light chain assay is done in the patient with MM.
- In the urine of the normal person:
  - **Albumin:** <30 mg/day.
    → They are negatively charged.
  - **Light chains:** <10 mg/day.
    → They are positively charged.

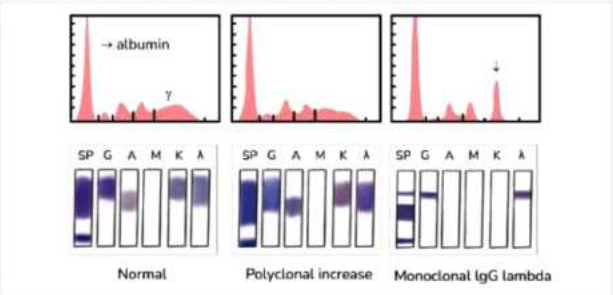
Triad for Diagnosis of Multiple Myeloma 00:09:15

1. Bone marrow biopsy shows plasmacytosis:
   - Absolute plasma cell in BM: >10%.
   - Plasma cell percentage in the bone marrow is >60%.
2. SPEP > UPEP: Shows the presence of M-Spike (Monoclonal Antibodies).
3. Features of **CRAB**, Myeloma like events:
   - C - Hypercalcemia
   - R - Renal failure
   - A - Anaemia
   - B - Bleeding.

Important Information

- If CRAB/ Myeloma like events have not developed, then the for diagnosis of MM - Plasma cell percentage in the bone marrow cut off taken is >60%.

Techniques to Demonstrate M-Spike 00:13:00



- M-Spikes are the monoclonal antibodies.
- Minimum tumor cells load to develop M-Spike: $>10^9$.
- Two techniques are used:
  - Immunoelectrophoresis
  - Immunofixation

Immunoelectrophoresis

- Superior technique
- Used to detect:
  - Albumin
  - Globulin (Subtypes - α,β,γ).
    → γ globulin is an antibody component.
  - M-Spike - Church spire appearance.

Immunofixation

- Advantage
  - Detect the Increased levels γ globulin.
  - Detects the Subtype of the light chain.
  - IgG is most common the defective antibody produced in MM.

Etiology of Multiple Myeloma 00:16:00

1. Exposure to radiation
   - The first risk factor for almost all blood cancers, haematological malignancies except for CLL.
2. Wood workers and farm workers.
   - Reason: Exposure to petrochemicals (Like turpentine oil - For wood Workers).
3. Hyperploidy - 13q14
4. Chromosomal swaps - t(11:14), t(4:14), t(14:16).
5. Deletion of chromosome 17p.
6. 1p amplification and 1q deletion.

Pathophysiology of Multiple Myeloma 00:18:35

Over production of defective light chains
Defective antibody production
↓
Bony lytic lesions are developed
↓
PET-CT can be done for early detection of MM
↓
In myeloma - Activation of osteoclast cells
↓
Bone destruction will occur
↓
Cytokine produced in MM: MIP-1α (Macrophage Inflammatory Protein), responsible for bone lytic lesions
↓
Bone pain is the common presentation (Vertebra > Pelvis > Skull)
↓
Hypercalcemia - Due to bone destruction
↓
Amyloidosis - AA variety which can damage the kidney
↓
Infections: Pyelonephritis contributes to scarring of the kidney
↓
Due to bone pain manifestation, the patient may use NSAIDs on a daily basis
↓
This may affect the prostaglandins (Maintains the gradient in the kidney for filtration)
↓
Filtration in the kidney is hampered

Extra Miles:-

- Normal viscosity of plasma: 1.8x more as the viscosity of water.
- Hyperviscosity syndrome: Viscosity of plasma is 4x more as the viscosity of water.
  Hypogammaglobulinemia, due to Increased catabolic rate of γ globulin.

Haematological feature in MM

- Normocytic normochromic anaemia
- Bleeding
  - Defective antibodies cause the accelerated clearance of platelets / Antibody coated platelets.

Clinical features of Multiple Myeloma 00:30:04

A 70 year old male patient presents with

1. Bone pain or Low backache.
- The features to be ruled out as a workup in the patient:
  - Osteoporosis
  - Disc prolapse
  - Metastasis to the spine because of the carcinoma prostate
2. Fracture of vertebra - Leading to compressive myelopathy
3. Lethargy or fatigue due to Anaemia.
4. Uraemia features if Renal Failure is not detected
5. Hyperviscosity syndrome, can present as:
   - Dizziness
   - Vertigo

6. Bleeding manifestations:
   - Epistaxis
   - Haematochezia
7. Carpal tunnel syndrome: Due to AA amyloidosis.
   - It can also be seen in:
     → Pregnancy
     → IT professionals
     → Hypothyroidism
     → Acromegaly

Workup

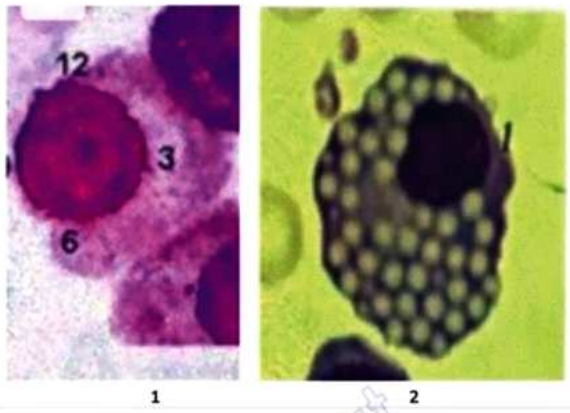
00:34:35

1. CBC with ESR:
   - 100 mm of fall/1st hour.
     → It is also seen in GCA, SABE, MM.
2. Peripheral smear: Rouleaux formation (Clumping of RBCs on each other like a stack of coins).
   - Plasma cell leukemia: Plasma cells in peripheral blood - >2,000/µL.
3. A:G Ratio
   - The increased levels of ← globulin are seen.
4. KFT: Deranged
5. PET-CT > MRI To detect the bony lytic lesions.
6. Coagulogram
7. AG (Anion Gap): $(Na^+) - (Cl^- + HCO_3^-) = \downarrow$
   - Reduced anion gap.

Paraproteins are elevated
↓
Contribute to more positive charges in the body
↓
Kidney To maintain, electroneutrality will increase negative charges in the body by increasing urinary reabsorption of chloride ions
↓
Hence anion gap will decrease

8. Screening test for diagnosis of MM
   - UPEP and SPEP: M-Spike.
   - Immunofixation - Used to determine the subtype of protein.
9. Flow Cytometry Marker: Cd138.
10. Serum light chain assay: ↑
11. Urine β_2 Microglobulin levels
12. Amyloid fat pad biopsy.
13. FISH
14. IOC: Bone marrow biopsy
15. Imaging modality: PET-CT

Histopathological finding



1 2

1. Myeloma cells have Eccentric Nucleus with clock face chromatin.
2. Mott cell with Intracytoplasmic inclusions
   - Inclusions can be:
     → Intranuclear - Dutcher body
     → Intracytoplasmic - Russel bodies

Important Information

X-Ray skull shows

- Geographical skull in histiocytosis.
- Hair on end appearance, seen in:
  - Thalassemia,
  - Sickle cell anaemia,
  - Hemolytic anaemia.
- Ivory skull (Due to increased bone density) is seen in osteopetrosis.

Spectrum of plasma cell Dyscrasias

Diagnostic Criteria for Monoclonal Gammopathy of Unknown Significance

- Plasma cells in bone marrow: <10%.
- M-component: <30 g/L.
- No evidence of CRAB or myeloma like events in the patient.

Diagnostic Criteria for Smouldering Myeloma

- Plasma cells in bone marrow: >10%.
- M-component: >30 g/L.
- No evidence of CRAB or myeloma like events in the patient.

Diagnostic Criteria for Multiple Myeloma

- Plasma cells in bone marrow: >10%.
- M-component: >30 g/L.
- Evidence of CRAB or myeloma like events in the patient.

Diagnostic Criteria for Plasma Cell leukaemia

- Plasma cells in peripheral blood - >2,000/µL.

Prognosis of the Multiple Myeloma 00:54:37

- **Salmon durie staging** (Earlier).
- **International staging systems**.
  - For MM, it is based on two components:
    → β_2 Microglobulin
    → Albumin

Treatment of Multiple Myeloma

- Induction: Drugs
  - Steroid - Dexamethasone.
  - Thalidomide - Lenalidomide.
  - Proteasome inhibitor - Bortezomib.
- If the patients are transplant eligible:
  - Autologous bone marrow transplantation.
- Autologous bone marrow transplantation used in:
  1. MM
  2. Relapsed lymphoma

Waldenstrom Macroglobulinemia 00:58:50

- Excess and defective IgM class of antibodies are produced with coomb positive hemolytic anaemia.
- It is a tumour of lymphoplasmacytoid cells with excess production of immunoglobulin: IgM.
- No bony lytic lesions are present.
- No Hypercalcemia.
- **Treatment:** Ibrutinib.

Heavy chain disease

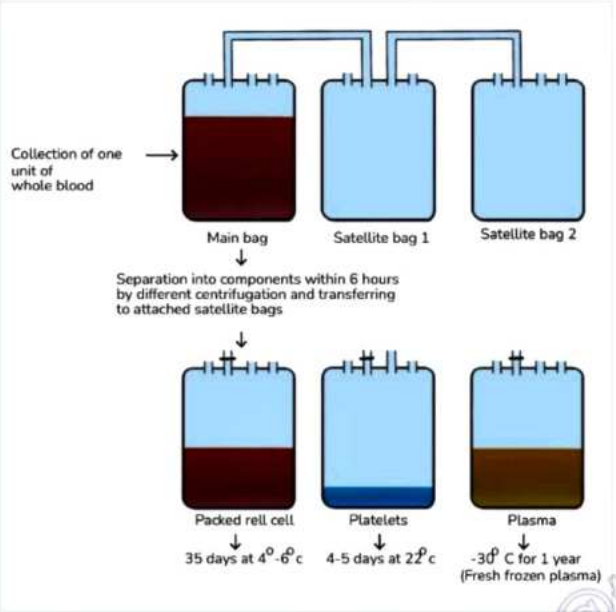
- γ Chain overproduction: Franklin disease.
- α Chain overproduction: Seligman disease (More common).
- μ Chain disease.

POEM syndrome 01:02:30

- **P - P**olyneuropathy.
- **O - O**rganomegaly
  - These can be:
    → Splenomegaly
    → Hepatosplenomegaly
    → Lymphadenopathy
- **E - E**ndocrinopathy
- **M - M**-Protein component
- **S - S**kin changes
  → Hyperpigmentation.
  → Acrocyanosis.

6 BLOOD COMPONENTS

Methods of Generation of Blood Components 00:00:17



- Satellite bags are attached to the main bag (whole blood)

Method 1

Whole blood
↓
High speed Centrifugation
↓
Packed RBCs (increased hematocrit)
Fresh Frozen Plasma FFP (stored at -30°C for 1 year)
Buffy coat (WBC) + Platelets

Buffy coat (WBC) + Platelets
↓
Low speed Centrifugation
↓
Platelets (pooled)

Method 2

Whole blood
↓
Low speed Centrifugation
↓
Packed RBC
Platelet rich plasma (PRP)

Platelet rich plasma (PRP)
↓
High speed Centrifugation
↓
Random Donor Platelets (RDP) + FFP

FFP (from both method 1 and 2)
↓
Thawed
↓
Cryoprecipitate

Packed RBCs 00:02:47

- **Storage temperature:** 4°C
- **Shelf life**
  - 35 days - CPDA (Citrate Phosphate Dextrose Adenine)
  - 42 days - SAGM (Saline Adenine Glucose Mannitol)

Whole Blood 00:03:18

- **Storage temperature:** 4°C
- **Shelf life**
  - 35 days - CPDA (Citrate Phosphate Dextrose Adenine)
  - 42 days - SAGM (Saline Adenine Glucose Mannitol)
- **Use:** Volume replacement in Acute hemorrhagic shock due to Peptic ulcer disease or gunshot injury

Hemorrhagic Shock

>25% of circulating fluid volume depletion
↓
Oxygen carrying capacity is affected
↓
Hypoxia and Metabolic acidosis. Loss of blood will also reduce body Temperature.
↓
Clotting ability is reduced

Extra Mile:
Trauma Triad of death
1. Acidosis
2. Hypothermia
3. Coagulopathy

Problems with storage of whole blood
1. Platelet count is decreased (longivity reduced)
2. 2, 3 DPG levels fall → increased O_2 affinity of RBCs

Increased O2 affinity of RBCs
↓
RBCs won't give blood to tissues, instead they keep it to themselves.
↓
Less delivery of O_2 to tissues, causes tissue hypoxia

3. Decreased factor 5 and 8 (heat labile factors)

Q. How much Hb is increased with 1 Unit of PRBCs?
Ans: 1gm%.

Q. How much Hematocrit is increased with 1 Unit of PRBCs?
Ans: 3%.

- PRBC is mainly used in Thalassemia major cases, where it increases Hb and PCV/Hematocrit.
- **Main advantage of PRBC over Whole blood -** Volume overload is avoided.

Q. What is the optimal target Hb to be achieved in a person who received PRBC?
Ans: Hb 7-8%

Platelets 00:09:10

2 methods:

- **Pooled platelets**
  - Taken from different people with the same blood group
  - Bag capacity: 50 to 70 ml
- **Single Donor Apheresis Platelets (SDAP)**
  - Donor undergoes Apheresis
  - Bag capacity: 200 to 400 ml

Q. When will we see spontaneous bleeding?
Ans: Platelet count is <5000/ cumm.

Q. If no fever/ no infection, then what is the threshold value of giving platelet Transfusion
Ans: 5000/ cumm.

- **Shelf life:** 5 days.
- **Storage temperature:** 20 to 24°C
- Stored in a state of constant agitation
- Should be transfused immediately
- Chances of infection are high with platelets due to storage at room temperature.

Fresh Frozen Plasma (FFP) 00:12:50

- Chances of infection are very low compared to others
- FFP can't transfer CMV, as this is transmitted via WBC (there are no viable WBC as FFP is stored for longer time)
- **Bag capacity:** 200 to 250 ml
- **Storage temperature:** -30°C
- FFP have more clotting factors (2% higher), thus preferred in patients with coagulopathy.
- **FFP provides:**
  1. Fibrinogen (preferred in DIC)
  2. Protein C and S
  3. Antithrombin III
  4. Albumin (used in patients with burn after 24hrs)
  - FFP can only be given after 24 hours in a burns patient, till then fluids and electrolytes are given.
- **Uses of FFP**
  1. Reversal of coagulopathy with respect to warfarin toxicity, in case Prothrombin complex concentrate is not available.
  2. DIC - Disseminated Intravascular Coagulation
  3. Plasmapheresis, especially in
     → TTP - Thrombotic Thrombocytopenic Purpura
     → GBS - Guillain-Barré syndrome
     → MG - Myasthenia Gravis

Cryoprecipitate 00:15:33

- **Formation:** FFP → Thawed → Cryoprecipitate.
- **Main Components**
  - Factor 8
  - Fibrinogen
  - Von Willebrand factor

Q. What factor is not present in Cryoprecipitate?
Ans: Factor 9

- Cryoprecipitate is not used in managment of bleeding in Christmas disease/ Haemophilia B as it doesn't contain Factor 9.

- **Uses**
  - Coagulopathies (fibrinogen is increased by 0.3 to 1gm %)
  - Type II Von Willebrand disease (dysfunctional VW factor)
  - Type III Von Willebrand disease (absence of VW factor)
  - Used as topical glue (to aid in hemostasis)

7 BLOOD TRANSFUSION COMPLICATIONS

Blood Grouping and Cross Matching 00:00:18

- Proper blood group cross-matching is essential to prevent complications.
- ABO system is used for blood grouping and cross matching.
- ABO system is located on chromosome 9q.
- Pattern of inheritance is co-dominant.

H antigen

- The antigen present on the red blood cell surface that decides the blood group is H antigen.
- H antigen decides if a person has blood group A, B, AB or O.
- H antigen composed of fucose sugar attached to a glycolipid.

Blood group	Components
A	H antigen (fucose + glycolipid) + N-acetylgalactosamine
B	H antigen + Galactose
AB	H antigen + N-acetylgalactosamine + Galactose
O	H antigen - (N-acetylgalactosamine + Galactose)

- Most common blood group is O^+
  - 45% of Indians are O^+
- Least common blood group is O_H-
  - Known as the Bombay blood group
  - H antigen is absent
- AB- is the second-best answer for least common blood group, if O_H- is not provided as a choice.

D antigen

- Another antigen present on the surface of the red blood cell.
- D antigen determines if the person is Rhesus $^+$ or Rhesus $^-$.
- A person can be D^+ (Rh^+) or D^- (Rh^-).
- D antigen is an alloantigen and isoimmunization can occur.
- D antigen is located on chromosome 1.
- 15% of the world population is D^- (Rh^-).
- Isoimmunization can occur in pregnancy or after blood transfusion in Rh^- people.

Important Information

- HLA antigen - Chromosome 6
- ABO blood groups - Chromosome 9 (co-dominant)
- Rhesus - Chromosome 1
- MNS blood groups - Chromosome 4

Duffy antigen

- Acts as a receptor for Plasmodium vivax.
- A person who is Duffy antigen + is susceptible to Plasmodium vivax infection.
- A person who is Duffy antigen – is resistant to Plasmodium vivax infection.

Pre-donation bag 00:06:52

- Initial part of blood that flows out into the tubing drains into the pre-donation bag.
- 10-30 ml of blood flows into the pre-donation bag.
- Advantage of pre-donation bag:
  - Reduces chances of any contamination e.g. bacterial contamination reaching the main bag.
- Blood released from the blood bank should be transfused within 4 hours.
- Keeping blood at room temperature for more than 4 hours allows the bacteria to grow, thereby inducing sepsis in the patient receiving the blood.
- Some bacteria can grow at 4°C in the blood bank refrigerator.
  - These bacteria can coat the bag surface.
  - Poking the bag allows their entry into the stored blood.
  - Quality control in the blood bank is necessary to minimize Pseudomonas sepsis.
  - The pre-donation bag helps to reduce the incidence of S. aureus or S. epidermidis or coagulase negative staphylococcus infections.
- Role of the pre-donation bag:
  - Enables diversion and collection of the first amount of blood which usually contains skin particles and bacteria.
  - It is especially crucial in reducing S, aureus, S. epidermidis or coagulase negative staphylococcus bacteria.

Leucodepleted Blood

- White blood cells can cause complications like febrile non-hemolytic transfusion reaction.
- Leucodepleted blood definition: < 1-5.10^6 donor leucocytes
  - A special filter is used in sensitized patients e.g., multiparous ladies. Ideally prestorage leucocyte reduction is recommended.
  - Sensitized people have a higher risk of complications.
  - Filter prevents the transfusion of white blood cells.
  - A bonus advantage is the blocking of specific viruses carried within white blood cells e.g., cytomegalovirus.
- Advantages of using leucodepleted blood
  1. Reduces febrile non-hemolytic transfusion reactions.
  2. Reduce cytomegalovirus/ Intracellular pathogens
  3. Reduce Alloimmunization and immunomodulation

Addditive Solutions

- The components of the blood aid in blood storage and prevent clothing
- Additive solutions in the donation bag:
  - Citrate-phosphate-dextrose-adenine (CPDA).
  - Saline-adenine-glucose-mannitol (SAGM).
  - Acidified citrate-dextrose (ACD).
  - Citrate-phosphate-dextrose (CPD).

Shelf Life of Blood with Additive solution 00:11:20

Solution	Shelf life
ACD	21 days
CPD	28 days
CPDA	35 days
SAGM	42 days

- CPDA is the most commonly used solution.
- Storage temperature within the blood bank is 4°C.
- Dextrose aids in providing nourishment for red blood cells.
- Citrate acts as the anti-clotting agent.
  - Binds calcium that is a co-enzyme in the clotting cycle.
  - This mechanism allows it to prevent blood clotting.
- Adenine aids in maintaining ATP storage which is crucial for maintaining the integrity of the red blood cells.
- 15 ml of ACD, 14 ml of CPD or CPDA used for preserving 100 ml of blood.

Citrate Toxicity

- If citrate is in excess, hypocalcemia and tetany occur.
- Tetany can cause laryngospasm and death.
- The patient presents with laryngospasm and difficulty speaking after transfusion.
- Citrate metabolized in the liver to produce bicarbonate.
- Excess bicarbonate causes metabolic alkalosis.
- Metabolic alkalosis may also contribute to encephalopathy.
- Both alkalosis and acidosis interfere with the integrity of the blood-brain barrier, causing encephalopathy.
- If blood is stored for a long time, the sodium-potassium pumps will fail.
- Pump failure cause increase in potassium levels in red blood cells.
- Transfusion with blood that is nearly expired leads to hemolysis of red blood cells.
- This leads to hyperkalemia causing bradycardia, diastolic arrest of the heart (K+ values > 8 mEq/L).
- Two reasons for hyperkalemia:
  - Prolonged storage leading to failure of sodium-potassium pump.
  - Transfusion of near-expiry blood.

Extra Mile:

Deleucocytation: To < 1-5/10^6 leucocytes per unit can be achieved by irradiation: X-Ray or gamma: 25-35 Gy. of units no older than 28 days: Harrism 21st update

Complications of Blood Transfusion 00:18:18

1. Febrile Non-hemolytic Transfusion Reaction 00:18:43

- Most common complication.
- Caused by antibodies to donor leucocytes or antibodies against HLA antigens.

People with increased risk

- Common in multiparous women
  - With each pregnancy, her immune system was sensitized, if she is Rh- and her husband and child are Rh+.
  - The mother may also have excessive bleeding after birth and receive a blood transfusion, stimulating her immune system with a large number of antigens.
  - Pre-existing antibodies attack the donor leucocytes.
  - This causes the release of cytokines e.g. interleukin-1 (IL-1) causing fever.
- Also common in people who have received multiple blood transfusions.
  - Could be due to hematological bone marrow-related disorders.

How the patient will present

- Temperature increase by > 1°C.
  - Blood transfusion does not need to be stopped.
  - Administer antipyretics.
  - Best method of prevention is the use of leucodepleted blood
  - Mild side effect

- Care should be taken to differentiate temperature increase due to febrile non-hemolytic transfusion reaction and anaphylactic shock.

2. Allergic Reaction 00:20:26

- Presents mainly as urticaria i.e., itching.
- Management: Stop transfusion temporarily as the itching will gradually reduce after a few minutes.
- Antihistamines may be given to manage the itching e.g., diphenhydramine.
- Can resume the blood transfusion after urticaria is subsided.

3. Anaphylaxis 00:23:37

- Anaphylactic shock is related to histamine release.
- Histamine causes vasodilation, leading to decreased blood pressure and increased heart rate.
- Patient vitals should be monitored every 5 minutes for the first 15 minutes.
- Thereafter, vitals can be measured in 15 minute or 30 minute intervals.
- Anaphylactic shock can also cause central cyanosis.
- Histamine release contributes to laryngeal edema that makes intubation difficult.
- Patient develops stridor and rhonchi.
- Rhonchi is caused by bronchospasms related to histamine release.
- Patient also develops associated pruritus.

Management

- Blood transfusion should be stopped immediately.
- Subcutaneous adrenaline is administered.
- Dilution of adrenaline is 1:1000.
- An ampoule containing 0.5 mg of Undiluted adrenaline is given.

Important Information

- Diluted adrenaline is used in cardiac arrest.
- Undiluted adrenaline is used in anaphylactic shock following blood transfusion.

4. Acute Hemolytic Reaction 00:25:45

- Mismatched blood transfusion.
- Example of type II hypersensitivity reaction.
- Related to immunoglobulin M (IgM).

Clinical manifestations

- Hemodynamic instability:
  - Heart rate increases
  - Blood pressure decreases
- Fever
- Chills
- Temperature decreases by 1°C.
- Rash develops on the arm or front of the body.
- Chest pain/Flank pain
- Hemoglobinuria

Management

- Blood transfusion should be stopped immediately.
- Patient work-up is done.

Work Up

- Demonstrate the presence of hemolysis.
  - Hemolysis causes haptoglobin consumption.
    → Haptoglobin binds to hemoglobin.
    → Therefore, haptoglobin values reduce.
  - Red blood cells burst releasing lactate dehydrogenase (LDH).
  - LDH levels increase
- The trigger can be substantial to cause disseminated intravascular coagulation (DIC) and coagulopathy.
  - Coagulogram should be used.
- Blood grouping and cross-matching should be done.
  - The main reason for mismatched blood transfusion is a clerical error.
- The final step in management is to initiate diuresis.
  - Prevent the shutting down of the kidney.
  - Patient is given fluids.
  - Furosemide/mannitol are administered.
  - Flushes out the kidneys.
  - Mannitol is not given to patients with established acute renal failure.

5. Graft Versus Host Disease (GVHD) 00:31:28

- Rare side effect seen after
  - After blood transfusion
  - In allogeneic stem cell transplantation.

  Transfusion associated GVHD is seen in recipients who are unable to reject allogenic lymphocytes like immunosuppressed patients
- If both individuals have common HLA antigens, a reaction occurs.

Cause

- Donor T_s leucocytes/lymphocytes recognized as foreign antigens.
- Donor T_s lymphocytes target specific organs.
- After receiving blood transfusion from family member, developmental GVHD occurs due to the presence of common HLA antigens.
- Hence Doctors discourage directed donations from family

members.

Clinical manifestations

Occurs after 8-10 days

1. Fever
2. Diarrhoea
3. Obstructive jaundice
4. Pruritus

- Death after 3 weeks.

Target organs affected in GVHD

- Skin
- Gastrointestinal tract
- Liver

Prevention

- Use of irradiated blood
  - Most radiosensitive blood cell is lymphocyte, which are responsible for GVHD development.
  - Most radioresistant blood cell is platelet.

6. Transfusion-Related Acute Lung Injury (TRALI)

00:37:22

- Common in the first 6 hours of transfusion.
- More common when using fresh frozen plasma (FFP) than whole blood.

Cause

- Blood donated from a multiparous woman.
- Blood donated from a person who has previously received multiple blood transfusions.
- These individuals have pre-existing antibodies.
- TRALI occurs due to to donor plasma containing
  1. Anti-HLA II antibodies.
  2. Anti-HLA I antibodies.
  3. Anti-neutrophil antibodies.
- They act against nucleated cells, HLA class I and HLA class II.

Clinical manifestations

- Leucocyte aggregation in the pulmonary capillaries.
  - Result in ventilation/perfusion (V/P) imbalance.
  - Leads to respiratory distress.
  - Acute respiratory distress syndrome
- Antibodies cause release of cytokines from the recipient's leucocytes.
  - Leads to increased capillary permeability in the lung parenchyma.
  - Fluid accumulates in the alveoli.
  - Fluid is normally absent in the alveoli as the surrounding endothelial cells do not allow movement of fluid across the tight junctions and gap junctions into the alveoli.
  - In patients with TRALI or ARDS, there is movement of fluid from the pulmonary capillaries into the alveoli, causing pulmonary edema.
  - In cardiogenic pulmonary edema, pressure in the blood vessels is higher causing the fluid to leak into the alveoli.
  - In this case, there is no damage to the heart.
  - Instead, the sequence of events is initiated by cytokine release.
  - TRALI is Non-cardiogenic pulmonary edema.

Prevention

- Avoid taking blood transfusions from multiparous women and people who have previously had multiple blood transfusions.

Confirmation of diagnosis

A. PaO_2/FiO_2 ratio determined.
   - PaO_2 is the partial pressure of oxygen.
   - FiO_2 is the fraction of inspired oxygen.
   - PaO_2/FiO_2 should be <300.

B. Evidence of absence of left atrial hypertension.
   - Left atrial hypertension occurs in cardiogenic pulmonary edema.
   - PCWP<AP is one of the criteria for ARDS.
   - There is no congestive heart failure.

- Insult will occur in the lung.
  - Should cause manifestations within 7 days.

C. Chest X-ray presents bilateral infiltrates present in the parenchyma.

D. Bilateral fine crepitations is an auscultatory finding in all patients of pulmonary edema.

E. Blood pressure may remain normal or be relatively lower.

F. Jugular venous pressure (JVP) is normal.

G. Brain natriuretic peptide (BNP) is normal.

7. Transfusion-Associated Circulatory Overload (TACO)

00:46:00

- Associated with increased blood pressure, JVP and BNP.
- Harrison 21st update: TACO is leading cause of death after blood Transfusion.

Q: A chronic kidney disease (CKD) patient is scheduled for dialysis next week. His hemoglobin levels were low as 7gm/dl. The doctor decides to transfuse 2 units of whole blood. (Ideally, one unit of blood is transfused over 4 hours.) Blood transfusion of 2 units occurred in a span of 4 hours. The patient then developed respiratory distress, elevated blood pressure and bilateral fine crepitations within the lungs. Condition?

Answer: TACO

If a blood transfusion is performed and the patient experiences breathlessness or respiratory distress, what are some complications that should be considered?

1. TRALI
2. TACO
3. Tetany

- TRALI can be distinguished by bilateral fine crepitations.
- In TRALI, blood pressure will be normal to low, JVP will be normal and BNP will be normal.
- Bilateral fine crepitations will also be observed in TACO due to circulatory overload.
- In TACO, blood pressure is elevated, JVP is elevated and BNP is elevated.
- Management of TRALI involves the use of ventilators.
- Management of TACO involves the use of diuretics to ease on the circulatory filling.
- Tetany contributes to breathlessness secondary to laryngospasms, causing decreased oxygen saturation.
- Tetany is caused by citrate toxicity.
- In this case, the patient also presents with stridor, cyanosis and tachycardia.
- BNP levels are normal.
- Chest X-ray is bilaterally clear.
- Conducted sounds due to laryngospasm can be auscultated.
- No fine crepitations

Q. If a blood transfusion is performed and the patient develops fever, what are some complications that should be considered?

1. Febrile non-hemolytic transfusion reaction
2. Anaphylactic shock
3. Mismatched blood transfusion

8. Electrolyte Imbalance 00:51:30

- If a person receives 2 or 3 units of blood in the recent 24 hours, they are likely to develop metabolic alkalosis.
- The dangerous effect observed with multiple transfusion protocol or trauma-induced coagulopathy is hypothermia.
- Following trauma, blood loss causes shock that subsequently causes metabolic acidosis.
- Trauma-induced coagulopathy is associated with metabolic acidosis.
  - Massive transfusion protocol is required
  - 6 units of packed red blood cells
  - 6 units of fresh frozen plasma (FFP)
  - 6 units of platelets
- Electrolytemia can lead to metabolic alkalosis secondary to excessive citrate present in unit of blood.
- Near-expired blood contributes to sodium-potassium pump failure.
- Leads to hyperkalemia
- Excessive citrate explains manifestations of tetany.
- Calcium levels decrease to < 7 mg/dl.

9. Iron toxicity 00:52:54

- Seen in patients that require recurrent transfusions e.g. a thalassemia patient.
- The patient may also develop secondary hemochromatosis.
- Serum ferritin levels increase.
- Serum ferritin is an acute phase reactant.
- 1 unit of blood provides 200-250 mg of iron.
- Features of secondary hemochromatosis develop if patient receives ≥ 100 units of blood.
- Iron content increases to 20 grams.
- For hemochromatosis manifestation to occur, 100 units of blood is needed e.g., in thalassaemic patients who are transfusion-dependent as their bone marrow does not produce normal red blood cells.

Clinical manifestations

- Bronze diabetes.
  - Skin hyperpigmentation
  - Iron deposited in the skin
- Liver cirrhosis
  - Iron destroys the hepatocytes
- Type I diabetes mellitus
  - Iron destroys pancreatic cells

Prevention

- Use of iron chelators
  - Desferrioxamine
  - Deferiprone
- Deferiprone is an oral iron chelator with vast side effects.
- Deferrioxamine is given as a subcutaneous infusion.

10. Infections 00:55:42

- HIV and Hepatitis B are ruled out by proper testing.
- 5 antigens that should tested mandatory
  - HIV
  - Hepatitis B
  - Hepatitis C
  - Syphilis
  - Malaria
- Some bacteria that can grow at 4°C and higher.
- Most common infection after blood transfusion is sepsis, followed by hepatitis B.
- Leading cause of transfusion-associated hepatitis is hepatitis B.
- Most common infectious complication after blood transfusion is bacterial.
- Fresh frozen plasma (FFP) does not transmit bacteria.
  - Devoid of cellular components i.e., acellular.
  - Advantage of FFP: Chances of bacterial infection are significantly minimized.
- Platelets are stored at room temperature (20-24°C).
  - The storage bag may harbour coagulase negative Staphylococcus from the skin.
  - Platelets should be transfused as early as possible, ideally within half an hour of arrival from the blood bank.
- Infections can be prevented by good quality control.

Viruses

- Human T-lymphotropic virus-1 (HTLV-1).
- Hepatitis E virus may be transmitted.
- Hepatitis A virus transmission is rare.
- HTLV-1 associated with development of:
  - Tropical spastic paraparesis/paraplegia.
  - Adult-onset T-cell leukaemia.

Other Complications after blood transfusion 01:00:25

11. Hypotension

- Occurs in patients taking angiotensin-converting enzyme (ACE) inhibitors.
- ACE inhibitors contribute to increased bradykinin as they inhibit bradykinin breakdown.
- Stored blood could have bradykinin.
- Bradykinin is a potent vasodilator that contributes to hypotension.

12. Immunomodulation

- Blood transfusion results in decreased immunity.
- False positive Mantoux test.
- Improved survival of kidney graft.
- People who have recurrent blood transfusions have reduced chances of reacting in a kidney transplantation.
- This is due to decreased immunity.
- Multiple bone transfusions are done before kidney transplantation surgery.

8 HODGKINS AND NON-HODGKINS LYMPHOMA

Hodgkin's lymphoma

00:00:10

- Cure rate: Greater than 85%
- The main concern for the treatment is the side effects of the anticancer drugs.
- The management mainly focused on using protocols that maintain a higher efficacy.

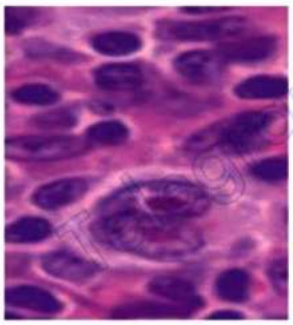
Aetiology:

1. Epstein Barr Virus
2. HIV

Extra mile:
AIDS Defining Cancers

1. Kaposi's sarcoma
2. Non-hodgkin's lymphoma
3. Invasive cervical cancer HPV 16 and 18: causing

- **Investigations:** Excision lymph node Biopsy
  - Presence of classical Reed sternberg cells (Owl eye like appearance)



→ These cells are abundant with cytoplasm and the nucleus is cleft or bilobed.
→ Prominent nucleoli is present inside the nucleus
→ Genetic aberration related to Reed sternberg cells: 9p 24.1

- Hodgkin's lymphoma is not the part of AIDS defining lymphoma.

Extra mile:

Q. A patient suffering from end stage renal disease, GFR is 10 ml/min and underwent kidney transplantation. Post kidney transplantation patient developed graft failure inspite of taking anti rejection drugs. Urine m/e shows owl eye appearance in Renal Tubular cells. Which organism is Responsible?

Ans: CMV

- Hodgkin's Lymphoma is a mature B cell tumor.
- Lymph nodes are filled with the cancerous cells.
- One single cell will have a clonal arrest (Multiply again and again without the differentiation)
- Acute lymphocytic leukemia: Whole bone marrow is filled with the Lymphoblasts.
- In Hodgkin's Lymphoma, mature B cell tumors will have a polyclonal inflammatory infiltrate that will be composed of multiple cells.
- The percentage of Reed sternberg cells are very limited in lymph nodes.

Clinical Presentation

1. Hodgkin's Lymphoma has a Bimodal age of distribution.
2. It may develop at 20 years of age or in the patient's with multiple comorbid conditions (i.e., 80 years)

3. Progressive cervical lymphadenopathy

- Early stage: Painless. Misdiagnosis as TB lymphadenitis.
- **Consistency of lymph nodes in Hodgkin's:** Rubbery consistency (Lymph nodes are discrete)
- In later stages, pain may be experienced on alcohol consumption.

4. Hilar Lymphadenopathy

A. The patient may suffer from noisy breathing (Development of Stridor)
B. Lymph nodes may press the superior vena cava, causing congestion of neck veins and even the development of collateral that will send the blood to the downstream (Facial plethora)
C. Compression of the thoracic duct (Development of Chylous ascites)

5. Porta Hepatis Lymph Nodes enlargement

- Compression of the common bile duct (Obstructive Jaundice, Pruritus)
- Retroperitoneal lymph node enlargement causing Hydronephrosis.

6. Category B Symptoms

A. Weight loss >10% over the previous 6 months
B. Drenching night sweats
C. Loss of appetite

Extra Mile:

Superior Vena cava Syndrome

- Leading Cause: Oat cell cancer of lung

Involuntary weight loss/Unintentional weight loss

- 5% over 6-12 months [Ref: Page 309, Harrison 21st edition]
- **Hematological malignancy:** 10% over 6 months

7. **Fever**
- Low to moderate grade
- Cyclic pattern of fever that rises and falls every one or two weeks.
- The above condition is known as Pel Ebstein fever.

8. **Paraneoplastic Manifestations**

A. Cerebellar degeneration
B. Guillain-Barré syndrome
C. Nephrotic syndrome: Membranous glomerulopathy
   - It is associated with the solid organ tumors (Hodgkin's lymphoma)
D. Hypercalcemia

Important Information

Malignancies related to hypercalcemia

1. Squamous cell cancer is responsible for the production of PTHRP (Parathyroid hormone related peptide)
2. Breast cancer
3. Multiple myeloma

9. Immune mediated anemia and thrombocytopenia
   - Anemia is common in any hematological malignancy
   - Disease progression causes cytopenia.
   - But in case if immune mediated, cell count will be decreased in CLL and in hodgkin's lymphoma.

Workup of Hodgkin's Lymphoma

Investigation:

1. CBC
2. LDH values are increased (Prognostic index)
3. Imaging: PET-CT (Accurate)
   - It helps in identifying the disease focus and in the staging (Ann Arbor classification)
4. **CT chest and CT abdomen**
5. Investigation of choice: Excision lymph node biopsy
   - Sample are analyzed through flow cytometry.
   - It results in CD 15 and 30 positivity (cHL)
   - CD 15 and 30 is negative in Atypical hodgkin's lymphoma.
   - As it is a B cell tumor: CD 19, CD 20 (Low or no expression)
   - PAX 5 positivity is expressed.
6. **Pulmonary Function Tests**
   - To check the baseline status of the lungs
7. **Echo**
   - To check the baseline status of the heart
   - To check whether the patient is fit to receive the full course of chemotherapy (6 cycles)
8. **Infection panel**

Modified Ann Arbor Classification

Stages	Explanation
Stage I	• Single group of lymph nodes (Cervical lymph nodes are enlarged) • Or the involvement of other lymphoid tissues like spleen, thymus
Stage II:	• Minimum 2 groups of lymph nodes • Present on the same side of the diaphragm. • Diagnosed through CT or PET-CT
Stage III:	• Minimum 2 groups of lymph nodes • Present on the both side of the diaphragm
Stage IV:	• Extranodal extension of the disease (Liver and bone marrow) • In Leukemia: Cancer begins in bone marrow and moves to lymph nodes. • Here, tumor is started in the lymph node and moves to the bone marrow. • Hence cytopenia is seen.

	• 2A or 3A: No category B symptoms
	• 2B or 3B
	  ○ Weight loss >10% over 6 months
	  ○ Persistent fever (Unexplained)
	  ○ Drenching night sweats
	• 2E or 3E: Extralymphatic site
	  ○ Sites other than liver and bone marrow

Differential Diagnosis

- Infection of TB should be ruled out.
- Infectious mononucleosis (NHL)
  - Common in young adults
  - Other Name: Kissing disease
- History of Recurrent seizures (If Phenytoin is used)
  - Commonly used drug for Epilepsy: Lamotrigine
  - Long-term use of phenytoin may induce lymphadenopathy
- In older age group, non-lymphomatous malignancies should be considered.

WHO Modified Real Classification

- It is the revised American and European classification.

1. Nodular sclerosis
   - Most common
   - Cell: Lacunar variant
2. Mixed cellularity
   - More common in India
   - Classical reed sternberg cells are present
   - HIV-positive patients may have both mixed cellularity and lymphocyte depletion.

- 95% of the classical Hodgkin's lymphoma is Nodular sclerosis and mixed cellularity

3. Lymphocyte rich
4. Lymphocyte depletion
5. Nodular lymphocyte predominant hodgkin's lymphoma

- Non classical or atypical variety
- Presence of traditional popcorn cells (Variants of reed sternberg cells)
- Alternative Name: L and H cells (Lymphocyte and histiocyte)
- It is CD15, CD30 negative
- CD19 and CD20 are better expressed.
- CD45 and CD79A are also identified.
- Progression of the tumor is slow (Indolent Presentation)
- May Transform into the diffuse large B cell lymphoma.

Extra mile:

- Popcorn like manifestation seen in Chest x ray: Benign tumor in the lungs (pulmonary hematoma)
- Popcorn like manifestation seen in Mammography: Benign tumors of the breast (Fibroadenoma)

Treatment

- It is based on if the disease is: Advanced or Localized.

Localized disease

- Chemotherapy(ABVD) and Radiotherapy (Field radiation)
- Disadvantages of Radiotherapy:
  - Cardiomyopathy
  - Atherosclerosis

Advanced disease

- ABVD protocol

Side effects of the drugs (Standard chemotherapeutic drugs)

- **Adriamycin:** Damages the heart
- **Bleomycin:** Pulmonary fibrosis
- Vinblastine, Dacarbazine

Other Protocols used: Stanford V regimen, BEACOPP

Treatment for the Relapse of Hodgkin's lymphoma

- Brentuximab (Monoclonal antibody)
- Autologous bone marrow transplantation

International Prognostic Index

- Helps to determine the chances for the survival of the patient.
  1. Age, gender of the patient is noted.
  2. Values of Lactate dehydrogenase
  3. **Lab reports which are added:** Hemoglobin, Albumin, TLC, and lymphocyte count
- Based on the entered information, the survival chances of the patients are given
- Disease can be cured in more than 85% of the patients

Nodular Lymphocytic Predominant Hodgkin's Lymphoma

- L and H cells (Lymphocyte and histiocyte)
- **Other Name:** Popcorn cells
- It is CD15, CD30 negative
- Transform into the Diffuse large B cell lymphoma
- If progression is present, two strategies are used
  - Radiotherapy (To shrink the size of the lymph node)
  - Chemotherapy (Both ABVD and R CHOP)
  - R CHOP is used for non hodgkin's lymphoma with high success rate

Non-Hodgkin's Lymphoma 00:44:20

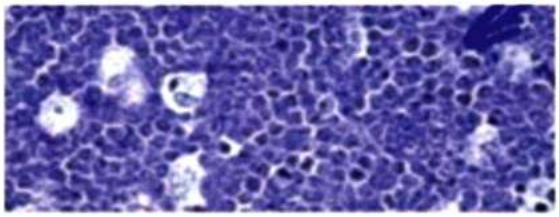
Aetiology

Viruses

1. Epstein Barr Virus
2. HIV
3. HTLV 1
   - Responsible for the development of adult T cell leukemia which on P. Smear shows Flower cells or Clover leaf pattern.
   - It causes Tropical spastic paraparesis.
4. HHV 8
   - It is responsible for the development of Kaposi's sarcoma.
   - **Current Name:** Kaposi's herpes simplex virus (KHSV)
   - It leads to the development of rare Non- Hodgkin's lymphoma known as primary effusion lymphoma.
   - HHV 8 is also responsible for Castleman disease (Onion skin appearance)
5. Hepatitis C Virus: Lymphoplasmacytic lymphoma
6. H. Pylori: Responsible for Gastric Mucosa associated lymphoid tumor (MALToma) and involving the Chromosomes swap t (11:18).
7. t (14:18): Most common chromosomal translocation involved in pathogenesis NHL
8. t (11:14): Responsible for Mantle cell lymphoma
   Mantle cell lymphoma can be differentiated from chronic lymphocytic leukemia based on the flow cytometric markers.

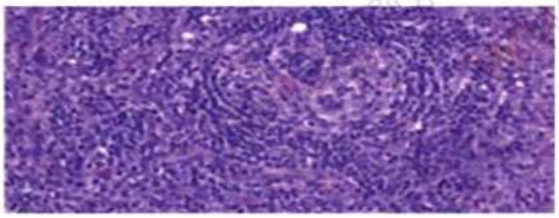
Extra Mile:
MC Histopathological subtype of NHL: Diffuse large B cell lymphoma. In pediatric age group, Burkitt lymphoma is seen with jaw swelling.

Histopathological Findings of Burkitt lymphoma:



- When the lymph node biopsy is done in the burkitt lymphoma, Sheets of blue cells (Basophilic nucleus and Basophilic cytoplasm) are seen.
- White spots present in between the blue cells are known to be Starry sky appearance.
- Chromosomal swaps include:
  - t(8:14): More common
  - t(2:8)
  - t(8:22)
- Overexpression of proto-oncogene can occur involving Chromosome 8q 24 causing overexpression of C myc.

Histopathological Findings of Castleman Syndrome:



- Mononuclear cell infiltrate is seen, and is arranged in a concentric fashion (Castleman syndrome)
- It has "onion ring" appearance.

Clinical Features of Non-hodgkin's lymphoma

- Bad prognosis
- Spread occurs through Hematogenous route.
- It is spread in a Non-contiguous fashion.
- Usually starts as Sub diaphragmatic lymphadenopathy.

Abdominal lymph node enlargement

1. Intestinal obstruction may be caused due to extreme amount of lymphadenopathy producing mass effect.
- Development of ascites may also occur.
- Hydronephrosis in case of retroperitoneal lymph node enlargement
- Non-hodgkin's lymphoma can also be presented as a testicular lump
- Acute Lymphocytic Leukaemia and Acute Myeloid Leukaemia will also have a Testicular presentation.

2. **Jaw swelling**
- Mostly presented in pediatric age group but may also present in the adults.

3. **Meningeal Spread**
- Features of Raised intracranial pressure or meningismus may be present.
- Blood cancer with meningismus is Acute lymphocytic Leukemia.
- Lumbar puncture is required to diagnose the spread of the tumor to the brain (Meninges)

4. **Category B symptoms**
- In Non-Hodgkin's Lymphoma, the initial presentation is ileocecal involvement contributing to the Stricture and features of subacute intestinal obstruction.

5. **Bone marrow involvement**
- Therefore, cytopenia will start developing (Progressive pallor and bleeding in the form of Epistaxis and bruises)

6. **Spinal cord compression**
- If Testicular involvement is positive, the lymph nodes present retroperitoneally press the the nerve roots causing the spinal cord compression like manifestations.
- Cranial nerve palsy (Due to Lymph nodes present at the base of the skull)
- The paraneoplastic manifestations caused are cerebellar degeneration and Guillain barre syndrome.

7. **Waldeyer's ring Involvement**
- Peculiar to non-hodgkin's lymphoma
- It means multiple tonsillar enlargement (Tubal tonsil involvement)

8. **Erythroderma**
- Tumor is originated from and is limited to skin is Mycosis fungoides
- Manifestations:
  - Extreme redness
  - Pruritic lesions. Misdiagnosed initially as Atopic Dermatitis
- When it spreads via blood it is called Sezary syndrome. It has Triad of Erythroderma, Lymphadenopathyand Sezary cells in blood/lymph nodes

Workup of the Patient's with Hodgkin's Lymphoma

Investigations

1. CBC
2. Elevated LDH levels (Prognostic marker in both hodgkin's and non-hodgkin's lymphoma)
3. **Imaging:** PET-CT scan
4. Instead of bone marrow biopsy to demonstrate colonization of cells, imaging is recommended.
5. **MRI spine:** For Neurological manifestations
6. **FISH:** To know the chromosomal translocation (11:18 or 14:18)
7. Investigation of choice: Excision lymph node biopsy along with flow cytometry

WHO Modified Real Classification

- It is the revised European and American classification.
- Predominantly it is a B cell tumor and some of them may be T cell tumors.
- Common: DLBCL (Related to Epstein Barr virus or HIV)
  - Immunoblastic subtype of diffuse large B cell lymphoma: HIV positive patients
- **Burkitt's Lymphoma:** Chromosomal swabs include:
  - t(8:14): More common
  - t(2:8)
  - t(8:22)
  - Overexpression of C myc will inhibit the apoptosis.
- **MALTOMA:** It is related to the H pylori.
- Lymphoplasmacytic lymphoma is seen with Hepatitis C

T cell Non Hodgkin lymphoma

Mycosis Fungoides	Sezary syndrome
• It is a cutaneous T-cell tumor	• It is a disseminated form of Mycosis Fungoides.
• Present with multiple eczematous lesions	
• Progression is very slow (Indolent course)	
• Manifestations: ○ Pautrier microabscess (If skin biopsy is done)	
• Later they may develop the erythroderma (extreme redness all over the skin) • **Peripheral smear:** Lymphocyte are seen with large nucleus (Occupy 90% of the cell) • Small construction is present in the middle (Sezary cell) • These cells will multiply and colonize in the liver and the spleen (Hepatosplenomegaly) • They may also move into bone marrow and contribute to the development of cytopenia.	

International Prognostic Index

- **Considerations**
  - Age
  - LDH values
  - Stage of the disease
  - Extra nodal site involvement
    → Common: GIT involvement
  - Eastern collaborative group (ECOG) Performance status
    → The comorbid patients will have poor prognosis than compared to relatively fit person.
    → Based on performance status of a patient, we can calculate the survival rate.

Treatment

- **Chemotherapy**
  - R CHOP
  → Rituximab (Anti CD20 molecule)
  → Cyclophosphamide (Alkylating agent)
    → Hydroxydaunomycin
    → Oncovin
    → Prednisolone

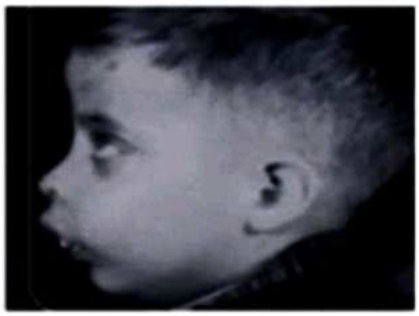
Extra Mile:

- Special feature of Hodgkin's lymphoma is Pel Ebstein fever.
- Chronic lymphocytic leukemia: Smudge cells on P. Smear
- Non-hodgkin's lymphoma: Waldeyer's Ring involvement

Investigational of Choice

- Chronic lymphocytic leukemia: Flow cytometry on blood sample
- Hodgkin's and Non-hodgkin's lymphoma: Excisional lymph node biopsy

9 THALASSEMIA



Chipmunk Facies seen in Thalassemia Major patients maxillary Bone expansion.

- Incisor teeth are more anteriorly placed.
- Frontal bossing

β-Thalassemia

00:01:28

- Autosomal recessive (25% chances in next generation)
- Chromosome 11
- HBB gene
- Missense or Nonsense mutation

Hemoglobin Electrophoresis

Hb	Birth (1st day)	Adult (6 months)
HbF (Fetal hemoglobin)	95%	2%
HbA (Adult hemoglobin)	2%	95% (α2β2)
HbA2	3%	3%

Q. HbA2 percentage is more than 3% in?
Ans: Thalassemia trait

- In β-thalassemia, Alpha chains coil among themselves producing α4 be Tetramers.
- These abnormal RBCs are destroyed in bone marrow, spleen and lead to severe anemia.
- Though the bone marrow produces RBCs quantity wise they are poor quality, and hence is known as Ineffective erythropoiesis.

Extra mile:

- The 1st hemoglobin to be formed in the embryo is Gower 1- Gower 2- Portland.
- These are known as Embryonic hemoglobins.
- By 14 weeks of gestation Fetal hemoglobin (HbF) is formed.

Hematopoiesis

- Starts in Yolk sac: 2nd week, Embryonic hemoglobins
- Liver, spleen: 14 weeks, HbF
- Bone marrow: 36 weeks, HbA appears.
- Sites responsible for hematopoiesis at birth
  - Skull
  - Vertebra, ribs
  - Pelvis and long Bones.
- Hematopoiesis shifts towards flat or long bones as we get older.
- In babies, all the bones are responsible for hematopoiesis.
- Skull is responsible for hematopoiesis in babies; hence malar prominence is seen is in β-thalassemia.
- The number of RBCs produced is normal, but the quality is poor.

β-Thalassemia Major

- 0% production of β chains
- α chains coil among themselves to produce α4 (tetramers), this is known as Ineffective erythropoiesis.
- Bone marrow detects these defective RBCs and destroys them.
- RBCs which enter peripheral circulation are destroyed by spleen (Extravascular Hemolysis).
- Babies <1 year show Severe anemia with
  1. CHF
  2. Chipmunk facies [Extra medullary hematopoiesis]
  3. Splenohepatomegaly

Extramedullary hematopoiesis is also seen in Myelofibrosis.

β-Thalassemia Intermedia

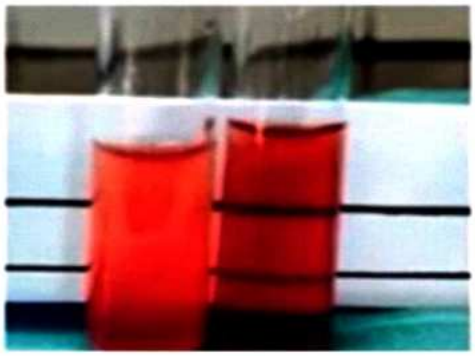
- 50% production of β chains
- Manifestations are less
- Age of presentation > 1year
- Child develops anemia, but not severe enough to cause CHF
- Splenohepatomegaly

β-Thalassemia Minor/ Trait

- Asymptomatic
- Relatively lower hemoglobin
- Microcytic Hypochromic anemia
- Generally, β-thalassemia minor/trait may be misdiagnosed as Iron deficiency anemia.
- If the patient takes iron supplements, there is no change in hemoglobin levels.

Screening test for β-Thalassemia

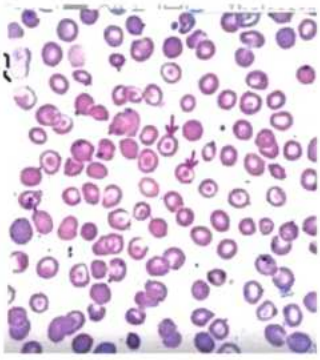
1. **NESTROFT**



   - NESTROFT (Naked Eye Single Tube Osmotic fragility test), is done.
   - Osmotic fragility of RBCs in thalassemia is reduced.

Note: In Hereditary Spherocytosis, osmotic fragility is increased, which makes RBCs to burst easily

2. Hemoglobin electrophoresis is best for identifying thalassemia minor.
   - **HbA2:** >3%
3. **Prenatal diagnosis**
   - Chorionic Villi sampling
   - Amniocentesis
4. **Peripheral Smear Test**



   - RBC is smaller
   - Dot in the center is due to the α4 tetramer (Target cells).
   - Target cells are more in number on a peripheral smear test.
   - Target cells are also seen in Chronic liver disease

Work Up of β Thalassemia

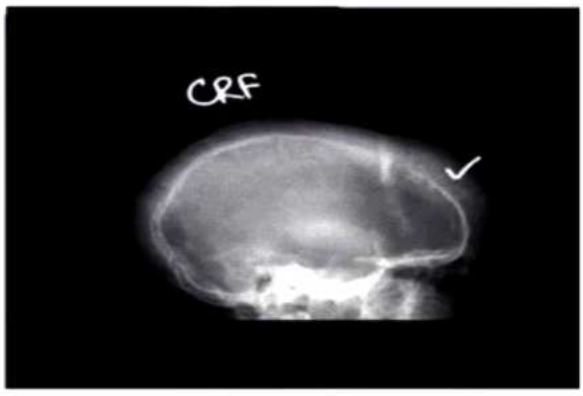
1. Hemoglobin reduced
2. Peripheral smear
   - MCHC (Microcytic hypochromic anemia)
   - Target cells
3. Reticulocyte count increased.
   - In thalassemia major, the reticulocyte count rise is lower compared to the severity of anemia.
4. NESTROFT: Osmotic fragility of RBC's is reduced
5. Investigation of choice
   1. PCR β globin gene sequencing, whenever available
   2. HPLC

Extra Mile:

- β globin gene (HBB) sequencing can be used to identify hemoglobin variants.
- Most commonly β Thalassemia sequence variants (beta plus and beta zero)
- This also identifies hyper unstable hemoglobin variants and dominant β-thalassemia sequence variants, other hemoglobin variants that cannot be identified by protein methods.
- Large deletions, alterations and crossover events will not be detected by β globin gene sequencing.
- The results of this test should always be interpreted within the context of the protein studies and RBC indices.

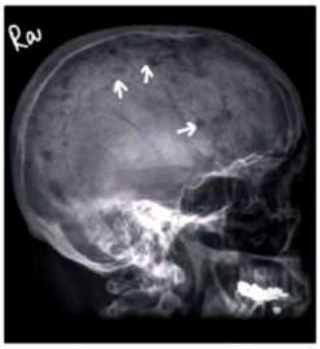
6. **Radiological investigations**

- **Crew cut appearance/Hair on end appearance on X-Ray skull**



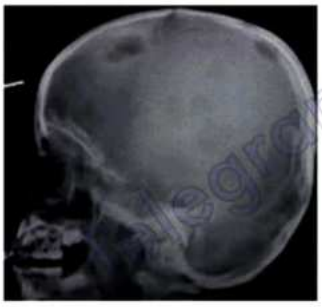
   - Widening of diploic spaces Squaring of Metacarpals on X-Ray hand

- **Multiple myeloma**



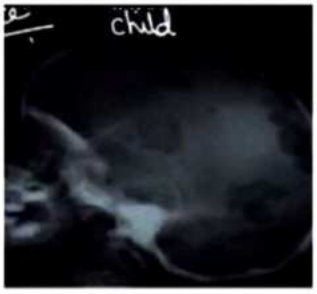
  - Multiple myeloma shows Raindrop (lytic lesions) like appearance.
  - Geriatric disease
  - CRAB features
    - → Hypercalcemia
    - → Renal failure
    - → Anemia
    - → Bony lytic lesions

- **Paget's disease**



  - Frontal bossing
  - Hearing issues
  - S.ALP is elevated disproportionately.
  - Geriatric disease

- **Histiocytosis-X**



  - Pediatric patient
  - Irregular lytic lesions that look like map of a country called Geographical skull.
- **Craniopharyngioma**
  - Lateral view of X-ray skull in a child shows, Sella turcica lesion in form of Intracranial calcification.

Treatment of Thalassemia Major

A. TOC: Allogenic bone marrow transplantation

B. Packed RBC, is initially transfused
  - Improve hemoglobin levels
  - Lifespan of transfused RBC: 60-80 days
  - Hypersplenism may occur which reduces the lifespan of transfused RBC
  - Transfusion required for every 1-2 months or even earlier.
  - Transfusion dependency may lead to:
    1. Secondary Hemochromatosis
    2. Bronze diabetes Triad
       - Liver Cirrhosis
       - Pancreas- Type 1 DM
       - Bronzing of skin
    3. Extra Iron can promote growth of bacteria, Yersinia enterocolitica

C. Prevention of Hemochromatosis by using Iron chelators
  - → Deferoxamine (subcutaneously)
  - → Oral Deferoxamine

D. To Prevent allergic reactions after Packed RBC
  - → Leuco depleted (Irradiated blood)
  - → Filters, stop WBCs.
  - → Triple saline washed RBCs.

E. Elective splenectomy is done in patients with increased transfusion dependency.
- Transfusion dependency increased >50% over last year.
- Elective splenectomy also used in
  - Hereditary spherocytosis
  - Chronic ITP

F. Lusapatercept: Enhances late stage Erythropoiesis [Harrison 21st edition update]

α-Thalassemia 00:42:36
- Autosomal recessive
- Chromosome 16
- **Genes involved**
  - HBA1
  - HBA2

Synthesis of α2β2
- 2 α chains- 4 α genes are required.
- 2 β chains- 2 β genes are required.

Variant	Production of α chains	Disease
- α α α	75%	Silent carrier
- - α α	50%	α- Thalassemia trait
- - - α	25%	Hb H (α-Thalassemia major)
- - - -	0%	Hb Barts (γ4)

Chromosome with one deleted α gene is called α^{+} Thalassemia
Chromosome with both deleted α gene is called α° Thalassemia

- Hb Barts (γ4) has high oxygen affinity
- Lack of oxygen to the tissues causes Heart failure in fetal life.
  1. Severe anemia
  2. CHF
  3. Edema (Hydrops fetalis - Non immunogenic)

Extra Mile:

- Rh incompatibility is immunogenic Hydrops fetalis.
- Hydrops fetalis is also seen in
  - Congenital Nephrotic syndrome (Finnish variety)
  - Complete Heart block
  - Congenital syphilis
  - α-Thalassemia

Diagnosis of α-Thalassemia

1. α- gene sequencing
2. HPLC
3. NESTROFT

Hereditary Spherocytosis 00:48:18

- Lesser surface area
- MCHC = MCH/MCV
- MCV is reduced, MCHC increased
- RBCs are flexible, which can travel through small capillaries
- Proteins in RBC membrane
  1. Spectrin
  2. Ankyrin
  3. Pallidin
  - Protein 4.2
  - Band 3 protein
- If any proteins are absent, RBC may become rigid.
- These rigid RBCs get stuck in the sinusoids of the spleen and cause Extravascular hemolysis.

Clinical Features

1. Pathological jaundice: Neonate will require Phototherapy.
2. Progressive Anemia
3. Splenomegaly
4. Pigmented gallstones (black)
   - Calcium bilirubinate
5. Non healing ulcer on Medial malleolus
6. Aplastic crisis (Human parvo B19)

Extra mile:

- Human parvo B19 causes:
  1. FSGS (Focal segmental glomerulosclerosis)
  2. Erythema infectiosum
  3. Aplastic crisis in children with H.S, Sickle cell Anemia

Work Up

1. Reduced Hemoglobin
2. **Peripheral smear:** Spherocytes: Lack of central pallor

Extra Mile:

- Spherocytes are seen in
  1. AIHA (Autoimmune Hemolytic anemia)
  2. CLL (Chronic lymphocytic leukemia)
  3. HS

3. **NESTROFT:** Osmotic fragility increased.
4. **MCHC:** Right shift in normogram (increased)

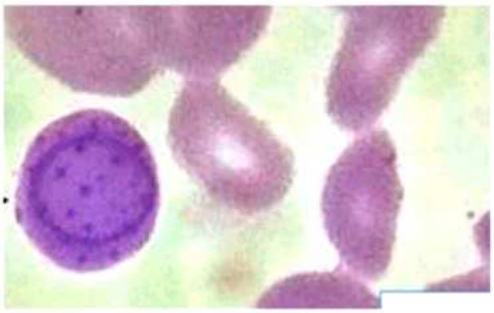
- Three criteria to be satisfied, to diagnose HS:
  - **Hemolysis**
    →Decreased Hb
    →Increased LDH
    →Increased bilirubin
    →Increased Reticulocyte count
  - Increased osmotic **fragility**
  - **MCHC:** Right shift in normogram

5. **Sensitive test:** NESTROFT > Osmotic gradient Ektacytometry
6. **Specific test:** Eosin 5' Maleimide (Flow cytometry)
7. **ELISA/ RIA:** Spectrin and Ankyrin assay
8. **Acidified glycerol test:** HS
   - Acid fragility test is for PNH

Treatment

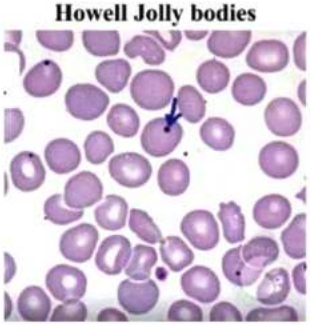
1. Elective splenectomy
2. Vaccines given for coverage for encapsulated organisms before Splenectomy
   - Pneumococcal vaccine
   - Meningococcal vaccine
   - Hib vaccine
   - Flu vaccine

Cabot Rings



- Post splenectomy (Asplenia)
- Vitamin B12 deficiency

Howell Jolly bodies



- Basophilic inclusions in RBCs seen after splenectormy
- In contrast Pappenhiemer Bodies are present in Sideroblastic anemia.
- Entire RBC is filled with bluish stipplings.

PREVIOUS YEAR QUESTIONS

Q. What is
mutation present in Beta Thalassemia?
Ans: Missense or Nonsense mutation

Q. In an 18 year person, which bones are responsible for hematopoiesis?
Ans: Flat bones

Q. Hematological conditions in which Autologous Bone marrow transplant is seen?
Ans:
1. Multiple myeloma
2. Hodgkin's lymphoma
3. Non-Hodgkin's lymphoma

Q. Where are brown gallstones seen?
Ans: Infections

Q. Adult patient with SLE, has peripheral smear with spherocytes.
Ans: AIHA

10 SICKLE CELL DISEASE, G6PD DEFICIENCY AND OTHER HEMOLYTIC ANEMIAS

Sickle Cell Anemia

00:00:13

- 1st case detected in 1952 at the Nilgiri hills in Tamil Nadu.
- Sickle cell trait or sickle cell anemia is highly prevalent in areas with high malaria incidences.
- Sickle cell trait is protective against malaria development.

Pathophysiology:

- Defective hemoglobin S (HbS) polymerizes.
- Red blood cells become rigid.
- Rigid red blood cells are trapped in the splenic capillaries and are destroyed at an accelerated rate within the splenic sinusoids.
- Extravascular hemolysis is also seen in
  - Thalassemia
  - Hereditary spherocytosis
- Red blood cells also become relatively stickier due to HbS.
- These cells may block off circulation at branching points.

- Multiple micro-infarctions occur in various organs, e.g., the spleen.
- Auto splenectomy can occur in this condition.
  - Child becomes susceptible to Opportunistic infections after Autosplenectomy.
- Fever and bone pain are some of the primary complaints.
- Blood supply of the bones, especially the small bones of the hand, may be compromised.
- Terminal branches of the nutrient artery are clogged as micro-infarctions occur in the bone.
- Avascular necrosis may develop, leading to severe bone pain and opioid abuse.

Clinical Manifestations

- Ethnicity: Afro-American, African, Tribal Indian child.
- Occur after a 6-month window of age
- Fetal hemoglobin protects against the clinical manifestations for the initial 6 months.
- Therefore, pathological jaundice is not presentation in sickle cell anemia.
- Pathological Jaundice presents in hereditary spherocytosis right after birth, requiring phototherapy and exchange transfusion.

1. **Fever**
   - Prevalence of infection increased as spleen develops micro-infarctions and is destroyed.
   - Acute abdomen and left upper quadrant pain due to micro-infarctions of organs due to sticky RBC.
   - This pain may be misdiagnosed as pancreatitis, or a condition related to renal etiology.
2. **Bone pain**
   - Avascular necrosis of the bone as the nutrient arteries and their terminal branches may develop micro-infarctions.
   - Investigation of choice for avascular necrosis is an MRI.
   - ANV of small Bones of hand is called Dactylitis

Extra Mile

- **Hand-and-foot syndrome**
  → Anticancer drugs, e.g., 5-fluorouracil, capecitabine.
  → Not to be confused with exanthematous disease associated with vesicular lesions on the sole of the foot, palms and inside the mouth, i.e., **Hand, foot and mouth disease** related to Coxsackie A virus.

- **Radiological finding in sickle cell Anemia**
  1. Fish vertebra
     - Blood supply of the upper and lower parts of the vertebral body is affected.
  2. Bone within a bone
     - Highlights the reactive and sclerotic changes due to avascular necrosis.
- Severe bone pain necessitates opioid use and risk of Addiction

Important Information

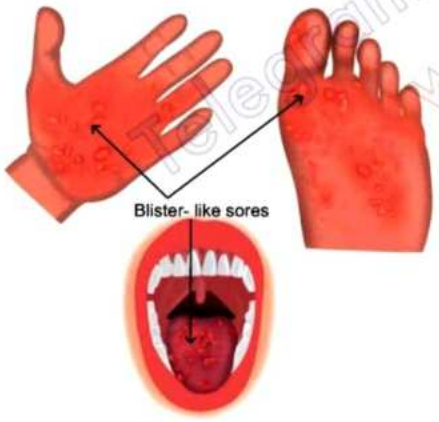
Radiological finding in Thalassemia vs Sickle cell Anemia
1. Thalassemia exhibits bone marrow expansion.
2. Its radiological finding is the squaring of the metacarpals.
3. In Sickle cell anemia, there may be a lytic lesion, bone versus a bone lesion or dactylitis.

3. **Acute abdomen**
   - Splenic crises as splenic blood supply is affected.
   - Left upper quadrant pain may be misdiagnosed as pancreatitis involving the tail of the pancreas or renal colic.
   - Child presents with recurrent splenic infarction with repeated hospitalizations.
   - Parenteral administration of painkillers.
   - Autosplenectomy occurs by 3 years of age, making the child susceptible to capsulated infections.
   - The infections common in this case are Pneumococcus, Meningococcus and Haemophilus influenzae.
4. **Cardiac involvement**
   - Terminal branches of Coronary arteries called perforators, can be occluded by Sickle RBC causing Ischemic damage to heart muscles and Dilated cardiomyopathy

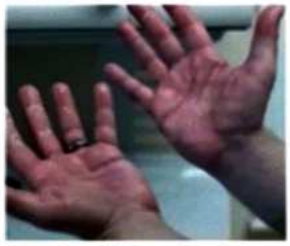
- Acute chest syndrome
  - → Not to be confused with the acute coronary syndrome.
  - → Atherosclerosis in the main coronary artery, i.e., the epicardial ones. It leads to thrombus formation, causing myocardial infarction or unstable angina.
  - → Presents the micro-infarctions that can lead to recurrent episodes of acute chest pain in child with Sickle Cell Anemia

5. **Pulmonary artery**
   - Vaso-occlusion of its small branches.
   - Pulmonary artery hypertension occurs.
   - Auscultatory findings – loud P_2
6. **Kidney**
   - Papillae affected.
   - These are the areas where all the collecting ducts open into.
   - Papillary necrosis occurs.
   - There are multiple causes of papillary necrosis, including sickle cell anemia.

- Mnemonic: Post Card: Causes of Papillary Necrosis.
  1. Pyelonephritis, with white blood cells casts in urine.
  2. Obstructive uropathy, caused by benign prostatic hyperplasia and bilateral strictures.
  3. Sickle cell anemia
  4. Chronic Alcoholism
  5. Renal vein thrombosis
  6. Diabetes mellitus



Hand, Foot and Mouth Disease

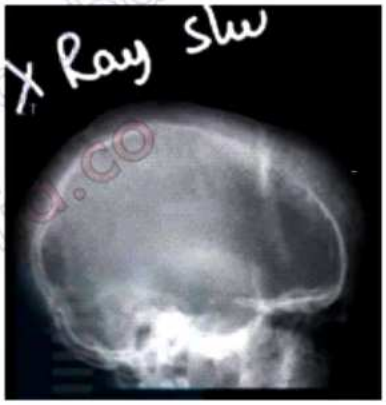


Hand And Foot Syndrome

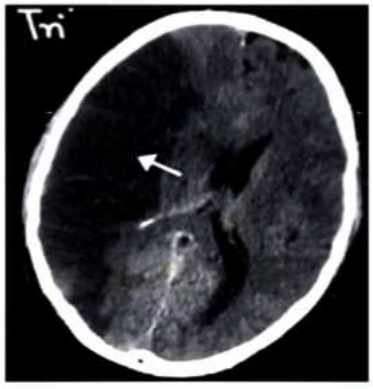
7. **Increased incidence of gall stones**
   - Pigmented variety, i.e. black stone.
   - Brown stones are seen with infection.
8. **Non-healing ulcer on medial malleolus**
   - In Adults it is seen with varicose vein causing Venous ulcer.
   - Non-healing ulcer in pediatric cases, over the medial malleolus, indicates 2 hematological conditions
     - → Hereditary spherocytosis
     - → Sickle cell anemia
9. **Aplastic crisis**
   - Caused by human parvovirus B19.
     - → Also causes focal segmental glomerulosclerosis and slapped cheek appearance in a child with viral erythema, i.e., erythema infectiosum (5th disease).

Specific Features

- **Crew cut appearance in skull X-ray**

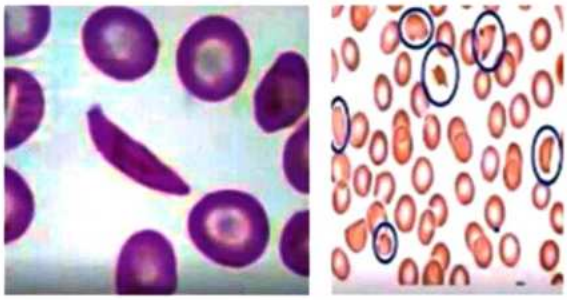


  - Seen in thalassemia and sickle cell anemia.
  - In both, bone marrow is affected.
  - Anemia stimulates bone marrow expansion.
  - Leads to the classical hair-on-end appearance or crew cut appearance.
- **Acute ischemic stroke**



- Patient may develop sudden onset hemiplegia.
- Cerebral circulation is affected.
- Hypodensity present on one side.
- Acute ischemic stroke risk is highest in first decade sickle cell anemia.

- **Red blood cell shape**



- Sickle-shaped red blood cells
- Schistocyte or Helmet cells
  - → Seen in several conditions
    1. Hemolytic Uremic syndrome
    2. Thrombotic Thrombocytopenic Purpura.
    3. Microangiopathic Hemolytic Anemia.
  - → Should not be confused with sickle-shaped red blood cells
  - → Schistocyte has pointed ends with a small beak present

Differences in Manifestations as Seen in Sickle Cell Trait Vs Sickle Cell Disease

	Trait	Disease
Hemoglobin electrophoresis	HbS, HbF, HbA, HbA_2 Present	HbS, HbF, HbA_2 Present HbA absent
Onset of symptoms	Symptoms can be triggered by • Pneumonia causing hypoxia. • Diarrhea causing acidosis. Hypoxia and acidosis cause HbS polymerization and sticky red blood cells.	
Severity	Mild	Severe due to the absence of HbA.

Work Up

1. Reduced hemoglobin.
2. Elevated lactate dehydrogenase (LDH) due to hemolysis.
3. Sickled red blood cells observed in peripheral blood smear.
4. Increased reticulocyte count.
   - Reticulocytosis is seen in all hemolytic anemia cases.
   - The only exception that presents with lower reticulocyte count as compared to anemia severity is thalassemia major.
   - For all hemoglobinopathies gene sequencing (if given in option) is to be given priority over HPLC. In SCA point mutation occurs in HBB gene on chromosome 11.
5. High-performance liquid chromatography (HPLC) is the investigation of choice.
6. Gene-sequencing can also be done.
7. Ultrasonography of the abdomen done to evaluate spleen size.
   - Shrunken spleen indicates a need for vaccination.
   - Hypersplenism may present initially.
   - If the diagnosis is made by the 1st year of life, splenomegaly is seen.
8. Hand X-ray shows dactylitis.
   - Hand X-ray in a thalassemia patient shows squaring of the metacarpals.
9. Spine X-ray shows fish vertebrae.

Treatment

Important Information

- HbS is created when glutamate is replaced with valine.
- HbS polymerization is the main cause of many clinical manifestations.

1. **Hydroxyurea**
   - Patients with increased cell counts, e.g. high total leucocyte count in blood cancer >50,000-100,000/µl.
   - Hydroxyurea decreases cell count.
   - Increases fetal hemoglobin (HbF), causing the migitation of clinical manifestations.
   - HbF gives a protective effect in the first 6 months after birth.

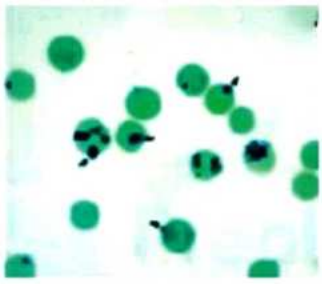
2. **For Sickling crisis**
   - Repeated hospitalizations for chest pain and bone pain.
   - IV analgesia using opioids.
   - IV fluids.
   - Fresh blood transfusion.
     - → In thalassemia, only packed red blood cells are transfused.
     - → Packed red blood cells should not be administered in sickle cell anemia.

→ It causes hemoconcentration, worsening the patient's condition.
→ Micro-occlusions make the blood flow sluggish.
→ Administration of packed red blood cells increases the sluggish nature.

3. **Opioids**
   - Examples
     → Morphine
     → Fentanyl
     → Codeine
     → Oxycodone
     → Methadone
     → Nalbuphine
   - Used depending on requirement and availability.
   - Fentanyl available as a transdermal patch.
   - Its efficiency is better than morphine.
   - It is relatively more expensive than its counterparts.
4. **Voxelotor**
   - Given to prevent HbS polymerization.
5. **Monoclonal antibodies**
   - Crizanlizumab
   - Reduce the frequency of vaso-occlusive crises in sickle-cell patients.
6. **Pulmonary artery hypertension**
   - Phosphodiesterase-5 inhibitors used in male erectile dysfunction.
     → Tadalafil
   - Endothelial receptor antagonist.
     → Bosentan
7. **Vaccines**
   - Against opportunistic infections.
   - 23-valent vaccine for Pneumococcus, i.e. Pneumovax-23.
   - Hib vaccine
     → Can be given nasally
   - Meningococcal vaccine
     → Protects against serotypes A, C, Y and W-135.
     → Does not protect against serotype B.
   - Vaccines should be given 2-4 weeks before elective splenectomy.

G6PD Deficiency 00:28:42

- Glucose-6-phosphate dehydrogenase deficiency.
- Example of Intra- and Extravascular hemolysis.



Supravital stain

- Supravital stain, i.e. crystal violet stain.
- Red blood cells appear green in color.
- Bluish inclusion bodies are Heinz bodies.

Bite cells

- Hematoxylin-eosin stain shows bite cells

G6PD role

- Free radicals are produced in the body.
- Main role of G6PD
  - Neutralize these free radicals.
  - Neutralize oxidative stress.
- Oxidative stress caused by intake of drugs, e.g. antimalarial drugs or may be naturally occurring.
- Antimalarial drugs destroy malaria parasites by oxidative stress.
- Red blood cells are not destroyed due to G6PD presence.

Hemolysis

- Hemolysis noted in G6PD deficiency is extravascular hemolysis.
  - Oxidative stress occurs naturally in the body.
- Triggers for intravascular hemolysis

- Consumption of fava beans.
- Consumption of antimalarial drugs
- Drug-induced damage is intravascular hemolysis.
- In this case, haptoglobin levels are absent.

Important Information

- Oxidative stress induced by antimalarial drugs may exceed the cell's natural capacity to overcome it.
- Hemolysis contributes to the generation of free hemoglobin in the blood.
- Hemoglobin in the blood is filtered via the glomerulus into the kidney tubules.
- Patient passes black-colored urine.
- Acute tubular necrosis may occur, leading to death.
- This can be prevented by conducting a G6PD assay in all babies, at birth as in Western countries.
- Once G6PD deficiency is identified early on, and parents are given a list of drugs that should be avoided.

Drugs contraindicated in G6PD deficiency

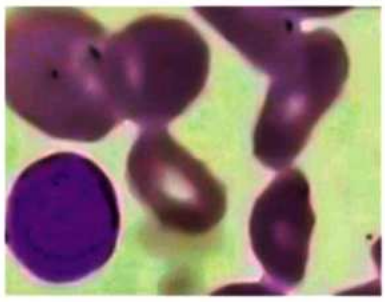
1. Aspirin
2. Nitrofurantion – urinary antiseptic
3 Antimalarial drugs e.g.
   - Primaquine
   - Chloroquine
   - Mefloquine

Q. Antimalarial drug that can be safely given in G6PD deficiency?
Ans. Artesunate

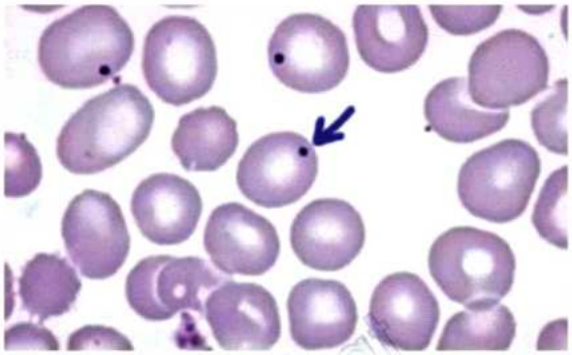
Difference between extravascular and intravascular hemolysis

- Serum haptoglobin levels blood test used to differentiate
- Haptoglobin binds to free hemoglobin.
- Haptoglobin levels are low in extravascular hemolysis but never absent.
- Haptoglobin is absent in intravascular hemolysis.

Cabot Ring, Howell-Jolly Bodies, Pappenheimer bodies



- Red blood cell with basophilic ring inclusion, called Cabot ring.
- Cabot rings are seen in Asplenia patients.



- Basophilic spot inside the red blood cell called Howell-Jolly bodies
- Both Cabot rings and Howell-Jolly bodies are seen in patients who have undergone a splenectomy, i.e. have asplenia.
- Pappenheimer bodies seen in sideroblastic anemia.
- In pappenheimer bodies, multiple blue-ish spots are seen in the red blood cell.

Autoimmune Hemolytic Anemia 00:37:48

	Warm	Cold	
		Pediatric case	Adult case
Antibody	IgG	IgG	IgM
Causes	1. Systemic lupus erythematosus 2. Chronic lymphocytic leukemia 3. Hodgkin's lymphoma 4. Non-Hodgkin's lymphoma 5. Drug-induced, e.g. α-methyldopa	Paroxysmal cold hemoglobinuria	Cold agglutinin syndrome

- Two types
  - Warm antibody type
  - Cold antibody type
- In CLL, immune-incompetent cells attack the 'self,' i.e. white blood cells, red blood cells.
- α-methyldopa was initially used as the drug of choice in pregnancy-related hypertension.
  - Labetalol is now used.

Paroxysmal Cold Hemoglobinuria (PCH)

- In PCH, when the patient is exposed to cold, and the red blood cells are sensitized, leading to hemolysis in warmer parts of the body.

Triggers of PCH

1. Previous pneumonia infection by Mycoplasma pneumoniae.
   - P antigen is present on the bacterial surface.
   - P antigen is also present on the red blood cell surface.
   - During infection, antibodies against the P antigen are produced.
   - Therefore, antibodies attack 'self' due to the presence of P protein antigen on the red blood cell surface.
   - Autoimmune hemolytic anemia occurs.
   - Antibody is known as the Donath-Landsteiner antibody.
   - This antibody gets sensitized at low temperatures causing hemolysis in warmer parts of the body.
   - Exposure to low temperature after Mycoplasma pneumoniae infection is followed by intravascular hemolysis.
   - Initial manifestations are seen after minutes to hours after cold exposure, e.g. abdominal pain or flank pain, Cramps or pain in the legs, headache and black-colored urine (hemoglobinuria).
2. Epstein-Barr virus
3. Varicella-Zoster virus
4. Human parvovirus B19

Cold agglutinin syndrome

- Adult patient > 50 years.
- I/I antigen is common between the red blood cells and the triggers.

Triggers

1. Mycoplasma pneumoniae
   - Known as atypical pneumonia as the patient later passes black-colored urine.
2. Infectious mononucleosis.
   - Kissing disease
3. Influenza viruses
4. HIV
5. Cytomegalovirus
6. Waldenstrom cryoglobulinemia
   - In multiple myeloma, there is overproduction of the light chains of IgG. Walden Strom has overproduction of defective IgM.
   - Cryo' means cold
   - History of cold exposure
   - Initial symptoms resemble frostbite or chill pains
   - Agglutination occurs at < 37° C
   - Cold exposure is required for the manifestation of this condition

Clinical manifestations

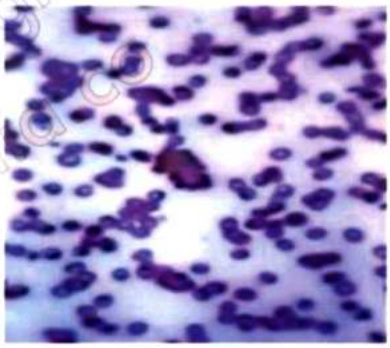
1. Initially, the profile is mottling with livedo reticularis present.
2. Mottling of extremities, the tip of the nose or ear lobes.
3. Cyanosis in the tips of the fingers, i.e. acrocyanosis.
   - Misdiagnosis of Raynaud's phenomenon possible.
4. Hemoglobinuria, i.e., black-colored urine.
5. Flank pain
6. Extreme fatigue

Tests for autoimmune hemolytic anemia

- For warm antibodies
  - Patient with malar rash, photosensitivity or other manifestations of SLE.
  - Blood cancer presenting with Cervical lymphadenopathy as in CLL.
- For cold antibodies
  - Patient who had cold exposure and exposure to P protein or I/I antigen.

Work Up

1. Peripheral blood smear



   - Rouleaux formation is often seen in multiple myeloma.
   - Rouleaux formation post-cold exposure or in a blood cancer or SLE patient indicates autoimmune hemolytic anemia.
   - Spherocytes are seen in the smear.
   - Agglutination of red blood cells is seen in adult patients with autoimmune hemolytic anemia with exposure to temperatures < 37°C.
2. Coomb's test
   - Direct Coomb's test is also positive in patients with SLE

Management

1. Administration of steroids
   - Primary management
2. Packed red blood cells should not be transfused.
3. Administration of monoclonal antibodies, e.g., rituximab or eculizumab.
   - Rituximab depletes the B cells that are eventually converted to plasma cells that produce antibodies.

Microangiopathic Hemolytic Anemia (MAHA)

00:49:41

- Formation of microthrombi inside the blood vessels.
- Red blood cells slam into microthrombi, leading to their fragmentation and destruction.
- Results in Helmet cell or Schistocyte formation.

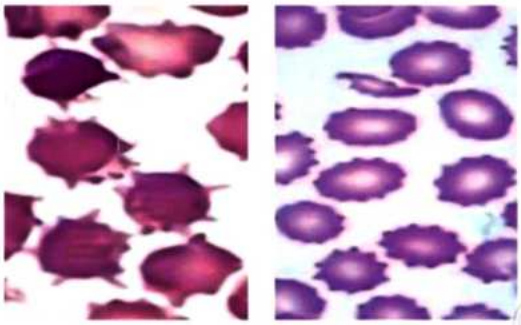
Disorders associated with MAHA

1. Hemolytic uremic syndrome caused by Escherichia coli O157:H7.
2. Thrombotic thrombocytopenic purpura.
3. Eclampsia.

Abnormalities of the Red Blood Cells

00:51:50

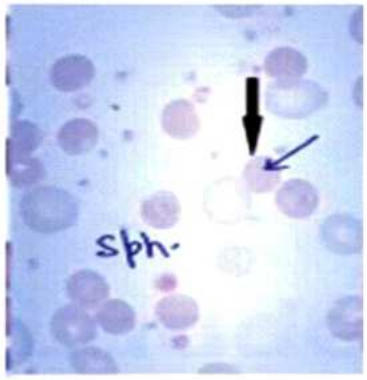
Spiky red blood cells



1 2

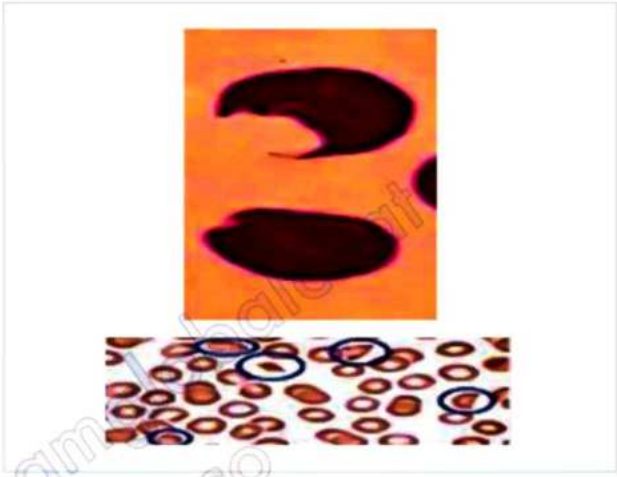
- Spikes on the red blood cell surface.
- Spikes in the 1st image are asymmetrically present.
- Spikes in the 2nd image are equidistant from one another or symmetrically placed.
- 1st image represents Acanthocytes.
- 2nd image represents Echinocytes.
- Acanthocytes are associated with abetalipoproteinemia.
- Two features of abetalipoproteinemia
  - Acanthocytes are present.
  - Cholesterol and triglycerides are reduced.

Spherocytes



- Red blood cells lacking a central color.
- Spherocytes.
- Conditions in which spherocytes are present include:
  1. Hereditary spherocytosis
  2. Chronic lymphocytic leukemia
  3. Autoimmune hemolytic anemia

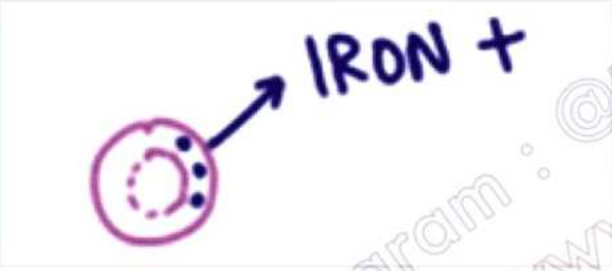
Bite cell VS schistocyte



- Bite cell are seen in G6PD deficiency.
- Schistocyte is a damaged red blood cell.
- Schistocytes are observed in:
  1. Hemolytic Uremic syndrome.
  2. Thrombotic Thrombocytopenic Purpura.

11 SIDEROBLASTIC ANAEMIA

- Normoblasts with iron deposits
- Haemoglobin synthesis occurs in the Intermediate Normoblast stage (polychromatophilic); will give rise to reticulocyte (haemoglobin occupying majority of the cell, nucleus disappears by pyknosis)
- Routine biconcave appearance of mature RBC
- If patient is on , A.T.T. INH will inhibit haemoglobin synthesis.



- Iron deposits present as it is not utilized for Hemoglobin synthesis
- RBC formed will be relatively smaller in size; iron deposits present (described as Papperhiemer bodies)
- In Sideroblastic Anaemia, RBC forms are loaded with iron, microcytic, hyperchromic (MCHC).
- Upon testing serum iron will be high and so is serum ferritin.
- Mitigation is observed upon B6; therefore, also known as pyridoxine-responsive anaemia.

Causes

- Genetic (X-linked)
- Drug Induced (INH, Chloramphenicol)
- Zinc Toxicity
- Lead poisoning

Prussian Blue stain is used to highlight iron deposits in the mature RBC.

Anaemia of Chronic Disease

- Seen in: Ulcerative colitis, Rhematoid arthritis, Systemic lupus erythematosus and Crohn's disease
- Hepcidin inhibits iron utilisation from the stores
- Serum iron level is less
- Serum ferritin will either be normal or the levels can be elevated.
- Normocytic Normochromic (NCNC) > MCHC (late manifestation)

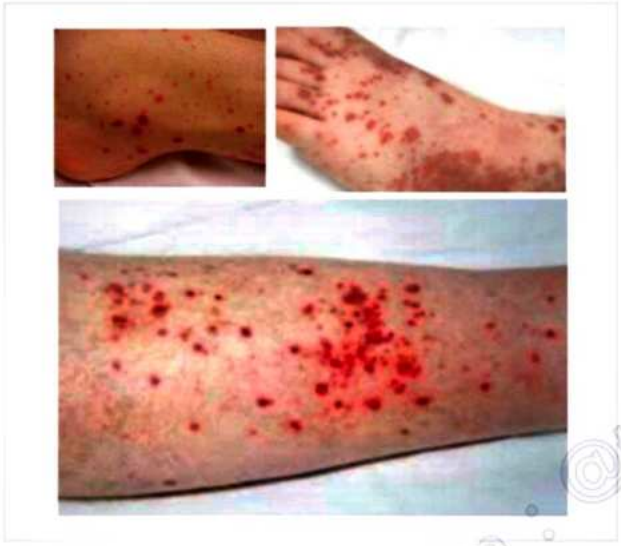
Difference in causes		
NCNC Anaemia	MCHC Anaemia	Macrocytic Anaemia
RBC count less due to deficiency of Erythropoietin : CKD AIHA: SLE, CLL ACD	Caused due to SITA (Sideroblastic anaemia, iron deficiency, thalassemia, anaemia) lead poisoning.	B12 deficiency (SIBO; Bacterial overgrowth syndrome, Type A gastritis, D. Latum worm, Orotic aciduria), Folic Acid deficiency (pregnancy, Anti-Epileptic Drugs, Celiac sprue, Tropical sprue), Chronic Liver Disease, Hypothyroidism, and aplastic anaemia.

	IDA	SA	ACD
Serum Iron Level	Low	High	Low
Serum Ferritin Level	Low	High	High/Unchanged
TIBC (opposite of ferritin levels)	High	Low	Low

12 PLATELET DISORDERS

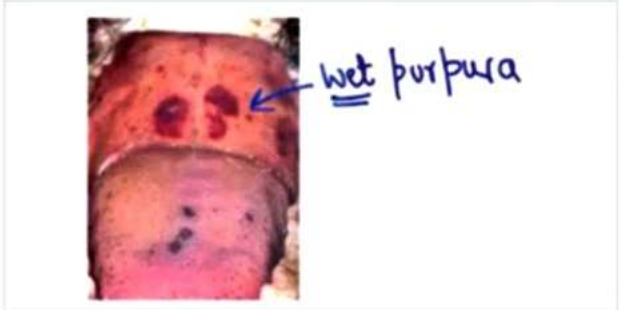
Platelet disorders

- Normal platelet count 1.5 to 4.5 Lakhs / cu.mm
- In hematological disorders (AML/ MDS) cases, Platelet transfusion can be started if the count drops below 5000.
- If the patient is diagnosed with Fever/ DHF, the platelet transfusion given if the count drops below 10,000.



- When a patient comes with a low platelet count, manifestations like petechiae (non-blanching) can be observed in ankles, slowly progressing to purpura (palpable bleeding; development of wet purpura)

Quick Facts



- Deficiency of Factor 8 (hemophilia A), Factor 9 (hemophilia B) and Factor 11(hemophilia C), and Factor 5 (Parahemophilia)
- Non-Palpable purpura: Acute Idiosyncratic Thrombocytic Purpura (ITP)
- Pinch purpura: Amyloidosis
- Non thrombocytopenic purpura: HSP
- Joint bleeding is presentation of Hemophilia
- Shortest half-life: Factor 7 (In Chronic Liver Disease, prothrombin levels are always elevated)
- Longest half-life: Factor 13 (Clot Stabilizing Factor)

Acute ITP 00:07:33

- Primary: Immune-mediated: EBV, CMV, Rubella
- Secondary: Myelodysplastic syndrome, SLE, HIV

Clinical Features

1. Recurrent Nosebleeds
2. Menorrhagia in females
3. Petechiae in Ankles, BP cuff
4. Purpura (non-palpable)
5. Spleen remains normal but, in some rare cases, may appear palpable.

Work Up

- Platelet count low.
  - In peripheral smear, the platelet count is less and is relatively larger size.
- Bone marrow Aspiration: Normal / megakaryocyte size increased and the count is high.

Treatment

1. IV Steroids
2. Rh +ve: Rhogam Rh Ig
   - MOA: Saturation of Fc receptors: Inhibition of Fc receptors function
3. Rh -ve: IV Ig (help in clearance of harmful antibodies)

- No Platelet transfusion is recommended.

Chronic ITP 00:16:29

Treatment

- Elective Splenectomy
  - The patient can be susceptible to infections and hence vaccines should be administered (Haemophilus influenzae, pneumococcal, meningococcal)
  - In Relapse /Contraindication of Splenectomy: Romiplostim, Eltrombopag

Elective Splenectomy is also done in Hereditary Spherocytosis

Hemophilia A 00:18:30

1. Factor 8 deficiency
2. X linked recessive
3. Girls are the carrier while the disease is presented in Boys.

Clinical Features:
1. Excessive bleeding post circumcision
2. B/L Haemarthrosis (Most Common)
3. Easy bruisability
4. Family history
5. Intracranial hemorrhage risk is increased

Investigations
- Screening Test: Coagulogram
  - BT (dependent on platelet count, Normal, Bleeding time: 2-9 min)
  - PT (dependent on Factor 5, 7, Normal, Bleeding time: 11-16 sec)
  - aPTT (dependent on Factor 8, increased levels, Bleeding time: 30-45 sec)
- Confirmation Test
  - IOC: Factor 8: Decreased levels; value less than 1%

Treatment
1. IV Factor 8 concentrate
2. For Mucosal bleeding: Desmopressin/ DDAVP
3. Life-threatening bleeding: FFP/ Cryoprecipitate (high infection rate)
- Cryoprecipitate is used in developing countries only in cases of life-threatening bleeding cases.

Important Information
- Autosomal Hemophilia (VWD Type 2N)
- Parahemophilia (deficiency of factor 5)

Acquired Hemophilia
- Antibodies against Factor 8, leading to enhanced clearance of the factor from the body.
- Causes:
  - Autoimmunity
  - Malignancy (carcinoma prostate, lymphoma)
- Clinical features: Soft tissue Bleeding
- Investigations: Diagnosed by Bethedsa assay (A/b factor 8)
- Treatment: Prothrombin Complex Concentrates
  - Also given in warfarin toxicity leading to ICH

Bernard Soulier Syndrome 00:31:07
- Autosomal Recessive (Receptor IB/IX/V binds to VWF tissue glue; adhesion does not take place due to genetic defects)
- History of consanguineous marriage may be given.
- Giant Platelet leading to pseudo-elevation of lymphocyte count.

Clinical features
1. Recurrent epistaxis
2. Menorrhagia
3. Postoperative excessive bleeding

Investigations
1. Platelet count normal, [Quality defect of Platelet.]
2. High Pseudo TLC count
3. Peripheral smear: Giant platelets
4. Coagulogram shows bleeding time is high whereas PT and aPTT time is normal:
5. Platelet function analyzer/PFA-100
6. Ristocein Aggregation Test:
   - Failure to agglutinate Ristocein.
   - ADP, adenosine, and collagen: agglutination takes place.

Treatment
- Platelet transfusion to manage excess post-op bleeding

Wiskott Aldrich Syndrome 00:39:27
- WAITER: Mnemonic
  - **W** = Wiskott
  - **A** = Aldrich
  - **I** = Immunodeficiency: IgM levels are low, whereas IgA and IgE levels will be high
  - **T** = Thrombocytopenia; small platelets
  - **E** = Eczema development
  - **R** = Recurrent pyogenic infection

Glanzmann Thrombasthenia 00:40:52
- α IIb/ ß3 receptor (helps in platelet aggregation)
- Autosomal Recessive Condition
- Defect in Chromosome 17
- Qualitative and Quantitative deficiency of the receptor
- History of Consanguineous marriage

Clinical Features
1. Menorrhagia
2. Gingival bleeding
3. GIT bleeding
4. Post Operative Bleeding
5. Recurrent Epistaxis

Investigations
1. Platelet Count normal.
2. The size of platelets on platelet smear will also remain normal.
3. Coaglugram shows BT is increased, whereas PT and aPTT are normal
4. PFA-100
5. Ristocein aggregation test
   - Ristocein agglutination normal
   - ADP, Adenosine, and collagen levels low

Treatment

- Platelet transfusion
  - Alloimmunization may occur so, primary: leucocyte depleted products are given.
- Non-life-threatening bleed: Desmopressin, E.A.C.A., Topical thrombin

Von- Willebrand Disease 00:47:11

- Most Common Inherited bleeding disorder
- VWF has two main functions:
  - Adhesion of platelet
  - Binds to factor 8, enhancing its half-life.
- Deficiency in VWF will lead to an increase in Bleeding time and increase in aPTT time.

Types

Type 1 (most common)	VWF function is low Protein levels are low Both Quality and Quantity are deficient
Type 2 (VWF multimers are destroyed by ADAM TS 13) • 2A (cleavage action by ADAM TS 13 increases) • 2B (Gain of function: spontaneous binding of platelets) • 2M (variant of 2B) • 2N (defective binding; autosomal hemophilia)	VWF dysfunctional Only Quality is deficient
Type 3	VWF absent (most severe cases)

Case study:

Q: A 13 year old female is suffering from wisdom tooth pain. Dentist prescribed NSAIDs and then tooth extraction. Postoperative bleeding is observed, and Coagulogram report shows BT and aPTT levels are high whereas PT level is normal. Ristocein when added to VWF deficient plasma, clotting takes place. What is the recommended treatment?

Ans. Treatment requires DDAVP

Heyde Syndrome 00:58:37

- Aortic stenosis: Shear stress generation on RBC due to turbulence leads to a decrease in VWF activity causing GI bleeding and hematochezia.

Refer Table 12.1

- Thromboelastography can diagnose the entire clotting system in case of emergencies.

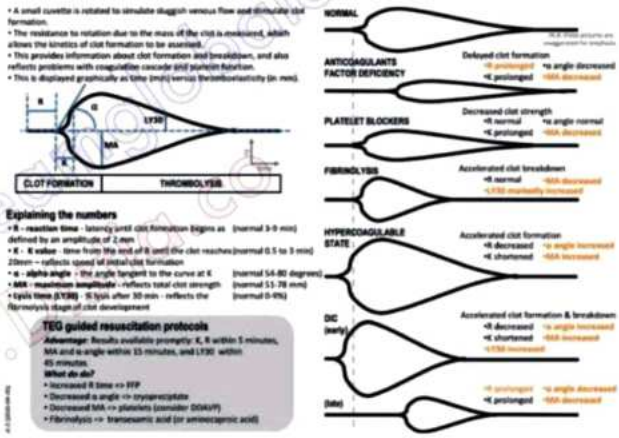


Table 12.1

	Dengue Hemorrhagic Fever	Hemophilia A	CLD	DIC	TTP	VWD
BT	high	normal	normal	high	high	high
PT	normal	normal	high	high	normal/ high	normal
aPTT	normal	high	normal	high	normal/ high	high
				Determined by S. Fibrinogen value. It will be decrease in DIC and normal in TTP		

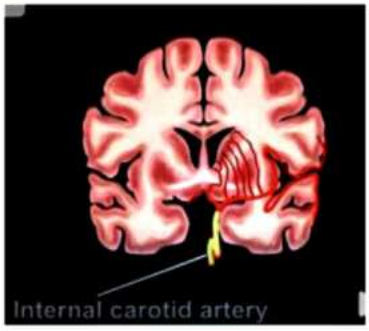
13 BASICS OF MIDDLE CEREBRAL ARTERY AND CRANIAL NERVE ARRANGEMENT

Branches of middle cerebral artery

Orientation:

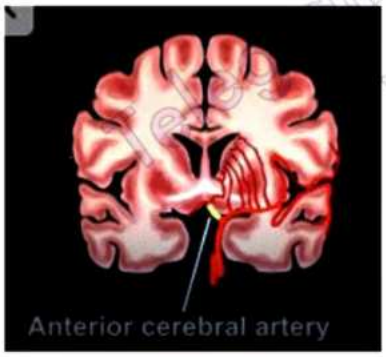
1. M1: Horizontal part
2. M2: Insular part
3. M3: Opercular part
4. M4: Cortical part

Internal carotid artery

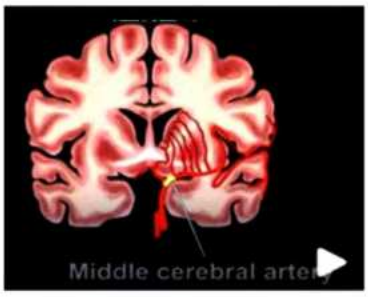


- Internal carotid artery is a thick blood vessels coming up vertically

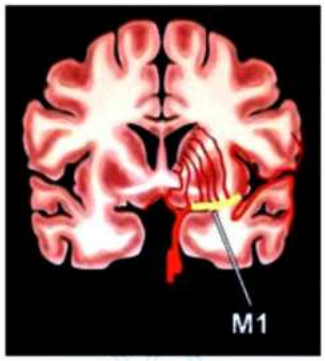
Anterior cerebral artery



Middle cerebral artery



M1 segment

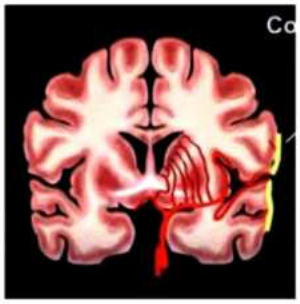


- Running horizontally and giving branches to basal ganglia
- The branches that are seen superiorly, the smaller tuex that are originating from the M1 segment are called lenticulostriate branches.
- They get involved in lacunar stroke.

Risk factors of lacunar stroke

- Hypertension
- Diabetes
- Smoking
- Atherosclerosis
- If lenticulostriate branches are involved, it will contribute to the development of basal ganglia manifestations in a patient.
- The moment the M1 branch ends, a branch M2 originates and moving superolaterally.
- The M2 branch is present on the Lateral surface of the insula.

- When this M2 segment ends, it takes the shape of a hair pin loop. From there, M3 is originated. M3 runs in Sylvian Fissure
- Sylvian fissure: It separates parietal from temporal lobe.



- The M4 branch supplies the Cortical Surface and is usually involved in the Cortical Stroke.

Rule of 4

- Valid for Brainstem stroke
- Brainstem: Midbrain, Pons, Medulla

- Any cranial nerve nuclei, if it is divisible by 12 or a direct multiple of 12, it will be medially located.

Important Information

- Hemiplegia, Ipsilateral ptosis are features of ventral midbrain syndrome.
- If a patient has Ipsilateral tongue deviation on tongue protrusion, then it will be medial medullary syndrome because there is 12th nerve Involvement.
- If 9,10,11 cranial nerve involvement (Gag reflex affected, dysarthria) are involved in Lateral medullary syndrome.

1. All structures that begin with letter M are midline. 4 motor syndromes are midline.

- Medial Longitudinal Fasciculus (Eye Motor)
- Motor Tract of the UMN (Corticospinal Tract)
- Medial Lemniscus (Proprioception/Vibration)
- Motor Nuclei of CN

2. All structures that begin with letter S are laterally located (side). 4 Sensory Syndromes are SIDE (LATERAL)

- Spinothalamic Tract (Pain & Temperature)
- Spinocerebellar Tract
- Sympathetic Chain
- Sensory CN Nuclei

Important Information

- Horner syndrome is seen in Lateral Brainstem Stroke Manifestations.

14 MECHANICAL THROMBECTOMY

MERCI and Mechanical Thrombectomy with Stent Retrieval

00:00:23

- **Full Form:** Mechanical embolus retraction in cerebral ischaemia
- **Most common type of stroke seen in clinical practice:** Acute ischemic stroke
  - In this condition, patient will lose 2 million neurons per min.
- **Successful recanalization is associated with:**
  - 4-to-5-fold decrease in the mortality
  - 4-to-5-fold increase in the functional outcome in the patients of AIS
- In the **first 4.5 hours**, Thrombolysis is done.

Management of Acute Ischemic Stroke with presentation after 4.5 hours or where thrombolysis has failed:

- **The basic dictum:** Time is brain.
- More neurons can be saved.

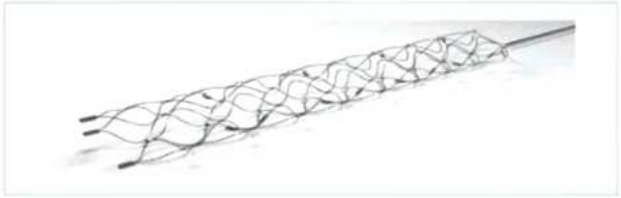
Need for Mechanical Thrombus Removal

- As Some clots are platelet rich, they are resistant to thrombolysis.
- Because they contain higher concentrations of platelet activator inhibitor 1.
- So, such clots formed are better organized and have low plasminogen content.
- Therefore, they are more resistant to thrombolysis.

Goal of Mechanical Clot Manipulation

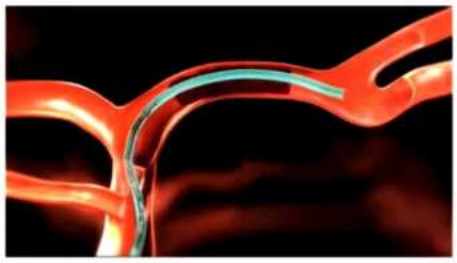
It is done quickly restore the cerebral blood flow in the involved atrial territory with a reduced dosage (Possibly without the use of any fibrinolytics)

- Quick clot manipulation is done to remove the clot
- To attain functional recovery



- An instrument known as the removable stent is used.
  - It is deployed in the blood vessel where the thrombus is present
  - It is made of Nitinol which is a nickel titanium alloy and has shape memory.
  - It is a super elastic material which helps to remove the clot in one piece.

Procedure for Mechanical thrombectomy with clot retrieval



Vascular access through femoral artery

Vascular access is taken from the blood vessel named femoral artery

↓

Guide wire is passed to the aorta

↓

It further moves into the common and internal carotid artery

↓

Once the wire reaches the brain circulation (Exact location where the clot is located)

↓

A micro catheter is passed through the Guide wire and the guide wire is removed

↓

Check the position of the catheter

↓

With the help of the microcatheter we will deploy the inflatable stent made of Nitinol

↓

This stent takes up the shape of the clot and ensnare the clot

↓

Negative force is applied to retract the clot which is entrapped in the mesh of the stent

↓

Prior to that we will deploy the balloon to cut off the proximal circulation

↓

These is done because while retracting the clot, may be broken into fragments and these fragments can embolize in the distal circulation

↓

Then clot or fragments can be removed

- If Removal of Clot with Running Circulation is done, the clot may break into pieces.
  - The fragments can embolize to distal circulation causing worsening of patient condition.

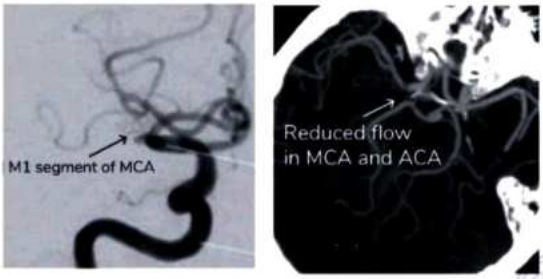
Case: A 60 years old man has hypertension and poorly controlled diabetes. In the early morning while going for the walk, he developed a sudden onset of left arm weakness, drooping of corners of the mouth and he was unable to speak. Then his wife rushed him to nearest hospital. What is the best course of treatment?

Ans: Thrombolysis is to be done when the patient arrives within 4.5 hours of the window period for acute ischaemic stroke.

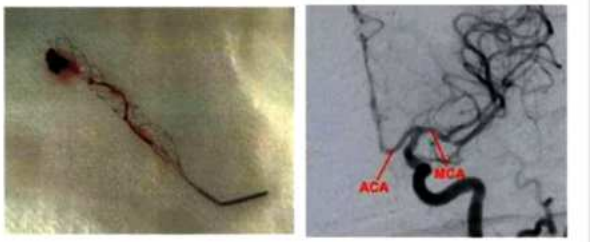
Management

Imaging

- **CT Scan:** Can be Normal in early presentation of Acute Ischemic Stroke.
- CT scan is done to rule out Hemorrhagic Stroke.



- A reduced flow in MCA and ACA can be seen.
- This because of the huge thrombus that is stuck in the lumen of the ICA terminus



Treatment for Acute Ischemic Stroke

- Thrombolysis is the first course of treatment if the patient arrives within 4.5 hours of onset of symptoms.
- In case of failure of thrombolysis or if the time period has exceeded 4.5 hours but before 24 hours, then, Mechanical thrombectomy is done after a CT Angiography is performed and the segment and artery involved in the stroke are confirmed.
- Physiotherapy is done for further improvement of the patient.
- Harrison 21st update: Mechanical Thrombectomy can be done upto 24 hours of symptom onset in stroke.

15 STROKE

- Also called - CVA - Cerebrovascular Accident

TIA 00:00:25

- Cut off for Resolution of Neurological symptoms by 24 hours
- Most cases neurological symptoms begin to resolve by 1 hour
- But if symptoms continue to increase → Evolving Stroke
- Symptoms will start improving in the 1st hour itself due to activation of Anti-clotting system of the body.
  - Protein C / Protein S / Antithrombin III
- Percentage of chances that person will develop stroke in next 48 hours after an attack of TIA
  - ABCD, SCORE
    - → Age
    - → Blood pressure
    - → Clinical symptoms
    - → Duration
    - → Presence or absence of Diabetes mellitus

- In case of stroke, Neurological symptoms progressively worsen
- Window period of treatment of TIA - 4.5 hours calculated from Onset of symptoms
- The radiological findings take more than 6 hours to appear
- If clinically patient worsens and CT is normal, then do CTA if available
- We do not wait for radiological finding to appear to start treatment - thrombolysis.

Symptoms

- **FAST**
  - Sudden onset **F**acial weakness
  - Sudden onset of **A**rm weakness
  - **S**peech deficit
  - **T**ime is neurons

Treatment

- **DAPT - dual antiplatelet therapy**
  - Aspirin and clopidogrel

- **NOAC**
  - Novel oral anticoagulants

Time period in TIA

- Improvement in symptoms - in 1 hour
- Resolves completely by 24 hours
- Highest chance of developing stroke after TIA - within first 48 hours

- If no improvement in 1 hour - think of development of stroke → NCCT → normal, no bleed → do thrombolysis
- Do not wait for radiological signs to appear
- Window period - 4.5 hours

Stroke management 00:07:24

- ABC (Airway, BP control, Circulation)
- Random Blood Glucose
  - Non-diabetic → Hypoglycemia → decrease the capacity of neurons to handle the stress
  - Diabetic → Hyperglycemia → increase the swelling in brain
  - In both cases, sugar level is important
  - Patient must be made euglycemic

- NCCT head
  - Normal/ Hypodensity: Ischemic
  - Hyperdensity: Hemorrhagic - thrombolysis is contraindicated. NCCT Head is done initially to rule out haemorrhagic stroke.
    In such case, Handle the raised ICT

Localization of stroke 00:09:25

Parietal Lobe

.

Parietal lobe - Dominant
Blood supply - Left middle cerebral artery (LMCA)
Functions

1. Acalculia
2. Agraphia
3. Left right disorientation
4. Finger agnosia

(1–4: Gerstmann Syndrome)

5. Global aphasia
   - Wernicke and Broca's area involved
   - Superior and inferior divisions of MCA supply
   - Understanding, expression of speech and fluency all are affected

Non - dominant parietal lobe
Blood supply - right middle cerebral artery (RMCA)
Functions

1. Constructional apraxia - loss of visuospatial skills
2. Hemineglect (requires prism glasses)- Visual inattention
   - e.g., Person shaves only on one side
   - Eats from one side of plate
3. Anosognosia - Inability to appreciate severity of motor and cognition defects
   - The person is not bothered about the deficit
   - Also seen in alzheimer's due to cortical atrophy

Temporal Lobe - MCA Territory

- **Anterograde amnesia**
  - Short term memory loss
    → Memory of food items consumed for Dinner last night or breakfast in the morning
- **Prosopagnosia**
  - Memory of face - Inability to recognize face of familiar person
  - Connection between occipital and temporal lobe lost
- **Complex hallucinations**
  - Complains of smell of rotten fish in ward or dead rat
  - Complains Metallic taste of food
  - Auditory hallucinations
- **Deja vu**
  - Undue familiarity
- **Jemai vu**
  - Unfamiliarity of familiar things

Pure word deafness

- Hearing is normal
- Defect in Reception area in temporal lobe
- Superior temporal gyrus
- Association areas of Wernicke's area

Pure word blindness

- Ocular apparatus or optic nerve normal
- Not able to understand written words
- Left occipital lobe affected
- Splenium - posterior most part of corpus callosum

Frontal Lobe – ACA

1. Traits of antisocial behavior / Aggression
2. Personality change
3. Urge incontinence
   - Paracentral lobule present in frontal lobe is responsible for control of urinary bladder
4. Apathy
5. Abulia: Lack of will/ desire to speak or do daily tasks
6. Appearance of Primitive reflexes
   - Primitive reflexes - disappear due to dominance of the frontal lobe
   - As dominance is lost - reflex comeback
   - Grasp reflex - normally persists up to 4 months of age
   - Rooting reflex - It persists up to 1 month of age.
   - Moro's reflex - it never reappears - it disappears by 6 months of age
7. Magnetic gait/Gait apraxia

Extra mile:

- Gait apraxia - ACA - FRONTAL LOBE
- Constructional apraxia - MCA - PARIETAL LOBE

Festinating gait in Parkinsonism

- Stooped posture
- No automatic arm swing
- Short shuffling steps

Occipital Lobe - P_2 PCA Territory

1. Visual hallucinations
2. Palinopsia
   - Persistence of image even when the image has been removed from field of vision
3. Asimultagnosia
   - Simultaneous visual information cannot be processed
4. Homonymous hemianopia
5. Cortical blindness: Bilatral P_2 PCA occlusion
   - Blindness with Normal pupillary reflex
   - As Edinger Westphal nucleus is in midbrain - spared

- Gun barrel vision - Central vision island preserved
- Denial of blindness as small islands of vision are still present and is called Anton syndrome
  - Denial of blindness in bilateral distal PCA blockade due to persistence of islands of vision

Summary

- ACA Territory Stroke
  1. Spastic monoplegia/Paraplegia
  2. Abulia
  3. Personality changes
  4. Urinary incontinence
- MCA Territory Stroke
  1. Contralateral face weakness
  2. Arm weakness
  3. Homonymous hemianopia - optic tract damage
  4. Gaze preference: Patient looks towards the side of lesion

- LMCA
  5. Global Aphasia

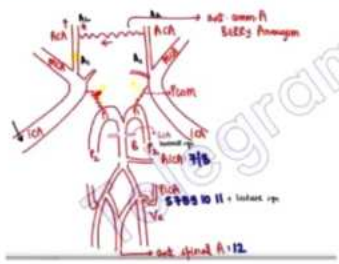
- RMCA
  6. Constructional Apraxia
  7. Hemineglect
  8. Anosognosia

- P_2 PCA Territory Stroke
  1. Visual hallucinations
  2. Palinopsia
  3. Asimultagnosia
  4. Cortical blindness

Lacunar stroke

- Lipohyalinosis - affects the smaller branches of the brain i.e. Perforator branches
- Risk factors -same as that of CVA and Stroke
- Lenticulostriate branch - branch of MCA
  - Supply - Internal capsule
  - Corticospinal pathway
- Pure motor or pure sensory stroke - Internal capsule
- Hemiplegia: Face, arm and leg due to involvement of posterior limb of internal capsule.

Blood supply of brain 01:06:09



Circle of Willis

- ICA - Internal cerebral artery
  - MCA - middle cerebral artery
  - ACA - anterior cerebral artery - A1, A2
    → ACOM- anterior communicating artery
  - Anterior choroidal artery

- Vertebral artery
  - ASA - Anterior spinal artery
  - PICA - Posterior inferior cerebellar artery

- Basilar artery
  - SCA- Superior cerebellar artery
  - AICA - Anterior inferior cerebellar artery
  - PCA - Posterior cerebral artery - P1, P2
    → P1 - midbrain
    → P2 - occipital cortex
    → Bilateral P2 blockage - Anton syndrome
    → PCOM- posterior communicating artery

- Berry aneurysm - Most common site - junction of anterior communicating artery and ACA
- Strokes that are well tolerated
  - A1 - well tolerated
    → Communicating artery will act as a bridge
    → Supply the brain even when A1 branch is lost
  - Anterior choroidal - well tolerated
    → Due to collateral circulation
    → By PCOM
    → And MCA -middle cerebral artery
- 3rd CN - runs adjacent to PCOM
- Cranial nerve - compressed by unruptured berry aneurysm - 3rd cranial nerve
- Even if it ruptures - will continue to compress 3rd nerve
- Raised ICT - 6th CN is affected
- Pontine stroke - Basilar artery
- Medullary stroke - Vertebral artery
  - Medial medullary syndrome - Anterior spinal artery involvement
  - Lateral medullary syndrome - Vertebral artery/PICA involvement
  - 5th,7th,8th,9th,10th,11th cranial nerves - PICA
  - 12th CN - ASA
- Basilar artery
  - AICA - 7th,8th CN
  - Superior cerebellar artery - Horner's syndrome, ipsilateral hypotonia ,gait ataxia
- Horner's syndrome also seen with PICA along with 5,7,8,9,10,11 nerve palsies
  - Involvement of Descending sympathetic pathway

Horner's syndrome

1. Pancoast Tumor
2. Lateral medullary syndrome: Vertebral A/PiCA involvement
3. Superior cerebellar artery stroke

Q. All of the following contribute to Circle of Willis except?

a. ACA
b. MCA
c. Anterior communicating artery
d. Posterior communicating artery

Answer- MCA

Total anterior circulation stroke - TAS when ACA+ MCA - Proximal to bifurcation of ICA is involved.

1. Unilateral spastic weakness - Face, Arm, Leg or Hemianesthesia
2. Optic tract involvement - Homonymous Hemianopia
3. Cortical involvement:
   - Apraxia
   - Global aphasia
   - Abulia

If only 2 features present - Partial anterior circulation stroke

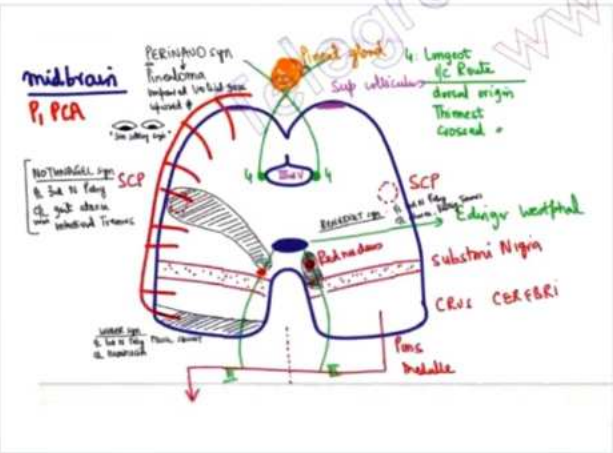
P1 PCA - MIDBRAIN STROKE 01:22:36

- Trochlear nerve features:
  1. Dorsal origin
  2. Thinnest cranial nerve
  3. Longest intracranial route
  4. Crossed origin
     → Left superior oblique supplied by right trochlear nerve

- Cranial nerve with longest Intracranial route - Trochlear nerve
- Longest Intraosseous route - Facial nerve
- Longest subarachnoid route - Abducens / 6th nerve
- Longest cranial nerve - Vagus
- Thickest - Trigeminal nerve
- Thinnest - Trochlear nerve

Weber syndrome -ventral midbrain syndrome

- Ipsilateral Oculomotor nerve palsy
  - Ptosis
  - Squint
- Contralateral hemiplegia



Nothnagel syndrome

- Oculomotor nerve + Superior cerebellar peduncle
- Ipsilateral 3rd palsy
- Contralateral gait ataxia, intentional Tremors
  - As area distal to decussation is involved
  - SCP crossovers

Benedikt syndrome

- Oculomotor + Red nucleus involvement
- Red Nucleus
  - Connecting midbrain to basal ganglia
  - Planning and programming of movements
- Ipsilateral 3rd nerve palsy+ Contralateral chorea
- If extends to substantia nigra → Vascular parkinsonism

Parinaud syndrome

- Parinaud syndrome - Occures due to Pinealoma

1. Impaired vertical gaze - Upward gaze palsy
2. Sun setting sign

Extra Mile
Pinealoma - vertical gaze palsy
Progressive supranuclear gaze palsy - downward gaze palsy - recurrent falling

Q. All of the following are features of weber syndrome except?

a. Ipsilateral ptosis
b. Squint
c. Hemiplegia
d. Impaired upward gaze

Answer - D

Impaired upward gaze - Feature of parinaud syndrome due to Pinealoma - superior colliculus involved

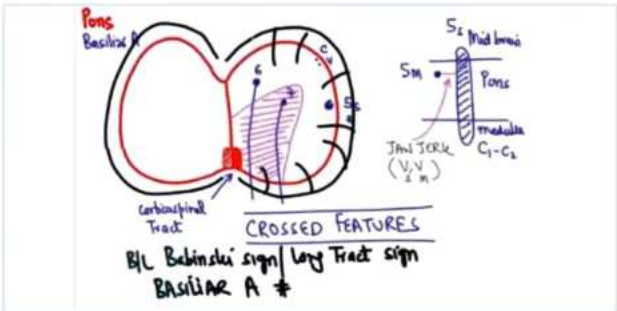
Claude syndrome

- Nothnagel + Benedikt syndrome [Reference: Page 229: Harrison 21st]
- Contralateral gait ataxia and chorea

Dejerine Roussy Syndrome

- **Thalamic stroke**
- P1- PCA Penetrating branches - supplying thalamus - pain relay center
- Agonizing searing pain/Lancinating pain/Burning pain

Pontine Stroke 01:41:28



Millard Gubler Syndrome

- Hearing and sensation of face not affected
- Ipsilateral nerve fascicles affected of 6th nerve
  - Lateral rectus weakness
- 7th lower motor neuron palsy
  - Facial palsy - LMN
  - Facial sensation not affected
- Contralateral hemiplegia
- Damage to nucleus / nerve fibers - LMN palsy
- Damage to corticobulbar fibers - UMN palsy
- Crossed features - midbrain stroke
  - Hemiplegia on one side
  - Cranial nerves on opposite side affected
- Nucleus of trigeminal nerve
  - Motor nucleus - pons
  - Horseshoe shaped -sensory nucleus of trigeminal nerve
    → Extends through - Midbrain , pons, medulla, extend up to C1 C2 part of spinal cord
- What test you do to check for connection between motor and sensory nucleus of trigeminal nerve
  - Jaw jerk

Basilar Artery

- If main trunk is involved
- Bilateral manifestations
- Both corticospinal tract involved - Bilateral Babinski Sign / Extensor plantar / long tract sign

Locked In Syndrome / Pseudocoma

01:48:32

- Midbrain, pons and medulla affected
- Quadriplegia
- Can't talk - 10th CN
- Can't eat - 9th, 12th CN
- Can't drink
- Only Vertical eye movement seen
- Cortex is functioning
- Patient is well awake
- Aware of his surroundings

Branch of basilar artery - SCA

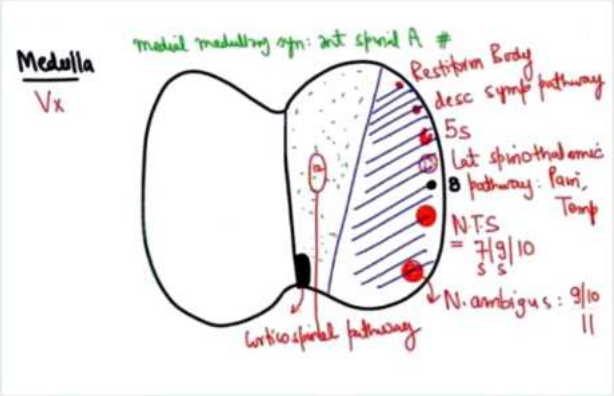
- Horner's syndrome
- Descending sympathetic pathway

PICA - Horner's syndrome + 5th,7th,8th,9th,10th,11th CN

- Lateral medullary syndrome

Medullary Stroke

01:52:44



Lateral medullary syndrome/Wallenburg syndrome

- 5th,7th,9th,10th,11th CN
- 8th CN - originates at pontomedullary junction - also involved
- 12th CN - not involved - originate medially
- Vertebral artery involvement
- Hemiplegia not seen as Corticospinal pathway runs medially

Medial medullary syndrome

- ASA
- Contralateral hemiplegia
- Ipsilateral 12th nerve palsy
  - Tongue deviation to same side

Lateral medullary syndrome features based on structures involved

1. Restiform body
   - Ipsilateral gait ataxia
   - Ipsilateral intention tremor
   - Ipsilateral hypotonia
2. Descending sympathetic chain - Horner's syndrome
   - PERFECT MEAL
     → Muller's muscle - sympathomimetic drive
     → Ptosis
     → Miosis
     → Pseudo enophthalmos
     → Anhidrosis
     → Loss of ciliospinal reflex
3. 5th CN - sensory nucleus of trigeminal nerve: Same side face sensation lost.
4. Lateral spinothalamic tract - pain and temp from opposite side

- Crossed hemianesthesia - PICA > vertebral artery
  - All sensations of face lost on same side - vibration, touch, pain, temperature
  - Pain and temp from opposite side of body lost

5. 7th,9th CN - nucleus tractus solitarius- sensory loss - Ageusia
6. 8th CN - Vertigo

7. 9th CN motor nucleus- speech production defective - soft palate palsy - nasal twang to voice, nasal regurgitation
8. Vagus involved
   - Vagus - control heart rate
     → Patient shows Tachycardia - palpitation
   - Stomach motility and intestinal motility
     → Stomach bloating - Gastroparesis
   - Cough reflex impaired
   - Gag reflex impaired
     → Risk of aspiration

Hemiplegia is seen with involvement of:

1. MCA
2. P1 PCA - Weber Syndrome - Crus Cerebri
3. Basilar Artery - Locked In Syndrome, Millard Gubler Syndrome
4. ASA - Medial Medullary Syndrome

- Hemiplegia is not seen in Vertebral / PICA - Lateral Medullary Syndrome

17 INTRAPARENCHYMAL HEMORRHAGE AND OTHER CNS BLEEDS

Intraparenchymal Bleeding

Causes of IPB

1. Trauma
2. HTN crisis (Rupture of penentrating branches of Lenticulostriate Artery.)
3. **Drugs**
   - Warfarin toxicity
   - Cocaine
   - Methamphetamines
4. Secondary to brain malformations like Arteriovenous malformations
5. Cerebral Amyloid Angiopathy

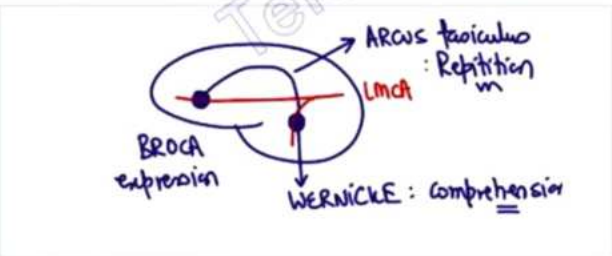
IPB in Non HTN and Non DM

Case-01: A military retired person (80 years of age) comes to your clinic for a regular checkup, He is not diabetic and non-hypertensive. But today morning he had a brain hemorrhage developed due to raised ICT and expired.

Ans. Weakening of brain vessels, Cerebral Amyloid Angiopathy (CAA). The genetic component involved here is Apolipoprotein E

Case-02: A 50 year old guy, a banker by profession taking a sales meeting today, has developed Embolic stroke due to atrial fibrillation. He speaks fluently, but no understanding or comprehension is seen. What blood is involved?

Ans. Inferior branch of left middle Cerebral Artery



Manifestations of occlusion of MCA branches:

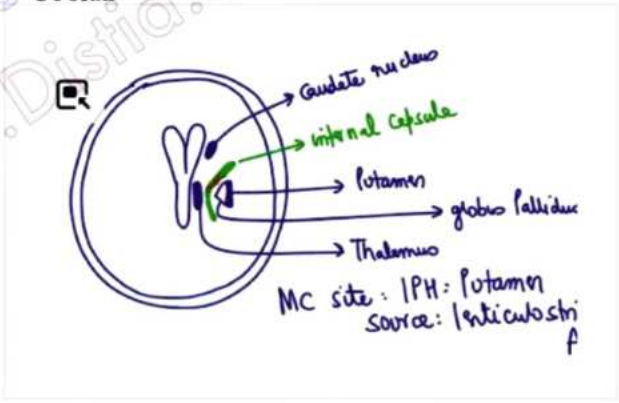
- **LMCA [Superior branch]**
  - Ability of expression (fluency) would be lost
  - Termed as Motor aphasia
- **LMCA [Inferior branch]**
  - Reception is lost - Receptive dysphasia.
  - The fluency is still present
  - The patient will say words with fluency, but there won't be any meaning or understanding.
  - Termed as Jargon speech.
- **LMCA [Main Trunk]**
  - Global aphasia

Case-03: A 50 year man with HTN (non-compliant) who is a sales manager is taking a sales meeting and scolding his juniors for the bad performance. While speaking he developed sagging of the muscles of face at one side and facial asymmetry is seen. Suddenly he became quiet. He trying to speak, but he wasn't able to. This discomfort was observed by one of the juniors, and he offered a glass of water, but the patient wasn't able to move his right arm Diagnosis?

LMCA territory stroke.

On Work up:

- Focal deficit in Right Arm is Noted.
- CT scan is to be done in 20-25 mins - Door To CT Scan Time
- And is to be interpreted in 45 mins - Door To CT Scan Interpretation Time
- **CT scan**



Important Information

- If an internal capsule stroke occurs, it causes pure motor paralysis (no aphasia and apraxia). Only face and arm paralysis are seen.

Q. Which is the most common site of IPH ?
Ans. Putamen

Q. Which is the bleeding blood vessel here?
Ans. Penetrating branches of Lenticulostriate arteries which in turn is branch of middle cerebral Artery.

Management

A. HTN crisis management

- **HTN crisis cutoff**
  → > 220/130 mmHg as per CMDT

Drug used:

- IV nicardipine
- IV labetalol

B. Increased ICP management

1. IV Mannitol or IV Hypertonic Saline for midline shift.
2. Ventriculostomy
3. Decompressive hemicraniectomy

Warfarin Toxicity with IPH

Case-04: A patient with atrial fibrillation was advised for Warfarin, but due to high dose the patient has developed IPH due to Warfarin toxicity. Best method to control bleeding?
Answer: Prothrombin complex concentrate

Extradural Hemorrhage

Case-05: A boy on his 25th birthday was traveling on his new bike, which he received as a present. Unfortunately, the bike skid and he fell on the concrete road without a helmet. He became unconscious due to concussion, but after some time he regains consciousness, he has lacerations and left knee pain. He came to the hospital for treatment by himself.

Doctor told the nurse to do basic first aid for him and made him rest on a bed. After 10-15 mins when the Doctor reached the patient, he was found asleep. But when examined he was unconscious, then sarted having posturing and went in coma.

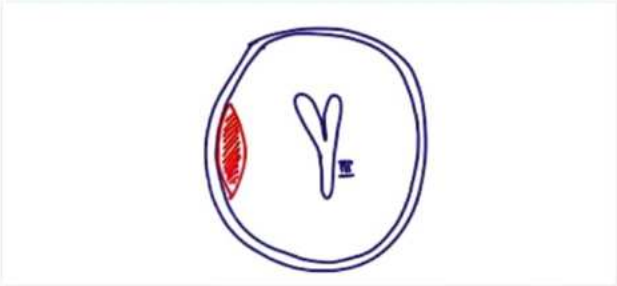
Consciousness between unconsciousness is seen - Lucid Interval.

- **Lucid Interval can be seen in both**
  1. Extradural hemorrhage (EDH)
  2. Acute subdural hemorrhage (SDH)
- CT helps to differentiate EDH and SDH
- Middle meningeal artery is bleeding vessel in EDH

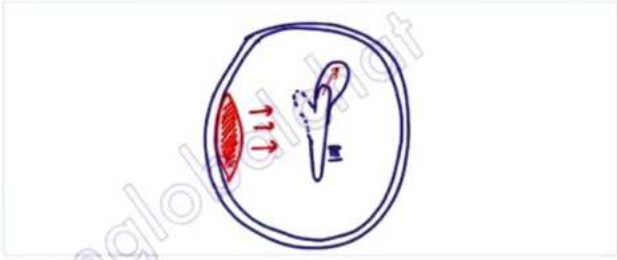
Case-06: A boy playing cricket got hit by a ball on his head. He lost consciousness for 1-2 mins and was conscious later. He played the whole match without any issue and even scored 50+ runs, but when he returned to the room he was groggy and dizzy so he laid down. Then he started posturing, went into a coma and when brought to hospital he was already dead.

CT Findings in Lucid Interval

- **EDH**
  - **Bleeding vessel:** Middle meningeal artery (branch of external carotid artery)
  - **Non Contract CT:** By Convex Hyperdensity can be present (Lenticular Hyperdensity)



  - If the bleed increases, it may pressurize the ventricles and one of the ventricles might be invisible on CT (midline shift) and other ventricle might be asymetrically enlarged - Obstructive Hydrocephalus.



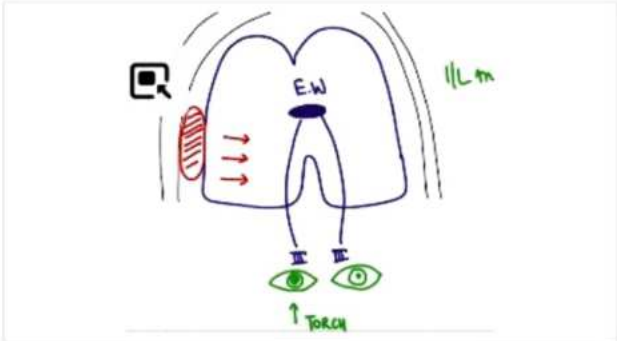
Treatment

- EDH with posturing: Burr hole surgery
- Burr hole is made at the weakest side of the pterion, or anterior or posterior of the pterion
- Done to reduce the pressure in brain
- Just a measure before the Neurosurgery is performed

- **TOC for EDH:** Decompressive Hemicraniectomy

Suspected Extradural Hemorrhage and Deciding the Side of Burr Hole

If CT scan isn't available where to perform the Burr Hole surgery?



- When there is a CNS bleed it will put pressure on the oculomotor nerve as well
- It will cause disparity of pupillary size. On the ipsilateral side, the pupil is sluggish and mid-dilated (Hutchinson pupil)

Deciding the Side of Burr Hole Surgery:

1. CT scan (primary)
2. Hutchinson pupil (secondary)
3. If both pupils show Hutchinson pupil - Select the left side

- Left side is selected as it is the most dominant part of the brain in many (as most people are right hand dominant)

Subdural Hemorrhage

Case-07: 70 year female with T2DM and neuropathy slipped in the bathroom and fell, at this moment her head slammed against the bathroom floor. She had a bump on her forehead. She didn't visit the hospital, and the next day she had a headache for which she took painkillers, but the headache is still persisting, she also vomited a couple of times.

Her son insisted that she visit the doctor, but she refused. She was enduring this for about 10 days, and on the 10th day she was having right arm weakness and wasn't able to lift it. Her son brought her to the hospital out of concern. Her GCS value is 15/15 but extensor plantars are noted.

NCCT Head:

- Concavo - Convex hyperdensity is seen - Signifies subdural hemorrhage

To Remember

- Concavo-Convex hyperdensity signifies Subdural hemorrhage.

1. **Acute -** White appearance of bleed
2. **Chronic -** Black appearance of bleed

Case Scenarios for Subdural Hemorrhage

1. Stunt actors
2. Boxers
3. Alzheimer's patients
4. Parkinson's patients
5. Obese people

} Falling in the bathroom

Treatment: Depands on volume of bleed and location of Bleed. In case of minimal bleeding acetazolamide will suffice and gradual improvement is seen.

- Acetazolamide can be prescribed

- **However if**
  1. Low GCS
  2. Volume of bleed is substantial (>30 CC)
  3. Location of bleed is infratentorial.
     - Decompressive surgery is necessary in this case

Summary

Refer Table 17.1

Table 17.1

Type of Hemorrhage	To Remember
EDH - Extradural Hemorrhage	**Main cause:** Trauma **Case** • Bike accident • Cricket player **CT** • Biconvex hyperdensity **Source of bleeding:** Middle meningeal artery

SDH - Subdural Hemorrhage	**Cause:** Fall
	Case
	• Lady with T2DM
	• Neurologically illness
	  ○ Alzeihmer's disease
	  ○ Parkinsonism
	CT
	• Concavo-Convex hyperdensity
	  ○ **White -** Acute
	  ○ **Black -** Chronic (blood reabsorbed)
	Source of bleeding: Cortical Bridging veins

IPH/ ICB - IntraParenchymal Hemorrhage/ IntraCerebral Bleed	**Main cause:** HTN **Case** • HTN crisis • Warfarin toxicity **CT** • Spilling of blood into parenchyma • **Common site:** Putamen • Intraventricular extension maybe present **Source of bleeding:** Lenticulostriate artery (one of the mid branches of middle cerebral artery)
SAH - Subarachnoid Hemorrhage *Explained in SAH chapter	**Main cause:** Trauma **Case:** Rupture of berry aneurysm **CT** • Blood in the Sylvian fissure • Blood in the Interhemispheric fissure **Source of bleeding** • Mainly MCA distribution
IVH - IntraVentricular Hemorrhage	**Neonate** • **Cause:** Birth trauma (faulty forceps application) • **Clinical Features:** Shrill cry/ Bulging anterior fontanelle. • **Diagnosis:** USG skull (as the anterior fontanelle is quite open till 18 months) • **Treatment:** Phenobarbitone (preferred to reduce convulsions in babies) **Adults** • **Cause:** Extension of IPH

18 HEADACHES & MIGRAINES

- Migraine: Throbbing Headache Associated with visual complaints in the form of Aura or zig zag lines in visual field.
- Pain sensitive structure in the brain is dura mater innervated by trigeminal nerve.
- The receptors that conduct pain are Nociceptive receptors.

Important Information

ICP:

- Normal = 10-20 mm of Hg.
- If ICP is >25 mm of Hg for >5 mins, is called Raised ICP.

Common Causes of Headache 00:00:51

- **MC: Tension headache** - Diagnosis of exclusion.
- **1° headache**
  - Leading cause - Tension headache.
  - Least common cause- Cluster headache.
    - → Cluster headache is characterised by the retro orbital pain.
    - → Pain intensity will be 10/10.
    - → It occurs for only a few months of the year.
    - → Cluster headaches are more common in male patients.
- **2° headache**
  - Leading cause: Infections
    - → Meningitis
    - → Sinusitis
    - → Upper respiratory tract infections
    - → Viral illness like fever.
  - Least common cause- Brain tumour.
- **Leading cause of headache gender wise:**
  - ♂ : Tension headache > Migraine >> Cluster headache.
  - ♀ : Tension headache > Migraine.
- **Leading cause of headache location wise:**
  - Frontal: **Tension headache** > **HTN** (Middle aged person) or **refractive error** (Myopic student) > **↑ICP** (Characterised by projectile vomiting, impaired sensorium, Cushing's reflex).
  - Occipital: Tension headache > HTN >> Basilar migraine.
    - → **Basilar migraine**
      - – Vertigo.
      - – Nasal twang.
      - – Nasal regurgitation of fluids.
    - → Predominant occipital headache, Basilar artery is situated posterior to the occipital lobe.
  - Temporal Headache:
    - → Leading extracranial cause - Giant Cell Arteritis or Temporal Arteritis.
      - – It is granulomatous vasculitis.

Case Scenario:

- A 70-year-old patient who is a senior citizen and a retired armed forces soldier who is very fit and has never gone to the doctor. He complaints of Temporal Headache and feel feverish off and on. ESR is elevated diagnosis.
- Answer : Giant Cell Arteritis.

Migraine 00:08:00

- It can occur with or without aura.
- Aura is also read with focal seizures. Person can experience the involuntary or jerky movements of the hands and fingers, but prior to the episodes, the patient may percieve smell of kerosene/ Plastic/ Burning rubber.

Clinical Features

- **Visual Complaints before the start of the attack -** Aura Features are:-
  - Blurring of vision or
  - Zig-zag lines or
  - Scotoma.
- Pulsatile or Throbbing headaches.
- Photophobia
- Phonophobia
- Nausea
- **Duration of attack:** 4 - 72 hours.
- **Average duration of the attack:** Approx 24 hours.
- If **duration of the attack is >72 hours** - Status Migrainosus.
- Neck movements worsen the headache of migraine.

Case: A female patient having recurrent episodes of Throbbing headache triggered by:

- Missing breakfast,
- Standing in the Sunlight for long duration,
- Excessive physical exertion.

Note: Thunderclap headache, is a feature of subarachnoid haemorrhage.

Summary

Mnemonic POUND:

1. P: Pulsatile / Throbbing headache
2. O: One day illness.
3. U: Unilateral headache
4. N: Nausea.
   - In Majority of patients, the smell or sight of food makes them pukish.
5. D: Disabling in character
   - Severity decides the need for the prophylaxis to maintain the interpersonal and professional relations and to reduce the intensity of the headache.

Note: 4 out of 5 symptoms are present with ≥ 5 episodes per year - Consinder migraine as first differential diagnosis?

Diagnosis

Diagnosis of Migraine according to the International Headache society guidelines:-

- Unilateral and
- Throbbing headache,
- Increased with physical movements,

Important Information

- Any 2 of the 3 characters (Above) and any 1 out of 3 characters the patient (Below) - Diagnosis can be made.

- Nausea / Vomiting
- Photophobia (Aversion to light)
- Phonophobia

Treatment

- Status Migrainosus: Migraine Attack Duration - >72 hours.
- DOC: Prochlorperazine
- **To prevent episodes of migraine:**
  1. Propranolol
  2. Flunarizine
  3. Pregabalin/Gabapentin
  4. Valproate and amitriptyline

Reasons for Attacks of Migraine

There are 3 theories which describes the reason for the migraine attack.

1. **Vascular theory - Based on Serotonin**

Vasoconstriction of intracranial blood vessels
↓
Reflex vasodilation of extracranial blood vessels
↓
It stretches the dura mater and nociceptive receptors.
↓
Increases the perception of pain.
↓
Triptans are used, which acts upon the extracranial blood vessels.

- Example: Sumatriptan, 5-HT 1B/1D agonist, which holds the action to neutralise the reflex vasodilation of extracranial blood vessels.

↓
↓Stretch of dura mater and ↓Perception of pain.

2. **Stimulation of nociceptive receptors i.e., Glutamate/ Aspartate**:
3. **Vasoactive peptide cGRP (Calcitonin Gene Related Peptide)**

cGRP irritates the nociceptive receptors of the Trigeminal nerve leading to perception of pain.
↓

The Migraine Disability Assessment Test

The MIDAS (Migraine Disability Assessment) questionaire was put together to help you measure the impact your headaches have on your life. The information on this questionaire is also helpful for your primary care provider to determine the level of pain and disability caused by your headaches and to find the best treatment for you.

Instructions:

Please answer the following questions about all of the headaches you have had over the last 3 months. Select your answer in the box next to each question. Select zero if you did not have the activity in the last 3 months. Please take the complete form to your healthcare professional.

1. On how many days in the last 3 months did you miss work or school because of your headaches?
2. How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches? (do not include days you counted in question 1 where you missed work or school.)

3. On how many days in the last 3 months did you not do household work (such as housework, home repairs and maintenance, shopping, caring for children and relatives) because of your headaches?
4. How many days in the last 3 months was your productivity in household work reduced by half of more because of your headaches? (do not include days you counted in question 3 where you did not do household work.)
5. On how many days in the last 3 months did you miss family, social or leisure activities because of your headaches?

Total (Questions 1-5)

What your Physician will need to know about your headaches:

A. On how many days in the last 3 months did you have headache? (if a headache lasted more than 1 day, count each day)
B. On a scale of 0 – 10, on average how painful were these headaches? (where 0-no pain at all, and 10-pain as bad as it can be.)

Scoring: After you have filled out this questionnaire, add the total number of days from questions 1-5 (Ignore A and B).

MIDAS Grade	Definition	MIDAS Score
I	Little or no disability	0-5
II	Mid Disability	6-10
III	Moderate Disability	11-20
IV	Severe Disability	21+

The patient is evaluated based on the MIDAS score - Migraine Disability Assessment Score.

MIDAS Grade	Definition	MIDAS Score
I	Little or no disability	0-5
II	Mild disability	6-10
III	Moderate disability	11-20
IV	Severe disability	>21

MIDAS - >21 (Severe):

- 1st line of approach: Triptans (Generally, sumatriptan).
- If the person is having nausea, the following choices can be considered:
  - Mouth dissolving tablets
  - Nasal sprays
    → Highly efficacious, works within a few minutes of administration.
  - SC Injector - Autoinjectors.
  - Transdermal patches
    → Easy to carry and very handy.

MIDAS - <20 (Mild to Moderate):

- 1st line of approach: COX-1 inhibitors
  - Indomethacin.
    → It can contribute to gastritis, which can be treated with antacids or PPIs.
  - Naproxen.
- Some patients are not tolerable for the pain killers, in such conditions;
  - COX-2 inhibitors
    → Etoricoxib
  - COX-3 inhibitors
    → Paracetamol 1g with caffeine.

Advice to the Patient: To prevent recurrent severe attacks in the patients, always have **autoinjectors 6 mg of sumatriptan**, which is administered subcutaneously for fast relief.

Important Information

- **Longest acting triptan** - Frovatriptan (Half life 26 hours).
  - This is beneficial for some migraine attacks which last longer.
- **Fastest acting triptan** - Nasal sprays (Rizatriptan/Zolmitriptan).
  - Fast relief, highly efficacious.
  - Prescribing triptans should be based on MIDAS.

- **Mechanism of Action:** 5-HT 1B/1D agonist causing Vascular Vasoconstriction.

Triptans are contraindicated in:

1. Pregnancy
   - COX-3 inhibitors can be given.
2. Prinzmetal Angina with concomitant migraine disease.
3. Peripheral arterial disease (PAD).
4. Basilar migraine
   - Vasoconstriction of the basilar artery causes **cranial nerve palsy (CNP)**.
   - Triptan mechanism of action is extracranial vascular constriction.
   - It constricts the already constricted artery, which may worsen the CNP.

- **Ergotamine**
  - Safe if taken in prescribed doses.
  - For **acute migraine attacks** - Sublingual route is recommended.
  - It is contraindicated in PAD, pregnancy.

Note:

- In severe attack: Triptans > Ergotamine.
- In Mild - Moderate attack: Routine painkillers work effectively.

Case Discussion

- A 25-year-old female patient generally wakes up at 7:30AM and goes to her work accordingly, but one day she has to wake up by 5AM. The patient presents an excruciating headache.
- The female has taken NSAIDS subsequently with a gap of 1-2 hours on empty stomach.
- According to the patient, above is the reason for 2 episodes of vomiting she had on the way to hospital.
- In further detailed examination- Nuchal rigidity is present.

First differential diagnosis?

a. SAH (Answer) b. Migraine
c. Meningitis d. ICSOL

Note:

- Blood in the meninges can result in the nuchal rigidity, Positive Kernig sign and Positive Brudzinski's sign in the patient.
- Migraine: ruled out as
  - POUND is not satisfied.
- Meningitis: rule out as
  - As it is present with fever and history of few days
- ICSOL ruled out
  - It should have a long history, where in this case the history involves only a few hours.

Important Information

- Worst headache of my life/Thunderclap headache. Peak onset of the effect can be seen within 1 min.

Case Discussion - Angle Closure Glaucoma

- A female who presented to the physician with retro orbital pain, vomiting, red eye (She was watching a movie when this episode occured).
- The 1st differential diagnosis - Angle closure glaucoma.

Reason:

As it is dark in the cinema hall, mydriasis would develop.
↓
Development of ciliary block.
↓
Dramatic increase in IOP.
↓
Vomiting

Important Information

- If retro orbital pain is presented in males - Cluster headaches.
- If retro orbital pain is presented in females - Angle closure glaucoma.
  - It begins as a severe attack, which causes extreme vision impairment.

Migraine Variants 00:39:45

- **Ophthalmoplegic Migraine**
  - POUND is resolved with the triptans.
  - 3rd nerve palsy - Neurological deficit post attack.
    → It might recover over hours or days.
  - Manifestations of ptosis and squints can also be seen.
- **Retinal Migraine**
  - It can be associated with:
    → Blindness
    → Scintillating scotoma (s).
  - The gradual resolution of manifestations can be seen as per the progression of the disease.
  - **Note:** Dramatic presentation of symptoms in 1st episode can be confused with stroke.
- **Familial Hemiplegic Migraine**
  - When the patient has developed 1st migraine attack associated with hemiplegia, the diagnosis can be confused with the stroke.
  - Work Up - Neuroimaging to rule out cerebrovascular accidents.
  - It is a calcium channel defect.

Important Information

- Calcium channel defects
  1. **Lambert eaton syndrome**
     → Anti P/Q antibodies affect the neuromuscular junction, which results in less release of Ach.
  2. **Hypokalemic Periodic paralysis type-1**
  3. **Familial Hemiplegic Migraine**

Note: Episodic ataxia - Potassium channel defect.

Case Discussion - Giant Cell Arteritis

- A 70-year-old patient who is a senior citizen and a retired armed forces soldier who has good physical health and has never gone to the doctor.
- He goes for a regular morning walk.
- The patient got a fever about a couple of weeks ago and started to have paracetamol, off and on.
- Patient also complained to Temporal Headache.

Explanation:

- Fever of Unknown Origin - Initial presentation.
- Tests for TB and connective tissue disorders are done, but the results are negative.
- On examination a cord like structure is felt anterior to the TM Joint.
- This is a case of a patient with Granulomatous Vasculitis involving a superficial temporal artery, a branch of the external carotid artery, which supplies skin of scalp and TMJ.
- In this case **narrowing of the arteries** results in the:
  - Ischaemia of the skin of the scalp
  - Jaw claudication.
- Internal carotid artery branches can be involved in this case, i.e., Ophthalmic artery.
  - If affected, it causes Monocular blindness.
- **Workup:** ESR - 100 mm fall in the first hour.
- **Invasive Investigation** - Vessel wall biopsy can be done in the patients.
  - It is done in multiple places as there is a segmental involvement of the artery.
  - **Under the microscope:** Giant cells/Granulomatous vasculitis are seen.
- Biopsy can be therapeutic in this case, as there is the removal of the nerve endings which may relieve the pain.
- The headache severity can be decreased post biopsy.
- **Treatment:** Steroids.

Important Information

- **ESR**:
  - Males: 0 - 8 mm fall/1st hour
  - Females: 0 - 20 mm fall/1st hour
- ESR - 100 mm fall in the first hour is also seen in;
  1. SABE
  2. GCA
  3. Multiple Myelome

Important Information

Two **important pointers towards the GCA:**

1. Temporal headache
2. Jaw claudication

Case Discussion - Tension Headache

- A 35-year-old lady approaches the physician and complains like "I have two children who are phone addicts and their academic performance has dropped and I'm very stressed about it."
- She then describes her headache as
  Band like compression over the head at:
  → Forehead
  → Occipital area
- On examination:
  1. BP - Normal.
  2. Refraction testing - Normal visual acuity.
  3. X-Ray PNS (For Sinusitis) - Normal.
  4. Fundus examination: Normal to rule out papilledema

Note: The patient should be ruled out for the common causes of headache before categorising the patient as suffering from tension headache.

Case Discussion - Cluster Headache

A 25-year-old guy, presents with retro orbital pain
↓
The patient is pressing the eye, the palm is wet because of tears- Epiphora.
↓
The tears can travel the puncta and enter nasolacrimal duct- Nasal stuffiness.
↓
Eyes are red with ciliary and bulbar congestion.
↓
Similiar attacks occurs for only a few months of the year, like two consecutive months.

Important Information

- **Frequency of the attacks:** 8-10 Weeks/Year.
- **Number of attacks per day:** 1-8.
  - In migraine - 1 attack per day.
- **Duration of the attacks:** 15-180 minutes.
- Pain intensity (10/10).
- The patient can't sleep, the pain will awaken the patient.
  - But in a migraine, after resting the pain may subside and the patient may feel fresh.
- Cluster headaches are more common in male patients, who become restless, get up form bed and start pacing to and fro in the room begging for pain relief.

- **Treatment**
  1. High flow oxygen: 12-15L/Min. 1st line
     → Decreases the severity of the pain.
  2. Triptans- Sumatriptan 6mg SC injection: Drug of choice/Best Treatment
- **To prevent the attacks:**
  1. Verapamil/Topiramate - 1st choice in the prophylaxis.
  2. Non-invasive VNS
     → Also used in refractory epilepsy.
  3. Additional drugs include:
     → Melatonin
     → Gabapentin
     → Pregabalin

Cluster Headache Vs SUNCT

01:00:41

SUNCT

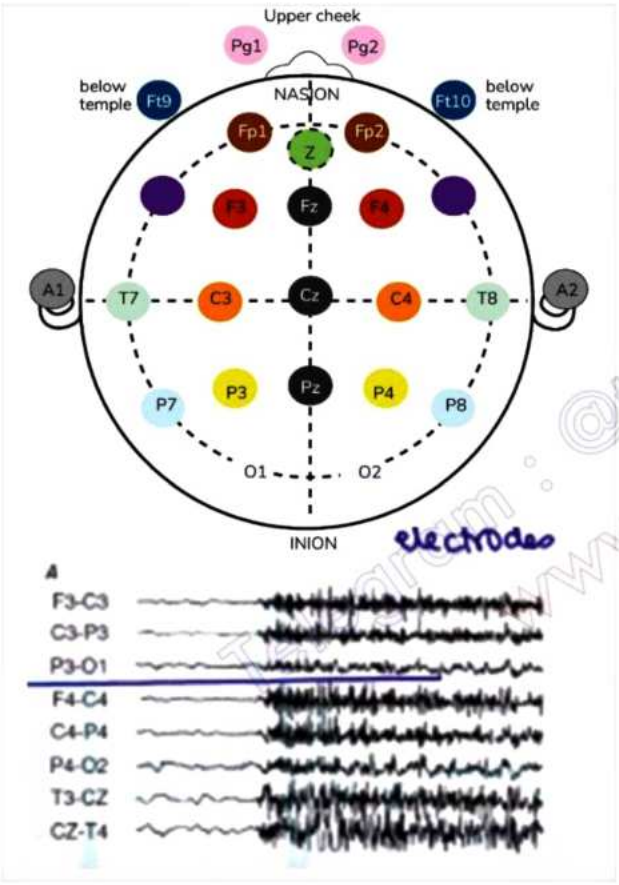
- Short Lasting
- Unilateral
- Neuralgiform
- Headache with:
  - Conjunctival injection and
  - Tearing.

Cluster Headache	SUNCT
Number of attacks per day: 1-8.	Number of attacks per day: 3-200.
Duration of the attacks: 15-180 minutes.	Duration of the attacks: 5-240 seconds.
Treatment • High flow oxygen: 12-15L/Min. ○ Decreases the severity of the pain. • Triptans - Sumatriptan 6mg SC injection. DOC/Best treatment	Stinging pain on the one side of the pain. • **Treatment** - IV Lignocaine. It is also used for management of ventricular tachycardia.

19 EPILEPSY AND EEG

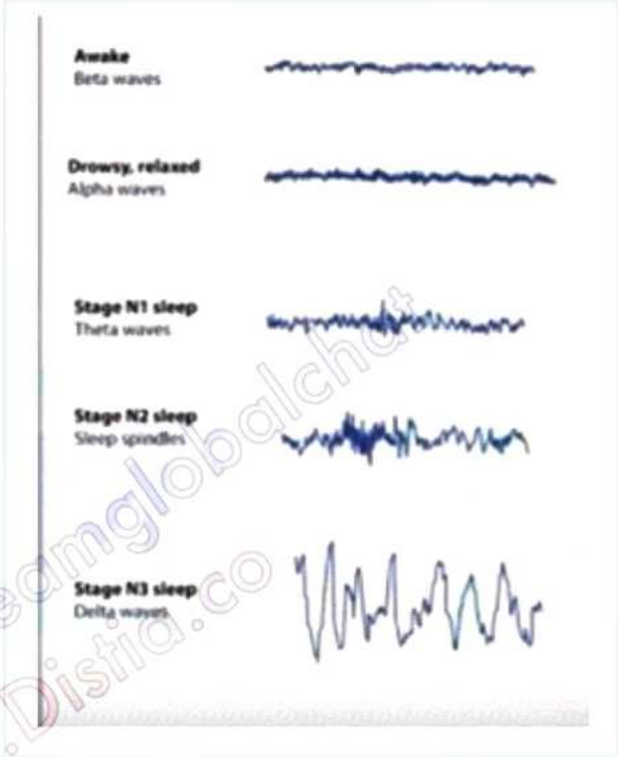
Introduction

- HANS BERGER - Invented EEG.
  - Developed 10-20 system where electrodes were placed on scalp
- Electrode are placed according to:
  - The ones in central - Z nomenclature
  - On Left side - odd number
  - Right side - even number



- Left side of the brain is represented by the upper part of the EEG.
- Right side is given below the left.
- Abnormal high voltage discharge - present on both left and right side of the brain. I.e., in the upper and lower parts of the EEG → generalized / diffuse abnormality.
- If, Abnormal high voltage discharge - present only on one side, it can lead to a diagnosis of → focal seizures.

Normal Brain Electrical activity



Refer Table 19.1

- EEG is usually normal in the interictal period.
- EEG is normal most of the times in focal seizures.
- Video EEG is superior to normal EEG as patient can be monitored for longer time.
- Myoclonus can also be physiological as:
  - It can be present during the NREM stage 1

Seizure vs convulsion vs epilepsy 00:08:26

- Seizure - Abnormal focus in the brain producing abnormal electrical discharg which can be picked by EEG
- Convulsion- It is the motor manifestation of abnormal electrical firing in the brain.
- Motor manifestation can be controlled by Lorazepam/ Diazepam.
- Electrical activity is controlled by lamotrigine, Levetiracetam, Phenytoin, Phenobarbital.

GTCS - Generalized tonic clonic seizure.

- Patient will not be able to maintain posture and may fall or slump on to one side.
- Up rolling of eyes can be seen.
- Due to sudden contraction of muscles of expiration or vocal cord → patient may make a loud sound known as ictal cry.
- There will be pooling of secretions as the patient is not able to swallow.
- Tongue may come in between teeth and cause Tongue bite
- Tongue may fall backwards - obstruct airway.
- Perioral cyanosis will be present.
- The Sympathomimetic stimulation will cause:
  - Heart rate ↑
  - BP ↑
  - Pupils - grossly dilated - mydriasis.
- Tonus phase lasts for 10 - 20 seconds
- After that, tonus is replaced by clonus.
- Clonus - It is the violent jerking of all limbs and truncal musculature
- Do not try to restrain the patient in a non-hospital set up rather wait for the convulsion to settle and then take the patient to the hospital.
- Restraining may cause:
  - Soft tissue injury
  - Ligament tear
  - Shoulder dislocation
- Convulsions in Hospital:
  1. Secure IV line
  2. Give IV Diazepam / Lorazepam to control convulsions.
  3. Abnormal electrical activity is controlled by lamotrigine, levetiracetam, phenytoin, phenobarbital.
- GCSE - generalized convulsive status epilepticus.
  - Convulsions lasting > 5 minutes

Post-ictal period

- Patient is unresponsive to commands - not able to tell name , place of living, phone number
  - Babinski relfex
  - Corneal reflex Absent
- When the patient regains Consciousness → Babinski disappears and corneal reflex reappears
- Even after waking up → patient will still be confused.
- Investigation - EEG
- DOC – Sodium Valproate

Epilepsy

- **When there is recurrence of seizure episodes in a patient, it is termed as epilepsy.**
- **≥2 unprovoked seizures**
- Provoked seizure – when there is a trigger present for seizure
  - Insulin overdose is a trigger in diabetics →provoked seizure
  - Head injury
  - CVA
- To terminate convulsion → Lorazepam
- If IV access not obtained, give Rectal diazepam

Classification of Seizures 00:17:20

Focal seizure

- With intact awareness
- With impaired awareness
- Motor
- Non motor
- Focal seizure with evolution into GTCS

Generalized seizure

- Motor
  - Tonic-clonic
  - Atonic
  - Myoclonic
- Non- motor
  - Absence
  - Atypical absence

Seizure of unknown onset

- Motor
- Non- motor

Focal seizure with intact awareness

- In such cases, Patient can explain the events
  - E.g, Clonic movements in left hand due to abnormal electrical activity on right motor cortex and patient can himself describe the symptoms.

Focal seizure with impaired awareness

- In such cases, the patient losses consciousness and description given by bystander or relative.
- Developed Clonic movements in hand may be associated with twitching of same side of face.

Non-motor manifestations of focal seizure

1. Pin and needle sensation.
2. Patient says he can perceive Smell of burning kerosene, burning rubber.
3. Visual symptoms may include
   - Brilliant flashes of light.
   - Micropsia- everything seems smaller
   - Macropsia - everything seems bigger
4. Loss of consciousness

To differentiate GTCS from 'focal seizure with evolution into GTCS'

- Focal seizure are always associated with aura
  - Symptoms like smelling kerosene or burning rubber
  - Things appearing smaller or bigger than normal

- Aura is followed by focal seizure and then gradually involuntary movements spread to whole body
- If the episode begins as GTCS then it is not associated with aura
- Management is also different.
- Focal seizure - Carbamazepine is usually used in young patients.
- But for Focal seizure with evolution into GTCS - sodium valproate is the drug of choice
- For GTCS - Lamotrigine / Valproate
- It was earlier called as focal seizure with secondary generalization but is now termed as Focal seizure with evolution into generalized variety.

Focal seizure	Generalized seizure	Unknown onset
• **With intact awareness** • **With impaired awareness** • **Motor** • **Non- motor** • **Focal seizure with evolution into GTCS**	**Motor** • Tonic-clonic • Atonic • Myoclonic **Non- motor** • Absence • Atypical absence	**Motor** **Non motor**

GTCS

1. Motor

- **Tonic-clonic seizures**
  - Patient initially becomes stiff (tonus)
  - Which is followed by jerky movements (clonus)
  - Tonus lasts for about 20 seconds
  - Clonus lasts for about 30-40 seconds
  - GTCS gets over within 1 minute

- **Atonic Seizures**
  - There is a transient loss of tone mostly of the muscles supporting the neck
  - So, it may be perceived as Head nodding or head drop
  - Tone lasts for 1 or 2 seconds.
  - If there is a loss of tone of whole-body, patient may fall.

- **Myoclonic Seizures**
  - **It is sudden jerking movement of some muscle groups in extremities.**
  - It can be focal or generalized.
  - It can also be Physiological
    → If a person is feeling very sleepy and tired and is drifting into sleep, he may feel as if he is falling.
    → This is myoclonic jerk that can jolt a person out of sleep.
    → It is seen in NREM stage 1
  - Myoclonus can also be seen when a person is awake.
    → Example, in a child of Juvenile myoclonic epilepsy
    → Child may have sudden jerky movement of hand while having breakfast that may spill breakfast or difficulty in tying shoelaces or buttoning a shirt.

2. Non-motor

- **Absence Seizures**
  - Common in 4-10 years of age
  - Vacant staring spells and post ictal deficit is absent.
- **Atypical absence**
  - Absence and Atypical absence can be differentiated by EEG

Focal seizure

- **Causes**
  1. Neurocysticercosis
  2. Hippocampal sclerosis -
     → It is the cause of Temporal lobe epilepsy.

Focal seizure with intact awareness

- Suddenly, Involuntary movement develops in one arm with twitching on one side of the face.
- This is due to abnormal electrical activity in the opposite side of motor cortex
- Patient may explain that he used the other hand to control but was not able to control the jerky movements.
- He may be aware of everything - intact awareness and motor component
- Jacksonian March - Abnormal movements start from Distal to proximal muscles
- Weakness persisting for hours to days or week after focal seizure - Todd's palsy
  - May be misinterpreted as stroke.
  - In Stroke the power will not return
  - But in Todd's palsy power will return after few days.
- If the manifestations continue for a longer period of time, it is known as Epilepsia partialis continua.
  - Weakness may persist even for days to weeks.
  - It is the counterpart of GCSE in GTCS

Non - motor manifestations could be:

1. Paraesthesia
2. Vertigo
3. Feeling of fall
4. Sensory Manifestations may include smell of burning rubber
   - As Temporal lobe integrates the sense of smell, abnormal electrical activity may begin in temporal lobe and cause this sensation.
5. Micropsia - things may appear small
6. Macropsia- things may appear bigger
7. Alice in wonderland syndrome - broad term - includes micropsia, macropsia

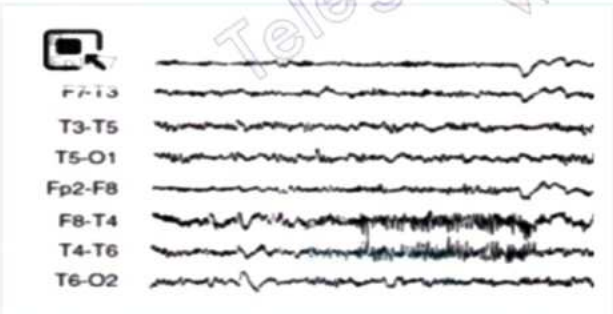
- It indicate that the person is having temporal lobe epilepsy
- The connection between temporal and occipital lobe may be affected.
- Or abnormal electrical activity is in the occipital lobe

8. Subjective internal events that cannot be observed by someone is called aura.
9. Aura is not seen in GTCS.
   - GTCS has premonitory symptoms.

Focal seizure with impaired awareness

1. It starts with an Aura.
2. And is then followed by Motionless stare.
3. This is then followed by various manifestations that are called automatism.

- **Automatism could be:**
  - Lip smacking movements
  - Chewing movements
  - Swallowing movements
  - Picking movements
  - Uncontrollable laughing or crying
  - This is followed by post ictal confusion.
    → The person feels dazed not realizing what actually happened.
    → No memory of recent event
  - The loss of short-term memory is called antegrade amnesia.
  - Transient neurological deficits in the form of aphasia may also be seen.
  - Period between two episodes of seizure - interictal period
  - EEG may be normal in this period.
  - Imaging of Brain will be able to pick the lesions responsible.



  - During ictal period - Abnormal high voltage may be seen in some leads
  - Image showing abnormal high voltage in right temporal leads.
  - Since the abnormal electrical activity is seen only in some leads it is focal seizure
  - Temporal lobe is also affected.
    → smell, taste, vision may be affected.

Generalized onset of seizures

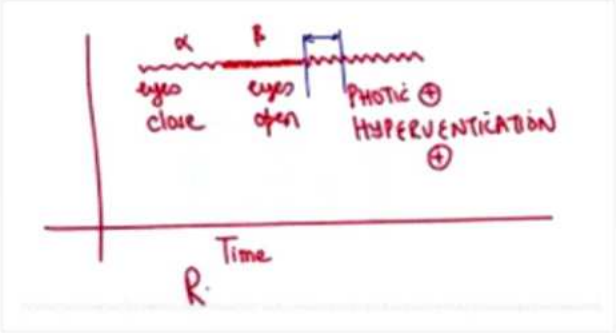
Typical Absence Seizure

- This is Loss of consciousness present without tonus or clonus.
- Transient loss of consciousness is only for 1 to 2 seconds
- Postural tone and control is maintained.
  - In Atonic seizure - loss of tone leading to head drop or fall
- Before attack begins, there may be repeated blinking of eyes

Case Scenario: For a child who's 4-10 years of age

- There is repeated blinking of eyes seen which is followed by sudden unresponsiveness as described by mother.
- Child may have been taking normally and then suddenly becomes unconscious
- Then the child resumes activity as if nothing has happened.
- Post-ictal deficit is not seen.
- Mother may describe that child becomes switched off for a few seconds.
- May be described as daydreamers.

- EEG- 3/sec spike of slow wave pattern
  - Child has eyes closed - alpha waves.
  - When asked to open the eyes the discharge become slightly lesser in voltage and slightly faster.
  - Child is then asked to hyperventilate.
  - After few seconds the EEG becomes relatively slow
  - Some bright light can be switched on or asking the child to hyperventilate for few seconds.
  - Photic stimulation or Hyperventilation can trigger absence seizure.



  - Spiked pointed and slow wave pattern
  - Frequency - 3/second

- Drug of choice - Valproate
  - Lower the age higher the chance of Fulminant hepatic failure due to valproate.
  - So, Ethosuximide used especially in <2 years age.

Typical vs atypical absence seizure

- It is clinically difficult to differentiate.

- So, it is differentiated by EEG
- In typical - 3 Hz spike and slow wave pattern
- In atypical - = <2.5 Hz spike and slow wave pattern

Atypical absence seizure

- There is loss of consciousness for relatively longer duration i.e., 10-15 seconds
- It is generally more severe and is associated with mental retardation.
- It is also associated with Lennox Gastaut syndrome.
- Posture is always maintained in absence seizure but lost in atonic seizure.

Atonic seizure

- The chance of injury is higher as person can fall suddenly due to loss of postural control.
- There is Loss of consciousness and loss of postural control for 1-2 seconds.
- The tone is not usually lost in whole body but is mainly lost in muscles of neck- sudden onset head nodding or head dropping may be seen.
- No postictal deficit is present.

Extra Mile:
No postictal deficit seen in:
1. Absence seizure
2. Febrile seizure - Typical
3. Atonic seizure

Extra Mile:

- Jerking movements of whole body, up rolling of eyeball and frothing- GTCS
- Involuntary movements only in one hand and person trying to control with other hand - focal seizure with intact awareness.
- If unconscious and only one hand is moving - focal seizure with impaired awareness
- Sudden jerky movements- myoclonic jerks
  - Can be unilateral or bilateral
  - Can cause spilling of food or water
- Atonic- sudden decrease in tone and no post ictal deficit

Myoclonic jerks

- Sudden brief jerky movement in arms and legs
- **Causes:**
  1. Neuro degenerative disorder VCJD - Variant Creutzfeldt Jakob Disease
     → Patient has history of consumption of poor quality beef
     → It may contain Prion particles which on entering into body multiply in cytoplasm of neurons.
     → And cause Irritation of neurons leading to their abnormal firing.
  2. Metabolic encephalopathy
  3. Anoxic or hypoxic injury to brain
     → Children - birth asphyxia
     → Adults - HACE - high altitude cerebral edema
     - Soldier posted in high altitude.
     - It causes swelling in brain due to sudden ascent to high altitude leading to sudden jerking movements - myoclonus
     - It may even cause death.

- **Myoclonic seizure can coexist with GTCS**
  - As in Juvenile myoclonic epilepsy
  - In childhood they have myoclonic jerks and when they become adults develop GTCS

Epileptic spasms

- There is mostly Involvement of truncal musculature so the patient bends forwards.
- Also called SALAAM SEIZURE
- It usually occurs in the infants, causing:
  - Body to bend forward and Jerky movement of arm - as if giving salute.

- EEG
  1. Grossly chaotic pattern: Hypsarrhythmia
  2. The background rhythm is also suppressed and is called Electrodecremental response.

Remember

- Decremental response in EMG - seen in Myasthenia gravis

GTCS

- Premonitory symptoms +
- Loud ictal cry due to sudden contraction of muscles of vocal cord and muscles of expiration
- Tonus - stiffness of body
  - Person may fall down
  - Lips may turn blue - cyanosis - as the person holds his breath continuously in expiration.
  - Duration of tonus - 10 seconds
  - Tongue falls backwards → leading to airway obstruction
  - Tongue bite + : clench teeth tightly that tongue may be bitten
  - Up rolling of eyes
- Clonus - involuntary jerking of whole body
  - Restraining will not be helpful.
  - No touch policy - wait and watch to be followed outside the hospital premise
  - Inside the hospital - give lorazepam to control the clonus
- Post ictal deficit
- Patient may have noisy breathing due to secretion in throat
  - Airway has to be cleared
- Sphincter relax at the end of clonus → incontinence causing Fecal matter or urine to pass

Vasovagal syncope vs GTCS - postictal period 00:56:41

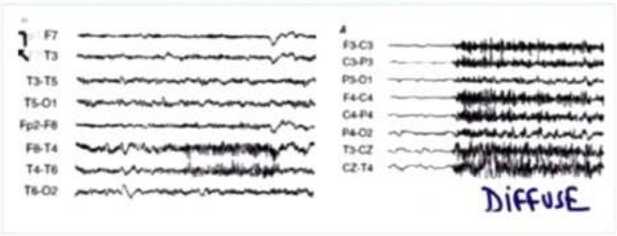
- History of sudden onset loss of consciousness present in both patient.
- Vasovagal syncope always has trigger like intense pain or on seeing blood.
- GTCS could be idiopathic without trigger or warning.
- Tonus - clonus in vasovagal syncope is due to sudden onset cerebral ischemia - may be due to pain during tooth extraction.
- The duration of symptoms is however very subjective and often cannot be differentiated based on the duration alone.
- In vasovagal syncope there is Tunneling of vision of patient as blood supply to brain reduces
- This causes Concentric shrinkage of field of vision.
- Recovery in vasovagal syncope can accentuated by leg arise as blood supply to heart increases and the ischemia to brain is resolved.

Symptoms	Vasovagal syncope	GTCS
Trigger	+	None
Tonus - clonus	<15 sec	30-60 sec
Tongue bite	rarely seen - as tongue falls backward	Tongue bite + as tongue may come between teeth during tonus
Headache	rarely	Headache ±
Urinary incontinence	+	+
Loss of consciousness	Gradual • Tunneling of vision • Concentric shrinkage of field of vision	Sudden
Recovery	Within seconds Accentuated by leg raise of patient	Takes hours Patient may sleep for hours and wake up dizzy

Q. All of the following can be used to differentiate between vasovagal syncope and GTCS except

a. Headache
b. Tongue bite
c. Recovery
d. **Urinary incontinence**

- Urinary incontinence is seen in both vasovagal syncope and GTCS
- Serum prolactin levels are increased post GTCS but are usually normal after vasovagal syncope.



- GTCS -diffuse abnormal activity in all electrodes
- Focal- some leads show abnormal high voltage activity against a background of normal rhythm.
  - EEG should be recorded during the episode of seizure or immediately after that.
  - During postictal period EEG is usually normal in focal seizure
  - As there is no abnormal electrical activity during interictal period
- Absence seizure - 3/sec spiked and slow wave pattern.
- Atypical absence - 2.5/sec spiked and slow wave pattern.
- Atonic - decrease in tone , may cause fall but no postictal deficit

Epilepsy syndromes 01:02:25

Lennox Gastaut Syndrome

- 3 kinds of seizure seen in same patient
  - Patient could wake up with **GTCS** in the morning.
  - **Atypical absence** - in the afternoon hours
    → with vacant stare
    → Blinking of eyes
    → Then behaving as if everything is normal.
    → EEG - <2.5/sec spiked and slow wave pattern.
  - **Atonic** - sudden decrease of tone of neck muscles
    → Head nod or head drop.
- Etiology - Multifactorial
- EEG - in atypical absence <2.5/sec spiked and slow wave pattern.
- Management - Monotherapy with valproate

JANZ syndrome

Juvenile myoclonic epilepsy

- Etiology- Polygenic inheritance
- Presents at 10 -19 years of age.
- Patient presents with Myoclonic Jerks
- Usually seen in the morning hours
- EEG - advised to do sleep EEG
  - Background rhythm - may be slow sawtoothed pattern as in REM sleep
  - 4-6 Hz polyspike pattern

- Patient may develop GTCS in adulthood.
- In about 30 % of patients, develop typical absence seizure.
- Treatment: Require lifelong valproate.

Myoclonus

- Myoclonus can be physiological in NREM stage 1

Based on age group myoclonus can be seen in

- Child <1 year - Infantile spasm / salaam seizure
  - Also called west syndrome
  - Epileptic spasm involving trunk
  - And jerky movement ike salute /salaam
  - EEG - hypsarrhythmia
    - → Gross chaotic pattern
    - → Background suppression of electrical activity - Electrodecremental response
- 8-year-old child who never had measles vaccine administered
  - Infected from slow virus disease.
  - Late complication of measles like SSPE-subacute sclerosing panencephalitis may occur
- 10-19 years - JME - juvenile myoclonic epilepsy
  - Early morning myoclonic jerks
  - May also have GTCS.
  - EEG - 4-6 Hz polyspike pattern
- 30 year - consumed poor quality/Tainted beef
  - Myoclonic jerks and dementia of cortical variety
  - VCJD - Variant Creutzfeldt Jakob Disease

MTLE- Mesial temporal lobe epilepsy

- It does not respond to medications so, Surgical intervention is required.
- MRI shows - hippocampal sclerosis
- It may be associated with history of febrile convulsions in childhood leading to development of focal seizure with impaired awareness.
- Automatism may also been seen in such patients which includes:
  1. Uncontrollable laugh or cry
  2. Lip smacking
  3. Chewing or swallowing movements
- EEG - abnormal electrical activity in temporal lobe area is seen.
- DOC - Valproate
  - It is used because safety profile is fairly good but it will not respond to medications on long term basis.
- Requires surgery - treatment of choice.
  - In MTLE, Increase the drug dose to the maximum before adding on another drug.
  - Polypharmacy can be implemented but it will amplify the side effects.

Treatment of Seizures 01:13:46

- Focal seizures:
  - L2COP
    - → Levetiracetam
      - Least interaction with other drugs
      - Preferred in elderly patients.
    - → Lamotrigine
      - Risk of SJS - steven johns syndrome
    - → Carbamazepine
      - Can develop anemia or leukopenia
      - It may lead to Hepatotoxicity.
      - If a person already has liver disease or anemia, avoid CBZ , instead give oxcarbazepine.
    - → Oxcarbazepine
    - → Phenytoin
- Generalized seizures:
  - L2V
    - → Levetiracetam
    - → Lamotrigine
    - → Valproate
- Woman of reproductive age group
  - Valproate is not preferred as it is teratogenic.
  - Levetiracetam or Lamotrigine have less teratogenicity
  - All of the antiepileptic drugs can cause folic acid deficiency and lead to neural tube defects.
  - If the patient has already started on antiepileptic like valproate and came to the doctor in second trimester, there is no need to change the drug as organogenesis takes place in first trimester
  - But if the patient is getting married or planning to conceive, then the first line drug to be used is Levetiracetam/Lamotrigine.

First line drugs

Refer Table 19.2

Febrile seizure

- For Prevention of episode of febrile seizure:
  - Oral Clobazam in intermittent prophylaxis as long as child is having fever
- During episode:
  - Rectal diazepam
  - Intranasal Midazolam

Infantile spasm

- ACTH is the DOC
- With tuberous sclerosis – Vigabatrin is the DOC
- Most common type of epilepsy in children - Benign Rolandic epilepsy
  - Age of onset is 2 - 13 years of age
  - It is a presentation of focal seizure
  - It causes Involuntary twitching contraction of one side of face

- A Workup to rule out any other cause/lesion should be done
- Treatment - carbamazepine

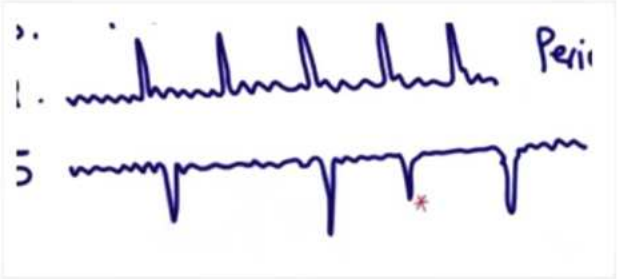
- Most common type of seizure in children - Febrile seizure
- Most common type of seizure in newborn - Subtle seizure
- **Subtle seizure**
  - It Shows mild manifestations.
  - There is JITTERINESS i.e.,
    → Tremors of lip or hands
    → Cycling movements
    → Boxing or kicking movements.
  - **Cause:**
    1. Birth asphyxia
    2. Hypoxic ischemic encephalopathy
    3. Metabolic causes
       - Hypoglycemia
       - Hypocalcemia
    4. Pyridoxine deficiency

EEG

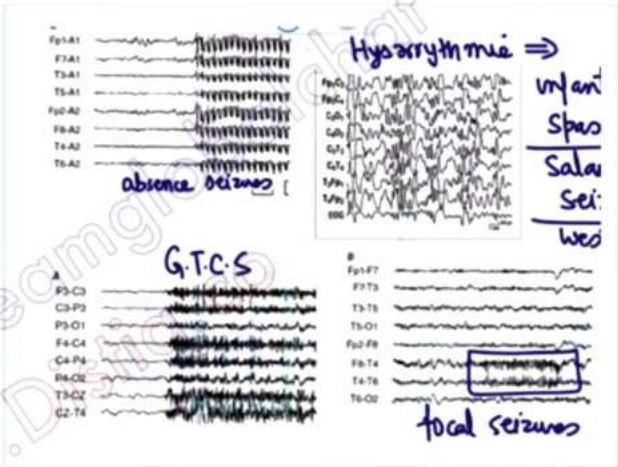
01:25:56

- < 3 Hz spike and slow wave pattern - absence seizure
- < 2.5 Hz spike and slow wave pattern- atypical absence seizure
  - Associated with Lennox gastaut syndrome
  - Drug of choice - Valproate
  - Atypical - More longer duration
- 4-6 hz polyspike pattern - Juvenile myoclonic epilepsy/ JANZ syndrome

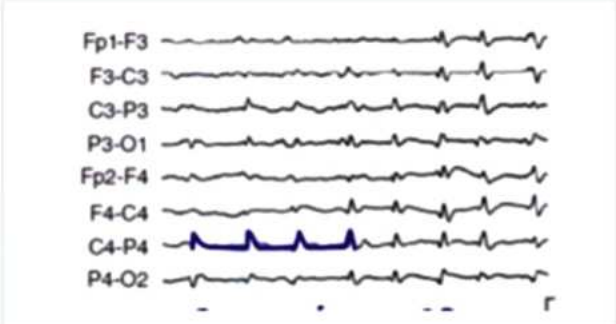
- **PSWC - Periodic sharp wave complexes**
  - High voltage burst in every few seconds
  - Shows Periodicity and hence called as periodic sharp wave complexes.
  - Seen in Neurodegenerative disorder called VCJD
    → History of consumption poor quality beef
    → The cow was having mad cow disease or bovine spongiform encephalopathy.
    → Prion particles are not killed by heat
    → Prion particles cross BBB - multiply in cytoplasm of neurons
  - Periodic waves - correspond to Myoclonic Jerks.
    → Dementia + Myoclonic Jerks + PSWC



- **Triphasic wave**
  - There are variable amplitude bursts with a positive wave preceded and followed by negative wave.
  - There is no periodicity seen.
  - Amplitude is different.
  - In EEG -
    → everything goes up is taken is negative
    → Everything that goes down is taken positive
  - This is called a triphasic wave
  - Positive wave that is preceded by and followed by negative waves
  - Seen in Metabolic encephalopathy, like Ammonia intoxication



- Spikes occurring 3/ sec - absence seizure
- Diffuse multi-amptitude bursts in all leads - GTCS
- Abnormal pattern only in temporal leads - Focal seizure
- EEG - Hypsarrhythmia - Infantile/epileptic spasm called West syndrome/Salaam seizure
  - Treatment - ACTH injection
  - With Tuberous sclerosis - vigabatrin



- Periodic sharp Wave complexes that occur periodically- PSWC

- Associated with VCJD
- Similar pattern seen in children with SSPE

Refer Table 19.3

SSPE - Subacute Sclerosing Panencephalitis 01:32:47

1. Clinical	Progressive, subacute metal deterioration with typical signs like myoclonus
2. EEG	Periodic, stereotyped, high voltage discharges
3. Cerebrospinal fluid	Raised gamma globulin or oligoclonal pattern
4. Measles antibodies	Raised titer in serum (1:256) and/or cerebrospinal fluid (1:4)
5. Brain biopsy	Suggestive of panencephalitis

Definitive Diagnosis: Three of the five criteria.

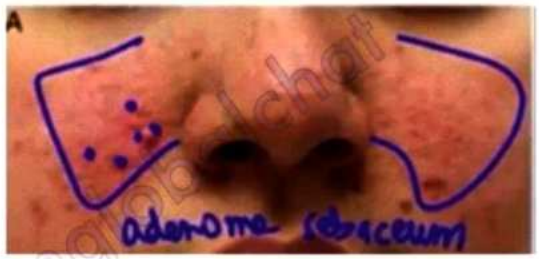
- EEG looks identical to that in VCJD
- It is a late complication of measles.
- It occurs when the child has never received measles vaccination.
- It is seen in areas where coverage of measles vaccine is low.
- At early years of life, the child may have got infected with measles and had no features or it got subsided due to his own immune system acting.
- The Virus that the child got infected might was mutated variant of measles virus as in area of low measles vaccine coverage → the virus gets mutated and converts to altered measles virus which can avoid the immune system of the body.
- It crosses the blood brain barrier and multiplies inside the neurons and causes neurodegeneration.
- So, at around 8 years of age the child develops
  1. Myoclonic jerks
  2. Lack of interest in playing with toys or children
  3. May lie on bed and keep staring at walls
  4. The interaction with parents gets affected
  5. Urinary and fecal incontinence/Vegetatove state
- EEG - identical to VCJD

- **Work up:**
  1. CSF study -
     → It shows slightly elevated protein
     → Antibody to measles virus is seen.
     → Antibody to measles virus in blood can be present in any person who have had measles disease but not in CSF.
  2. Brain biopsy:- Done Postmortem.
     - It Shows the features of panencephalitis.
- The cases of SSPE can be brought down by increasing the vaccine drive in a community.
- Early complication of measles also include- Pneumonia and Otitis media.

Phakomatosis / Neurocutaneous Disorders 01:38:34

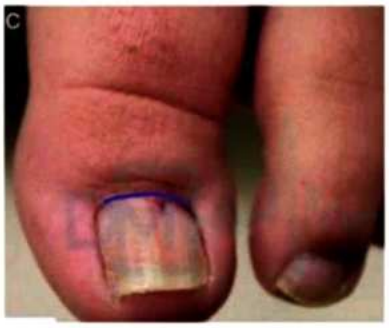
Tuberous Sclerosis

- Autosomal dominant.
- **Genetics:**
  - TSC1 - chr 9
  - TSC 2 - chr 16
- **Cutaneous manifestation:**

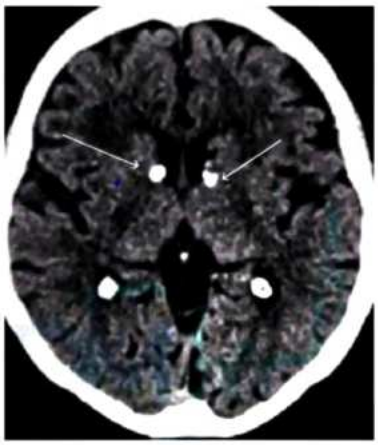


- In Butterfly distribution - acneiform lesions called adenoma sebaceum are present.
- Irregular appearance of skin is called with orange peel consistency shagreen patch.

- There is fleshy growth in nails called subungual fibroma or Koenen's tumor



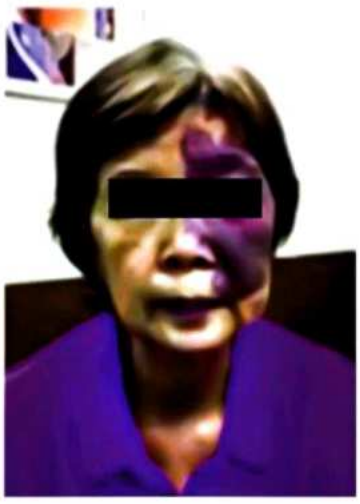
- Earliest cutaneous manifestations include - presence of ash leaf macules
  - Hypopigmented macules
  - On trunk of child
- There is family history of epilepsy present in the patient.
- **Neurological manifestations in the patient include:**
  - <1 year - infantile spasm - vigabatrin
  - > 1 year - Focal seizure - carbamazepine
- Mental retardation develops
- **MRI**
  Periventricular lesions called Subependymal astrocytoma.



- A lesion in the Kidney called angiomyolipoma (blood vessels + muscle + fat) may also be seen which can cause Bleeding.→ WUNDERLICH SYNDROME

Sturge Weber Syndrome

- It is a Neurocutaneous disorder where Port Wine stain is seen.
- There is a Cavernous angioma in brain on the same side as port wine stain on face.



- The Cutaneous manifestation is - Port Wine stain
- The Neurological manifestation is - cavernous angioma
- Features - **STURGE**
- **S**- Seizure - Recurrent episode of focal seizure
- **T**- Trigeminal nerve distribution - Port Wine stain on Trigeminal nerve distribution
- **U**- Unilateral weakness - cavernous angioma may press on corticospinal tract
- **R** - mental retardation
- **G** - glaucoma
- **E** - eye feature- buphthalmos
- CT HEAD - Visible calcification in brain can be seen and is called Tram Track Appearance.

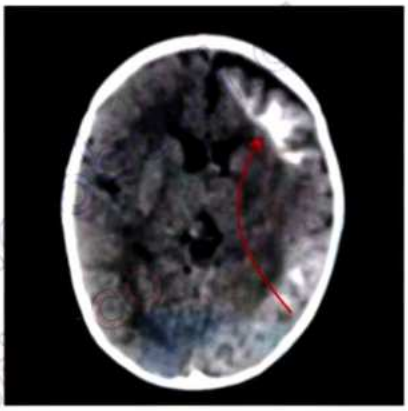


Table 19.1

Given situation	Rhythm	Frequency
Eyes closed and relaxed	Alpha	8-13 Hz
Awake, listening and alert eye opening +	Beta rhythm	13-30 Hz
When sleeping, drifting to sleep NREM stage 1	Theta rhythm	4-7 Hz amplitude is slightly increased
Deeper NREM NREM stage 2	Sleep spindles Mu waves	12 -14 Hz
NREM Stage 3 Deepest stage of sleep	Delta waves	0.5 - 4 Hz Max amplitude and slowest part of EEG
REM - Tone of muscle is least on EMG	Saw tooth pattern.	

Table 19.2

GTCS L2V	Focal seizure L2COP	Typical absence VLE	Atypical absence Atonic Myoclonic VLT
Lamotrigine	Levetiracetam	Valproate	Valproate
Valproate	Lamotrigine	Lamotrigine	Lamotrigine
Levetiracetam	Carbamazepine	Ethosuximide < 2 years (avoid valproate due to hepatotoxicity)	Topiramate
	Oxcarbazepine		
	Phenytoin		

Table 19.3

Selection of Antiepileptic drugs			
Generalized-onset Tonic-Clonic	Focal	Typical Absence	Atypical Absence Myoclonic Atonic
First-Line			
Lamotrigine Valproic acid	Lamotrigine Carbamazepine Oxcarbazepine Phenytoin Levetiracetam	Valproic acid Ethosuximide Lamotrigine	Valproic acid Lamotrigine Topiramate

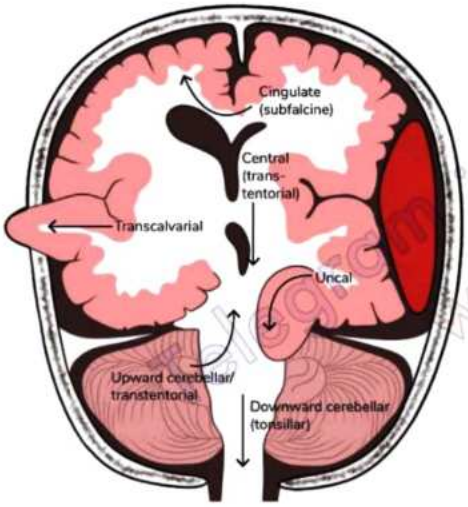
20 RAISED ICP AND BRAIN DEATH

Raised Intracranial Pressure

00:00:38

- **Normal pressure:** 10 to 20 mm Hg
- **Raised intracranial pressure:** Greater than 25 mmHg more than 5 minutes
- **Goals of treatment** keep ICP below 20 mm Hg and CPP > 60 mm Hg
- **Cerebral perfusion pressure** = Mean arterial pressure - Intracranial pressure
- CPP = 95 mm - 20 mm = 75 mmHg
- Range of CPP is 60 to 80 mmHg
- **Brain infarction:** Less than 60 mmHg
- **Hemorrhage:** More than 80mmHg (Blood vessel may pop off)
- Hence, less than 60 and more than 80 are detrimental to the Brain

Brain Herniation



- **Most common herniation:** Transtentorial herniation >> Subfalcine herniation

Raised ICP

- Brain stem is crushed such that the vasomotor and respiratory center is compromised

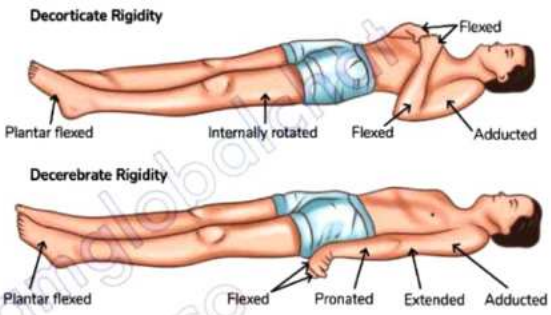
Management of Raised ICP

00:06:07

1. Osmotherapy for midline shift
   - Mannitol
   - 3% saline
   - Glycerol
   - Acetazolamide (used in N.P.H.)
   - Mannitol is not given in active CNS bleed. It is given to manage midline shift caused by mass effect of bleed.
2. Don't use hypotonic fluids 5% Dextrose in contraindicated
3. Head of the patient should be slightly elevated

- It improves the jugular venous outflow and improves brain perfusion.

Decorticate and Decerebrate Posturing



- Recommended Procedure: Ventriculostomy

4. Ventriculostomy

Refer Image 20.1

- Most effective method to lower Raised ICP done to reduce chances of develop posturing
- Choroid plexus is the site for the synthesis of CSF
- It is produced 20 ml per hour
- Reabsorption of CSF: 20 ml per hour
- As the rate of production and reabsorption is equal
- Hence the pressure is constant
- If there is any imbalance, either production is more or reabsorption is slow
- **Subarachnoid hemorrhage:** Causes the obstructive hydrocephalus (Ventricle flow obstruction)
- It leads to the raised ICP because it obstruct the flow of CSF
- Hence the pressure will be increased
- In tuberculous meningitis, pus blocks the outflow of the CSF again leading to communicating Hydrocephalus.

5. Management of Cerebral Edema

- Vasogenic cerebral oedema DOC is steroids
- **Cerebral edema:** It is of two types
  - Vasogenic cerebral edema: eg NCC and H.A.C.E
  - Cytotoxic cerebral edema: eg Stroke and Head injury

- Glucocorticoids are not recommended for cytotoxic cerebral edema

Cytotoxic cerebral edema

- It is commonly seen in the
  - Stroke
  - Head injury
- Treatment include osmotherapy
- Neuroimaging shows loss of gray matter and white matter differentiation

6. Sedation and Neuromuscular paralysis

- Coma patients are prone to the risk of aspiration and hence securing airway is important. To keep ETT in place and ventilate patient sedation and N_M paralysis is required.
- Anaerobic pneumonia can develop because the organisms in the oral cavity is anaerobic
- **Sedation drugs**
  - Midazolam
  - Propofol
  - Morphine
- **Drugs for neuromuscular paralysis**
  - Pancuronium
  - Vecuronium
  - Atracurium
  - Succinylcholine
- Patient is electively intubated
- After that patient is kept in the positive pressure ventilation and we deliberately increase the respiratory rate
- Because this will cause the carbon dioxide washout.
- Carbon dioxide washout will decrease the rate of CSF production and lower Raised ICP

7. Elective hyperventilation
   - It is effective method but has short limited effect

Important Information

- Ventriculostomy is more effective than compared to the elective hyperventilation
- Elective hyperventilation is effective but for short duration
- You can shuffle the procedures depending on their availability

8. Pressor Therapy

- Cerebral perfusion pressure = Mean arterial pressure - Intracranial pressure
- CPP = 95 mm hg - 20 mm hg = 75 mmHg
- If the ICP raises, CPP will be reduced
- To prevent this mean arterial pressure is increased
- It will *counterbalance* the increased intracranial pressure of the patient
- Dopamine is used in head injury
- It is used both in the cardiogenic and septic shock
- Standard vasopressors
  - Dopamine
  - Phenylepinephrine
  - Norepinephrine

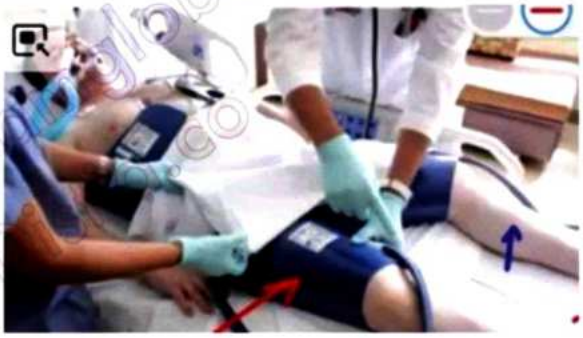
Tier II Therapy

9. **Pentobarbital coma**

Explanation

- Pentobarbital coma because barbiturates are cerebro protective and act by reducing the metabolism of the neurons

10. Therapeutic Hypothermia



Procedure

In this technique, temperature of the brain will be decreased to

33 degrees

↓

Then the energy requirements will be decreased such that longevity of the cell will increase

- Vascular access of an artery and special pads are used for cooling the blood
- Objective: Decrease the metabolism of the neurons
- This technique is also used in cardiac arrest (Targeted temperature management)

11. Decompressive Hemicraniectomy

Clinical Features 00:40:33

1. Frontal headache

- Pain sensitive structure in the brain is dura mater
- When the pressure in the brain is raised, the stretching of the dura mater will occur
- Duramater is innervated by the V cranial nerve

- This lead to the activation of nociceptors in the trigeminal nerve

2. Projectile vomiting

3. 6th nerve palsy

- False localizing sign
- Abducens nerve has the longest subarachnoid/subdural course
- When the pressure in the CSF increases then the pressure in the subarachnoid space will also be raised
- Hence the 6th nerve will get stretched
- This sign is known as the false localizing sign because problem is not in the nerve but due to stretching of nerve
- Clinical Manifestations: Diplopia laterally

Important Information

- **Longest subarachnoid course:** 6th cranial nerve
- **Longest intracranial course:** 4th cranial nerve
- **Overall longest nerve:** Vagus nerve
- **Longest intraosseous course:** 7th cranial nerve (Petrous part of the temporal bone)

4. Drowsiness/Altered Sensorium: Most reliable symptom of Raised ICP

- Very sleepy then goes into stupor further into the coma

Examination findings 00:43:52

1. Bradycardia
2. Elevated BP (Cushing reflex)
3. Cheyne stoke breathing also known as periodic breathing

Important Information

Cheyne stoke breathing is also seen in the

1. Congestive heart failure
2. Acute mountain sickness
3. Increased ICP

4. It can progress into Biot's breathing
   - It is also known as Irregularly Irregular breathing

Important Information

- Irregularly irregular pulse is seen in atrial fibrillation and multi focal atrial tachycardia

5. Hutchinson's Pupil

Refer Image 20.2

- Pupil become dilated at the side of bleeding or hemorrhage (ipsilateral mid dilated pupil)
- It reacts poorly to the light
- This pupil is of three varieties

Stages	Description
Initial stage I	• Irritation to the oculomotor nerve • Constriction of the pupil will occur • Pupil on the other side will become normal
Stage II	• Pupil will become dilated • Dilation is due to the paralysis of oculomotor nerve
Stage III	• Dilation of pupil on the both sides • No reaction to light

6. Brisk DTR

7. Sign: BCG
   - **B**abinski sign
   - **C**haddock sign
   - **G**ordon sign

   They indicate corticospinal injury

8. Fundus Examination: Papilloedema

Important Information

- Bradycardia, increased BP, and cheyne stoke breathing are together known as Cushing's triad
- Cushing's ulcer is not included in triad (Developed due to raised ICP)

Important points for Pupil Status

- Bilateral small pupils which is reactive to light: Metabolic encephalopathy
- Metabolic encephalopathy can occur due to
  - Ammonia intoxication of Fulminant hepatic failure (FHF)
  - Acute kidney injury causing uraemic encephalopathy
  - Carbon dioxide (CO_2) narcosis can be found in status asthmaticus and in impending respiratory failure

Pinpoint Pupils

- **Diagnosis:** Opioid poisoning and pontine hemorrhage

Features	Opioid Poisoning	Pontine Hemorrhage
Temperature	Decreased	Increased
Respiratory rate	Decreased (Less than 10)	Hyperventilation or normal
CT scan will evaluate the final results		

Cortical stroke	Patient will always look towards the site of the lesion
Brain stem stroke	Patient will always look opposite to the site of the lesion (Crossed Feature)
Ocular dipping	• Downward movement of the eye is slow (Both the eyes) • Upward movement of the eye is very fast • Seen in Diffuse Cortical anoxia
Ocular bobbing	• Downward movement of the eye is fast (Both the eyes) • Upward movement of the eye is very slow (Nystagmus) • Seen in Basilar artery stroke

Ipsilateral Pupil Image 00:58:20

- It is a Hutchinson Pupil
- It reacts poorly to the light
- It indicates that the 3rd cranial nerve is compromised (One side)
- **Trans calvarial Herniation:** Brain tissue is protruded out (Skull)
- **Subfalcine or Cingulate herniation:** One part of the brain is pushed below the other (Gyri and sulci)
- **Trans tentorial herniation:** Brain stem is comprised
- **Most common:** Trans tentorial herniation and Subfalcine herniation or midline shift

Important Information

- CT scan is the best method to diagnose the raised ICP

Brain Death 01:00:41

- Brain death means brain stem death (Vital centers of the brain was destroyed)
- Gross movements are absent but spinal reflexes are present
- DTR: Elicitable and twitching of the fingers or toes may be noticed in some cases

Features for confirming Brain death

1. Patient should have irreversible coma with GCS<8.
- Reversible coma causes:

Reversible Coma	Treatment
Diabetes ketoacidosis	Treated with insulin drip
Hyperosmolar coma	Treated with insulin drip
Uremic encephalopathy	Dialysis
Fulminant hepatic failure	• Liver dialysis (Ammonia intoxication) • Lactulose • Neomycin
Carbon dioxide narcosis	Ventilator
Drug overdoses (Opioid poisoning)	Naloxone
Endocrine cause (Myxedema coma)	Levothyroxine or levothyroxine

Tests to rule out reversible causes of coma

- Random blood sugar
- Kidney function tests
- Liver function tests
- ABG analysis
- Urine toxicology (Drug overdose)
- TSH T3 T4
- Serum electrolytes because hypernatremia or hyponatremia can be treated
  - **Hyponatremia <125:** Hypertonic saline
  - **Hypernatremia >160:** 5% dextrose
  - Hyponatremia and Hypernatremia patients can also go into coma secondary to seizures
- Testing and imaging should be done for diagnosing irreversible coma

2. **Imaging:** CT or MRI/MRA shows structural damage and no blood supply to brain stem.
3. Corneal reflexes, you can use wisp of cotton. Absent Bilaterally
4. **Gag reflex:** Posterior pharyngeal wall is checked with the wooden spatula. Absent gag
5. **Cough reflex:** Trachea suction is done. Absent cough reflex

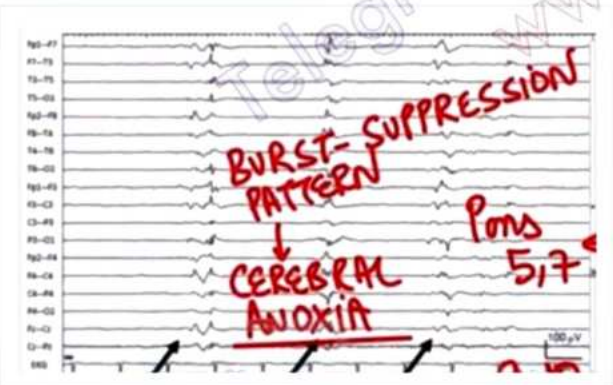
Reflexes	Diagnosis	Root values
Light reflex	Pupils will be fixed, no response to light	Midbrain (2, 3)
Corneal reflex	Absence of blinking bilaterally	Pons (5, 7)
Gag reflex	Absent	Medulla (9, 10)
Cough reflex	Absent	Medulla (9, 10)

6. **Caloric stimulation test:** Absent
- Irrigation of the ear canal with cold or warm water
- **Cold water:** Nystagmus to opposite side
- **Warm water:** Nystagmus to same side
- **Technical term:** Oculovestibular reflex

7. **Oculocephalic test:** Absent
- **Other Name:** Doll's eye reflex
- Eyes move independently to the head movement
- Cranial nerve 3, 6, 8 are interlinked with each other
- **Contraindication:** Cervical spine trauma

8. **Apnoea Test:** Negative
- Important test to demonstrate the brain death
- Preoxygenate the person (Two doctors will do independent examination)
- **100% oxygen:** 10 minutes
- **PO_2:** 200mmHg
- Disconnect from the ventilator and check for the spontaneous breathing
- You will find absence of the spontaneous breathing (Brain stem was completely damaged)
- Hence spontaneous drive of the pre botzinger complex in the medulla is damaged
- **PCO_2:** > 60 mmHg or raise of over 20 mmHg from the preexisting value
- It is done because carbon dioxide is the most potent stimulus for respiratory center

9 **EEG**



- Sensitivity of the electrodes is changed to 2 micro volts (Smaller discharges will look bigger)
- Flat isoelectric line is seen in brain death patients (Some bursts may also occur)
- Burst suppression pattern is seen in cerebral anoxia (Intermittent electrical discharges)

10. **MRA**
- No blood supply to anterior and posterior circulation

11. **Cerebral Scintigraphy**
- Reduced activity of the cortex and brainstem

Important Information
- Two doctors must certify the patient is brain death (Neurologists)
- They should certify with two different neurological examinations

Organ Transplantation
- A brain death person can save 8 lives

Organ transplantation	Causes
Heart	Cardiomyopathies
Lungs	Idiopathic pulmonary fibrosis, COPD, Cystic fibrosis
Liver	Hepatitis C induced cirrhosis of the
Kidney	Diabetic nephropathy
Pancreas	• Beta cells of the islets are taken from the donor and passed into the recipient through hepatic portal vein • It is done for type 1 diabetes mellitus • These cells will move to the liver and produce insulin
Small intestine	Crohn's disease
Heart and lung transplantation should be done within three hours	

- Organs are donated in the University of Wisconsin solution (Organs are perfused)

Image 20.1

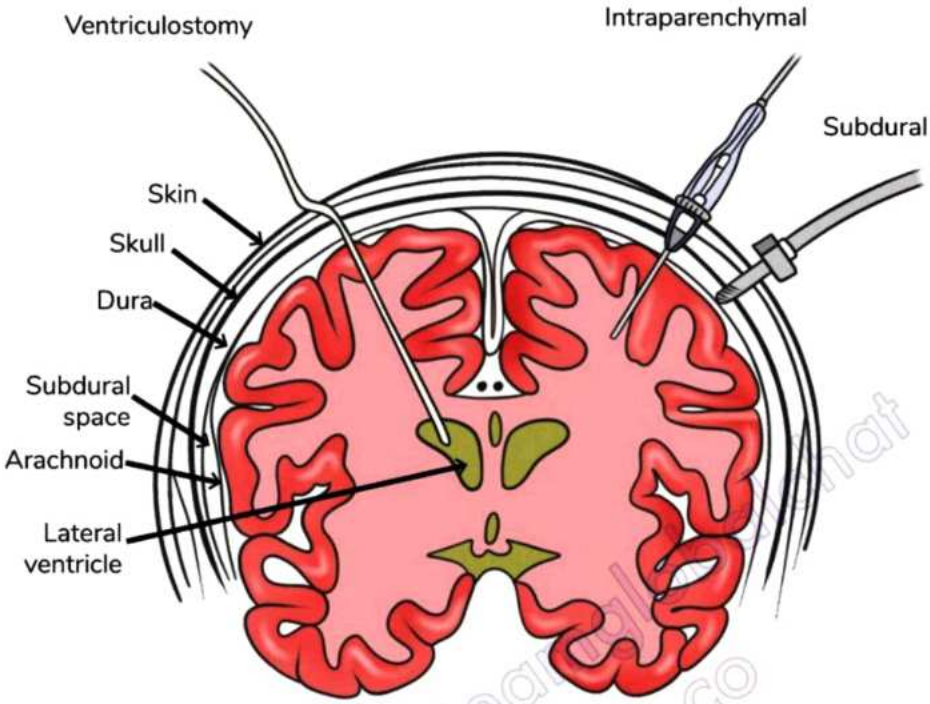
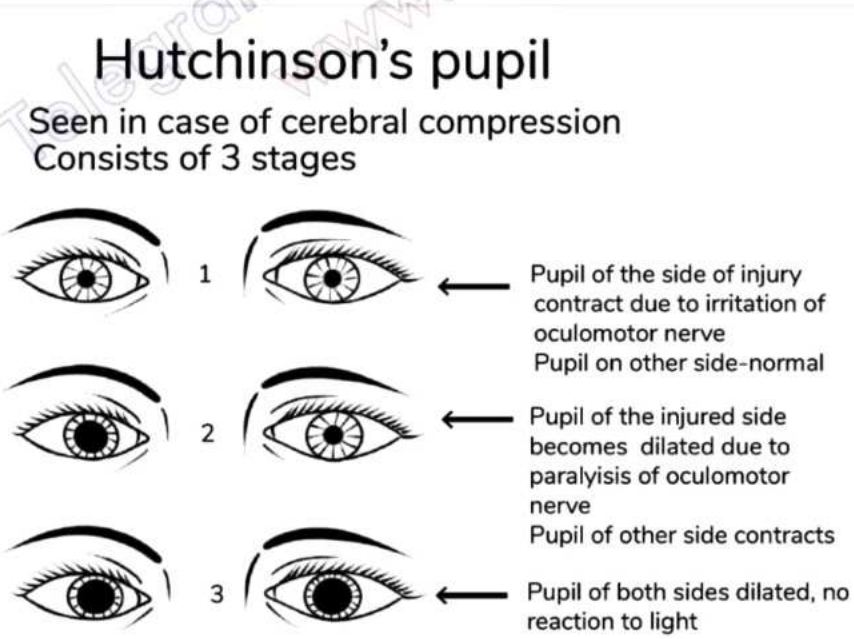


Image 20.2

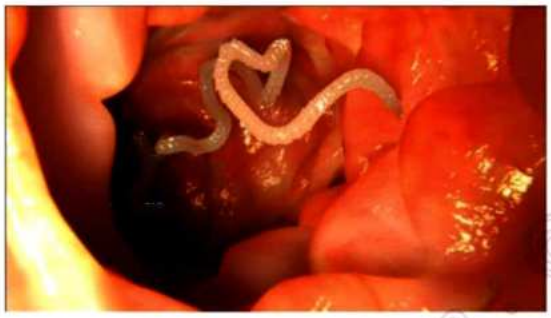


21 INTRACRANIAL SPACE OCCUPYING LESION

Neurocysticercosis

00:00:13

- Leading cause of intracranial calcification
- Larva growing in the brain is causing Vasogenic cerebral edema that can lead to seizures.
- Imaging modality of choice for Vasogenic cerebral edema: Gadolinium-enhanced MRI
  - Identify the scolex
  - Demonstrate the vasogenic cerebral edema
- Patients will have focal seizures
- Initially, no albendazole is given.
- Steroids are given initially - Dexamethasone to minimize the cerebral edema and reduce the frequency of seizures in the patients.



- Tapeworms developing in the gut of an individual.
- Found in both non- vegetarians and vegetarians.
- Length is 3 metres.
- Sticky segments are proglottids that attach to the person's perianal area after he defecates.
- If he doesn't wash his hands afterward, there is a high risk of ingesting these worms, resulting in the development of adult worms in his guts again.
- Where does this worm live?
  - It lives in the small intestine in the Upper Jejunum.
- **In vegetarians** → Cabbage/Lettuce in street food → If these leafy vegetables are grown in fecally contaminated soil → which means the person ingests the eggs
- **In non-veg eaters** → who eat semi-cooked pork, ingesting the larvae, they will form into adult tapeworms in the GI tract of the patient.
  - These larvae can migrate out → via the bloodstream → reach the muscle area
  - Person will develop lumps/bumps in muscles.
  - The larva cannot cross the blood-brain barrier hence there will be no neurocysticercosis.
  - A person who consumes the eggs of Tenia solium is the one whose brain will be infected
    - → The eggs are coming into the bloodstream
    - → Crossing the blood-brain barrier
    - → Hatch into the larva in Brain
    - → In later stages, when immunity will kill the worms – Intracranial calcifications can be seen.
- Cysticercosis cellulosae involves brain parenchyma and it contributes to cerebral edema, and cerebritis – seizures episode.
- Racemose Form: Parasitic Infiltration can obstruct CSF flow in the ventricular system hence raising the ICP and cause hydrocephalus in the patients.

Case Scenario

A 30 years old Rickshaw puller presents with multiple episodes of focal seizures. He went to a local doctor, but his medicines didn't bring any relief.

Physical examination:

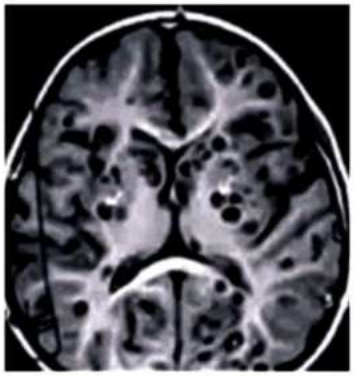
- GCS = 15/15
- Cranial Nerves examination was normal, DTR normal
- Fundus Examination: Papilledema ±
- Lumps and bumps all over body
- There is a possibility of Focal neurological deficit (weakness)

Admit and work up

Work Up

00:11:27

1. CSF Immunoblot for NCC antigen
2. Imaging = Gadolinium-enhanced MRI



- Starry sky appearance.
- There will be black spots: hypointense lesion with Scolex
- Perilesional cerebral edema is seen.

Stages of larva development in NCC

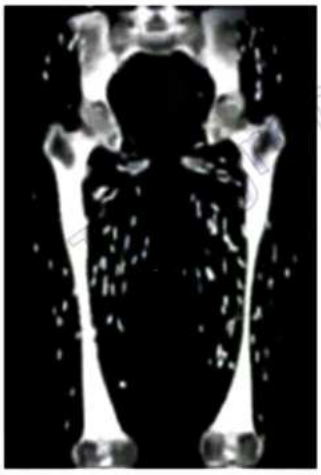
1. Vesicular
2. Colloidal vesicular: Cerebral edeme develops and cause symtoms
3. Granular Nodular
4. Nodular calcified

Absolute criteria for NCC

1. There should be a histopathological demonstration of the parasite: brain parenchyma or CSF.
2. Fundus examination: Subretinal cysticercosis
3. Neuroimaging: Preference is gadolinium-enhanced MRI
   - Will show Scolex/ evidence of vasogenic cerebral edema.

Starry sky appearance is seen in many other conditions
Lymph Node Biopsy: Burkitt Lymphoma
USG of Liver: Acute Viral hepatitis
Kidney Biopsy: P.S.G.N
MRI head: NCC

X-ray Bilateral Lower extremities



- "Rice Grain Calcification" due to dead larva in soft tissues and muscles of patients.

Differentiate from tuberculoma - Magnetic resonance spectroscopy (MRS)

- Tuberculoma is seen after giving ATT
- Tuberculoma causes Lipid leak - Choline to Creatine ratio spiked.
- NCC: Amino acids, Lactate, and Pyruvate.

Q: A 16-year-old girl presents with multiple episodes of focal seizures. MRI image is shown. MRS shows peak in lactate, amino acids, pyruvate and acetate levels. Diagnosis?

a. Tuberculoma
b. Neurocysticercosis
c. Toxoplasmosis
d. Cryptococcomas

The correct answer is (B)

Explanation:

Toxoplasmosis: Basal ganglia lesion, eccentric dot, CD_4 count < 100.

Cysticercosis	Tuberculoma
Round in shape	Irregular in shape
Cystic	Solid
20 mm or less with ring enhancement or visible scolex	Greater than 20 mm
Cerebral edema not enough to produce midline shift or focal neurological deficit	Associated with severe perifocal edema and focal neurological deficit

Target lesions:

Lesions with a central nidus of calcification or a dot enhancement

- If sensorium of suspected TBM patient on ATT is not improving, always rule out drug induced hepatic encephalopathy
- If it is ruled out, then consider tuberculoma.
- MRS is used to detect Chemical metabolism: Lipid peak is seen in tuberculoma.

Treatment

1. IV Dexamethasone
   a. To reduce incidence of Allergic reactions.
   b. To reduce Vasogenic cerebral edema.
   c. After 48 hours, when Cerebral edema subsides, start with albendazole.
   d. Steroids for a few days to 8 weeks.
2. Albendazole: not concurrently but sequentially
   a. Duration - 8 days
3. Focal seizures: Carbamazepine/ lamotrigine/ oxcarbazepine
   a. AED: asymptomatic for 2 years then gradual withdrawal
   b. Never stop antiepileptic drugs immediately
4. Raise ICP: Ventriculoperitoneal shunting
   a. Give Dexamethasone
   b. Suppress cerebral edema

Brain Tumor

00:31:40

- Most common brain tumour: Metastasis
  1. Small cell cancer of lung
  2. Breast cancer
  3. Malignant melanoma
- Most common primary malignant tumor Grade IV: Glioma
- Most common Primary Brain cancer:
  - Meningiomas - Intracranial calcification
- Incidence wise: METS > Meningioma > Glioma

Extra mile:

- Causes Intracranial calcification
  1. NCC- leading causes in India and globally
  2. TORCH
     → Toxoplasma: Location at basal ganglia, corticomedullary Junction
     → Cytomegalovirus: Periventricular location
  3. Craniopharyngioma
  4. Meningioma

- Meningioma
  - CT head - Dural tail sign
  - Brain tumor originating from dura can cause erosion of calvarium
  - Risk factors:
    1. CNS irradiation in childhood
    2. Neurofibromatosis - 2
  - If exposed to radiation in adult age group, commonest tumor seen is: Papillary carcinoma thyroid

Clinical Features of Brain Tumor

1. Impaired cognition
2. Early morning headache/ Holocephalic location
3. Migraine-like symptoms in old age
4. Personality change (anti-social behaviour)
5. Aphasia (dominant parietal lobe is involved)
6. Weakness- Monoplegia, Paraplegia and Quadriplegia (Cortico-spinal pathway is involved)

Q: Which brain tumor in an adult will have the worst prognosis?

- Grade 4 Glioma/Glioblastoma multiforme

7. Focal seizures related to brain tumor: Cerebral edema: the drug used is levetiracetam (antiepileptic that has minimal interaction with other drugs)

- To prevent interaction with drug
- Because brain tumor patient may already be undergoing chemotherapy and exposed to multiple drugs

Work up

- IOC Brain Tumor: Gadolinium-enhanced MRI

Necrosis vs Tumor progression

- Necrosis – metabolism will decrease
- Tumor progression - metabolism will increase
- Investigation of choice: MRS (magnetic resonance spectroscopy)
- How do you diagnose brain tumor? Gadolinium-enhanced MRI
- How do you differentiate between Brain tumour progression vs brain necrosis? - MRS

Syndromes

Refer Table 21.1

Paediatric Brain Tumor

Benign brain tumour

- Cerebellar astrocytoma / Pilocytic astrocytoma:

Malignant Brain Tumor

- Medulloblastoma
  - Bad prognosis
  - Cranio-spinal axial spread
- Supratentorial tumor - Craniopharyngioma - tumors visible in X-ray of the skull
- Worst prognosis - Brain Stem Glioma
  - Brain tumor is located near the respiratory centre, vasomotor centre
  - 6 months mortality rate is 100%

Craniopharyngioma

- Develops from Rathke pouch
- I/C calcification
- Precariously situated near optic chiasm
  - Visual deficit – Bitemporal hemianopia
- Short stature
- Central diabetes insipidus Polyuria and Polydipsia

Summary

- MC primary malignant brain tumor
  - For adults Grade 4 glioma
  - For paediatrics age group: Medulloblastoma
- Important cause of Leptomeningeal metastasis: Breast cancer
- Epidural tumour spinal cord compression: Breast cancer
- Brain tumor progression vs necrosis – MRS
- Brain abscess will be a hypointense lesion
  - DW MRI
  - Clinical history will be of pre-existing focus of Infection
  1. Infective endocarditis
  2. Bronchiectasis
- Perilesional edema will be present on MRI and is managed by Dexamethasone

Table 21.1

Syndrome	
COWDEN	Cerebellar Ganglioblastoma
VHL	Cerebellar hemangioblastoma Not originating from cells of cerebellum but from the blood vessels
TURCOT	Medulloblastoma - infratentorial tumors
GARDNER	Medulloblastoma + osteomas/ desmoid tumor
NF - 1	Optic glioma, Phacomatosis
NF - 2	Acoustic neuroma, meningioma is also seen after radiation exposure
TSC	Subependymal astrocytoma

22 MENINGITIS PART 1

Bacterial Meningitis

00:00:12

Neonatal Meningitis

- Globally, the organism responsible is Group B Streptococcus or Streptococcus agalactiae.
- In India, studies are done in limited hospitals only.
- Mostly found organisms in India are Klebsiella, Acinetobacter.
- Rarely, Listeria monocytogenes causes Meningitis in neonates.
- This does not exhibit sensitivity to 3rd generation cephalosporins and needs Ampicillin.

Children

- In children, Pneumococcus is the leading cause for Meningitis than Hemophilus influenzae.
- Incidence of Hemophilus influenzae has been decreased due to good coverage of Hib vaccines given by the government.
- Hemophilus influenzae causes sensorineural deafness.

Adults

- Pneumococcus is the leading cause of meningitis in adults
- Neisseria meningitidis causes epidemics of meningitis in winter in overcrowded population.
- Neisseria meningitidis, spreads through droplets, the doctor is vulnerable.
- The doctor who is infected, may also develop sepsis and DIC
- DIC contributes to adrenal gland bleeding, which leads to Addisonian crisis called Water House Freidschen syndrome
- The petechiae and purpura develop all over the body, especially on the lower extremities and patient goes into septic shock.
- Prophylaxis for meningococcel meningitis Chemoprophylaxis with Ceftriaxone in healthcare workers.
- Family contact can be prevented by using Ciprofloxacin.
- Pregnant women are given Ceftriaxone.
- Rifampicin has 70% efficacy, not recommended for healthcare workers.

Viral Meningitis

	Viral Meningitis	Viral Encephalitis
Organism	Enteroviruses	Global: HSV-1 encephalitis India: Japanese B encephalitis

HSV-1 Encephalitis

- Bloody CSF
  1. Traumatic Lumbar puncture
  2. Subarachnoid hemorrhage
  3. Viral encephalitis caused by HSV-1
- Three tube tests is done to differentiate Traumatic LP from SAH, serial contiguous samples are taken.
- If Subarachnoid hemorrhage, all the samples will uniformly have RBC.
- If Traumatic Lumbar puncture, RBC's in the 2nd or 3rd tube will gradually disappeared.
- Source of blood in Traumatic Lumbar puncture is epidural venous plexus.

- Empirical Acyclovir is started for viral encephalitis and reports of PCR are not required immediately.
- HSV-1 has Temporal lobe predilection that may cause memory loss.
- Periodic Lateralized epileptiform discharge is the EEG finding.
- Investigation of choice for encephalitis is PCR HSV-1, but do not wait for reports.

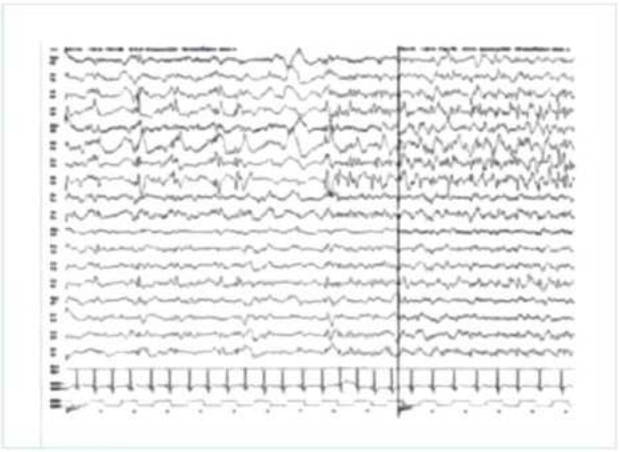
Recall: Periodic Sharp Wave complexes (PSWC) are seen in Variant Creutzfeldt-Jakob disease (VCJD)

Clinical Manifestations of HSV-1

- History of HSV is short duration
- Fever since 1 day
- Patients may have violent behavior (Psychotic behavior Scratching, Hitting his family members).
- Aphasia, Apraxia is seen due to cortical damage.
- Dysregulation of Hypothalamic Pituitary axis which causes:
  - Hyperthermia (107-108°F)
  - Diabetes insipidus/ Syndrome of inappropriate ADH secretion (SIADH)

Extra mile

- SIADH causes Euvolemic hyponatremia, which may lead to seizures
- Triad of meningitis includes Fever, Headache, and Nuchal rigidity.
- Fever for 1 with Altered sensorium is seen in cerebral malaria and viral encephalitis.
- HRP-2 Dipstick test, Peripheral smear test is available for quick malaria.
- Leading cause of SIADH, is CNS infections like Encephalitis or Brain abscess.
- PSWC in VCJD



- Burst suppression pattern is seen in anoxic cerebral injury
- PLED is seen in HSV-1 encephalitis.

Fungal Meningitis

- **Organism:** Cryptococcus neoformans or Cryptococcus gatti
- **Investigation of choice:** CSF ELISA for CrAg (Cryptococcal Antigen)
- **Treatment**
  - LAMB (Liposomal Amphotericin-B) and 5-Fluorocytosine for 2 weeks
  - Fluconazole is given subsequently for 6 weeks

PREVIOUS YEAR QUESTIONS

Q. A child has CSF Culture showing growth of Listeria monocytogenes. Which antibiotic should be given?
Ans: Ampicillin

Q. A child recovered from Meningitis, but is suffering from deafness. Organism Responsible?
Ans: Hemophilus influenzae causes gliosis of the 8th nerve and leads to deafness.

Q. Leading organism responsible for Meningitis in children is?
Ans: Pneumococcus

Q. Community-acquired Pneumonia in children and Meningitis is caused by?
Ans: Pneumococcus

Q. Group vesicles on the glans penis of a patient or on the vulva of a sex worker is a feature of?
Ans: HSV-2

Q. Grouped vesicles on dermatomal distribution is a feature of?
Ans: HZV (Herpes Zoster virus), Chickenpox

Q. 18 year boy, works in the city and went to his village on weekend. After swimming in stagnant water, he developed high grade fever, frontal headache with forceful projectile vomiting, nuchal rigidity. Lumbar puncture was done after giving mannitol. CSF shows presence of trophozoites. Diagnosis is?
Ans: Naegleria fowleri

23 MENINGITIS PART 2

Work Up

00:00:15

1. Blood Culture
2. NCCT Head/Fundus examination
3. Giving Empirical Antibiotics
4. First, give mannitol to lower the intra-cranial pressure and then do guarded Lumbar puncture

Lumbar Puncture Needle

- Comparing the two needles:
  1. Quincke - Traumatic lumbar puncture needle due to pointed edge and sharp bevel
  2. Sprotte is an atraumatic lumbar puncture needle with blunt edge.
- Site of doing lumbar puncture is L3 & L4
- Prefered Position: Lateral decubitus with knees up to the chest.
- Needle is introduced bevel up, while piercing the skin
- Progression: Cephalad (aim for the umbilicus).

Sequence in which Layers that are pierced from outwards to inside:

1. Skin
2. Subcutaneous Tissue
3. Supraspinous ligament
4. Interspinous ligament
5. Ligamentum flavum
6. Duramater and subarachnoid space is reached.

LP Contraindications

1. Raised ICP
2. Bleeding diathesis
3. Local site infection (poor patients sweaty or sticky)
4 Kyphoscoliosis
5. Polio (any invasive procedure is not done in this case)

Advice to the patients to minimize post L.P. Headache

1. Bed rest for 8-12 hours
2. Painkillers

After all of this, the headache still persists.

3. Next course of action is - intravenous caffeine (preferred drugs) - tea and coffee
4. Codeine: But can lead to constipation - more strain more will be the leakage
5. Opioids can be given
6. Low Volume Blood patch, where patient's blood is injected via LP needle to seal the tear in dura matter.

How much CSF can be removed?

- For diagnostic purpose - 20 ml
- For therapeutic purposes - 30 ml
- Therapeutic relief in Normal pressure hydrocephalus
  - Triad of Ataxia, inconti and dementia
  - Fisher Test is removal of CSF that causes improvement in gait of patient, with NPH

Rate of CSF production/ absorption	20 ml/hour
Total amount of CSF	150 ml
Attach Manometer	To check opening pressure

Queckenstedt Manoeuvre - lumbar puncture

- Bilateral pressure on internal jugular veins.
- Appreciable rise of CSF column.
- Failure to rise of CSF column can be due to lumbar canal stenosis.

Refer Table 23.1

Tuberculous Meningitis

00:28:00

- Rich focus
- History child-Long standing illness for weeks
  - Irritable child
  - Head banging
  - Drowsy
  - Episodes of Focal seizures
  - Altered sensorium
  - Monoplegia or paraplegia due to Endarteritis
  - Nuchal rigidity
  - Crackpot sign, Macewan sign
  - Sutural diastasis
  - Sun setting sign
  - Non obstructive/Communicating hydrocephalus
  - NCCT Head shows: Basal Exudates

- IOC: PCR CSF for MTB
- Treatment:
  1. ATT for 6 months
  2. Steroids to reduce Cerebral Edema and enhance the penetration of anti-tuberculous drugs into the meningeal space.

Acute Bacterial Meningitis 00:33:47

Child < 3 months of age -listeria monocytogenes: the antibiotics given Ampicillin + cefotaxime

Child > 3 months and adult up to 55 years of age: Ceftriaxone/cefixime and Vancomycin

Patients > 55 years old patient is given: Ampicillin + Cefixime + Vancomycin

Pseudomonas
- Hospital based infection: Ampicillin + Ceftazidime + Meropenem

Chronic Meningitis 00:36:12

- Manifestation may develop after a couple of weeks.
- Etiology
  1. Infection- TBM
  2. Malignant - Carcinoma breast
  3. Autoimmune - Behcet
  4. Drugs like ibuprofen contribute to nuchal rigidity - contribute to chronic meningitis

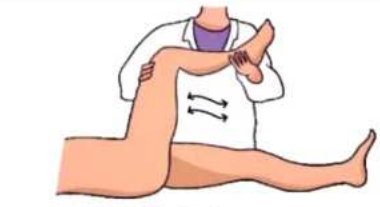
CSF eosinophilia

1. Fungal infection - Coccoides immitis
2. Rat lungworm
3. Hantavirus

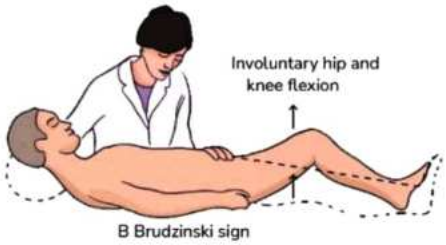
- CSF chloride values are decreased in Bacterial meningitis.

Clinical Features: Acute Bacterial Meningitis 00:41:18

- Two classic signs are:



A Kernig sign



B Brudzinski sign

- Kernig Sign:
  → Extension of the leg of the patient.
  → Position of leg - one hand is below the ankle and one is above the knee
  → When it is elevated - extreme amount of pain due to stretching in the hamstrings
- Brudzinski Sign:
  → Flex the neck
  → Involuntary flexion in the knee and hip joint

- Fever
- Headache
- Nuchal rigidity

} Triad of ABM (present in only 40% of cases)

- Raised ICP - projectile vomiting
- Pupils: bilaterally uniformaly dilated
- Sluggish/poor reaction to light
- Stupor/photophobia
- Pressure on cranial nerve - sixth nerve palsy also called False Localising Sign
- First: Draw blood sample culture then give empirical antibiotics

Question: Antibiotics should be given in the suspected case of ABM within how much time?

Answer: Within 60 minutes of admission

- Antibiotics given early will reduce the mortality substantially
- Does not cause significant Changes in the CSF Biochemistry

If a person has Headache, Fever and ± Nuchal rigidity.

- If it's a child, he may involuntarily stiffen his neck.
- There is no nuchal rigidity if a person comes relatively early.
- But if a person has altered sensorium, the differentials to be considered are:
  1. Acute disseminated encephalomyelitis (post vaccine)
  2. Meningoencephalitis
  3. Metabolic encephalopathy
  4. Intracranial space occupying lesion
  - Early part of illness may show :
    → Papilledema on fundus examination
    → Focal Neurological deficit
    → Sinusitis and history of antibiotics
    → Head trauma

Investigation of ABM 00:48:55

1 Step: Obtain blood culture
2 Step: Administer empirical antibiotic within 60 min of arrival to hospital
3 Step: NCCT head to rule out raised Intracranial pressure
4 Step: Perform lumbar puncture

CSF findings of ABM:

- > 1000 PMN/cumm and turbid CSF: Bacterial meningitis
- CSF lymphocytosis and sugar is relatively low and long history: Consinder Tubercular aetiology
- CSF lymphocytosis and history is of one day, Sugar is normal: Consinder Viral aetiology
- Hypoglycorrhachia - Low CSF sugar
- CSF glucose/serum glucose value
  - If < 0.4, then it is Bacterial Meningitis
- Protein value will spike
- CSF 20-30 mL can be removed safely
- Normal pressure hydrocephalus - gait abnormality, we can remove 30 ml to improve the gait (Called Fisher Test)
- Antibiotics used for 3 months - 55 years of age: Ceftriaxone and vancomycin

Table 23.1

	Pressure	Cells	Sugar	Protein	Gross physical appearance of CSF
Normal	50-180 mm H_2O	0-4 lymphocytes	2/3rd of blood sugar in acute bacterial meningitis Hypoglycorrhachia can have zero sugar	15-45 mg%	Clear
Acute bacterial meningitis	↑	> 1000 PMN	↓	↑ Spiked protein level	Turbid Sample for gram staining and CSF
Tuberculous meningitis • Malnourished child with PEM- grade 4 • BCG scar is absent • Contact with Koch's	↑	> 100-1000 lymphocytes per cubic mm	↓	↑↑ Clot like a basketball net– cobweb coagulum Bacteria is trapped inside cobweb	Straw coloured
Subarachnoid haemorrhage	↑	RBC - predominantly	N / ↑	N / ↑	Bloody in the initial phase after 48 hours. Xanthochromic CSF
Viral meningitis	↑	50-500 lymphocytes	N	↑	Normal or Turbid
GBS (Albumin cytological dissociation)	Normal	Normal	Normal	↑	Normal

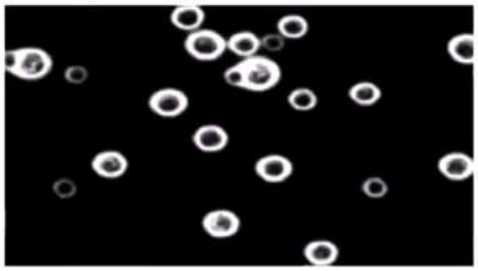
CNS leukaemia: Sugar is low

The findings of fungal and viral meningitis will be almost same.
Cryptococcal meningitis: Sugar is low

24 CNS INFECTIONS IN AIDS POSITIVE PATIENTS

Introduction

00:00:12



- India Ink, stain showing capsulated organisms responsible for causing Fungal meningitis
- The organisms incriminated:
  1. Cryptococcus Neoformans
  2. Cryptococcus gatti
- CD_4< 100 / in AIDS-positive patients
- Nowadays, because of the advent of the Antiretroviral therapy - the opportunistic infections found in AIDS-positive patients are dramatically low.
- Microbiology details related to Cryptococcus Neoformans:
  - Entry Via the lungs.
  - Organisms Excreted in pigeon droppings.
  - From lungs infection reaches the blood stream and then crosses blood brain barrier.

Case discussion

00:02:28

- 30 year old truck driver who is AIDS positive has not been feeling well and has a headache. He didn't go to the doctor but rather went to a chemist suffering from fever and took PCM. His headache worsened and he developed severe photophobia.

On physical examination -

- Nuchal rigidity/ Brudzinki sign and Kerning sign are present
- DTR reflexes are brisk

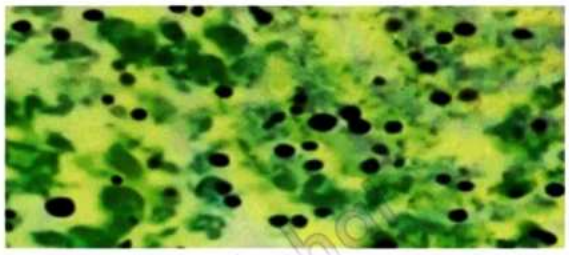
Work Up

00:04:24

1. LP: Total cells are increased, mainly lymphocytes
- CSF sugar is relatively low
- Protein - will be increased
- 1,3 β glucan test is done to pick systemic fungal infection - CAP - Candida/Aspergillus/Pneumocystis Jiroveci
- Organism not going to be identified by the 1,3 β Glucan test – Mucormycosis - Rhino cerebral mucormycosis

2. Send a CSF sample for India ink stain - negative stain, does not stain the organism but will highlight the capsule

- Other stains used to highlight the capsule:
  1. Mucicarmine
  2. Gomori methenamine



3. CSF ElisA for Cryptococcal antigen
4. Lateral flow Cryptococcal antigen detection test
   - Sandwich immunochromatographic Assay
5. CT Scan / MRI Head: Soap Bubble Appearance

MRI Head

Treatment

00:12:33

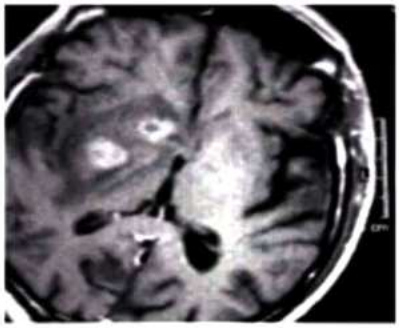
1. Liposomal amphotericin B + 5 fluorocytosine for 2 weeks.
2. Fluconazole is used once the patient is over the acute phase for 8 weeks.

Case Scensrio:

- There is a 30 years old truck driver who is AIDS positive. He has raised ICP, fever, headache, photophobia, nuchal rigidity. He was admitted. Lumbar puncture was done and obtained CSF. India ink stain: CSF sample is shown below

- Capsulated diplococci are seen. Contrast this with previous case scenario where cryptococcus was seen.
- Doc for Pneumococcal Meningitis - Ceftriaxone

Cerebral Toxoplasmosis 00:15:46



- AIDS ⊕ patient presented with seizures.
- MRI Head: Lesions can be seen in the area of the Basal Ganglia.
- CSF IgM/IgG class of antibody for toxoplasma
- Cryptococcomas: skin (umbilicated papules that look like Molluscum contagiosum), brain (cranial palsy)

Treatment

- Sulfadiazine + Pyrimethamine

Progressive Multifocal Leukoencephalopathy 00:19:20

- Multiple sclerosis, Natalizumab (monoclonal antibody) is given but the side effect is the deterioration of the patient.
- Side effects are reactivation with the JC virus (John Cunningham virus) Also known as polyomavirus
- Lower immunity due to AIDS or Natalizumab, leads the virus to cross the blood-brain barrier and contribute to demyelination and damage to white matter brain.
- Clinical features are Seizures, Ataxia, Visual defects, Hemiparesis.
- CSF-PCR: JC virus DNA positive
- IOC-MRI head: Subcortical demyelination

Treatment

- No Treatment available

Extra Mile:

- TB + AIDS – CART, but to prevent IRIS:
  - ATT to the patient decreases the bacterial load
  - After 2 weeks, start CART.

CNS Lesions in AIDS Positive 00:24:44

HIV-associated dementia: subcortical dementia
Cortical dementia is seen with Alzheimer's and Pick's disease with frontotemporal dementia

Seizures: HIV-associated encephalopathy

Intracranial Space Occupying Lesion in a AIDS positive patient which is contributing to seizures: Cerebral Toxoplasmosis

Intracranial Space Occupying Lesion which turned out to be brain tumor: Primary CNS Lymphoma

- Diagnosis: Guided biopsy

Meningitis in AIDS positive = Cryptococcus neoformans, Cryptococcus gatti with respect to HIV positive patient

Coccoides Immitis – Fungal meningitis and CSF eosinophilia

Reversible Dementia

- Hypothyroidism
- Vitamin B12 deficiency
- Normal Pressure Hydrocephalus
- Dementia /ataxia/incontinence

25 PARKINSONISM AND PARKINSON'S DISEASE

Comparison with Alzheimer's Disease

Parkinson's Disease

- Dopamine levels are low.
- Substantia nigra is damaged.
- Lewy bodies are seen
- Composed of alpha synuclein.
- Activity of Thalamus decreases.
- Activity of globus pallidus interna increases.

Alzheimer's Disease

- Less Acetylcholine.
- Nucleus of meynert basalis damaged.
- Hirona bodies are seen.
- Composed of Tau protein.

Causes of Parkinsonism 00:05:46

1. **Parkinson's Disease:** Age related neurodegenerative disorder.
   - Can be genetic or sporadic.
   - **Genes involved**
     → PARK SCN4A gene - Autosomal dominant.
     → PARKIN - present on chromosome 6.
   - Leads to 1° parkinsonism / typical parkinsonism.
     → Has good response to levodopa.

2. **Secondary Parkinsonism**

A. **Drugs:** MC Cause for Secondary parkinsonism.
   - Haloperidol, Chlorpromazine and Metoclopramide.
   - These drugs reduce Dopamine and Increase Ach.
   - Benzhexol is DOC for drug induced Parkinsonism. Another drug used Trihexyphenidyl.

B. Hypoparathyroidism- Elevated phosphate casues basal ganglia calcification.

C. **Toxins:** CO, CS2, MPTP

D. Manganese

E. Trauma / Vascular damage / Tumor

Atypical Parkinsonism 00:16:01

A. Multiple System Atrophy/Shy drager syndrome.

Case: A 60-year-old patient presents with bradykinesia, rigidity, autonomic insufficiency + Intentional Tremors with gait ataxia.

- This can be a case of:
  - **MSAc** - Having Cerebellar manifestations (intentional tremors with gait ataxia) + Basal ganglia features.
  - **MSAp** - Only Basal ganglia features expect tremors.

Autonomic Insufficiency Features:

1. Orthostatic hypotension - BP of a patient is measured in supine position and after 3 minutes BP is measured in erect position.
   - If Systolic BP falls > 20 mmHg
   - If Diastolic BP falls > 10 mmHg
   - Indicates presence of orthostatic hypotension.

2. Constipation and diarrhea

- **MRI Head in MSA-** shows Hot Cross BUN sign.
- Poor response to levodopa.

B. Progressive Supranuclear Gaze Palsy

- Patients have tendency of falling backwards.
- Superior colliculus is involved along with basal ganglia.
- Since vertical gaze is impaired the chances of falling increases.
- Mostly downward gaze is affected.
- Tau protein is involved.

Case: A 65 year male patient presents with Rigidity, Bradykinesia, recurrent falls, eyelid apraxia, slow saccades, hyperextension of the neck.

- MRI Head shows - Hummingbird appearance EOG - square wave jerks
- Poor response to levodopa.

Diagnosis: Progressive Supranuclear gaze palsy.

C. Alien Hand Syndrome / Corticobasal degeneration

- Let's understand with an example:
  - A person kept a cigarette between lips and lit it with right hand.
  - Suddenly his left hand takes out the cigarette and throws it away. Patient says I feel as if left hand does not belong to me.
- Area involved is corpus callosum.
- Tau protein is involved.
- Other clinical features resembles of Parkinsonism like rigidity, bradykinesia etc.

Extra Mile:

Tauopathy

1. Alzheimer's Disease
2. Corticobasal degeneration syndrome
3. Progressive Supranuclear Gaze Palsy.

D. Pick's Disease

- Also called Frontotemporal Dementia.
- Affected parts are frontal and temporal regions leading to changes in personality, language disturbances and memory deterioation.

Wilson's Disease

- Has parkinsonism like symptoms but at 10-20 years of age.
- Copper deposition occurs in the Lenticular nucleus.
- MRI finding - Giant face of panda appearance.
- Compare with Neurodegeneration in brain with Iron accumulation:
  - Iron accumulation occurs in globus pallidus
  - Previously called Halloverden Spatz disease
  - MRI finding - Eye of a tiger appearance.
- Both are pediatric onset neurodegenerative disorders.

Huntington Chorea 00:35:02

- Autosomal dominant, Trinucleotide Repeat disorder
- Affected Age - 40 to 50 years.
- Gene involved - Huntington gene present on chromosome number 4.
- Protein involved - Huntington protein.
- The Huntington protein affects Ubiquitin proteasome system that prevents misfolded protiens.

Neurotransmittors involved:

- GABA decreases, Dopamine is excess.
- Levodopa is contraindicated.

Extra Mile:

- **Other Trinucleotide repeat disordes:** Myotonic dystrophy and Fragile X syndrome
- **Hexanucleotide repeat disordes**: Motor neuron disease / Amyotrophic Lateral Sclerosis

Clinical Features of HD

1. Anticipation - Severity of disease increases with successive generations.
2. Chorea - Fast involuntary movement in hands causing difficulty in eating, typing on keyboard.
3. Dementia - Subcortical dementia.
4. Behavioral changes
5. Rigidity
6. Bradykinesia - slowness in preforming Tasks.

MRI Head - shows Boxcar ventricles due to caudate atrophy

Treatment: Tetrabenzine is DOC for HD

Refer Table 25.1

Typical Parkinsonism 00:45:27

Clinical Features

- **Non motor symptoms**
  - Anosmia
  - Constipation
  - Mood and sleep disorders
- **Motor symptoms develop in late Sixties**
  1. **Resting tremors** - 4 to 6 Hz (Low frequency).
     → Asymmetric
     → Pill rolling tremors
     → Most common and earliest motor manifestation

Extra Mile:

High frequency tremors[≥ 8 Hz]

1. Anxiety neurosis
2. Graves disease or thyrotoxicosis

Low frequency tremors[< 8 Hz]

1. Intentional tremors of cerebellar damage~ 5Hz
2. Resting tremors of PD~4– 6Hz

2. **Bradykinesia** - slow movement.
   → May progress to akinetic mutism.
3. **Rigidity**
   → Cogwheel/Lead pipe rigidity
4. **Postural instability**
   → Short shuffling steps
   → Stooped posture is seen
   → Minimal automatic arm swing.
   → Festinating gait.

- From the first 3 motor symptoms atleast if 2 are present consider diagnosis as Parkinson's Disease.
- All the 4 motor symptoms are called - Cardinal symptoms.

5. On and off phenomena as effect of medication wears off
6. Hesitancy / Freezing / Postural Instability
7. Mask like facies
8. **Depression**
9. Bradyphrenia (Slowness in thought and spontaneous speech)
10. Myerson sign is present: Unable to resist blinking when tapped repetitively on glabella.

Treatment 00:31:17

- Gold standard for treatment of PD: Levodopa.
- Rasagaline exhibits neuroprotective effect not documented in all clinical studies
- **Preferred drug in younger patients** - Pramipexole or Ropinirole.
  - Stimulates D2 receptors.
  - Has less side effects.
  - Rotigotine - has longer action.
  - Transdermal patches are easy to use and make patient take better care of himself as disability is reduced.

- **Preferred drug in older patients** - Levodopa + Carbidopa.
  - Levodopa is converted to Dopamine in the body.
  - When levels reach more than normal in blood - causes Levodopa induced dyskinesia.
  - Also causes - nausea, vomiting and orthostatic hypotension.
- Carbidopa reduces the side effects of levodopa.
  - It is a peripheral decarboxylase inhibitor.
  - Inhibits the formation of Dopamine in blood.

- **COMT (Catechol o Methyltransferase) Inhibitors** - Entacapone, tolcapone.
  - Tolcapone has hepatotoxic potential
  - On time increased.
  - Off time decreased. Ensure patient can perform activity of daily living.
- **MAO-B (Monoamine oxidase) inhibitors** - Selegiline, Rasagiline, Safinamide [reduces levodopa induced dyskinesia].
- **Other drugs:**
  - **Amantadine** - Anti flu drug, used in influenza A (H3N1).
  - **Bromocriptine** - Side effect Raynaud's phenomenon.
  - **Cabergoline** - Side effect Cardiac valvular defects

Case: 90 years old Patient with Parkinson disease is having intolerable side effects on maximum dosages of antiparkisonism medication.
In this case deep brain stimulation can be done in which an electrode will be displayed in Basal ganglia.
This name is a misnomer as it causes inhibition but not stimulation. the electrode is displayed in Subthalamic nucleus, globus pallidus interna

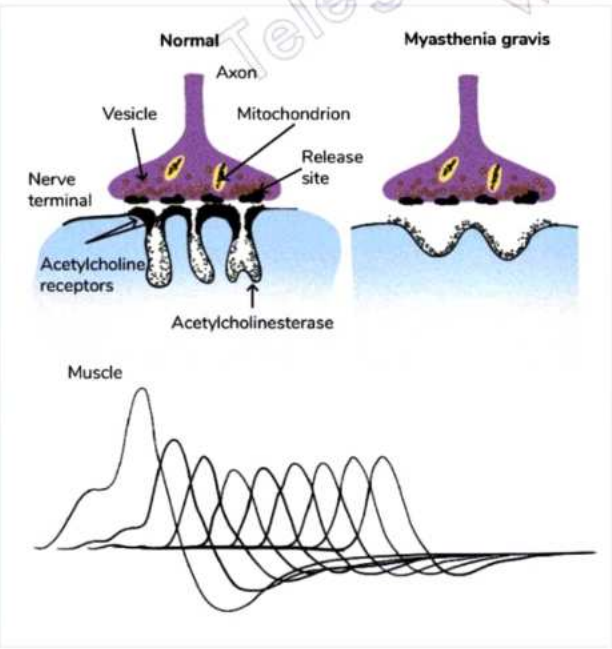
Table 25.1

Important Findings			
Disease	**Area Involved**	**MRI finding**	**Clinical Feature**
Progressive supranuclear gaze palsy	Superior colliculus	Hummingbird appearance.	Impaired downward gaze
Multisystem atrophyc	Brain stem/ Pontocerbellar Tracts	Hot Cross Bun sign	Autonomic insufficiency
Huntington chorea	Caudate nucleus	Boxcar ventricle	Chorea and dementia

26 MYASTHENIA GRAVIS

Introduction 00:00:15

- Type II Hypersensitivity Reaction. [latest:Type 5]
- Autoimmune disorder with waxing and waning course.
- It can have exacerbations especially in pregnancy and infection leading Myasthenic crisis that may require ventilatory support.
- Post-junctional defect.
- Acetylcholine receptor has a total of five subunits:
  - Alpha
  - Beta
  - Gamma
  - Delta
  - Epsilon
- When Alpha subunit is activated, Sodium influx would be occurring subsequently causing a depolarization at neuromuscular endplate, which allows the muscles to contract.
- The Anti AchR antibody affects N_M Transmission by
  1. Blockade of alpha subunit of receptors.
     → leading to weak contraction of muscles called myasthenic fatigue.
  2. There would be an increase in the turnover of the receptors as well thus time for the acetylcholine to activate the receptor is reduced.
  3. Physical damage to the postsynaptic muscle membrane.
  4. Presynaptic rundown.



Repetitive Nerve Stimulation test.

- Stimulate a nerve at a lower frequency then at a high frequency.
- Stimulated muscles keep on performing & their performance reduces
- Usually the performance reduction is less than 10%.
- A substantial reduction in the performance of the muscle is as nerve is continuously stimulated.
- The reason for this is that the acetylcholine is not being able to activate its receptors properly.
- The technical term is Decremental Response.

Causes 00:05:32

1. Thymic hyperplasia (65%)
2. Thymoma (10%)
   - Thymoma is a benign tumour, it can spread locally, it can press on the recurrent laryngeal nerve.
   - The thymus is having the cells that are called myoid cells as antigens.
   - On the surface of these myoid cells, there is an alloantigen.
   - This is the antigen against which antibodies are formed and, the chemical structure of this antigen resembles the acetyl choline receptor.

- Antibodies present are T cell dependent and IgG class and they can cross the placenta.
- If a mother has autoimmune disease, she can transfer this antibody to her baby, and neonatal Myasthenia Gravis will be a presentation in this case.

Antibodies seen in M.Gravis:

1. **Anti acetylcholine receptor antibody (Seen in 85% patients)**
- This will block the alpha subunit of Ach receptors.
2. **Anti M.U.S.K antibody (Seen in about 10% patients)**
- The full form is muscle specific kinase antibodies.
- Mostly it is found in those patients who are AchR negative.
3. **Anti LRP4 antibody-**
- The full form here is Low density lipoproteins related protein 4 antibody.
4. **Anti Netrin-1 receptor antibody**
5. **Anti Caspr-2**
6. **Anti striated muscle antibody**

Prevalence 00:10:20

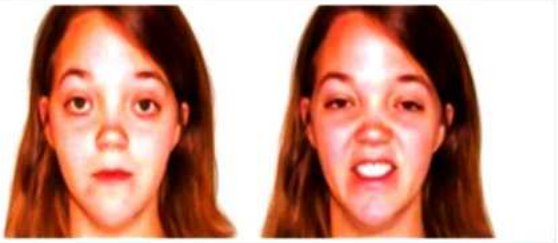
- 200:100,000 in Western populations.
- It is common in young women or in men after 50 to 60 years of age.

- The exacerbations can be triggered by infection or by pregnancy M.crisis can lead to diaphragmatic paralysis.

Clinical Features: 00:11:13

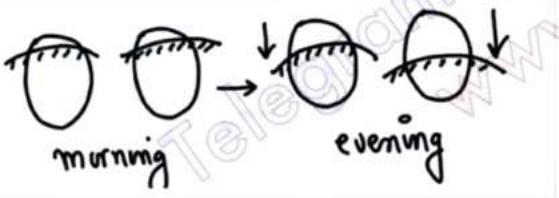
1. Ptosis-

- It is the earliest manifestation present.

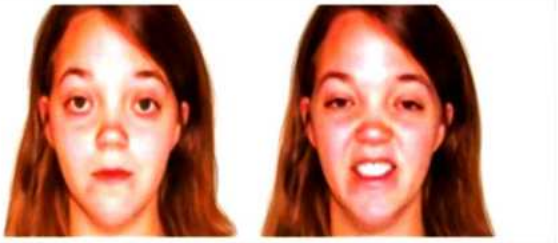


  - Notice the elevated eyelids to keep her eyes open when she was asked for medical photography.
  - Initially, most patients having Myasthenia Gravis don't realise that they're having ptosis.
  - Persons having ptosis use the forehead muscles to elevate the upper eyelids.
  - Myasthenic weakness is more in the evening hours as compared to morning hours.
  - There is a diurnal variation of Symptom description and easy Fatiguability

2. Diplopia-



- Upper 2mm of cornea is covered by upper eyelid
- On examination: Asymmetrical ptosis is seen.
- Because of asymmetrical ptosis, double vision develops.
- Sustained Upward gaze for 30 seconds triggers development sustained of ptosis in the patient.
- Ocular myasthenia gravis: If the extraocular muscle weakness persists for atleast 3 years.
- In this case, we should do a CT or an MRI to rule out any CNS cause that can also contribute to ptosis.



- Patient is asked to smile, giving a snarling facies appearance.

3. Chewing Muscle Weakness-

4. Nasal twang of voice-

- Because of the weakness of the soft palate, there can be development of nasal twang.

5. Nasal Regurgitation of fluids

6. Aspiration Risk

7. Oropharyngeal dysphagia

8. Dysarthria/ Unclear speech

9. DTR Preserved

10. Proximal Muscle Weakness-

- There is arm and leg weakness in Myasthenia Gravis. If we ask this patient to spread out arms and keep arms abducted up, then we will notice shoulder muscle fatigue will start developing and there will be drooping of the arms of the patient.
- Muscles of hip joint & shoulder joint involve as late manifestation.
- In Contrast in Lambert Eaton syndrome, the primary complaint will be proximal muscle weakness.
- A female with long hair feels the comb is heavy while combing, this is because of deltoid muscle weakness.

Work up 00:21:31

1. Anti AchR Antibody-

- It is a screening test positive in 85% cases

2. Anti M.U.S.K antibody-

- This is known as a muscle specific kinase antibody.

3. Anti LRP4

4. S.F.EMG - Single fibre electromyography.

- The findings in this case would be referred to as a jitter and blocking which means that the amplitude of contraction will be lesser as compared to normal muscles performance.
- It is a confirmatory test.
- Electro diagnostic tests are always to be given preference over anti cholinesterase test or Tensilon test.

5. RNS- Repetitive nerve stimulation test: Decremental response

6. Anticholinesterase Test / Tensilon Test-

- Asked patient to do sustained Upward gaze for >30 seconds that will trigger Ptosis in the patient; meanwhile secure IV line
- Edrophonium is injected.
  - It is a short acting drug Onset of action: after 30 seconds Peak effect at: 5 minutes.
  - Do not push 10 milligrams right away because it can trigger a cholinergic crisis.
  - First give two milligrams which will inhibit the degradation of acetylcholine.
  - As we are inhibiting the degradation of acetylcholine, so it will be able to act on the receptor for longer duration.

- Most of the time on giving two milligram of edrophonium, there will be a marked improvement in the patient.
- If there is no improvement, then give the remaining eight milligram of edrophonium to the patient and wait for a clinical response.
- Look at the ptosis or See how long is the patient able to hold arms in abducted position. Ptosis will disappear on injection edrophonium.

- Cholinergic crisis can be identified when the patient will develop SLUDGE symptoms
- During the performance of this test, if the patient is having cholinergic crisis, Atropine has to be given to the patient.

7. Ice Pack Test-

(Ice Pack test- alternative of Tensilon Test)

- Acetylcholinesterase enzyme is sensitive to temperature. If we decrease the temperature, then the activity of acetylcholinesterase enzymes tends to reduce. This will reduce degradation of Acetylcholine. More Ach at neuromuscular junction will improve symptoms.
- The test of the ice pack has a sensitivity equal to that of the tensilon test.

8. CT/ MRI Head-

- To rule out causes like arteriovenous malformation or any space occupying lesion contributing to third nerve Palsy or ptosis occurring in a patient.
- This is a baseline test that is mandatory in all cases of ocular myasthenia gravis.

9. CT Chest-

- It is done in the patient to pick up Mass Effects of thymoma.
- Thymectomy is done in all cases because even if it is a patient who will require steroids, the dosage of steroids is reduced. Lesser requirements of steroids, then the side effects of steroid toxicity are substantially reduced.

10. Antibody testing for Hashimoto / Grave / SLE / RA

- These patients can have co existent autoimmune diseases

11. PFT-

- Done in all patients, to plan thymectomy.
- Look at the lung reserve of the patient.
- If he's an obese person because possibly the person who has Myasthenia Gravis might have been on steroids for a long duration. So the obesity component might have developed in a patient.
- Check this before we plan a surgery for a patient.
- Steroids will worsen tuberculosis or diabetes mellitus by increasing the blood sugar values.

12. HbA1C, TST-

- The glycosylated haemoglobin values and a baseline test for TB like tuberculin skin test will be done.
- So diabetes mellitus and tuberculosis should be ruled out by the investigation part before initiation of immunosuppressive therapy is done for these patients.

Treatment 00:41:00

1. Pyridostigmine: DOC for symptom relief in Generalised M.gravis
- Patients who are having Anti MUSK antibodies may not show a good response to this drug.
- In generalized Myasthenia Gravis the response is going to be much much better.

2. Thymectomy-
- Thymectomy is the treatment of choice for generalized Myasthenia Gravis.
- There are two aspects why thymectomy is used:
  - Resection of thymoma because it can expand locally.
  - Decrease in the requirement of immunosuppression drugs. Long term intake of steroids can cause cushing syndrome, visual defects, cataract, myopathy in patients.
- Before doing a thymectomy a pulmonary function testing must be done thoroughly.
- Anaesthesiologist should be ready as surgery can trigger myasthenic crisis.
- So the anaesthesiologist has to be good at ventilation both intra and postoperatively for these patients, it might take a while for these patients to come out of anaesthesia also.
- Interaoperative & postoperative complications are more as compared to diaphragmatic involvement.

3. In ocular myasthenia gravis, we first give Pyridostigmine and if it's a poor response, then straight away go for immunosuppression.
- Do not recommend thymectomy in ocular myasthenia gravis.
- Myasthenia gravis, the first line drug is pyridostigmine for symptomatic relief.
- Though if a person is anti muscle specific antibody positive there might even be worsening, so a watch out for the same.
- If a person is having a poor response to its administration then start these patients on immunosuppressive molecules like steroids and azathioprine.

4. In generalised Thymectomy -first give pyridostigmine and you will get a substantially good response in the patient.
- Now educate the patient regarding the benefits of thymectomy.
- If the FVC of the patient is good, and the consent of the patient is there, then a thymectomy can be performed in the patient.
- Post thymectomy, in these patients, we will still be giving steroids but the dosage of steroids that would be required in this particular case will be minimal.
- The requirement of immunosuppressive therapy after thymectomy is substantially reduced.

5. In Myasthenic crisis patients, we will use plasmapheresis for these patients to get rid of the dangerous antibodies.
- Triggers: Infection & pregnancy.
- If facilities for plasmapheresis are not available. It is intravenous immunoglobulin.
- The first to be done in the Myasthenia crisis is elective intubation and ventilation of the patient.
- Put the patient on assisted controlled mechanical ventilation because the PCO2 to the patient is beginning to rise in co2 in the patient is significantly low. .

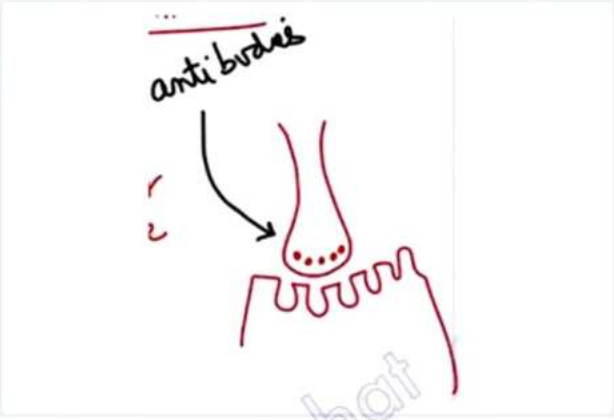
Treatment for Neonatal Transient Myasthenia Gravis 00:47:47

Mother of this child was having Myasthenia Gravis and at the time of delivery and before delivery, she has transferred the antibodies to a child.

- The antibodies that are found in this condition are immunoglobulin G class which can very easily cross the placenta.
- Because of the transplacental spread of this antibody, the neonate will also suffer from a possible difficulty in establishing respiration.
  - Breastfeeding will still be a challenge because every time she will breastfeed this baby, there might be regurgitation of milk, there might be choking episodes
  - Neostigmine drops 4 hrly.
  - Antibody has not been produced by the immune system of the baby the antibody has been produced or has been transmitted from body of the mother to the baby
  - Every antibody is a half life IgG usually gets destroyed in next 3-4 weeks.
- Drug of choice for neonatal Transient Myasthenia Gravis is neostigmine.

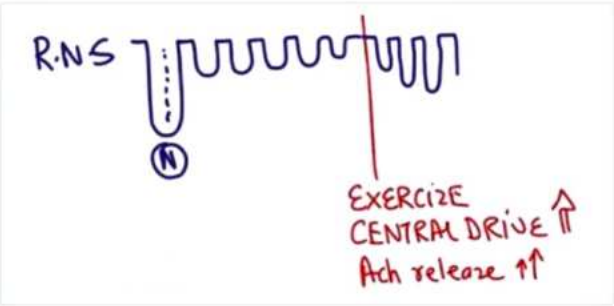
Lambert Eaton Syndrome 00:50:59

- Paraneoplastic manifestation related to Oat cell lung cancer.
- In this, the problem is that the production of acetylcholine is lesser.
- This is a pre Junctional disease whereas Myasthenia Gravis is a, post junctional disease where the receptors of acetylcholine are defective.



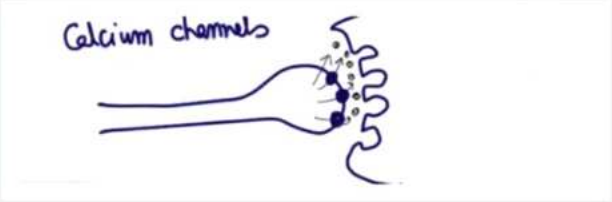
- **Clinical Features-**

1. Proximal Muscle Weakness
2. Subsequently the feature will be ptosis, diplopia, Chewing muscle weakness might be there.
3. DTR- are reduced
   - Deep tendon reflexes are preserved in patients with myasthenia gravis, but here the deep tendon reflexes in these patients will be substantially reduced. So, reflexes can be one point of differentiation.
4. Autonomic Features-
   - It can include dry mouth, or male patients having erectile dysfunction.
5. RNS- Repetitive nerve stimulation response shows incremental response
   - It is the main differential point in MCQ from M.Gravis



   - Patients of Myasthenia Gravis, when they wake up in the morning they are fine but by evening the performance goes down. In Lambert Eaton syndrome it is opposite. When they wake up in the morning they are weak and when they start doing activity the performance starts increasing.
   - So a decremental response for Myasthenia Gravis and incremental response is seen after making the person do some light exercise in Lambert Eaton syndrome.

- The name of the antibodies involved here is antibody P/Q antibody and this is acting voltage sensitive calcium channels which help in release of acetylcholine at the neuromuscular junction.



- **Treatment-**

The drug of choice be 3,4 diaminopyridine.

  - This will increase the amount of acetylcholine at the neuromuscular junction.
  - This drug basically acts on potassium channels.
  - Along with this we can add pyridostigmine.
  - The advantage of Pyridostigmine treatment will be that it will inhibit the degradation of the release acetylcholine.

Neurasthenia 01:00:00

- The symptoms that are described by a neurasthenia patient might be the same as that of myasthenia gravis.
- So, it will be easy fatigability tiredness occurring in a patient. But there is no organic cause in this case. Electrodiagnostic testing in patient is normal.
- And the history of this patient will keep on changing like sometimes a patient will say he is weak in the morning or afternoon or evening.

Botulism 01:00:51

- Case scenario will be of home delivery and the grandmother had given honey to the baby.
- This would be a disaster because if the quality of the honey is bad, honey was given and the spores of botulinum toxin will germinate in the GI tract and will produce the toxin.
- Therefore, the patient will develop paralysis that will be a descending paralysis.
- Most patients of Botulism would be newborn babies who would be having bulbar palsy.
- The bulbar Palsy would explain the aspiration of milk, inability to feed or nasal regurgitation of fields in this child and they can also be diaphragmatic paralysis which can be life threatening.
- The main treatment for botulism would be to give antitoxin for this patient.
- This is also a pre junctional defect or a pre synaptic defect, so the amount of acetylcholine the toxin acts on the neuromuscular junction, and it reduces the amount of acetylcholine release at the neuromuscular junction.

MG vs LEMS 01:02:31

Refer Table 26.1

- Anti acetylcholine receptor blocking antibody if it is negative, does not rule out the possibility that disease or disease could still be present in a patient
- It is single fibre electromyography which is the confirmatory test for diagnosis of this patient.

Table 26.1

Myasthenia Gravis	Lambert Eaton Myasthenic Syndrome
Mainly Associated with Thymus Abnormalities	Associated with small cell lung cancer, especially with male patients
Acetylcholine release is completely normal. Problem is with the receptor known as Post Junctional Defect.	Acetylcholine release is less. Receptors are however normal.
Multiple antibodies but main are: AchR antibody Anti Musk Anti LRP4	Antibody: Anti P /Q voltage gated calcium channel
Might be having Ptosis, extra ocular Muscle weakness, Diplopia, Chewing muscle weakness	Might be having Ptosis, extra ocular Muscle weakness, Diplopia, Chewing muscle weakness
Ptosis & diplopia are main complaints	Shoulder Girdle weakness, Proximal Muscle weakness are main complaints
Reflexes are Normal or preserved. Decremental response on repetitive nerve stimulation Drug of choice should be Pyridostigmine Surgical Treatment should be Thymectomy. Steroids used in Ocular M.Gravis	Reflexes are reduced impotence, dry mouth, orthostatic hypotension. Incremental response on repetitive nerve stimulation Steroids are not used, rather 3,4 diaminopyridine. Pyridostigmine can also be used because all pyridostigmine does is inhibit the enzyme responsible for breakdown of acetylcholine so the muscles get stimulated for longer duration. Chemotherapy is used for small cell cancer as it can metastasize very fast. Drugs include: cisplatin & irinotecan

27 GUILLAIN BARRE SYNDROME

- It is a progressive neurological disease of fast onset.
- There is demyelination which involves the spinal cord and the peripheral nerves. So, there will be manifestations of Lower motor neuron lesion.
- It can result in the development of flaccid paraplegia/ quadriplegia, and even a diaphragmatic paralysis in a person, which could necessitate an elective intubation and then a requirement of a positive pressure ventilation.
- Etiological agents responsible for GBS
  1. COVID-19
  2. Zika: Neurological manifestations
     → If a pregnant lady gets infected with Zika virus, then a baby can be born with microcephaly.
     → Patients suffering from Zika virus infection can subsequently develop Guillain Barre Syndrome.
- GBS is an example of Type IV hypersensitivity reactions.
- It can have both a humoral immunity component as well as a cellular immunity component.
  3. Epstein Barr Virus
  4. Hepatitis E virus
  5. SLE
  6. Neural derived Rabies vaccine
  7. Campylobacter Jejuni
  - Initially there will be clinical recovery but two to four weeks later, the patient starts to develop neurological complications.
  - This gastroenteritis like dysentery episode triggers and results in antibodies development which with Type IV hypersensitivity results in Demyelination.

Clinical Presentation 00:05:15

1. **Flaccid Paraplegia:** Weakness in both legs
   - E.g., A 25-30 year old person wakes up in morning with no power in legs and by evening patient might not be able to sit in chair
2. **Truncal Paralysis:** Truncal muscles also have flaccid paralysis leading to inability to sit up in bed
3. **Arm Paralysis**
   - If biceps is paralyzed then one of the root values of biceps i.e., C5, C6 is involved
- If C5 is involved, then demyelination occurs at the cervical part of the spinal cord and C5 shares a common root with a phrenic nerve.
  - Once there is arm weakness, there is fast onset quadriplegia in 24 hours and the patient will end up with diaphragmatic paralysis.

4. **Diaphragmatic Paralysis**
   Segmental demyelination: There will be patchy involvement of spinal cord and nerve roots.
   - The patient will be electively intubated and put on positive pressure ventilation.
   - If recovery is delayed then tracheostomy can be done.
   - If the patient is not intubated on time the carbon dioxide values in the body will continue to rise which will contribute to the development of respiratory acidosis.
   - Acidosis can damage the blood brain barrier causing brain swelling and encephalopathy.
   - It can damage the heart contributing to Arrhythmias.
   - If the patient is not given ventilatory support than these patients can expire due to type 2 respiratory failure secondary to the diaphragmatic paralysis.
5. **Neck Floppiness**
6. Bilateral 7th nerve Palsy/**Facial Diplegia/**
   - Bell's Palsy is a unilateral 7th Nerve Palsy
   - Medical disorders causing Facial Diplegia -
     1. Sarcoidosis: Non-caseating granulomas involving 7th nerve bilaterall
     2. Melkersson-Rosenthal syndrome
     3. Guillain Barre Syndrome.
     4. Lyme disease

- The most common cranial nerve involved in sarcoidosis and GBS is the 7th nerve.

7. **Bulbar Palsy**
   - There will be feeding problems, patient will not be able to sip tea or coffee.
   - Manifestations of bulbar palsy are seen due to 9th, 10th or 12 cranial nerves involvement.
   - Hence this patient will be at the risk of developing an aspiration pneumonia, especially on feeding.
8. **Autonomic Insufficiency**
   → Fibers from T1 to T4 are called cardiac accelerator fibers.
   → The Sympathomimetic drive coming from T1 to T4 via cardio accelerated fibers can increase the heart rate.
   → But in this case as these fibers are demyelinated, the patients can develop bradycardia which can further cause low BP i.e., Neurogenic shock.
   → As BP is falling, there can be a reflex vasoconstriction which in same patient results in spike of blood pressure.

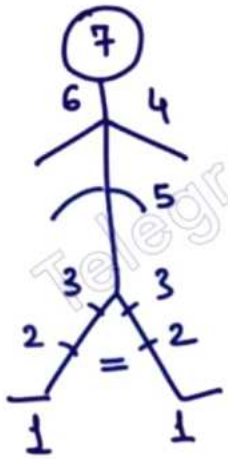
→ Hence, Wide fluctuations of BP can be seen in patients of GBS.

9. **Sensory Implications**
   - If patient presents late, then there will be no the sensory complaint as pateint cannot talk.
   - But if patients presents early and can talk, then there will be sensory complaints like pain in muscles.
   - Pain experienced by patient will be similar to the pain after prolonged exercise or exercise done after a long duration.
   - There can be some tingling sensation in the extremities.
   - As peripheral nerve is involved, there can be paresthesia.
10. **Bladder & Bowel**
    - Bladder and bowel is usually spared in this condition as there is a segmental demyelination.

- In Contrast Transverse myelitis, bladder and bowel involvement is seen in the majority of cases.

Summary of clinical evolution of GBS

- Earliest manifestation seen in Distal areflexia
- Initially ankle jerk is lost and then it involves the knee jerk, paralysis goes from bottom upwards.



- Initially, paralysis will occur in the muscles supplying the ankle joint then there will be paralyzes related to muscles of the knee joint then the hip joint muscles.
- Hence the patient won't be able to stand.
- Even arms can be involved.
- Ascending Symmetrical Flaccid Paralysis: Left leg paralysis = Right leg Paralysis.
- Power in left leg muscle will be equal to power in right leg muscles.
- In Poliomyelitis: There is descending paralysis of asymmetric nature.
- Descending paralysis is also seen with Botulism, Diphtheria.

Subtypes of GBS 00:19:37

- Motor, sensory, autonomic manifestations are not seen in all the cases of GBS.

1. AMAN (Acute Motor Axonal Neuropathy)
2. AMSAN (Acute motor sensory axonal neuropathy).
3. AIDP (Acute Inflammatory Demyelinating Polyneuropathy) – commonest presentation of GBS
   - All motor, sensory, autonomous manifestation are seen.
4. MFS (Miller Fisher syndrome): Rare.

Important Information

- Axonal damage is seen in AMAN and AMSAN
- Demyelinating polyneuropathy: Damage is seen in axons and Schwann cells

Miller Fisher Syndrome 00:22:18

- It is a triad of
  - **O** - Ophthalmoplegia - 3rd nerve Palsy causing ptosis.
    → AIDP: Main presentation is facial diplegia and there is 7th nerve involvement.
  - **A** - Areflexia
  - **A** - Ataxia (sensory ataxia).
- Triad of GOA is seen with Wernicke's encephalopathy.
- In OAA along with areflexia, muscle weakness or limb weakness is usually not seen.
- The antibodies involved in this condition are responsible for this.
  - Anti GQ1 antibody- Damage gangliosides present in the nerve lining.
  - Nerves supplying the arms have less concentration of GQ1, so, the antibodies cause less damage, but the nerves supplying the muscles of the eyeball have a higher concentration of GQ1 so antibodies will cause more damage.
  - As a result, eye muscles are involved but the arm muscle is usually spared in this condition.

Extra Mile:

Wernicke's Encephalopathy 00:25:45

- **G:** Global confusion
  - E.g., If the individual did not get access to alcohol for the previous 48 to 72 hours.
- **O:** Ophthalmoplegia -6th nerve involved.
- **A:** Ataxia
  - It is a combination of sensory, cerebellar, vestibular. All these circuits play an important role in maintaining balance and alcohol can contribute to damage to all these circuits.
- **Treatment**
  - IV thiamine
  - IV sugar (infusion)

- If sugar is given first, it will cause worsening of neurological features because when sugar is metabolized, thiamine will be consumed even more, resulting in development of less availability of thiamine.
- RBC Transketolase levels
- The first manifestation to respond is Ophthalmoplegia (not ataxia).

Work Up 00:28:49

1. **Lumbar Puncture**
   - CSF: Albumino cytological dissociation will be seen
   - The standard findings are
     → The opening pressure was found to be normal.
     → The cells that were found on microbiological examination were normal.
       - Normally zero to four cells are found in the CSF, that is lymphocytes primarily
     → Sugar: Normal
     → Colour: Normal
     → Protein is increased.
   - Traditionally in CSF, when cells will increase that is when proteins will increase, but in this condition cells are normal, but still the proteins are elevated.
   - So, Albumino Cytological dissociation is an important features of Guillain Barre syndrome.
   - Albuminous cytological dissociation can also be seen in FROIN syndrome.
     → Froin syndrome: It is a condition of the spinal block which occurs because of a tumor or maybe tuberculosis.
2. **Electro-diagnostic test /NCV** (Nerve conduction velocity)- Increased Latency Period of the F reflex. It means that the time taken for the current to go into the spinal cord and coming out of the spinal cord is increased.
   - In this case because there's a Demyelination the speed will be less.
3. **MRI Spine**
   - MRI spine is not necessary for diagnosis of this condition.
   - But because there are so many other conditions where Demyelination can occur including vitamin B_{12} deficiency, it is recommended.
   - Then along with Serum Vitamin B_{12} deficiency you can definitely make a diagnosis of the combined Demyelination
   - But one of the clinical pointers which is against diagnosis of Subacute Combined Demyelination for this condition is corticospinal pathways involvement, this causes Brisk DTR and Babinski sign whereas in GBS, there is no upper motor neuron manifestations.
   - Corticospinal pathway wherever it is damaged, whether in the brain or in the spinal cord, the manifestations will still be Babinski sign/ Extensor plantars.
4. **ANTI GM1 Ab-** There are 3 main antibodies
   - Anti GM1 antibody: Causes motor, sensory, autonomic manifestations (AIDP).
   - Anti GQ1 antibody: Miller Fisher syndrome where there was a triad of OAA minus the arm weakness.
   - Anti GD_1 antibody is the one responsible for acute motor axonal neuropathy.

Brighton Criteria for GBS 00:34:51

1. **Bilateral Flaccid Paralysis Limbs**
2. **Areflexia**: Distal areflexia
3. **Monophasic Illness**

- There would be a deterioration of the patient over a span of hours to weeks, but not years. The weakness in the legs developing over years is seen in Amyotrophic Lateral Sclerosis or Motor Neuron Disease.
  - In GBS Monophasic illness spans over 12 hours - 28 days.

4. **Electrodiagnostic Testing**
   - Nerve conduction velocity, and increased F-reflex latency in the reports.
5. **Lumbar Puncture:** It shows Albumino cytological dissociation.

- **Treatment**
  - Steroids are not useful in this case.

1. Intravenous immunoglobulins
   - Chances of recovery: 85% recovery.
2. Plasmapheresis

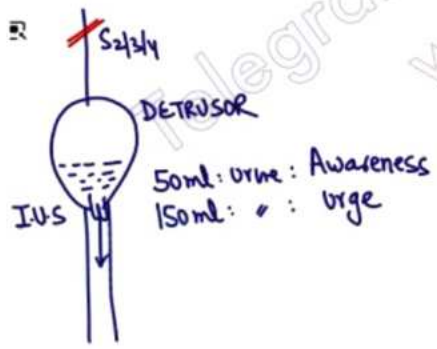
- Efficacy of IVIG and Plasmapheresis are equal.
- IVIG is relatively more practical

3. Ventilator support is given.
4. Tracheostomy may be required.
5. Speech rehabilitation is also required.

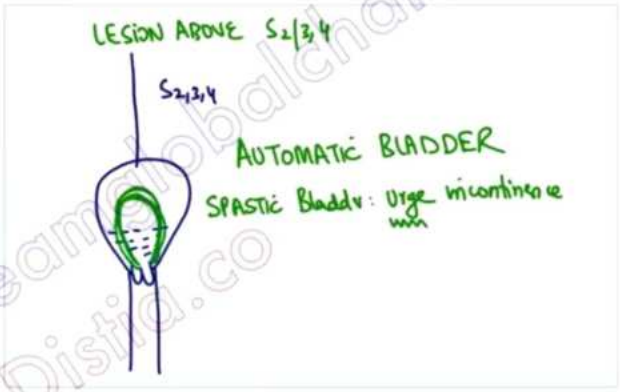
Transverse Myelitis 00:41:02

- It is an inflammatory disorder of spinal cord
- Occurs after URTI / AGE
  - E.g., A person having an upper respiratory tract infection or gastroenteritis went to the physician who prescribed him zinc supplementation and the person has recovered.
  - After two to four weeks, the antibodies which are produced in this condition will contribute to development of inflammation of the spinal cord which means steroids will be useful in this condition.
- **Clinical Presentation**
  1. **Flaccid Paraplegia**
     → Patient wakes up in the morning with inability to move his legs or get out of the bed.

2. **Truncal Paralysis:** Initially, he could at least sit in the chair, but now truncal paralysis has also occurred.
3. **Quadriplegia**
4. **Diaphragmatic paralysis**
5. **Sensory Complaints:** This is a characteristic feature of T.myelitis
   → Patient feels as if somebody has poured acid over his legs or somebody's taken a blade or a piece of glass and is making cuts over his legs or somebody is pouring boiling water over his legs.
   → Radicular pain or root pains
   → Lancinating pain, burning pain.
   → There will be a sensory level that will be documented in this case, unlike in GBS where there was just vague musculoskeletal pain.
   → Patient feels as if somebody is tying a military grade barbed wire around his legs and is trying to cut them.
6. **Autonomic Dysfunction**
   → Autonomic insufficiency is seen both in GBS as well as in transverse myelitis.
   → There will be fluctuating blood pressure, labile blood pressure of the patient
   → Heart rate and the BP can be on the lower side.
7. **Bladder / Bowel involvement:**
   → The bladder and bowel involvement is usually seen in Transverse myelitis whereas it is not usually seen in patients with Guillain Barre syndrome.



- Detrusor muscle contracts on stimulation and the urine will be ejected into the urethra.
- When approximately 50ml of urine is collected in the bladder of a normal person, then there is an awareness.
- If the amount starts exceeding 150ml of urine, then in a normal human being there will be an urge.
- During urination, detrusor will contract, internal urinary sphincter will relax and urine will pass out in urethra
- Because of damage to S2, S3, S4, there will be no awareness and there will be no urge.
- The bladder could be totally filled with urine, the maximum capacity of the bladder is 500 ml but the patient will not make an attempt to even pass the urine.
- When the bladder is full to the maximum capacity, the bladder can contract on its own, and the person will pass urine in his clothes that is called overflow incontinence.
- In this overflow incontinence, not all 500 ML will pass out, maybe only 300 ML or 400 ml urine might pass out while 100 ML might still be left behind.
- So therefore, there will be post void residual urine.
- Post voidal residual urine is also seen in Benign Prostatic Hyperplasia where there is Obstructive Uropathy.
- But this particular patient have autonomous bladder i.e., the bladder is contracting on its own without a nerve supply as the muscle also has the ability to contract.



- E.g., If the damage is above the level of S2, S3, S4 i.e., upper motor neuron lesion.
- The control of the bladder is gone.
- Whenever the lesion is above, there will be spasticity.
- There is a spastic bladder Normally the urge comes at 150 ml but due to contracted spastic bladder the urge will come at less than 150 ml.
- Therefore, the manifestations is that the patient will urinate every few minutes: Urge incontinence.
- This is an Automatic Bladder.

Investigations

- IOC for Transverse Myelitis – MRI spine.

Treatment

- **Steroids:** IV methyl prednisolone.
- Manifestation of Ascending paralysis in GBS is over 12 hours – 28days.

CIDP (Chronic Inflammatory Demyelinating Polyneuropathy) 00:51:12

- If the duration of illness is > 9 weeks.
- In a case with ascending paralysis usual progression of illness is up to a 28 day period.

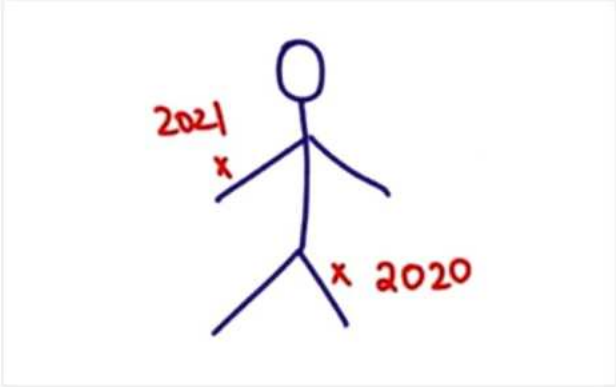
- If it spans over a much longer duration than Chronic inflammatory demyelinating polyneuropathy should be considered and Steroids will be given.
- Methyl prednisolone is used in Transverse myelitis and CIDP.
- Clinical features are identical to features of Guillain Barre Syndrome.
- Presentation: Symmetrical flaccid paralysis developing in the person.
- The worsening period will be over a duration of months in most of the cases.
  - In nerve conduction velocity , there can be increased latency period or there will be a conduction slowing present.
  - Lumbar puncture: AC dissociation
- Nerve biopsy shows Onion Bulb appearance.

Extra Mile:
Onions Bulb appearance
1. Nerves: CIDP and HSMN
2. Bite ducts: PSC

Comparison of GBS vs T.M vs Polio vs Botulinum 00:56:39

Refer Table 27.1

- In poliomyelitis paralysis progression will stop by itself, it may involve only one leg so patient might walk with crutches or stick.
- In botulism toxin case, there is history of home delivery and subsequently honey is given to the child.
- When mother feeds the child, milk might come out of the nose.
- Child may be choking on breast milk or there may be nasal regurgitation of fluid.
- When the child is crying there will be no voice.
- There is a high risk for Aspiration pneumonia.



- If paralysis progresses over years e.g., paralysis of legs in 2020, patient uses stick to walk and then there is paralysis of opposite arm in 2021, the disease that needs to be considered is motor neuron disease.
- In ALS, patients usually die within 3 years due to respiratory failure.
- It is asymmetrical but slow in onset.
- This disease attacks the anterior horn cells of spinal cord.
- Pyramidal neurons in the brain are affected
- High mental functions remain normal.

Table 27.1

	GBS	TM	Polio	Botulinum Toxin
Initial trigger	Initial trigger - Dysentery	URTI AGE (Acute Gastro Enteritis)	Fever	Honey
Clinical presentation	• Ascending Sym. Flaccid Paralysis • No root pain. • Sensory complaint: Sore muscles or pain in muscles after exercise	• Same features with o Root pain present o Sensory level will be present. o Bladder and Bowel involvement is present	• Asymmetrical Descending paralysis	• Bulbar Palsy

28 ALZHEIMER DISEASE

- It is a leading cause of Cortical dementia
- As this disease progresses, the patient not only forgets his personal details, but will develop Akinetic Mutism and Incontinence

Pathophysiology of Alzheimer's

1. Acetylcholine, noradrenaline and serotonin levels are reduced
2. Parietal and Temporal lobes are affected
3. In Hippocampus, Nucleus of Meynert Basalis is affected
4. In Alzheimer's, initially, short-term memory is lost and later progresses to long term memory deficit.
5. Earliest and most serious damage is seen in medial temporal lobe or entorhinal cortex

Extra Mile:

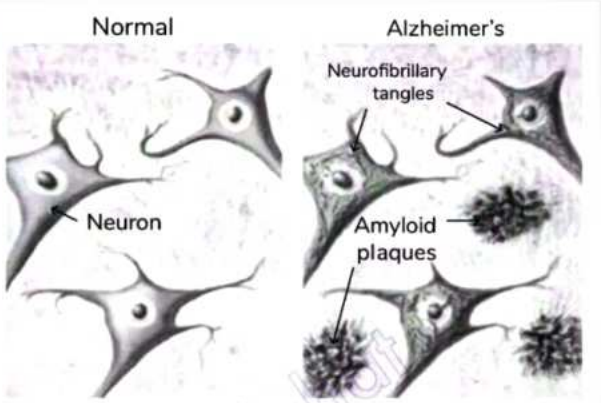
- Cortical dementia is also seen in Pick's disease or Fronto-temporal dementia (Frontal and Temporal lobes are involved unlike Alzheimer's where Parietal and Temporal lobes are involved)

Etiology 00:05:31

1. Aging
2. Genetic predisposition
   - Chromosome 1
     → Defective gene is Presenilin-2
   - Chromosome 14
     → Defective gene is Presenilin-1
   - Chromosome 19
     → Defective gene is Apolipoprotein E
     → Apolipoprotein E 4 allele
   - Chromosome 21
     → **Down syndrome**
     → Down Syndrome patients usually die before 35 years due to pneumonia or congenital heart disease
     → When Down Syndrome patients survive even at 35 years, they can develop Alzheimer's - Presenile dementia.
   - Amyloid precursor protein

Histopathology

1. Amyloid protein (Aβ) is deposited in between the Neurons leading to formation of neuritic plaques.
   - A-β_2 amyloid deposition leads to dialysis dementia but A-β is related to Alzheimer's.
2. Neurofibrillary tangles (NFT) are the intracytoplasmic findings in Alzheimer's Number of NFT's is directly is to severity of dementia. NFT are composed of Tau protien



Neurofibrillary tangles and Amyloid plaques

Clinical Manifestations 00:10:25

Mnemonic: 4A's

1. **Amnesia**
   - **Loss of episodic memory**
     → **Ex:** If a patient who has been living in a place for more than 60 years and is buying groceries from same store, on developing amnesia, forgets his way back to home. Most patients develop inability to track finances
   - **Short term memory loss**
     → **Ex:** Searching the entire house for a mobile phone after a few minutes of keeping it in the pocket.
   - **Long term memory loss**
     → Patient forgets his name or phone number
2. **Aphasia**
   - This is because of the damage to the dominant Parietal lobe.
3. **Apraxia**
   - Loss of visuospatial skills due to involvement of Non-dominant parietal lobe
     → **Ex:** The patient may not be able to perform Clock Face test. When the patient is asked to draw a clock that is drawn by a normal person, the patient may make all numbers on only one side of the clock, loss of visual spatial skill.
4. **Anosognosia**
   - The patient is unaware of neurological deficit and mental illness.
   - The patient forgets to eat when a food plate is present before him and when he is fed out of concern, the patient even forgets to chew the food. He may urinate while eating.
5. **In advanced stages** there can be

- Rigidity
- Mutism and Incontinent
- **Incapacitated bed ridden** state that leads to Deep vein thrombosis, pulmonary embolism, Urinary tract infection, Decubitus ulcers.

Workup 00:21:19

1. **Mini mental score examination (MMSE)**
   - It should be only considered as a screening test.
   - Total score is for 30
   - Score <24 - dementia
     → **21-24,** mild
     → **10-20,** moderate
     → **<10,** severe
   - Patient will be asked about current date or month or year or address
   - Patient will be asked to do basic calculations
     → **Ex:** Serial subtractions (100-7=93-7=86)
   - Asking the patient to draw intersecting pentagons.
   - MMSE should be only considered as a screening test rather than test of choice as this may lead to false diagnosis (A depression patient may also score less than 21).

2. **Functional MRI**
   - Helps in identifying metabolism in Parietal and Temporal lobes
   - Plain MRI is not preferred because it shows the findings lately.
   - As in Alzheimer's, blunting of gyri and sulci are seen, it leads to pseudo-enlargement of ventricles of the brain and be misinterpreted as hydrocephalus when a plain MRI is performed.

3. **Other imagings**
   - CT
   - Volumetric MRI
   - FDG Glucose PET
   - Amyloid PET is investigation of choice: Harrison 21st edition update

Treatment 00:25:11

Drug of choice

1. Donepezil
2. Memantine (new drug)

- Mostly prescribed in initial stages

3. Rivastigmine + Galantamine

- Tacrine used previously has been withdrawn due to its hepatotoxicity

Extra Mile:

1. Cortical Dementie is seen in Alzheimer's (Parietal and Temporal) and Pick's disease
2. Presenile dementia is seen in Down syndrome
3. Subcortical atrophy is seen in Parkinson's disease, Huntington's disease, AIDS related dementia
4. Pseudodementia is the presentation of Depression
5. Lewy bodies are seen in Parkinson's disease and also Lewy body dementia
6. Hirona bodies are also seen in Alzheimer's Disease
7. A young age patient (around 30 years) has Dementia+Myoclonus, then it is Variant creutzfeldt-Jakob disease
8. If a patient around 50 years old has Dementia+Chorea, then it is Huntington's disease.

Pick's Disease/ Fronto-temporal dementia (FTD)

- Damage to the frontal lobe makes the patient aggressive or socially inappropriate (patient may physically expose themselves without any guilt)
- Patient may experience psychotic features like
  - OCD
  - Delusions and hallucinations

29 MULTIPLE SCLEROSIS

Multiple Sclerosis 00:00:15

- Autoimmune Demyelinating Disorder
- Myelin is produced by oligodendrocytes
- Main target of disease is MBP - Myelin Basic Protein

Myelin - Advantage

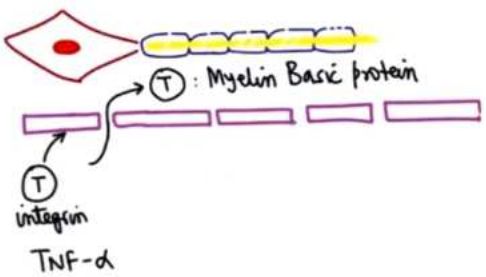
- Myelin allows Saltatory conduction
- Normal conduction speed across axons is 1 m/ sec
- But in myelinated fibers, the speed is 70 m /sec
- When myelin fibers are damaged, the conduction will be significantly hampered

Risk factors

1. Autoimmunity
2. Women > men
3. Associated with Vitamin D deficiency
   → Common in North America, Northern parts of Europe , Scotland - where sunlight exposure is less than Asia or India
   → Vitamin D plays a role in immune modulation

- Increased permeability of BBB
- Blood brain barrier composed of
  - Foot processes of Astrocytes
  - Endothelial cells

- **Investigation of choice** - Gadolinium enhanced MRI
  - To identify increased uptake in areas where there is a breach in BBB and increased permeability
  - Normally, the gadolinium does not cross BBB and there is no enhancement



- T cells bind via integrin to endothelial cells and cause damage.
- NATALIZUMAB - Interferes with binding of T cell to endothelial cells and prevent further damage
- T cells produce damage to myelin by producing cytokines likes TNF - α which target MBP.

Pathophysiology 00:02:58

1. Myelin damage
2. Axon damage
3. B cell also start producing antibodies in this disease
   - They are not from blood stream
   - They are the endogenous B cells of brain
   - It targets Myelin Oligodendrocyte Glycoprotein - MOG
4. Oligodendrocytes initiate repair
   - It causes gliosis and plaque formation in white matter
5. Plaques are Visualized in MRI as Periventricular Dawson fingers

Features

- Usually affects young females
- Neurological symptoms worsened or triggered by physical activity or with fever

Example,

- If plaques affects optic nerve
  - Then patient may complain that he is unable to see after hot shower
- Or if it affects corticospinal tract
  - There could be cramps in leg due to spasticity
  - Young female after joining gym or dance class would come to you with complaints of muscle cramps
- Neurological symptoms are triggered by heat exposure - this is called UHTHOFF phenomenon
  - Triggers could be
    → Taking a hot shower
    → Or steam bath / sauna bath
    → Fever
  - This is not same as heat intolerance seen with thyrotoxicosis

Clinical features 00:12:13

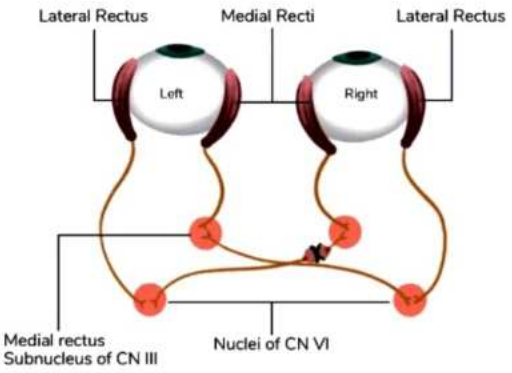
1. Sensory - 37 %
2. Optic neuritis - 36 %
   - Sensory symptoms are more prevalent than optic neuritis
3. **Sensory symptoms**
   - Paresthesias
     → Tingling sensation

→ Pins and needle sensation in one arm or both arm
→ Definitive sensory level in the torso just like in transverse myelitis
→ Below the level patient may describe that someone has tied metal wire and is tightening it all the time

- Pain - multifocal and varying intensity
  → Example, pain initially would be in left hand and then in other hand on a different day/times of examination.
  → May be confused as psychiatric manifestation of Malingering
- Dissemination over time and space
  → Plaques keep developing over time
  → Time - symptoms developing at different times
  → Space - it gradually affecting different parts of brain

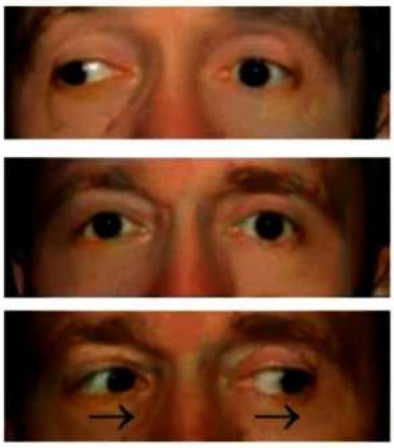
4. **Optic neuritis**
   - Optic nerve - most common cranial nerve involved in multiple sclerosis
   - Decrease in visual acuity
   - Unilateral > bilateral
     → The person may go to an ophthalmologist with visual complaints and get glasses
     → But his vision deteriorates over time and he needs frequent change of power of spectacles
   - Change in color perception
     → May even develop color blindness
     → May not be uniform
     → Not like scotoma / blind spot
     → This is called desaturation
     → Especially in central field of vision
   - **No uveitis**
     → If present → think of neurosarcoidosis
     → If red eye → unlikely to be multiple sclerosis
   - Optic neuritis can be severe and cause blindness in young female
   - Unilateral > bilateral
   - Variant - Neuromyelitis Optica
     → Brain, spinal cord and eye involvement
       - CNS manifestation
       - Spinal cord affected - sensory level
       - Optic nerve involved → cause blindness
     → Non specific symptoms progressing to visual loss
   - Fundoscopy - fundus is normal
     → As the Retina is normal
     → Involvement is retrobulbar
     → Plaques in optic nerve cause blindness in this case
     → Evidence of papillitis may be noticed
5. On a retrospective history - patient may complain of **periorbital pain increasing with eye movements**
6. **Internuclear Ophthalmoplegia - INO**
7. **One and half syndrome**
8. **Eight and half syndrome**

Internuclear Ophthalmoplegia – INO



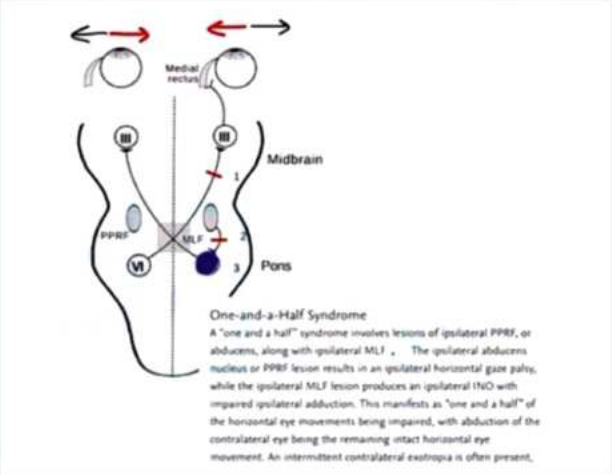
- Damage to Medial Longitudinal Fasciculus
- Coordination of eye movements are done by MLF
- MLF - coordinates:
  - 6th nerve on same side → lateral rectus → abduction with 3rd nerve on contralateral side → medial rectus → adduction
- If you are looking to the left
  - The lateral rectus of left eye help in moving left eye
  - And medial rectus of right eye help in moving right eye medially - to the left
- When MLF is damaged due to plaques right after the crossing over
  - On the affected side -fibers to 3rd nerve nucleus damaged
  - There will be impaired adduction on the ipsilateral side
- Contralateral eye movements will be intact

One and half syndrome



- Eyes are looking straight
- When looking to the left → Lateral rectus of one eye and medial rectus of other eye is functioning to look to the left

- When asked to look to the right - one eye is unable to adduct
  - The right eye moves to right
  - But left eye unable to adduct → impaired adduction
  - Normal eye may show nystagmus
    → As a compensatory mechanism
    → By Hering's law of equal innervation
    → When one eye shows impaired adduction the other eye may show compensatory abduction or nystagmus



- Plaque in 6th nerve nucleus
  - 6th nerve → lateral rectus → helps in abduction of eye
  - On the affected side → inability to look laterally
  - 6th nerve is connected to contralateral 3rd nerve also
  - Helps in adduction of contralateral eye
  - Both these movements are impaired
- Second lesion - plaque in MLF also
  - Affects the function of 3rd nerve
  - Adduction of the ipsilateral eye impaired
  - In effect , No movement of the eye on affected side - both adduction and abduction impaired

- **The impact is**
  - one eye is not moving at all
  - And in the other eye only one movement is possible
- The abduction of other eye is possible as the 6th nerve on contralateral side is not involved
- This is called one and half syndrome

Summary of One and Half syndrome
- Ipsilateral 6th nerve nucleus
- Or PPRF - parapontine reticular formation
  → The affected side - eye cannot look laterally
  → Connection of opposite side that has to feed 3rd nerve is also affected → contralateral adduction impaired
- Ipsilateral MLF lesion
  → Leads to ipsilateral adduction impairment
- On eye not being able to move at all
- Other eye only able to abduct
- The only movement possible is contralateral abduction

Eight and half syndrome
- 7th nerve involvement + one and half syndrome
- 7th nerve nucleus affected by plaque
- So 3 plaques in total
  - 6th nerve nucleus
  - MLF
  - 7th nerve nucleus

9. **Weakness on limited physical activity**
   - Increased activity causes weakness eg Tired even after chopping vegetables
   - Due to involvement of Corticospinal tract
   - May complain of cramps on examination
     → Spasticity: hypertonia
     → Hamstring cramps on climbing stairs
   - Spasticity in these patients are a blessing in disguise
     → It helps them to stand
     → Had there not been spasticity → they would not be able to stand
   - Spasticity may be so severe in late stages that the person will not be able to walk
     → Abnormal gait would be seen
- **UMN lesion findings**
  - Brisk DTR
  - Babinski sign
- **Plaque in spinal cord - lower motor neuron findings could also be seen**
  - Areflexia
  - Simultaneous upper motor and lower motor neuron findings in the same patient
  - Example - spasticity in right arm and fasciculations in left arm

10. **Facial nerve palsy**
    - Different from Bell's palsy
    - Damage to nucleus of 7th nerve in pons
    - Taste sensation is preserved
      → Helps to differentiate from Bell's palsy

11. **Development of cerebellar involvement**
    - Ataxia
      → Walking difficulty - may fall
      → Drunken gait or broad based gait
      → Gait ataxia is due to damage to paleocerebellum (GP)
      → Due to truncal ataxia there may be difficulty in sitting
      → Truncal ataxia is due to plaques in archicerebellum
    - Scanning speech
      → Speech will be deliberate with effort
      → The words will be phonated separately

12. **Vertigo / Deafness due to 8th nerve involvement**
13. **5th nerve nucleus involved - Trigeminal neuralgia**
    - Can be bilateral
    - Patient feels as if somebody has cut their face with a piece of glass
    - Or trying to pull skin
    - Carbamazepine maybe given for management
    - Inspite of giving CBZ, symptoms may persist

14. **Glossopharyngeal neuralgia may lead to pain during swallowing**
    - May be explained by the patient as if drinking acid or a piece of glass

15. **Ancillary symptoms**
    - LHERMITTE SIGN
      → Neck flexion resulting in shooting pain in the legs of patient

LHERMITTE SIGN seen in

- Tabes dorsalis
- Cervical spondylosis
- Multiple sclerosis

    - FACIAL MYOKIMIA
      → Twitching of muscle of face
        - e.g,Fluttering of eyelids
      → Different from fasciculations
        - Selective area would only be involved
      → Visible as well as perceived by the patients
      → Flickering movements can be seen in normal person related to stress
      → But in this patient, it would be a regular event
      → May last for few seconds or minutes

16. **Bladder involvement**
    - There has to be coordination between the contraction of the detrusor and the relaxation of the internal urinary sphincter for micturition to occur
    - In this patient there can be
      → Detrusor hyperreflexia
        - Due to loss of inhibitory control
        - Difficulty in control of urination → nocturnal enuresis
        - Later it can lead to urinary incontinence
      → Detrusor sphincter dyssynergia
        - Detrusor contracts but sphincter not relaxing → leads to urinary retention
    - So both urinary incontinence and urinary retention may be seen in this patient
    - Urinary incontinence could be due to
      → Spasticity and inability to walk faster
      → Detrusor hyperreflexia → inability to control urination

Expanded disability severity score - EDSS

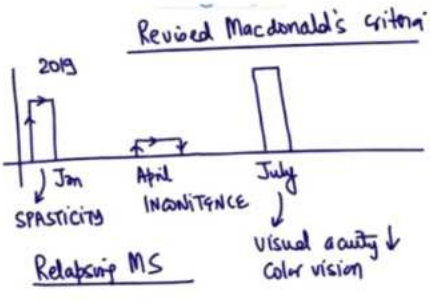
- Rate the patient with respect to manifestation of the patient
- From 0 to 10
- 10 means - death
- 9.5 - completely bedridden
    - cerebellum and corticospinal tract involved
    - Not able to talk - vocal cord palsy - bulbar palsy
    - Can't drink - may need to feed via RT or Nasogastric tube
- 9.0 - completely bedridden
    - But can at least talk
    - At least able to drink with help of straw
    - No aspiration
- 3.5 - fully ambulatory
    - Can walk to washroom
    - Not able to run or jog
- This is to identify the functional status of the patient
- Treatment aims in improving the quality of life

Disease modifying drugs

- Beta interferon
    - Once a week or once a month
    - Intramuscular injections
- Acute attack of multiple sclerosis (causing blindness) - drug of choice is steroid
    - IV methylprednisolone
- Uhthoff phenomenon do not require steroids

Revised Mcdonald's criteria for identification of multiple sclerosis 00:47:52

- Manifestation will not develop simultaneously
- Example
    - Young lady developed spasticity or muscle cramp in 2019 January and it gradually settled
    - In April 2019, new symptom developed - passed urine in bed
      → Nocturnal enuresis or urinary incontinence
    - The patient in July complains of inability to see color in central part of field of vision
    - This shows waxing and waning of symptoms
    - This is relapsing type of multiple sclerosis
    - This is the most common subtype



- In 2019 , many symptoms developed with asymptomatic intervals
- In 2020, the symptoms add on to each other
- If the patient shows no symptom free interval right from the beginning
- It is Primary Progressive Multiple Sclerosis
  → Less common - 10 %
  → Most severe

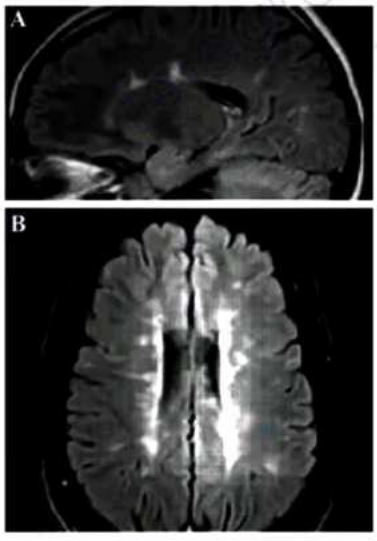
- **3 types**
  1. Relapsing type of multiple sclerosis
  2. Primary Progressive Multiple Sclerosis
  3. Secondary Progressive Multiple Sclerosis

Criteria

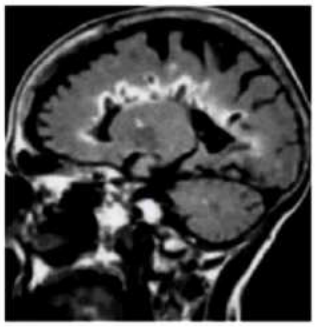
- 2 symptoms present in a patient
- Symptoms lasting for > 24 hours (to differentiate from TIA) Both symptoms not occurring simultaneously
- Symptoms separated by > 4 weeks (to differentiate from stroke)
- Any of the following work up showing involvement of specific sites.

Work up 00:53:15

1. **Gadolinium enhanced MRI**
   - Presence of plaques /Dawson fingers at following sites
   A. Periventricular - or white matter area
   B. Juxtacortical - junction between gray and white matter
   C. Infratentorial - cerebellum
   D. Size of plaque > 6 mm



- **FLAIR** image showing Plaques
- FLAIR - Fluid Attenuated Inversion Recovery System
  - Suppress the signal of the CSF
  - Periventricular lesions identified better
- In corpus callosum - white matter area - whitish lesions - dawson finger



2. **VEP - visual evoked potential**
   - If plaques are small and cannot be visualized
   - So we use VEP - increased latency period

3. **CSF study** - mild to moderate pleocytosis and slight increase in protein
   - > 75 cells - unlikely to be multiple sclerosis
   - Protein > 100 mg - unlikely to be multiple sclerosis
   - Normal - 0-4 lymphocytes

- **CSF - ELECTROPHORESIS**
  - Oligoclonal band in CSF
  - Helps in identifying antibodies produced by B cells
  - That attack MOG - myelin oligodendrocyte glycoprotein

Treatment 00:59:57

- **Acute attack**
  - IV methylprednisolone
  - If not responding → plasmapheresis may be needed

- **Disease modifying drugs for relapsing type**
  - Aim - To Prevent progression
  - Beta interferon (Modesty effective)
    → Intramuscular - once a week
    → Subcutaneous - 3 times a week
  - GLATIRAMER (Modesty effective)
    → Glutamic acid
    → Lysine
    → Alanine
    → Tyrosine
    → Immunomodulatory action -prevent further deterioration
  - Oral FINGOLIMOD
  - Oral DIMETHYL FUMARATE
  - NATALIZUMAB
    → Once a month infusion
    → Inhibit T lymphocyte binding to endothelial cells of BBB

→ Side effect - PML
- JC virus - John Cunningham virus
- Shed in urine of normal people
- But in patient taking natalizumab - due to immunosuppression
- This virus cross BBB and cause - PML
- Progressive Multifocal Leukoencephalopathy
- Can lead to worsening of neurological symptoms
- Incidence is less
- So the drug is recommended only for JC virus negative individuals

○ OCRELIZUMAB
→ Attack mature B cell - that express CD20
→ Selective targeting
→ Initially Used for the treatment of primary progressive multiple sclerosis but now used in all forms.
→ Mitoxantrone: cardiotoxic, thus not currently recommended for the treatment of multiple sclerosis.
→ Highly effective drug used as initial Treatment

Harrison 21st update
- Siponimod is a selective S1P1 S1PS Receptor Modulator used in SPMS

FREQUENTLY USED AGENTS IN RMS
- Highly effective : Ocerlizumab, Ofatumumab, Rituximab, Natalizumab
- Moderately effective: Siponimod, Dimethyl Fumarate
- Modestly effective: Glatiramer, β – INTERFERON

LESS COMMONLY USED AGENTS for RMS
- Highly effective: Alemtyzumab, mitoxantrone (cardiotoxic)
  Moderalety effective: Cladiribine
- Modestly effective : Terifluonomide

30 NEUROMYELITIS OPTICA

- Also known as Devic's disease
- Female to male ratio is 3:1
- Astrocytopathy
- **Target:** Foot process of Astrocytes (responsible for the formation of blood brain barrier).
- **Manifestations**
  1. Blindness (sudden onset) may be bilateral
  2. Tingling sensation
  3. Transverse myelitis like presentation (Monoplegia, paraplegia and quadriplegia)
  4. May develop cervical myelitis (diaphragm would be paralyzed)
- **Reason for the death:** Respiratory paralysis
- Aquaporin 4 is the main target for the disease
- Anti Aquaporin antibodies can be measured.
- **Diagnosis:** NMO (Neuromyelitis Optica Spectrum Disorder)
- Due to damage to Aquaporin 4, blood brain barrier is compromised.

Core Clinical Findings

00:02:40

1. Optic Neuritis

- Sudden onset blindness
- Bilateral involvement

Multiple sclerosis	Neuromyelitis Optica
• Gradual onset of optic neuritis	• Sudden onset of optic neuritis
• Unilateral blindness • Bilateral (Asymmetrical progression with visual acuity in both eyes)	• Bilateral blindness

2. Transverse Myelitis

- Longitudinally extensive transverse myelitis
- More than 3 consecutive segments of the spinal cord is involved
- Clinical presentations:
  - Unpleasant pin and needle sensation
  - No feeling in the legs (Woody legs - Spasticity)
  - Inability to walk
  - Presence of ambulation issues
- Development of the symptoms is very fast

3. Area Postrema Syndrome

- Lesion in Vomiting center
- Manifestations: Nausea, Protracted vomiting, Hiccups
- No Features of raised ICT are present

4. Endocrinopathy

- Hypothalamus regulates intake of food (Satiety Centre)
- Hypothalamus of the patient is damaged Extreme anorexia and weight loss is present.
- This is known as Diencephalic syndrome

5. Narcolepsy

- Sudden onset of increased day time sleep

6. Acute Brainstem Syndrome

- 3rd nerve palsy may occur
- Development of hemiplegia (in midbrain crus cerebri is affected)

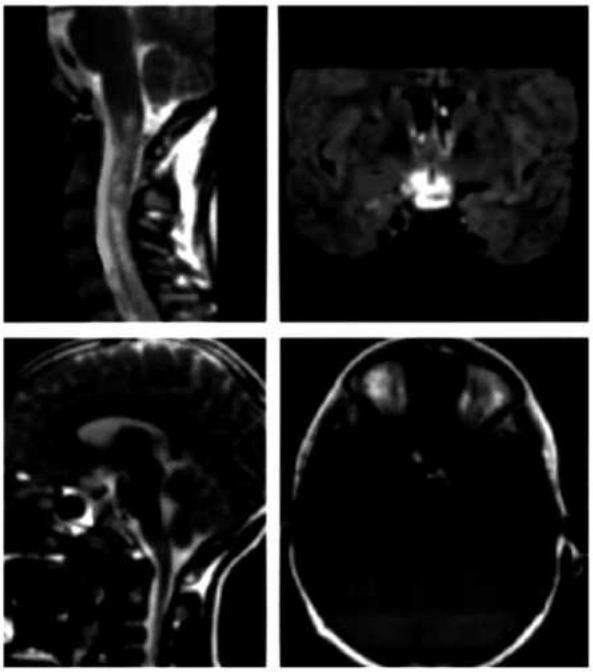
7. Cerebral Syndrome

- Cortical involvement leads to the development of seizures and encephalopathy in the patients.
- Earlier:
  - They were misdiagnosed as stroke
  - Or development of acute disseminated encephalomyelitis.

Diagnosis of NMO

00:10:20

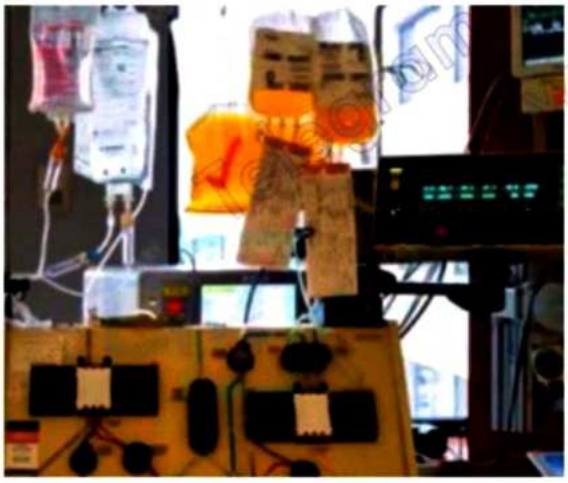
- **At least 1 core clinical feature + anti aquaporin 4 antibody**
- **At least 2 Core clinical features + MRI findings**
  - Dissemination over space
  - Gadolinium-enhanced MRI findings
    - → More than half the length of the optic nerve inflammation should be definitely demonstrated
    - → Longitudinally extensive transverse myelitis (LETM) spreading over more than 3 segments
    - → Cloud like lesions developing in the brain parenchyma of the patients
    - → Damage to area postrema is seen
    - → Periependymal brain lesions



Treatment

00:14:13

- Methylprednisolone: Drug of choice
- In case of poor response with methylprednisolone, back up with plasmapheresis is given.



Extra Mile

- Plasmapheresis is used in the management of the:
  1. Hemolytic uremic syndrome
  2. Thrombotic Thrombocytopenic Purpura
  3. Neuromyelitis Optica

- Mycophenolate: To prevent future episodes of blindness
- Death may occur due to respiratory insufficiency
- Anti- MOG - Myelin Oligodendrocyte Glycoprotein Antibody is seen in patients who are Anti Aquaporin 4 negative NMO.
- Beta Interferon and Glatiramer are disease modifying drugs used for multiple sclerosis and redevelopment of symptoms: Disease modifying treatment
- All Disease modifying drugs discussed in Multiple Sclerosis are contraindicated in NMO.

Extra Mile

- Anti- MOG has also been demonstrated in pediatric cases of ADEM
- ADEM is associated with:
  1. Vaccines
  2. Antibody - Anti- MOG.
     → Target of antibody - Affects the oligodendrocyte and astrocytes in the brain.

31 AMYOTROPHIC LATERAL SCLEROSIS

- Most common type of Motor Neuron Disease is ALS
- Stephen Hawking
  - Diagnosed with MND in 1975
  - Longest survivor of MND

Extra Mile:
- People who suffer from MND usually die due to respiratory failure after getting bedridden.
- Muhammad Ali had Parkinson's died due to pneumonia when he was bedridden

Understanding ALS 00:01:42

- **Amyotrophic**
  - Denervation of Muscles (Damage to the anterior horn cells of the spinal cord)
  - Lower motor neuron (LMN) lesion symptoms
    → Fasciculations
    → Areflexia
- **Lateral Sclerosis**
  - Involvement of Corticospinal pathway (thinning of the lateral columns)
  - Upper motor neuron (UMN) lesion symptoms
    → Brisk reflexes
    → Babinski sign

Pathogenesis of ALS 00:04:04

1. **Genetic**
   - AD SOD1 GENE
   - C9 or F72 gene: Hexanucleotide Repeats
2. **Sporadic**

SOD 1 Gene

- Controls the activity of superoxide dismutase
- Superoxide dismutase controls and neutralizes the free radicals in the body

SOD 1 gene defect
↓
Activity of superoxide dismutase is ↓
↓
↑ Free radicals
↓
Damage to Anterior horn cells of spinal cord
Damage to Pyramidal neurons in brain
Thinning of the Lateral columns
↓
ALS

Extra Mile

- **Hexanucleotide repeat disorders**
  - Amyotrophic Lateral Sclerosis/ MND
- **Trinucleotide repeat disorders**
  1. Huntington Disease
  2. Fragile X syndrome - Tall male with mental retardation + large ears and large testicles
  3. Myotonic dystrophy

Pathology

1. Defective protein degradation in neuron
2. Defective RNA processing
3. Excitatory damage due to amino acids - Excitotoxicity
   - Glutamate levels ↑
   - Aspartate levels ↑

Treatment 00:07:51

1. Drugs
   - Riluzole (↓ both glutamate and aspartate levels)
   - Edavarone
2. Foot drop splints - As foot drop is seen
3. Physiotherapy
4. Finger extension splint - For contractions
5. Tracheostomy - To support the respiratory functions
6. Cough assistive devices - For Bulbar palsy effects

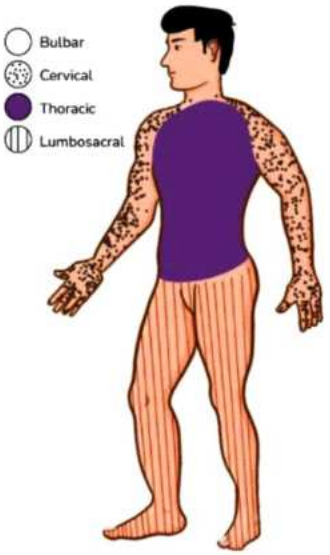
- ALS has no effects on Higher mental functions.
- Only LMN + UMN are affected.

Q. Which is the most common cause of death in ALS patients?
Ans. Respiratory failure (Pneumonia)

Clinical Manifestations 00:11:35

1. Asymetrical Gradual onset weakness in extremities
   - Leg weakness
   - Fasciculations
   - Knee jerk was absent in one leg
   - Slapping gait
2. Same patient after 1 year will develop:
   - Hand weakness
   - Brisk Bicep jerk
   - Asymmetrical weakness
3. Eye movements are preserved
4. Bladder and bowel control is present till late
5. Higher mental functions are Normal
6. Later (after a few years)
   - Bulbar palsy
     → 9th and 10th cranial nerves - Can't drink water
     → 12th cranial nerve - Can't talk and eat

- If any ≥ 3 of the below 4 segments is showing above mentioned features it is Confirmatory diagnosis of ALS
  - Bulbar
  - Cervical
  - Thoracic
  - Lumbosacral



Work Up

00:18:22

1. S. Electrolyte
2. NCV
3. CPK MM Muscles Biopsy an EMG: Denervation pattern in LMN involved
4. Anti Ach R A/b, Anti - Musk A/b, Anti - P/Q A/b
5. Genetic studies for SCN 4A channel
6. S. vit B_{12}

Extra Mile:

1. Damage to Anterior horn cells of spinal cord: LMN lesions (Progressive muscular atrophy)
2. Damage to Pyramidal neurons in brain: UMN lesions (Progressive lateral sclerosis)
3. Combination: LMN + UMN lesions (Amyotrophic lateral sclerosis - ALS)

Clinical Tips:

- Guillain Barre Syndrome: LMN lesions will progress over 4 weeks
- Chronic Inflammatory Demyelinating Polyneuropathy: LMN lesions will be noticed in almost 9 weeks
- ALS: LMN and UMN lesions will be noticed in almost years, not immediate

Bulbar Palsy

00:26:35

- Damage to 9th, 10th, 11th, and 12th cranial nerve
- Bulbar palsy: Damage to the Nucleus of nerve + Nerve
- Pseudobulbar palsy: Corticobulbar fibers are involved

Bulbar palsy	Pseudobulbar palsy
Pure LMNL	Pure UMNL
Gag Reflex -ve	Gag Reflex is Brisk
Tongue is flaccid (deviated)	Tongue is spastic (diffcult to take it out)

Other Diseases with LMNL + UMNL

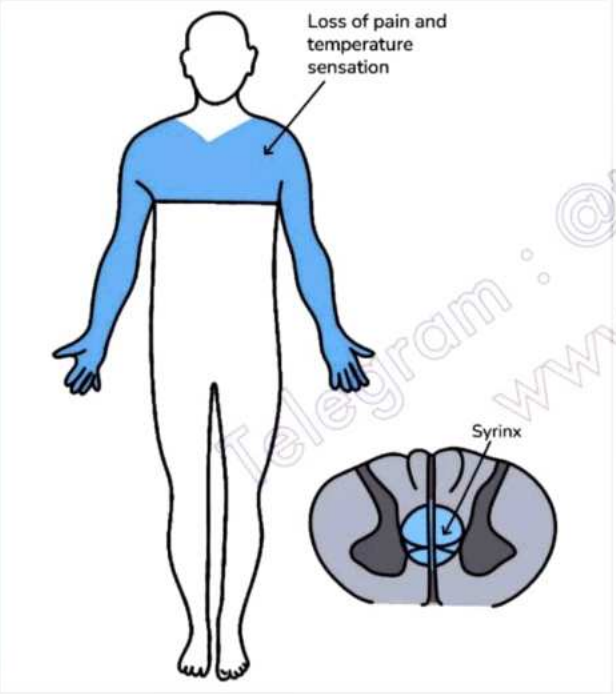
00:28:31

1. **Sub-Acute Combined Demyelination Spinal cord (SACD)** - Due to Vit B12 deficiency
2. **Friedreich Ataxia** - Due to frataxin gene defect
3. **MND/ALS** - Damage to Anterior horn cells (spinal cord) and Pyramidal neurons (brain)

32 SYRINGOMELIA AND CONUS MEDULLARIS SYNDROME

Syringomyelia

- Dilatation of central canal of spinal cord
- Lateral spino-thalamic pathways (responsible for pain and temperature sensations) will be pressed due to dilatation.
- As a result, Pain and temperature senses are lost on hands.
- Painless burn(s) in hand is characteristic feature this case.
- In the Lateral spino-thalamic pathway,
  - Cervical nerve fibers are present medially (close to central canal of spinal cord)
  - Thoracic and lumbar, and sacral are lateral (away from central canal)
- Cape distribution: When the central canal dilates, cervical fibers are affected first causing reduced sensation in the hand and arms.



- Central canal expands asymmetrically and in the initial stage only some part of the cervical area is involved leading to a patchy loss of pain and temperature sensation.
- It progresses to bilaterally symmetrical symptoms based on the extent of compression.

Causes

1. Congenital cause is Arnold Chiari Malformation Type I
   - It is not a neural tube defect.
2. Arachnoiditis, Meningitis
3. Spinal cord injury

Clinical Features

Sensory manifestations

1. Painless burn in hand.
2. Non healing ulcer on hand and Develops as result of painless burn
   - Non healing ulcers on foot may be due to diabetes but on hand, it is characteristic of Syringomyelia.
3. Charcot joints
   - Painless, paralyzed Joints
   - In Diabetes, Charcot joints are seen in foot
   - In Tabes dorsalis, Charcot joints of ankle are seen
4. Asymmetrical patchy loss of pain and temperature sensations
   - Sensory deficit of pain and temperature progresses from shoulders (proximal) to palm (distal).
   - When the disease progresses, sensory deficit becomes symmetrical - Cape distribution.

Motor manifestations

5. Occurs when Central canal compression progresses to the Cortico-spinal pathway.

- Either one or both Cortico - spinal pathways can be involved leading to unilateral or bilateral features.

6. Features include:
   - Ipsilateral or bilateral spasticity
   - Ipsilateral Brisk Deep Tendon Reflexes.
   - Ipsilateral or Bilateral Babinski sign.
   - Wasting of hand and arm muscles.

Investigation of Choice

1. **MRI spine** Syrinx fluid-filled cyst in spinal cord

Management

- Surgical decompression: It is not the same as decompressive surgery of a prolapsed intervertebral disc.
- Sometimes patients refuse surgery due to absence of pain leading to Syringobulbia
- In Syringobulbia
  - Syrinx expands vertically
  - Compressed brain stem
  - 9, 10 and 12th cranial nerves are involved
    → 9 - Nasal regurgitation
    → 10, 12 - Speech problems and Risk of Aspiration

Extra Mile

There are four types of Arnold Chiari Malformations (I,II III and IV)

- Type III and Type IV are not compatible with life.
- Type I is associated with Syringomyelia and Type II is associated with Myelomeningocele

Arnold Chiri Malformation Type II

- CSF is produced in Choroid plexus at a rate of 20 ml/hour travels through the 3rd and 4th ventricles of brain and exits at Luschka (lateral) and Magendie (medial) into basal cisterns
- Rate of production and reabsorption of CSF is the same.
- In ACMT II, there is inferior displacement of Cerebellar Tonsils thus compressing the 4th ventricle.
- As a result, there will be dilatation of 3rd and lateral ventricles which may cause hydrocephalus.
- As the 4th ventricle is compressed, small posterior fossa is seen.
- It is not a neural tube defect but is associated with neural tube defect:
  - E.g., When associated with myelomeningocele in which the baby has a malformation on back and spinal cord can be visible. The sac may rupture and CSF leaks. Meningitis will lead to death of the baby.
  - Congenital hydrocephalus (Leading cause is Aqueductal stenosis).

Important Information

- Large posterior fossa is seen in a Congenital malformation called Dandy Walker Syndrome.

Conus Medullaris Syndrome 00:19:22

- Length of the spinal cord is 45 cm.
- Sub arachnoid space ends at S2 level and spinal cord ends at L1 for adults and at L3 for newborns.
- The terminal part of the spinal cord at L1 level is called Conus Medullaris.
- S1- S5 nerve roots arise from Conus Medullaris regions.
- E.g., In a prostate carcinoma patient and the cancer has metastasized to the Conus Medullaris region (S1-S5 nerve roots), the patient presents with bowel and bladder complaints.
- We examine for:
  - Knee jerk: Associated with L2-L4, Preserved
  - Ankle jerk: Associated with S1-S2, Lost
  - Perineal sensory examination: Associated with S2-S4, Saddle anesthesia is encountered
  - Bowel and bladder complaints: S2-S4, No discomfort or pain even when the bladder is full and Overflow incontinence or Autonomous bladder is seen (large volume of urine is passed without warning).

Cauda Equina Syndrome 00:24:38

- When the damage has occurred to the L1-L5 and S1-S5 nerve roots (unilateral or bilateral),
- We examine for:
  - Knee jerk: Associated with L2-L4, Lost
  - Ankle jerk: Associated with S1-S2, Lost
  - Perineal sensory examination: Associated with S2-S4, Saddle anesthesia is encountered
  - Bowel and bladder complaints: S2-S4, No discomfort or pain even when bladder is full and Overflow incontinence or Autonomous bladder is seen (Large volume of urine is passed without warning).

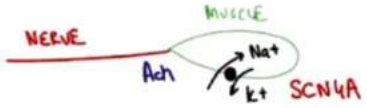
Conus Medullaris Syndrome vs Cauda Equina Syndrome

Conus Medullaris Syndrome	Cauda Equina Syndrome
Mainly due to Mets	Mainly due to Trauma
Bladder complaints	Radicular pain
Knee jerk preserved	Knee jerk lost
S1- S5 lesion	L1-L5 and S1-S5 lesion

Other Disorders Involving Spinal Cord 00:27:27

1. **Guillain Barre Syndrome:** Patients will have lower motor neuron (LMN) manifestations.
2. **Spinal shock:** Patients will have LMN manifestations in the initial stage and after 1 week will develop Upper motor neuron manifestations
   - E.g., A construction worker fell from a height and has develops spine fracture. In the initial stage the patient will have LMN manifestations. UMN manifestations may develop after one week
   - The reflexes that come back in spinal shock after one week can be bulbocavernosus reflexes.
   - If the patient has a cervical cord fracture, then initially, at the lesion level, there would be flaccid biceps and below the lesion level, there can be spasticity after one week in legs because cortico-spinal pathway is involved.
3. Transverse Myelitis Occurs after URTI / Infections process.

33 CHANNELOPATHIES



Important Information

- The defect in Sodium channel SCN5A results in Brugada syndrome causing sudden cardiac death.

Hypokalemic Periodic Paralysis 00:01:38

There is a Loss of function of SCN4A channel

- There would be a Defective depolarisation /repolarisation
- The amplitude of contraction will be hampered.
- So Less Sodium goes inside, and less potassium comes out.

Clinical Features:

- After breakfast, the patient says he feels as if he has no energy/ as if paralysis had hit the body. Initially doctor may get impression that patient is Malingering.
- Carb. rich diet is triggering the weakness leading to an increase in insulin.
- It is called periodic because every time the patient has a meal, he feels weak.
- Spike of insulin causes potassium to go inside the cell; worsening the Hypokalemia.

Work up:

1. Electrolyte imbalance should always be ruled out.
2. **Serum potassium**: either it will be normal or less
3. CPK-MM- it will be normal
4. Nerve conduction velocity - normal
5. Electromyography: defective depolarisation and repolarisation
   - Not a disease involving proteins in muscle but a defect in the function of muscle
6. Genetic studies - Autosomal Dominant inheritance

Treatment:

- Potassium chloride is given orally, during attack.
- Acetazolamide to prevent attack: Exact mechanism of action is not known.
- Recent studies have shown another channel defect in these patients. Due to defect of CALC1A3 gene, calcium that operate in sarcoplasmic Reticulum are also defective leading to muscles weakness. This has been designated as Type 1 Hypokalemic periodic paralysis.

Q. What channel is defective in Hypokalemic period paralysis?
Ans.
Type 1: Hypokalemic periodic paralysis-Calcium channel defect
Type 2: Hypokalemic periodic paralysis-Sodium channel defect

Hyperkalemic Periodic Paralysis 00:13:29

There is a Gain of function of SCN4A channel which in turn causes different manifestations.

- The patient will have Myotonia and muscle weakness.
- Relaxation of muscles is hampered due to exaggerated or depolarisation due to gain of function of sodium channel.
- It is not to be confused with myoclonus or myokymia as Myoclonus has involuntary jerky movement of hands and myokymia is the periocular muscle fluttering.

Treatment:

- Acetazolamide is used.
- The dosage will be higher in hypokalemic PP than used in Hypokalaemic PP.
- Drugs like Thiazides and Lasix can also be used, but they will cause Hypokalemic.
- Mexiletine- useful in Myotonia

Important Information

- Both of these channel disease are not potassium defects, they are sodium and calcium defect

Paramyotonia Congenita

It is a variant of Hyperkalemic Periodic Paralysis seen in children

- The Clinical presentation will be Myotonia.
- It is triggered by cold exposure– having ice-cream or going to a cold areas.
- There is a gain of function of SCN4A

Diseases of sodium channel	Diseases of calcium channel
1. Hypokalemic PP type 2 variety 2. Hyperkalemic PP 3. Paramyotonia congenita	1. Hypokalemic PP type 1 variety 2. Lambert Eaton syndrome 3. Familial Hemiplegic migraine

Potassium channel defect is episodic ataxia

Chloride channel defect - Thomson disease and Becker disease

Important Information

SCN5A: Brugada syndrome

- Sudden Cardiac Nocturnal Death.
- South-east Asian male –previously healthy
- Sodium influx is defective leading to defective inward current in the right ventricular epicardium leading to a development of electrical gradient. This can trigger Polymorphic VT/VT
- The patient maybe asymptomatic or syncopal attacks. Family history of sudden cardiac death in sibling
- ECG of asymptomatic patient -V_1V_2 shows ST elevation (cove pattern)

Treatment:

- I.C.D (Implantable Cardioverter Defibrillator) to

Important Information

- Potassium channel defect involving Heart leading to S.C.D ANDERSON TAWI SYNDROME sudden cardiac death.

Neuropathy	Myopathy
Distal muscle weakness	Proximal muscle weakness
Difficulty in turning a door knob	Difficulty in climbing of stairs
Recurrent falls, foot drop Slapping gait	Difficulty in combing of hairs
ARREFLEXIA	PRESERVED DTR
Gloves & stocking anaesthesia	-
Test - Nerve conduction velocity Nerve biopsy- sural nerve	CPK MM level and Muscle biopsy

In case patient having neuritic subtype of leprosy– nerve biopsy is made from Superficial Branch of Radial Nerve followed by ULNAR NERVE.

Fundamental difference between myopathy vs muscular dystrophy

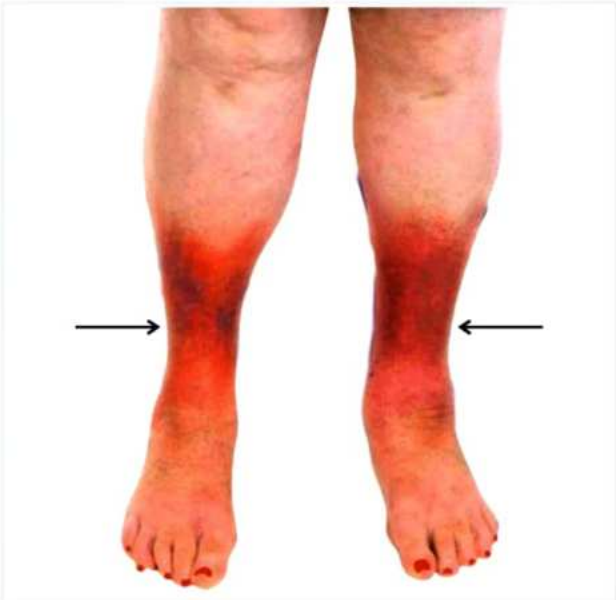
- In myopathy, the severity of weakness will remain the same.
- In Dystrophy, the weakness will progressively increase and patient will develop PseudoHypertrophy of muscles.

Leading cause of neuropathy is: Diabetic neuropathy.

- There is involvement of sensory system > motor system > autonomic system.
- Autonomic system involvement is dangerous as it can lead to silent myocardial Infarction/orthostatic hypotension.
- In sensory system, there is Distal sensory loss in the patients.
- The 1st loss is loss of the vibration sense.
- In motor involvement, Most common cranial nerve involved is 3rd nerve palsy with pupillary sparing, but the light reflex fibres are spared.
- It may also be seen in arterio-venous malformations in Brain

Charcot Marie Tooth Disease/HSMN: Hereditary Sensori-Motor Neuropathy

00:35:25

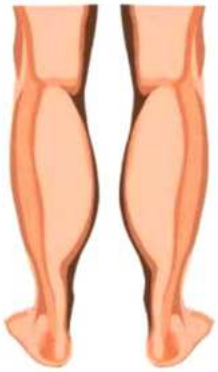


- There is Champagne bottle appearance or stork-leg appearance because of presence of a peroneal muscle atrophy.
- It contrasts with Pseudo hypertrophy of calf muscle seen in Duchenne Muscular Dystrophy
- Contractures in foot may also develop due to nerve involvement leading to difficulty in walking.
- Thickened nerves may also be seen which on biopsy will show onion bulb appearance

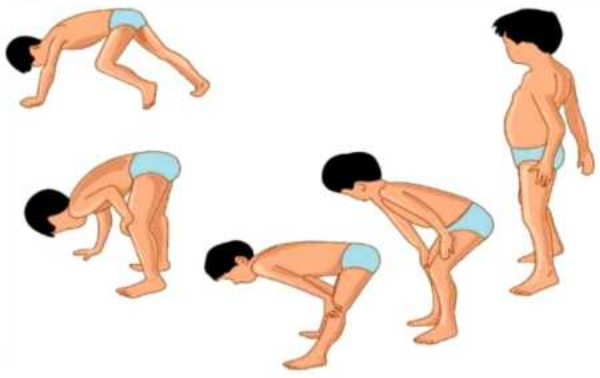
Extra Mile

Onion bulb appearance also seen in **Chronic inflammatory demyelinating polyneuropathy,** a variant of Gullian Barre Syndrome

Duchenne's Muscular Dystrophy 00:38:29



- It is a progressive weakness
- Pattern of inheritance – X-Linked Recessive Disorder: with girls being the carriers passing the disease on to the next generation
- Dystrophin gene is the gene involved leading to defective coding of protein -dystrophin which is a sarcolemmal protein working as a regulatory protein, so ability of the muscle to perform will be hampered.
- Age of presentation – 4-5 years
- Complaint of child falling on stairs again and again
- There is also Hip joint muscle weakness leading to Waddling Gait.



- **GOWER SIGN**– Child takes support of arms, puts hands on knee or may try to take help of near by furniture in an effort to get up from ground.
- The child become Wheelchair-bound after 10-12 years of age
- Later the patient may become completely bedridden and expire.
- Leading causes of death:
  1. Congestive heart failure due to dilated cardiomyopathy
  2. Pneumonia
  3. Respiratory failure

Work up:

1. CPK -MM – initial stages may show elevated values
   - But by 10 years of age, due to muscle wasting, CPK value will return to normal
2. Investigation of choice for Duchenne muscular dystrophy PCR for dystrophin gene > western blot on muscle Biopsy

Treatment:

- There is no definitive treatment for this disease, and the steroids will not alter the course of the disease.
- Most of the children die by the age of 20 years.
- Chest physiotherapy will delay inevitable helping the muscles of chest to be in good shape.

Milder variant of Duchenne's dystrophy

BECKER MUSCULAR DYSTROPHY

- This is very different from BECKER'S disease which is:
  - It is a variant of myotonia congenita.
  - It is a Chloride channel defect.

Becker Muscular Dystrophy 00:46:38

- A Child will present by 10 years of age with symptoms and CPK MM value will be elevated
- By 25 years, the patient will be wheelchair-bound with CPK MM levels becoming normal due to muscle wasting.
- By 40 years the patient might die of congestive heart failure or pneumonia

Q. A child of 10 years of age is having issues with ambulation has large leg muscle. CPK MM value is normal. What is the Diagnosis?

Ans. Duchenne muscular dystrophy, not Becker Muscular dystrophy

- If, in the same question, the CPK MM value is elevated, then the answer is Becker Muscular Dystrophy

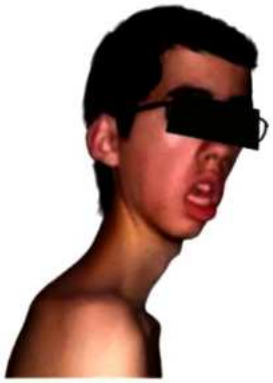
Extra mile

Child with large leg muscles and reduced dystrophin levels: BMD

Child with large leg muscles and *absent* dystrophin levels: DMD

Myotonic Dystrophy

00:51:26



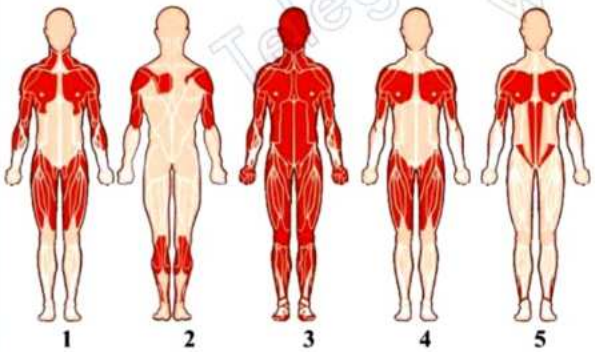
Clinical Features:

1. Tenting of the upper lip
2. Myopathic facies/Hatchet facies
3. Cataract: Christmas Tree Appearance
4. Cardiac Conduction defects
5. Type 2 Diabetes Mellitus

Important Information

Calf Muscle Weakness. Not PseudoHypertrophy.

- EMERY DREIFUSS
- Causing the patient to walk on his toes.
- Defect in protein EMERIN/LAMIN – X-Linked Recessive Disorder



Pattern of muscle involvement in Muscular Dystrophies

Diagram 1 is XLR	Neck muscle + forearm muscle involvement: Duchenne Muscular Dystrophy
Diagram 2 is XLR	Calf muscle weakness: Emery Dreifuss Muscular Dystrophy
Diagram 3	Gross paralysis: Congenital Muscular Dystrophy
Diagram 4 is AR	Axial Muscular involvement: Limb Girdle Muscular Muscular Dystrophy
Diagram 5	Weakness of muscle related to mouth(chewing) + Abdominal muscle + Chest muscle + Back muscle(winging of scapula): Facio scapula humeral dystrophy

Q. Patient: Adult female with GOWER sign, and skin Rash
Ans. Dermatomyositis

Q. Patient: Boy Calf muscle weakness with Toe walking
Ans. Emery-Dreifuss

Q. Only Axial musculature weakness
Ans. Limb- muscular dystrophy

Q. Chewing chewing muscle weakness plus winging of scapula
Ans. Facio scapula humeral dystrophy

Work up in any patient with gradual onset weakness:

1. Rule out electrolyte imbalance: Hypokalemia
2. Rule out neuropathy by Nerve Conduction Velocity
3. CPK MM levels as well as muscle biopsy if clinically indicated to elicit the problem of muscle
4. Antibodies Assay: Receptor blocking anti Ach antibodies
5. R.N.S test has a detrimental response in case Myasthenia gravis
6. EMG: Myopathic pattern vs Neuropathic pattern
7. Genetic studies for ruling out channelopathy and motor neuropathy
8. Autoimmune panel for Dermatomyositis/polymyositis

Extra mile:

Clinical Pointers in Dermatomysositis

- Gottron papules found on knuckles of the patient
- Heliotrope rash on upper eyelid of the patient
- Shawl sign seen on shoulder

Q. A patient having Asymmetrical distal weakness but no muscle pain and on Muscle biopsy, some inclusion bodies are found, then what is the diagnosis ?
Ans. Inclusion Body myositis

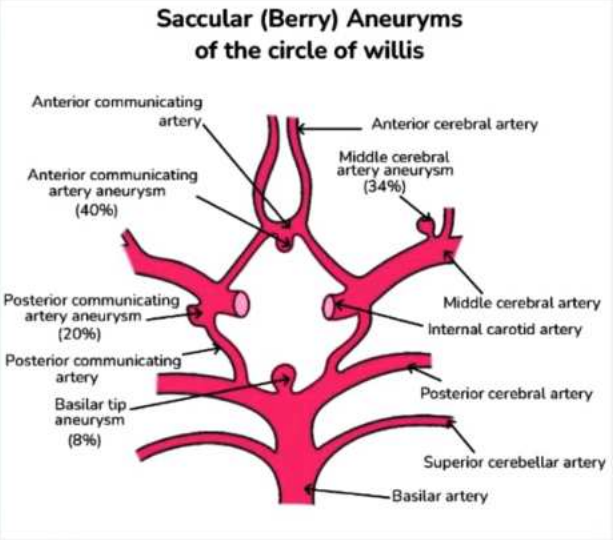
Q. A female present with Muscle pain but no muscle weakness. What could be the probable diagnosis?
Ans.

- Fibromyalgia
- Polymyalgia rheumatica

Q. A lady is 50 years old with frozen shoulder having stiffness and pain in Lower back /hip joint with increased ESR. CRP is Positive and NCV & CPK MM are Normal. What is the probable Diagnosis?

Ans. Polymyalgia Rheumatica

34 SUBARACHNOID HAEMORRHAGE



Causes

1. **Trauma:** MC
2. **Rupture of berry aneurysm**
3. **Arteriovenous malformation**
4. **Charcot Bouchard aneurysm**
5. **Extension of intracerebral haemorrhage: Hypertensive crisis**
6. **Mycotic aneurysm**
   - Complication seen with Subacute bacterial endocarditis
   - There is embolization of infection from the heart to the blood vessels of the brain

Site of Berry Aneurysm

- 85% of Berry aneurysm is found in Anterior circulation
- Leading site is the Anterior communicating artery where it meets the anterior cerebral artery.

Site of mycotic aneurysm

- Distal to the first bifurcation of the major arteries of the circle of willis.

Giant Aneurysm

- Size >2.5 cm
- Common site is the Terminal internal Carotid artery.
- Common sites:
  1. Terminal internal carotid artery
  2. Middle cerebral artery
  3. Top of basilar artery

Incidence of Rupture

- If Berry aneurysm size is >7mm:
  - The incidence of rupture increases.
  - The Berry aneurysm which has highest chances of rupture is located at the top of the basilar artery and contributes to severe brain stem ischemia.
  - Mortality rate with subarachnoid haemorrhage can increase up to 45%.
- Berry Aneurysm will rupture at the dome and tear occurs.
- Microleaks are present before the actual rupture causing headache known as Sentinel headache.
  - It is a severe excruciating headache having a duration of few seconds to a minute and then goes away.
  - After few days of Sentinel headache, the Berry bursts causing Classical Thunderclap Headache.
- The layer of blood vessel which is defective in this condition is the Internal elastic Lamina.

Thunderclap Headache

- It reaches peak intensity within 1min of onset

Case Scenario: A young female working on a laptop or watching TV develops excruciating headache. She has multiple episodes of vomitting: On examination nuchal Rigidity is noted. Diagnosis: SAH

- **Causes of Thunderclap Headache**

1. Subarachnoid haemorrhage
2. Post coital headache.
3. Exertional headache
4. Benign cough headache
5. Intracerebral haemorrhage
6. Migraine
7. Hypophyseal apoplexy
   → Bleeding in the pituitary
   → Bleeding in the meninges
   → Brain haemorrhage
8. Dissection of cerebral vessel
9. Segmental reversible vasospasm

- Features based on location of Berry Aneurysm:

1. If the Site is Anterior communicating artery, then features will be related to speech deficits.
   - This blood vessel is related to the frontal lobe and its blood supply damage causes Abulia.
   - Aphasia may also occur: Broca's aphasia
   - The blood supply to the corticospinal cord can be also be

hampered. So, it can also result in Hemiparesis.

2. If the berry aneurysm is present in posterior communicating artery, as the Oculomotor nerve is present in close vicinity, 3rd nerve palsy may occur with respect to berry aneurysm.

Q. What is the Most common Cranial nerve involved in an unruptured berry?

Ans: Oculomotor nerve.

Q. What is the Most common Cranial nerve involved in ruptured berry?

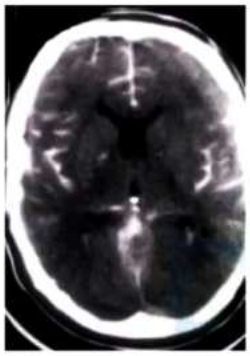
Ans: 3rd nerve palsy

- Both unruptured and ruptured Berry aneurysm lead to 3rd nerve palsy.
- But as the 6th nerve has the longest subarachnoid course, later when the pressure in brain raises, it causes stretching of the 6th nerve contributing to 6th nerve palsy.
- 3rd nerve palsy would lead to loss of light reflex and retro orbital pain.

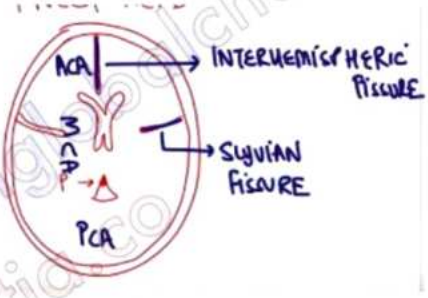
3. If berry aneurysm involves internal carotid artery while it transverses the cavernous sinus multiple cranial nerves can be involved
   - 3^{rd},4^{th},5^{th} cranial nerves are present laterally.
   - The 6^{th} nerve is a free-floating structure, Which when involved will cause diplopia occurring on looking laterally.
   - In case of Raised ICT, As the problem is not in the 6th nerve but in the Subarachnoid space, it is called a False Localising Sign.
4. If berry is present in posterior inferior cerebellar artery(PICA) or anterior inferior cerebellar artery(AICA):
   - PICA is a branch of vertebral artery.
   - AICA is a branch of basilar artery.
   - Clinical Features include Occipital headache or cervical headache.
5. Risk of seizures in SAH
   - The Seizures occurring are due to increased levels of B type natriuretic peptide, that causes urinary sodium loss.
   - So, patients will have severe hyponatremia. (Normal sodium: 135-145 meq)
   - If Na gets <125 meq, it contributes to development of dyselectrolytemia and seizures.

- Posturing might be misinterpreted as patient having convulsions.
  - Posturing indicates brain herniation and rising ICT.
- Sentinel headache history may or may not be elicited.

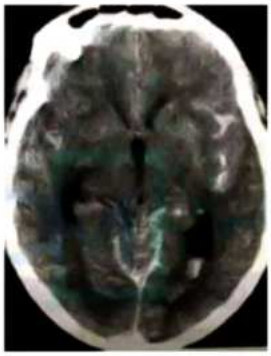
Work Up



1. Non contrast CT head
   - Patients, Presence of blood in sylvian fissure.



   - Blood can also be present in inter hemispheric fissure.
   - The arteries involved are Anterior cerebral artery and distribution of the Middle cerebral artery.
   - Sylvian fissure, the source of bleeding is MCA.



2. **Lumbar puncture findings of the patient**
   - Bloody CSF is seen.
   - Rule out traumatic lumbar puncture.

- Xanthochromic CSF
  - RBC lysis Produces bilirubin and gives yellow colour to CSF.
  - It starts after 6-12 hours of bleed
  - The peak is obtained in 48 hours.

Normal CSF | Xanthochromic CSF

3. **CT Angiography / Four vessel Conventional Angiography**
   - To identify any other Aneurysm which could be present in the patient.
   - Either CT Angiography or Four vessel conventional X-Ray Angiography is done.
4. **ECG**
   - Due to the presence of excess catecholamines which may contribute to myocardial ischemia.
     A. ST depression and T wave inversion are seen.
     B. Peaked T waves may also be seen.
     C. QT prolongation
     D. Broad QRS complex
5. **Serum Electrolytes**
6. Echocardiography
   - Presence of regional wall abnormalities will be seen due to myocardial ischemia
   - LVH, as some patients are already hypertensive.

- Hypertension may also cause CNS bleeding.

Hunt Hess Scale & World Federation of Neurosurgical Society (WFNS)

- Helps in grading the severity of headaches.

Hunt Hess Scale	Grade	WFNS	Description
Mild headache	1	GCS 15	No motor deficits
Severe headache	2	GCS 13-14	No motor deficits
Somnolent, confused	3	GCS 13-14	Motor deficits
Stupor	4	GCS 7-12	With or without motor deficit
Comatose	5	GCS 3-6	With or without deficit

- The scoring helps the doctor to evaluate the patient to check out the deterioration.
  - After 24-48 hours, the patient can worsen due to spasm of the surrounding blood vessels, called delayed cerebral ischemia.

Delayed Neurological Deficits seen in SAH

1. Rebleeding
   - Strict bed rest is required.
   - Loud laughing, straining must be avoided during urination and defecation.
2. Development of hydrocephalus
   - Ventriculostomy is done to prevent it.
3. Cerebral ischemia/ vasospasm
   - Leading cause of neurological deterioration and death.
   - Occurs usually after 24 hours.
4. Hyponatremia
   - Secondary to BNP release
   - It is also known as Cerebral salt wasting syndrome
5. CVS: Myocardial ischemia or myocardial infarction can develop in patient.

Treatment of Subarachnoid Haemorrhage

The main aim of treatment is Early Aneurysmal Repair to minimise the chances of rebleeding.

- **Endovascular Coiling:** An access from femoral artery is taken and a platinum coil inside the berry aneurysm or any AV malformation in the brain is introduced.
  - **It is then** packed up in the platinum coil which prevents the berry from rupturing.
  - It also reduces the incidence of subarachnoid haemorrhage.
  - It would also be done for Co-existing unruptured Saccular Aneurysm that may be present in same patient on opposite side.
- **Aneurysmal clip**
  - It is done to prevent aneurysm from bursting
  - Craniotomy is required to be done for putting aneurysmal clip.
  - So, Neurosurgical morbidity is increased.
  - As it is a ferromagnetic device, MRI can't be done again

Medical Management

Objectives:

1. Airway Protection: To minimise the chances of Aspiration and Elective Hyperventilation can be done, if necessary to lower the raise ICP
2. BP Control: It is done before and after the aneurysmal treatment.
3. Management of Vasospasm
4. Management of Hydrocephalus
5. Correction of Hyponatremia

Cerebral perfusion pressure = mean arterial pressure - intracranial pressure

6. Management of Pulmonary embolism

- If mean arterial pressure is decreased, then perfusion pressure of the brain also gets reduced.
- So, the target is to maintain cerebral perfusion pressure between 60-70 mmHg.
  - If the patient is comatose, Ventriculostomy/EVD can be done.
  - If SBP is high, Target blood pressure to be achieved is 160 mm of Hg.
    → IV Nicardipine is used.
    → Labetalol, Esmolol can also be used.
    → But Sodium nitroprusside is not recommended.
  - If the patient develops seizures, Anticonvulsants are to be used.
  - To prevent Delayed Cerebral Ischemia/ Vasospasm, which is the main cause of mortality & morbidity Nimodipine should be started at 60mg 4hourly PO.
  - Euvolemia should be targeted with IVF and Norepinephrine or Phenylephrine if required.
  - If DCI persists in spite of treatment, Direct Angioplasty can be done.
  - For prevention of pulmonary embolism, Pneumatic Compression Stockings

- **Contraindications in management of SAH**
  1. Heparin: It is not used as it increases the risk of rebleeding.
  2. Free water restriction
- **Not useful in SAH:**
  1. I/A Papaverine
  2. Steroids
  3. Anti-Fibrinolytics

MCQ

Q1. Patient presents with BP of 160/110 mmhg & on CT head SAH is detected. What is the next step in management of this patient?

A. Nimodipine
B. Conventional angiography for aneurysm
C. Urgent surgical intervention
D. Mannitol

Ans. B

Q2. Not required in management of SAH?

A. Pneumatic compression stockings
B. Fluid restriction
C. Nimodipine
D. Esmolol

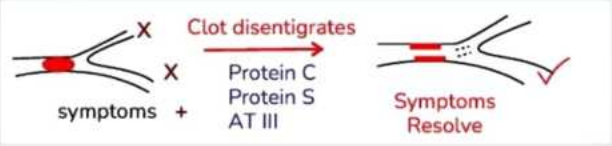
Ans. B

16 TRANSIENT ISCHEMIC ATTACK AND STROKE INTERVENTIONS

Introduction 00:00:13

FAST

- **F** -sudden onset Facial weakness
- **A** -Arm weakness
- **S** - Speech deficit
- **T** - Time is neurons (more delay does more damage to neurons)



- In transient ischemic attack usually Improvement begins in 1st hour
- If there is no improvement, it might be progressing to stroke
- Cut off for TIA <24 hours
- Imaging: normal

Case Scenarios based on Artery involved:

- 60-year-old male
  - Smoker/HTN: non-compliant for Medication
  - Ophthalmic artery blockage: Transient blindness called as amaurosis fugax
  - Middle cerebral artery thrombus: Contralateral Arm weakness, face weakness and aphasia
    → Resolution of symptoms 1 to 24 hours, cut off <24 hours
  - Anterior cerebral artery: Paraparesis
  - Vertebral artery thrombus: Nasal regurgitation of fluids/Nasal twang voice
  - Pins and needles
- Patient with TIA can develop stroke anytime but high chances in next 48 hours.

$ABCD_2$ SCORE: Used to predict / chances of stroke development 00:13:20

1. Age should be more than 60 years: 1 point
2. BP more than 140/90 mmhg: 1 point
3. Clinical feature: Arm weakness: 2 points
4. Aphasia: 1 point
5. Duration: <10 minutes: 0 points
   - 10-59 minutes: 1 point
   - >60 minutes: 2 points
6. Diabetes mellitus: yes/no, 1/0 points, respectively.

- Maximum score possible = 7, 22% chances of developing stroke in next 48 hours.

Work up 00:17:05

1. ECG: Rule out atrial fibrillation: clots leading to cardio-embolism
2. ECHO: Transthoracic Echocardiography / Transesophageal echocardiography: Rule out mural thrombus
3. Carotid Artery doppler to rule out atherosclerotic narrowing of carotid Artery.
4. Lipid profile
5. Homocysteine levels

Treatment

1. DAPT (Dual Anti Platelet Therapy)- Tab. Aspirin Clopidogrel / Ticagrelor
   - Resistance to clopidogrel: CYP2C19, polymorphism
2. Atorvastatin: high intensity 40/80mg
3. Vitamin B6/B9/B12
4. Evidence of LA thrombus due to Non Rheumatic etiology then use NOAC: Rivoxaban (factor X inhibitor), Dabigatran (direct thrombin inhibitor)

Case scenario 00:24:42

- A 60-year-old HTN / Smoker gets up to get ready for morning walk at 6 am
- At 6:30 am there occurs sudden onset: Aphasia, along with right arm weakness.
- At 7:30 am he is brought to Hospital

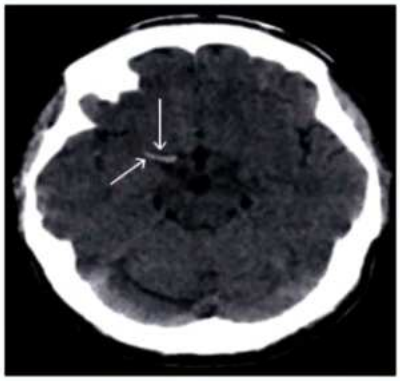
Activate the stroke protocol

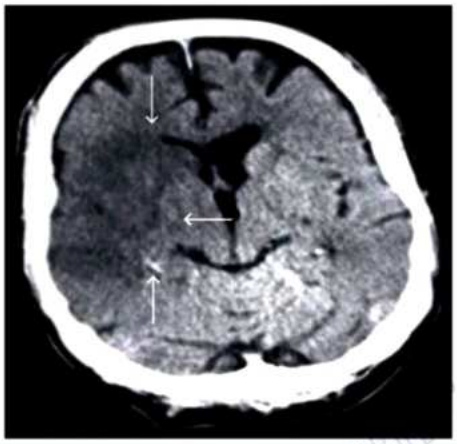
1. Assess airway, BP, establish time the person was seen normal
2. NIHSS: >5; eligible for IV Plasma activators, endovascular therapy
3. Neuroimaging: Door to CT scan: <25 minutes of arrival
4. On examination: Focal neurological deficit findings: present
   - 7: 50am = NCCT HEAD
   - 8:15 am = NCCT head interpretation time (under 45 minutes)

Two possibilities can occur on CT scan 00:29:37

- Hypodensity
- Hyper density

Acute ischemic stroke (hypodense)





- Initially normal
- Then Dense MCA sign
- Hypodensity takes time to develop

Management

1 Airway, BP control
2 Random Blood Sugar values
   - <60mg%,
   - >200mg%
3 Thrombolysis: *Likely* benefit: <4.5 hrs *Possible* benefit: <6 hrs
4 Not a candidate for Thrombolysis or failed recanalization of occluded vessel: initial 6 hrs then, next investigation done is CT angiography is done (from left atrium to skull base)

↓

Thrombus or occlusion in ICA, M1M2 branches of middle cerebral artery or in Basilar artery.

↓

Perfom Thrombectomy

↓

Thrombectomy

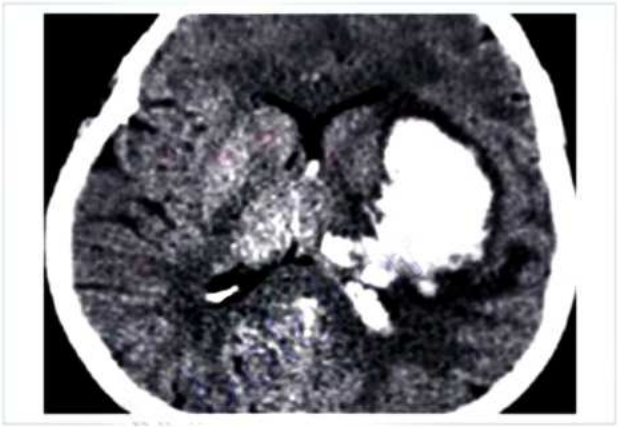
↓

6-24 hrs of stroke onset:
CT no evidence of hemorrhage
CTA/CTP

↓

ICA/M1M2/Basilar artery occlusion

Hemorrhagic stroke (hyperdense)



- BP increased ++
- Deficit increasing gradually
- Decreased level of consciousness
- MC site: putamen

Treatment

- Osmotherapy
- Ventriculostomy
- Hemicraniectomy
- Nicardipine, labetalol

Thrombolysis Indications 00:40:26

1. NIHSS>5: clinical stroke
2. Age > 18 yrs
3. Onset of symptoms < 4.5 hrs time of drug given
4. CT scan: no hemorrhage or edema for >1/3rd MCA territory

Contraindicated in: Mnemonic: STORM

- Sustained BP> 185/110 mmhg despite treatment
- Bleeding diathesis, INR 1.7
- Gastrointestinal bleeding: <21 days(last)
- Recent head injury/ICH
- MI recent
- Major surgery in last 14 days

Etiology for development of stroke

- **Hemorrhagic:** 15 % incidence

1. HTN, Trauma
2. Warfarin toxicity: Prothrombin complex concentrate>Fresh frozen plasma
3. Dabigatran toxicity: Idarucizumab

4. Cerebral amyloid angiopathy: spontaneous ICH in 80 year old man who is non diabetic, non hypertensive

- **Ischemic: 85%**

1. **Most common**: Non-rheumatic atrial fibrillation,
2. Paradoxical embolism

DVT→ IVC→RA→RV→PA

↓

PFO: an opening between RA & LA known as patent fossa ovalis: bubble contrast echocardiography

↓

LA→LV→AORTA→BRAIN

3. Carotid artery atherosclerosis (surgery for this is carotid endarterectomy, but now endovascular stenting is used more)
4. Cerebral artery thrombosis: Atherosclerosis, Thrombotic cytopenic purpura, Tet spell
5. Genetic cause:
   - CADASIL: Cerebral Autosomal Dominant Arteriopathy with subcortical infarcts
   - Notch 3 gene involved
   - Type of small vessel stroke
   - In younger age, these patients have migraine like illness with aura
     → Weakness
     → Dementia
     → Brisk dtr

Medical care in case of AIS 00:54:55

1. IV Reteplase: dose 0.9mg/kg (max) = 90mg (Tenecteplase can be used)
2. BP monitoring
   - If candidate for thrombolysis: Lower the BP < $\frac{185}{100}$ mmHg
   - Not a candidate: Threshold for lowering if BP >220/130 mmHg
3. No antithrombotic for 24 hours
4. If a patient undergoing Thrombolysis has Worsening of symptoms: Low GCS: Stop infusion give cryoprecipitate
5. Cerebral edema in case of Acute ischemic stroke

- Cytotoxic cerebral edema
- Seen on day 2
- Mass effect day 10: Malignant cerebral edema
- Manage with Mannitol / Hemicraniectomy

ICH Score: To be calculated in Hemorrhagic stroke 01:02:24

Age	<80 year	>80 year	
Hematoma volume	<30cc	>30cc	
Intraventricular Hemmorhage	NO	YES	
Infratentorial	NO	YES	
GCS	13-15	5-12	3-4
	0	1	2

Toxicity Antidote:

- VKA/ Warfarin: PCC
- NOAC: IDARUCIZUMAB

Cerebral Venous Thrombosis 01:05:36

- Involvement of sagittal sinus/ Lateral sinus

Causes

1. OCP/ Pregnancy/ Post-partum/protein C/S/AT III decreased
2. Factor V leiden mutation (protein C resistance)
3. Prothrombin G 20210 mutation
4. APAS, polycythemia

Clinical feature

1. Headache
2. Seizure
3. Paraplegia
4. Increased ICP
5. COMA

Work up

1. NCCT head: Normal or empty delta sign
2. Investigation of choice: Magnetic resonance venography

Treatment

- Heparin IV and later start warfarin, 3-6 months
- Aspirin

35 SYSTEMIC LUPUS ERYTHEMATOSUS

Introduction

00:00:13

- Selena Gomez developed active SLE
- Progressed to lupus nephritis and had to Undergo kidney transplantation
- Most common cause of death in active SLE in the first decade- Renal failure [pg 2740: Harrison 21st edition]
- If not active SLE - Cause of death - infections
  - This can be explained by use of potent Immuno suppressants used in treating flare ups of SLE
- Female : Male Ratio = 9:1

Important Information

Skewed female to male ratio in
1. Takayasu arteritis - (Cause of renal artery stenosis)
2. SJOGREN - SICCA syndrome - Dry eyes and Dry mouth
3. SLE

- Severity of SLE directly related to the number of X chromosomes
- Suppose there are four patients
  - Turner with SLE 45XO
  - Klinefelter with SLE
  - Edward syndrome with SLE
  - Down's syndrome with SLE
- Klinefelter's with SLE will be more severe - 47XXY - as there are more number of X chromosomes

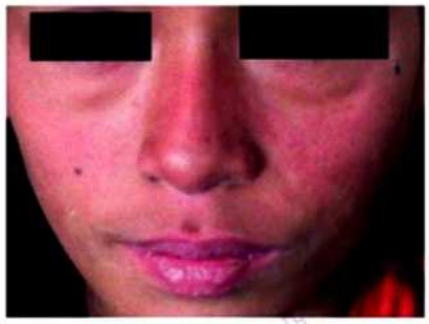
Most common presentation

00:03:36

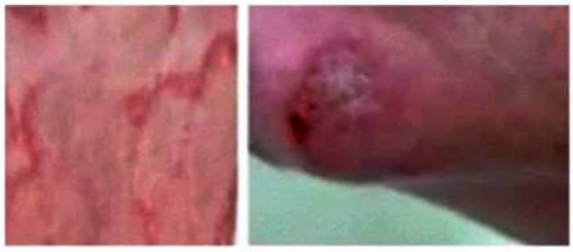
- Musculoskeletal manifestation - pain-along with fever, pg 2741, Harrison 21st
- Hematological - Anemia
- Subsequently - Skin manifestations

Acute, Subacute, Cutaneous LE

- Malar rash
  - → Malar flush is a Presentation with mitral stenosis, not to be confused for malar rash



- Butterfly rash
  - Erythematous rash on cheek involving bridge of nose
  - Nasolabial folds are spared
- All rashes in SLE shows Photosensitivity
  - Burning sensation persists even after sun exposure and coming under shade
- Malar rash as it is seen on Malar eminence
- Erythematous rash with raised margin
- Also seen on Hands and V of neck
  - Do not confuse with Seborrheic dermatitis
  - In Seborrheic dermatitis -yellow greasy flakes that peel off are seen
  - And they begin from nasolabial folds



- **Subacute cutaneous lupus erythematosus**
  - Psoriasis like lesions
- Discoid lupus - circular lesion
  - Periphery - erythematous
  - Center - scarring - atrophic scarring
    - → Dermal appendages are lost
    - → May be confused for Fungal infection
    - → But fungal infections show central clearing
- Atrophic scarring seen in discoid lupus but non-scarring alopecia is associated with SLE
- Non scarring alopecia
- **ACR 2019** - diagnostic criteria that has higher sensitivity and specificity

Autoantibodies 00:09:44

1. **ANA**
- 98 % sensitivity
- Most sensitive
- Not only positive in SLE but also in:
  1. Scleroderma
  2. Sjogren's syndrome

Important Information
- Do not confuse with AMA
- Antimitochondrial antibody-is seen in primary biliary cirrhosis

2. **Anti smith antibody**
- Most specific

3. **Anti ds DNA**
- As SLE is Autoimmune -it shows waxing and waning course
- The value of Anti ds DNA tends to correlate with disease activity
- Anti ds DNA Value can be used to check if SLE worsens / gets better during pregnancy
- And to see response when treating with steroids

4. **Anti Ro antibody/anti-SS-A antibody**
- Antibody responsible for photosensitivity
- Acute, subacute, chronic, psoriatiform or discoid-all rash in SLE shows photosensitivity
- All lesions worsen with sunlight
- Anti Ro can spread Transplacentally
  - Causes Damage to AV node in fetus
  - This causes SA node to control atria
  - Bundle of his control ventricle
- Leads to Complete heart block
- Fetus develop Neonatal Lupus
  - Severe bradycardia at birth
    → As Bundle of His can fire 15 - 30 / minute only
  - Child develops Syncope
- Treatment: Pacemaker
- Usually goes undiagnosed and child may not survive
- Anti Ro antibody - also seen in SICCA syndrome

5. **Anti Lupus anticoagulant/anti SS- B antibody**
- Decreased risk of nephritis

6. **Anti Histone antibody**
- Drug induced lupus
- Will not develop lupus nephritis or Lupus cerebritis
- Prognosis is better
- Once drug is discontinued→ after 8 weeks→ resolve on its own
- Drugs
  - Sulfa drug
  - Hydralazine
  - Isoniazid
  - Procainamide (used in WPW, LGL)

7. **APLA - Antiphospholipid antibody syndrome**
- Anti Cardiolipin Antibody
- Anti β-2 glycoprotein antibody
- Lupus anticoagulant
  - Young lady with recurrent abortions > 3 consecutive abortions
  - History of absent fetal movements in third trimester → IUD in previous pregnancy
  - Work up in such cases of BOH -Bad obstetric history - includes - VDRL false +
  - Antibody that cause cross reaction with VDRL kit
  - These antibodies trigger Uterine artery / Venous thrombosis → fetoplacental insufficiency → IUD
  - Without trauma, autoantibodies cause activation of intrinsic system of clotting mechanism
- APLA syndrome
  - Dilute Russell viper venom time test - DRVVT

8. **Anti erythrocyte antibody**
- RBC's destroyed
- Common anemia in SLE - anemia of chronic disease
- But autoimmune hemolytic anemia can also occur

9. **Antiplatelet antibody**
- Thrombocytopenia
- Petechiae around ankles

10. **Anti neuronal antibody**
- Cross BBB
- Cause Cerebral edema

11. **Anti Glutamate receptor antibody**

12. **Anti Ribosomal P antibody**
- Cause psychosis

Important Information
- Anti ribonucleoprotein antibody (RNP)- related to Mixed connective tissue disorder (MCTD).

Clinical features 00:27:59
- **MD SOAS BRAIN**
- **M - Malar Rash Sparing Nasolabial Fold**

Important Information
- In Seborrheic dermatitis, nasolabial folds are involved
- Lupus pernio
  - Cutaneous manifestation of sarcoidosis-also involve face
  - But are associated with Massive Hilar Lymphadenopathy
  - Breathlessness and stridor

→ Psoriasis like lesions
→ Shows Photosensitivity
- **D - Discoid lupus erythematosus**
  - Periphery - Hyperpigmented, Erythematous
  - Center- Atrophic scarring, dermal appendages will be lost

- Alopecia - Non scarring alopecia
- Discoid - Rash central scarring

- **S- Serositis**
  - Affects lung and heart

Lung	Cardiac
• Pleuritis → pleural effusion (most common)	• Pericarditis → effusion (most common) • Echo- Bag of water appearance in pericardial effusion
• Shrinking lung syndrome (least common) • Timed vital capacity ↑	• Libman sacks endocarditis (least common)
• Pleuritic chest pain - worsens with inspiration	• ECG: ST elevation - Concave upwards

Libman sacks endocarditis

- Sterile vegetations - Fibrin deposits
- Predominantly on inferior surface involvement
- In Libman-Sacks - malfunction of chordae tendineae leads to hampering of valve integrity
- This leads to Mitral regurgitation
- Only symptomatic mitral regurgitation needs intervention.
- Steroid will not treat the pulmonary edema in this case as it is due to leakage of blood
- Valvuloplasty is the treatment of symptomatic MR.

- **O - Oral aphthous ulcers**
  - Also seen in Stress
  - due to Constipation
  - Idiopathic: Usually resolves with Topical benzocaine jelly
  - In SLE aphthous ulcers are
    - → Recurrent
    - → There may be crops of aphthous ulcers
      - Some develop and resolve and then come again in the same side or opposite side
    - → It is usually Painless
    - → Recurrent aphthous ulcer and recurrent vulval ulcers that are painful is presentation of Behcet's disease
- **A - Alopecia - non scarring**
- **S - Synovitis**
  - Joint pain
  - Most common presentation of disease
  - Associated with Low grade fever
  - ≥ 2 joints
  - Could be small or large
  - Symmetrical or Asymmetrical
  - Intermittent polyarthritis
  - Tenderness
  - Soft tissue swelling
    - → Patient could complain of knee joint pain one day and the next day complains of elbow or wrist joint pain
  - Joint deformities develop in only 10% cases [pg 2740: Harrison 21st edition]
    - → Also in rheumatic fever, arthritis is non erosive
  - Deformities can occur - but are rare

Important Information

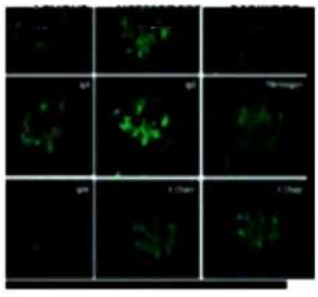
Rheumatoid Arthritis
- Involve small joints
- Bilaterally Symmetrical
- Erosive arthritis

Rhupus = Rheumatoid Arthritis + SLE
- Rheumatoid Arthritis can coexist with multiple autoimmune diseases
- Like SLE or Sicca syndrome

Secondary Sicca or secondary Sjogren syndrome
- Dry eyes and dry mouth with joint involvement
- Pain is severe

- **B - CNS involvement**
  - Most common CNS manifestation - Cognitive defects
  - Lupus cerebritis
    - → Antineuronal Antibody - cerebral edema
    - → Headache and seizures
    - → Dexamethasone reduces cerebral edema
  - Psychotic features : Anti Ribosomal P antibody
- **R - Renal involvement**
  - Lupus nephritis
  - Contribute to mortality
  - Hematuria - Cola colored urine
  - Hypertension
  - ESRD - End Stage Renal Disease
    - → Uremia
    - → Hyperkalemia
    - → Metabolic acidosis
  - Work up-Urine microscopy
    - → hematuria - RBC > 5/ hpf
    - → dysmorphic RBC due to glomerular damage
    - → RBC in normal urine - 3-5/hpf
    - → Freshly passed urine when centrifuged
    - → sediment contain RBCs
  - C3 low
  - Creatinine ↑
  - BUN ↑

Important Information



- 6 stages of Lupus Nephritis
- Most common - Stage 4
  - Diffuse lupus nephritis > 50 % of glomeruli are damaged
  - IF - IgG/A/M
  - C3 ,C1 deposited
  - Since many type of antibodies are deposited, it is called Full house effect like in game of cards

- **A - Anemia**
  - Commonly in SLE - Anemia of chronic disease
  - Normocytic normochromic anemia
  - Other causes of anemia - autoimmune hemolytic anemia
    - → Antibodies against erythropoietin and erythropoietin receptor
      - Enhanced clearance of erythropoietin
      - Impaired response of erythropoietin - antibody act against receptor
    - → Antibody destroy RBCs
  - Peripheral smear - Some RBCs seen without central pallor and smaller in size - Spherocytes

Spherocytes are seen in any Type of Autoimmune hemolytic anemia
- If a 2 year old girl comes with history of progressive anemia , splenomegaly , presence of spherocytes in peripheral smear → think of Hereditary spherocytosis
- If a 25 year old female with progressive anemia and Peripheral smear shows spherocytes : Autoimmune hemolytic anemia
  - Steroids are the mainstay of treatment in such patients
  - Packed RBCs may worsen the condition
  - More RBCs will be destroyed by pre-existing Antibodies.
  - Patient may even develop Jaundice

Important Information

Steroids not recommended in
1. Symptomatic mitral regurgitation due to Libman sacks endocarditis
2. Photosensitivity
   - Anti Ro antibody +
   - Drug for photosensitivity - Hydroxychloroquine
   - Hydroxychloroquine also given if patients plans to conceive or is pregnant
   - Hydroxychloroquine was used in COVID-19
3. End stage renal disease
   - Uremia - hemodialysis or preferably transplantation-to prevent recurrence of Uremia manifestations
4. Psychotic manifestations - Steroids themselves cause psychosis.

- **I - Immunological**
  - Antibodies
  - Anti Smith antibody - most specific
  - Anti ds DNA =course and progression of disease
  - Low C3 and C4
- **N - antinuclear antibody**

Criteria for diagnosis 00:56:42

1. Malar rash - acute SLE rash
- psoriatiform or discoid
- Photosensitivity
2. Discoid lupus erythematosus
3. Serositis - pleuritis and pericarditis
4. Oral aphthous ulcers - painless
5. Non scarring alopecia
6. Synovitis
   - ≥2 joints - intermittent polyarthritis
7. Brain - cognition defects, psychotic
8. Renal - Lupus Nephritis or ESRD
9. Anemia - Anemia of chronic disease , Autoimmune hemolytic anemia
- Autoantibody damage self WBCs → Leukopenia
- And platelets → thrombocytopenia
10. Immunological
- Direct coombs test
- Positive in AIHA
- Anti smith antibody
- ANA
- Lupus anticoagulant
- ELISA Anticardiolipin - ACL - give false positive VDRL
- Anti β-2 Glycoprotein
- Low C3 and C4
- TOTAL 4 + features
- At least 1 clinical and 1 immunological feature
- E,g. Joint pain anemia and malar rash and ANA positive
- One clinical + 3 immunological

Refer Table 35.1

- Chronic cutaneous - discoid rash - face and chin
- Glomerulonephritis - biopsy + for diffuse lupus nephritis → SLE

Latest ACR criteria - 2019

- Includes Fever
- Criteria are almost same
- Highest weightage for renal biopsy - 10 points
- Take highest rating from each if more than 1 are present under one category like Hematological or Neurological or Cutaneous
- Diagnosis of SLE = Total score >10 with ANA +
- DOC of SLE in pregnancy - hydroxychloroquine
- Steroids not given, as they are deactivated by placental enzymes
- Hydroxychloroquine-given in Photosensitivity and Pregnancy
- Cause of death
  - Early years after diagnosis - highly potents steroids cause immunosuppression and life threatening infections
  - Active lupus - renal failure
  - >45 years - Accelerated atherosclerosis
- Fetus
  - IUD / abortion - anti β_2 Glycoprotein, Anticardiolipin, Lupus anticoagulant
  - Complete heart block - Anti Ro and Anti SS-A

Frequency (%) of autoantibodies in rheumatic diseases

Refer Table 35.2

- ANA+
  - SLE
  - Sjogrens
  - Sarcoidosis

Antiphospholipid Syndrome Criteria (Sydney revision of Sapporo criteria 2006)

Clinical criteria	Lab criteria
1. Vascular thrombosis 2. Pregnancy Morbidity a. Death of normal fetus at ≥ 10 wks b. Premature birth at ≤ 34 wks due to preeclampsia c. 3 consecutive abortions at < 10 wks d. Placental insufficiency at < 34 wks	1. Anti-Cardiolipin IgG/IgM 2. Anti-beta-2 glycoprotein 1 (GP1) 3. Lupus anticoagulant (LAC) • Medium to - high titer • At least X 2 times • 12 wks apart

Cause of death in SLE [Source :CMDT]

- Early years - infections
- Active SLE - renal failure
- >45 years - accelerated atherosclerosis

APLA syndrome criteria

- Primary = without SLE
- Secondary = Coexist With SLE
- Sydney revision of Sapporo criteria
  - Vascular thrombosis
    → MI, stroke
    → Low dose aspirin taken lifelong
  - Pregnancy morbidity- IUD/ abortion due to placental insufficiency
  - Lab values of Anti β-2 glycoprotein, anticardiolipin , lupus anticoagulant
    → Elevated 2 times 12 weeks apart Shows False positive VDRL
- Catastrophic - 3 body system affected serially
  - Brain, heart and kidney

Table 35.1

Additive criteria Do not count a criterion if there is a more likely explanation than SLE. Occurrence of a criterion on at least one occasion is sufficient. SLE classification requires at least one clinical criterion and ≥ 10 points. Criteria need not occur simultaneously. Within each domain, only the highest weighted criterion is counted toward the total score			
Clinical domains and criteria	**Weight**	**Immunology domains and criteria**	**Weight**
Constitutional Fever	2	Antiphospholipid antibodies Anti-cardiolipin antibodies OR Anti-β2GP1 antibodies OR Lupus anticoagulant	2
Hematologic Leukopenia Thrombocytopenia Autoimmune hemolysis	3 4 4	Complement proteins Low C3 OR low C4 Low C3 AND low C4	3 4
Neuropsychiatric Delirium Psychosis Seizure	2 3 5	SLE: Specific antibodies Anti-dsDNA antibody* OR Anti-Smith antibody	6
Mucocutaneous Non-scarring alopecia Oral ulcers Subacute cutaneous OR discoid lupus Acute cutaneous lupus	2 2 4 6		
Serosal Pleural or pericardial effusion Acute Pericarditis	5 6		

Table 35.2

	ANA	Anti- Native DNA	Rheumatoid Factor	Anti -Sm	Anti-SS-A	Anti-SS-B	Anti-SCL-70	Anti-Centromere	Anti Jo-1	ANCA
Rheumatoid arthritis	30-60	0-5	70	0	0-5	0-2	0	0	0	0
Systemic lupus erythematosus	95-100	60	20	10-25	15-20	5-20	0	0	0	0-1
Sjogren syndrome	95	0	75	0	65	65	0	0	0	0
Diffuse scleroderma	> 95	0	30	0	0	0	33	1	0	0
Limited scleroderma (CREST syndrome)	> 95	0	30	0	0	0	20	50	0	0
Polymyositis/ dermatomyositis	80	0	33	0	0	0	0	0	20-30	0
Granulomatosis with polyangiitis	0-15	0	50	0	0	0	0	0	0	93-96[1]

36 RHEUMATOID ARTHRITIS

Rheumatoid Arthritis

Rheumatic Arthritis Vs Rheumatoid Arthritis

- Rheumatic is non-erosive, and Rheumatoid Arthritis is erosive. In the later stages, RA can lead to Periarticular Osteoporosis

Clinical manifestations

00:00:41

- Auto-immune disease which is seen more common in women (25 to 55 age group or post- menopausal women)

Clinical features

1. Involvement of Small joints of the hand: PIP, MCP and wrist joint.
2. Bilaterally symmetrical involvement.
   - The patient will describe inflamed joints, pain , tenderness and redness especially in morning Hours.
   - This is bilaterally symmetrical in contrast to rheumatic arthritis, seen due to Group A beta-hemolytic streptococcus which leads to Migratory polyarthritis in large joints.
3. The range of movement will be affected.
4. Morning stiffness which might persist for an hour, and as the day progresses, the manifestations will subsequently reduce.
   - Symptoms of such patients decrease with painkillers but also with activity.

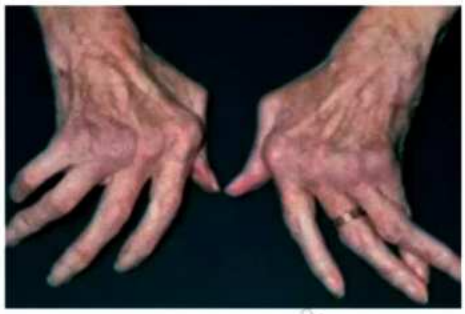
Important Information

It is important to count how many groups of joints are involved because,

- If less than 4 joints are involved, then it is Oligoarticular arthritis.
- But if it is at least 5 or more than 5, then it can be Polyarticular arthritis.
  - This is not the final diagnosis, but under the condition the patient has a positive RA factor and positive Anti-cyclic citrullinated peptide, it can be called polyarticular arthritis.

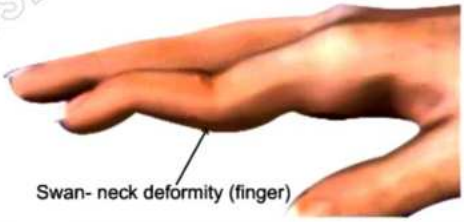
5. Hallmark presentation

- Flexor Tenosynovitis
- The early manifestation or the hallmark manifestation of the disease is that the Grip strength will reduce.
- The muscle strength will be normal
- A trigger finger can be related to this as well.



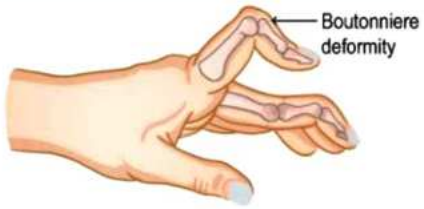
Erosive arthritis of Rheumatoid Arthritis

- Two things can be noticed
  - Ulnar deviation of the hand
  - Deformation of hands and fingers, including deformity in the thumb that is known as z-line deformity.
  - Rheumatic is an example of non-erosive arthritis.
  - Rheumatoid is erosive, there will be pannus formation, and damage to the cartilage, in later stages the bones can also be affected.



Swan-neck Deformity (finger)

- While looking at the DIP (Distal interphalangeal joint) and PIP (Proximal inter-phalangeal joint), an extension at PIP can be noticed.
- Near the DIP, there is a flexion.



Boutonniere Deformity

Here, the PIP has a flexion and an extension in the DIP

It is important to note than a person can have both a Swan-neck

Deformity and a Boutonniere Deformity in the same hand in different fingers.


Mallet Finger

Mallet Finger

- Here there is no extension at the PIP
- There is flexion at DIP
- Mallet finger is due to the avulsion of the extensor tendon related to the DIP.
- When a person needs to grab a ball, there might be a possibility that there might be an avulsion of the tendon related to the DIP.
- Therefore, a flexion defect may be occurring.
- Mallet's finger is more common in sportspersons like goalkeepers or wicketkeepers.

Z line deformity

- There are 3 features of Z line deformity:
  1. Subluxation of the First metacarpophalangeal joint
  2. Subluxation of Distal radio ulnar joint
  3. Hyperextension of the Interphalangeal joint

Joints of the feet involved in Rheumatoid Arthritis

- First Metatarsophalangeal joint is involved
- Flat foot or Pes planus
- Cervical spine is extremely vulnerable.
- Cervical spine is in patients who have Rheumatoid arthritis.
- Practicing yoga can help, because it helps release endorphins. These endorphins can reduce the pain component.
- Atlantoaxial dislocation which results in compressive myelopathy
  - Atlanto axial is common with Down syndrome. It can be there in ankylosing spondylitis.
- Rheumatoid is more common in females and Ankylosing Spondylitis is more common in males.

Extra Articular features of Rheumatoid Arthritis 00:18:50

- **Rheumatoid nodules**
  - These are Non-tender and can be seen from the extensor aspect.
  - Positive RA factor.
  - In rheumatoid nodules lung involvement can be there
  - These are inflammatory nodules so there can be breakdown as well and lead to exudative pleural effusion
  - These nodules can press on peripheral nerves contributing to mononeuritis multiplex.
  - It means multiple neuropathy happens concomitantly.
  - Posterior tibial nerve involvement will cause tarsal tunnel syndrome
  - If there are nodules on the median nerve then it would contribute to Carpal Tunnel syndrome.
- **Livedo Reticularis:** It means you can see fine blood vessels which will give a characteristic fishnet appearance.
  - This is a physical skin appearance.
- Purpura can be possible which can bleed
- Ulcers can be visible in the tip of the finger

Manifestations

Eye involvement

- Autoimmune diseases
- In sarcoidosis one have noncaseating granulomas that lead to uveitis
- **But there is no uveitis** in rheumatoid arthritis.
- Keratoconjunctivitis sicca is the most common ocular issue. Apart from that scleritis, episcleritis, scleromalacia perforans are also possible.
- Involvement of Salivary glands causing compromised production of saliva and Xerostomia.

Lung manifestation-Pleuritis-This is an inflammatory nodule causing pleural rub.

- When they break down, blunting of the costophrenic angle on the chest x-ray
- Cardiac involvement in the patient.
- Nodules occur in the pericardium - pericarditis.
- The nodules occur and damage the myocardium-heart failure
- The valvular region that can be involved is MR.
- Almost with any condition if heart is involved then the most common valve involved is mitral valve and the lesion seen is regurgitation.
- The incidence of ischemic heart disease will dramatically increase in women or men with rheumatoid arthritis.
- The bad news is because hypoxic tachyarrhythmia can occur and can lead to sudden death.
- In these patients especially after the age of 45 there can be a higher chance of Accelerated Atherosclerosis.
- Cardiovascular mortality is the main cause of death in rheumatoid arthritis.
- For RA we do not use steroids.
- Intra-articular steroids used by some doctors has temporary effect and are not recommended.
- Kidney involvement in Rheumatoid Arthritis
  - MGN is the lesion seen.
  - MGN can be associated with any auto-immune disorder
  - Secondary amyloidosis can occur with chronic inflammatory disorder
- Genitals can be involved as well.
- Due to Hypoandrogenism, there can be issues related to conception for female patients
- Hematological manifestations can also occur

- Anemia of chronic disease: Normocytic normochromic anemia.
- Osteoporosis can be seen due to disease or treatment
- Purpura can occur
- Livedo reticularis is associated with rheumatoid arthritis.
- The most common Extra Articular Feature is rheumatoid nodules.

Caplan Syndrome

- Associated with RA
- Associated with coal workers' pneumoconiosis
- **Felty Syndrome**
  - Associated with RA
  - Associated with splenomegaly
  - Neutropenia is associated with this syndrome
- One of the important lesions here is pannus formation
  - It will cause synovial inflammation
- Tenderness or pain is related to this part only
- As the disease progresses, there is cartilage erosion, bone erosion, and periarticular osteoporosis.
- Once this disease progresses, what is the diagnosis?
  - JSAD (mnemonic)
    - → Document the joint involvement in the patient. It could include both small and large joints. There could be 1 large joint, 2 to 10 large joint, 1 to 2 small joints, 4 to 10 small joint involvements. It could be even more than 10 joint involvements as well. The more the number of small joint involvement, the more credibility.
    - → Serological evidence
      - There are two tests
        1. RA factor
        2. Antibody - cyclic citrullinated peptide antibody
      - Low titre - means the value is less than 3 times upper limit of normal
      - High titre - means more than 3 times of upper limit of normal
      - High titre of RA factor and anti- CCP then the credibility of diagnosis is increased
      - If both are low then the credibility is decreased
    - → Acute phase reactants
      - ESR can be normal
      - CRP can be normal
      - They can be substantially elevated
    - → Duration of illness
      - Follow the patient for 6 week and see how many joints are getting involved.
      - If it is more than 6 weeks of involvement then the diagnosis will be more credible.

These parameters have scores, for instance,

- RA factor low titre will be given less marks
- RA factor high titre will be given more marks

Work Up

1. X Ray is not useful, except in Late stages
2. MRIs can pick up Synovitis or Joint inflammation.
3. RA factor: IgM class of antibodies. This test may be biologically false positive in 5% of the normal population. This cannot be used as the best diagnosis. It is a screening test but it can't be the investigation of choice
4. Anti CCP - Cyclic Citrullinated Peptide will be helpful
5. Joint aspiration- Synovial fluid on M/E
   - The cells can range from 5000 to 50,000.
   - In fact initially there could be a predominant neutrophil count.
   - These high counts tell about evidence of inflammatory processes.
6 X ray of the hand can help pick up on erosions on the later part of the disease
7. There would be a reduction in joint spaces
8. Periarticular osteoporosis can be identified later

Treatment

- Now NSAID's have no role.
- Intra-articular steroids can reduce joint pain and not recommended.
- The drug used is Methotrexate but it cannot be used in pregnancy
- In those cases hydroxychloroquine can be used
- Methotrexate needs to be taken once a week as compared to any other drug needed on a daily basis.
- Compliance perspective is better though side effects are there.
- Other drugs like Leflunomide or levamisole can be given.
- Methotrexate dose can be increased and sulfasalazine can be given as well.
- Another drug is hydroxychloroquine. This is known as triple therapy where all three meds are given, Methotrexate, Hydroxychloroquine, Sulphasalazine.
- Continue with Methotrexate along with biologicals if cost is not a problem
- One important biological is - TOCILIZUMAB
- Other biologicals are
  - Certolizumab
  - Abatacept
  - Rituximab
- Addition strategy is-Methotrexate+Tofacitinib (JAK 3 inhibitor)
- JAK 3 inhibitor means it will inhibit the signaling of the receptor of cytokines involved in the disease
- Piano key movement ulnar styloid process of the hand can develop in late stages.

37 CRYSTAL ARTHROPATHY

Crystal arthropathy

Acute Gout

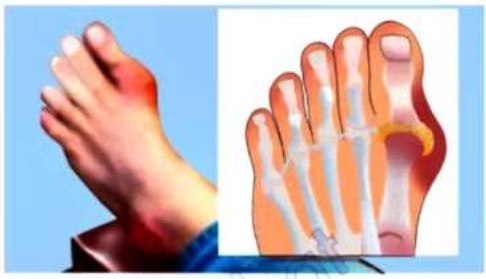
00:00:20

- Swelling of the big toe
  - Technical term - Podolagia or podagra
- In Acute Gout presentation will be of middle-aged male but in most rheumatological disorders young females in the reproductive age group is the stage of presentation.
- In rheumatological disorders Ankylosing spondylosis is more common in younger male
- Question an Acute gout can present as Postmenopausal female who recently was diagnosed with hypertension by a General physician has been started on diuretics.

- Why are diuretics not preferred in comparison to CCB's?
  - Long-term thiazide usage can lead to glucose intolerance, so diabetic people can have problems. HbA1c values will turn out to be higher than they actually are.
  - Drugs can contribute to impaired lipid profile as well
  - Incidence of Coronary artery disease will be increased.
  - Diuretics can also trigger an acute attack presentation of gout
  - It can contribute to an increase in Uric acid levels.
  - Thiazides can be used as a backup only and not as a primary drug for control of Hypertension.

- Swelling of the first Metatarsophalangeal joint, which is characteristically involved, can look like cellulitis.
- Joint Swelling will be red, tender, and warm to touch (looks like an infection)
- Swelling in the ankle joint or knee joint may be present.
- On the knee joint or around the knee joint, there could be soft tissue deposition of uric acid or monosodium urate. This is called as tophi. It can be present in extensor aspects like ankle joint, shin, just related to the joint just below the patella, or tophi can be described on the hands of the person or earlobes of the patient.
- Tophi specifies that patient has a chronic or acute on chronic presentation
- Because uric acid will already be high to get deposited in the tissues

Image Based Discussion



- Image shows hand of a old man/woman with deformities.
- No boutonniere or Z-line deformity
- Bouchard nodes which are related to the proximal interphalangeal joint are evident
- Heberden's nodes related to the distal interphalangeal joint are also evident
- There is a possibility that in this old woman or man with osteoarthritis in the area with Heberden's nodes, there could be a development of redness, yellow point in the middle which might look like a pus
- This is a presentation of Acute gout.
- Tophi could develop in Heberden's nodes or even Bouchard's nodes
- In old age, multiple diseases co-exist

Clinical Features of Acute Gout

00:07:07

1. Pre-existing hyperuricemia in this person
2. Excruciating pain in the middle of the night, mimicking cellulitis.
3. Tophi that is deposits of monosodium urate monohydrate crystals in the ear lobes, hand, pre-existing Bouchard's nodes or Heberden's nodes, etc.
4. Nephrolithiasis possibility as well.

Investigation of Choice 00:07:40

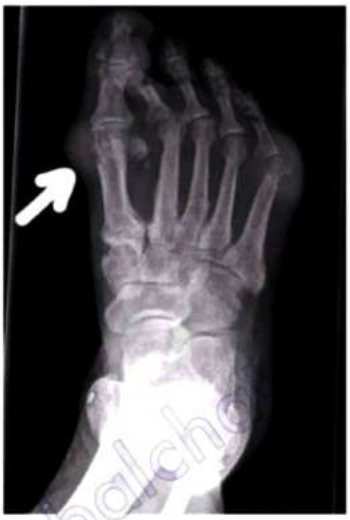
Joint Aspiration:

- The uric acid level in the blood might be average or even less than normal because all the uric acid is mobilized into the joint space, so there is synovial inflammation.
- It is uric acid that is elevated in the joint space.
- The IOC is a joint aspiration. Once the joint aspiration is done, we will evaluate the synovial fluid under the microscope and then a polarised microscope.
- The synovial fluid under the standard microscopy will reveal an increase in the number of cells.
- Do we have cells in synovial fluid? Yes, less than 200 cells usually.
- In inflammatory state, it will increase. There can be up to 10 times regular. (2000 - 6000 cells/mm3)
- Sometimes fluid may be turbid or chalky white as well and fever may be present.
- To rule out septic arthritis, prepare a gram stain, culture, and then isolate the organism.
- In this case, Monosodium urate crystals is seen
- Synovial fluid under a polarized microscope negatively birefringent needle-shaped crystals.
- Description of a person having joint pain, and big toe involvement was not mentioned. When joint aspiration fluid was seen under an electron microscope the doctor found needle-shaped crystals. The disease here is not acute gout. It is Calcium apatite crystal deposition.

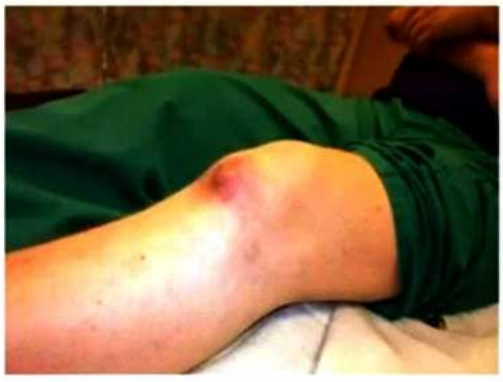
Other investigations

- Joint aspiration and evaluation under a microscope, including a polarised microscope
- A serum uric acid levels should be done. In chronic gout, it is elevated, but in acute gout, it is falsely normal.
- 24-hour urinary uric acid level to diagnose whether he is over producer of uric acid or under excretor.
- There is a possibility for Kidney stones, so a standard urine microscopic examination should be done.
- KFT will also be done because many hypouricemic therapy drugs like allopurinol requires dose adjustment
  - As there is a risk of the S. Creatinine going up
  - The dose of drugs needs to be changed as well
- Lipid Profile and LFT - Old man can have concomitant atherosclerosis as well.
  - Evaluation for non-alcoholic fatty liver disease
  - Syndrome X means abdominal circumference will increase
  - He will develop centripetal obesity, will become hypertensive, along with that hyperlipidemia, and there could be impaired glucose tolerance. So, everything needs to be treated as a whole.

- X-ray findings and USG (Ultrasound) findings for acute attacks.



- Soft tissue swellings can be observed
- Also, notice some erosive lesions present.
- This guy is a patient of acute on chronic gout, and there were many flare-ups of the disease earlier.
- Because of the Recurrent flare-up of the disease, there could be lytic lesion concerning the Metacarpophalangeal joint.
- Martel sign can also be written as a rat bite margin lesion that might be encountered.
- Erosions can occur in SLE as well, but fundamentally SLE is an example of non-erosive arthritis.
- Martel sign is rarely to be seen because most of the time, you will not get an x-ray of a person of gout and start treating the patient right away.
- Ultrasound of the swollen joint can show a double contour sign



- The lesion present is a tophi

- Tophi might not be just in the lower extreities but may also be present in the hands
- They may later develop a yellowness in the middle which is the inflammatory component
- At the same time, earlobes can be involved

Management 00:18:02

- Do not use a hot pack, as pain will increase if there is swelling or inflammation
- Use ice pack
- COX-1 inhibitors like indomethacin or naproxen which can be used. They are highly effective but can cause gastritis a well
- Some patients are hyper-sensitive to painkillers like indomethacin, which can cause bee hives, rashes, breathing problems, swollen lips, etc.
- Some patients may have an intolerance to COX-1 inhibitors.
  - Trying out COX-2 inhibitors is also a choice. But it is not as effective, so steroids can be given.
    - → Here steroids can be used primarily in someone who is hypersensitive to painkillers.
    - → Steroids are anti-inflammatory agents
    - → These can be given orally or intra articularly
  - Colchicine. 0.6 mg TDS (introduce after 2-3 days)
    - → The disadvantage of this dose is the development of diarrhea.
    - → A patient already limping due to pain in foot and suffering from diarrhea can cause trouble.
  - Aspirin is not given in Acute Gout.
    - → Studies have shown Aspirin can cause more precipitation of uric acid crystals in the synovial fluid.
    - → It can worsen the patient's condition.
    - → So, Aspirin is contraindicated.
  - Allopurinol is used for Chronic Gout.
  - Aspirin and Allopurinol are contraindicated in Acute Gout.

Hypouricemic Therapy 00:21:19

- Once patient is better, you can start Hypouricemic therapy
  - This can be given till tophi completely disappears
  - Once uric acid level touches normal, it has to remain normal for 6 months consecutively.
  - From that day when the values of serum uric acid levels touch normal upto 6 months, hypouricemic therapy will continue
  - Limit non-vegetarian food
  - Purine intake should be controlled
  - Control of weight is important
  - The diuretic dosage might need adjustment
  - Diuretics can be used, after dose adjustment or the patient can be switched to calcium channel blockers
  - The next steps will depend upon the results of 24-hour urinary uric acid levels
    - → If the values turn out to be elevated it indicates that the person is an overproducer,
    - → On the other hand, if the values turn out to be lesser, the person is an under excretor
    - → Which indicates that the kidney tubules are not working to excrete uric acid.

Drug Treatment 00:24:36

Drugs for overproducers	Drugs for under procedures

• Allopurinol
  ○ Can cause granulomatous hepatitis
  ○ It can cause toxic epidermal necrolysis, where a person can develop blisters in the body,
  ○ And if more than 30% of the body is involved, it is Steven Johnson Syndrome.
  ○ However, it is rare.
  ○ Problematic with patients having deranged kidney problems
• Febuxostat is safer in renal failure
• The medically refractory patient is a case of chronic gout where the uric acid is permanently elevated, and you have tried all the drugs. So, an IV molecule is available.
• PEGLOTICASE can be used, which will help restore the uric acid levels to normal.
	• Probenecid will enhance the excretion of uric acid
	• Benzbromane is not permitted in some countries. But it is safer for chronic kidney disease.
	  ○ It is withdrawn due to hepatotoxicity potential
	• Lesirunad

Crystals in Synovial Fluid 00:27:58

- Needle-shaped crystals with Negative birefringence under **polarised microscopy** - Monosodium urate (MSU)
- Needle-shaped crystals with negative birefringence under an **electron microscope** - Calcium apatite
- The shape of the crystal is rhomboid rectangular, which is weakly birefringent positive. This is a case of pseudogout. (Steroids are the primary treatment for this)
- Bipyramidal crystals on a light microscope - encountered with calcium oxalate

Saturnine Gout

- Overlap with forensic medicine that is Saturnine gout seen with Lead poisoning.

Normal findings with respect to Synovial fluid aspiration

	Colour	Clarity	Viscosity	WBC Count (mm^3)	Neutrophil Count	Gram Stain	Crystals
Normal	Colourless	Translucent	↑	<200 cells/mm^3	<25%	Negative	Negative
Non-inflammatory	Straw like/ yellow	Translucent	↑	200 - 2000 cells/ mm^3	<25%	Negative	Negative
Inflammatory	Yellow	Cloudy	↓	2000-50,000 cells/mm^3	>50%	Negative	Positive
Septic	Yellow/ green	Cloudy/ opaque	↓	>50,000 cells/mm^3	>75%	Positive	Negative
Haemarthrosis	Red/ xanthochromic	Bloody	Variable	200-2000 mm^3	50-75%	Negative	Negative

- Viscosity of synovial fluid ensures minimum friction during joint movement.
- Cell count can be elevated due to inflammation
- If viscosity is reduced, it is inflammation or a septic process

38 VASCULITIS

- Most common vasculitis subtype among the adult population is
  - Previously, giant cell arteritis was considered the answer.
  - The current edition of Harrison states that idiopathic cutaneous vasculitis is the most common variety.
- The most common vasculitis subtype among the paediatric population of Asian descent is Kawasaki disease.
- Most common vasculitis subtype among children is Henoch-Schonlein purpura (HSP).

Giant Cell Arteritis 00:01:25

- Involves superficial temporal artery (auriculotemporal artery).
- Artery palpated on the temporomandibular joint.
- Affects geriatric population > 70 years.

Important Information

For instance, An MCQ can mention a geriatric male above 70 years who is a retired military officer i.e. physically fit for all his life. The patient presents with low-grade fever for the past couple of weeks. Previous investigations were done for tuberculosis and brucellosis were negative. The patient also reports non-pulsatile pain on the side of the head i.e. over the temporal area.

- The first speculation can be that the superficial temporal artery supplying the skin of the scalp undergoes vasculitis and becomes progressively narrow.
- Leads to ischemic pain in the skin of the scalp.
- Giant cell arteritis is an extracranial cause of headache.
- Examples of intracranial causes of headache
  - Migraine
  - Raised intracranial pressure
- Ischemia due to arterial narrowing causes Jaw claudication.

Clinical manifestations

1. Low-grade fever lasting a few weeks.
2. Temporal headache
3. Jaw claudication (Jaw claudication can also be seen in temporomandibular arthritis.)
4. Mono-ocular blindness, if the ophthalmic artery (branch of internal carotid artery) is involved.
5. Superficial temporal artery supplies the Skin of the scalp and the Temporomandibular joint.

On examination

Cord-like structure felt at the temporomandibular joint.

Work Up

Erythrocyte sedimentation rate (ESR): 100 mm fall in 1st Hour

Important Information

Conditions with 100 **mm fall in 1st Hour**

1. Subacute bacterial endocarditis
2. Multiple myeloma
3. Giant cell arteritis

Biopsy Findings

- May be repeated in several places.
- Therapeutic effect as nerve endings are cut, reducing burning pain sensation.
- Giant cells demonstrated.
- Neutrophilic infiltration in all three layers of blood vessel walls.
- Uniform inflammation or panarteritis.

Management

- Sumatriptan is not given for headache management.
- Steroids are administered.

Causes of Headache

- The most common cause of headache is Tension headache.
- The most common cause of Secondary headache is Infection e.g. sinusitis, rhinitis.
- The most common cause of Pulsatile headache is Migraine.
- Thunderclap headache occurs in Subarachnoid haemorrhage or stroke
  - Headache develops very fast i.e. achieves maximum intensity in just one minute.
- The main cause of Temporal headache in geriatric population is Giant cell arteritis.
- The main causes of Occipital headache is Tension headache, Hypertension, Basilar migraine.
- The Intracranial cause of headache in geriatric patients is Brain tumour.
- The leading Extracranial cause of headache in geriatric patients is Giant cell arteritis.

Henoch-Schonlein Purpura (HSP) removed IgA vasculities 00:10:03

- Non-thrombocytopenic purpura.
- Increased IgA levels.
  - Also elevated in Berger's disease in kidney.

Organs affected by IgA-mediated vasculities

1. **Cutaneous Blood vessels**
- Rupture due to damage.
- Extensor purpura i.e. bleeds present in the skin of the buttocks, back of thighs, calves and back.
- May be misidentified as a viral exanthema

2. **Vasculitis related to gastrointestinal vessels**
- Abdominal pain.
- Fussy eating with no oral intake.
- Hematochezia i.e. fresh blood in the stool.

3. **Blood vessels related to the joints or synovium**
- Joint pain or arthralgia.

Criteria for diagnosis of Henoch-Schonlein purpura

Criteria	Definition
Palpable purpura	Palpable hemorrhagic skin lesions in the absence of thrombocytopenia.
Bowel angina	Diffuse abdominal pain or the diagnosis of bowel ischemia.
Diagnostic biopsy	Histological changes showing granulocytes in the walls of arterioles or venules; IgA deposits in the vessel wall.
Pediatric age group	Age <20 years at onset of symptoms.

- The diagnosis of HSP is based on the presence of two of four criteria.

Important Information

- Conditions causing non-palpable purpura
  - Idiopathic thrombocytopenic purpura.
- Conditions causing pinch purpura
  - Amyloidosis
- HSP is an example of non-thrombocytopenic purpura. Bleeding occurs due to fragility of blood vessels caused by vasculitis, not thrombocytopenia.

Work Up

- Elevated IgA and low C3 levels are not definitive diagnostic criteria for HSP.
- Investigation of choice is a skin biopsy.
  - In Robbins pathology uses the term 'leukocytoclastic vasculitis'.
- Coagulogram may be mildly deranged.

Management

- Steroids administered

Scarlet Fever 00:17:04

- Can be compared with features of Kawasaki disease.
- Both diseases present at 4 years of age.
- Caused by Streptococcus pyogenes.

Differences between Kawasaki disease and Scarlet fever

Kawasaki disease	Scarlet fever
Fever present for 5 days or more.	Fever lasts 4 days.
Mucocutaneous lymph node syndrome Strawberry tongue Bulbar congestion Periungual peeling of the skin Perianal peeling of the skin	Strawberry tongue. Scarlet rash all over the body with a sandpaper consistency. Pastia lines along flexural areas with mild desquamation.
Unilateral cervical lymphadenopathy.	Bilateral cervical lymphadenopathy.

Important Information

In Kawasaki Disease
- Mucocutaneous lymph node involvement should be demonstrated for Kawasaki disease diagnosis.
- Intravenous immunoglobulin is the effective treatment for Kawasaki disease and Guillain-Barre syndrome. Aspirin (low dose) is also used in Kawasaki disease.

Management

- Ampicillin

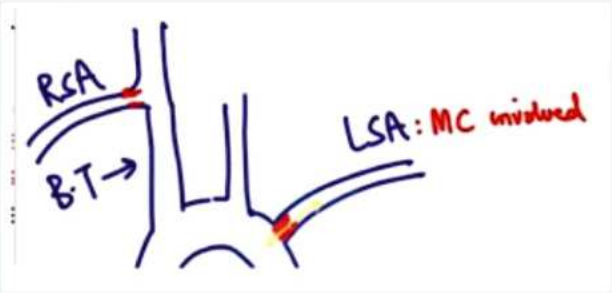
Important Information

- Strawberry gall bladder: Cholesterolosis.
- Strawberry cervix: Trichomonas vaginalis.
- Strawberry gingiva: Granulomatosis with polyangitis (Wegener's granulomatosis).
- Strawberry nose: Rhinosporidiosis.
- Strawberry tongue: Kawasaki disease or Scarlet fever.

Takayasu Arteritis (Pulseless Disease) 00:22:00

- Leading cause of Renal artery stenosis in India.
- Causes Ostial narrowing, compromising renal blood flow.
- Low glomerular filtration rate causing High renin hypertension.

Ostial narrowing



- Most common blood vessel involved is the left subclavian artery.
- Less blood flows into the left subclavian artery.
- Leads to unequal pressure between the left arm and right arm.

Clinical manifestations

Arm claudication due to Vascular cause

- May be misdiagnosed as Neurogenic claudication due to disc prolapse.
- Neurogenic claudication presents as pain in the arms even at rest.
- Vascular claudication presents as pain only when using the arms.
- Orthopedician may recommend an MRI of the cervical spine, suspecting Neurogenic Claudication.
- No pain improvement despite gabapentin and pregabalin use.

Disparity of blood pressure between the left arm and right arm

- Lower blood pressure on the left arm.
- Blood pressure may also be low on the right arm due to ostial narrowing on the right side too.

Pulseless disease

- Ostial narrowing on the left side is substantially more, such that the doctor is unable to appreciate the pulsations of radial artery.

Renal artery stenosis

- Ostial narrowing occurs in the renal artery.
- Leading to reduced renal blood flow, low GFR and high renin hypertension.
- If a person aged > 60 years who is a frequent smoker presents with renal artery stenosis, the diagnosis is atherosclerosis of the renal artery.
  - The entire length of the blood vessel narrows in atherosclerosis.
  - Only the ostium narrows in Takayasu arteritis.
- If a young female (< 20 years) living in the USA develops renal artery stenosis, the diagnosis is fibromuscular dysplasia (FMD).
- For a young female in India with renal artery stenosis and clinical features discussed above the diagnosis is Takayasu disease.

Work Up

- Investigation of choice is MR-angiography (MRA).

Treatment

- Steroids are administered.

Additional Facts 00:27:03

- Normally, blood pressure (BP) in legs > blood pressure in arms due to gravity.
- The difference between the two BPs is <20 mm/Hg.
- Condition in which arms BP > legs BP
  - Coarctation of the aorta.
- Condition in which legs BP > arms BP with a difference greater than 20 mm/Hg:
  - Hill sign observed in aortic regurgitation.
- Conditions with unequal BP between the left and right arms:
  - Supravalvular aortic stenosis (SVAS) with coanda effect as jet of blood preferentially goes to the right side.
  - Takayasu arteritis
  - Coarctation of the aorta of the preductal variety i.e. paediatric presentation.

Comparison between Wegener's Granulomatosis (Granulomatosis with Polyangiitis) and Polyarteritis Nodosa 00:28:57

Characteristics	Granulomatosis with polyangiitis	Polyarteritis Nodosa
Affected body parts	Damage to the blood vessels of • Upper respiratory tract. • Lower respiratory tract. • Kidneys.	• Kidney • Pulmonary artery & Glomerulonephritis and hemoptysis not seen .
Clinical manifestations	• Epistaxis. • Sinusitis. • Nasal ulcers. • Recurrent episodes of hemoptysis. • Lung lesions in the form of multiple lung cavities. • Hematuria.	• Hematuria. • Digital ulcers. • Digital gangrene. • Hypertension. • Myocardial infarction. • Stroke. • Livedo reticularis.
Antibody	c-ANCA.	p-ANCA (perinuclear-ANCA).
Cytoplasmic antigen	Proteinase-3.	Myeloperoxidase.
Treatment	1. Rituximab. (1st line) 2. Cyclophosphamide 3. Steroids.	Steroids

- Rituximab is first line as per Harrison 21st edition update.

- Hematuria and hemoptysis are also observed in Goodpasture syndrome.
- Cyclophosphamide causes Hemorrhagic cystitis.
- In polyarteritis nodosa, there is:
  - Damage of the renal blood vessels, not the glomerulus.
  - Necrotizing vasculitis affecting blood vessels supplying the fingertips.
  - Coronary artery vasculitis.
  - Vasculitis of brain blood vessels.
  - Fishnet appearance of skin blood vessels i.e. livedo reticularis.
- 2 clinical manifestations not seen in polyarteritis nodosa:
  1. Glomerulonephritis.
  2. Pulmonary artery involvement.
- Combination of Gangrene and Hypertension indicates Polyarteritis nodosa.

Important Information

Conditions where p-ANCA is strongly positive
1. Microscopic polyangiitis.
2. Churg-Strauss syndrome (Eosinophilic granulomatosis with polyangitis).
3. Primary sclerosing cholangitis.

Microvascular Vasculitis

00:34:29

- Diseases include
  - Granulomatosis with polyangiitis (GPA).
  - Microscopic polyangiitis (MPA).
  - Eosinophilic granulomatosis with polyangiitis (EGPA).

Refer Table 38.1

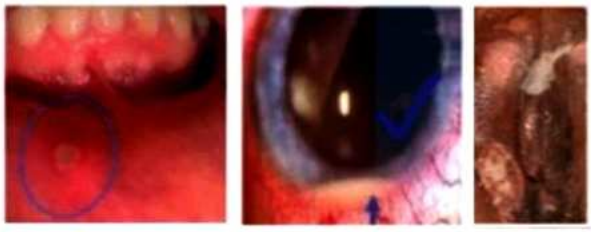
- EPGA is associated with Eosinophilic infiltration.
- EPGA patient may develop
  - Eosinophilic gastroenteritis
  - Eosinophilic esophagitis. Presents with feline oesophagus with corrugated appearance.

Behcet's Disease (Silk Route Disease)

00:37:47

- Affects Arab population or populations in China, Turkey or Mongolia.
- HLA B5 positivity.

Clinical manifestations



1. Recurrent painful oral aphthous ulcers
- Occur in crops i.e. at least 3 times per year.

2. Recurrent vulvul ulcers
- Often misdiagnosed as herpes in females.

3. Scrotal ulcer(s)

4. Hypopyon
- Ocular manifestation.
- Pus in the anterior chamber of the eye.
- Anterior inflammation or anterior uveitis.
- Behcet's disease is also known as oro-oculo-genital syndrome.

Work Up

Pathergy test
- Should not be confused with a patch test for contact dermatitis.
- Both are Type IV hypersensitivity reaction.
- In a normal person, hypodermic needle prick on the forearm resolves on its own in a few days.
- In Behcet's disease patients, a sterile pustule is formed after 48 to 72 hours.

00:43:18

- Behcet's disease can affect both small and large blood vessels.

Arteries involved in Behcet's disease
- Behcet's disease causing large vessel vasculitis is rare.
  - The blood vessel involved is the Pulmonary artery.
  - Pulmonary artery rupture can occur leading to life-threatening hemoptysis.
- Small vessel vasculitis may occur.
  - Involves brain blood vessels leading to CNS manifestations e.g. unconsciousness, abnormal behaviour, cortical venous thrombosis and encephalopathy presentations. Neuro-Behcet's disease.
  - May be misdiagnosed as Herpes Encephalitis.
  - Administration of IV prednisolone.
  - Administration of Steroids.

Treatment
- Topical steroids
  - Management of oral and genital lesions.
  - Not used for ocular manifestations as steroid use in the eye may cause corneal perforation.
- Azathioprine
  - Ocular Behcet manifestations.
- IV methylprednisolone
  - Neuro-Behcet's disease.

Kawasaki Disease

00:46:12

- Mucocutaneous lymph node syndrome.
- ECG findings of myocardial infarction present in a 4-year old child.

American Heart Association Criteria for Identifying Kawasaki Disease

Age of Presentation: > 4 years

1. Fever t ≥ 5 days.
2. Unilateral cervical lymphadenopathy.
3. Strawberry tongue
4. Scarlet rash.
5. Peeling of skin at the fingertips, palms and genitals i.e. desquamation.

- Bulbar congestion.

Important Information

Mnemonic

- Mucocutaneous lymph node syndrome.
- Muco - Strawberry tongue, Bulbar congestion.
- Cutaneous - Rash, Desquamation.
- Lymph node syndrome-Unilateral cervical lymphadenopathy.

Kawasaki can be differentiated from Scarlet Fever

- Scarlet fever
  - Bilateral cervical lymphadenopathy.
  - Pastia lines.
  - Rash has sandpaper consistency.
  - Does not cause Coronary A. Vasculitis

Untreated Kawasaki disease

- The child develops chest pain.
- Fall unconscious i.e. syncope.
- Coronary artery vasculitis triggers myocardial infarction.

- Characteristic ST elevation with T wave inversion.

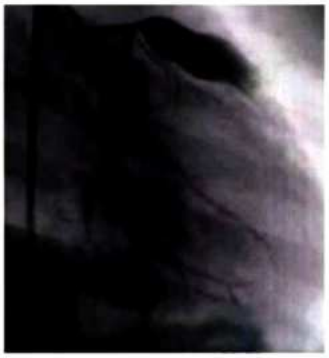
Treatment of ST elevation MI

- Primary percutaneous coronary intervention is not done in children.
- Thrombolysis is done.
  - A major side effect of thrombolysis is brain haemorrhage.

Treatment of coronary vasculitis

- Intravenous immunoglobulin (IVIG).

Echocardiography and angiography



- Coronary Artery Aneurysm > 1 cm in size.

Treatment on day 5 or 6

- Combination of Aspirin and IV immunoglobulins.

Important Information

ECG finding of myocardial infarction in neonates

- Indicative of anomalous origin of left coronary artery from the pulmonary artery (ALCAPA).
  - Normally, the left coronary artery originates from the aorta.
  - In this case, the left coronary artery has deoxygenated blood, contributing to myocardial ischemia.

Table 38.1

	Granuloma formation	Renal involvement	Pulmonary manifestations	Association with asthma	Antibody
GPA	+	80%	ENT manifestations e.g. • Sinusitis. • Nasal ulcer.	-	C-ANCA.
MPA	-	90%	50% of cases have ENT manifestations.	-	P-ANCA.
EGPA	+	45%	70% of cases have ENT manifestations.	+	P-ANCA.

39 SCLERODERMA

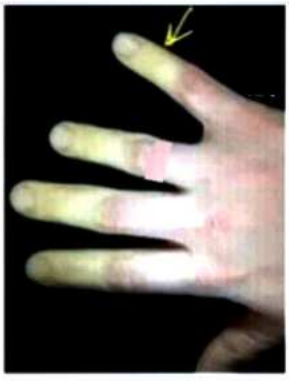
Scleroderma

- **Two types**
  - Systemic scleroderma (Systemic sclerosis)
  - Limited scleroderma
- Predominant in females
- Anti Topoisomerase-1 is the antibody seen
- Screening test for the Patient will be Antinuclear antibodies (ANA) just like in case of SLE, Sjogren's syndrome and Rheumatoid arthritis
- The proportion (%) of ANA in various diseases as follows

	ANA	Native DNA	Rheumatoid Factor	Anti-Sm	Anti-SS-A
Rheumatoid arthritis	30-60	0-5	70	0	0-5
Systemic lupus erythematosus	95-100	60	20	10-25	15-20
Sjogren syndrome	95	0	75	0	65
Diffuse scleroderma	>95	0	30	0	0
Limited scleroderma (CREST syndrome)	>95	0	30	0	0
Polymyositis/ dermatomyositis	80	0	33	0	0
Granulomatosis with polyangiitis	0-15	0	50	0	0

Clinical features: 00:01:12

1. **Raynaud's phenomenon**



- Extremities of the hand become pale or white when placed in cold water.
- It is due to extreme vasoconstriction
- Later, due to accumulation of deoxygenated hemoglobin 4.0 gm%, finger tips may turn bluish and ultimately become red due to vasodilation.
- Primary Raynaud's phenomenon
  → It is idiopathic (cause is not known)
  → Also termed as Raynaud's disease
- Secondary Raynaud's phenomenon
  → It has a definitive cause
  → Associated with connective tissue disorders (Scleroderma)
  → In late phases of Scleroderma, Ischemic digital ulcers may develop
  → A construction worker using a drill machine or a hammer and crane worker can develop Secondary Raynaud's phenomenon as the hand is subjected to vibrations.

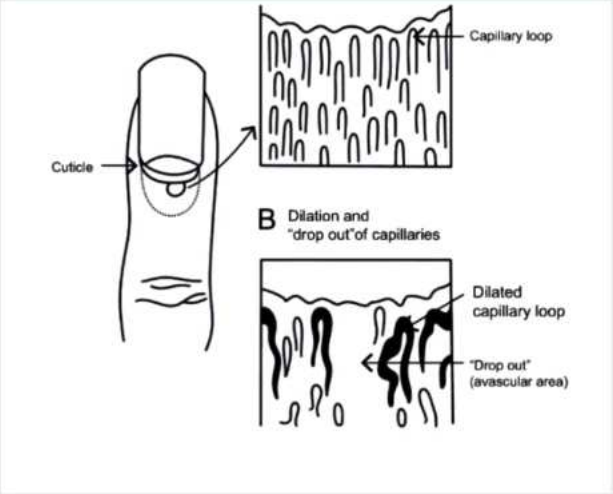
Important Information

Features seen in Polycythemia vera:

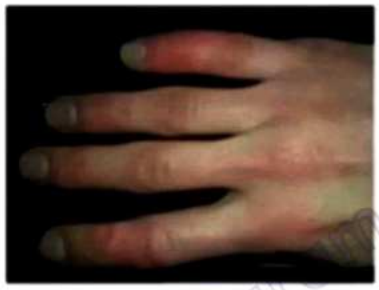
- **Erythromelalgia**
  - Toes may turn into Red or violet or purple due to heat exposure
- **Aquagenic Pruritus**
  - When patient takes bath with warm or hot water, muscle degranulation takes place leading itching all over the body
- Raynaud's phenomenon can also be seen in lower limb extremities

Buerger's disease, toes will become black due to gangrene

- Apart from color sequence (white, blue, red), other investigation is Nailfold capillaroscopy
  → Capillary loop below the nail cuticle will be in such a way that there will be avascular area(dropout) and fibrosis of capillaries



2. **Leather like skin or Sclerodactyly** is seen and most common involvement in Scleroderma is Skin involvement
   - Range of movements will be reduced



3. **Tendon friction rub or Contractures**
   - Noise during the movement of fingers due to fibrosis
4. **Pitting scars or Pits** on the fingertips due to reduced blood supply and subcutaneous fibrosis.
5. **Microstomia or Pinched facies,** reduced mouth or lip opening during eating because of fibrosis
6. In advanced stages, Fibrosis of salivary glands can also be seen resulting in reduced saliva production.
   - Due to this feature, patients may experience **Oropharyngeal dysphagia** when they eat dry food items.
7. **Esophageal dysmotility**
   - Also seen in Achalasia cardia in which sphincter tone in increased
   - But in scleroderma, sphincter tone is reduced due to fibrosis
   - GERD manifestations may develop
     → Sour brash
     → Enamel damage
     → Retrosternal pain
     → Chemical tracheitis or laryngitis
8. **Pulmonary fibrosis** in advanced stages
   - Not similar to shrinking lung syndrome as seen in SLE
   - Reduced residual volume due to increased timed vital capacity.
   - Pulmonary artery fibrosis can be seen leading to pulmonary artery hypertension (PAH)
     → It causes hypoxia and all blood vessels will be dilated except pulmonary artery
     → Loud P2, Early diastolic murmur and reduced DLCO are characteristic in such patients
     → Leading cause of death, 30% of mortality rates in Scleroderma is due to PAH
9. **Restrictive cardiomyopathy** due to fibrosis in heart
   - Patient exhibits Positive Kussmaul sign (Paradoxical rise in JVP on inspiration)
10. **Malignant hypertension or Scleroderma crisis**
    - Due to fibrosis of kidney, there will be reduced GFR and increased Renin
    - Progressive increase in BP and the patient may require antihypertensive dose modifications frequently.
    - Drug of choice for Scleroderma crisis is ACE inhibitor

- Scleroderma crisis is not the leading cause of death in scleroderma but PAH followed by Interstitial lung disease (ILD) or Pulmonary fibrosis are, irrespective of age.

Extra Mile:

- Drug of choice
  - Scleroderma crisis- ACE inhibitor
  - Hypertension + Documented hemorrhagic stroke- Nicardipine
  - Hypertension during intra operative pheochromocytoma- Sodium Nitroprusside
  - Eclampsia (Hypertension + Pregnancy)- Labetalol for hypertension and MgSO4 for Seizures

- In SLE patient
  - With active lupus, End stage renal disease is leading cause of death
  - If death occurs in the first 10 years after diagnosis, then death is due to infection (Due to usage of steroids)
  - If death occurs above 45 years, then cardiovascular mortality is predominant due to accelerated atherosclerosis- same as that of Rheumatoid arthritis

Case Scenario

- For Anti Topoisomerase 1 antibody
  - A female patient with positive ANA, Secondary Raynaud's phenomenon, leather like skin (sclerodactyly), PAH (reduced DLCO), increased timed vital capacity, malignant hypertension
  - Treatment
    → Steroids
    → Methotrexate

→ Cyclophosphamide
- Showed beneficial results
- Side effect: Hemorrhagic cystitis

Limited Scleroderma 00:28:31

- **Limited cutaneous systemic scleroderma (LC SSc) or CREST syndrome**
  - **Calcinosis cutis**
    → It is calcified plaque in skin
    → Despite the normal serum calcium levels, there will be calcification on skin

Case Scenario

- A female patient with positive ANA, calcinosis cutis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly (leather-like skin), Telangiectasias (Dilated blood vessels in face or sclera of eye). Work up shows presence of Anti centromere antibody

Mixed Connective Tissue Disorder (MCTD) 00:31:34

Case scenario

- U1 RNP (Ribonucleoprotein) antibody is involved
- A female patient with positive ANA, Malar rash, Raynaud's phenomenon, Bilateral Proximal interphalangeal and Metacarpophalangeal pain, wrist proximal muscle weakness (polymyositis)
  - Features of SLE, Rheumatoid arthritis and Polymyositis are present in this case

Important Information

- Psychosis in SLE is due Anti ribosomal P antibody
- U3 RNP is antibody against fibrillarin and seen in limited cutaneous systemic sclerosis and diffuse cutaneous systemic sclerosis

Localized Scleroderma/ Morphea 00:34:45

- Idiopathic scarring on face even without any injury leading to disfigurement
- Other manifestations of systemic scleroderma will not be seen in this type

40 SARCOIDOSIS

- Characterized by non-caseating granuloma (also seen in ulcerative colitis)

Important Information

- Caseating granulomas are seen in Histoplasmosis, TB, cryptococcosis

- Lung followed by skin (Erythema Nodosum) are the most common organs affected.
- Heart is the least common organ involved
- Respiratory failure due to lung manifestation is the leading cause for mortality in sarcoidosis.
- Angio-invasive mycetoma (Aspergillus niger) can also cause death in sarcoidosis patients treated with steroids, due to Massive Hemoptysis
- Sudden death in Sarcoidosis is due to Arrhythmias

Important Information

- Rhinocerebral Mucormycosis (Black fungus) is seen in COVID19 patients as a result of steroid treatment which may result in loss of vision or even death.
- Aspergillus fumigatus is related to development of Allergic bronchopulmonary aspergilloma (ABPA)

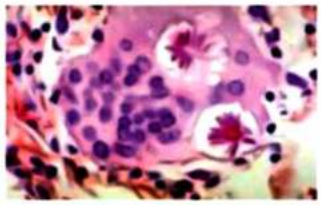
Etiology 00:03:32

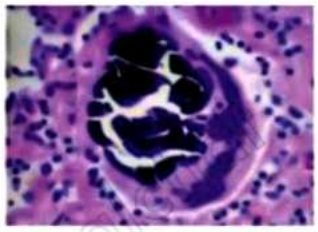
- Caused by
  - Propionibacterium acnes
  - Mycobacterium tuberculosis: MCAT antigen

Pathophysiology 00:03:56

- Antigen presenting cells present these antigens to CD4 cells in lymph nodes
- CD4 cells produce
  - Gamma interferon (γIFN)
    → Responsible for granuloma formation
  - IL-2
    → Helps in CD4 cell proliferation

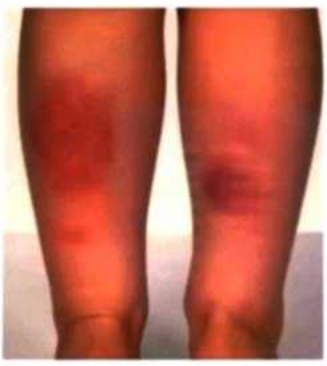
- Macrophages and eosinophils accumulate to form a giant cell and non caseating granuloma is formed
- Intracytoplasmic Asteroid bodies and Schaumann bodies (blue in color) are characteristic to these giant cells





Clinical Manifestations 00:06:46

- A patient may present with
  1. Progressive increase of Cough, Dyspnea on exertion or rest, Stridor
     → Due to bilateral hilar lymphadenopathy
  2. Night sweats, weight loss
     → May be misdiagnosed as Pulmonary TB due to these symptoms
  3. Skin manifestations differentiates from TB
     → **Lupus Pernio**
       – Involved in face and is painless
       – Involved in tip of the nose and cheek just like a butterfly rash but there will be distinct normal gap between nose and cheek
     → **Erythema nodosum**
       – Seen on Shin part and is painful
  - **Lofgren's syndrome**
    → It is a variant of sarcoidosis
    → Erythema nodosum
    → Bilateral hilar lymphadenopathy
    → Can be associated with arthritis



4. **CNS manifestations**
   → Lymphocytic meningitis
   → May involve optic nerve, Optic neuritis (also seen in multiple sclerosis) can be observed
   → Granuloma may damage Posterior pituitary leading to central diabetes insipidus.
5. **Ocular involvement**
   → Uveitis
   → Pars planitis

Important Information

- Optic neuritis is also seen in multiple sclerosis but Uveitis and Pars planitis are not.

- Features of Sicca Syndrome
  → Dry eyes and dry mouth

6. **Parotid gland involvement**
   → May lead to bilateral 7th nerve palsy or facial diplegia
   → Facial diplegia is also seen in Guillain-Barre syndrome and Lymes disease
7. **Lymph Node enlargement**
   → Hilar Lymph Node enlargement impinge on airways causing cough that doesn't respond to cough drugs
   → Recurrent laryngeal nerve and thoracic duct can be pressed leading to hoarse voice and chylous ascites, respectively

Important Information

- Upper Lung lobe fibrosis occurs in: **SAT**
  - Sarcoidosis
  - Ankylosing spondylitis
  - Tuberculosis (after healing)

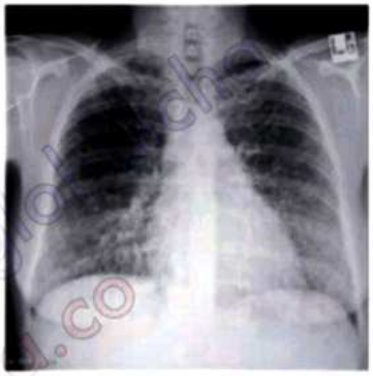
- Cardiac involvement
  → Death due to Tachyarrhythmias
  → Ischemic heart disease
  → Conduction blockade may lead to Bradyarrhythmias
  → Pulmonary artery hypertension (PAH)
    – Loud P2
    – Reduced DLCO
- Liver involvement
  → Granulomatous hepatitis
- Bone marrow manifestations
  → Lymphopenia
    – Thus patient should be treated with lowest dose of steroids
- Endocrine manifestations
  → Granulomas have 1-alpha hydroxylase enzyme that synthesizes Vitamin D_3
  → Thus hypercalcemia is noted leading to calcification
    – When treated with steroids, calcium levels will be normalized- Steroid responsive hypercalcemia

Important Information

- Vitamin D_3 intoxication is also treated with steroids- Steroid responsive hypercalcemia
- Cranial nerves involved in Sarcoidosis-CN VII, CN II

Workup 00:23:05

1. **Chest X-ray**



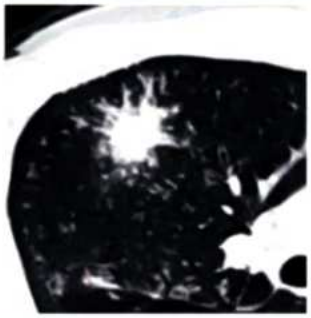
- Most common investigation to identify lung manifestations
- Hilar lymphadenopathy is seen as radio opaque shadow due to calcification
  → Termed as egg shell calcification (also seen in Silicosis)
- Radiological stages of lymphadenopathy progression
  → **Stage I**
    – Hilar lymphadenopathy (Early presentation)
  → **Stage II**
    – Hilar lymphadenopathy + Peripheral infiltrates
  → **Stage III**
    – Peripheral infiltrates alone
  → **Stage IV**
    – Fibrosis (late presentation)

2. Investigation of choice-**Biopsy**
   - Transbronchial biopsy
     → Opted when there is parenchymal involvement in Chest X-ray
   - Endobronchial biopsy
     → Opted when there is Lymph Node enlargement
   - Bronchoalveolar Lavage can also be done
     → Lymphocytosis can be observed (more likely to be sarcoidosis)
     → CD4:CD8 ratio > 3.5 in BAL fluid

Important Information

- Lymphopenia is a hematological manifestation but in Bronchoalveolar Lavage, Lymphocytosis can be seen.
- Transbronchial biopsy and Endobronchial biopsy are preferred over Bronchoalveolar Lavage

3. **HRCT chest**
   - Galaxy sign is observed



4. **Gallium-67**

   - Panda sign is observed in parotid or lacrimal glands
   - Lambda sign is seen due enlargement of bilateral hilar lymph nodes and right paratracheal lymph nodes
   - CXR 1-2-3 sign.
5. **PET scan**
   - To analyze extrapulmonary involvement
6. **Diffusion lung capacity for carbon monoxide (DLCO)**
   - Reduced DLCO due to PAH or Pulmonary fibrosis
7. **Cardiac MRI**
   - To examine granulomas in heart that pertain to tachy or bradyarrhythmias
8. **ACE levels**
   - Will be elevated

Important Information

- ACE levels are elevated in: Mnemonic SGLT
  1. Sarcoidosis
  2. Gaucher's disease
  3. Leprosy
  4. TB

- **Kveim's test**
  - It is not done currently due to risk for prion particle transmission that lead to Cruezfelt Jacob disease

Treatment 00:33:55

1. **Steroids**

- If lymphopenia is present
  - Steroid sparing agent hydroxychloroquine hydroxychloroquine

Note: Hydroxychloroquine is also used in photosensitivity due to SLE

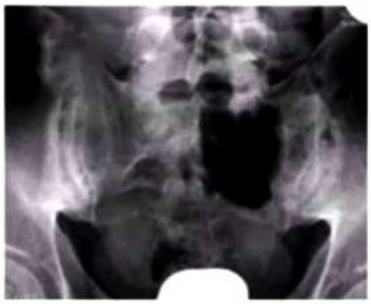
2. **Methotrexate**
3. **Azathioprine**
4. **Infliximab**

Important Information

- Infliximab is also used in Ankylosing spondylitis, IBD (healing of enterocutaneous fistulas), Sarcoidosis

41 ANKYLOSING SPONDYLITIS

Ankylosing Spondylitis 00:00:17



Young male patient presents with

- Low backache persisting for the previous 3 months.
  - May be initially mis diagnosed as with disc prolapse,
  - No sign of relief observed even after using;
    → Gabapentin,
    → Pregabalin,
    → Other painkillers.
- Pain is nocturnal but ↑ Inactivity and ↓ Activity.
  → In Vascular claudication seen in buerger's disease, here walking causes the pain.
  → In Neurogenic claudication, the pain worsens on standing.
    - Mostly in sciatica, the pain travels from the buttocks to the back of the thigh.
  - Pain in sciatica and disc prolapse is nocturnal.
  - In this case, the male patient says that "After standing or walking, the pain tends to reduce, but lying on the bed worsens my pain."
  - Pain Decreases on physical activity, exercise or taking a hot bath - Clinical hint for AS.
- MRI Spine with Pelvis helps in the diagnosis of the AS.

- It picks up Bone Marrow Edema - Early presentation of the AS.
- Sacroiliitis, Bamboo spine on X-Ray are late features
- **Neck or nuchal stiffness** - Range of movement in cervical is lesser.

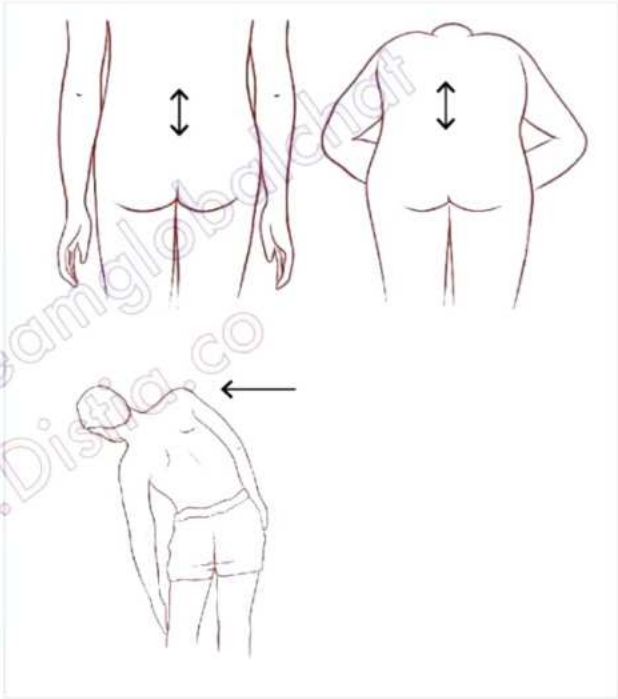
Important Information

- The patients are not advised to participate in the competitive or body contact sports (Example: Hockey and Football).
- If they collide with somebody their rigid osteoporotic spine can be fractured - Leading cause of death in AS.

- **Enthesopathy:** Pain at the insertion of tendon / ligament.
  - **Example:** Achilles tendon is inserted into the heels
- The AS patients may have nocturnal pain, there is a chance of over usage of the NSAIDs. The patient may experience the side effects of the painkillers.

Findings on Physical Examination 00:05:43

- Modified Schober's Test and Lateral Spine Flexion



- **Tenderness or pain at**
  - Sacroiliac joint or sacroiliitis - Earliest involvement in the AS.
    → Radiologically: Bone marrow oedema.
  - Sternoclavicular joint.
  - Tips of the spinous process of the vertebra.
    → If such patients are involved in body contact sports, chances of irreversible injury or even the chances of fracture of the spine are higher.
  - Tibial tuberosity.
  - Heel.
- **Substantial buttock muscle atrophy.**
  - Presented as buttock pain.
  - **Examination:** Modified Schober's Test is performed
  - The distance between the two points or markings is <4 cm.

Modified Schober's Test

Steps of the Modified Schober's Test

Select the posterior superior iliac spine of the patient.

↓

Mark a point on the midline of the PSIS and draw a line 5 cm below to the point and 10 cm above the point (Making the total length of marking 15 cm).

↓

Ask the patient to bend forward and ask to try to touch the toes.

↓

In **normal individuals**, the total length of the marking may increase substantially to 21 or 22 cm (Spine is flexible), i.e. the distance between the markings can increase >5 cm.

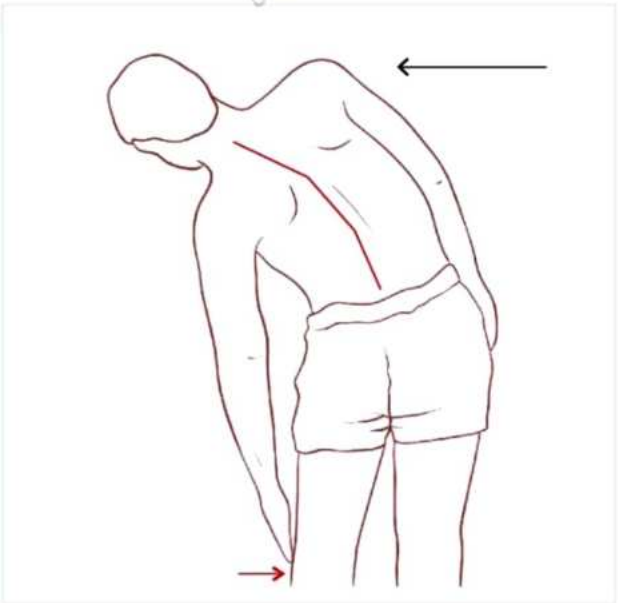
↓

In **AS patients**, the total length of marking doesn't increase like normal (Spine length may increase to 18-19 cm). The distance between the markings is <4 cm.

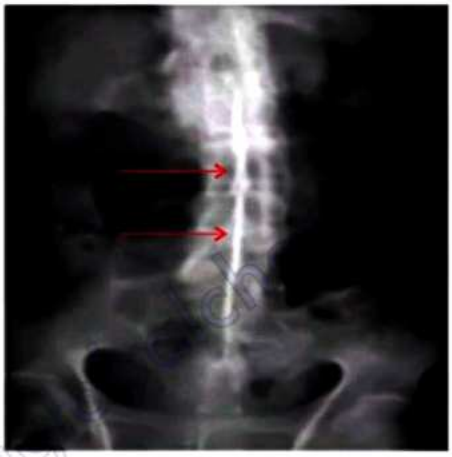
- **Lateral bending:** ↓
  - Ask the patient to bend laterally and touch the knee with the palms.
  - In AS, the patient cannot be able to touch the knee, as a normal person.
  - As, the curvature of the spine is substantially reduced.

- **Height of the patient:** ↓
  - Due to
    → Substantial thoracic kyphosis.
    → Loss of lumbar lordosis.

Decrease in Height of the Patient



- It is due to increase in the thoracic kyphosis and decrease in the lumbar lordosis component.
- In late diagnosis, the following characteristics can be presented - Seen rarely;
  - Bamboo spine,
  - Dagger sign



Important Information

- Modified schober's test and Lateral bending are used for evaluating spine flexibility.

- Chest expansion is substantially reduced: <5 cm.
- Spondyloarthropathy - Important diagnostic feature for AS.
  - **Mnemonic: SPINE ACHE.**
    → S - Sausage digits.
      - Also studied in psoriatic arthritis (Example of seronegative arthritis - RA factor is negative).
    → P - Psoriasis.
      - Skin lesions with silvery mica like plaques.
      - If peeled off, then the bleeding point is seen and called as an auspitz sign.
    → I - Inflammatory backache.
      - Biological molecules are required for symptomatic relief.
    → N and E - NSAIDs Responsive Enthesopathy.
      - Enthesopathy - Pain at the insertion of the joint in the tendons.
    → A - Arthritis.
      - Axial musculature is mainly involved.
    → C - Crohn's Disease and Ulcerative Colitis - HLA-B27+.
    → H - HLA-B27+.

→ E - Eye manifestation: Uveitis.
- It can cause blurred vision.
- Most common extra articular manifestation.

Important Information

In AS
- Most common extra articular manifestation - Uveitis.
- Most common cause of death;
  - Fracture of osteoporotic rigid spine.
  - Valvular lesions associated with Ankylosing Spondylitis-AR
    → AR can contribute to CHF > CAD.
  - In order; AR > CHF > CAD.

In IBD
- Extra intestinal manifestation of IBD is;
  - Osteoporosis (Harrison 21st update)
  - Arthritis,
  - Sacroiliitis.

In RA
- Most common extra articular manifestation - Rheumatoid nodules.
- Eye manifestation - Keratoconjunctivitis sicca > Scleritis.
- Leading cause of death - Accelerated atherosclerosis.

Summary of Important Findings in AS

Ophthalmic issues
- Uveitis
  - Opposite to keratoconjunctivitis sicca or Scleritis or episcleritis is seen in RA.

Cardiac issues
- Valvular lesions,
- AR,
- IHD (Ischemic Heart Disease)
- 3° Heart block development,
- Bradyarrhythmia.

Pulmonary manifestations
- Upper lobe fibrosis.
  - Also seen in SAT (Mnemonic);
    → **S** - Sarcoidosis.
    - Non caseating granulomas are seen.
    → **A** - AS.
    → **T** - TB.
    - Once healed, the cavity in the upper lobe turns to upper lobe fibrosis.

- **Thoracic or lumbar or lumbosacral spine** can be involved in AS;
- Cauda equina syndrome or conus medullaris syndrome
- Bladder and bowel involvement is also seen.

Skin involvement
- Psoriatic lesions - May or may not be associated with AS.
  - If Spine ache is present, then AS is confirmed.
- Fingertips show Clubbing-like symptoms with sausage digits.
  - Traditionally seen in pulmonary and cardiac diseases.
  - Sausage digits also seen in psoriatic arthritis - Classical pencil And cup appearance on X-Ray.
- Psoriatic arthritis shows Peripheral arthritis, whereas AS shows Axial spondyloarthropathy

Work-Up 00:22:53

1. Ideally, **MRI Lumbosacral Spine:** Bone marrow edema.
2. **X-Ray Lumbosacral Spine:** Sacroiliitis.
   - Bamboo spine and dagger sign are rarely seen due to the medical care given in the early stage of the disease.
   - Both conditions are important radiologically.

- Sacroiliitis is generally bilateral but the radiological picture may not accurately depict the disease process.
  - Thus MRI is ideal imaging for accurate AS diagnosis.

3. HLA-B27 + is an important diagnostic criteria.
   - **Also seen in;**
     → JRA,
     → Reiter syndrome (Rewritten in the books as "Reactive Arthritis" occurs after STDs like chlamydia, genitourinary infection or GI illness.)
     → IBD - Both Crohn's disease and ulcerative colitis patients may show HLA-B27 +
     → Psoriatic arthritis.

4. **ESR/CRP/SAP/IgA/C, with RA Factor:** Negative.
   - **Seronegative arthritis:** RA factor is negative in 5 subtypes of seronegative arthritis;
     → Ankylosing spondylitis.
     → Reactive arthritis/ **Former name:** Reiter's syndrome.
     → Psoriatic arthritis.
     - Peripheral joint is mainly involved.
     → IBD associated arthritis.
     → Undifferentiated variety.

Important Information

- Except AS, the other 4 subtypes of seronegative arthritis, present with predominant features - Peripheral arthritis components.
- Whereas AS - Spondyloarthropathy (Predominant Spine involvement).

Diagnosis 00:27:26

Diagnostic Criteria for Ankylosing Spondylitis

- MRI Spine - Bone marrow edema or sacroiliitis with **one** spondyloarthropathy feature.
- Blood Test - HLA B27+ with **two** spondyloarthropathy features.

Important Information

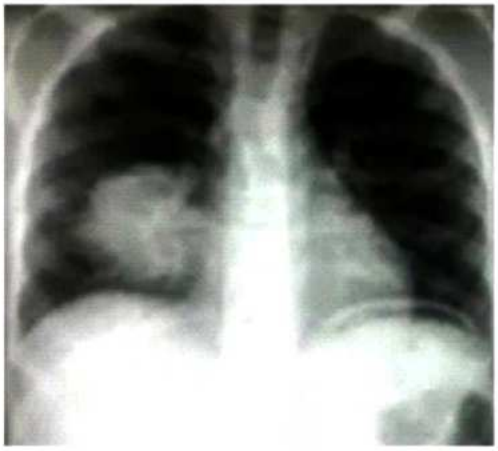
- Imaging > Blood test.

Treatment 00:28:55

- **1st line management:** NSAIDs.
  - There is a limit to the use of NSAIDs, as the nocturnal pain can be disabling - Leads to loss of productivity.
- Sulphasalazine (Described in the Management of IBD, RA).
  - It helps to ease the manifestations.
- **BADSAI Index**
  - Created by Dr. Bath.
  - BADSAI: Bath Ankylosing Spondylitis Disease Activity Index.
  - It is used to analyse the treatment response form the patients with prescribed medications.
  - Patients are quizzed regarding the symptoms on a regular basis.
  - BADSAI Index: >4.
    → This means, biologicals should be started in the patient.
    → Example: Infliximab infusion.
- Methotrexate / Gold salts / Steroids (Intra-articular or oral).
  - There are no disease modifying roles with these medications
  - Using these drugs, only symptomatic alleviation can be done.

42 IgG_4 RELATED DISEASE

Chest X Ray



- CXR shows Circumscribed mass is present on the right lower zone
- By observing the mass on the CXR, the doctor will plan for HRCT or bronchoscopy guided biopsy
- The results show that there is no tumor
- As it is a pseudo tumor, steroids are recommended
- This tumor is caused by plasma cell infiltration in the tissues

IgG_4 Related Disease 00:01:43

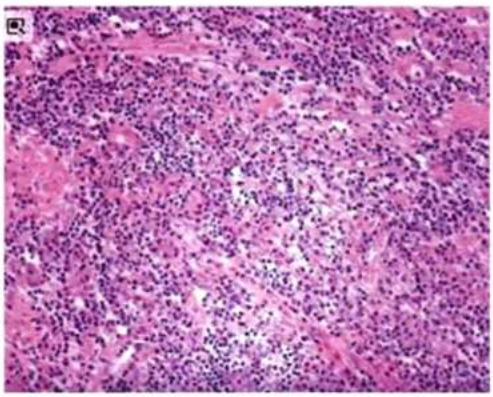
- They will form a tumor like lesions (pseudo tumors)
- These are formed due to the overexpression of immunoglobulin G_4
- IgG_4 is produced from the plasma cells in larger quantities and these plasma cells are infiltrated into the tissues
- Tumefactive lesions will be seen
- **Various Sites include**
  1. Salivary glands
  2. Lacrimal glands
  3. Thyroid gland
  4. Lungs
  5. (Sausage) Pancreas
  6. Hepatobiliary involvement

Diseases	Description
Mikulicz syndrome	• It is the outdated term • It is a subtype of Sicca syndrome/ Sjogren's syndrome • Standard presentation: Dry eyes and dry mouth • It has a progressive enlargement of parotid glands
Ormond Disease	• They were the part of immunoglobulin G_4 related diseases • Tumor or mass is present in the retroperitoneum & grows substantially and cause retroperitoneal fibrosis

To Remember

- These two are historically important diseases
- Recently, these disease are categorized as part of spectrum of the Immunoglobulin G_4 diseases

Histopathological Findings

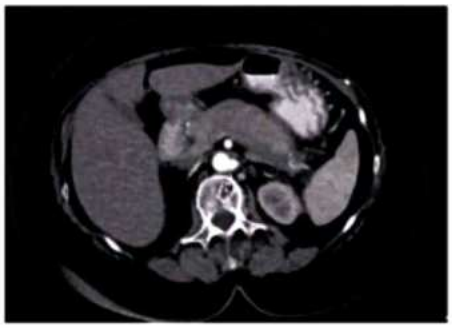


- Blue color spots are the mononuclear infiltrate varieties found in the light microscope
- Multiple fibrotic sites are present in between the fibrotic bands in a criss cross fashion

Histopathological findings

- It helps to differentiate the tumor from pseudo tumor
- This findings include
  1. Storioform fibrosis
  2. Infiltrate plasma cells
  3. Obliterative phlebitis (Damage to veins)

CT abdomen



- Big pancreas present in the image are known as sausage pancreas

Clinical Findings 00:07:50

1. More common in the Males
2. False alarm in the midlife of the male patients
   Rheumatological disorders are more common in women
3. Eyelid or orbital mass will increase in the size (Pseudotumor)
4. Submandibular gland enlargement (Subsequently turned out to be a pseudotumor)
5. Thyroid mass
6. **Fibrosis found in the thyroid gland:** Riedel thyroiditis (Stony hard consistency)
7. **Chest X ray:** Lung pseudotumor
   - Administer steroids and Rituximab (Tumor size will be decreased)
8. **Pancreas:** Sausage pancreas (Incidental findings)
9. Retroperitoneal fibrosis

Investigations 00:10:00

It is a Histological diagnosis

1. Whole body PET Scan
2. Biopsy
3. **Values of IgG and IgG4:** These values will increase 40 times than the normal values
4. **CT abdomen**
5. Bronchoscopy is not required if the mass is located in lung Periphery.

Treatment of Choice 00:11:26

- Steroids and Rituximab

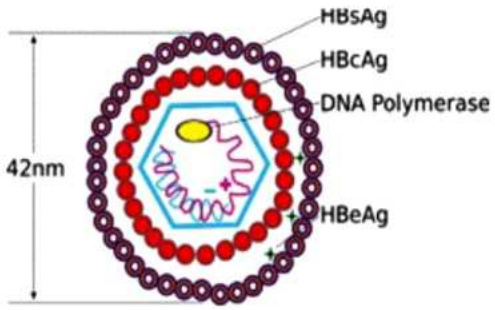
Extra Mile

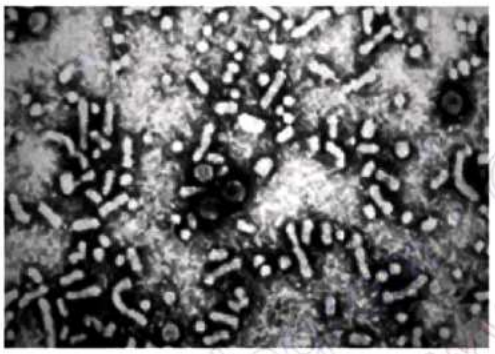
Must know points of IgG_4 related disease:

1. Tumefactive lesions are present
2. Storioform fibrosis
3. Sausage shaped pancreas
4. Steroids and Rituximab

43 HEPATITIS-B

- Leading cause of transfusion-associated hepatitis is Hepatitis B
- On electron microscopy view:
  - A complete virion of hepatitis B termed as Dane particle.





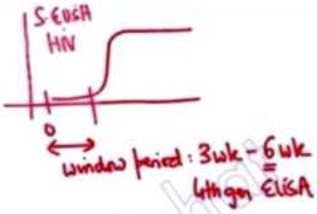
  - **HBsAg**: Surface antigen
    → It is either spherical or tubular in shape.
  - **HBcAg**: Core antigen Found in the nucleus of hepatocytes but never found in the blood.
    → However, antibody to it is seen in the blood.
  - **HBV DNA PCR DNA will be positive in the early phase of disease even before HBSAg**
  - **HBeAg**: Marker for replication or infectivity of the virus
    → Presence of HBeAg is highly infectious.
  - **Pre-core mutant**: HBeAg absent
    → More Severe
    → Replication not detected routinely.
    → Seen in Russia and Central Europe
  - **Escape mutant:** Avoid neutralization with antibody to hepatitis B surface antigen.
    → The manifestation that occurs in this is termed occult infection.

Genome

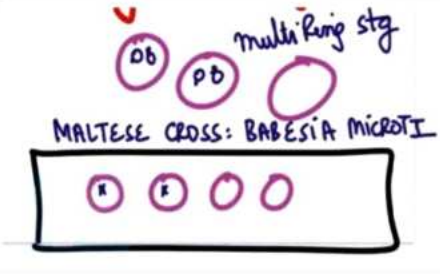
- Partially SS and partially ds circular DNA (3.2 kb): Double-shelled virion and the usual size is 42nm.

Route of Transmission 00:04:35

- Most common: Percutaneous exposure
- Parenteral: I.V. drug abusers.
- Blood transfusion
- **For transfusion, Blood is tested for**



  - HBV (HBsAg is Australian antigen)
  - HCV (EIA anti-HCV antibody, PCR HCV RNA)
  - HIV (ELISA HIV, PCR HIV for earlier identification of disease especially in the window period)
  - Syphilis (FTA- ABS), VDRL for Neurosyphilis and Vertical transmission
  - Malaria: HRP-2 dipstick test
    → On Peripheral smear, banana-shaped gametocytes, and maltese cross appearance.



    → Differential diagnosis is babesia microti.
    → Ixodes scapularis is the vector responsible for it.
    → Management: atovaquone and azithral
- **Vertical transmission: mother to baby**
  - Case scenario: Commercial sex worker in 3rd trimester of pregnancy and her test report as: HBsAg and HBeAg positive
  - Mother has a 90% chance of transmitting to baby during delivery baby or in pregnancy.
  - Management: HB Ig I.M. to be given ASAP within <12 hours (To the child) + Hepatitis B vaccine 3 doses (0, 6, 10 or 14 wks.)
- **Accidental needle stick injury**
  - Occurs mostly while recapping the needle.
  - Chance of transmission is 30%

- Conjunctival inoculation: Due to splattering of blood on the face while handling trauma patient- the risk of infection present
- Management: HBIg I.M. ASAP (within 6 hours)

- Most common cause of chronic hepatitis or chronic liver disease or end-stage liver disease or orthoptic liver transplant is the hepatitis C virus.

Serum markers

00:17:40

- **HBsAg**
  - 1st to appear: 1-12 weeks of infection
  - Earliest serological evidence of hepatitis-B infection
  - Precedes SGPT rise by 2-6 wk.
  - Sequence of appearance: HBsAg positive followed by SGPT raised followed by jaundice.
  - Disappear in the reverse direction.
- **HBcAg**: Never appears in the blood.
- **HBeAg**: Replication or highly infectious
- **HBxAg**: CD 95 inhibitor, it inhibits the extrinsic pathway of apoptosis
  - Triggers development of Hepatocellular carcinoma (HBV >HCV)
- **PCR HBV DNA:** Quantify the viral load

Important Information

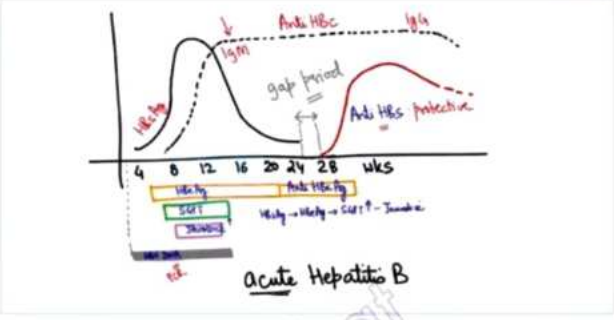
- **Cut off viral load for starting treatment in chronic hepatitis B**: Patient is diagnosed with a case of chronic Hepatitis B and HBe Ag: reactive and viral load is $>2 \times 10^4$ IU/ml with raised SGPT 2x.
- Management: Tenofovir (Drug of choice) or Entecavir
  - Pegylated interferon + Lamivudine (In earlier times)

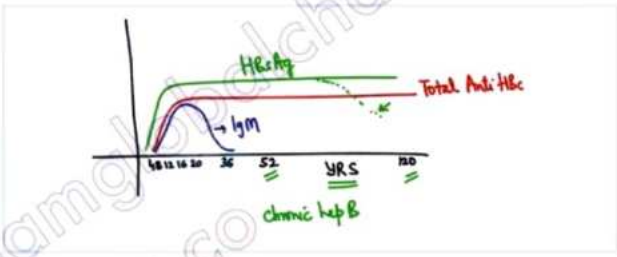
Antibodies Against Hep B

00:23:44

- Anti-HBsAg: Protective antibody
- Anti HBcAg
  - Antibody against the HBcAg.
  - Initially it's an IgM type of antibody later it converts into IgG.
  - IgM: Diagnosis of Acute viral hepatitis and Antibody present in Gap Period or Window period.
  - IgG: Chronic hepatitis
- Anti-HBeAg: Replication rate reduces, and Infectivity reduces.
  - Jaundice will appear at last and is the first to disappear.
- Gap period: it is the period between when the HBsAg disappears and anti-HBsAg appears
  - Only the IgM type of antibody against the HBcAg is present in this period.
- SGPT starts rising before icterus appears.
- Jaundice will disappear but SGPT will take time to get normal.
- Biochemical recovery will take time, but clinical recovery will occur early.
- HBsAg → anti HBeAg → SGPT elevated → Jaundice (but first to disappear)

00:25:35





- Above diagram shows chronic hepatitis B which leads to cirrhosis and ultimately develops End-Stage Liver Disease.
- In chronic hepatitis B the HBs Ag remains detectible for a long time period.
  - In some cases, it shows a decline in a couple of months or years.
- IgG type of antibody against the core antigen persists for a long time period.

Important Information

- Hep B **usually recovers (90%)** even without any medications: due to seroconversion and medication is only given in chronic phase not given in patients of Acute Hep-B.

Case Scenario

00:31:39

- 22-year male comes with complaints of nausea, change in olfaction and taste, Multiple episodes of vomiting, aversion to smoking, Low-grade fever present with right upper quadrant discomfort for the past 1 week.

  On examination:

  1. Icterus present (usually when Serum Bilirubin > 2-3 mg/dL. Sclera (High conc of Elastin that binds with bilirubin) is yellow
  2. Tender hepatomegaly

3. Liver span increased (normal is 12-15 cm)
   - If the liver regress in next few weeks then it means it progression into Fulminant Hepatic failure.
4. No pedal edema
5. No ascites
6. No caput-medusae

Probable diagnosis: Acute Viral Hepatitis

Work–Up of Patient

LFT

1. In hepatocellular jaundice
   - Serum bilirubin ↑
   - SGOT ↑
   - SGPT ↑↑ most specific
   - Serum alkaline phosphatase normal
- In obstructive jaundice
   - Serum bilirubin ↑ (conjugated)
   - SGOT normal
   - SGPT normal
   - Serum alkaline phosphatase increased 4 times
- In hemolytic jaundice
   - Serum bilirubin ↑ (unconjugated)
   - SGOT normal
   - SGPT normal
   - Serum alkaline phosphatase is normal and Splenomegaly can also be seen

2. **USG:** to check echo texture and span of liver
- On USG, Starry Sky Liver appearance seen.
- Free fluid absent.
- Liver span ↑↑ seen in Viral hepatitis

3. Simplified diagnostic algorithm for finding etiology of acute viral hepatitis
- Non-A, Non-B, Non-C" infection means it is either due to Hep-D or E. As in India Hep E is more common due to feco-oral contamination.

HBsAg	IgM Anti HAV	IgM Anti HBc	Anti HCV	
+	-	+	-	Acute Hepatitis B
-	+	-	-	Acute Hepatitis A
-	-	-	+	Acute Hepatitis C
-	-	-	-	Non-A Non-B Non-C

Treatment

00:49:39

Acute Hepatitis B

- 90% cases recover spontaneously
- Bed rest
- Management: Itopride or Mosapride for Nausea
- I.V. fluids (10% dextrose or NS) for dehydration.
- Monitoring

HBsAg	Anti Hbs	Anti Hbc	HBe Ag	
+	-	IgM	+	Acute Hep B Highly infectious
+	-	IgG	+	Chronic Hep B
-	+	IgG	-	Recovery
-	-	IgM	-	Gap period
-	+	-	-	Vaccinated
-	-	IgG	-	Low level carrier/ Remote infection

Important Information

- HBs Ag⊕ + IgM anti HBc: Acute Hepatitis B
- Hbs Ag⊕ + IgG anti HBc: Chronic Hepatitis B
- IgM anti HBcAg present: Gap period
- Anti HbsAg > 10 IU/ml: Vaccinated
- IgG Anti Hbc: Low level carrier

Treatment

- **Chronic Hep B**
   - HBeAg: Reactivity
   - PCR HBV DNA shows >2 x 10^4 IU DNA/ml
   - SGPT shows doubling.
   - Management: Tenofovir 300 mg O.D. for 48 weeks.
   - Monitor KFT while Tenofovir is recommended.
- **Compensated cirrhosis patients.**
   - HBeAg: Reactivity
   - PCR HCV DNA shows 2 x 10^3 IU DNA/ml
   - SGPT raised shows doubling.
   - Drug of choice: Tenofovir 300 mg OD for 48 weeks or Entecavir

Hepatitis A

- Transmission by the fecal-oral route
- Chances of fulminant hepatic failure is 0.1%
- No carriers.
- No progression to chronicity.

- No progression to carcinoma.
- More symptomatic in adults.
- IgM anti-HAV is present.
- Vaccine is available: inactivated vaccine present.
  - Given 2 shots to children.

Hepatitis E

- Most common cause of Acute viral hepatitis.
- Chances of fulminant hepatic failure is . 0.1 – 1%
- Leading cause of fulminant hepatic failure in pregnancy (up to 30%)
- Incidence of Fulminant hepatic failure associated with ~ 20 % HDV.
- Vaccine: Available

Important Information

- Fulminant hepatic failure encountered with all Hepatotropic viruses.
- Chronic hepatis is not associated with hepatitis A, E.
- No vaccine is available against Hepatitis C.
- Complete clinical and biochemical recovery is expected in all cases of HAV, HEV in 1-2 months of post-jaundice.
- Prescribe high-carbohydrate and low-fat diets in all of the patients.

Physical findings to be evaluated in all liver diseases

1. Icterus seen in sclera and frenulum.
2. Spider angiomas are dilated cutaneous arterioles. Found in both acute and chronic liver disease.
3. Palmar erythema
4. Tender hepatomegaly
5. Ascites: Shifting dullness and/or Fluid thrill
6. Encephalopathy: earliest feature is an alteration in sleep pattern.
   - Trail making/Number Connection Test is done
7. Caput medusae, widened pulse pressure.
8. Hyperpigmentation in cholestatic disorders
9. Slate gray Skin in haemochromatosis, xanthoma, xanthelsma, KF ring.

Extra Mile:

- Triggers of Hepatic encephalopathy
  - → GI bleed: Blood is good culture media which helps the bacteria to multiply.
  - → Diuretic excess: loss of water from the body will raise the ammonia levels.
  - → Loss of potassium
  - → Dehydration
  - → Infection
  - → Constipation
  - → Narcotics

Approach to deranged LFT

Hepatocellular jaundice:

- Predominantly rise in ALT
- ALT elevated.
- Alkaline phosphatase elevated.
- Tests done are:
  - IgM Anti HAV
  - HBs Ag, IgM Anti Hbc
  - Anti HCV
  - ANA (anti-nuclear antibody), SMA
  - Ceruloplasmin, alcohol history, drug history.

Obstructive jaundice:

- Alkaline phosphatase increased by 4X.
- GGT is elevated.
- ALT is elevated.
- Tests done:
  - AMA: for primary biliary cirrhosis
  - Drug intake
  - USG: 1st investigation to be done.
  - MRCP

44 HEPATITIS-C-D AND FULMINANT HEPATITIS

Hepatitis C

00:00:24

- Single-stranded RNA virus
- Leading cause of End-stage liver disease (ESLD)
- Liver Transplant (OLT)- MC cause for liver transplant in the world is HCV-induced cirrhosis.
- Most common cause of Transmission is Parenteral
  - IV drug abusers (IVDU) > B.T (Blood transfusion)

Clinical Features

00:04:09

- Extrahepatic manifestations like Arthralgia, Myalgia, Paresthesia's, Pruritus and sicca syndrome-like manifestations
- Other manifestations like MPGN, Lichen planus, porphyria, cutenea tarda and mixed Cryoglobulinemia can be seen
- **Cirrhosis**
  - Hand sign: Palmar erythema, Duputyren's contracture leukonychia, clubbing, asterixis
  - Ascites, pedal edema, caput medusae, oesophageal varices

Workup

00:11:06

- E.I.A (enzyme immunoassay) anti-HCV antibody positive; can be false positive in patients with autoimmune hepatitis
- Investigation of choice is PCR HCV RNA: "no cut off" for management of patient.
- LFT: SGPT may be normal or increased. All patients with chronic HCV infection, detectable HCV RNA with or without elevated ALT, at any stage of fibrosis needs treatment

Treatment is based on Genotype

Harrison 21st edition update: Treatment Naive or relapsed after prior PEG-IFN-Ribavarin Therapy

Genotype 1-6: Sofosbuvir + Velpatasvir 12 weeks Glecaprevir + Pibrentasvir 8 weeks

- Objective is to obtain a sustained virological response > 90%
- Post-exposure prophylaxis: not available.
- Chances of getting infected by HCV after needle stick injury is 3%.
  - Do PCR HCV RNA test if results are positive in within 3 months: then treat as the case of HCV positive.

Hepatitis D - Delta

00:18:22

- Transmission is through Parenteral
- Hepatitis D is an incomplete virus.
- For Eradication: 100% coverage of the population with HBV vaccine should be done

Example

- I.V. drug abuser, Jaundice with HBsAg +. also, IgM anti HBcAg + in Feb 2021. He had to shift his workplace due to police patrolling. While taking IV drugs, he got delta virus in Mar 2021. IgM anti-HDV Ag +

Co-Infection

- IgM anti HBc Ag + IgM anti HDV Ag
- Fulminant liver failure

Example

- IV drug abuser with HBsAg +. also, IgG anti HBcAg + in Feb 2021. He had to shift his place due to police patrolling. He got hepatitis D in Mar 2021. IgM anti HDV Ag +

Superinfection

- IgG anti HBc Ag + IgM anti HDV Ag
- Chronic Hep B + Acute Hep D
- Chronic hepatitis

Drug of Choice

00:26:04

Hep D	α Interferon
Hep B	Entecavir or Tenofovir
Hep C	Sofosbuvir + Velpatasvir
Multiple sclerosis	ß interferon

Important Information

- Most common cause of acute viral hepatitis is Hepatitis - E (Pg 2574: Harrison 21st edition)
- Most common cause of fulminant hepatic failure (FHF) is Hepatitis – D (20%)
- Most common cause of FHF in pregnancy is HEV.

Fulminant Hepatic Failure

00:28:36

Cause

- Toxins > Viral hepatitis, Hepatitis D, Hepatitis E(pregnancy)
- Toxins are:
  - PCM toxicity
  - Halothane
  - A.T.T: Pyrizinamide
  - Amanita (Mushroom) poisoning
- Cut off: < 8 weeks of liver insult, development of
  - Coagulopathy and/or
  - Encephalopathy
- Sub fulminant: cut off: 8-26 weeks

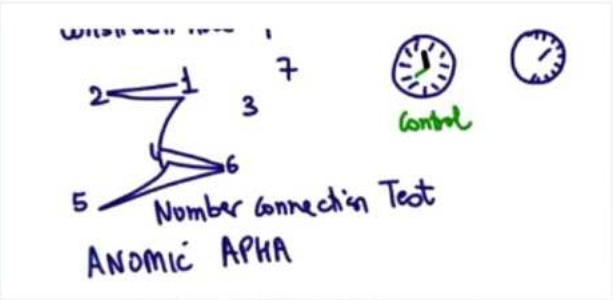
Features of Fulminant Hepatic Failure

00:31:53

1. Jaundice: worsens

2. Bleeding will occur because all clotting factors are produced in liver except Factor VIII: endothelial cell, Factor IV: calcium- Epistaxis
3. Ammonia intoxication/Hepatic Encephalopathy

- **The earliest manifestation of encephalopathy:**
  - A. Alteration of sleep: awake cycle
  - B. Euphoria, slurring of voice.
  - C. Constructional apraxia: Number connection test and Clock face test.



  - D. Anomic aphasia difficulty in naming an object.
  - E. Most Reliable sign: Asterixis (Flapping Tremors)
  - F. Stupor: Coma GCS<8


Asterixis or Flapping Tremors

Extra Mile:
- Fine tremors can be seen in
  - Anxiety neurosis
  - Grave's disease
  - Pheochromocytoma
- Site of ammonia (NH_3) synthesis is Gut flora.
- Hepatic encephalopathy can be triggered by GI bleeding.
  - Internal GI bleeding can worsen hepatic encephalopathy. Thus, stabilizing coagulogram is important.

Work-up of FHF 00:41:03

1. LFT:
   - SGOT is raised.
   - SGPT is raised.
   - Serum Bilirubin is raised.
   - Serum alkaline phosphatase is normal.
2. Coagulogram

		Early	Late
BT (2-9 min)	Platelets	N	N
PT (11-16 sec)	Extrinsic 5,7	↑	↑
aPTT (30-45 sec)	Intrinsic 8	N	↑

   - Factor 7 has the shortest t½ and PT is the first to get deranged.
3. Investigation of choice in fulminant hepatic failure is Blood ammonia levels which are raised.
- On EEG, Triphasic waves and delta waves (Metabolic encephalopathy)

Extra mile:
- Delta waveIn ECG = WPW
- Delta wave in EEG = NREM II
- Discharge frequency of delta waves in EEG is 0.5 – 4 Hz

4. USG: Liver Span decreases
5. KFT: Serum Creatinine levels are raised.

MELD Score: Used to register a patient for liver Transplantation. We can use this score prognosis and referral of the patient.
- The parameters include are:
  - Bilirubin
  - I.N.R or PT
  - Serum creatinine
- If the MELD score is more than 17 is an indication of an orthoptic liver transplant.

Extra Mile
- **MELD-Na: Incorporates serum sodium used to Stratify transplant candidates for organ allocation.**

Child-Pugh Score
- The parameter includes are:
  - Bilirubin
  - INR
  - Albumin
  - Ascites
  - Asterixis
- Class A (score 5-6), class B (score 7-9), class C: ≥10 score. Class B is an accepted level criterion for listing a patient for liver transplantation.

Management 00:48:36

1. Drug of choice: lactulose (Ammonia binder)

- It gives through the Nasogastric tube.
- It causes diarrhea thus, gut bacterial load is reduced.
- More the gut is clear, the lesser will be ammonia production.

2. Rifaximin (bacteriostatic antibiotic) and Neomycin
   - Give through the NG tube.
   - To prevent the multiplication of bacteria in the gut.
3. L.O.L.A (L-ornithine -L-aspartate)
   - It binds to ammonia resulting in the production of glutamine. This glutamine is excreted by the kidney.
4. MARS: Molecular absorbent re-circulating system (liver dialysis)/Extracorporeal hepatic support system.

- Care of bowel, back and bladder for a comatose patient. To prevent the bed sore in the patient.

5. Orthotopic liver transplant is done on the base of the MELD score of the patient.
   - HLA matching is not mandatory.

Important Information

HLA matching is not necessary in:

- Cornea transplant
- Cardiac transplant
- Liver transplant

Discriminant function or score: Used for alcoholic's hepatitis severity

- Serum bilirubin
- INR

- If the discriminant function score >32, it is indication for treatment.
- Management: Prednisolone or Methyl Prednisolone 00:53:17

Scores	Decision-making Tool for
1. NAZER index	Lliver Transplant in Wilson disease
2. MELD	Liver Transplant in Fulminant Hepatic Failure
3. Discriminant function	Alcoholic hepatitis for severity of disease
4. Child – Pugh	For Liver Transplantation

45 HEPATORENAL SYNDROME AND HEPATOPULMONARY SYNDROME

Hepatorenal Syndrome

00:00:17

- It is a complication of Decompensated cirrhosis.
- Seen in 10% cases of advanced cirrhosis.
- Overall poor prognosis and requires Orthoptic liver transplant.
- It is Characterized by oliguria followed by anuria in a patient with liver failure which is primarily because of toxins and due to an imbalance between vasoconstriction and vasodilatation mechanisms in the body
- 40% of cirrhosis patients have refractory Ascites
- HPE: On light Microscopy, glomerulus is normal.
- These patients would develop Pre-renal Acute kidney injury.
- Prostaglandins are important for the maintenance of the glomerular filtration rate.
  - PGE_2 and PGI_2 these are vasodilatory prostaglandins.
  - They will help increase the renal blood flow and increase the glomerular filtration rate to maintain perfusion.
  - In hepatorenal syndrome, Vasodilatory prostaglandins are lost in urine.
  - This causes predominant renal vasoconstriction and the blood supply of the kidneys is hampered.
  - That is why it leads to Pre-renal Acute Kidney injury.
- The damaged cirrhotic liver will be producing endothelin-1
  - This will upregulate the endothelial nitric oxide synthesis enzyme in the splanchnic blood vessels.
  - There will be more nitric oxide synthesis, which will cause splanchnic vasodilation.
  - Shunting of blood away from the kidney cause less perfusion of Glomerulus.
- Orthoptic Liver Transplant (OLT) Leads to restoration of kidney function.

Revised Criteria for diagnosis of HRS

- **Refractory Ascites**
  - Ascites persisting patients even after optimal management of ascites are vulnerable to developing hepatorenal syndrome.
  - Substantial ascites contributes to:
    → Tense ascites
    → Respiratory difficulty
    → Hepatic hydrothorax
- **Serum creatinine**
  - The values of serum creatinine are progressively raised.
  - The values more than 1.5 mg%
  - Muscle mass in the patient is reduced. Rise in 0.3 mg% over the baseline values in 6 hours.
  - Urine output is less than 0.5 ml/kg/hour over 6 hours defines kidney malfunction.
- **Stop diuretics**
  - Diuretics contribute to dehydration which leads to kidney malfunction.
  - Stop the diuretic for the next 2 days.
- **Volume expansion**
  - Use Foley's catheter and central line.
  - Do not give 1.5 liters of normal saline sometimes, it contributes to heart failure.
  - It is safer to do volume expansion with albumin.
  - Dose: 1 g/kg
  - Maximum dose that can be used is ~ 100 grams.
  - Albumin contributes to an increase in oncotic pressure and reduces the amount of ascites in the patient.
  - Ascites is third space loss.
  - If we get this fluid back in the vascular compartment, there is the chance that kidney perfusion will increase and urine output will also increase.
  - If we use foley's or a condom catheter in the patient it will help us to check the rise in the urinary output in the patient
  - Central line in the patient, it will help to check the central venous pressure.
- **No shock**
  - Do vital monitoring to rule out this.
- **No nephrotoxic drug**
  - If the patient is taking any nephrotoxic drug then has to be immediately stopped.
- **No parenchymal disease**
  - It can be ruled out by doing USG.
  - Objective evidence: no parenchymal disease as indicated by proteinuria > 500 mg/day.
  - Demonstrate that there is no evidence of microhematuria at least > 50 RBC/HPF.
  - No abnormality detected in Renal ultrasound.

Clinical Scenario

- Chronic liver disease patient presents with be refractory ascites. He had 2-3 episodes of hematemesis. On examination, vitals are deranged with anuria

Work up:

- Urinary sodium is elevated.
  - In Pre-renal variety of AKI the urinary sodium is less.
  - In acute tubular necrosis, salt is not absorbed, so urinary sodium is high
- Fraction of sodium (FeNa) ≥ 1%

Diagnosis

- Volume depletion contributing to Acute Tubular necrosis, This is not HRS which causes pre-Renal AKI and FeNa is <1%

Types of HRS 00:15:28

Type – 1 HRS

- It is also known as HRS acute kidney injury.
- It is fast progressive in nature and develops over 1-2 weeks

Type – 2 HRS

- It is also known as HRS Non-acute kidney injury.
- This is having a relatively better prognosis than Type -1.
- The disease is slowly progressive, over 3-6 months.

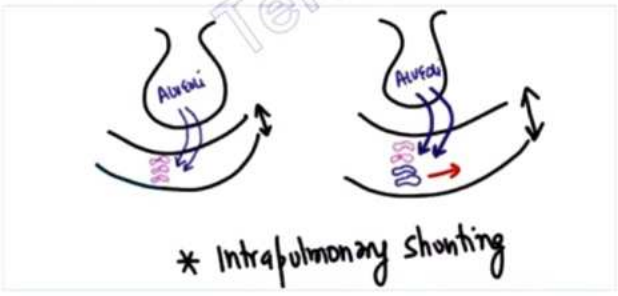
Treatment 00:16:53

1. Albumin with octreotide or midodrine.
2. Octreotide or midodrine: They cause vasoconstriction mainly acting on the splanchnic arteries
   - It results in decrease in venous flow.
   - Manifestations will reduce due to reduction in portal hypertension.
   - It neutralizes the vasodilation occurring in splanchnic arteries.
3. Subsequently, this patient will require liver transplant

Hepatopulmonary Syndrome 00:18:41

Triad of HPS

1. Intrapulmonary shunting
2. Platypnea or Orthodeoxia
3. Cirrhosis



- The damaged cirrhotic liver will be producing Endothelin-1
  - This will upregulate the endothelial nitric oxide synthesis enzyme which is present in the splanchnic blood vessels and pulmonary bed
  - There will be more nitric oxide synthesis, which will cause dilation of pulmonary vessels.
  - If the blood vessel diameter gets increase. A lot of RBCs farther away from the basement membrane might be passing through blood vessels without getting oxygenated.
  - So, there would be hypoxia.
  - It is termed intrapulmonary shunting.
- Platypnea or Orthodeoxia: Due to gravity, there is dilation of pulmonary blood vessels.
  - If the patient is in sitting position, the Weight of dilated blood vessels will mainly affect the basal part of the lung.
  - When this patient lies down flat, the effect of gravity will become relatively equally distributed over the lung.
  - When the patient sits up the SpO_2 will fall by > 5%
  - Fall in pO_2 > 4mm Hg on sitting.
  - PaO_2 < 80 mm hg
  - A-a gradient is raised.

Extra mile:

Causes of Platypnea 00:25:11

1. Atrial myxoma
2. Atrial septal defect
3. Emphysema
4. ARDS

Work up

1. Investigation of Choice: Bubble contrast Echocardiography
   - Risk of air embolism is absent.
   - Pushing up agitated saline into the heart. Simultaneously, do echo-cardiography.
   - The bubble in agitated saline in size of approximately 25 microns.
   - The diameter of pulmonary vessels in normal individuals are 5-8 microns.
   - If there is gross dilation in the pulmonary vessels. The agitated bubbles can pass through it and seen into left atria.
   - It shows that there is intrapulmonary shunting.
2. Lung scan
   - With Tc_{99} labelled particles
   - This having particular size which cannot cross the pulmonary vessels in normal individuals.

Management

- Supplemental oxygen is given.
- Definite treatment: Orthoptic liver transplant.

HPS	HRS
Production of NO is excess	
• Substantial renal vasoconstriction because of urinary loss of prostaglandins. • Decrease in systemic vascular resistance.	• Intrapulmonary shunting

46 AUTOIMMUNE HEPATITIS

- Also known as Lupoid Hepatitis or Plasma Cell Hepatitis
- Untreated autoimmune hepatitis: mortality rate of 6 months is 40% (high)

Pathophysiology 00:01:44

- Cell-mediated damage to liver parenchyma causing interface hepatitis

Causes

1. Idiopathic
2. Loss of immunological tolerance to self-liver Ag's.
3. It is T8 cell-mediated attack on liver antigens directly.

Triggers or Conditions associated with

- HAV, HBV, HCV
- Drugs: minocycline (used in management of acne)
- Autoimmune hepatitis is associated with common autoimmune disorders like:
  - Hashimoto's thyroiditis
  - Celiac spruce
  - Ulcerative colitis
  - Membrano Proliferative Glomerulo Nephritis (MPGN)

Type 1 Autoimmune Hepatitis	Type 2 Autoimmune hepatitis
• Young female • Ethnicity: North America • Ab: associated with ANA (which is also seen in SLE, so it`s also known as lupoid hepatitis) o Anti SMA (actin) o Anti-soluble liver antigen o Atypical p-ANCA (x-ANCA)	• More common with children • Mediterranean or central Europe • ANA absent • Anti LKM1 (can contribute to a false positive diagnosis of Hepatitis C) • Anti-liver cytosol – 1 Ab
HLA associated with • HLA DR3 • HLA Dr4	**HLA associated with** • HLA DR B1 • HLA DQ B8

Important Information

- x–ANCA: Autoimmune Hepatitis
- c–ANCA: Wegner`s Granulomatosis
- p–ANCA: Microscopic polyangiitis and Churg Strauss

Important Antibodies association

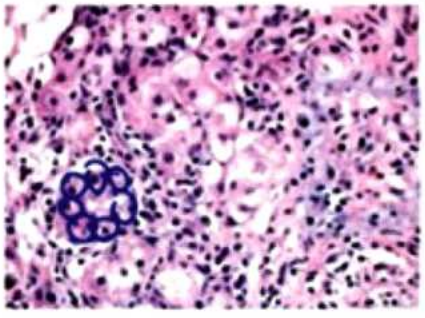
- Anti LKM1: HCV
- Anti LKM2: Drug-induced hepatitis
- Anti LKM3: HDV

Clinical Feature 00:08:49

1. Initially, the patient is asymptomatic.
   - On Routine LFT: SGPT is raised.
2. Symptomatic: Non-specific symptoms
   - Fatigue
   - Anorexia
   - Acne
   - Amenorrhea
3. Jaundice (waxing and waning course)
4. SICCA syndrome (Dry eyes and mouth)
5. Erythema nodosum
6. Cirrhosis (decompensated: Ascites, pedal edema, variceal bleeding)
7. Incidence of HCC is increased

Work Up 00:11:13

1. LFT:
   - S. bilirubin: might be increased.
   - SGPT: Significantly raised.
   - S. Alkaline Phosphatase normal or raised.
2. Albumin ↓ and γ- globulin ↑↑ (change in albumin globulin ratio) and as no catabolism of this protein occurs, therefore it keeps on elevating.
   - Differential diagnosis is Multimyeloma: Albumin is normal and γ- globulin ↑↑
3. Viral serology
4. PT is increased.
5. RA factor is positive.
6. ANA ⊕, SMA (actin), Anti LKM-1 Ab, Liver cytosol 1 Ab.
7. Liver Biopsy
   - Interface hepatitis
   - Rosette formation (this indicates regenerating hepatocytes)



Diagnostic Criteria 00:14:46

- Diagnosis of Exclusion

Excluded causes

- Virus
- Drugs
- Alcohol
- Genetic ds {α-1 AT def, Wilson disease, Menke's disease}

Include

- Antibodies profile, Biopsy findings

Management 00:16:06

- Steroids + Azathioprine
  - Steroid used is prednisolone.
  - Steroid given for a long time leads to steroid toxicity. Cushing syndrome-like manifestation will occur.
  - Steroids will be given at lower dosages. To prevent side effects.
- Late representation: Orthoptic Liver Transplantation In case of decompensated cirrhosis
  - On basis of child Pugh score: Class B Listed for liver transplantation.
  - Disease can re-occur, the incidence is rare

MCQ

Q. Which disease has propensity to reoccur in a transplanted liver? (Recent NEET)

Ans. Autoimmune Hepatitis

47 CIRRHOSIS AND ITS COMPLICATIONS

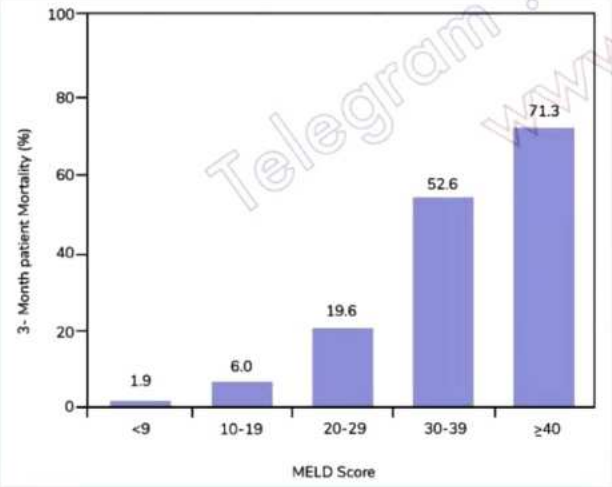
Introduction 00:00:13

- Cirrhosis is reversible.
  - Hepatitis C is the leading cause of the requirement of an orthoptic liver transplant, as it pregresses into chronic hepatitis C
  - Hemochromatosis
  - Alcohol liver disease

Scores determining Mortality 00:02:22

MELD Score (Model for End-Stage Liver Disease)

- Parameters are:
  - Serum bilirubin
  - INR
  - Serum creatinine
- Lower limit is 6 and the higher limit is 40.
- Higher the score enlists for an orthoptic liver transplant.
- United network for organ sharing MELD Score > 17: enlist for an orthoptic liver transplant.
- If a Liver transplant has to be done, it should be planned before the value of 20, because after this steep rise in mortality rate occurs.



MELD – Na

- Parameters are:
  - Bilirubin
  - INR
  - Creatinine
  - Serum sodium
  - Need for kidney dialysis.

Dialysis at least twice in the past week	No	Yes
Creatinine	Norm: 62 - 115	µmol/L
Bilirubin	Norm: 5.13 - 32.49	µmol/L
INR	Norm: 0.8 - 1.2	
Sodium	Norm: 136 - 145	mmol/L

PELD score

- Parameters are:
  - Bilirubin
  - INR
  - Albumin
  - Age
  - Growth failure

Child-Pugh score

- Parameters are:
  - Bilirubin
  - INR
  - Albumin
  - Ascites
  - Asterixis
- Category
  - A: 5-6 (Compensated cirrhosis)
  - B: 7-9 (Decompensated cirrhosis)
  - C: >10
- Category B: Enlist for liver transplantation

	1	2	3
Encephalopathy	None	Grade 1-2 (or precipitant induced)	Grade 3-4 (or chronic)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	> 3
Albumin (g/dL)	> 3.5	2.8-3.5	< 2.8
INR	< 1.7	1.7-2.3	> 2.3

Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)
Class A = 5 to 6 points (least severe liver disease)

- If decompensated cirrhosis will occur the manifestation of encephalopathy and/or Coagulopathy will develop.
- If there is an internal GI bleed, it contributes to more bacterial growth. The bacteria proliferate to produce more ammonia in the intestine. It will precipitate hepatic encephalopathy.

Invasive test

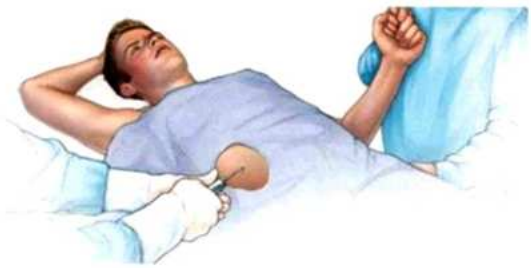
00:14:27

Liver Biopsy

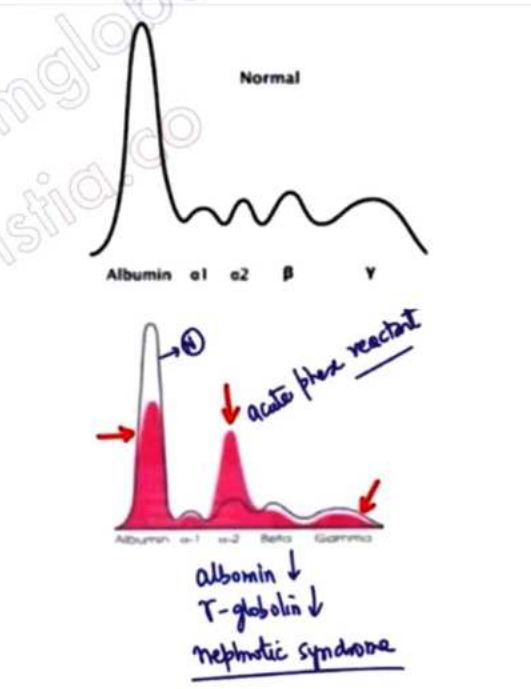
- Must always be done USG guided.
- Coagulogram should always be normalized before liver biopsy, as bleeding chances will be high in cirrhotic patients.
- Preferred site: midaxillary line 7th or 8th intercostal space.
- Liver biopsy is the most accurate to assess the severity of the chronic liver disease.
- Grading is done by using the METAVIR or ISHAK score.

Metavir score system	Fibrosis stage
F0	• No fibrosis can be detected
F1	• Fibrosis exists with the expansion of portal zones
F2	• Fibrosis exists with the expansion of most portal zones, and occasional bridging
F3	• Fibrosis exists with the expansion of most portal zones, marked bridging, and occasional modules.
F4	• Presence of Cirrhosis

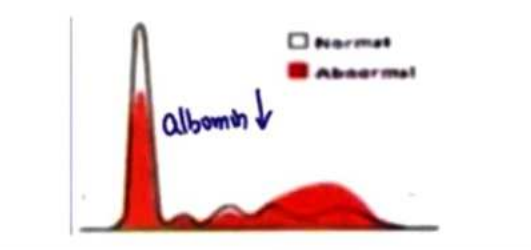
Ishak grade	Categorical description
0	No Fibrosis
1	Fibrosis expansion of some portal areas, short fibrosis septa
2	Fibrosis expansion of most portal areas, short fibrosis septa
3	Fibrosis expansion of most portal areas with an occasional portal to portal (P-P) bridging
4	Fibrosis expansion of portal areas with marked bridging (P-P) as well as portal-central (P-C)
5	Marked bridging (P-P and/or P-C) with occasional nodules (incomplete cirrhosis)
6	Cirrhosis, probable or definite



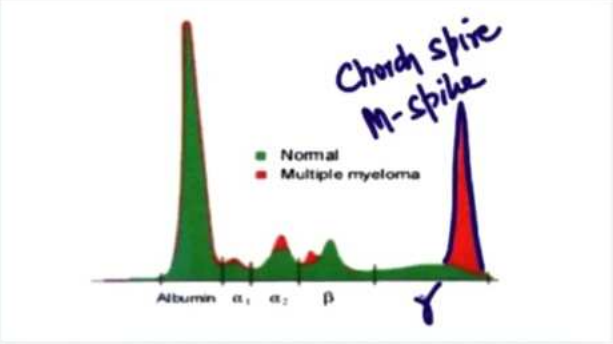
- Transient elastography (Fibroscan): Measure the speed of shear wave which is generated by vibration.
- Fibrotest:
  - Bilirubin
  - Gamma-GGT
  - Haptoglobin
  - Apolipoprotein A
  - α_2 Macroglobulin,
- **Serum electrophoresis**:



- In Nephrotic syndrome: Albumin decreases, γ Globulin decreases



- In chronic liver disease: Albumin decreases and γ Globulin is elevated.
  - Because catabolism of globulin occurs in the liver and if the liver is damaged it will not occur.



- In multiple myeloma: There is spike in the γ Globulin give a characteristic church spire of M spike appearance.

Albumin	Globulin	Condition
↓	↓	Nephrotic syndrome
↓	↑	Cirrhosis
Normal	↑↑↑	Multiple myeloma/plasmacytoma

Important Information

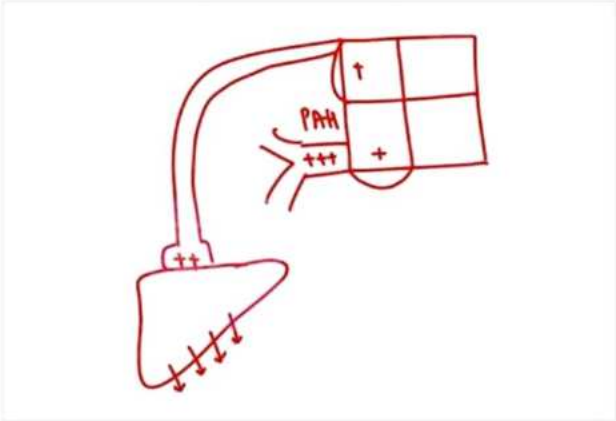
- Most common cause of cirrhosis is Alcoholic Liver disease.
- Most common cause of Orthoptic Liver transplant is Hepatitis C.

Causes of cirrhosis

00:26:55

1. Alcoholic liver disease
   - Alcohol once goes into the body then it will be metabolized through cytosolic alcohol dehydrogenase.
     - → This is going to produce acetaldehyde which will be causing reactive oxygen species to contribute to damage to liver cells primarily.
     - → Kupfer cells are also activated producing Cytokines These Cytokines trigger activity in hepatic stellate cells that cause fibrosis and causing micro-Nodular cirrhosis.
     - → In the initial part of alcoholic cirrhosis, it's micronodular cirrhosis.
     - → If there is a complete absence of alcohol this can be reversed back to normal
     - → The definition of micronodular size would be less than 3 millimeters.
2. Hepatitis B or C or D
3. Autoimmune hepatitis
4. Primary biliary cholangitis / Secondary biliary cholangitis / primary sclerosing cholangitis
   - Primary biliary cholangitis that can deteriorate into primary biliary cirrhosis.
   - Antimitochondrial antibody was seen in Primary biliary cirrhosis.
   - P-ANCA antibody is seen in Primary sclerosing cholangitis.
5. NASH
   - Obesity contributes to non-alcoholic steatohepatitis.
6. Wilson or hemochromatosis
   - For Wilson disease: Done specialized test 24-hour urinary copper.
   - For hemochromatosis: check out the percentage saturation of transferrin along with ferritin values.
7. Alpha 1 antitrypsin deficiency
   - Which can be associated with both emphysema and bronchiectasis.
   - The production of alpha 1 antitrypsin is normal but excretion is hampered.
   - It will accumulate in the hepatocytes, so it is PAS-positive inclusion present in hepatocytes.
   - There is a special phenotype of this that is called double ZZ phenotype which has a higher incidence for the development of cirrhosis.
8. Cardiac cirrhosis
   - This is rare.
   - COPD patients could be having cardiac cirrhosis.
   - Read in pathology as nutmeg liver.
9. Cryptogenic cirrhosis / non-cirrhotic portal fibrosis (NCPF).

- Line diagram for cardiac cirrhosis: There is a patient with COPD who is suffering from pulmonary artery hypertension.



- Starting from Cor Pulmonale then there was pulmonary artery hypertension, then there was a right ventricular decompensation that was occurring in the patient and leads to hepatomegaly.
- The stellate cells cause fibrogenesis that will result in shrinkage of the liver.
  → Liver span will regress.
  → In pathology, term nutmeg liver and in medicine, the term cardiac cirrhosis.

Manifestation of compensated cirrhosis

00:36:36

1. Spider Naevi or Spider angioma: Fine dilated cutaneous arterioles
   - Site: Over the shoulders and over the neck of the patients so they would be present on superior vena cava distribution.
   - Oestrogen is responsible for it.
   - It is not a pathognomonic finding that may also be seen in pregnancy and rheumatoid arthritis.
   - If you press on the center you see there is a central filling of arteriole
   - if you press on it will blanch, but when you let it go, it will start filling from inside to outside.
2. Palmar erythema: Areas of redness and in some areas blanching present alternatively in the palms.
3. Duputyren's contracture: Can begin in the ring finger and then can involve the little finger as well.
4. Clubbing: There is release of platelet-derived growth factor causing proliferation of tissues at the base of the nail leading to bulbous appearance of the Nail.
   - Clubbing is also seen in inflammatory bowel disease.
5. Parotid enlargement
   - There is an inter-stromal fatty infiltration present in alcoholic cirrhosis.
6. Testicular atrophy: Gynecomastia, decreased body hair and muscle wasting which will be predominant proximal muscle wasting and temporal muscle wasting.

- If the patient goes into decompensation then 50% of these patients would be dead over next 3 to 4 years.

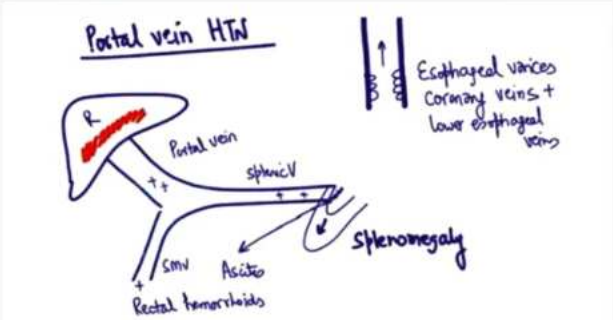
00:13:47

Refer Table 47.1

- Decompensated cirrhosis leads to development of Portal hypertension
- The oesophageal varies which develop initially is non-bleeding. So, we can start the patient with Propranolol or Nadolol.
- Once the pressure becomes substantially high usually more than 12 mm Hg these varices can burst to result in life-threatening hematemesis and hemorrhagic shock.

Portal Hypertension

00:44:52



- The Normal pressure in the portal vein is usually less than 5 mm Hg.
- Fibrosis in the liver will increase the resistance leading to increase pressure in the portal vein.
  - This will be transmitted to the splenic vein resulting in enlargement of the spleen.
  - Splenomegaly is one of the early findings of portal hypertension.
  - When the size of the speed increases, it can also contribute to the development of hypersplenism.
- The increase of the pressure in the splenic vein there is transudation of fluid from the capillary bed into the peritoneal cavity there would be also the development of Ascites.
  - Puddle sign present
  - Shifting dullness, fluid thrill present.
- Subsequentially, the pressure will increase in the superior mesenteric vein resulting in rectal hemorrhoids.
- The oesophageal veins are thin, they can rupture resulting in oesophageal vertices. Once it ruptures cause life-threatening hematemesis and contributes to hemodynamic compromise occurring in the patient.
- Nitric oxide is liberated from a damaged liver cirrhotic liver ultimately causes vasodilation so there would be more blood flow pressure in this entire circuit and the higher blood flow also contributes to an increase in hydrostatic pressure resulting in ascites.
- Definition of portal hypertension is
  - Hepatic venous pressure gradient (HVPG) of more than 5 mm Hg
  - Esophageal varices when the pressure should usually be in excess of 12 mm Hg.

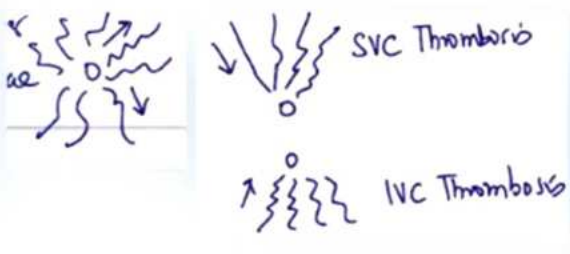
Investigation of choice

1. On USG, the Liver span is reduced.
   - Free fluid in the peritoneal cavity.
2. On the Doppler scan (investigation of choice for diagnosis): Used to measure the pressure gradient.

Extra mile

Porto-systemic collateral sites are

1. Esophageal veins
2. Rectal hemorrhoids: so fresh blood in the stool can be present.
3. Bare area of the liver
4. Caput medusae: This would be dilated veins present around the umbilicus.



   - Dilated veins which are present only above the umbilicus: due to superior vena cava thrombosis.
   - Dilated veins which are present only below the umbilicus: due to inferior vena cava thrombosis.
5. Omental veins
6. Retroperitoneal veins
7. Lumbar vein

Important Information

- Overall, the Most common cause of Hematemesis is peptic ulcer disease.
- The common cause of Hematemesis with Splenomegaly is Portal hypertension

Causes of Portal Hypertension 00:54:09

Pre hepatic	Hepatic	Post hepatic

• Portal vein thrombosis
• Splenic vein thrombosis
• Banti syndrome (massive splenomegaly)
  ○ Idiopathic and more common in Japan.
	• Pre- sinusoidal
	  ○ Schistosomiasis
	• Sinusoidal
	  ○ Cirrhosis
	• Post sinusoidal.
	  ○ Veno occlusive disease
	  ○ Radiation, Herbal tea
		• Budd Chiari Syndrome
		• Inferior vena cava webs
		• Restrictive cardio myopathy
		• Constrictive pericarditis (compliance will reduced)

Important Information

Bantu syndrome:

- Found in Africa.
- There is iron overload. Due to the consumption of local beer which is stored in iron utensils.

Management

For non-bleeding oesophageal varices:

- Endoscopic variceal ligation or
- Drugs: Nadolol or Propranolol

For bleeding esophageal varices with having haemodynamic compromise:

- Massive blood transfusion: Meanwhile, you can secure grey cannula access preferably putting 2 wide bore cannulas in a patient.
  - It is the initial step of management.
  - Give I.V. fluid which will be normal saline in decompensated shock.
- Drugs: I.V. octreotide
- Upper GI endoscopy
- Endoscopic variceal ligation
- Sclerotherapy: Sclerosing agent is Ethanolamine oleate
- Patient might even be having a Portal Gastropathy that is even if you do ligation of all the esophageal varices, since the blood vessels of the stomach will also be dilated so the blood might be coming from the stomach.
  - So, in some cases if there is recurrent bleeding inspite of EVL it is mainly due to portal gastropathy.

For recurrent variceal bleeding patients:

- In esophagus, after endoscopic variceal ligation there is a possibility that the new veins are developed which are grossly dilated and rupture. So, we can repeat endoscopic variceal ligation.
- If bleeding is controlled: (Child Pugh staging in the patient has to be done)
  - In Class A (compensated cirrhosis): Plan a peritoneal Venous shunt to decrease the portal vein pressure
    → If the patient is not willing for it then the TIPS procedure can be done.
  - In Class B and C (decompensated cirrhosis): Do Transplant evaluation.
    → If the child Pugh score is more than 7 then enlist the patient for orthoptic liver transplantation
    → TIPS is recommended in this particular case.
- In both cases, Orthoptic liver transplantation is a required.

Ascites 01:08:44

- Amount of peritoneal fluid is present in normal man is nil.
- Amount of peritoneal fluid is present in normal female is nil.

- In mid cycle ovulatory female: 10 – 20 ml
- Normal Pleural fluid is 5-15 ml.
  - Minimal pleural fluid effusion
    → Investigation of choice is CT chest > USG.
- Normal Pericardial fluid is 20-50 ml.
  - Pericardial effusion
    → Investigation of choice is echocardiography.
- > 100 ml of peritoneal fluid: Puddle sign is detectable.
- > 500 ml of peritoneal fluid: Shifting dullness is detectable.
- Fluid thrill or fluid wave sign: There is a high chance of false positive results.
- Superficial veins of the anterior abdominal wall become more prominent and gradually it becomes tortuous.
- There is everted umbilicus which is due to an increase in ascites fluid.
- Subsequently, there is the development of Respiratory distress in the patient, when it deteriorates into Tense Ascites
- Some of the fluid passes through fenestrations into the pleural cavity leading to respiratory distress results in Hepatic hydrothorax in the patient.
- Minimal fluid to be present in the peritoneal fluid to be detected clinically is ~ 1500 ml.
- If we don't intervene it deteriorates into abdominal compartment syndrome (pressure in the peritoneal cavity is so much that it compresses the veins).
  - Abdominal compartment syndrome is grade higher than intra-abdominal hypertension.
  - If the pressure due to ascites fluid is more than 25 mm Hg.

Management 01:18:13

1. Salt-restricted diet
2. Diuretics: Spironolactone + Furosemide
   - Maximum amount Dosage of spironolactone given is 400 mg.
   - Maximum amount of Dosage of furosemide given is 160 mg.
3. **Refractory Ascites:** after medical treatment there, ascites is occurring again.
   - Spironolactone causes painful gynecomastia as a side effect. So, Amiloride instead of spironolactone is used.
   - Midodrine: it is vasoconstrictor.
     → It α_1 agonist.
     → It will cause constriction of the splanchnic artery. Flow to the splenic vein is also reduced.
     → Reduced portal hypertension.
     → Transudation occurring in the capillary bed around the spleen is also reduced.
     → Development of ascites is also less.
   - Clonidine: also, a vasoconstrictor.
     → It α_2 agonist.
   - If inspite of maximum dose of these drugs, Large volume paracentesis is recommended.
   - Either, large-volume paracentesis or TIPS has to be performed.
- Large volume paracentesis: Draining the fluid from the body it aggravates the dehydration.
  - Rise of ammonia concentration in the body.
  - Substantial rise in ammonia can trigger asterexis.
  - IV albumin is given with LVP to neutralize.
    → IV albumin raises the oncotic pressure. It will cause the mobilization of fluid back into the intravascular space.
- TIPS is superior to prevent the reaccumulation of fluid in the liver.
- Side effect is hepatic encephalopathy.
- Mortality reduction with LVP with albumin is equal to TIPS.
- β blockers are contraindicated in refractory ascites as they will increase mortality. Notice that β blockers were DOC for Non bleeding O.varices.

Serum albumin ascites gradient (SAAG) 01:29:36

Refer Flow Chart 47.1

- Albumin present in the ascitic fluid is subtracted from the Serum albumin.

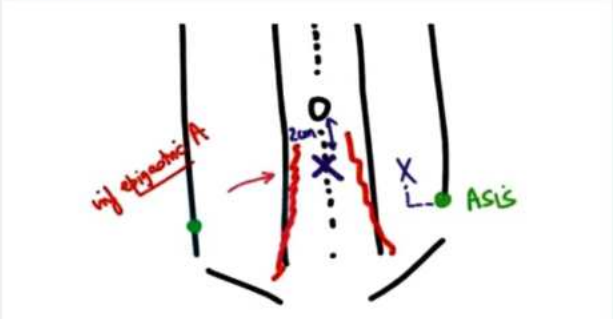
Management

- Serial LVP with albumin
- Peritoneo venous shunting can be done.

Black ascitic fluid

- Causes
  - Pancreatic necrosis due to hemorrhagic pancreatitis.
    → May be secondary to Peptic ulcer disease.
    → SAAG value is less than 1.1 g/dl.
    → Amylase in ascitic fluid is raised.
  - Malignant melanoma

Paracentesis



- Position: The head end is slightly elevated of the patient so that fluid tends to move down into flanks so it is easy to tap.
  - Preferably Done from the left side because there is a higher incidence of gut perforation on right side.

- Angle: Needle introduced at 45° in Z tracking to minimize the leakage subsequent to tap.
- Anatomical localization: 2 cm below the umbilicus in the midline (linea alba) or in left lower flank as shown in diagram
  - This area is avascular, so it is safe.
  - Inferior epigastric artery is present lateral to the rectus abdominis muscle.
  - So, Either do the procedure medial or lateral to it.
  - Another site is 4 cm supero medial to the anterior superior iliac spine to avoid trauma to the inferior epigastric artery.
- Collected fluid sent for the microscopic examination, cytology, gram stain, and culture is done.
- Sugar and protein value has to be checked.
- In Secondary peritonitis, sugar values are very low and LDH values are raised.
- Dark brown: Seen in biliary tract perforation.
- Coagulopathy is a relative contraindication.
- Always perform Paracentesis USG guided, to avoid medico legal issues.

Spontaneous abdominal bacterial peritonitis (SBP) 01:51:05

- Case scenario: Patient having refractory ascites presents with breathing difficulty. On examination patients is grossly malnourished with alcoholic liver disease.
- SBP be prevented by performing Paracentesis in a patient within 12 hours of admission.
- Bacteria (E.coli) present in the gut exhibit transmigration or translocation to lymph nodes then disseminate to peritoneal fluid. This leads to peritonitis.

Clinical features

1. Fever
2. Nausea or vomiting
3. Worsening of ascites/Increase in girth of the abdomen.
4. Encephalopathy

Diagnostic ascitic tap:

- Fluid is Turbid in nature.
- More than 250 PMN cells/ cubic mm.
- Do gram stain and culture.

Management

- IV cefotaxime.
- To prevent the patient from developing SBP: Norfloxacin is recommended.

Systemic inflammatory response syndrome (SIRS)

- Presents with
  - Fever
  - TLC Raised
  - Increased respiratory rate
  - Increased pulse rate.
- For diagnosis of SIRS: 2 out of the above 4 have to be present.
- If not intervened during this it will lead to sepsis.
- Sepsis: SIRS with positive blood culture report.

Septic shock

- It will decrease the perfusion of the kidney leading to acute tubular necrosis.
- Sepsis criteria will be satisfied with hypotension less than 90/60 mm Hg in spite of using vasopressor.
- Vasopressor of choice in septic shock is Norepinephrine.

Extra mile

Summary 01:57:45

- Bleeding esophageal varices: Endoscopic variceal ligation.
  - Nadolol or propranolol.
- Refractory ascites: LVP with albumin
  - TIPS
- Spontaneous bacterial peritonitis: cefotaxime
  - Primary prevention: Norfloxacin.
- Hepato – renal syndrome: Albumin with octreotide or midodrine.
- Hepato – pulmonary syndrome: oxygen supplementation.
- Bleeding or coagulopathy: Fresh frozen plasma.
- Encephalopathy: lactulose
  - Rifaximin
  - Neomycin
- Malnutrition
- Osteoporosis
- Hematological: macrocytic anaemia.
- ZIEVE syndrome: severe alcoholic hepatitis.
  - Acanthocytes and spur cells present.

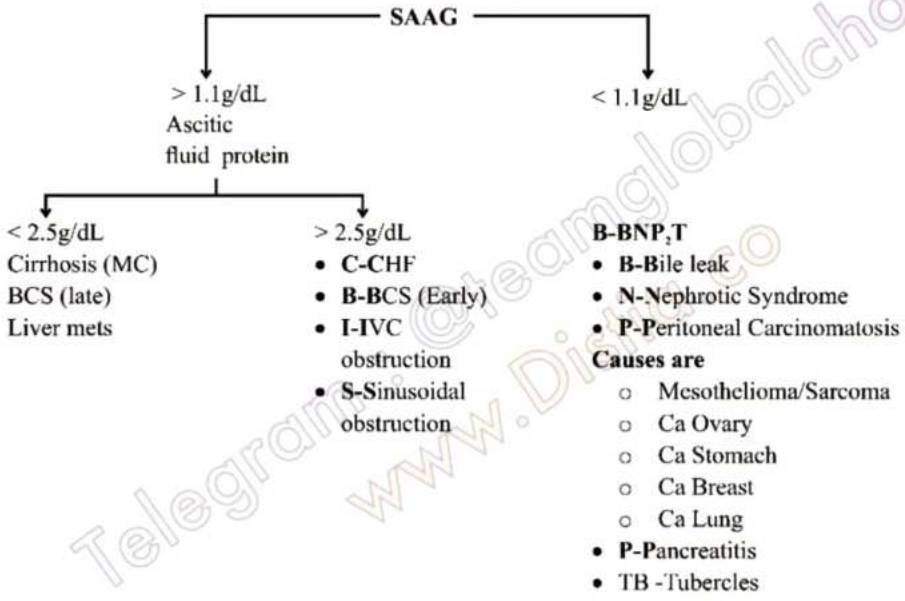
Orthoptic liver transplant (OLT)

- HLA matching is not mandatory.
- UW solution cold ischemia time ~ 20 hours.
  - Ideal is ~ 12 hours.
  - Components: lactobionate
    → Raffinose. 02:07:06
- Donor adult: Right lobe
- Donor adult for the child: Left lateral lobe.
- There might be postoperative biliary complications.

Table 47.1

	Compensated Cirrhosis		Decompensated cirrhosis	
Stage	**Stage 1**	**Stage 2**	**Stage 3**	**Stage 4**
Clinical	No Varices No Ascites	Varices + No Ascites	Ascites +/- Varices +	Bleeding +/- Ascites +
Death (at 1 year)	1%	3%	20%	57%

Flow Chart 47.1



48 PBC AND PSC

Primary Biliary Cholangitis 00:00:49

- Autoimmune disorder: due to Anti Mitochondrial Antibody (AMA)
- It is primarily an intrahepatic lesion.
  - Damage to cholangiocytes
  - Initial manifestation is features of cholestasis.
  - There is development of granuloma formation and ductsopenia.
  - Last cirrhosis occurs.
    → Micronodular (Most common)
    → Macronodular

Important Information

- Antimicrosomal antibody is responsible in Hashimoto thyroiditis.

Staging

- Stages I – Portal stage of Ludwig
- Stage II – Peri portal damage
- Stage III – Septal damage
- Stage IV – Cirrhosis

Clinical features 00:03:58

Occur in 40 – 60 years age group.

- Most common in female

1. Fatigue: Most common and earliest manifestation.
2. Pruritus followed by Lichenification of skin
   - When there is liver damage, there is the production of the endogenous opioid peptides responsible for pruritis
3. Jaundice and hepatomegaly
4. Palmar Erythema
5. Spider naevi
6. Temporal and proximal muscle wasting.
7. Ascites, caput medusae
8. Collaterals present
9. Xanthoma or xanthelasma (over eyelids): LDL is elevated in these patients. Receptors of LDL uptake are hampered.
   - Initially, LDL and HDL values are elevated.
   - In a later stage, LDL values are elevated and HDL value is reduced.
10. Steatorrhea, deficiency of fat-soluble vitamins.
11. Osteopenia: Due to vitamin D deficiency.
12. SICCA syndrome manifestations present. (Dry eyes, dry mouth)
13. Kayser - Fleischer Ring: a rare manifestation of the disease

Work up 00:11:38

1. LFT
   - Bilirubin: it keeps fluctuating over the course of time.
   - SGOT, SGPT is normal or maybe slightly increased.
   - Serum Alkaline phosphatase: elevated (shows up to 4 times elevation).
2. AMA is positive.
   - Mitochondrial antigens ($M_1 - M_9$).
3. ANA positive in ~ 20 – 50% of the patients.
4. Prothrombin time is elevated.
5. INR increased.
6. Platelet count is reduced: Hypersplenism due to portal hypertension.
7. Deranged Lipid profile.
8. USG: To rule out any extrahepatic cause.
9. Liver biopsy: Investigation of choice

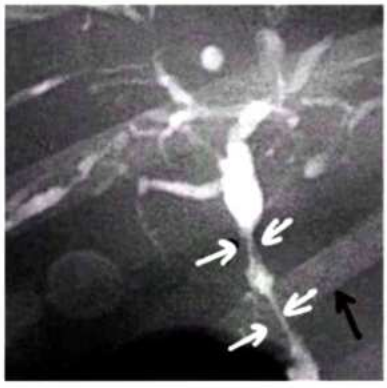
Management 00:17:15

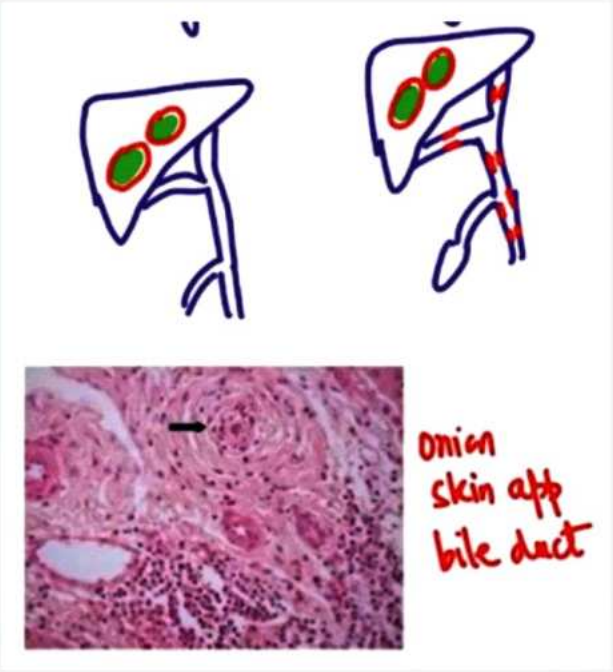
- UDCA (Ursodeoxycholic acid): Slow the progression of the disease.
- Obetocholic acid: if there is intolerance to UDCA.
- Cholestyramine: is a sequestrant.
- Anti histaminics
- Dronabinol: neutralizes the endogenous opioids peptide.
- Naltrexone
- Plasmapheresis: Given in case the patient deteriorates in spite of medical treatment.
- Treatment of choice is an Orthoptic liver transplant.

Differential diagnosis

1. Autoimmune hepatitis
2. Primary sclerosing cholangitis
3. Sarcoidosis

Primary Sclerosing Cholangitis (PSC) 00:21:45





- On ERCP in patients: multiple strictures present in the extrahepatic biliary pathway give a characteristic beaded appearance.
- Characteristic onion skin appearance of the bile duct on biopsy.
- It Is a multifactorial disease.
- Autoimmune is one of the components.
- Genetic predispositions play an important role in the development of the disease.
- Risk of cholangiocarcinoma incidence increased.
  - Because of PSC association with ulcerative colitis.
  - Ulcerative colitis is a premalignant condition and predisposes to Colon Ca.
- When cholestasis is present in the patient conjugated bilirubin is not get excreted.

Clinical features 00:25:38

1. Pruritis
2. Icterus: Waxing and weaning course values may touch normally in between.
3. Steatorrhea
4. Vitamin D deficiency manifestation occurs: Osteopenia.

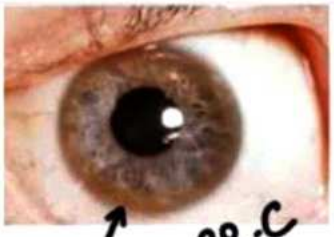
Work up 00:27:20

- LFT deranged
- Serum Alkaline Phosphatase elevated up to 4 times.
- Gamma GTP elevated.
- Hypergammaglobulinemia (IgM) is elevated.
- PT is increased.
- Albumin value is reduced.
- pANCA is positive in 65% of total cases.
- 50% of total cases: are associated with Ulcerative colitis.
- Investigation of choice is MRCP > ERCP.
  - On ERCP: Beaded appearance or multiple strictures
- Liver biopsy: Onion skin appearance

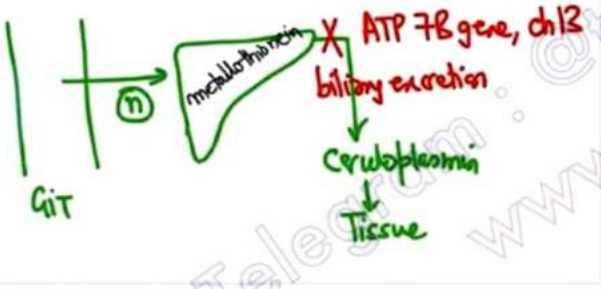
Management 00:30:15

- UDCA
- ERCP: dilation of strictures
  - Balloon dilatation
- Orthoptic liver transplant (OLT): is the mainstay of treatment.

49 WILSON DISEASE AND HEMOCHROMATOSIS



- In Wilson disease, absorption of copper from the gut is absolutely normal.This copper binds to a protein named metallothionine in the liver.
  - From the liver copper in excreted and is transported to the tissues bound to ceruloplasmin.



- In Wilson disease hepatobiliary excretion of copper is less causing accumulation of copper in Hepatocytes.
- Ceruloplasmin levels are reduced in Wilson disease.
- Ceruloplasmin is also reduced in:
  1. Alcoholic cirrhosis
  2. Nephrotic Syndrome
  3. Kwashiorkor
- Hence Ceruloplasmin has less utility for diagnosis.
- In the Body, total Copper is 50-100 mg. Consumption of Cu: 2-5 mg/day.
- The problem in Wilson disease is defective biliary excretion of copper due to a defect in the ATP7B gene (on chromosome 13)
- It is autosomal recessive in inheritance.
- There is P-type ATPase enzyme activity linked to this gene and this activity is defective.
- Amount of copper in the liver increases leading to the development of cirrhosis.
- Subsequently, decompensated cirrhosis and portal hypertension will be occurring.

Extra mile:

- ATP 7A: Menkes disease (Cu deficiency)
  - Case scenario: A boy with mental retardation with kinky hairs

Clinical Features

00:07:12

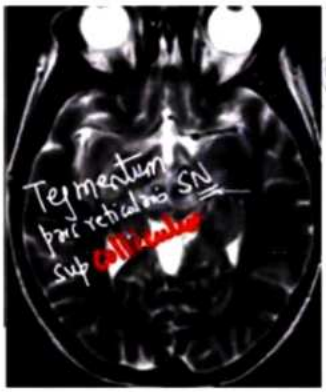
Occur in >5 years and < 50 years of age.

1. In the liver: chronic hepatitis manifestations develop
   - Icterus
   - Deranged liver enzyme.
   - Viral markers are negative.
   - Copper will damage the hepatocytes resulting in cirrhosis.
   - Initially, it is compensated later it becomes decompensated.
   - Child presents with a history of repeated hospitalization.
   - Compensated cirrhosis
     → Spider naevi
     → Palmer erythema
   - Decompensated
     → Portal hypertension
     → Splenomegaly
     → Refractory ascites
2. Neuropsychiatric manifestation
   - Damage to Basal genglia: Lenticular nucleus
   - Midbrain and Cerebellum may also get involved.
   - Earliest neurologic manifestation: Resting tremor, postural, kinetic.
     → Parkinsonism-like manifestations
     → Dysarthria, rigidity related to the vocal cord as well.
     → Drooling of saliva
     → Incoordination
   - Psychiatric manifestations
     → Impulsiveness, disinhibition.
     → Emotional lability: child cries without any reason.
     → Migraine like headaches (Pulsatile)
     → Temper tantrums
3. Hemolytic anemia
   - Free copper in the blood is toxic to RBCs.
   - Copper level is increased Hemolytic episode.
   - In the late phase, the serum copper is less because it is deposited in the tissues and excreted into the urine.
4. Joint: premature osteoarthritis
   - Because copper gets deposited in the synovium.
5. KF Ring: it is present as 10 – 12 years of age but not visible.

- KF ring initially, develops into the upper part of the cornea.
- Upper 2 mm is not visible to the naked eye because it is covered by eyelids.
- Usually, by 15 years of age or older the lower part of the cornea gets involved.
- Increases in the circumferential fashion involves the cornea.
- Descemet membrane gets involved. (Examined under slit lamp).
- Greenish brownish ring.

6. KF ring with neuropsychiatric features are diagnostic accuracy of 95 – 98%.
7. Kidney: Urinary copper is significantly increased leading to damage to PCT and glomerulus.
   - Which leads to gross hematuria, Fanconi syndrome, Renal glycosuria, and aminoaciduria.
8. Other rare clinical features seen in Wilson disease:
   - Azure nail: lunule is blue in color and present in the nail bed.
   - In females: amenorrhea, cholelithiasis, nephrolithiasis.
9. Cardiac involvement: there is a conduction defect in the form of bradyarrhythmia and tachyarrhythmia.

- Radiological finding on MRI Head face of giant panda.



Important Information

3 common movement disorders seen in Wilson disease are
1. Tremors
2. Dystonia
3. Incoordination

Organs involved in Wilson disease 00:27:06

- Liver: Cirrhosis (most common)
- RBC: Hemolytic anemia
- Basal ganglia: Tremors
- Nails: Azure lunulae
- Kidneys: RTA type 2
  - Renal tubular acidosis type – 2 is the alternative name for PCT damage.
- Eye: KF ring

Important Information

In hemochromatosis
- Iron damaging the β cells of the pancreas resulting in insulinopenia. So type I DM is one of the manifestations termed as bronze diabetes.
- It involves skin: slate gray.
  - Due to overexpression of melanin.
  - Because iron triggers the melanocytes.
- Liver: contributes to cirrhosis.
  - Higher incidence of HCC is present

Workup 00:30:05

1. 24-hour Urinary copper value (screening test)
   - Elevated more than 100 mcg/day.
- D-Penicillamine challenge test
2. Liver Biopsy
   - It is the investigation of choice.
   - Use for Estimation of Hepatic Copper
   - Content: > 250 mcg/g of the dry weight of the liver
   - Stains used are:
     → Rhodamine
     → Rubeanic acid
3. Serum ceruloplasmin: < 20 mcg/dl
   - It is useful if there is a positive family history.
4. MRI Head: Face of panda appearance
   - Parts involved are:
     → Tegmentum
     → Pars reticularis of substantia Nigra
     → Superior colliculus is also involved.
- Panda Sign: Seen in gallium scan: In sarcoidosis patients.
- Panda Sign or Raccoon eyes: Seen in Anterior Cranial fossa fractures.
5. Slit lamp biomicroscopic examination.
6. DNA testing for ATP 7B gene
   - Haplotype testing in siblings.

Management 00:40:52

1. If the patient is having hepatitis-compensated cirrhosis: Zinc acetate
   - Mode of action: it competitively inhibits the absorption of copper from the gut.
     → Inducer of metallothionein

→ Copper is a teratogenic so give zinc acetate in pregnancy.

2. In case of hepatic decompensation (it means portal hypertension already occurred): Trientene > D penicillamine.
3. If CNS manifestations present: Tetrathiomolybdate

Liver manifestations and severity of manifestation will be reduced after medical management.

In 2nd year the KF ring will remain static but later reduced as well.

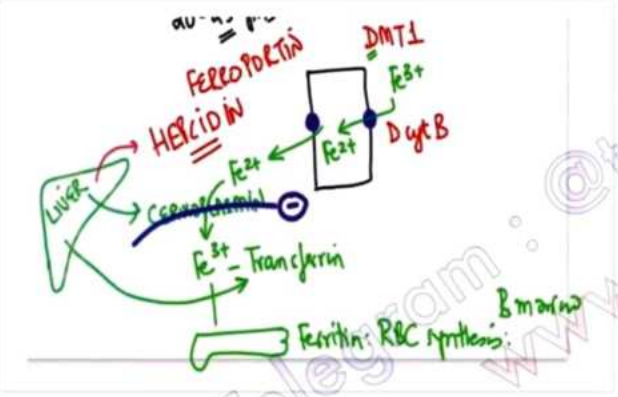
- Need for liver transplantation is evaluated by:
- NAZER index
  - Parameters are
    1. Serum bilirubin
    2. INR
    3. SGOT

    → <7: Medical treatment

    → >9: Register for orthoptic liver transplant

Hemochromatosis

00:49:06



- Total amount of iron content in body is 3 – 4 gm %.
- In hemochromatosis iron content is increased to 20 – 25 grams.
- Duodenum is the main site for the absorption of iron.
  - Divalent Metal Transporter: it helps In the transport of Fe^{3+} into enterocytes in Fe^{2+} form.
  - Duodenal Cyt B helps in the reduction of Fe^{3+} to Fe^{2+}.
- Ferroportin: Importer of iron from enterocyte into circulation.
- Ceruloplasmin converts Fe^{2+} into Fe^{3+} and Fe^{3+} binds to Transferrin for transport to bone marrow.
- Ferritin is the storage form of iron. This will help with RBC synthesis.
- All this is regulated by hepcidin.

Etiology

- Aceruloplasminemia: Deficiency of ceruloplasmin. Conversion into Fe^{3+} will not occur.
  - So Fe^{2+} gets deposited in tissue and causes Neurodegeneration.
- Subsequent damage to the liver: Leads to inability to produce ceruloplasmin and transferrin.

Hereditary Hemochromatosis

00:55:47

- There is Hepcidin deficiency.
- Unregulated iron is absorbed in excess and will get deposited in the tissues.
- Etiology: Gene mutation: HFE gene present on chromosome 6p, C282Y homozygosity (most common)
  - Hemojovilin mutation
  - Transferrin mutation
  - Ferroportin mutation

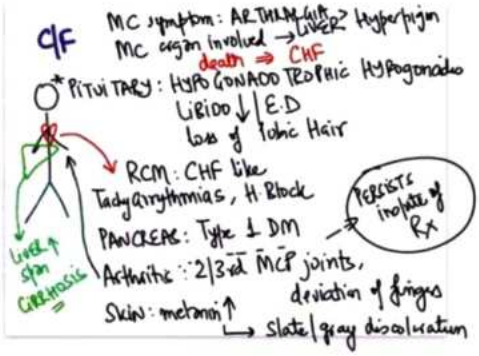
Type of hemochromatosis

Hereditary	Acquired
Type I ○ HFE gene 6p, AR, C282 Y Homozygosity	**Chronic liver disease** ○ Alcohol ○ Hepatitis C (MCC) ○ N.A.S.H (Non acholic steatohepatitis) ○ Cirrhosis
Type II ○ Hepcidin/ Hemojuvelin mutation	**Thalassemia (transfusion related iron overload)** ○ Myelodysplastic anaemia ○ Aplastic anaemia ○ Sideroblastic anemia ○ Chronic hemolytic anemia
Type III ○ Transferrin Receptor mutation	
Type IV ○ Ferroprotein mutation	

Clinical features

01:03:14

- Most common symptom: Arthralgia > Pigmentation of skin
- Most common organ involved: Liver.
- Most common presentation: Hepatomegaly



- Pituitary damage: hypogonadotropic hypogonadism (LH and FSH decreased)
  - Testosterone and estrogen decreases
  - Decrease of Libido
  - Erectile dysfunction
  - Amenorrhea
  - Loss of body hair
  - Testicular atrophy
- Heart
  - Congestive Heart failure (Right sided)
  - RCM (Restrictive cardiomyopathy)
  - Arrhythmia (tachyarrhythmia or bradyarrhythmia)
  - AV block
- Pancreas
  - Insulinopenia: Type – 1 DM
  - Bronze diabetes (because there is also bronzing of skin along with diabetes)
- Arthritis: Joints: 2nd and 3rd MCP joints (Most common) would be erosive arithritis.
  - Persists in spite of treatment
  - Ulnar deviation of fingers
- Skin: production of melanin is increased (Hyperpigmentation)
  - Slate or gray discolouration of skin
- Liver: increase in liver span hepatomegaly.
- As the disease progresses, Stigmata of development of spider naevi, Dupuytren contracture and palmer erythema.
- In later stage, caput medusae, variceas or variceal bleeding and refractory ascites developed in patients.
- Most common cause of death in hemochromatosis: Congestive Heart failure

Work up 01:13:10

1. Iron studies
   - Serum Iron ↑
   - TIBC ↑↑
   - Percentage saturation of Transferrin: raised > 45% (Screening)
   - Serum Ferritin is elevated >1000-6000 micro gm/dl (Screening)
   - Liver Biopsy with an estimation of Iron content is the investigation of choice.
   - Hepatic Iron index > 2
2. HbA1C
3. Echocardiography
4. X-ray hand

Treatment

- Phlebotomy
- Deferoxamine is the iron chelator.
  - Given as Subcutaneous infusions.
- Deferasirox (oral)
  - Side effects are present
- Deferiprone (oral)
- Death is generally due to: Heart Failure › Liver failure › HCC

50 ALCOHOLIC HEPATITIS

Introduction 00:00:14

- Marker for determining heavy alcohol consumption is γ GGTP.
- Best test for determining alcoholic hepatitis is SGOT/SGPT ratio is more than 1.
- Alcohol is the third largest disease burden in world after CAD & DM
- Male: 40-80 grams per day: fatty liver and 160 grams per day for over 10 -20 years develop alcoholic hepatitis.
- Female: 20 grams per day
  - Female is having higher chance of developing alcoholic liver disease.
  - Because BMI is less so alcohol distribution per unit body weight is more.
  - Estrogen is also responsible for it.
- There is 50 % chances that patient of alcoholic hepatitis is deteriorates into alcoholic cirrhosis.
- 60 % mortality rate over the next 4 years once alcoholic cirrhosis occurs.
- Binge drinking cause sudden cardiac death due to Atrial fibrillation.

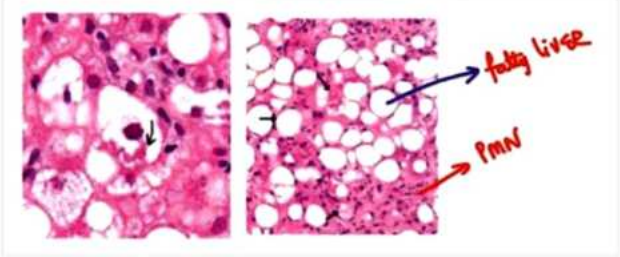
Risk factors for Alcoholic cirrhosis

- HCV
- Genetics
- NAFLD
- Obesity

Spectrum 00:04:08

- Fatty liver is caused by alcohol is reversible.
- Fatty liver deteriorates into alcoholic hepatitis.

Pathological Features 00:08:06



- There is ballooning of hepatocytes.
- Macro vesicular fat deposition can be seen.
- Neutrophilic infiltrate can be seen.
- Spotty necrosis once this appear. At this stage stellate cells in liver becomes active.
- Mallory denk bodies: not seen by low magnification.

Causes of Mallory Denk bodies (I Will Break Alcoholic Status)

- Indian childhood cirrhosis: increase in copper (due to use of copper utensils)
- Wilson Disease
- Primary Biliary cirrhosis (Anti mitochondrial Ab)
- Alcoholic Hepatitis
- Non-Alcoholic Steatohepatitis (NASH)

Clinical features 00:16:10

1. Asymptomatic
2. Right upper quadrant discomfort
3. Nausea
4. Vomiting
5. Jaundice Absent initially. If patient continues to drink and damage increases then Bil can rise.
6. Tender Hepatomegaly
7. History of heavy alcohol intake

- If patient presents late palmer erythema, spider naevi, duputyren contracture, temporal muscle wasting is seen and Parotid gland enlargement is seen.
- Decompensated cirrhosis leads to Portal HTN causing Splenomegaly, variceal bleed and Caput medusae

Work up 00:18:33

1. Liver function test
   - SGOT / SGPT ratio is more than 1.
   - Most specific LFT is ALT or SGPT.
   - AST or SGOT: 2-7 times elevated (most specific test) for alcoholic hepatitis
2. USG: Check liver span
   - Liver span is increased in patient
   - Echotexture: portal vein reversal seen on doppler.
   - It indicates the portal hypertension is already developed.
3. Transient electrography: to check the echotexture of the liver and amount of fibrosis occur in liver.
4. Liver biopsy
5. Coagulogram: PT elevated INR elevated Elevated (Normal: 11-15 sec)
6. Kidney function test: Serum creatinine is Normal and later on increases.
7. γ GGTP: it is the non-specific marker for alcoholic hepatitis.

Maddrey`S/ Discriminant Function/ Score 00:24:14

- To check the severity of alcoholic hepatitis
- 4.6 x [↑PT above the upper limit of control] + Serum Bilirubin
- If value > 32: indication to start the treatment.

MELD Parameters 00:26:03

- Serum Bilirubin
- INR
- Serum Creatinine
- If M.E.L.D score > 21: indication To start the treatment

Extra mile

Glasgow Alcoholic Hepatitis Score 00:27:53

- Age
- WBC count
- BUN
- Bilirubin
- PT

Management 00:28:33

1. Alcohol Deaddiction: Naltrexone, Acamprosate
2. Drug of choice for Alcoholic Hepatitis: Prednisolone 32 mg/day for 4 weeks
3. TNF-α inhibitor: Pentoxyphylline (Efficacy not proven)

Laboratory Diagnosis of Alcoholic Fatty Liver and Alcoholic Hepatitis

Test	Comment
AST	Increased two to sevenfold, < 400 IU/L, greater than ALT
ALT	Increased two to sevenfold, < 400 IU/L
AST/ALT	Usually > 1
GGTP	Not specific to alcohol, easily inducible, elevated in all forms of fatty liver
Bilirubin	May be markedly increased in alcoholic hepatitis despite modest elevation in alkaline phosphatase

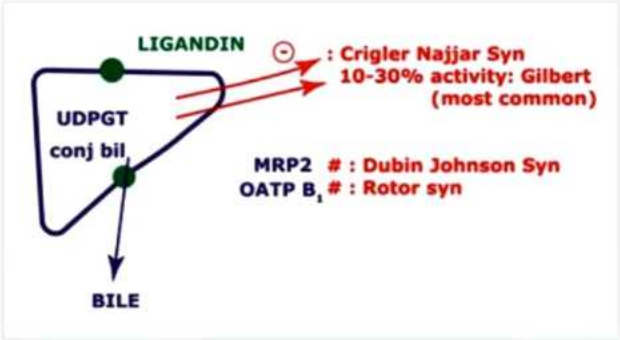
Selected Noninvasive Methods of Assessing hepatic Fibrosis and Cirrhosis

Method	Parameters	Advanced fibrosis	Cirrhosis
APRI (AST to platelet Ratio Index)	AST, Platelet count	>1	>1.5 (1-2)
ELF (Enhanced Liver Fibrosis)	Age, Hyaluronic acid, MMP-3 [Metalloproteinase], TIMP (Tissue Inhibitor of Metalloproteinase)	>7.7	>9.3
FIB – 4	Age, AST, ALT, platelet count	>1.45	>3.25
Fibro Test	Haptoglobin, α2- macroglobulin, apolipoprotein A1, γ GT, total bilirubin	>0.45	>0.63
TE (Transient Elastography/Fibrosure)	Measure speed of a shear wave generated by vibration through liver tissue	>7.3 kPa	>15 KPa (9-26.5 kPa)
ARFT [Acoustic Radiation force imaging]	Measure speed of shear wave generated by acoustic radiation force through liver tissue	>1.3 m/s	>1.87 m/s

51 HEREDITARY HYPERBILIRUBINEMIA

Hereditary Hyperbilirubinemia 00:00:13

- Hemolysis
  - Unconjugated Bilirubin is produced
  - It can cross blood brain barrier causing kernicterus/ bilirubin encephalopathy
  - Normally, not transported in free form.
  - It binds to plasma proteins and does not cause encephalopathy



Gilbert Syndrome 00:04:42

- If promoter molecule mutation is present: Autosomal Recessive
- If Missense Mutation is present: Autosomal Dominant
- UDPGT (UDP-glucuronosyltransferase) activity is 10-30%, in comparison with normal person
- Fluctuating/increased levels of unconjugated bilirubin maybe due to stress, medications
- Phenobarbitone
  - Enzyme inducer activity is used to promote the enzyme activity of UDP- glucuronosyltransferase
  - So that it can normalize the Serum Bilirubin levels
  - Elevated Unconjugated Bilirubin most of the times is incidental diagnosis or seen after fasting, febrile illness and physical exhausation.

Crigler Najjar Syndrome 00:09:12

- Leading cause of kernicterus
- Complete absence/Profound reduction of UDP-glucuronosyltransferase enzyme activity in Type 1. UGT1A1 gene defect.
- Increase in unconjugated Bilirubin which can cross BBB if exchange transfusion is not done. The sequelae of Basal ganglia damage is Athetoid cerebral palsy

Clinical Features

1. Neonate on day 0
   - Palms/ soles start turning yellow causing Pathological jaundice
   - In these patients despite giving Phototherapy and Exchange Transfusion, the levels of bilirubin remain high and tends to cause: Bilirubin encephalopathy
   - The bilirubin damages Putamen and it leads to sequelae called as Athetoid cerebral palsy.
   - Most common cause of pathological jaundice is Rh incompatibility
   - There is no effect of phenobarbitone because there is complete absence of enzyme
2. Opisthotonus and Seizures may develop
3. Delayed milestones

Dubin Jonhson 00:14:01

- Gene defect: ABCC-2
- Protein defect: MRP-2 (Multi drug resistance associated protein 2) - Canalicular protein responsible for excretion of conjugated bilirubin

Clinical Features

1. Obstructive jaundice occurs but since the bile salt / acid handling is normal, so pruritus is absent.
2. Increased conjugated bilirubin [Bilirubinemia] → Bilirubinuria → Mustard yellow urine
3. Icterus developing after Pregnancy, Oral Contraceptive Pills, stress

Work up

1. LFT: Serum Conjugated Bilirubin > 15% of Total serum bilirubin
   - SGOT, SGPT: Normal
   - SAP (Serum alkaline phosphatase) and 5'nucleotidase, normal
2. MRCP imaging: Normal
3. **Investigation of Choice**
   - Bromsulphalein (BSP)Test
   - Normally dye is cleared, excreted into bile by MRP-2 protein but in DJS – as the defect lies in the transporter protein- BSP regurgitates back into blood stream
4. Urine total coproporphyrin value- Normal, but ratio of coproporphyrin is changed.
   - In normal person the value of Coproporphyrin III > I

- In DJS values of Coproporphyrin I > III

5. Oral cholecystography – Gall Bladder not visualized
6. Black liver because of accumulation metabolites epinephrine

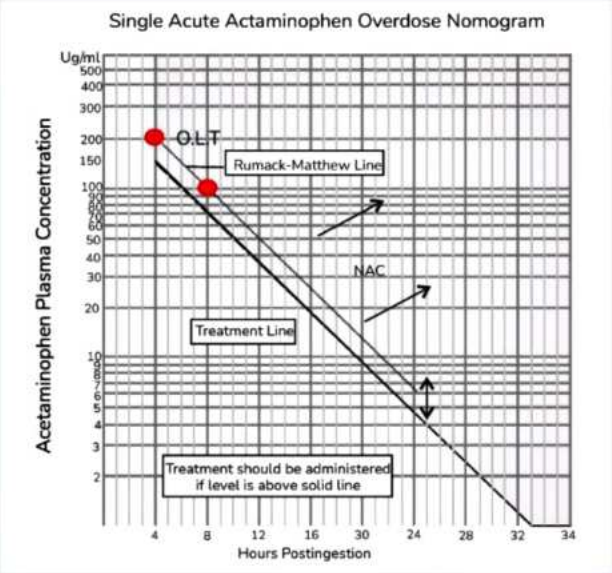
Rotor Syndrome 00:24:32

1. Autosomal Recessive
2. Defect in OATP B_1 - organic anion transport protein B_1
3. Liver Color: Normal, Echotexture also remain normal
4. Gall Bladder can be visualized because the cholecystography dye is excreted by MRP-2 and not excreted by OATP B_1
4. Total urinary coproporphyrin increased: significantly elevated
5. Coproporphyrin I/III ratio is more (I>III)

52 PARACETAMOL TOXICITY/ ACETAMINOPHEN TOXICITY

Introduction

00:00:20



- Rumack Mathew line:
  - If the values are at least 100 Hg/mL at 8 hours and 200 Hg/mL at 4 hours: do an orthoptic liver transplant
  - If the values are lower than this: N-acetylcysteine is given.
  - Area in grey denotes that we have to do an intervention.
  - Treatment line threshold kept 25 % lower than the Rumack Mathew line.
  - If the persons falls to left side of the treatment line: Only conservative treatment is required.
- Safe dose of paracetamol: 3 grams per day
- Safe dose in the alcoholic patient: 2 grams per day
- PCM in combination with opioid tablets: because of dependence there is a risk of causing paracetamol toxicity.
- To decrease the risk of toxicity the maximum dose of PCM as marketed is 325 mg tablet.
- 10 - 15 grams per day: requires Hospitalization.
- > 25 grams per day: has higher chances of fatality.
- Antidote: N-acetyl cysteine
  - If indicated in the patient start within 8 hours of intake and can be given up to 24-36 hrs.
  - There is a reduction in mortality.
- Blood PCM >300 µg/ml at 4 hours of ingestion: High chance of liver damage.
- Blood PCM < 150 µg/ml at 4 hours of ingestion: damage is unlikely.

Metabolism of PCM

00:08:50

- Metabolized by phases 1 and 2 of metabolism.

In Phase 1

- Cytochrome P450: Produces NAPQ I (N-acetyl-P-benzoquinone Imine) neutralized by Glutathione.
- Low glutathione levels in person (In alcoholics, in starvation, consumption of anti-TB drugs (INH) and Barbiturates: Ability to cause more damage to the liver.
- N-acetyl cysteine generates glutathione.

In Phase 2

- It Involves conjugation: Responsible for
  - Sulfate moiety
  - Glucuronidation

Clinical features

00:11:47

1. At 4-12 hours: Nausea, vomiting, diarrhea, abdominal pain and shock.
2. At 24 -48 hours: Fulminant hepatic failure

Coagulopathy	Encephalopathy
• Bleeding from gums and Nose etc.	Altered sensorium progressing to Coma

3. Acute kidney injury: Oliguria or anuria
4. Myocardial injury: Troponins are elevated.

Treatment

00:13:55

1. Gastric lavage (not effective after half an hour of intake)
2. Cholestyramine
3. N-Acetylcysteine <8 hr: Antidote
   - MOA: replenish levels of glutathione which will neutralize NAPQ 1, by providing sulfhydryl groups to glutathione
4. If Fulminant hepatic failure is already present: An orthoptic liver transplant is done.

Iron toxicity

00:15:22

- Leading cause of poisoning in children less than 6 years.

Stages

- Stage-1: Nausea, vomiting, hemorrhagic manifestation in conjunction with diarrhea and shock.
- Stage- 2 (Latent phase): Deceptive phase.
  - Occurs in ~ 6 – 12 hours. Patient appears relatively better.
- Stage – 3: Metabolic acidosis cause cardiac depression.
  - The most common cause of death is iron toxicity.
- Stage – 4: Damage to the liver.

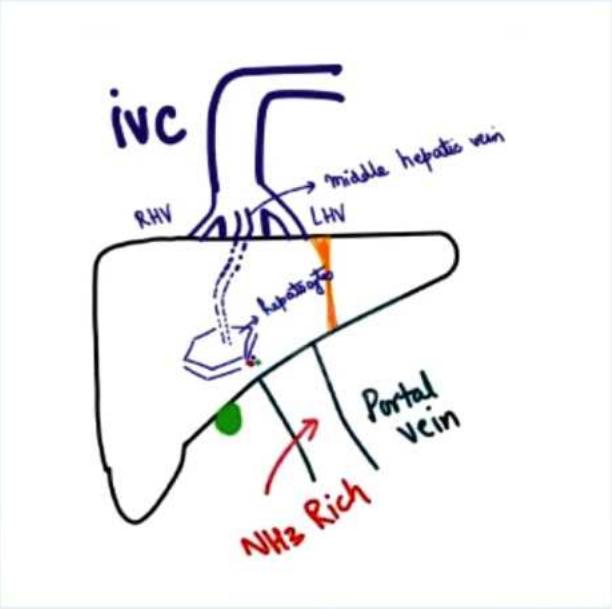
- Coagulopathy
- Encephalopathy

- Stage-5 (Delayed phase): scarring of the gut.
  - The patients end up with gastric outlet obstruction.

Management

- I.V. fluids
- Oxygen supplementation.
- No role for activated charcoal and ipecac.
- Deferoxamine: chelate the iron.
  - Indications: > 350 µg/dl: toxicity
  - >500 µg/dl: irrespective of toxicity
- Deferasirox oral: used in chronic overload and >2-year thalassemia transfusion dependent
  - Primary bronze diabetes

53 BUDD CHIARI SYNDROME



- Normally: In the Portal vein there is ammonia rich blood
- In liver, $NH_3 + CO_2 \rightarrow$ Urea
- In Budd Chiari syndrome: there would be Thrombus formation in hepatic veins.
- Secondary to obstruction there is congestion developing in the liver.
- There will be the development of centrilobular necrosis resulting in fulminant hepatic failure.
- Either have acute or chronic manifestations.
- It is Post hepatic cause of Portal hypertension.

Definition

- Thrombosis of ≥2 hepatic veins
- Usually, Caudate lobe drains in IVC. If thrombus involves IVC, then on USG, with help of doppler Enlargement of the caudate lobe is seen.
- Hydatid cyst is a secondary cause of Budd Chiari syndrome
- Liver tumor: it could be HCC or multiple metastases pressing on multiple hepatic veins.

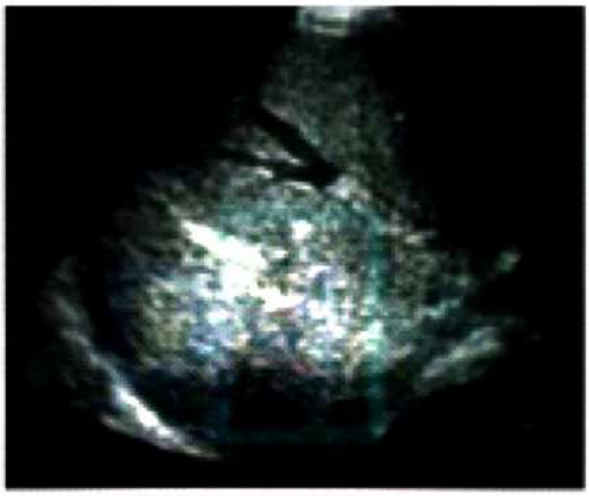
Causes of B.C.S 00:05:33

1. Hematological disorders
   - Polycythemia vera (JAK 2 mutation)
     → Erythrocytosis explains the sluggish circulation in the liver and thrombosis.
   - Paroxysmal nocturnal Hemoglobinuria (P.I.G.A gene defect)
     → Defect in CD 59 which is present on the platelets and it will inhibit the platelet aggregation.
     → Thrombus formation chances will increase.
2. Deep vein thrombosis
3. Thrombotic diathesis
   - Protein C, S and AT III all decreases it contributing to a hypercoagulable state.
   - Factor V Leiden mutation: defective binding with protein C leads to extrinsic system activation and initiates the clot.
4. Postpartum, OCPs: High estrogen leads to a hypercoagulable state.
5. Tumors: Hepatocellular carcinoma, RCC, Wilm's tumor (TUMOR PRESSING HEPATIC Vein)
6. Infections: Hydatid cyst
7. Connective tissue disorders: Anti-phospholipid antibody syndrome
   - Anti β2 glycoprotein antibody stimulates the Intrinsic System of clotting and turns into automatic mode.
   - May or may not be associated with SLE.
   - Sarcoidosis
   - Bechet's disease
8. Membranous defects in IVC or portal Vein
9. Total parenteral nutrition: IVC catheter

Clinical Features of B.C.S 00:13:45

1. Triad
   - RUQ pain (Sudden onset)
   - Ascites (due to portal HTN)
   - Hepatomegaly: the gross detention of the liver and liver span is increased.
2. Jaundice due to necrosis in the central lobular part of the liver.
3. Hepatorenal Syndrome
   - Splanchnic vasodilation: in the kidney, there is apparent hypovolemia.
     → In the kidney there is hypoperfusion
     → Acute kidney-like manifestation occurs.
4. Pedal edema
5. In Chronic presentation: Caput Medusae or ascites

Work up 00:19:52



1. USG with doppler: Helps to rule out gallstones and cholelithiasis.
2. Ascitic Tap: SAAG > 1.1 caudate lobe may be enlarged
   - In the initial phase, the Ascitic fluid protein can be more than 2.5 grams.
3. LFT
   - Serum bilirubin values can be increased.
   - SGOT and SGPT are grossly elevated.
4. MRI abdomen
5. Investigation of choice is Hepatic venography

Treatment 00:23:30

- EASL Guidelines for Acute Budd Chiari syndrome
  - Balloon angioplasty
  - Anticoagulation
- In Chronic Budd Chiari syndrome
  - TIPS
  - Spironolactone with furosemide
  - Orthoptic Liver Transplantation in ESLD

54 CYSTIC FIBROSIS

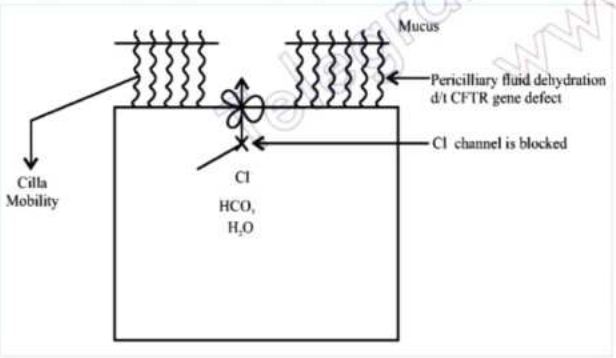
Introduction 00:00:20

- **Also known as Mucoviscidosis**
  - Because the body's secretions, especially those related to the Pancreas, are very thick and contribute to various manifestations.
- **Also known as Exocrinopathy**
  - Because this condition is having the propensity to involve the exocrine glands.

Pathogenesis 00:00:55

- AR, CH-7 # CFTR gene: With 1480 AA sequence CFTR protein malfunction
- [CFTR-Cystic Fibrosis Transmembrane Conductance Receptor]
- In Cystic Fibrosis- phenylalanine present at the 508th position is deleted
- So, the Most common mutation is the F508 mutation.

In Cystic Fibrosis
↓
Defect in CFTR gene
↓
Defective Cl-Channel
↓



↓
Efflux of HCO_3, Cl^-, H_2O From cell not possible
↓
Low water Content in the lumen
↓
Periciliary dehydration
↓
Highly Viscid mucus
↓
Cilia will not be able to work normally

- Kartagener syndrome - disease due to defect of dyenin protein. So mucociliary clearances are poor.

Important Information

Common organs involved in Cystic Fibrosis :
1. Lungs
2. GIT
3. Pancreas - results in T2DM in future
4. Liver: Biliary stasis can cause liver damage (biliary cirrhosis).

Root Cause Of This Condition

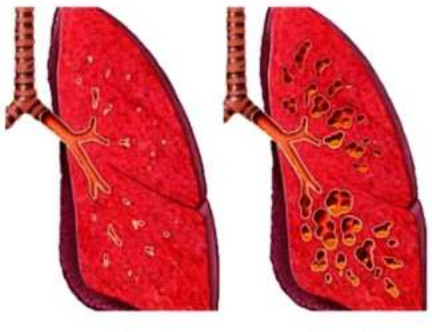
1. Low water content of PCL (Periciliary fluid)
2. Acidic Environment of Periciliary fluid due to defect in HCO_3 release.
3. Mucociliary clearance is hampered.

- Inhaled bacteria S. Aureus, Pseudomonas, Burkholderia undergo a mucoid transformation, and can Forms Biofilm which is Impermeable to antibiotics.

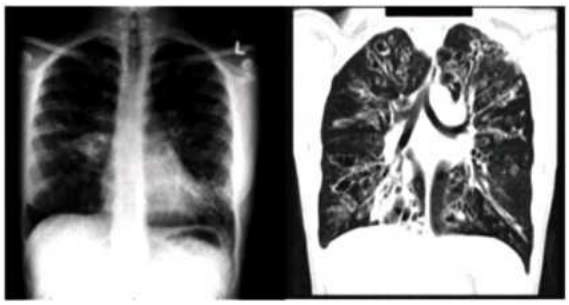
Pathologic Features 00:08:16

1. **1st Involved in Lungs**

- Bronchiolitis: Follicular plugging in the airways by thick tenacious secretions
↓
Bronchitis
↓
Bronchiectasis
(Large, Dilated airways filled with pus)

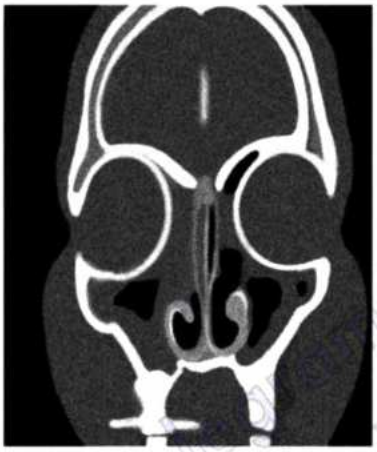


- At a later stage, the Patient can develop Cor-pulmonale.
- Ultimately leads to recurrent Pneumonia and causes the death of Patient.



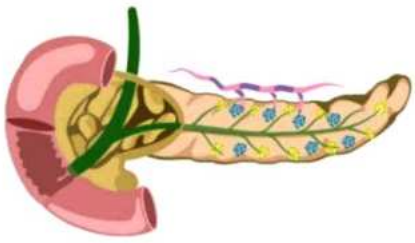
(Bronchiectasis - Tram track appearance)

- **Upper respiratory tract (URT) is also involved in the form of**
  - Nasal polyps
  - Recurrent Sinusitis



2. GIT

- **Pancreas: relatively small, replaced by Fibro fatty tissue**
  - Pancreatic secretion becomes **thick and viscid**.



- **Exocrine Function**
  - Decrease in Amylase, Lipase
  - Malabsorption syndrome can occur - failure to thrive.
- **Endocrine Function**
  - (In 2nd decade Diabetes mellitus can also occur) → 2° diabetes mellitus.

- **Liver**
  - Patients end up with **2° biliary cirrhosis.**
  - Obstructive jaundice/ prolongation of physiological jaundice
  - **Management:** Organ transplantation is required in these patients.

Important Information

- 1° PBC - (Autoimmune condition) AMA ab anti mitochondrial antibody

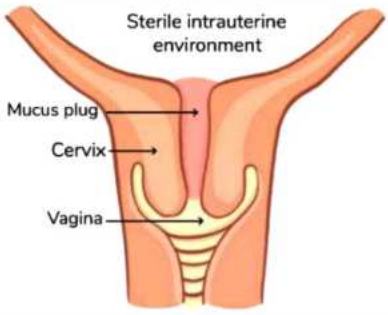
3. **Esophageal/ duodenal glands (Brunner's Gland): filled with thick mucus, Unable to secrete their own secretions and acid from the stomach will not be neutralized and leads to duodenal ulcers.**
4. **Genito urinary System**

In females

- Formation of Thick Cervical mucus plug causes Conception issues (Infertility)

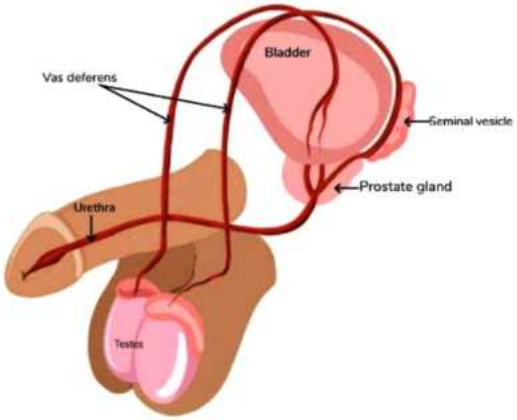
Management: ART

- Pregnancy can happen or not depending upon her lung function status.
  (Shrunken lungs with decreased lung volume are high Risk for pregnancy)



In males:

- Agenesis of vas deferens and epididymis leading to Azoospermia and Infertility



Important Information

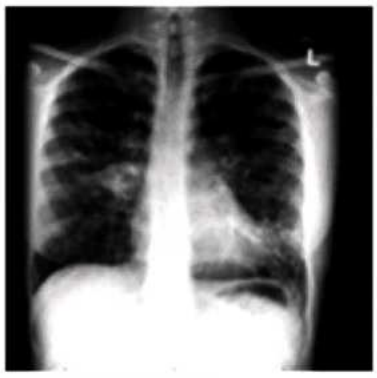
- Infertility is not included in Triad: It is present in males but not in females.
- **Kartagener syndrome Triad :**
  1. Recurrent Sinusitis
  2. Recurrent Pneumonia
  3. Situs Inversus

Clinical Features:

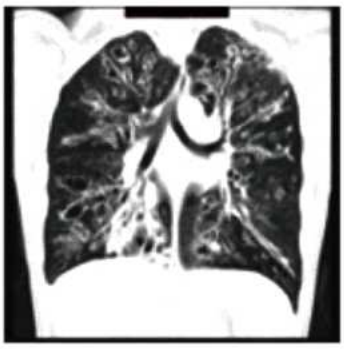
00:18:22

1. **Chronic cough productive (Purulent)**

- Foul-smelling pus present
- Shortness of breath
- Cor pulmonale: RVF - Non cardiogenic edema (Need for Lung Transplant)
- AP diameter increase (Barrel shaped chest)
- Chest, Hyper resonance
- Clubbing present
- Sudden deterioration can occur due to
  → Pneumothorax: Worsening of pre-existing Respiratory distress
  → Massive Hemoptysis

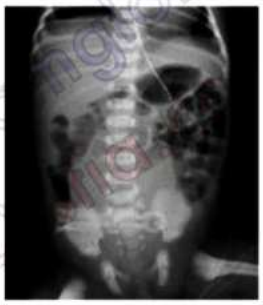


2. **Nasal Stuffiness / Epistaxis / Polyps**

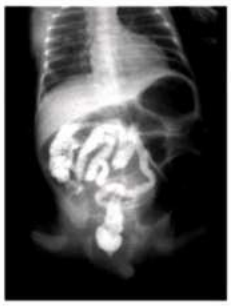


3. **Meconium ileus-**

- Abdominal distension & Delayed Passage of meconium (Normal < 48 hours)
  Investigation of choice: GASTROGRAFFIN enema
  Treatment of choice: GASTROGRAFFIN ENEMA
- As it Softens the stool



Abdominal distension



Meconium ileus

4. **GIT:** Osmotic diarrhea due to the absence of pancreatic secretions.

- Steatorrhea
- Failure to thrive/P.E.M

5. **Vitamin Deficiency**

- Vit E ↓ → Hemolytic anemia (Acanthocytes formation occurs)
- Vit K ↓ → Bleeding

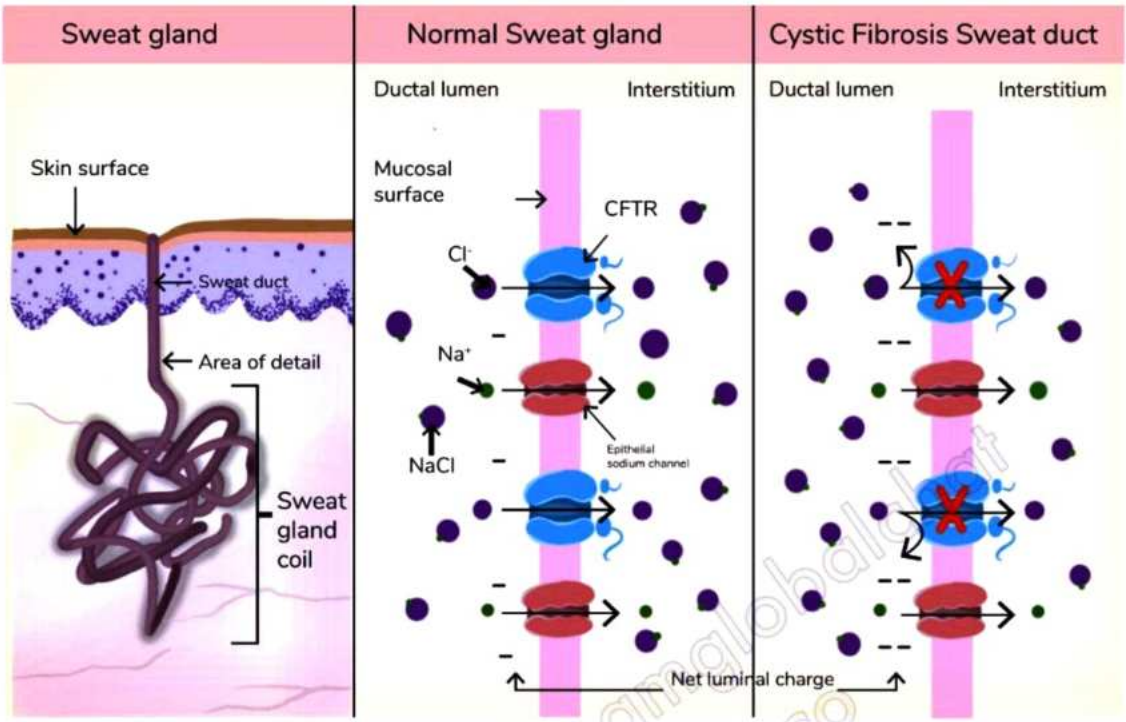
6. **Liver cirrhosis:** ICTERUS

- Ascites/ Hypersplenism/ Caput medusae, Esophageal varices

7. **GU system:** INFERTILITY (Agenesis of vas deferens)

8. **Sweat gland.**

- Sodium and chloride Reabsorption both inhibited.
- In laymen terms it called salty baby syndrome



- Increased Na/Cl^- loss causes RAAS activation
  ↑ Aldosterone in kidney
- Aldosterone action in the kidney: This leads to
  - Hypochloremic
  - Hypokalemic
  - Metabolic Alkalosis

Diagnostic Criteria For Cystic Fibrosis (CF) 00:35:37

- Presence of Typical clinical features
  - Respiratory: COPD, Bronchiectasis
  - Gastrointestinal: Meconium ileus, Malabsorption (osmotic diarrhea steatorrhea)
  - Genitourinary: Infertility

  (or)
- A history of Cystic Fibrosis in a sibling

  (or)
- A positive newborn screening test

  plus
- Laboratory evidence for CFTR (Cystic Fibrosis transmembrane regulator) dysfunction
  - Two elevated sweat chloride concentrations obtained on separate days **> 60 mEq/L**

    (Or)
  - Identification of two Cystic Fibrosis mutations by DNA sequencing

    (Or)
  - An abnormal nasal potential difference measurement.

WORK UP 00:38:31

1. **Sweat chloride test**
- Method used here is PILOCARPINE IONTOPHORESIS
- **Sweat Cl > 60 mEq/L** (should come positive 2 times for diagnosis)
- **False positive: Sweat Cl- > 60.**
  - Anorexia Nervosa
  - Addison Disease
  - Congenital Adrenal Hyperplasia
  - Nephrogenic Diabetes insipidus
- **False negative**
  - Malnutrition
  - Edema
- If the equivocal report comes here
  - Report 1 → 50
  - Report 2 → 65
  - Then we do the 2nd test (trans epithelial nasal potential test)

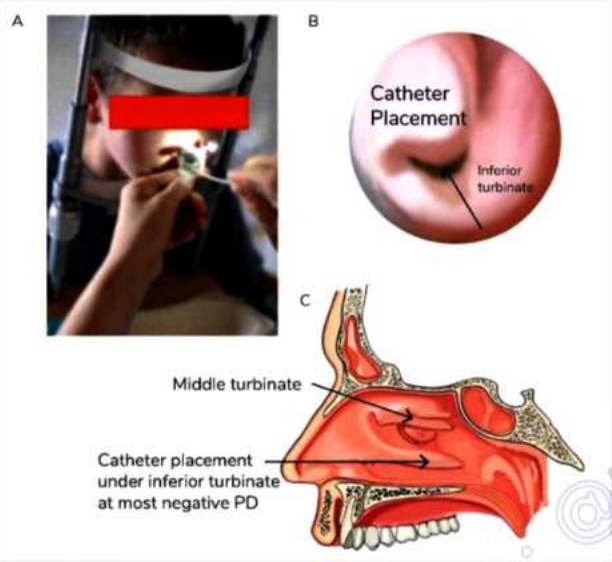
2. TRANS EPITHELIAL NASAL POTENTIAL TEST
- Done in case of equivocal test chloride report.

3. DNA testing (Most accurate Test)
- **CFTR Mutation:** Positive of at least 2 mutations

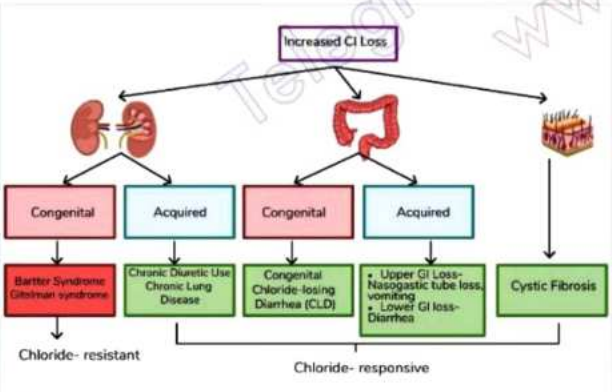
4. Fecal Elastase level (Serum ELISA)
- To identify the malabsorption component of the disease

5. **Pulmonary Function Testing**
- Obstructive manifestation earlier part of the disease/ Restrictive lung disease in the later part of disease
- In the case of pregnancy, it is important test.

6. **HbA1C > 6.5%: 2° Diabetes mellitus**
7. **CXR/ HRCT chest:** Shows dilated airways.
8. **Sputum culture:** Staph Aureus, Pseudomonas infections can occur.



Causes of Hypochloremic [Metabolic Alkalosis] 00:43:58



Extra Mile:
- The cause of Hypochloremia Metabolic Alkalosis is:

1. Barrter syndrome
2. Gitelman syndrome
3. Polyps
4. Diuretics
5. NG tube
6. Aspirate
7. Cystic fibrosis

Management: 00:46:31

- **Human recombinant DNA: Daily Aerosol Spray**
  - DNAase
  - DORNase
  - It will decrease the viscosity of sputum so antibiotic penetration and cough out of sputum are relatively easy.
- **N-acetyl/cysteine** followed by **β2 agonist nebulization** (Causes vigorous cough and expectorate sputum out)
  - **Nebulized Hypertonic Saline of 7%** can draw water into periciliary mucus.
  - **Nebulized TOBRAMYCIN and AZTREONAM** weekly (Reduces chances of colonization)
  - **Chest PERCUSSION and physiotherapy**
  - **Handheld Oscillometric devices** (Vibrations help to mobilize secretions)
  - **If Burkholderia cepacia infection is present:**
    → **The antibiotic of choice** – meropenem
  - **Steroids: ABPA (allergic bronchopulmonary aspergillosis)**
    → In Cystic fibrosis and Asthma (Because a lot of patients might be having upper airway colonization by aspergillus with the highlighted feature of **central bronchiectasis** - Serum precipitin antibody against aspergillosis has to be done
- **Ivacaftor**

[CFTR G551 Mutant proteins loss of Cl- conductance]

  - 150 mg B.D **IVACAFTOR** will improve Cl- conductance So, advantage is FEV1 increases cause decrease in Pulmonary exacerbation.

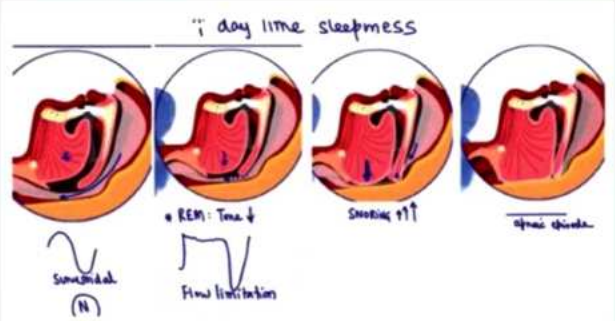
Important Information

- Prenatal diagnosis of cystic fibrosis: Chorionic villus sampling and amniocentesis.

55 OBSTRUCTIVE SLEEP APNEA

Clinical Scenerio

00:00:18



- Increased day time sleepiness due to recurrent cortical arousals at night time which are secondary to disease - obstructive sleep apnea.
- Patient is morbidly obese with BMI > 30.
- Normal Individuals have pharyngeal dilator muscles which prevent the tongue from falling backward when we are in the supine position. They promote the normal delivery of oxygen to the lungs by keeping the airway patent.
- In a patient with obstructive sleep apnea, normal sinusoidal inspiration & expiration will not occur.
- REM phase: The tone of muscles is least to a level which causes narrowing of the airway
- Patients with OSA has sharp inspiratory uptake, sequentially plateau wave then scooped out pattern of breathing seen on polysomnography which has flow limitation.
- This leads to hypoxia in the body and contributes to cortical arousal.
- Magnitude of obstruction increased even further, and soft tissues are falling backward (Secondary to obesity, or patient with smaller jaw - micrognathia)
- When air tries to go through a narrow airway, there is the vibration of soft tissues and especially the uvula giving characteristic Loud snoring. As the airway progressively gets narrowed intensity of snoring increases.
- The further narrowing leads to the apneic episode which causes.
  - Bradycardia
  - Oxygen saturation falls causes:
    → There will be Cortical arousals (Sleep will be interrupted)
    → Continuous twisting and tossing in bed.
  - Grunting at the end of the apneic episode that Helps to forceful opening of mouth and passage of air inside airways:
    → This will lead to an increase in SpO_2 and an increase in heart rate.
    → A sudden increase in heart rate leads to a tremendous load on the heart.
    → Patients develop left ventricular hypertrophy (LVH) or left ventricular (LV) strain.

Important Information

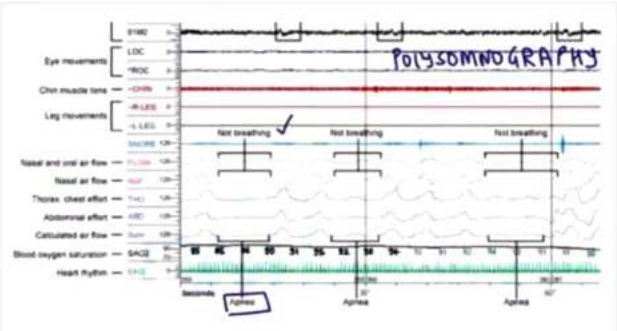
- RV failure is least likely/ not seen in OSA

Important Information

- Cortical arousal there is Strain on the Left ventricular and also other body systems not getting rest causing:
  - Extreme fatigue at night
  - Never waking up fresh
  - Body pain, thought process -"when will i get back to sleep".
- Obstructive Sleep apnea is one of the causes of **secondary HTN.**
  - Sleep apnea increases cardiovascular mortality.
  - In some congenital CVS disorders, children have OSA by birth and might have some **Behavioral Issues**
  - Increase in the neck and abdominal circumference (Characteristic of obesity) is a risk factor for obstructive sleep apnea.

Investigation Of Choice: 00:08:46

- Polysomnography (For obstructive sleep apnea and Hypopnea syndrome)



  - **Polysomnography**: Records nasal airflow chest expansion, Abdominal expansion and multiple other parameters
  - When the person is not breathing or having apnea the machine records a dip in oxygen saturation. Once the breathing resumes, on cortical arousal, increased efforts in inspiration cause oxygen saturation to increases.

- If oxygen saturation decreases > 3% then diagnosis is Obstructive sleep apnea.

Apnea 00:10:20

- Absent breathing effort for > 10 sec
  - associated with a 3% decrease in SaO_2 on pulse oximetry.
  - Cortical arousal (By checking on EEG pattern changes)

Hypopnea 00:11:34

- >30% decrease in airflow for more than 10 sec
- associated with a 3% decrease in SaO_2
- Cortical arousal

Obstructive Sleep Apnea-Hypopnea Syndrome (OSAHS) 00:12:30

1. Symptoms
- Nocturnal: Snoring, grunting, snorting, Breathing pauses (Partner usually notices)
- Increase in daytime sleepiness.

2. Polysomnography
- 5 episodes of Apnea per hours of sleep

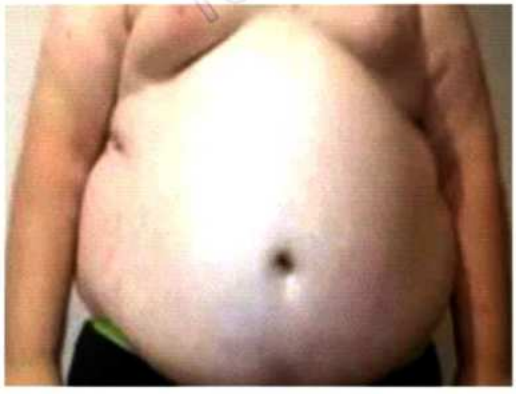
3. Apnea Hypopnea Index (AHI)

a. Calculated by the number of Apneic or hypopnea episodes divided by number of hours of sleep

b. If more than 15 episodes per hour of sleep minus symptoms

Risk Factors 00:17:10

1. Centripetal obesity (Most common)



Central obesity

- Narrowing of pharyngeal inlet due to Fat deposition.
- Decreased chest wall compliance which decreases the Caudal Traction required for Patency of the Upper Airway

2. Micrognathia or Retrognathia
- Tongue disproportionate to the size of the mandible
- Tongue falls backward during the REM phase of sleep.

Important Information
- MICROGNATHIA: Mandibular hypoplasia
- RETROGNATHIA: Abnormal mandibular alignment with respect to maxilla.

3. Down syndrome
- Have protuberant tongue.

4. TREACHER COLLINS

5. Menopause (> 45 years-as decrease in estrogen is associated with development of OSA in post-menopausal females)

6. Acromegaly

7. Hypothyroidism

8. High Nasal Resistance: DNS (deviated nasal septum) and polyps
- Development of mouth breathing in sleeps causing the tongue to fall backwards leading to occlusion of airway.

Clinical feature 00:23:55

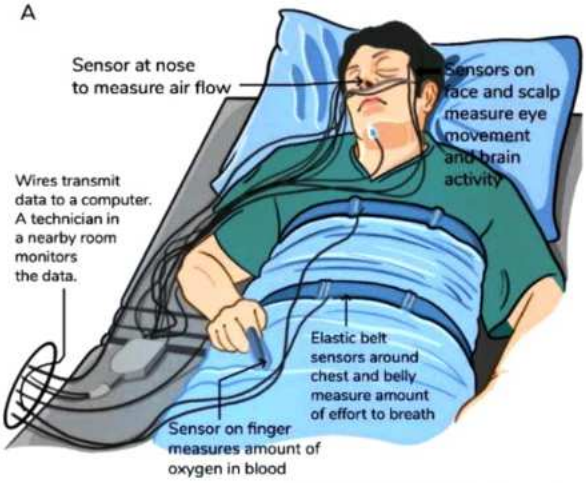
1. Increased Day time Sleepiness
2. Weight Gain
3. Snorting or Gasping
4. Dyspnea will not be present.
- Nocturnal dyspnea will be due to P.N.D, Nocturnal asthma or GERD
- Absent in OSAHS
5. Frequent Awakening
6. Dozing off involuntary during task
7. Dry mouth, Halitosis, Mood swings
8. Erectile Dysfunction

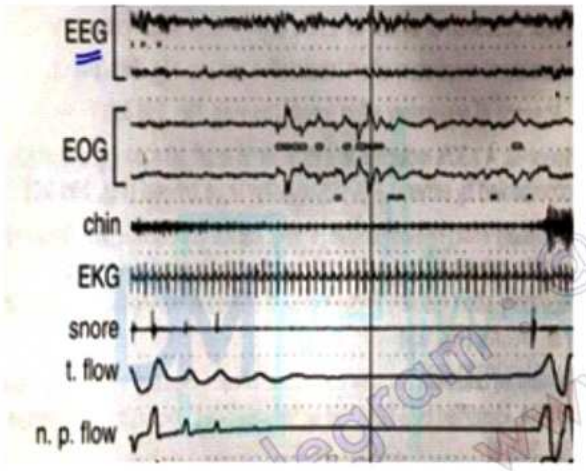
On Examination 00:26:30

1. Increase in BP (Can be pre-existing to the current symptoms)
2. Increase in Abdominal Girth
3. Increase in Neck Circumference
4. Large Tongue size, Low lying palate with bulky uvula
5. Enlarged tonsils

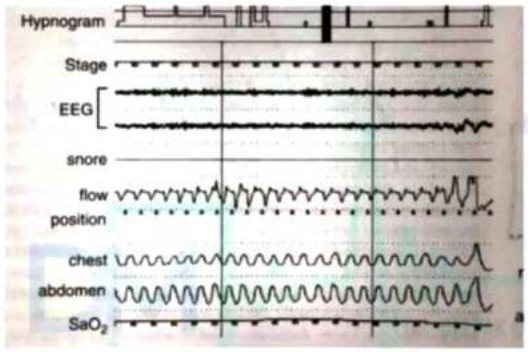
Work up 00:28:10

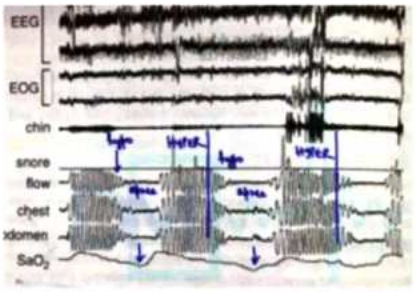
- BY POLYSOMNOGRAPHY:
  - EEG, EOG EMG, ECG, SpO2, Nasal Airflow, Chest and abdominal movements
  - On BP monitoring, there is the absence of a nocturnal dip in BP.
  - On ECHO: Chamber size (RVF is not seen)





- Whenever there is apneic episode
  EEG: In REM
  - Cortical Arousal will be present
- ECG: R-R interval will be prolonged (Bradycardia)
- Naso-Pharyngeal Airflow sensor: Shows declining activity
- Snore flow:





CHEYNE STOKES BREATHING

Image Noting: Hypoventilation then apnea followed by hyperventilation followed by hypoventilation then apnea and again hyperventilation.

- SaO_2: Dip in the SaO2 at the time of the episode leads to CHEYNE STOKES BREATHING (Hypopnea-apnea-hyperventilation)

Note: There are sinusoidal movements between the chest and abdomen.

Treatment: 00:36:44

1. Weight loss
   (Increase in Weight by 10% leads to a 30% increase in OSA incidence)
2. Avoid sleeping in a supine position; try to sleep in a lateral position.
3. Nasal allergy
4. Avoid alcohol (3hrs before sleep)

5. C.P.A.P (Treatment of choice): more than 15 Hypopneic episodes per hour (or) >5 apneic episodes per hour: Splint airway open
6. Uvulo-Palato pharyngoplasty
7. Upper Airway Device: Surgical implantation, Stimulates the hypoglossal Nerve (prevents the bending of tongue backward)
8. Oral Devices: Reposition of mandible (efficacy is very less)

Continuous positive airway Pressure

Epworth Sleepiness Questionnaire 00:42:42

- Fill up a Questionnaire and if **score is > 8,** medical consultation is recommended and a polysomnography should be done.

Refer Table 55.1

Central Hypoventilation Syndrome 00:46:52

- As known as the ONDINE curse
- Genetic condition involving PHOX 2B gene.
- Patient has an absent response to hypoxia or hypercapnia.
- Sensors that respond to hypoxia do not work properly.
- Management
  - NIPPV (Non-invasive Positive pressure ventilation)
  - Phrenic nerve/ Diaphragm pacing (New Technique): not done for OSA

Obesity Hypoventilation Syndrome 00:49:13

- BMI of more than 30
- PCO_2 more than 45 mmHg:
- Patient has Chronic Daytime hypoventilation.
- Patient may or may not have apneic episodes.

Pneumomediastinum 00:50:22

- Associated with a decrease in oxygen saturation below the tissue.
- Can occur due to
  - Alveolar Rupture leads to dissection of air.
  - Perforation of Esophagus (Boerhaave syndrome)
  - Trauma to the Neck or Neck tissues may get damaged leading to dissection of air.

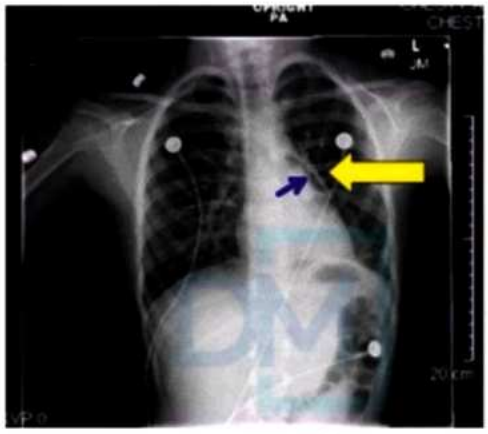
- **Clinical features:** Substernal chest pain with or without radiation to arms

- **On Auscultation**
  - Hamman Crunch Sign is a characteristic finding.
  - Crunch sound due to Air movement synchronous with heartbeat (Better heard on lateral decubitus position)

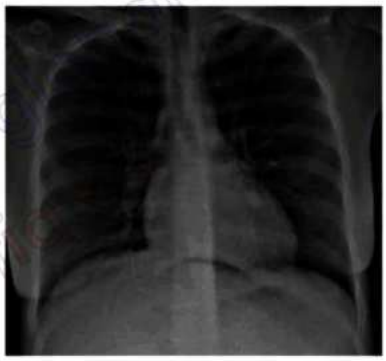
- **On Chest X-Ray:**

Notice

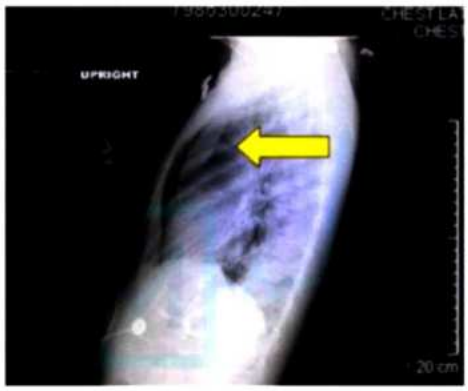
1. Air below the heart of the patient called Continuous Diaphragm sign
2. Air at heart borders (Thick arrow)
3. On Lateral view air present in mediastinum: Spinnaker sail sign is seen air will lift up the thymus.



Air Around The Heart



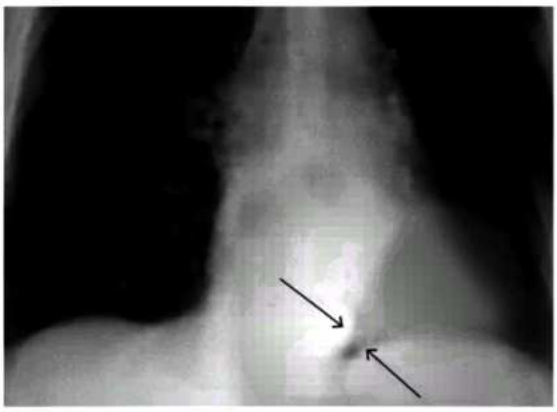
Continuous diaphragm sign



Spinnaker sail sign

- **Management:**
  - No treatment required (Self- reabsorption of air)
  - If high flow O_2 is given, rate of reabsorption is increased
  - If obstructive shock occurs, then needle decompression will be required due to concomitant is Pneumothorax

Naclerio's V sign



Lucent band of gas extending along descending aorta and intersecting band of gas that extends along medial left hemi-diaphragm together forming V

Table 55.1

Epworth sleepiness Questionnaire for a Medicare subsidised sleep study a patient must score 8 or more.				
How likely are you to doze off in the following situations?	**No chance**	**Slight chance**	**Moderate chance**	**High chance**
Sitting and reading	0	1	2	3
Watching television	0	1	2	3
Sitting inactive, in a public space	0	1	2	3
Lying down to rest in the afternoon when circumstances permit	0	1	2	3
Sitting and talking to someone	0	1	2	3
Sitting quietly after a lunch without alcohol	0	1	2	3
As a passenger in a car for an hour without a break	0	1	2	3
In a car, while stopped for a few minutes in traffic	0	1	2	3
			Total score:	

56 PULMONARY EMBOLISM

INTRODUCTION 00:00:16

- Pulmonary thromboembolism originating from DVT (deep vein thrombosis) which is a leading risk factor.
- Most common cause of preventable death in hospitalized patients is Pulmonary thromboembolism which can be treated with LMWH, Fondaparinux, and prevented in all post-op patients with pneumatic compression stocking.

ETIOLOGY 00:02:30

1. Deep vein thrombosis: "Virchow Triad"

- Prolonged Immobilization can cause thrombosis in mainly soleal veins and popliteal veins and a piece of clot has broken and passes via the IVC into the right side of the heart resulting in a Ventilation-perfusion mismatch.

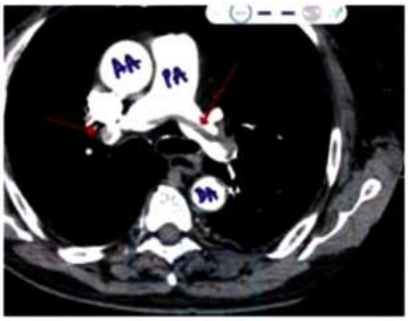
2. Prothrombotic states :

- Autosomal dominant conditions
  - Factors V Leiden mutation
  - Prothrombin Gene mutation

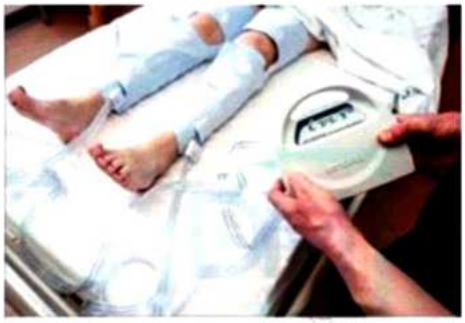
Important Information

- Most common congenital hypercoagulable state is Factor V Leiden mutation.
- Unopposed activity of factor V leads to a procoagulant state where protein C can't inhibit factor V

- Antiphospholipid antibody syndrome
  - Anti β2 Glycoprotein antibody is the troublemaker in this.
  - It Stimulates the intrinsic pathway.
- Oral contraceptives
- Hormone replacement therapy in Post-menopausal female
- Cancer surgery:
  - Cancer surgeries can be a disaster. Because cancer is a hypercoagulable state
  - After the removal of cancer, the clot can be formed.



Pulmonary Thromboembolism

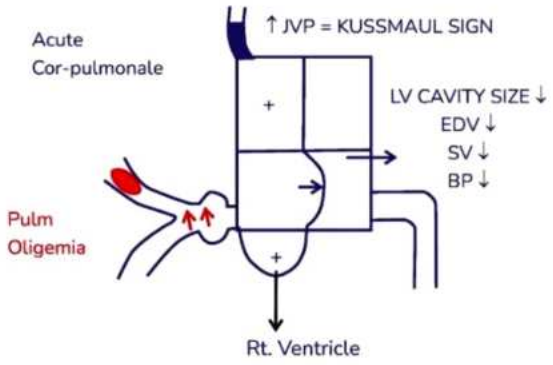


Pneumatic compression stockings

- Ortho implant surgeries (Massive PE can develop on 2nd to 3rd post operative day)

Physiological Basis Of Pulmonary Thromboembolism 00:09:40

- Increased A – a gradient ($PAO_2 - PaO_2$)
- Normally, A-a gradient (pAO_2-paO_2) 5-15 mmHg.
- PaO_2 reducing because there is no blood reaching alveoli.
- Increased dead space ventilation.
- Pulmonary vessel constriction increases due to hypoxia.
- Alveolar Hyperventilation
- Decreased lung compliance



- Thrombus in pulmonary artery branches and occluded it.
- It will cause an increase in pulmonary artery pressure leading to pulmonary oligemia
- Increase pressure causes dilation in the pulmonary artery.
- Once the right ventricular is going to fail there is rise in JVP (Kussmaul sign present)
- There is a lot of congestion in right ventricle causing septal deviation.
- It leads to a decrease in LV cavity size and causes.
  - Decrease in EDV, SV, BP

Findings In PTE 00:15:33

- Pulmonary oligemia
- Pulmonary artery HTN
- Sudden Right Ventricular failure
  - JVP raised.
  - On Echo, there is McConnell Sign (Right Ventricular hypokinesia, Right Ventricular apex hyperkinetic)
- Septal deviation
- Decrease In LV (left ventricle) cavity size and causes:
  - Decrease in EDV, SV, BP

Important Information

- **3 + 4 +5 presentation** together called as **acute cor pulmonale.**
- **COPD** is the leading cause of the **Cor pulmonale**. While **acute cor pulmonale** is associated with **PTE**

- Right Coronary artery compression due to sudden dilatation of the right ventricle leads to microinfarctions

Clinical Features 00:18:55

- "GREAT MASQUERADER" it mimics MI by chest pain but here the pain is due to pleural infarction while pulmonary artery blood supply is compromised.
- Case: 75 years old man underwent Bilateral total Hip replacement. On day 3, at 8 pm develops dyspnea and chest pain.

On Examination

1. Heart rate is 120/min, BP 90/60 mmHg and JVP elevated.
2. Kussmaul sign present, S_1 Loud
3. S2 wide fixed split because P2 closure takes more than 30 msec.
4. Heard with bell of the stethoscope S3 ⊕
5. Lungs: Bilateral clear lung fields

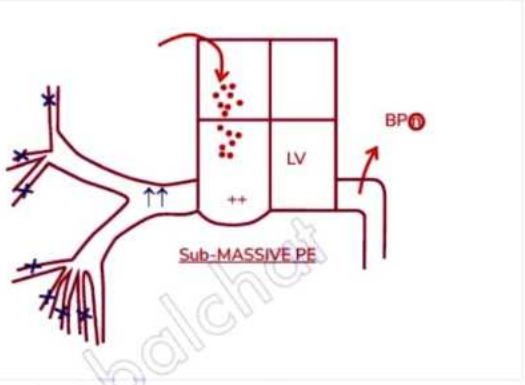
Well's Criteria 00:23:48

B - Blood in sputum
D- Deep vein thrombosis sign and symptoms present like Homan Sign (Pain on the calf while dorsiflexion of the ankle)
C- Cancers
H- HR>100 /min on the 3rd or 4th day is suggestive of atelectasis or PTE.
I- Immobilization > 3 days, surgery < 4 weeks
P- Prior pulmonary embolism Or Prior DVT

- If Score > 4 = High probability of Pulmonary Embolism

Sub-Massive PTE 00:27:50

- Multiple small pulmonary emboli enter into the Right heart leading to blockage of small arteries of the Pulmonary artery that result in mild distension of the right ventricle without affecting the left ventricle.
- Seen in around 65 % of cases.
- Blood pressure tends to remain normal in the patient.



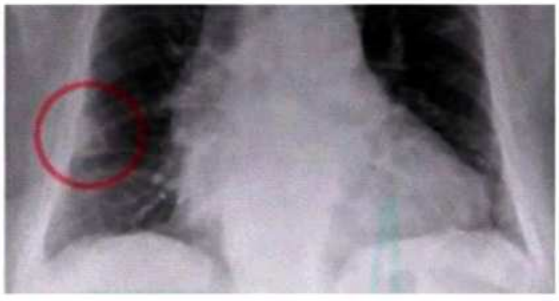
Work-Up 00:29:45

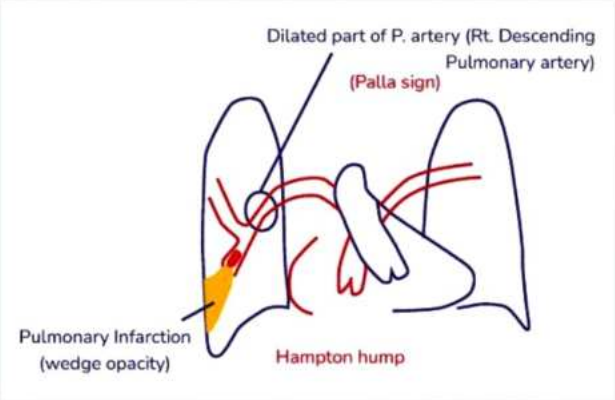
1. E.C.G = $S_1 Q_3 T_3$,
- Deep S wave in lead I
- Deep Q wave in lead III } RV Strain pattern
- Inverted T wave in lead III

2. Chest X-ray
- Palla sign
- Hampton hump
- Wester mark sign

There is a block by dislodged emboli on the pulmonary artery which presents dilated to the proximal emboli called Palla sign - commonly seen in the Right descending pulmonary artery and wedge-shaped infarction to the distal emboli called Hampton hump.

Westermark sign – due to focal oligemia seen in only one lung where emboli lodged into the Right descending pulmonary artery.



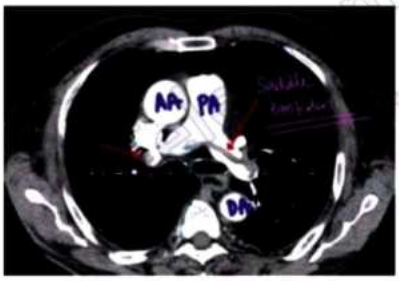


3. Trop I or HFABP or B.N.P: Elevated due to Right ventricular micro infarction
4. USG or Doppler of legs: Non compressibility of big veins (normally these veins are compressed by placing the USG probe)
5. Screening test: D – Dimer assay elevated.
6. Investigation of choice: CT angiography

Important Information

- **Triple rule-out CT Chest**

1. Pulmonary Embolism
2. Acute aortic syndrome
3. Acute coronary syndrome



7. **Gold standard test: Pulmonary Angiography**
8. **Echo: McConnell sign**

- Right ventricular wall hypokinesia
- Right ventricular Apex hyperkinesia

Management Of Massive PTE 00:42:18

1. **Primary therapy: Pharmaco mechanical approach**

- **Alteplase 100 mg**: given for Massive PTE

2. **New approach:** Catheter directed thrombolysis with 25 mg alteplase.
3. **Primary prevention: Pneumatic Compression Stockings**
4. **Secondary prevention:** Anticoagulation (UFH, enoxaparin) or I.V.C filters

Clinical Scenario: 00:45:37

Massive P.E	Sub massive P.E
1. BP decreased. 2. R.V Hypokinesia 3. ECG: S1 Q3 T3 4. CXR: Hampton Hump	1. BP normal 2. R.V dilatation 3. ECG: sinus tachycardia 4. Chest x-ray normal

5. Old age = Immobilization or malignancy
   Post-operative sudden onset respiratory distress with chest pain on day 3 or day 4

Screening test: D- Dimers assay
For diagnosis: CT Angio

Treatment: Thrombolysis & anticoagulation

Treatment: Anticoagulation

Drug Used 00:51:36

1. **Unfractionated heparin** = Requires monitoring aPTT – 60 to 80msec has to be done (Normal value of aPTT: 30- 40 msec)

- U.F.H can cause H.I.T (Heparin-induced thrombocytopenia)
- To control H.I.T: **Bivalirudin** is given.

2. **Enoxaparin**
3. **Fondaparinux**

} Can be given OD, Subcutaneously, with No Monitoring required

4. **Warfarin →** it will take at least 5 days to work so it can be bridged by any of the above-mentioned drugs. So, for the first 5 days, UFH / Enoxaparin/ Fondaparinux can be given parenterally with warfarin.

- Target INR = 2-3
- Requires monitoring

5. **Novel oral anticoagulants:** Start action within hours.

- Dabigatran, Betrixaban
- Given for 1st six months.

Anticoagulant	Antidote
• Dabigatran • Betrixaban	• Idarucizumab • Andexanet

Indication of IVC Filters 00:56:18

Recurrent episodes of Pulmonary Embolism

57 FAT EMBOLISM SYNDROME

CASE SCENARIO

18 years old male had bike accident: Fracture Shaft of Femur for which he was operated. Post operative 12-72 hours

- Sudden onset dyspnea
- Altered Sensorium Cognitive defect, Coma
- Petechiae: Axilla > rest of the body

Provisional Diagnosis

- Fat Embolism syndrome

Differential Diagnosis:

1. Pulmonary thromboembolism
   - Immobilization for long time
   - Deep vein thrombosis
   - Respiratory distress present.
2. Pulmonary contusion will also occur after trauma.
   - Respiration distress occur as early as 6 hours.
   - On Chest X-ray: Localised ground glass opacity.

PATHOGENESIS 00:08:02

Bone fracture
↓
Fat molecules come into circulation
↓
Lipoprotein lipase
↓
Free fatty acid generation+ Cytokines
↓

- Damage to pulmonary circulation especially pulmonary endothelium leads to alveolar edema and haemorrhage.

↓
Ventilation perfusion imbalance/respiratory distress

CNS Manifestation:

- 20-30 % of individual having the fat embolism syndrome patient might be having patent fossa ovalis (PFO)
  - Documented on transoesophageal echo.
  - The fat globules transferred left side of the heart and then to the systemic circulation.
  - Cerebral circulation will suffered.
  - Cognition defect, stupor and Coma.
  - Patient will require intubation. Sometime patient will aspirate and causes the pneumonia.
- During intramedullary nailing: asymptomatic fat embolism can occur

Causes

1. Polytrauma: Fracture of long bones, pelvis.
2. Acute pancreatitis, Diabetes mellitus. Increase in Triglycerides more than 500 mg %.
3. Joint reconstruction surgery
4. Liposuction
5. IV fat infusion: Patient on Total parenteral nutrition (TPN).

- Decompression sickness or Caisson's disease: Seen in Deep Sea divers
  - Nitrogen bubbles contributing to blockage of coronary circulation, renal circulation. Patient can have chest pain, flank pain etc.
- In poly trauma:
  - Incidence is 90% of Fat embolism
  - Incidence is 2% of Fat Embolism Syndrome

CLINICAL FEATURES 00:19:19

Based on Gurd Wilson Criteria

Major Criteria:

1. Respiratory: There is fast breathing, accessory muscles of respiration being used
   - Patient is having Type I respiratory failure because of hyperventilation.
2. CNS:
   - Coma (GCS <8)
3. Petechiae: Axilla

Minor Criteria :

1. Increase Heart rate
2. Raised Temperature (>38°C)
3. Retinal changes
   - Retinal artery (breach in column)
   - Petechiae
4. Kidney dysfunction
   - Anuria
   - Oliguria
5. Jaundice
6. Decreased Hb, Decreased platelet count, Raised ESR
7. Fat in Urine or sputum specimen

Fat globules in urine or oval fat bodies:

1. Nephrotic syndrome
2. Chyluria
3. Fat embolism

For diagnosis: 1 major criteria + 4 minor criteria

WORK UP 00:26:05

1. Chest X Ray
   - Normal or diffuse infiltrates
2. Helical CT Nowadays recommended : Ground glass opacity
3. CT Head: Normal or diffuse white matter petechiae present .
4. Transoesophageal echo: Patent Fossa Ovalis (20-30%)
5. Doppler to Rule out Deep vein Thrombosis.
6. Bronchoalveolar Lavage: stained for fat

TREATMENT 00:30:06

There is no definite treatment.

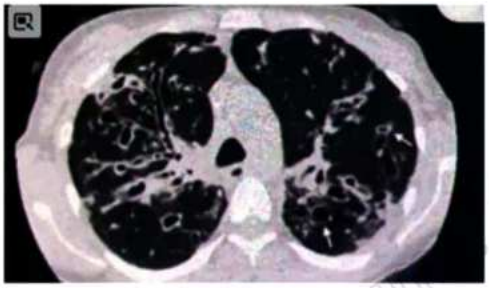
1. High flow O2 at approximately 12 L/min
2. I.V. fluids: to prevent dehydration.
3. Steroids: Given for Vasogenic cerebral edema
4. Heparin: Anti lipemic effect (Dissolve the fat globules)
5. To Prevent D.V.T: Stocking compression is recommended.
6. Stress GI bleeding: Pantoprazole (PPI) I.V. is given.

58 BRONCHIECTASIS

- **Definition:** Destruction or Dilatation of proximal & medium sized bronchi (>2 mm) airways which are filled with pus & results in the features of bronchorrhea.
- Mucopurulent sputum and bronchorrhea are the characteristic features.
- **AREAS INVOLVED ARE**
  - Lower lobes
  - Right middle lobe
  - Lingula

Important Information

- Bronchorrhea also seen in chronic bronchitis.
- Dry bronchiectasis: TB



Histopathological Examination 00:04:35

1. Cylindrical or Tubular: Most common subtype
2. Varicose
3. Saccular or cystic variety

Important Information

- Massive hemoptysis:
- Treatment: Bronchial artery embolization.

Etiology 00:09:20

- Focal obstruction
  - Tumor
  - Foreign body aspiration
  - LN enlargement
- Diffuse
  - Infection
    - → Pseudomonas
    - → Mycoplasma pneumonia
    - → Bordetella pertussis
    - → Burkholderia cepacia
  - Decreased immunity
    - → HIV
    - → Hypogammaglobinemia
  - Recurrent microaspirations
    - → Scleroderma
    - → Bulbar palsy
  - Rheumatological causes
    - → RA (Rheumatoid arthritis)
    - → Sjogren syndrome
    - → IBD (Inflammatory Bowel disease)
    - → IPF (traction bronchiectasis) Idiopathic pulmonary Fibrosis.
      - There is distortion of the airway which will hamper the ventilation and reduces the clearance of the lungs leads to Traction Bronchiectasis.

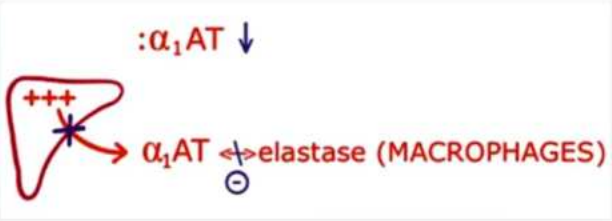
Important Information

Two more causes of Traction Bronchiectasis.
1. Radiation
2. Sarcoidosis

- Autoimmune: Patient is asthmatic, exacerbation.
  - ABPA (Allergic Broncho pulmonary aspergilloma): There is Hypersensitivity reaction against Aspergillus fumigatus.
    - → Serum precipitins against aspergillus used for the diagnosis.
    - → IgE levels are raised.
    - → Fungal hyphae are seen on sputum examination.
    - → On HRCT, Central Bronchiectasis is seen.
    - → Treatment: Steroids are recommended.
- Genetic causes
  - Alpha 1 AT deficiency
  - Cystic fibrosis
  - Kartagener syndrome
- Miscellaneous causes
  - Yellow nail syndrome
- Idiopathic (25-50%)

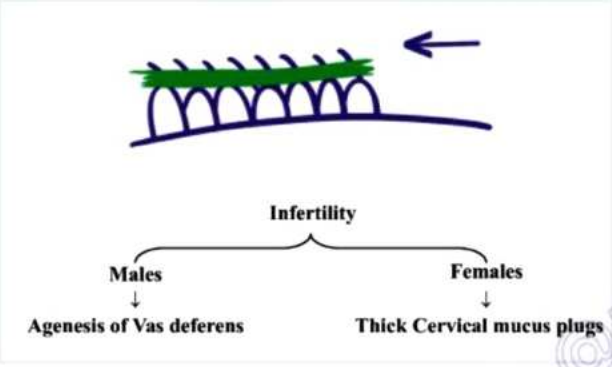
Alpha-1 Antitrypsin Deficiency

- The main function of α-1 antitrypsin is Neutralization of Elastase from macrophages. This function is impaired in this condition.
- The production is normal but not released out and accumulates in hepatocytes.
- Effects
  1. Cirrhosis
  2. Panacinar emphysema
  3. Bronchiectasis



Cystic Fibrosis: (Mucoviscidosis)

1. AR
2. F508 mutation, defect in chromosome 7.
3. Cilia motility is normal
4. Mucus become thick and viscid, so there is stasis of mucus.
5. Infertility seen in both male and female.



Kartagener Syndrome

- Immotile cilia due to dynein arm defect, secretions are normal.
- Triad
  1. Recurrent sinusitis
  2. Bronchiectasis: due to recurrent lung infections.
  3. Situs Inversus
- **Infertility:** not a part of Triad
- **Male:** Seen due to defect of sperm motility
- **Female:** Not seen because movement of ova is depending on both peristalsis of fallopian Tube and cilia motility so even if cilia motility is affected still ova can move in fallopian tube.
- So, infertility is not included in triad.

Lobes of Lungs Involved 00:31:20

Upper lobe Bronchiectasis

1. Cystic fibrosis
2. Tuberculosis
3. Post Radiation Fibrosis: causes traction bronchiectasis because radiation can destruction of airway.
4. ABPA (Central)

Middle lobe Bronchiectasis

1. Non-Tuberculosis mycobacteria
2. Kartagener syndrome
3. William Campbell syndrome (Defect in cartilage cause defective ventilation)

Lower lobe Bronchiectasis: Usually seen in the people with recurrent microaspirations.

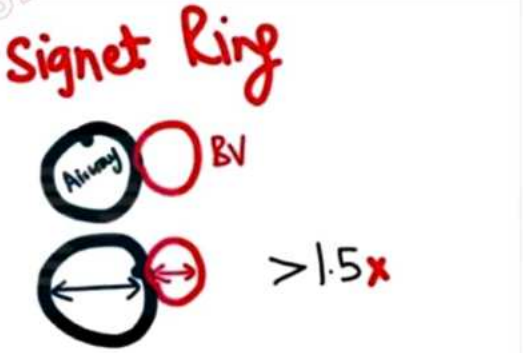
1. Scleroderma
2. Hypo gammaglobulinemia
3. ILD

Clinical features 00:34:18

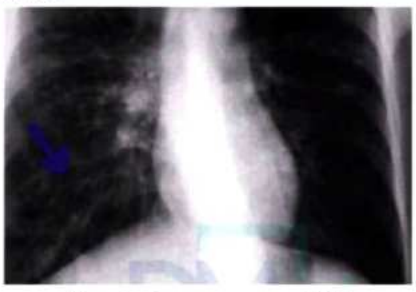
1. Productive cough
2. Bronchorrhea, purulence increase, fetid present
3. Dyspnea on exertion
4. Crept present or rhonchi present
5. Clubbing
6. Weakness
7. Weight loss
8. Cyanosis may or may not be present.
9. Cor pulmonale

Work Up 00:37:36

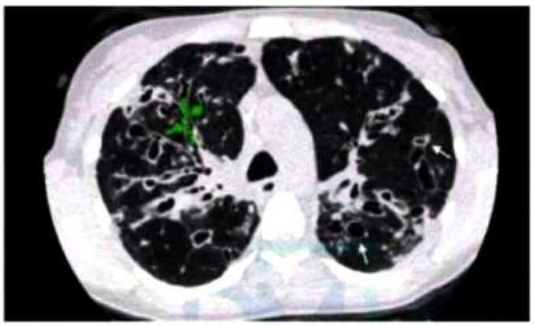
1. **On Chest X-Ray**: mostly normal, in few cases present with Tram track appearance on lower lobe.
2. **CT-scan** (HRCT – Investigation of choice)
   - Tram track appearance
   - Signet ring appearance



- Diameter of airway should be >1.5x to all the dimension of Blood vessel.



Tram track appearance on CXR



Tram track appearance on HRCT

3. **Pulmonary Function test:** Obstructive Pattern
   - $\frac{FEV1}{FEC} \rightarrow < 0.7$
   - No improvement with bronchodilators
4. **Sputum culture:**
   - Keep sputum for some time: Dittrich plugs (concretions, yellow)
   - M/E: Eosinophils in ABPA, fungal hyphae
5. **HIV:** to test with 4th generation ELISA.
6. **Autoimmune panel**
7. **Genetic causes evaluation**
   - Alpha 1 AT quantitative assay
   - Pilocarpine iontophoresis
   - Nasal electrode potential test/lung biopsy: videomicroscopic analysis
8. **Quantitative Ig level**

Treatment 00:46:25

1. Non-TB Mycobacterium: Macrolide with Rifampicin with ethambutol
2. Mucolytics: Dornase, DNAase
   - for stuck secretion: 3% saline nebulization with bronchodilators
3. Percussion device (high frequency chest oscillatory device): Helps in dislodgement of mucus.

Percussion Device

4. Chest Physiotherapy
5. Incentive spirometry
6. Vaccines
7. Gamma globulins
8. Antibiotics
   - Ciprofloxacin BD: 2 week on, 2 week off
   - Macrolide OD
   - Tobramycin nebulization in CF prevent colonization
   - I.V. antibiotics
9. Steroids in ABPA exacerbation

59 PNEUMONIA

Common Microbes causing Pneumonia

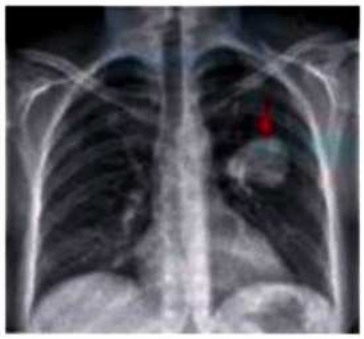
Case 00:00:20

- AIDS positive Patient with CD4 count low (200/mm3) with auscultatory finding of bronchial breathing. Organism Responsible for opportunistic infection?
- Diagnosis: Pneumococcal pneumonia

Case 00:02:35

Young child came with complaints of breathlessness, productive cough, difficulty in speech, fever and CXR shows circumscribed opacity in left upper zone.

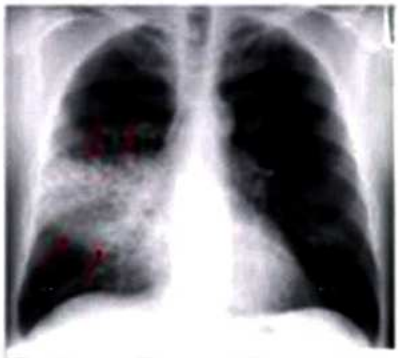
- Characteristic features of round pneumonia
- Round pneumonia caused by Pneumococcus



Case 00:03:30

Consolidation present in the right middle lobe with Silhouette sign.

- Lobar pneumonia = community acquired pneumonia (CAP)
  Causative organism : Pneumococcus

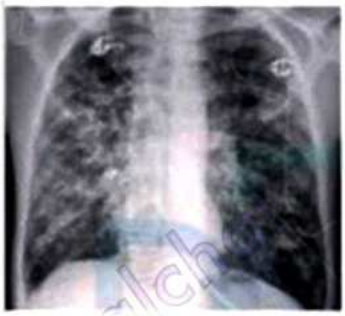


Case 00:04:50

- Ventilator Associated pneumonia (VAP). It is not associated lobar predilection.
- It begins as respiratory bronchiolitis.
- With bilateral infilterates.

VAP:

- MDR associated with Pseudomonas > Acinetobacter
- Drug of choice: Piperacillin with Tazobactam
- **Non MDR associated with Pneumococcus**



Pathology

- **Phase of Edema**: Proteinaceous exudates develop in the alveoli.
- **Red hepatization:** RBC with Neutrophils (PMN)
- **Grey Hepatization:** It signifies containment of infection. RBC lysis with PMN (Neutrophils) present, fibrin deposition in the alveoli
- **Resolution:** alveolar Macrophages predominantly present, restore the normal tissue of lung

- **Community Acquired Pneumonia commonly** associated with following organisms:
  1 . Pneumococcus (MC)
  2. Mycoplasma pneumoniae
  3. Hemophilus influenzae: gradually emerging cause.
- **ICU:** Pneumococcus: because patient got infection from community, but he is admitted to ICU only because of severity of the symptoms with having high CURB - 65 like score of 3.
- **CAP (Routine wards/Non-ICU):** Pneumococcus
- **AIDS:** In AIDS positive patient common cause of infection is still pneumococcus, but pneumocystis jiroveci present only when CD4 is < 200. Differentiation based on auscultation, chest X-ray and BAL findings

Atypical Pneumonia (Walking Pneumonia) 00:16:28

- Patient has symptoms of Mild fever, cough and came to hospital as walk in patient and hence called as Walking Pneumonia. Even
  Patient having mild manifestation but Xray showing significant changes. Organism responsible.
  1. Mycoplasma pneumoniae: Drug of choice is Azithromycin

2. Legionella pneumophila: URTI, Legionnaire's disease associated with SIADH. Na^+ decreases causing seizures. It can spread via water droplets..
3. Chlamydia pneumoniae
4. Influenza, Influenza A: H3N1, H1N1 RSV, adenovirus, Meta Pneumo virus, COVID -19

- Management: Macrolides or Fluoroquinolones, Doxycycline

Important Information

- Influenza A can superadded infection with Staph aureus. Can cause pneumatocele formation and pneumatocele may rupture and worsen the respiratory distress, due to development of Pneumo thorax.

Anaerobes Causing Pneumonia 00:23:22

- Secondary to micro-aspirations.
- Are present in the oral cavity, in between tooth which aspirated into lungs and cause anaerobic pneumonia.
- Causes of Aspiration pneumonia

1. Drug Overdose/ Overdose of alcohol: cause impaired airway defenses.
2. Seizures episodes.

- Lung abscess:
  - Primary lung abscess: Oral anaerobes
  - Secondary lung abscess: Staphylococcus aureus
  - Embolism to lungs: Infective endocarditis (S. aureus).
- **CASE SCENARIO:** A 20 years old male on Holi festival, consumed alcohol excessively with his friends and took some drugs like charas, due to effect of intoxication, he was continuously sleeping for 2 days. While waking up the patient had productive cough, fever, chills, rigors and purulent bronchorrhea. On CXR finding shows air fluid levels. All these features are suggested of Lung abscess. The organism is responsible for these features is Anaerobic organisms. So, drug of choice for anaerobic organisms is Clindamycin

Questions with following key words:

- Alcohol, Developing Lobar Pneumonia: Pneumococcus pneumonia.
- Alcohol, Red Currant Jelly sputum: Klebsiella pneumonia / FRIEDLANDER pneumonia.
- Alcoholic and drug overdose manifest with decreased airway defense so patient ends up with Anaerobic lung abscess
- COPD & smokers end up with → H. influenzae
- Structural lung disease, Eg. Cystic fibrosis with mucus plugs thickening present = Pseudomonas Aeruginosa / Burkholderia cepacia
- Contact with Birds: Chlamydia psittaci
- Contact with Bats: Histoplasmosis
- Contact with Rabbits: Francisella tularensis (TULAREMIA)
- Contact with Goat/ sheep: Coxiella burnetii can cause Q fever.
- Hotel/ cruise: Legionella pneumophila

Clinical Features 00:39:15

- Fever
- Palpitations
- Cough
- Hemoptysis: present only in the CA-MRSA
  - Rusty sputum: Pneumococcal pneumonia
- Chest pain: due to pleuritis.
- SOB
- Nausea, vomiting and diarrhea vomiting
- Abdominal pain
- Headache
- Myalgia
- Seizures

On Examination 00:41:44

1. Respiratory rate: Increased
   - Use of Accessory respiratory muscles
   - If ABG is done there is findings of Respiratory Alkalosis
2. Subcoastal recessions
3. Tactile fremitus is increased.
4. On Percussion: Dull (Usually resonant note in normal lungs).
5. On Auscultation: Bronchial breathing present
6. Air entry is normal.
7. Crackles may also heard.

Refer Table 59.1

8. Egophony: Due to lung consolidation there is the modifications in the vocal sounds which heard through stethoscope Eg: EE heard as AAA
9. Whispering Pectoriloquy where a patient sits with back to doctor and whispering sounds of patient is heard through stethoscope.

- The sound is of low intensity than the Bronchophony.

Important Information

- Old man with pneumonia discharged from the hospital after 15 days came to hospital again for MI
- This is Because of pneumolysin the toxins released by pneumococcus which will activate platelet results platelet plug in coronary vessels and lead to MI.

Work up:

1 CBC - elevated TLC levels.
2. On Chest X-ray:
   - Round pneumonia
3. Bronchopneumonia
4. Parapneumonic Effusion if untreated → Empyema
5. Lobar pneumonia
6. Sputum evaluation: Imp work up for choice of antibiotics.
   - Culture
   - Gram Stain

"Adequacy of sputum sample" is analysed by On M/E:
- 25 PMN
- 10 sq. epithelial cells

7. Blood culture (First step to done in the case of bacterial meningitis)
8. Urine antigen
   - Legionella pneumophila
   - Pneumococcus
9. PCR sputum or BAL
10. Biomarkers: CRP, Procalcitonin

CURB – 65 Score 00:57:45

- Parameters used to decide need for hospitalization.
- Parameters

Confusion	1 point
BUN ≥ 7 mmol/L	1 point
Respiratory rate >30 / min	1 point
BP <90/60 mm Hg	1 point
Age > 65 years	1 point

Score	Mortality	Rx
0	1.5%	OPD Basis
1-2	9.2%	IPD basis
	22%	ICU Basis

Important Information

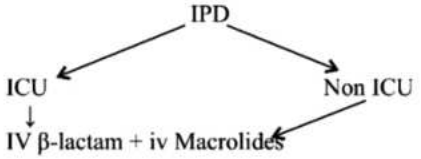
- If only age alone > 65 and results in score 1 then patient can be treated in OPD basis.

Empirical Treatment 01:03:10

- **OPD treatment**

No Comorbidities or Not received antibiotic in last 3 months ↓ Macrolides (Clarithromycin / Azithromycin) Or Doxycycline (If macrolides is not available)	Co – morbid condition or Taken Antibiotics in last 3 months ↓ Moxifloxacin or β lactam + Macrolides

- If local Prevalence of Pneumococcal Resistance is <25%
- Comorbidiaties : Chronic Heart, Lungs, Liver or Kidney disease, DM alcoholism , malignancy or asplenia
- **IPD treatment with no risk factors**



1. Recent Hospitalization, Antibiotic Treatment : Add coverage for pseudomonas: Add Meropenem/piperraclillin- tazobactam with levoflox
2. CA-MRSA: linezolid/vancomycin

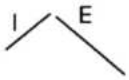
- **Ventilator associated pneumonia** 01:08:30

MDR	Non-MDR
Pseudomonas	Pneumococcus
Treatment • Piperacillin- Tazobactam • Amikacin	Treatment • Piperacillin-Tazobactam

Risk Factors For Early Deterioration Of CAP (Community acquired pneumonia) 01:11:10

- Multilobar infitrates
- SpO2 < 90%
- pH<7.3
- confusion
- RR>30/min
- Decreased albumin
- Decreased neutrophils
- Decreased platelets
- Decreased sodium
- Sugar low

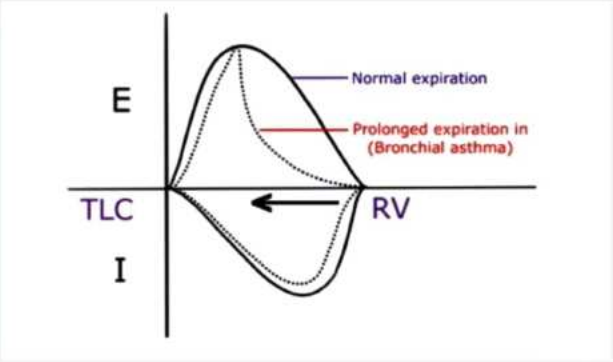
Table 59.1

Breath Sounds			
VESICULAR SOUNDS		Normal- heard over periphery Gentle rustling Sound Fades on expiration	There is no gap present in between inspiration and expiration, while inspiration takes longer time than expiration.
BRONCHIAL SOUNDS		Normal - heard over substernal notch LOUDER Expiratory lasts longer	There is a *audible gap* in between 1/4th to 3/4th distance and here expiration takes longer time. If this sound heard in any other place consider as abnormal.

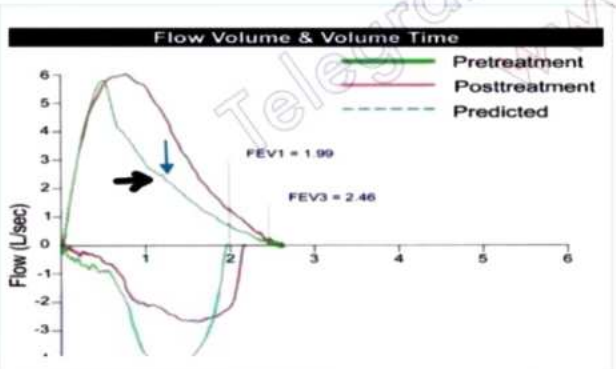
60 BRONCHIAL ASTHMA

Introduction 00:00:16

- Main diagnostic criteria for Bronchial Asthma is reversibility of airflow obstruction which is demonstrated by spirometry.
- Patient is made to perform forceful inspiration and expiration and flow volume curves are obtained



- In asthmatic patient, Baseline curve for inspiration part remain same but in expiration part: Patient is not able to push out the air as Asthma is disease of expiration So, marked concavity in expiration part is present.
- Now salbutamol is given and test is repeated in 10-15 min, concavity will reduce significantly



- Investigation of choice for bronchial asthma is Spirometry.
- FEV1: FEV1 normal before and after giving SABA
- Change in FEV1 > **12%** or 200 mL increment over baseline value of FEV1 is diagnostic of bronchial asthma
- Methacholine provocation test: Not done now because of severe bronchospasm as may lead to imminent respiratory failure.
- Eucapnic hyperventilation test: Person is made to breathe in cold air. Asthmatics has bronchial hyper reactivity to cold air and FEV1 will fall.

Diagnostic Criteria of Asthma 00:04:07

- Reversibility (Absolute criteria): Asthma is reversible airflow obstructive disease whereas COPD is nonreversible obstructive airflow disease.
- Asthma is episodic.
- Most attacks are nocturnal. Possible explanation is that at nighttime air is colder.
- Main test for diagnosis is spirometry.
- Chest X- ray may show hyperinflation and flattening of diaphragm or it can be normal also, so it has no role in diagnosing asthma
- No role of HRCT chest in diagnosis of Asthma
- Allergic bronchopulmonary aspergilloma: Hypersensitivity reaction to Aspergillus fumigatus which is associated with *Central bronchiectasis.*
  - Steroids and itraconazole are given for treatment.
  - Investigation of choice of ABPA: Serum precipitin Ab

Update GINA Guidelines 00:06:30

- New studies have suggested that patients treated only with salbutamol (SABA) are found to have higher asthma related death incidence.
- GINA no longer recommends SABA as only treatment of Asthma in adults or highly effective for quick relief of asthma symptoms

Step 1: Controller options for children 6-11 years

- Possible controller options for this age-group include taking ICS whenever SABA is taken, based on evidence from a single Step 2 study with separate inhalers that showed substantially fewer exacerbations compared with SABA only treatment. (Evidence B). Regular ICS with as-needed SABA is also a possible option for this age-group (Evidence B), but the likelihood of poor adherence in children with infrequent symptoms should be taken into account

Not recommended

- GINA no longer recommends SABA-only treatment of asthma in adults or adolescents. Based on the evidence (A), Although SABAs are highly effective for the quick relief of asthma symptoms, patients whose asthma is treated with SABA alone are at risk of asthma-related death and urgent asthma-related healthcare, even if they have good symptoms control. One long-term study of regular SABA in patients with newly-diagnosed asthma showed worse outcomes and lower lung function than in patients who were treated with daily low dose ICS from the start.

- In adults, inhaled anticholinergic agents like ipratropium, oral SABA or short-acting theophylline are potential alternatives to SABA for relief of asthma symptoms; however, these agents have a slower onset of action than inhaled SABA and oral SABA and theophylline have a higher risk of side-effects. No long-term safety studies have been performed to assess the risk of severee exacerbations with these reliever medications in patients not also taking ICS.
- The rapid-onset LABA, formoterol, is as effective as SABA as a reliever medication in adults and children, but use of regular or frequent LABA without ICA is strongly discouraged because of the risk of exacerbations.
- Controller medication: Low dose inhaled corticosteroid (ICS) with formoterol (Formoterol is a Rapid acting LABA)
- Reliever: low dose inhaled corticosteroid (ICS) with formoterol (Raise dosage up to 4 times)

Controller Medication

00:11:57

	Symptoms	Interference	FEV1	Treatment
Intermittent	< 2 d / week	None	N (>80%)	STEP 1
Mild persistent	> 2 d / week	None	Normal	STEP 2
Mod. Persistent	Daily	Some limitation	60-80%	STEP 3
Severe persistent	All Through day	Extreme Limitation	<60%	STEP 4 or 5

- STEP 1: Low dose ICS (Budesonide) with formoterol: As needed. (Ask the patient to rinse the mouth after medication to reduce the chances of oropharyngeal candidiasis)
- STEP 2: Low dose ICS (on daily basis)
- STEP 3: Low dose ICS with LABA (on daily basis)
- STEP 4: Medium dose ICS with LABA (on daily basis)
- STEP 5: High dose ICS with LABA with add on therapies (daily)
- Sputum microscopic examination: Eosinophils >3% indicates requirement of upgradation of therapy.
- Sputum guided therapy is used to dose standardization of therapy.

ADD ONS

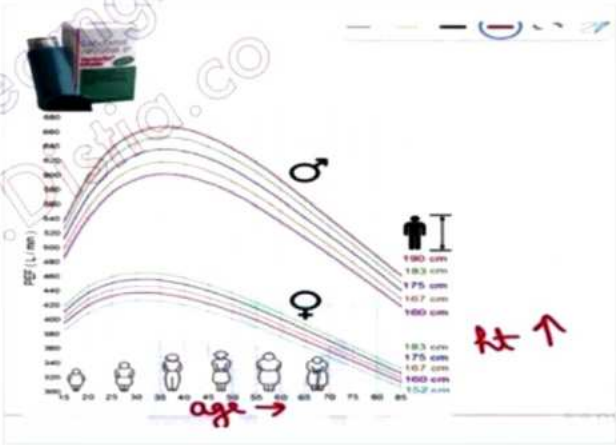
00:19:28

- Tiotropium: LAMA
  - It is an anticholinergic.
  - Reduces the bronchospasm.
- Omalizumab: Anti IgE Given Subcutaneously.
- Mepolizumab: Anti IL-5/5R
- Dupilumab: Anti IL–4/4R (Useful in severe type 2 Asthma)

Acute Asthma Exacerbation

00:21:31

- PEFR (peak expiratory flow rate) meter is advised: objective test to analyses worsening of asthma patients.
- Baseline PEFR should be noted. Value will decrease during exacerbation.



- Flow rates can be observed according to age, sex & height

Management

- Increase the dose of controller medication: can be increased up to 4 times of normal dose.
- Add S.A.B.A (Salbutamol) Color coding of inhalers is done for easy recognition
- Add oral corticosteroids

Exacerbation	FEV1	PaO2
Mild	>70%	Normal
Moderate	40-69%	>60 mmHg
Severe	<40%	>60 mmHg

Indications of Hospitalization in Severe Acute Asthma

00:25:27

1. Inability to lie flat in bed
2. Cannot speak / talk, agitated by doctor's questions, hunched up position.
3. FEV_1 < 25% of predicted value (Personal best; pre-treatment)
4. Post treatment FEV_1 < 40%

Severe Acute Asthma

00:27:48

- Talks in words.
- Agitated
- Sits in tripod position
- Accessory respiratory muscles used by patient
- Resp. rate > 30 / min
- Heart rate > 120/ min
- Pulsus paradoxus may or may not present.
- Loud Rhonchi

Treatment

1. Nebulization with salbutamol, O_2 driven (Humidified).
2. Done every 20 min for atleast 3 times in first hour. (Air driven nebulization can lead to ventilation perfusion mismatch)

Important Information

- Curschmann spirals are casts of mucus plugs which can block the airways

3. Inj. Terbutaline subcutaneous (given only if there is no improvement)
4. I.V. Hydrocortisone should be given 100 mg stat. (Can also potentiate effect of bronchodilators)
5. Consider $MgSo_4$ I.V.: As Mg+2 antagonize effect of calcium mediated bronchoconstriction.
   - I.V. Aminophylline ± (Toxicity), not recommended because it can lead to arrhythmia (PSVT)
6. Ipratropium bromide

Imminent Respiratory Arrest/ Failure

00:35:39

1. Patient Can't talk, totally silent.
2. Drowsy due to CO_2 narcosis.
3. >30/min resp. rate, bradycardia.
4. Shallow rapid breathing (Soon it will develop respiratory arrest)
5. Cyanosis may or may not be appreciated.
6. Pulsus paradoxus disappears.
7. Peak expiratory flow or FEV_1 <25%. PaO_2<60 mmHg, pCo_2 >45 mmHg.

Treatment

1. Hydration: As neuromuscular blockade for intubation causes vasodilation and severe fall in B.P. can occur so before intubation I.V. fluids should be given to patient.
2. Neuromuscular paralysis achieved in the patient and electively intubate the patient (E.T. tube) with Assisted controlled mechanical ventilation (ACMV)
3. To minimize risk of Barotrauma, permissive hypercapnia is allowed pH=7.3; pCO_2 = 50 mm Hg

Important Information

- Controller or prevention: Low dose inhaled corticosteroids (ICS) with formoterol (LABA)
- Acute Asthma: Low dose ICS with formoterol or SABA
- Severe Acute Asthma: Nebulization with salbutamol with I.V. hydrocortisone
- Imminent respiratory arrest: Elective intubation is recommended with ACMV (Assisted controlled mechanical ventilation)
- Brittle asthma (PEFR >40 %): Epi-PEN

Brittle Asthma / Type 2 Asthma

00:42:15

- Diurnal variation of PEFR > 40%
- Epi – PEN is advised to keep along and injected subcutaneously when patient feels attack.

61 COPD

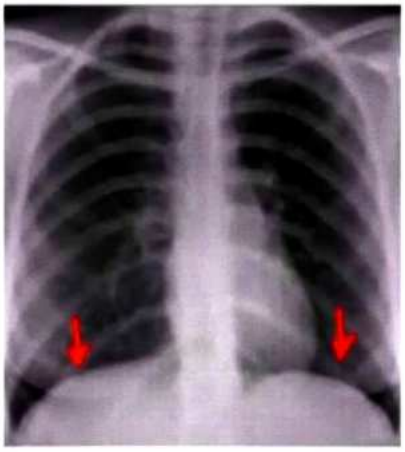
Introduction 00:00:10

- COPD involves small airways (≤ 2 mm in diameter).
- It is an Irreversible disease.
- Post bronchodilator
  - FEV1/FVC <0.7
- Triple therapy:
  - LAMA
  - LABA
  - ICS
- Biomarker of disease severity: Eosinophil count
  - > 300: Indication to start ICS.
- Biomass combustion (indoor pollution) in villages leads to Increased risk of COPD.

Emphsema 00:07:00

Tar inhaled by the individual.
↓
Alveolar macrophages
↓
Elastase production
↓
Centriacinar emphysema

- After 20 years of smoking, there is structural damage to the respiratory bronchioles leads to formation of blebs.
  - These blebs unite to form the bullae.
  - Distort the alveoli causing scarring of the alveoli.
  - The basic unit of gas exchange is hampered.
  - Delivery of oxygen is hampered leads to hypoxia. (Decrease in pO_2)
  - Hyperventilation occurs in response to hypoxia.
  - There will be carbon dioxide washout leads to normal or decrease in the pCO_2
  - This causes Type-1 Respiratory failure (Respiratory alkalosis)
- There is no change in FEV_1 before and after giving salbutamol.
- Ventilation perfusion affected.
- It is also known as pink puffers.
- On Chest X-Ray of emphysema findings are:
  1. Hyperinflation
  2. Flattening of diaphragm
  3. The lungs will look more black than normal. (Because of air trapping)
  4. Tubular heart



- Imaging modality: HRCT chest is recommended.
  - Bullae present. (This bulla can rupture anytime)
- Sudden onset of respiratory distress in smoker patient is due to rupture of the bullae leading to development of Spontaneous pneumothorax.
- Most common Complication of emphysema is Cor pulmonale contributing to RVF (Right ventricular failure)
  - Starting Low flow oxygen in COPD patients will reduces the complications and mortality.

Chronic Bronchitis 00:21:32

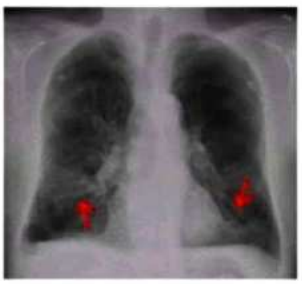
Mucociliary escalator in action
↓
In heavy smoker → Tar induced Ciliary damage
↓
Failure of muco-ciliary escalator
↓
Stasis of secretions
↓
Infection (presence of purulent bronchorrhea)
↓
Pus
↓
Occlusion of respiratory bronchioles leading to hypoventilation of alveoli
↓
Very severe hypoxia → central cyanosis (Decreased pO)

Chronic Bronchitis

- Increased pCO_2: Drowsy, Decreased physical activity, Weight gain, Hence called Blue bloaters.

gain, called blue bloaters.

- Severe hypoxia leads to Increased erythropoietin production, increased RBCs and Secondary polycythemia.
- Smoker: having cough, sputum expectoration, exertional dyspnea.
- On Chest X-Ray, increase in bronchopulmonary markings.



- This causes Type-2 Respiratory failure (Respiratory acidosis)

Case Presentation of Emphysema 00:29:54

- Tall Thin smoker, decrease exercise Intolerance, breathlessness.
- On examination:
  1. Tachypnoea
  2. Accessory Muscle working excessively.
  3. Sitting in tripod position
  4. Barrel shaped chest (AP diameter > Transverse diameter)
  5. Liver may or may not be palpable (due to Hyperinflation of lungs)
  6. Cyanosis absent
  7. Cachexia
  8. Bitemporal muscle wasting } Poor prognostic indicator
  9. Diffuse loss of subcutaneous fat.
  10. Hoover sign: Paradoxical inward movement of ribcage

Work up:

1. Spirometry:
   →FEV_1 /FVC <0.7
   →Residual volume is increased.
   →Total lung capacity is increased.
   →Functional residual capacity is increased.
2. On HRCT: bullae are seen.
3. On chest X-ray: hyperinflation seen.
4. DLCO (diffusion capacity of Lung for CO) is decreased because of trapping of CO in blebs. So, less diffusion of CO across alveoli
5. ABG:
   →
   → pCo_2 is reduced.
   → Type-1 respiratory failure.

- **Treatment:**
  - Nicotine deaddiction:
    →Nicotine buccal spray
    →Varenicline ($\alpha_4\beta_2$ partial agonist of nicotine R)
    →Bupropion
  - Video assisted Thoracoscopic surgery: Bullectomy.
  - Lung Transplantation

Important Information

- Most common cause of Lung transplantation is Idiopathic Pulmonary Fibrosis

Case Presentation of Chronic Bronchitis 00:43:17

- Fat or obese smoker with:
  - Cough
  - Bronchorrhea
  - Halitosis
  - Hemoptysis may or may not present.
  - Clubbing
  - Both inspiratory and expiratory Rhonchi

- **Work up:**
  - Spirometry: $FEV_1/FVC < 0.7$
  - Chest X ray: increased Broncho vascular markings (Dirty Lungs)
  - Investigation of choice is HRCT.
  - DLCO: Normal
  - ABG: not routinely done.
    →Done only when there is exacerbation.
    →pO_2 is reduced.
    →pCo_2 is grossly elevated.
    →Type 2 Respiratory failure (Respiratory acidosis)
- **Treatment**
  - Antibiotics with mucolytics
  - LAMA: Ipratropium Bromide
  - LABA
  - ICS
  - Mainstay of treatment: Low flow O_2 (reduces the incidence of mortality)
    → with a Nasal Cannula (1L / min): It will Increase dissolved O_2 and will increase the work capacity of patient.
    → Indication:
      - If SpO_2 less than 89% if PAH.

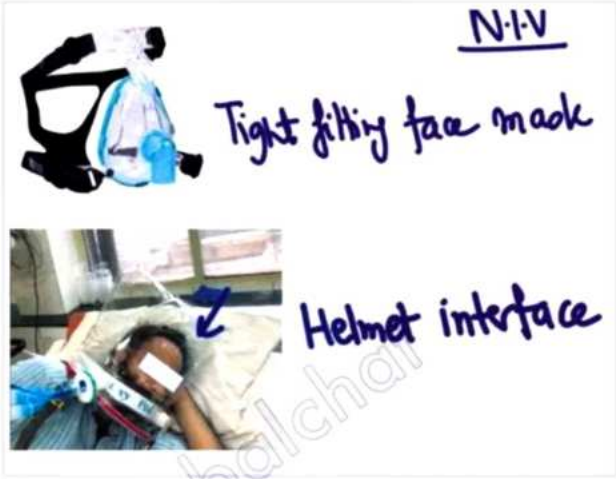
GOLD Classification

1.Mild COPD	FEV1 / FVC < 0.7	FEV1 ≥ 80%
2.Moderate COPD	FEV1 / FVC < 0.7	FEV1 = 50-80%
3.Severe COPD	FEV1 / FVC < 0.7	FEV1 = 30-50%
4.Very Severe COPD	FEV1 / FVC < 0.7	FEV1 < 30%

- Management of COPD: LAMA or ICS or LABA or roflumilast

Acute Exacerbation

- **NIV**
  - Target PO_2: 88-92%
  - Using tight fitting mask or helmet interface



  - Indications to start NIV in Severe COPD Exacerbation
    →$FEV_1 \leq 30\text{-}50\%$
    →pH <7.35
    →PCO_2 > 45mmHg
  - **Other NIV uses:**
    1. Bilateral pneumonia
    2. Acute pulmonary edema
    3. Myasthenic crisis
    4. Weaning from ventilator
  - **Contraindication of NIV:**
    1. Unresponsive patient
    2. Inability to open airways
    3. Facial trauma or facial surgery
    4. Apneic episode
    5. Hemodynamic instability
    6. MI or unstable angina or severe GI bleeding

62 COPD UPDATE

mMRC (Modified Medical Research Council) Grading

00:00:15

- Used for dyspnea
  - Grade 1: Incline (Breathlessness on going upstairs)
  - Grade 2: Slow walking than peers of same age group (Breathlessness on walking on flat surface)
  - Grade 3: Stops intermittently even after few steps.
  - Grade 4: Too Breathless to go out his house or when dressing (wheelchair bound)

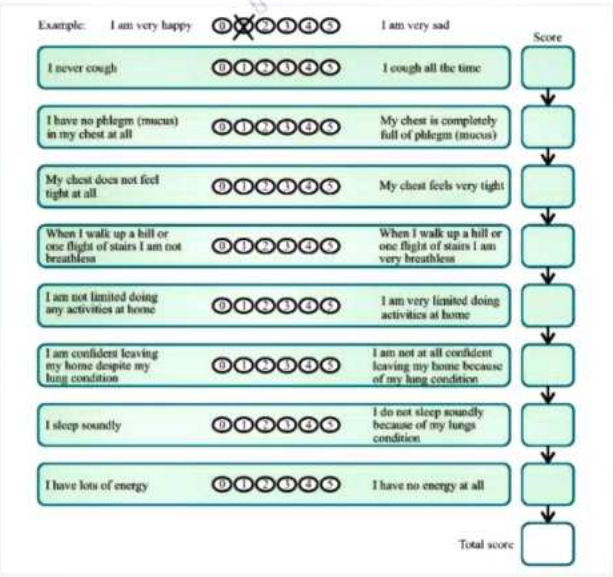
Low Risk	High Risk
• mMRC: 1	• mMRC ≥ 2
• Exacerbation: 0-1, no hospitalization	• Exacerbation: ≥ 2 requiring hospitalization in one year

COPD Assessment Test (CAT)

00:05:38

How is your COPD? Take the COPD Assessment Test (CAT)

- This questionnaire will help you and your health care professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your well-being and daily life. Your answers, and test score, can be used by you and your health care professional to help improve the management of your COPD and get the greatest benefits from treatment.
- For each item below, place a mark (x) in the box that best describes you currently. Be sure to only select one response for each question.



COPD Patients Categories

00:07:10

- A: Low risk, Low symptoms
- B: Low risk, high symptoms
- C: High risk, low symptoms
- D: High risk, High symptoms
- High risk means: Patient has had hospitalization.
- High symptom means: mMRC more than 2.

Treatment of COPD

00:08:40

- A: Bronchodilators
- B: LABA or LAMA
- C: LAMA
- D: LAMA with LABA or LABA with ICS (if eosinophils > 300/μL)
- Eosinophil count <300/μL: increased risk of pneumonia
- Test all the patients of COPD for α_1 AT deficiency (serum α_1 AT levels)
- Vaccines: Tdap, influenza, pneumococcal

α_1 AT deficiency

- Alpha 1 AT augmentation therapy on weekly basis
- Panacinar emphysema
- Defect in SERPINA 1 locus/Pi on Chromosome 14
  - M allele: normal
  - S allele: reduced levels
  - Z allele: severely reduced levels
  - P_i^Z MC form of severe α_1 AT deficiency

Pack Years

- $\frac{\text{No of Cigarettes/day} \times \text{years}}{20}$

BODE Index

To predict mortality in COPD patients

- BMI
- FEV_1 : evaluate Obstruction
- mMRC grading : evaluate Dyspnea
- 6 min walk test : evaluate Exercise Capability

63 RESPIRATORY FAILURE

Introduction 00:00:13

- Respiratory failure is divided into 4 types

Type 4 00:00:53

- Due to Under perfusion of Respiratory Muscles
- Cause: Shock (mainly cardiogenic shock: pulmonary edema, decreased supply to respiratory muscles causing hypoxia)

Management:

- ET with intermittent positive pressure ventilation is the first line management.
- Treatment of shock: Impella or ionotropes

Type 3 00:03:33

Cause:

- Due to Peri-op atelectasis (Most common in obese or elderly patients)
  - Under General anesthesia: decreased FRC cause collapse of basal lung segments
  - Oxygen saturation will relatively less.
- Inadequate analgesia: because of pain the patient will cause patients to Hyperventilate.
  - Carbon dioxide washout from the body leads to Respiratory alkalosis.

Management:

1. Supplemental O_2
2. Chest physiotherapy
3. Incentive spirometry

Differences Between Type 1 & Type 2 Respiratory Failure 00:08:12

Type I	Type II

• Reduced pO_2
• pCO_2 either normal or decreased
• Acute asthma
• ARDS
• CHF
• Fat embolism syndrome
• Pneumonia
• Spontaneous pneumothorax
	• Decreased pO_2
	• Increased pCO_2
	• Severe acute asthma
	• Diaphragm paralysis:
	  ○ GBS
	  ○ T. Myelitis
	  ○ ALS
	  ○ Polio
	  ○ Botulinum
	  ○ Cervical cord injury: C3 – C5
	  ○ Hypokalemia
	  ○ Duchenne muscle dystrophy
	• Status asthmaticus
	• Chronic bronchitis exacerbation
	• OSA
	• Pulmonary embolism

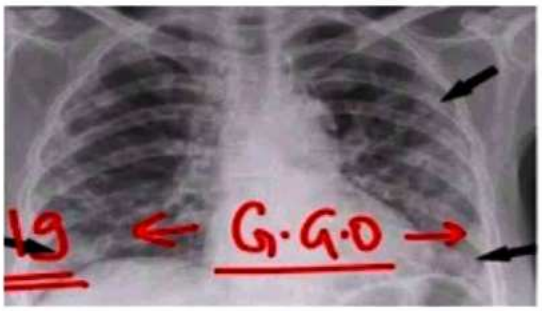
Summary Of Respiratory Failure 00:16:30

Respiratory failure	Example:	Management
Type I	ARDS, CHF	• Low volume ventilation • Prone position and Neuromuscular blockage
Type II	Status asthmaticus, acute exacerbation of COPD	• Tight fitting face mask (Non-Invasive Ventilation) • E. tube with I.P.P.V (if due to diaphragmatic paralysis)
Type III	Peri-operative atelectasis	• O_2 supplementation • Chest physiotherapy
Type IV	Decreased perfusion of respiratory muscles	• E. Tube with I.P.P.V

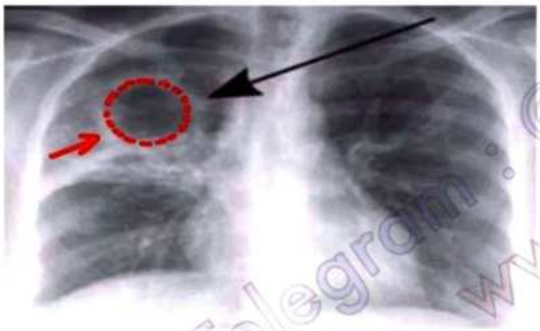
64 TUBERCULOSIS

Introduction 00:00:16

- Ro (Reproductive period per se) number is defined as the number of cases infected by one case of that infection.
- In the Overall world, the Ro number for covid is 2.56.
- In India, the Ro number for covid is 1.29.

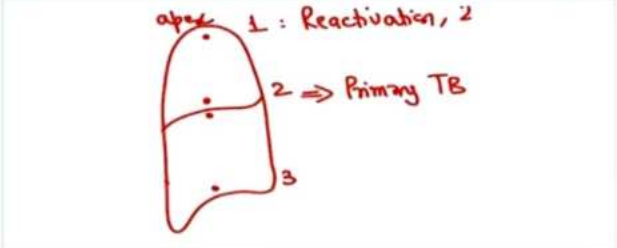


X-ray of COVID-19 patients having ground glass opacity

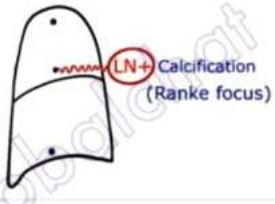


On chest x-ray, in right upper lobe, there is a distinct circumscribed lung cavity present

- Ro for TB is 1.2 (Number of cases one case of TB can infect)
- **Most common site of primary TB or Ghon focus:** Lower part of the upper lobe.
- **Apex** is the site for secondary TB, reactivation TB, or post-primary TB.



- **Most common presentation of extrapulmonary TB** is the development of Cervical Lymphadenopathy.
- If Ghon focus develops in Tonsils causes Cervical lymphadenopathy (Extrapulmonary TB)
- Lymph nodes get bigger, ultimately rupture and pus escapes into soft tissue leads Cold abscess in the neck (Extra pulmonary TB)
- Management of Cold abscess is ATT (given for 6 months) with antigravity drainage.
  - Don't do incision and drainage because it contains live bacteria that can cause fistula formation.

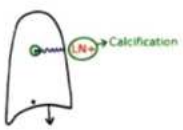
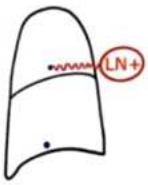


Ghon's focus with concomitant same-sided lymphadenopathy.

Ghon Complex

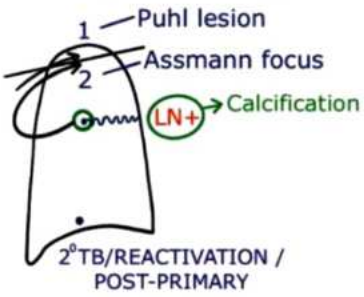
- Most common presentation is asymptomatic.
- Since it is subpleural, can erupt and cause pleuritis in the individual.
- Patient develops fever and chest pain (pleuritic chest pain)
- Erythema nodosum on the shin
- Phylctenular conjunctivitis (Reaction to tubercular bacilli)

Two possibilities of Ghon's focus in the body 00:08:03

I. Body will try to limit it	II. If CMI decreased (low immunity): Primary progressive pulmonary TB
	
• By Calcification around focus and LN • Ranke Complex (Good immunity) develops.	• Pleural effusion • There is a Cavity formation called Primary progressive pulmonary TB. • L.N enlargement: exhibit Ball valve defect and Lobar inflation. • Segmental Collapse • Tubercular pneumonia

Post Primary TB or Reactivation of TB/Adult TB 01:13:43

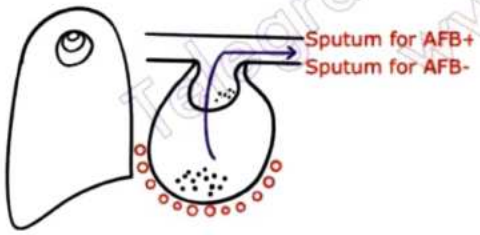
If CMI decreases later on
↓
Reactivation of TB / Post 1° TB
↓
Bacteria can be disseminated to the following Sites.



- PUHL Lesion: Supraclavicular lesions (active lesion)
- ASSMAN focus: Infraclavicular
- Weigert focus: Pulmonary vein
- Rich focus: CNS (TB meningitis)
- Simmonds focus: Liver

} Related to the dissemination of disease

- Simon focus: Supraclavicular (Inactive lesion)
- Cavity formation keeps increasing in size, resulting in damage and eroding adjoining tissue.
- So, the sputum is loaded with bacteria.



  - Sputum for AFB is positive which means it has a large cavity with a more bacterial load.
  - Sputum for AFB is negative which means it has a small cavity.
- Can also erode into blood vessels (Most common blood vessel involved Bronchial Artery)

Clinical Presentation of TB 00:19:30

1. Fever: Evening rise in temperature
2. Night Sweats
3. Weight loss
4. Decreased appetite
5. Hemoptysis
6. Clubbing
7. SIADH

Important Information

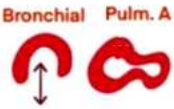
Massive hemoptysis

- The leading cause is TB.
- The source of bleeding is the Bronchial artery.
- Loss of blood is 600 ml/day.
- Treatment of choice is Bronchial artery embolization.

Hemoptysis	
Massive or Life-threatening	**Non-Life-threatening**
• Palliative Measure: Rigid bronchoscopy (to keep airway patent) • Treatment of choice is Bronchial Artery Embolization	• First investigation: HRCT chest (helps to differentiate whether it's a vascular or parenchymal lesion) • Fiberoptic bronchoscopy: Biopsy with Local hemostasis

Important Information

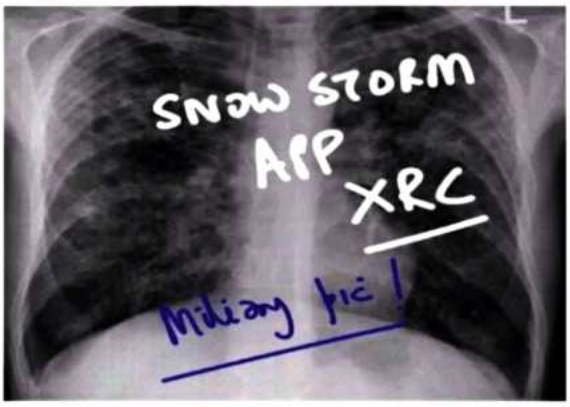
- **Rasmussen's aneurysm:** present in the pulmonary artery and commonly seen in Bronchial TB.
- Occur in the pulmonary artery because the bronchial artery is having less connective tissue.



Rassmussen aneurysm

Disseminated TB 00:28:59

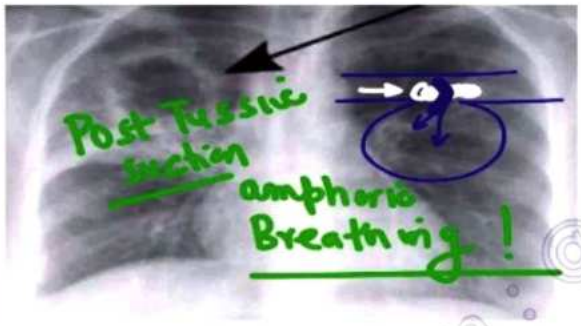
- If dissemination occurs via the Bronchial vein
  ↓
  To Heart
  ↓
  All over the body
- Pathognomic feature: Choroid Tubercles (on Fundus examination)
- If dissemination through pulmonary artery: to both lungs causing Miliary Tb (Snowstorm appearance on CXR)



Breathing in Cavity in TB

00:32:30

- Amphoric breathing
- Post tussive suction



Important Information

- Most common site of extrapulmonary TB: **L**ymph node > **P**leura > **G**enitourinary Tract (LPG)
- Snowstorm appearance is seen in
  1. TB
  2. Silicosis
  3. Hemosiderosis
  4. Varicella zoster pneumonia (in older age group)
  5. Pulmonary alveolar proteinosis.
  6. Fat embolism syndrome (rare)

Pleural TB

00:35:33

- Diagnosis by pleural biopsy and CBNAAT on the sample.
- It can be involved in 1°, 2° or extrapulmonary TB.
- **Clinical features**
  - Fever
  - Weight loss
  - Evening rise in temperature
  - Night sweats
  - Pleuritic chest pain
  - Pleural rub heard on deep inspiration
- **On Thoracocentesis**: Straw-colored fluid.
- **In Fluid**: Lymphocytes present, Sugar decreased, Protein elevated.
- **Screening test for diagnosis of Pleural TB:** Adenosine deaminase levels (elevated).
- **Investigation of choice:** CBNAAT on the pleural biopsy specimen

HIV and TB

00:38:42

- Cavity size: Smaller
- Sputum for AFB: negative
- Montaux test: False negative
- Chest X-ray: Normal
- Dissemination is more common and so, do CBNAAT of CSF or gastric lavage.
- Treatment: ATT with combination anti-retroviral therapy (CART)
- If cART is initiated: causes IRIS (immune reconstitution inflammatory syndrome)
  - So, to prevent this, start ATT, and after 2 weeks start HIV treatment.
- Rifampicin with protease inhibitors can cause a drug interaction, so use Rifabutin instead of Rifampicin.

Summary

00:43:52

- 1° TB: The Lower part of the upper lobe
- 2° TB: Reactivation on the APEX, post-primary TB
- Extrapulmonary TB: Cervical group of LN enlargement
- Disseminated TB: Fundus- Choroid tubercles.
- Site of Congenital TB: Liver
- HIV with TB: the cavity is small.
- Ghon focus seen in: Lungs, Tonsils, Ileum (via swallowed sputum, M.Bovis in unpasteurized milk), liver

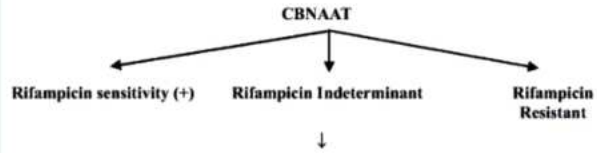
Important Information

In HIV
If CD4 count is < 500: TB
< 200: P. jiroveci
< 100: toxoplasmosis
< 50: MAI (Mycobacterium avium intracellulare), CMV retinitis

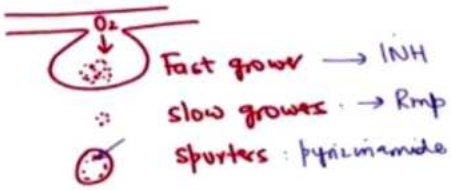
Work Up: Using CBNAAT (Gene XPERT)

00:49:40

Smear + CXR+	Smear + CXR -	Smear - CXR +	Smear - CXR: not available clinical suspicion
Microbiological confirmed TB		CBNAAT	PLHIV/MDR TB Suspicion
			CBNAAT



Repeat CBNAAT or do liquid culture: BACTEC



Indications of CBNAAT

00:54:22

1. Person living with HIV (PLHIV)
2. Smear negative, X-ray positive.
3. Smear negative, X-Ray unavailable.
4. MDR-TB suspicion
5. Extra pulmonary TB: CSF sample
6. Pediatric Tuberculosis: In child having
   - Fever for more than 2 weeks
   - Unremitting cough
   - Weight loss of 5% over 3 months

Important Information

- Involuntary weight loss in adult is 5% over 6 months.
  - 10 Lbs weight over 6 months
  - In category B symptoms: in Hodgkin lymphoma: 10%

Treatment

00:59:30

- Category 1: Newly diagnosed (Smear positive or negative) or even previously treated cases
  - Give: 2 (HRZE) + 4 (HRE) for a total of 6 months
- Combining the drug is important to deal with different species of bacteria having different rates of multiplication.
- Drug Sensitivity testing is important.
  - Rifampicin Resistance is due to RPO B gene.
- MDR TB: Resistance to either isoniazid / Rifampicin

Levoflox
Kanamycin
Ethionamide
Cycloserine
Pyrazinamide
Ethambutol
} 6 months (L K Et Cs Z E) + 18 months (L Et Cs Z)

XDR TB: Resistance to INH or RMP, 2nd line drugs (Fluoroquinolone), and to one of the second line injectables (Amikacin, Kanamycin, Capreomycin)

- Treatment of XDR TB
  - **3C** → **C**apreomycin, **C**ycloserine, **C**lofazimine, **2E** → **E**thionamide, **E**thambutol } 6-12 months
  - **PUB** → **P**yrazinamide, **B**edaquiline, **E**thionamide, cycloserine, clofazimine, linezolid, ethambutol (18 months)

DOTS 99 is used for checking the compliance of the patient

65 INTERSTITIAL LUNG DISEASE

Causes of ILD

Known Causes 00:00:57

Exposure
- Cement (Asbestosis)
- Glass Industry (Silicosis)

Therapeutic
- Radiation to chest (Ca breast, Superior vena cava syndrome)
- Drugs
  - Amiodarone
  - Methotrexate
  - Nitrofurantoin (Causes Fleeting Pulmonary Opacities)

Connective tissue disorder
- Rheumatoid arthritis: associated with usual interstitial pneumonitis (UIP).
- Scleroderma
- Polymyositis
- Dermatomyositis

} histopathological domain seen is nonspecific interstitial pneumonitis (NSIP).

Vasculitis
- Wegener Granulomatosis (also known as Granulomatosis with polyangiitis)
- Churg Strauss Syndrome (Eosinophilic Granulomatosis with polyangiitis)

Granulomatous Causes
- Sarcoidosis
- Hypersensitivity Pneumonitis (Type IV HSR)

Hypersensitivity Pneumonitis
- Causes
  - Farmer Lung: Barn: Hay having Thermophilic Actinomycetes.
  - Bagassosis: Sugar Cane dust having Thermophilic Actinomycetes
  - Bysinosis: Cotton dust in the mill (Monday chest tightness in a factory worker)
- In Contrast to bronchial asthma, the symptoms here get relieved as soon as causing factor is eliminated.
- Repeated attack of HP ultimately leads to Pulmonary Fibrosis.

Unknown Causes 00:12:55
- IPF (Idiopathic Pulmonary Fibrosis): Most common and the Mortality rate due to it is 50%
- NSIP: common in females >> male
  - Having a Good prognosis
- Desquamative interstitial pneumonitis (DIP): Associated with smoking.
- Cryptogenic organizing pneumonia: after the pneumonia is recovered there is the development of pulmonary fibrosis.
- Acute interstitial pneumonitis (mimics ARDS)
  - (Hamman-Rich syndrome)
- Lymphocytic interstitial pneumonitis: Diagnosis of exclusion in AIDS + patient with Shortness of breath.
  - First Rule out P. Jiroveci, TB, Histoplasmosis, MAC by BAL
    → If all is ruled out, LIP Can be the diagnosis.
- Lymphangioleiomyomatosis (LAM)
  - Female > Male
  - Female, on HRCT chest there are Cystic Changes
  - Development of Spontaneous pneumothorax can occur.
- Langerhans Cells histiocytosis (associated with smoking)
- Pulmonary Alveolar Proteinosis: Surfactant is produced but clearance is defective so it keeps on accumulating leading to obstruction of the airway

Important Information
- Hamman crunch sign: it is an auscultatory finding seen in pneumo-mediastinum.
  - As someone walking on freshly fallen snow with leather boots on.
- Hamman sign: it is a palpable finding seen in subcutaneous emphysema

Important Information
ILD Associated with Smoking
1. DIP (Desquamative interstitial pneumonia)
2. RB ILD (Respiratory Bronchiolitis - ILD)
3. LCH (Langerhans Cell Histiocytosis)

Clinical feature 00:23:37

History
- Age > 60 years: Suggestive of IPF
- 20-40 years: CTD, Sarcoidosis, LAM, LCH
- Female: CTD except for RA with lung involvement is more common in males
- Duration: Acute conditions are acute interstitial pneumonitis, hypersensitivity pneumonitis, GPA (granulomatous polyangiitis)

Symptoms
1. Shortness of breath
2. Dry Cough

3. Haemoptysis (GPA, LAM, Goodpasture syndrome): must rule out cardiovascular causes, infections, lung cancer.
4. Past medical history
- Asthma in Churg Strauss syndrome
- Raynauds (CTD)
5. Smoker (Desquamative interstitial pneumonitis (DIP), Respiratory bronchiolitis interstitial lung disease (RBILD), Langerhans cell histocytes (LCH))
6. Occupation History: Pigeon Breeder Lung (HP)

On Examination 00:30:47

1. End inspiratory fine crackles at lung bases (Bibasilar Crepitations)
2. Wheeze: Sarcoidosis (Lymphadenopathy present)
3. Cyanosis
4. Clubbing
5. Cor Pulmonale (RVF: Pedal Edema)

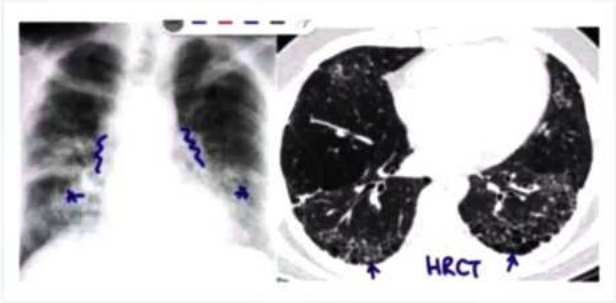
Work Up 00:33:45

1. Autoimmune Panel
2. Pulmonary function tests-Restrictive Pattern
   - TLC levels decreased.
   - FEV_1 / FVC Ratio is normal or increased.
   - Obstructive Pattern: Seen in Sarcoidosis (hilar lymphadenopathy)
3. Chest X-ray
   - Hilar LAP in sarcoidosis
   - Asbestosis: Basilar Reticular Opacities, Shaggy heart (irregular border of the heart)
4. HRCT (recommended imaging mortality): Subpleural reticular opacities
   - Traction Bronchiectasis (airway distortion)
   - Honey combing pattern
   - Reverse Halo Sign (Cryptogenic Organizing pneumonia)

Important Information

- Halo Sign → Aspergillus

5. Investigation of Choice → Biopsy (Fiberoptic Bronchoscopy with Cryobiopsy)



Treatment 00:41:34

- IPF (idiopathic pulmonary fibrosis): Pirfenidone with Nintedanib
- NSIP: Prednisolone with Mycophenolate with Rituximab
- CTD: Steroids
- Lung Transplantation: Most common cause of lung transplantation is ILD (Most common type – IPF)

Vasculitis with ILD 00:43:49

GPA

- URT involved: Epistaxis.
- LRT involved: Hemoptysis
- Kidney involved: Hematuria
- Strawberry gingiva
- HRCT: nodules, Ground glass opacities

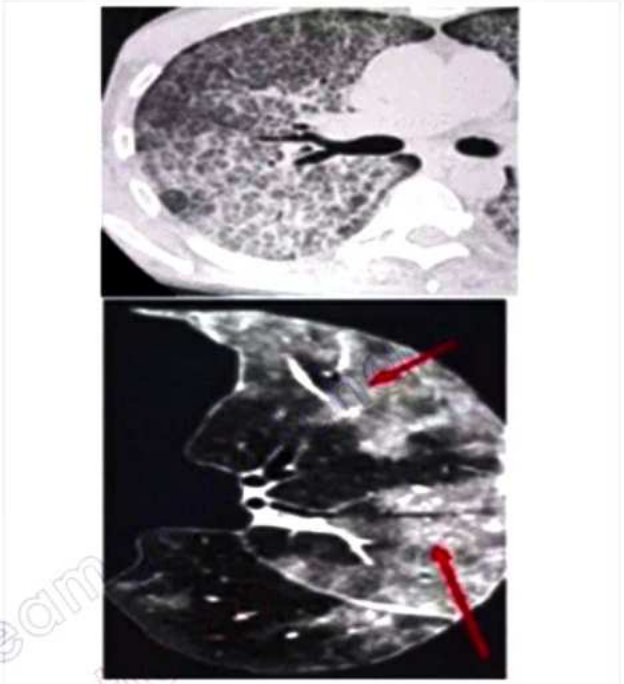
EGPA

- Chronic sinusitis
- History of asthma
- Peripheral eosinophilia

66 PULMONARY ALVEOLAR PROTEINOSIS

Introduction And Pathophysiology 00:00:13

Type 2 Pneumocytes
↓
Produce DPPC (Dipalmitoyl phosphatidylcholine) with Surfactant Proteins
↓
GM - CSF (Granulocyte-Macrophage colony-stimulating factor) produced by alveolar macrophages clears surfactant.
↓
Clearance of surfactant decreased due to decreased bioactivity of GM-CSF and
Accumulation of surfactant in alveoli
↓
Later- Pulmonary fibrosis



CAUSES

- Congenital (Autosomal recessive)
- Acquired
  - Silicosis
  - Inhalation dust
  - Lysinuric acid intolerance
  - Haematological malignancies
  - Crystals of Quartz

Clinical Features 00:05:48

30–50-year male presents with

1. Dyspnoea on Exertion
2. Fatigue
3. Weight loss
4. Fever
5. Chunky gelatinous sputum plugs

Work Up 00:07:55

1. PFT (Pulmonary function tests): Restrictive pattern (FEV_1 / FVC is Normal or increased)
2. Chest X-Ray: Snowstorm / "Bat wing" appearance of lung infiltrates
3. HRCT: "Crazy pavement" pattern (thickened interlobular septa)
4. Investigation of choice is BAL (Bronchoalveolar lavage): Presence of PAS positive Lipoproteinaceous material

Important Information

PAS positive is seen in:

- Pulmonary alveolar proteinosis
- Liver: α_1 Antitrypsin deficiency
- GIT: Whipple's disease

Management

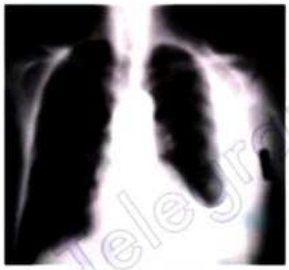
Whole lung lavage

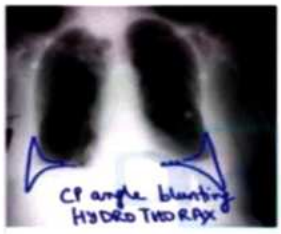
67 PLEURAL EFFUSION

Introduction

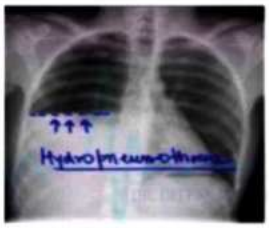
00:00:14

- Normal amount of fluid in Pleural space: 5-15 ml
- Pleural fluid secreted by: Parietal Pleura
- Rate of synthesis of pleural fluid is 0.01 ml/kg/hour (Some of this secreted fluid is reabsorbed by lymphatics)
- Minimal Amount of fluid present in the pleural cavity for Clinical Detection is 300ml.
- Investigation Of Choice for Minimal Pleural Effusion: CT chest > USG chest
- Minimal Amount of fluid that should be present to confirm pleural effusion on CXR in the Upright position.
  - CXR Upright: Lateral view > 100ml
  - CXR Upright: Frontal view > 200ml
  - CXR Upright: Frontal view (Amount of fluid needed for the obliteration of Hemi-diaphragm: > 500 ml
- Characteristic of Pleural effusion on CXR
  - Obliteration or Blunting of CP angle (CP Angle: Costophrenic Angle)
  - Meniscus sign
  - Notice the highest point on meniscus laterally is higher

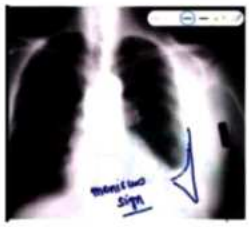




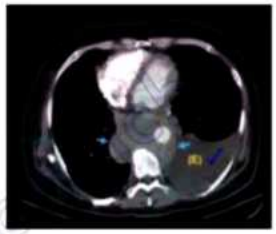
B/L Pleural Effusion (Hydrothorax)



Hydro pneumothorax



Meniscus sign



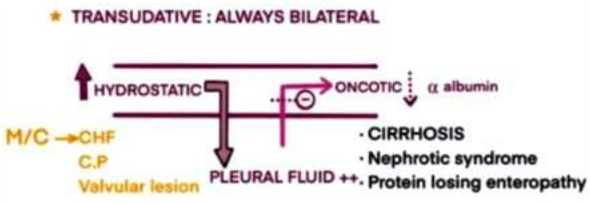
CT chest showing Left sided Pleural Effusion

Etiology

00:07:18

- 2 types of Pleural effusion:
  1. Transudative
  2. Exudative

Transudative Variety



- Hydrostatic Pressure will drive the fluid out of vascular space/capillaries while Oncotic pressure will drive the fluid back into the Intravascular compartment.
- Any condition causing.
  - Increase In Hydrostatic Pressure or Decrease In Oncotic pressure Would lead to Excess Pleural fluid accumulation in the Pleural space of the patient.
- Conditions causing an increase in Hydrostatic Pressure
  1. CHF (Most common)
  2. Constrictive Pericarditis
  3. Valvular lesions
- Conditions causing a decrease in Oncotic pressure.
  4. Oncotic Pressure ∝ Blood Albumin

5. Decrease in Blood Albumin (Hypo Albuminemia) leads to decrease in Oncotic Pressure

Important Information

Hypoalbuminemia is seen in conditions like:

- Cirrhosis
- Nephrotic Syndrome
- Protein Losing enteropathy
- Transudative Pleural Effusion is always B/L as pressure is distributed equally to left & Right Side.
- Leading cause of B/L Pleural effusion → Heart Failure
- Exudative Pleural effusion can be U/L or B/L

Exudative Variety

Causes of Exudative Pleural Effusion

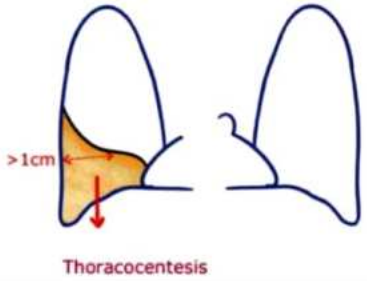
1. Parapneumonic Effusion (Pleural Effusion with Pneumonia)
2. Malignancy
3. TB
4. Rheumatoid Effusion
5. Meig Syndrome

Important Information

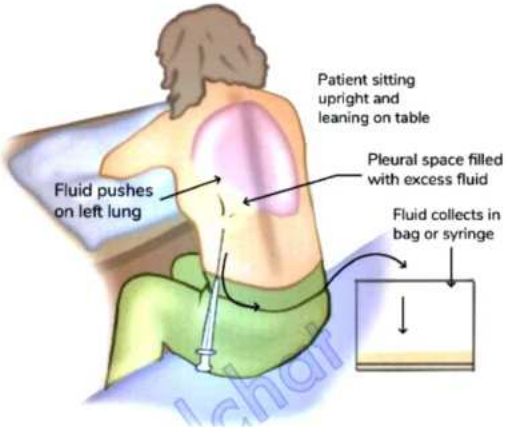
- Leading cause of Malignant Pleural Effusion is Adenocarcinoma lung.
- Adenocarcinoma lung is Peripherally located so it would keep on causing Irritation of the pleural surface resulting in Exudative pleural Effusion.
- On Thoracocentesis
  - Fluid Clots on standing in an Exudative variety.
  - Fluid is transparent like water and Never Clots in the Case of Transudative variety.

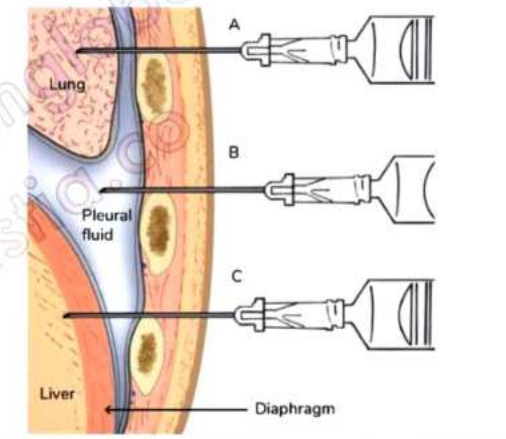
Thoracocentesis

- Thoracocentesis is always done USG guided.
- >1 cm distance between Pleural surface and lung border i.e. 1 cm of Fluid separating Lung border from Pleural Surface on CXR is an Indication of Doing Thoracocentesis
- Preferred site of Thoracocentesis is 8th ICS (Inter Costal Space) in Scapular line. Some sources mention 8th ICS space. Best would be decided on ultrasound report.



- Always do this by standing behind the patient
- If we have done on mid axillary line, the chances of causing pneumothorax are very high

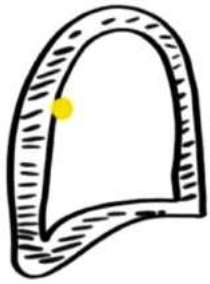




Different varieties of pleural effusion 00:17:00

Pleural Effusion related to Malignancy

- Usually there is occurs Massive Pleural Effusion in Malignancy (peripherally located cancer)



Important Information

- Leading cause of Malignant Ascites is Ca Ovary
- Leading cause of Malignant Pleural Effusion is Ca Lung (Adenocarcinoma)

- Symptoms are Patient complains of TREPEPNEA (Dyspnea of Patient is Increasing on lateral Decubitus position.)
- Management
  - Diagnostic Thoracocentesis
  - Send the fluid to the laboratory to confirm the Exudative variety based on light's Criteria
    → Check for:
    - Pleural Fluid Protein
    - Pleural Fluid LDH

Light's Criteria	• Pleural Fluid Protein > 0.5 times of serum protein • Pleural Fluid LDH > 0.6 times of serum LDH • Pleural Fluid LDH > 2/3 times upper Reference limit of serum LDH

  - Ideally any 1 of 3 present is sufficient for Diagnosis of Exudative Pleural Effusion.
    → However, in about 25% of cases light's criteria may misdiagnose Transudate as Exudate.
  - Other parameters checked
    → Pleural fluid Sugar < 60 mg%
    → Cytology: Microscopic examination: Malignant Cells are present
    → Pleural effusion in these cases of Malignancies recurs a lot after Thoracocentesis. To prevent this, we inject a sclerosing agent in the pleural space which causes obliteration of the pleural cavity and the fluid doesn't reaccumulate. This procedure is known as Pleurodesis.

Important Information

- Maximum Amount of fluid that can be removed per episode of Thoracocentesis is < 1500 ml (As per BTS Guidelines -British Thoracic Society Guidelines)
- We don't remove fluid > 1500 ml due to the risk of development of Re-expansion pulmonary edema.

- Management of malignant pleural effusion: After Removing the fluid from the pleural space, give the following drugs:
  - Injection of Doxycycline into pleural space via chest tube: Leads to the formation of adhesions in various layers of pleura ultimately causing Pleurodesis

Pleurodesis

Important Information

- Orthopnea: Breathlessness increasing in supine position
  - Seen in Acute CHF
- Platypnea : Increase in Breathlessness in a sitting position Seen in
  1. Atrial Myxoma
  2. Hepato pulmonary syndrome

Parapneumonic Effusion

- If Diagnosed later or failed to Diagnose: Can lead to Empyema which then is managed by Chest tube insertion in the 5th ICS in Mid Axillary line.

Tubercular Pleural Effusion

- Classified as Extra-pulmonary TB.
- Adenosine Deaminase Levels increase in Pleural fluid.
- Investigation of choice is Pleural Biopsy gene Xpert or CBNAAT (Not Pleural Fluid gene Xpert)

Rheumatoid Pleural Effusion

- Inflammatory nodules in Lungs, Heart
- On Skin present in Extensor Distribution
- Inflammatory nodules undergo breakdown that results in the development of exudates
- On Microscopic Examination
  - Cholesterol crystals present in Pleural Fluid

Important Information

- Low pleural Fluid Sugar: Seen in
  1. Infection
  2. Malignancy
  3. Rheumatoid Arthritis associated Pleural Effusion

Meigs syndrome

- Associated with
  1. Ovarian Tumors
     - Fibroma or Thecoma
  2. Ascites
  3. Right-sided Pleural effusion

Important Information

- Left-sided pleural effusion:
  - Acute Pancreatitis (Involving the Tail of the Pancreas): Sympathetic Pleural Effusion
  - Boerrhaave Syndrome (Rupture of Esophagus)
  - Esophageal Malignancy
- Bilateral pleural effusion: CHF
- Hemorrhagic Pleural Effusion
  - Has a Hematocrit Value 0.5 times that of blood.
  - Seen with TB or Cancer lung or Mesothelioma or Trauma
- Mesothelioma is associated with Asbestosis. Other features seen are:
  - Pleural Plaque Calcification
  - Hemorrhagic Pleural Effusion

Normal pleural fluid has the following characteristics 00:33:20

- Clear Ultrafiltrate of plasma that originates from the Parietal pleura.
- A pH of 7.60-7.64
- Protein content of less than 2% (1-2 g/dL)
- Fewer than 1000 white blood cells (WBCs) per mm^3.
- Glucose content similar to that of plasma
- Lactate dehydrogenase (LDH) less than 50% of plasma

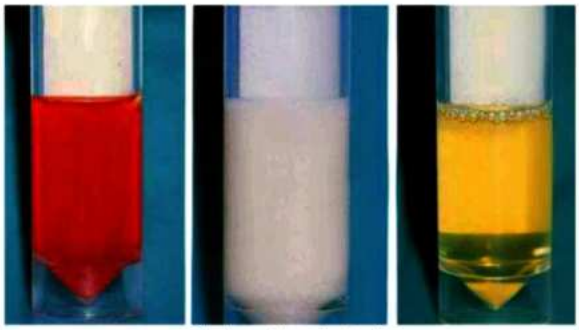
Indications of ICD tube insertion

1. Loculated Pleural Fluid / Empyema
2. Pleural fluid PH < 7.20
3. Pleural Fluid glucose < 3.3 mmol/L (< 60 mg / dl)
4. Positive Gram stain or culture of pleural fluid
5. Presence of Gross pus in the pleural Space

Characteristics of important exudative pleural effusion

Refer Table 67.1

Gross appearance of pleural fluid



Hemorrhagic | Chylous- thoracic duct obstruction | Transudate in CCF

- Haemorrhagic pleural effusion
- Chylous pleural effusion
- Transudative Pleural effusion
- Chylous Thoracic duct obstruction leads to Chylothorax: This Pleural Fluid is Milky White Colored and has increases Triglycerides
  - Cause of Chylothorax is Damage to lymphatics by Conditions such as Filariasis.

Empyema drainage

Normal chest tube insertion

Table 67.1

Etiology or Type of effusion	Gross Appearance	White Blood Cell Count (Cells/mcL)	Red blood Cell Count (Cells/mcL)	Glucose	Comments
Malignancy	Turbid to bloody: occasionally serous	1000 to 100,000 M	100 to several hundred thousand	Equal to serum levels: <60 mg/dl. In 15% of cases	Eosinophilia uncommon: positive result on cytologic examination
Uncomplicated parapneumonic	Clear to turbid	5000-25000 P	< 5000	Equal to serum levels	Tube thoracostomy unnecessary
Empyema	Turbid to purulent	25,000 – 100,000 P	<5000	Less than serum levels: Often very low	Drainage necessary: putrid odor suggests anaerobic infection
Tuberculosis	Serous to serosanguineous	5000 – 10,000 M	<10,000	Equal to serum levels: occasionally 60mg/dL	Protein > 4.0g/dL (may exceed 5g/dL) eosinophils cells (>5%) make diagnosis unlikely: see text for additional diagnostic tests
Rheumatoid	Turbid: greenish yellow	1000-20,000 M or P	<1000	< 40 mg/dL	Secondary empyema common: high LD, low compliment, high rheumatoid factor, cholesterol crystal are characteristic
Pulmonary infarction	Serous to grossly bloody	1000- 50,000 M or P	100-100,000	Equal to serum levels	Variable findings: no pathognomonic features

Esophageal rupture	Turbid to purulent red-brown	<5000 to 50,000 P	1000 – 10,000	Usually, low	High amylase level (salivary origin): pneumothorax in 25% cases: effusion usually on left side: pH <6.0 strongly suggests Diagnosis
Pancreatitis	Turbid to serosanguineous	1000 – 50,000 P	1000 – 10,000	Equals to serum	Usually left-sided: high amylase level

PREVIOUS YEAR QUESTIONS

Q. What is correct about transudative pleural effusion?

A. Pleural fluid protein to serum protein <0.5

B. Pleural fluid LDH to serum LDH >0.6

C. Pleural fluid LDH >2/3 of the upper limit for serum LDH

D. Pleural fluid protein to blood protein ratio more than 0.5

Q. A 30-year-old patient was having breathing difficulty on doing day to day activities. His doctor noticed dullness on percussion in right infra-axillary area with reduced air entry. Chest X-ray showed pleural effusion and pleural tapping was done. What finding will suggest an exudative pleural effusion. (FMGE JUNE 2021)

A. Pleural fluid protein= 3.5 gm %and LDH = 100 IU

B. Pleural fluid protein = 4.5 gm.% & glucose = 30mg%

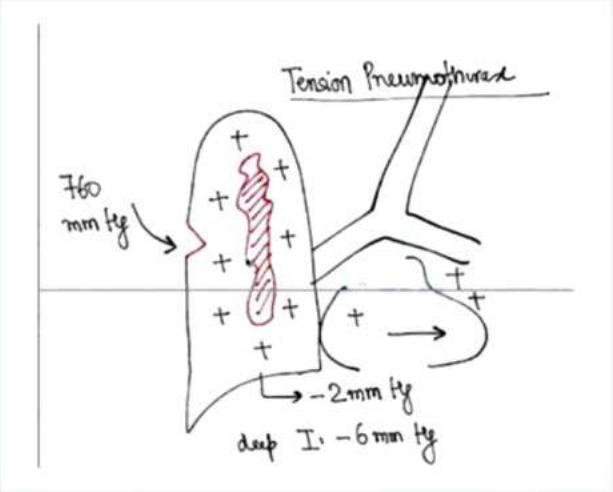
C. Pleural fluid LDH= 90 IU & glucose = 60 mg%

D. Pleural fluid protein = 3.5gm% & glucose = 90 mg%

68 PNEUMOTHORAX

Tension Pneumothorax

00:00:32



- Intrapleural space is having a pressure of -2 mm Hg. On deep inspiration, the pressure is -6 mm Hg.
- If there is a breach in the chest wall the high-pressure air entering the chest results in the collapse of the entire lung.
- The entry of air leads to the creation of a tissue flap. Functions as a one-way valve. (The air enters into the lung but can't escape out of it)
- The pressure of intrapleural space is turning out to be positive from negative.
- Push the heart to the contralateral side, along with kinking of SVC/IVC Shifts the trachea to the contralateral side.

Clinical features

- Sudden onset respiratory distress after Chest Trauma
- Kinking of great veins (SVC or IVC)
- Decreased Venous return
- SBP decreased.

} Obstructive Shock

Important Information

Causes of Obstructive Shock
1. Cardiac Tamponade
2. Tension pneumothorax
3. Budd Chiari Syndrome

Examination findings

1. Trachea shift to the contralateral side
2. Apex Beat displacement to contralateral side
3. On Percussion: HYPER RESONANT NOTE
4. HAMMAN CRUNCH SIGN: PNEUMOMEDIASTINUM (Sounds like walking on snow with Leather boots)
5. Air Entry: Absent and Breath sounds are Absent.

Management

- Wide Bore Needle at 2nd intercostal space near MCL (midclavicular line), into the chest of the patient. As per Harrison. ATLS guidelines mention 5 ICS MCL. Choose 5th over 2nd spa
  - This system creates an exit mechanism of air, thus reducing the severity of obstructive shock.
- I.C.D (intercostal drainage tube in) 5th intercostal space, anterior to MAL (mid-axillary line), connected to underwater seal, creating negative suction.

Spontaneous Pneumothorax

00:15:05

- In emphysema patients, the lung has many cystic dilatations leading to rupture of bulla resulting in the escape of air from the lung parenchyma into the pleural cavity causing a change of pressure in the pleural cavity.

Clinical presentation

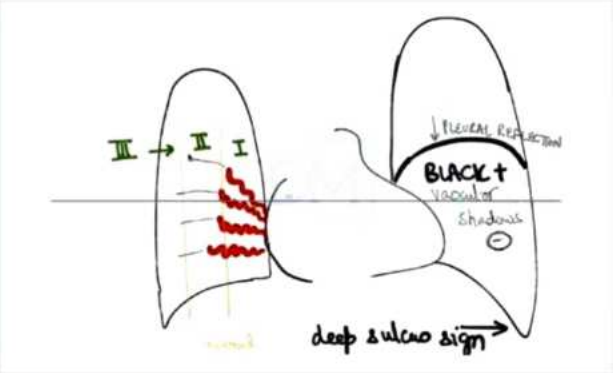
A 60-year-old smoker had a coughing Bout after which his lips turned blue and could not speak due to sudden onset Respiratory Distress

On Examination

1. Respiratory rate is increased to 30/ min.
2. Sternocleidomastoid or Scalenus anterior or Alae Nasi being used.
3. Chest Hyper-Resonant on Percussion
4. Absent Air-Entry or Absent Breath sounds in corresponding area of Bullae/lung pathology

Chest X-ray

1. Deep sulcus sign
2. Absent Vascular Shadows
3. Collapsed lung with visible Pleural Reflection



Management 00:23:04

- <25% lung collapsed: Supply O_2
- 25%-50% lung collapsed: Needle aspiration.
- >50% lung collapse or central cyanosis: Intercostal drainage 5th space in mid-axillary line with underwater seal. (Negative suction)

Important Information

- In Pediatric cases, Pneumatocele due to Staph. aureus can rupture: Spontaneous Pneumothorax
- Case: 6-month-old body with pneumonia on Vancomycin for 2 days. The child is taking feeds and there is sudden onset cyanosis and Respiratory Distress
  CXR: Deep sulcus sign
  - Diagnosis: Sudden rupture of Pneumatocele resulting in Spontaneous Pneumothorax.

Causes of spontaneous pneumothorax

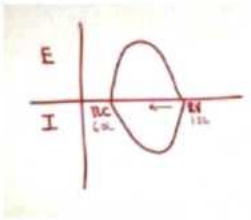
- Bulla Rupture Tall thin smoker: COPD
- Tall, thin & Arm span > height (Fibrillin Defect: Marfan Syndrome)
- Ehler Danlos syndrome
- Pneumatocele Rupture

69 FLOW VOLUME CURVE, SPIROMETRY AND DLCO

Flow volume curves

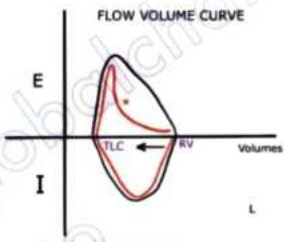
00:00:40

Normal curve



Asthma

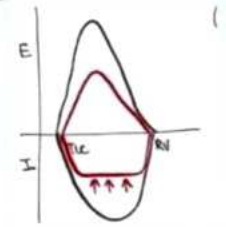
- Prolonged expiration (Scooped out concavity)



Retrosternal Goiter (Extra thoracic

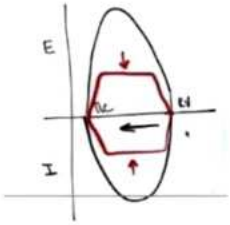
variable obstructive airway disease)

- On Inspiration: Compression of airway
- On Expiration: Relief of air compression



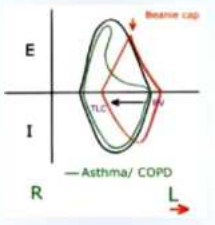
Intra thoracic fixed obstruction

- Tracheal stenosis or prolonged intubation



Restrictive Airway Disorder/ Disease: IPF, ILD, NSIP, COP, UIP (RV reduced, TLC reduced)

- Shift of curve
- Beanie cap appearance



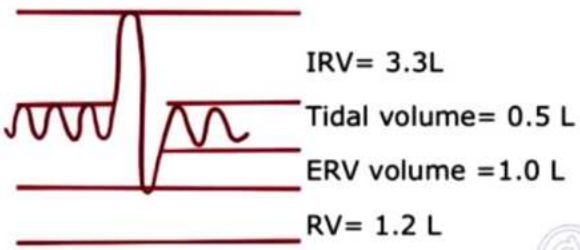
Spirometry

00:11:56

Obstructive	Restrictive
Asthma, COPD	ILD
1. FEV_1 reduced.	1. FEV_1 reduced.
2. TLC: N/Increased	2. TLC: Reduced.
3. FEV_1/FVC: Reduced	3. FEV_1/FVC: Increased.

Spirometric parameters

- TLC = IRV + TV + ERV + RV = 6L
- VC = IRV + TV + ERV = 4.8L
- IC = IRV + TV = 3.8L
- FRC = ERV + RV = 2.2L



IPF/Asbestosis / Silicosis	Asthma
1. RV decreased	RV increased
2. FRC decreased	FRC increased
3. TLC decreased	TLC increased
4. Timed vital capacity increased	Timed vital capacity decreased

Methods to measure Residual volume:

1. Body plethysmography: Most accurate way
2. Helium dilution test
3. N_2 washout test

Case

00:21:02

ANKYLOSING SPONDYLITIS
↓
Costochondral joint (chest) stiffness
↓
Residual Volume increased.

Important Information

- Extra parenchymal restrictive lung disease-RV↑
- Parenchymal restrictive lung disease – RV↓

Important Information

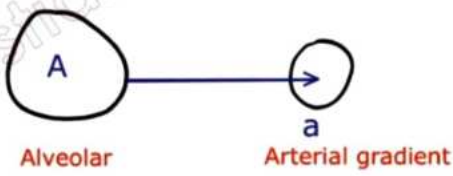
RV

↓ RV	↑RV
• ILD / IPF	Asthma
• UIP	COPD (Blebs)
• NSIP	Ankylosing Spondylitis (HLA B27+)

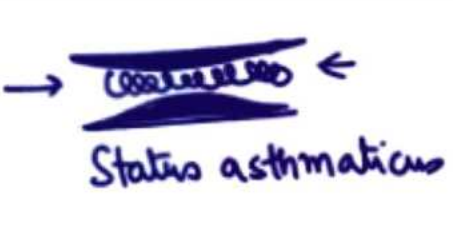
Alveolar arteriolar gradient

00:23:24

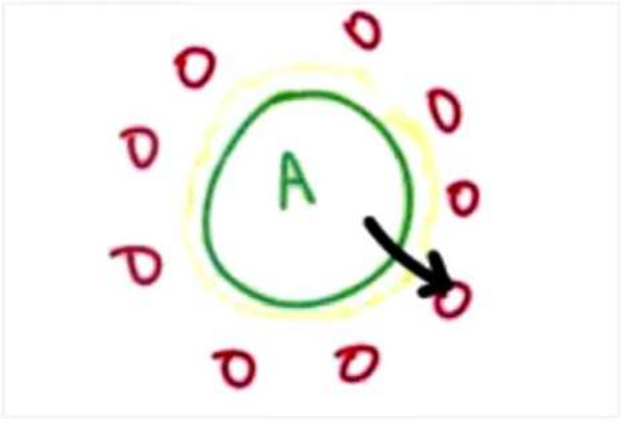
- A-a gradient = 5-15 mmHg
- A- alveoli, a- blood vessels around alveoli



- **Status Asthmaticus/ Impending Respiratory Arrest in Asthma (type 2 Respiratory Failure)**
  - Due to physical obstruction air will not go inside.
  - Alveolar and arterial values both are reduced.
  - So, the A-a gradient is normal.



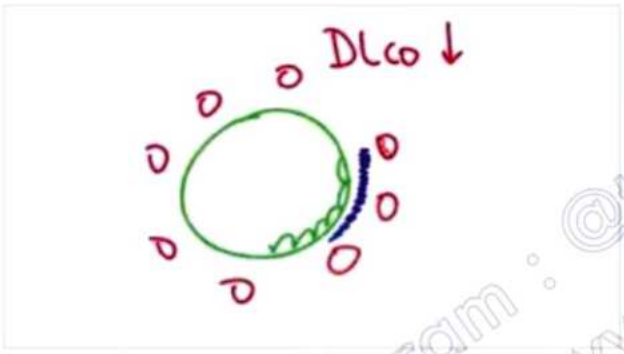
- Type 1 respiratory failure
  - Increase A-a gradient because of the alveolar damage or interstitial space getting involved, only the value of 'a' will be reduced



Examples: Covid-19, P. jiroveci, TOF (tetralogy of Fallot).

DLCO 00:27:10

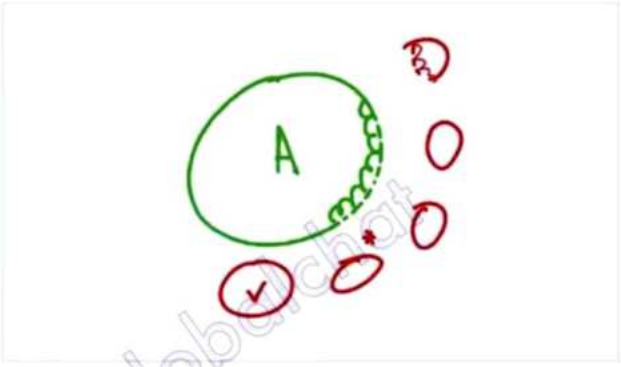
- Diffusion capacity of the lung for Carbon monoxide



Causes for decreased DLCO:

1. Interstitial pneumonia: P. Jiroveci
2. UIP, NSIP, COP
3. Emphysema or COPD
4. Pulmonary arterial HTN
5. Anemia

Causes of increased DLCO:



1. Good pasture syndrome
2. Pulmonary hemorrhage
3. CHF
4. Polycythemia

70 ABG ANALYSIS PART-1

Respiratory acidosis

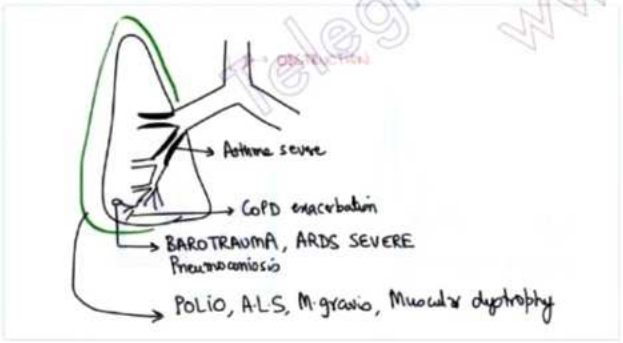
00:01:05

$CO_2 + H_2O \longleftrightarrow H_2CO_3 \longleftrightarrow H^+ + HCO_3^-$

- In Respiratory Acidosis
  - Once the carbon dioxide will spike there would be excess production of hydrogen ions leading to a fall in pH (acidosis).
  - There is a compensatory increase in the values of bicarbonate to neutralize the values of hydrogen by the reabsorption from the kidney (From PCT).
- In acute compensation
  - 10 mm Hg increase in CO_2: 1 mEq increase in HCO_3^-
- In chronic compensation
  - 10 mm Hg increase in CO_2: 4 mEq increase in HCO_3^-

Causes:

- **Central causes**
  - CVA (cerebrovascular accident): Stroke contributing to damage to the respiratory center.
    →The hypoventilation leads to the accumulation of carbon dioxide.
  - Drugs:
    →Morphine
    →Sedatives, Anesthesia
  - CNS Infection
- **Respiratory Causes**



- **Miscellaneous**: OSA, obesity

Summary of causes

- **D - D**rugs
- **D - D**isease of NMJ
- **E - E**dema: may be Cardiogenic or Non-Cardiogenic
- **P - P**neumoconiosis
- **R - R**espiratory center depression
- **S - S**pasm

Clinical features

Due to high Co_2 levels

1. CO_2 narcosis
2. Increased ICT (Intracranial tension)

Management

1. Elective Intubation and IPPV
2. Aggressive treatment is not recommended. Otherwise, CO_2 washout cause loss of vasodilator property of cerebral blood vessels.
3. It leads to a decrease in Cerebral perfusion.
4. It causes Seizures, anxiety, asterixis, increased daytime sleepiness, papillary edema

Respiratory Alkalosis

00:12:32

$CO_2 + H_2O \longleftrightarrow H_2CO_3 \longleftrightarrow H^+ + HCO_3^-$

- In respiratory alkalosis
  - There is a carbon dioxide washout due to hyperventilation and leads to a decrease in hydrogen ions (alkalosis).
  - To compensate for this Hydrogen ions, bicarbonate loss occurs from the kidney. (Via PCT)
- **Acute:** For 10 mm Hg decrease in CO_2: HCO_3 decreases by 2 mEq
- **In chronic:** 10 mm Hg decrease in CO_2: HCO_3 decreases by 4 mEq

Causes

1. Pain, anxiety, hysteria, fever, CVA
2. Pulmonary edema, CHF
3. High-altitude pulmonary edema
4. Pulmonary embolism
5. Flail chest
6. Miscellaneous: Sepsis, Heat exposure

Clinical features (Decrease in CO_2: Cerebral hypoperfusion)

1. Dizziness, vertigo
2. Intracellular shift of sodium, potassium, phosphate: Arrhythmias can occur.
3. Increase in protein binding of Ca++ leads to decrease in availability of ionized Ca++ causing Tetany.

Important Information

- Most common ABG disorder in chronically ill patients in ICU is Respiratory Alkalosis

Management

Paper–bag breathing

Procedural aspects

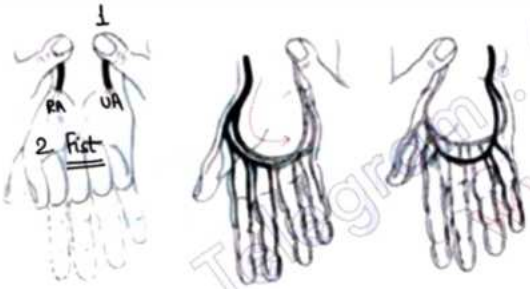
00:22:56

Modified Allen test

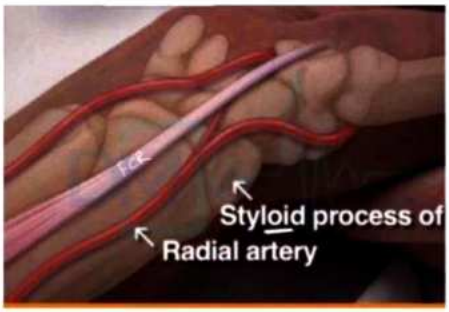
- To check the integrity of the palmar arch

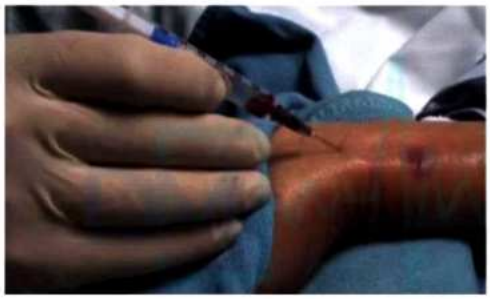
Steps:

- Obliterate both Arteries (Ulnar and radial artery)
- Ask the patient to form a fist.
- Entire palm became pale
- Release arteries simultaneously
- If collaterals are present whole hand will have a blush from the release of either artery.



- Always take the ABG sample from where the collaterals present. Otherwise, it can cause spasm of the artery and in chronic case it will cause gangrene.
- Preferred site is radial artery.
- Palpate the artery between the tendon of flexor carpi radialis and styloid process.





Take the sample at 45°

Instruments needed:

- 3 ml syringe (pre filled with electrolyte balanced Heparin)
- Rubber stopper
- Rolled towel
- Bag of ice

Alternate techniques to study vascularity of hand

- Colour doppler study of flow
- Plethysmography
- MRI

Numericals

00:28:20

Q.1 A 24-year-old beggar is found unconscious at the gate of Metro station Green Park. In the ER, room air arterial blood gas is performed and reveals pH 7.25, PCO_2 60, PO_2 65, HCO_3 26, Base Excess 1. On the chemistry panel, the sodium is 137, chloride is 100, bicarbonate is 27. What is the diagnosis?

Solution:

pH: 7.25 (acidic)
PCO_2 – 60 (elevated) } Respiratory acidosis
HCO_3 – 26: Normal

Here AG (anion gap) = 137-(100+27)
= 10 meq

So, uncompensated respiratory acidosis

Q.2 A 60-year-old man with amyotrophic lateral sclerosis is brought to the clinic by his family who are concerned that

he is more somnolent than normal. On further history, they report that he has been having morning headaches and does not feel very refreshed when he wakes up. An arterial blood gas is performed and reveals pH 7.37, PCO_2 57, PO_2 70, HCO_3 34. What is the diagnosis?

Solution:

pH: 7.37
PCO_2: 57 } Respiratory acidosis
HCO_3: 34

- As patient is suffering from ALS
- So, CO_2 increase (~ 20 mm Hg)
- HCO_3 to be increased by 2 x 4 = 8 mEq
- HCO_3: 34 mEq
- So, it is Fully compensated respiratory acidosis.

Q.3 A patient has readings of pH 7.3, $PaCO_2$ 68 mmHg, HCO_3 28 mmol/L, and PaO_2 60 mm Hg. How would you interpret this?

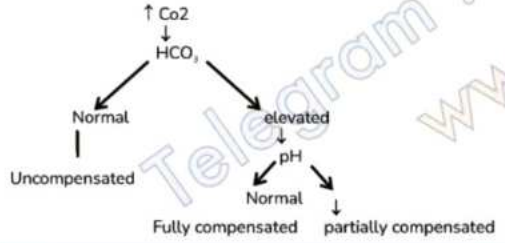
Solution:

pH – 7.3 (acidic)
$paCO_2$ – 38 mm Hg (elevated) } Respiratory acidosis
HCO_3 – 28 mm / L (elevated)

- As pH is acidic
- So partially compensated.

Important Information

- IN RESPIRATORY ACIDOSIS



Q.4 A 68-year-old man with a history of very severe COPD (FEV1~1.0L, <25% predicted) presents to the ER complaining of worsening dyspnea and an increase in the frequency and purulence of his sputum production over the past 2 days. His oxygen saturation is 78% on room air. Before he is placed on supplemental oxygen, a room air arterial blood gas is drawn and reveals pH 7.25, PCO_2 68, PO_2 48, HCO_3 31.

Solution:

- pH: 7.25 (Acidic)
- PCO_2: 68 mm Hg (elevated) } Respiratory acidosis
- HCO_3: 31 mm Hg (Elevated)
- So, pH acidic: So partially compensated.

Q.5 A 15-year-old juvenile with a history of inhalant abuse presents to the emergency room complaining of dyspnea. He has a SpO_2 of 99% on room air and is tachypneic. A room air arterial blood gas is performed and reveals pH 7.25, PCO_2 17, PO_2 128, HCO_3 2. A chemistry panel revealed sodium of 130, chloride 98, HCO_3 2. What is the diagnosis?

Solution:

- pH: 7.25 (Acidotic)
- PCO_2:17 mm Hg (Low)
- HCO_3: 2 mm Hg (Very low)
- So metabolic acidosis
- pH: acidic, so partially compensated.
- AG = 130 – (98+2)

30 increased A.G

So, Diagnosis is HAGMA (High anion gap metabolic acidosis)

- Predicted PCO_2 = HCO_3 + 15 (for both metabolic acidosis with alkalosis)
  = 2+15
  = 17

Q.6 A three-year-old child is admitted to the hospital with a diagnosis of severe asthma exacerbation. The mother of the child reports to the nurse on duty that she has witnessed slight tremors and behavioral changes in her child over the past four days. The attending physician orders routine ABGs following an assessment of the ABGs. The ABG results are pH 7.35, $PaCO_2$ 72 mm Hg and HCO_3 38 mEq/L What acid-base disorder is shown?

Solution:

- PH: 7.35 (N /Acidotic)
- PCO_2: 72 mm Hg (Elevated)
- HCO_3: 38 meq (Elevated)
- So respiratory acidosis
- As pH: Normal
- So fully compensated respiratory acidosis

Q.7 A resident working in the ER decides to draw a room air arterial blood gas from a sick patient, which reveals pH 7.46, PCO_2 49, PO_2 68, HCO_3 34. On his chemistry panel, the sodium is 139, chlorides 95, HCO_3 34. What is the diagnosis?

Solution:

- pH: 7.46 (Alkalotic)
- PCO_2: 68 (Elevated)
- HCO_3: 34 (Elevated)

→ So metabolic alkalosis

Q.8 A climber is coming down from the summit of Mt. Everest. At an altitude of 8,400m, he has a blood gas drawn while breathing ambient air as part of a research

project. The blood gas reveals pH 7.55, PCO_2 12, PO_2 30 and HCO_3 20. What does it demonstrate?

Solution:

pH: 7.55 (Alkaline)
PCO_2: 12 (Low)
HCO_3: 20 (Low)

- Respiratory alkalosis
- For every 10 mm decreased in Co_2
- HCO_3 to be decreased by 2 meq.
- So PCO_2 decreased ~ 30 mm Hg.
- HCO_3 to be decreased by 2x3=6
- So HCO_3: 26-6 = 20
- But pH increased.
- So partially compensated.

Q.9 A 57-year-old woman presents with 2 days of fever, dyspnea and a cough productive of rust- colored sputum. Her room air oxygen saturation in the emergency room is found to be 85% and the intern decides to obtain a room air arterial blood gas while they are waiting for the CXR to be done. The blood gas reveals: pH 7.54, PCO_2 25, PO_2 65, HCO_3 22, Base excess 1. What is the diagnosis?

Solution:

pH: 7.54 (alkalotic)
PCO_2: 25 (Low)
HCO_3: 22 (N)

- So uncompensated Respiratory alkalosis as HCO3 (Normal)

Q.10 A patient has pH 7.6, PaO_2 120 mm Hg, $PaCO_2$ 31 mm Hg, and HCO_3 25 mmol/L. What does this mean?

Solution:

pH: 7.6 (Alkaline)
CO_2: 31 (Low)
HCO_3: (N)

- So uncompensated respiratory alkalosis

Q.11 Patient X is admitted to the hospital and is to undergo brain surgery. He is very anxious and scared of the upcoming surgery. He begins to hyperventilate and becomes very dizzy. STAT ABGs reveal pH 7.51, $PaCO_2$ 22 mm Hg and HCO_3 25 mEq/L. What is the ABG interpretation based on the findings?

Solution:

pH: 7.51 (Alkaline)
CO_2: 22 (Low)
HCO_3: 25 (N)

- As hyperventilated & HCO_3: Normal
- So uncompensated respiratory alkalosis

Q.12 Lab values: pH 7.42, $paCO_2$ 25, HCO_3 18

a. Metabolic acidosis, partially compensated
b. Respiratory acidosis, partially compensated
c. Respiratory acidosis, fully compensated
d. Respiratory alkalosis, fully compensated.

Solution:

pH – 7.42 (Normal)
$PaCO_2$ – 25 (Low)
HCO_3 – 18 (Low)

- Decrease in CO_2 = 40-25 = 15 mmHg
- For a chronic change for every 10 mmHg fall in Co2 decrease by **4** mEq. HCO3
- HCO_3 to be decrease by 4 x 1.5 = 6
  HCO3
  So (16-20)
  HCO_3 = 18
- **So** fully compensated respiratory alkalosis

Q.13 Lab values: pH 7.56, $paCO_2$ 20, HCO_3 20

a. Respiratory alkalosis, uncompensated
b. Respiratory alkalosis, uncompensated
c. Respiratory alkalosis, partially compensated.
d. Metabolic alkalosis, partially compensated.

Solution:

pH: 7.56 (Alkaline)
$PaCO_2$: 20 (Low)
HCO_3: 20 (Low)

- So, this is Respiratory alkalosis.
- $PaCO_2$ decrease by 20 mm Hg
- So HCO_3 to be decrease by 4 x 2=8
- HCO_3 to be between (14 -18)
- HCO_3 in question 20
- pH: alkaline
  → So respiratory alkalosis but partially compensated.

71 ABG ANALYSIS PART-2

00:00:21

Q.14 A 47 year old man with a history of heavy alcohol use presents with a two day history of severe abdominal pain, nausea and vomiting. On examination, his blood pressure is 90/50 and he is markedly tender in his epigastrium. His initial laboratory studies reveal a sodium of 132, chloride 92, HCO_3 16, creatinine 1.5, amylase 400 and lipase 250. A room air arterial blood gas is drawn and reveals pH 7.28, PCO_2 31, PO_2 88, HCO_3 16. What is the diagnosis?

Solution:

- Alcohol & severe abdominal pain: Point towards possibility of acute pancreatitis
- BP of 90/50 means patient is having shock probably of distributive etiology
- From lab studies; quickly calculate Anion gap
  $Na + - (cl + HCO_3)$
  $= 132 - (92+16)$
  $= 24$ meq. Which is elevated [(N) = 10 mEq] Therefore, high anion gap
- Then look at pH of 7.28 reflecting an acidotic pH [(N) pH = 7.35-7.45]
- PCO_2: 31 which is low [Normal 38-42 (average – 40)]
- This low PCO_2 cannot explain acidotic pH also: HCO_3 = 16 which is low (Normal 22-28)
- This explains acidotic pH

Therefore, acidic pH is due to metabolic problem: metabolic acidosis

In this case a compensatory process is also going on which is Hyperventilation leading to CO_2 washout thus low CO_2 Since pH is still not normalized, meaning compensation is partial.

Final answer would be: HAGMA (High anion gap metabolic acidosis) with partial compensation.

00:03:43

Q.15 pH = 7.27, PCO_2 = 33 and HCO_3 = 17 what is the Diagnosis?

Solution:

- pH= 7.27 Acidotic pH
- HCO3 = 17 PCO2= 33 Low PCO_2 (Cannot explain acidotic pH)
- Low HCO_3 (Can explain acidotic pH)
- Therefore, metabolic acidosis.
- Accompanied by hyperventilation (Kussmaul breathing)
- Since pH still not normalized, compensation is partial.

00:06:20

Q.16 Lab values: pH = 07.37, $paCO_2$ = 33, HCO_3 = 17

a. Metabolic acidosis, fully compensated
b. Metabolic acidosis, partially compensated
c. Respiratory acidosis, fully compensated
d. Respiratory alkalosis, uncompensated

Solution:

- pH : =7.37 normal
- PCO_2 = 33: low meaning CO_2 washout is occurring
- HCO_3 = 17: low
- Metabolic acidosis
- Along with compensatory hyperventilation respiratory alkalosis Since pH is normal, means it is fully compensated
- Therefore Answer is Metabolic acidosis fully compensated

00:08:06

Q.17 Lab values: pH = 7.23, $PaCO_2$ = 37, HCO_3 = 18

a. Respiratory alkalosis, partially compensated
b. Respiratory alkalosis, uncompensated
c. Metabolic acidosis, uncompensated
d. Metabolic alkalosis, partially compensated

Solution:

pH: = 7.23 acidotic
pCO_2 = 37: normal (38-42) HCO_3 = 18: low
Metabolic acidosis. Since pCO_2 is normal means: compensatory process has not started. Therefore uncompensated
Answer: metabolic acidosis, uncompensated

00:09:50

Q.18 Lab values: pH = 7.30, PCO_2 = 36, HCO_3 = 16

a. Respiratory acidosis, uncompensated
b. Respiratory alkalosis, uncompensated
c. Metabolic acidosis, uncompensated
d. Metabolic alkalosis, partially compensated

Solution:

pH: 7.3 – acidotic pH
pCO_2: 36 – normal – means compensatory process not started
HCO_3: 16-low
Diagnosis is Metabolic Acidosis
Since pH is not normal it is uncompensated

00:10:27

Q.19 An 8-month female baby presented with 1 day history of lethargy. She had vomited several times. Her drug addict mother said she appeared "intoxicated"

Examination: The baby was obtunded but she was easily arousable and muscle tone was normal. Respiratory rate was 60/min. pupils are normal. No dehydration BP was 112/62

mmHg. Heart and chest examination was normal. planter response was normal.

Investigations:

Na^+: 135 mmol/l
K^+: 4.2 mmol/l
Glucose 5.9 mmol/l
Cl^-: 116 mmol/l
HCO^-_3 6 mmol/l

Urinalysis: pH = 5.0; negative for glucose & ketones. Calcium oxalate crystals were seen on urine microscopy.

Arterial Blood Gases:

pH: 7.19
pCO_2: 16 mm Hg
PO_2: 100 mm Hg
HCO_3: 6.2 mEq/l

Solution:

Important points in history:

- Drug addict mother
- Tachypnea
- Pupils normal: no CNS depression by opioids
- Calcium oxalate crystal due to ethylene glycol poisoning
- Calculation: Anion gap: $Na^+ (Cl^- + HCO_3)$
  = 135-(116+6)
  = 135-122 = 13

Ethylene glycol poisoning leads to acute tubular necrosis
From ABG: Metabolic acidosis partially compensated

00:14:13

Q.20 Mr. Sharma, who underwent post-abdominal surgery, has a nasogastric tube In-situ. The nurse on duty notes that the nasogastric tube is draining a large amount (900 cc in 2 hours) of coffee ground secretions. The patient is not oriented to person, place, or time and hence STAT ABGs are ordered. The results from the ABGs show pH 7.57, $PaCO_2$ 37 mmHg and HCO_3 30 mEq/L. What is your assessment?

Solution:

pH = 7.57 (Alkalotic pH)
pCO_2 = 37 (Normal)
HCO_3 = 30 mEq/L (Elevated) explains Metabolic alkalosis
Compensatory mechanism in M. alkalosis is increase in CO_2 that is Respiratory acidosis but in this case, CO_2 is not raised, so Diagnosis is uncompensated M. alkalosis.

Excessive secretion from NG tube
↓
Dehydration
↓
↓ GFR
RAAS +
↓
Aldosterone ↑
↓
Loss of K+ and H+

Hypokalemia **Metabolic alkalosis**

Expected $pCO_2 = 15 + HCO^-_3$
= 15+30
= 45
But actual = 37 not equal to 45 thus, compensatory process not started

00:18:12

Q.21 Lab values: pH 7.52; PCO_2 = 48, HCO^-_3 = 28

a. Respiratory alkalosis, partially compensated
b. Respiratory alkalosis, uncompensated
c. Metabolic acidosis, partially compensated
d. Metabolic alkalosis, partially compensated

Solution:

Alkalotic pH; ↑ pCO_2; slightly elevated HCO^-_3
Primary problem: Metabolic alkalosis with partial compensation
Predicted pCO_2 = 15+28 = 43 which is not equal to 48, therefore partial compensation

00:20:54

Q.22 You are reviewing the latest arterial blood gas results for a sick Cushing's Syndrome patient. Which result indicates that the ABG derangement is compensated?

a. pH 7.32
b. $PaCO_2$ 18 mmHg
c. HCO_3 8 mEq/L
d. $PaCO_2$ 48 mmHg

Solution:

Cushing syndrome patient
↓
↑ Cortisol
↓
Stimulate ENaC
↓
↑ Na^+ & H_2O absorption
loss of K^+ & H^+
↓
M. Alkalosis
Compensation by ↑ Co_2

00:22:17

Q.23 A patient is post-op from knee surgery. The patient has been receiving analgesia 4 mg IV every 2 hours. You notice the patient is exhibiting a respiratory rate of 8 and is extremely drowsy. Which of the following condition is the patient at risk of?

a. Respiratory acidosis
b. Respiratory alkalosis
c. Hypokalemia
d. Metabolic acidosis

Solution:

Analgesia cause CNS depression leads to CO_2 narcosis resulting in respiratory acidosis

If the patient receive inadequate anesthesia, the patient complains of pain which leads to hyper ventilation resulting in respiratory alkalosis.

00:23:36

Q.24 A patient attempted to commit suicide by ingesting a bottle of Aspirin. Which of the following conditions is this patient at risk for?

a. Hyperkalemia
b. Hypercalcemia
c. Respiratory alkalosis
d. Respiratory acidosis

Solution:

Aspirin toxicity
↓
acetyl salicylic acid accumulates
↓
Stimulates Respiratory center: hyperventilation & CO_2 washout
↓
Respiratory alkalosis

- Intracellular shift of Na^+ /K^- /PO_4
- Increase In protein binding of calcium, decrease ionized Ca_2+ leading to tetany

00:25:43

Q.25 Respiratory alkalosis can affect which electrolyte levels in the body?

a. Calcium and sodium levels
b. Potassium and sodium levels
c. Calcium and potassium levels
d. Potassium and phosphate levels

Solution:

Respiratory alkalosis affects Ca_2+ & PO_4 3 -
↓
Tetany and hypokalemia

00:27:05

Q.26 A Patients is experiencing respiratory alkalosis. What is the most classic sign seen ?

a. Bradypnea
b. Chvostek sign
c. Bradycardia
d. Hoover sign.

Solution:

CHVOSTEK sign positive: sign of tetany which present in respiratory alkalosis

Respiratory alkalosis contributes to tetany in the patient.

ECG finding of tetany is prolonged QT interval.

Hoover sign: Rule out hysterical leg weakness

00:28:52

Q.27 A patient has the following blood gases: $PaCO_2$ 25, pH 7.50, HCO^-_3 19. Which of the following could not be the cause of this condition?

a. Anxiety attack
b. $paO_2/Fi\,O_2$ ratio <100
c. Hysteria
d. Aspirin toxicity

Solution:

First read pH always

- Alkalotic pH
- Low pCO_2
- Low HCO^-_3

Respiratory alkalosis partially compensated

Caused by:

- Anxiety attack
- Hysteria
- Aspirin toxicity stimulate respiratory center leads to hyper ventilation

Severe ARDS
↓
Blood vessel collapse
↓
Ventilation Perfusion imbalance
↓
CO_2 build up
↓
Respiratory acidosis

00:31:24

Q.28 A patient on mechanical ventilation has the following blood gases: $PaCO_2$ 29, pH 7.56, HCO_3 23. Which of the following conditions is the patient experiencing?

a. Respiratory alkalosis not compensated
b. Respiratory alkalosis partially compensated
c. Respiratory alkalosis fully compensated
d. Respiratory acidosis partially compensated

Solutions:

Alkalotic pH
Low CO_2
HCO_3 normal
} Respiratory alkalosis uncompensated

00:32:49

Q.29 A patient is experiencing respiratory acidosis due to brain trauma. Which of the following lab values correlates with this acid imbalance?

a. Potassium level of 6.0
b. Potassium level of 2.5
c. Potassium level of 5.0
d. Potassium level of 3.5

Solutions:
Respiratory alkalosis: Intracellular shift Na^+ K^+ PO_4^{2+} inside
Respiratory acidosis: Intracellular shift Na^+ K^+ PO_4^{2+} outside
Therefore potassium is increased

00:33:59

Q.30 Which of these patients is experiencing partially compensated respiratory acidosis?

a. $PaCO_2$ 30, pH 7.35, HCO_3 26
b. $PaCO_2$ 53, pH 7.23, HCO_3 28
c. $PaCO_2$ 45, pH 7.49, HCO_3 21
d. $PaCO_2$ 50, pH 7.30, HCO_3 23

Solution:
pH = Acidotic
pCO_2 = Elevated
HCO_3 = Elevated
} (B) option

00:35:45

Q.31 Which of the following is not a cause of respiratory acidosis?

a. Pulmonary emboli
b. Asthma
c. Chronic obstructive pulmonary disease (COPD)
d. Hyperventilation

Ans: Hyperventilation cause Respiratory alkalosis

00:36:49

Q.32 A patient with COPD has the following blood gases; PCO_2 59, pH 7.26, HCO_3 32. Which of the following conditions is presenting?

a. Respiratory alkalosis
b. Respiratory acidosis
c. Metabolic alkalosis
d. Metabolic acidosis.

Solutions:
Acidotic pH
Elevated pCO_2
Elevated HCO_3
} Respiratory acidosis partially compensated

00:37:46

Q.33 A 28-year-old woman was admitted electively to a HDU following a caesarian section. A diagnosis of 'fatty liver of pregnancy' had been made preoperatively. She was commenced on a continuous morphine infusion at 5 mg/hr and received oxygen by mask. This was continued overnight, and she was noted to be quite drowsy the next day. Arterial blood gases were.

pH 7.16
pCO_2 61.9 mmHg
pO_2 115 mmHg
HCO_3 21.2 mmol/l

Solution:
Acidotic pH
Elevated CO_2
Low HCO_3
} Respiratory acidosis with Metabolic acidosis

00:41:08

Q.34 Comment on the diagnosis:

pH 7.31
pCO_2 56 mmHg
pO_2 87 mmHg
HCO_3 13 mmol/L

Solution:
Acidotic pH
Increase in Co2
Decrease HCO_3
} Respiratory acidosis with Metabolic acidosis

Extra Mile: CKD patient presents with protracted vomiting CKD leads to metabolic acidosis due to inability to excrete Hydrogen ions. Severe vomiting leads to metabolic Alkalosis. Hence pH can be falsely normal at pH=7.40.

00:41:55

Q.35 A 70-year-old man was admitted with severe congestive cardiac failure. He has been unwell for about a week and has been vomiting for the previous 5 days. He was on no medication. He was hyperventilating and was very distressed. Admission biochemistry is listed below. He was on high concentration oxygen by mask.

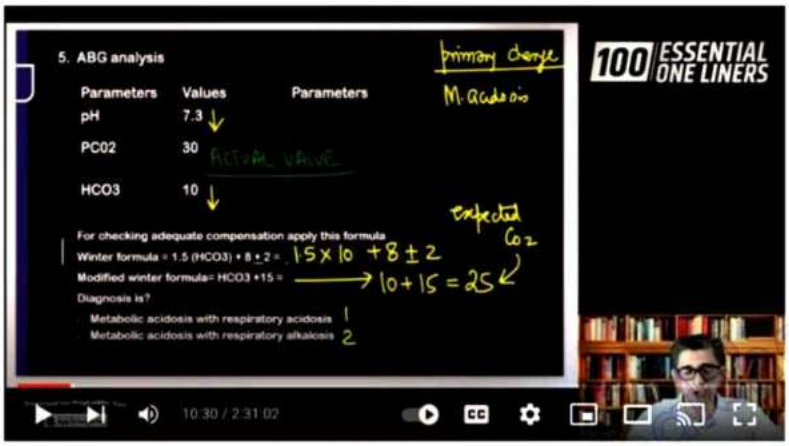
Biochemistry results: Na^+, 127, K^+5.2, CI: 79, HCO_3 20, urea 50.5, creatinine 0.38 & glucose 9.5mmol/l. Anion gap 33 mmol/l

Arterial blood gases
pH 7.58 (alkalotic)
pCO_2 21 mmHg (low)
pO_2 154 mmHg
HCO_3 32 mmol/L(elevated)

Solution:
Vomiting causes dehydration leads to RAAS activation resulting in Metabolic alkalosis
Hyperventilation resulting in Respiratory alkalosis
Anion gap = 127 – (79+20)
= 28 (elevated)
Alkalotic pH
Low Co_2
Elevated HCO_3
} Respiratory alkalosis + Metabolic alkalosis

Extra Mile:

https://www.youtube.com/watch?v=3iV9zd5yuBw



One liners for "MEDICINE" by Dr. Marwah [Crucial for NEET PG, FMGE & INI-CET]

72 FEVER OF UNKNOWN ORIGIN

Diurnal variation in body

00:00:16

- Max Temp in Evening
- Min Temp in Morning usually around 4:00 am.
- Normal Diurnal Variation < 0.9 F

Note: Reason for Increase in Temperature in Evening

- BMR is high.
- Muscular Activity

Measure of activity and work

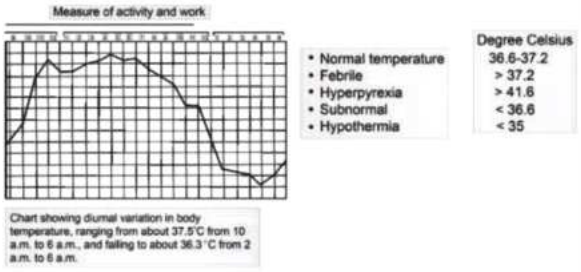
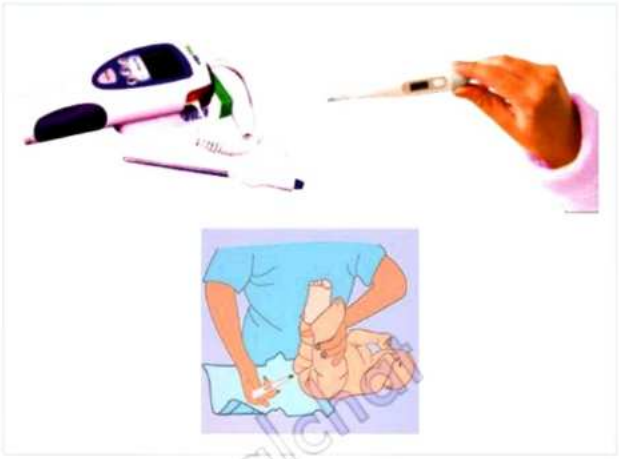


Chart showing diurnal variation in body temperature, ranging from 37.5°C from 10 a.m. to 6 a.m., and falling to about 36.3°C from 2 a.m. to 6 a.m.

- Fever/Temperature
  - In AM > 98.9° F
  - In PM > 99.9°F (Because of circadian rhythm)
- Hyperpyrexia more than 107° F is associated with heat stroke Cause
- Hyperpyrexia > 107°F
- Hypothermia: < 35° C
  - Mild 32 - 35° C
  - Moderate 28 - 32° C
  - Severe < 28° C
- ECG changes in Hypothermia: J wave/ Osborn wave
- **To measure core temperature**
  - Ideal Site
    → Pulmonary Artery
  - Preferred site
    → Lower esophagus
  - In fever
    → Pulse Rate is increased If Temp Increase > 100° F
- For every 1° F rise of temperature above 100° F PR increases >10 bpm Note: Rectal Temp > 0.7° F than the oral reading temperature.
- Rectal temperature is more accurate than oral temperature.



Faget Sign/ Relative bradycardia

00:06:26

- Disease manifestation of hyperthermia with bradycardia (More common with gram –ve bacteria and infections of bacteria that are transmitted by Ticks).

Causes

T – Typhoid or **T**ularemia or **T**yphus Scrub.
B – **B**rucellosis or **B**abesia
M - **M**ycoplasma pneumonia or **M**alaria
C - **C**oxiella Brunetti (Q fever), **C**orynebacterium Diphtheria
L - **L**egionella pneumophila, **L**eptospira
R - **R**ickettsia

- All are gram-negative or Tick-Borne Infections
- **Tularemia**:
  - Caused by Ticks (Living on the Body of Rabbits, Deer)
  - Person Hunter by Profession, shot a rabbit or deer while handling the meat, the tick bite the person, leading to bacteria entering the body of the hunter so he developed Axillary Lymphadenopathy
- **Typhus Scrub**
  - Transmitted by baby mites (Chiggers)
- **Brucella**
  - Caused by consumption of Raw milk.
- **Babesia:** Differential diagnosis of malaria [On Peripheral smear Maltese cross appearance is seen]
- **Coxiella Brunetti/ Q fever (Query fever)**
  - Spread by animals.
- **Legionella**
  - Spread by inhalation of water Droplets.
- Viral causes of Relative bradycardia are Dengue, Yellow fever
- Other causes are Drug fever/ Factitious Fever/ CNS Lesions
- Drug fever

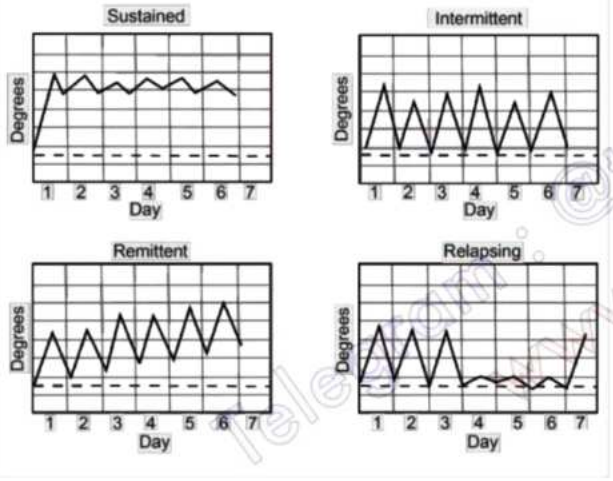
- Allopurinol [history of postmenopausal women with gout], β Blocker, Sulfa Drugs
- Non-Hodgkin Lymphoma

Factitious fever

00:12:06

- Seen in Health care workers or access to Health care services.
- Mostly Female
- Due to the Injection of Infected Distilled water
- CNS Lesions:
  - Pontine Hemorrhage (Parabrachial nucleus- present at the junction of the midbrain & PONS. It is in direct connection with the hypothalamus. It regulates body temp) leads to expanding hematoma will press the nucleus and the resetting hypothalamus causing central fever.
  - Non-Hodgkin's lymphoma.

Patterns of fever



Continuous fever or sustained fever

00:16:29

- Never touches the Baseline.
- Diurnal Fluctuation < 1° F

Remittent fever

- Fever never touches the baseline.
- Diurnal Fluctuation > 1°F

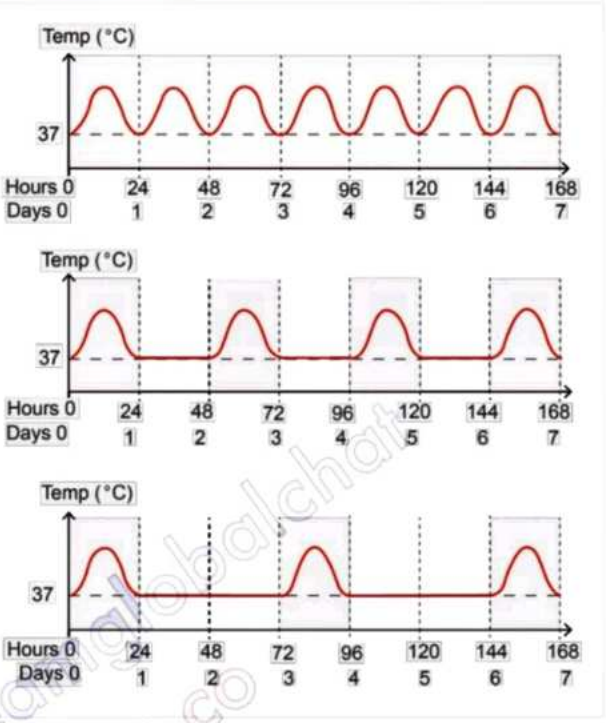
Intermittent fever

- It touches the baseline.
- Diurnal variation >1°F
- For example, Malaria.

Relapsing fever

- Fever can be developed in an interval of 3 days.
  - For example, Borrelia recurrentis, Rat Bite Fever

The pattern of Fever in Malaria



Quotidian fever

- Fever will occur once every day and it will touch the baseline. Example of Intermittent fever
- For example, Falciparum infection
  - P. Knowlesi

Double Quotidian fever

- Fever will be spiking Twice per day that Fever will be touching the baseline and again spike in a single day. i.e. Two spikes of fever in a single day.
  - For example, Adult onset STILL disease, Juvenile rheumatoid arthritis.

Tertian fever

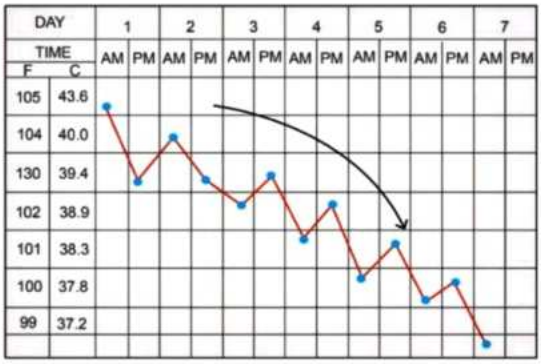
- Fever is occurring every 48 hours.
  - For example, P. vivax, P. Ovale

Quartan fever

- Fever will be occurring after every 72 hours Fever.

Resolution with Lysis

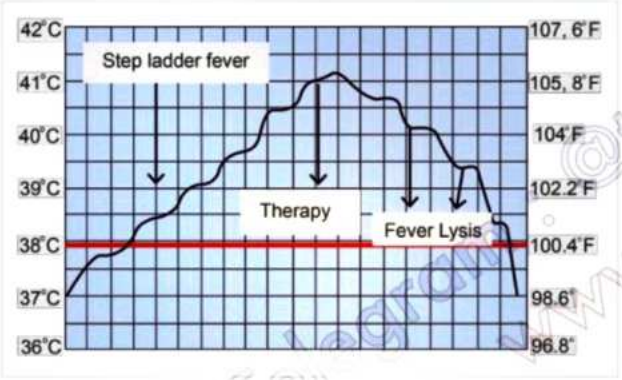
- Fever is resolving in person over a couple of days. Crisis implies fever resolves over 24 hours, or even faster.



- Gradual step ladder pattern of decrease of fever seen mostly post antibiotics.

Step ladder pattern of fever

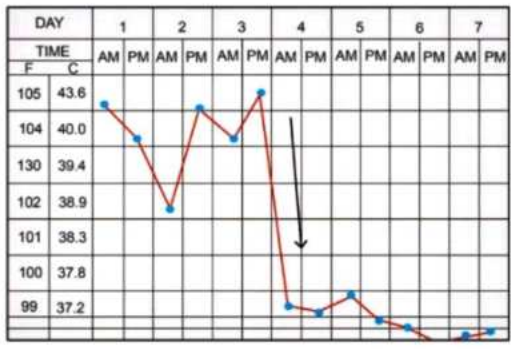
- Seen in Typhoid.
  Ciprofloxacin → lysis takes 5-6 days
  Ceftriaxone → It is faster



Fever resolution by crisis

00:23:11

- Fever is suddenly falling, over 24 hours or even faster.



  - Acute Tonsillitis
- Katayama fever
  - Resolving case of Pneumonia
  - Associated with Schistosomiasis
  - Q Fever
    → Coxiella burnetii
  - Parrot Fever
    → Chlamydia psittaci

Pyrexia of unknown origin

00:25:02

- Fever: Temperature more than 101° F on >2 occasions
- Duration: more than 3 weeks
- Absence of immunocompromised state.
- Uncertain diagnosis: Thorough history taking.
  - Thorough physical examination.

Obligatory investigations

00:27:09

1. Hb, TLC, DLC, Platelet count, and ESR to rule out hematological illness
2. CRP, Elevated LDH, and Elevated Ferritin to rule out inflammatory illness.
3. KFT with serum electrolytes
4. LFT: SGOT, SGPT, Serum Alkaline Phosphatase, With total serum protein: Albumin, Globulin
5. Serum Electrophoresis gammopathy: To identify monoclonal gammopathy [multiple myeloma]
6. For Autoimmunity: Creatine Kinase
   - RA factor
   - ANA (Antinuclear Antibody)
7. Urine Microscopic Examination & culture: Only 1 culture with Mid-Stream Urine
8. Blood culture: 3 times, is sterile.
9. Imaging: CXR for Diagnosis of Miliary Tuberculosis
10. USG for - Liver Abscess
    - Pyogenic Liver Abscess
    - Hydatid Cyst
11. Tuberculin skin test, Interferon Gamma Release Assay

PUO causes

- Infection > Inflammation
- Atypical presentation of Infection
- Rare causes: SAPHO (Synovitis, acne ,pustulosis, hyperosteosis, osteomyelitis) or PAPA PAPA (Pyogenic arthritis, pyoderma gangrenosum and acne) or SCHNITZLER SYNDROMES (urticaria, bone pain and monoclonal gammopathy)

In PUO, Steps to be followed

1. Exclude Thermometer manipulation.
2. After this Stop all medications
3. If still fever is present for more than 72hrs Then do a Fundus examination for roth spots to rule out SABE
4.. Cryoglobulins
5. FDG PET/ CT: To rule out.
   - Malignancy of Bone marrow
   - Lymphoreticular malignancy

- Any occult cancer
- Vasculitis
- But FDG PET/ CT cannot differentiate between infection and Inflammation.
- FDG PET/CT > Scintigraphy

6. Scintigraphy is done by
   - Gallium 67
   - Indium–III
   - 99Tc labeled RBC.
7. Chest CT/ Abdominal CT
8. Temporal Artery Biopsy: To rule out Temporal arteritis.

PDC [Potential diagnostic clues] 00:39:33

- Fever associated with Headache. (GCS is on the Lower side or Neurological deficit) Therefore Lumbar puncture can be done and a CSF examination to rule out.
  - TBM (tubercular meningitis)
  - Cryptococcal meningitis
  - Mollaret meningitis
- Fever with cytopenia/Hepatosplenomegaly/ LN enlargement
  - Then do bone marrow aspiration/ BM biopsy / BM culture.
- Fever with Feature of T.B (for example Matted Lymph nodes Disseminated T.B)
  - Investigation of choice is Liver Biopsy (by CBNAAT)

Important algorithm 00:42:17

Refer Image 72.1

Infections 00:46:23

- T.B
- Endocarditis
  - Culture negative by HACEK Group
  - Q fever (valvular Lesion)
  - Bartonella
  - Sterile Endocarditis aka Marantic endocarditis → Adenocarcinoma.
  - SLE, APLAS (Antiphospholipid Antibody Syndrome)

HACEK

- **H** - **H**aemophilus Aphrophilus
- **A** - **A**ggregatibacter
- **C** - **C**ardiobacterium
- **E** - **E**ikenella
- **K** - **K**ingella
- GIT Cause: Diverticulitis (In long standing constipation)
- Vertebral Osteomyelitis
- Q fever: valve lesion
- Whipple Disease: By Treponema Whippelii
- Travel History
  - MALARIA
  - KALAAZAR
  - HISTOPLASMOSIS
  - COCCIDIOIDOMYCOSIS

NIID (Noninfectious Inflammatory Disorder) 00:50:56

- Large Vessel vasculitis (Most common in India is Takayasu Arteritis, most common in central Asia is BEHCET disease)
- Sarcoidosis
  - Breathlessness in young females
  - Hilar Lymphadenopathy developing in a patient.
- Adult-onset Still disease (Adult-onset Juvenile Arthritis)
- Polymyalgia Rheumatica

Tumor

- Malignant Lymphoma (Most common)
- Leukemia

Drugs

1. Allopurinol
2. Antiepileptic Drugs:
   - Lamotrigine
   - Phenytoin
3. Sulfa drugs
4. Furosemide
5. Quinidine

PUO history

History

- Pattern or duration of fever
- Medical history: medication
- Sexual history
- Travel history
- Contact with animals: pets or hobby.

Examination

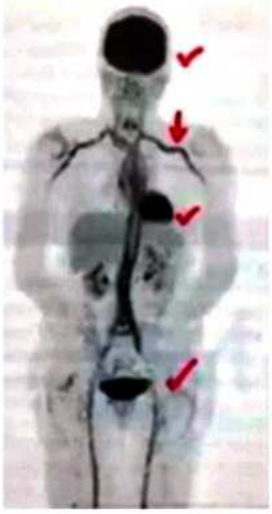
- Eyes
- Lymph nodes
- Temporal arteritis
- Liver and spleen
- Any previously surgical scar
- Skin and mucous examination

P.D.C

- Headache : CSF
- TB dissemination : Liver biopsy
- Cytopenia/ HSM : Bone marrow biopsy

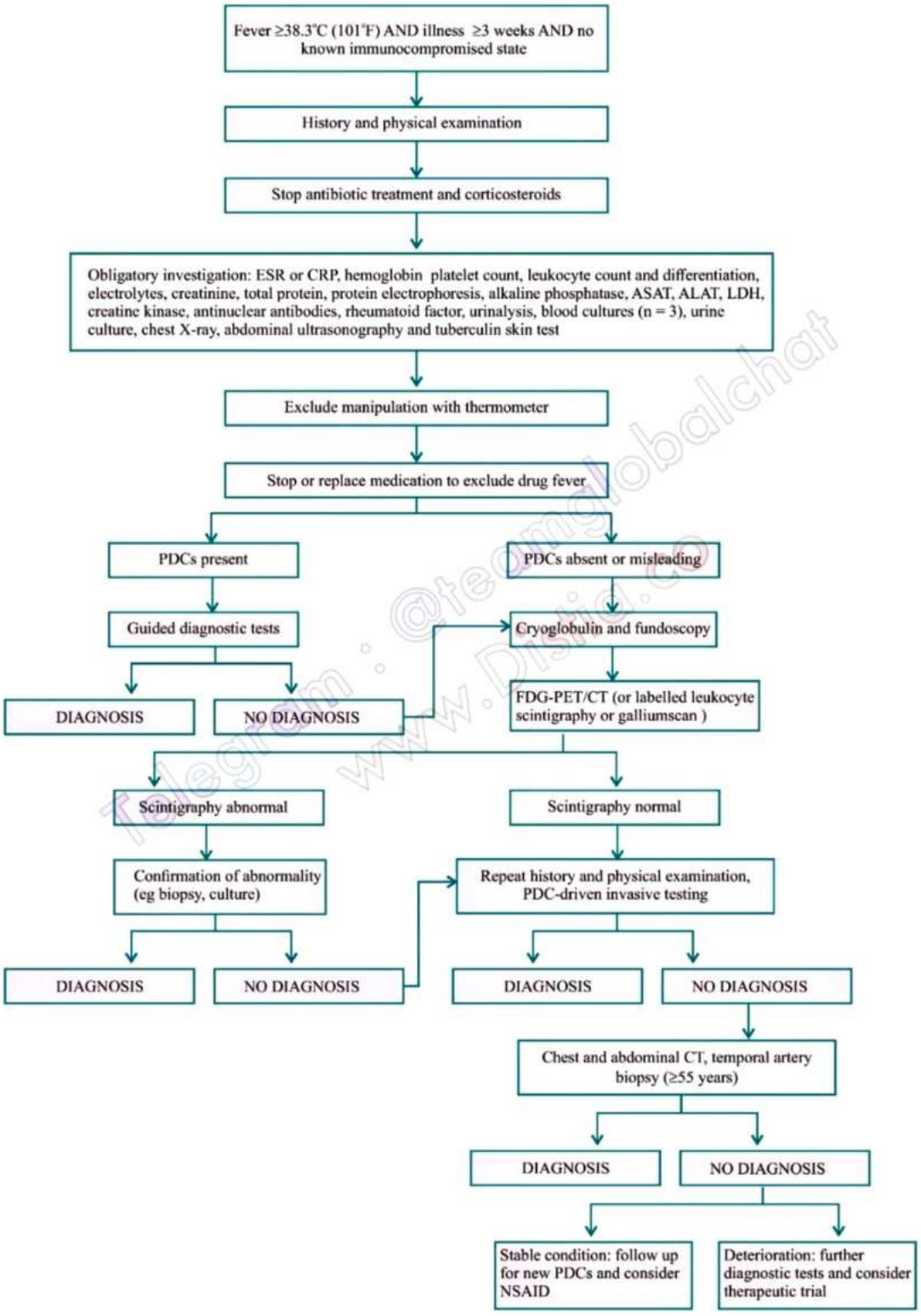
Clinical scenario

72-year-female patient complains of low-grade fever and fatigue for 3 months. No history of drug intake or travel or contact with pets. No features of temporal arteritis. On obligatory investigations: CRP is positive. Normocytic Normochromic anaemia. FDG PET image is shown:



- Substantial uptake in subclavian artery indicating Large artery vasculitis, i.e. Takayasu Arteritis

Image 72.1



73 DENGUE FEVER

Introduction: Arbovirus Infection 00:00:19

- It is the most common arbovirus infection in the world.
- Majority of cases occur in southeast Asia.
  - Due to heavy rainfall and rapid urbanization.
- Has 4 serotypes 1,2,3,4
- Transmitted by Aedes mosquito.
- Mortality: Usually < 1%
  - Severe dengue: 5%
  - Undiagnosed dengue: 20%
- Incubation period: 3-14 days
- Person is infected to mosquitoes for 4-5 days.

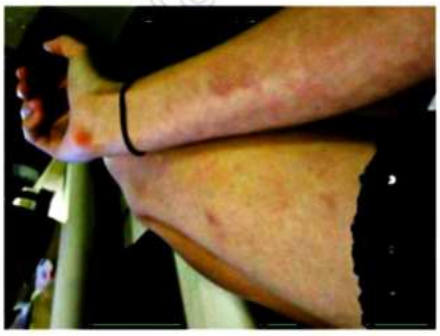
Warning Signs 00:07:27

1. Restlessness or obtundation (under perfusion of the brain)
   - Capillaritis: causes fluid loss into the cavity leading to Ascites and pleural effusion.
   - Resulting in the hypo-perfusion of the brain.
2. Epistaxis
3. Nausea or vomiting protracted.
4. Pleural effusion: Shortness of breath
5. Hepatomegaly
6. Ascites
7. Hematocrit Rise >20% admission value
8. Platelet count decreases.

Dengue Fever 00:12:18

Clinical features

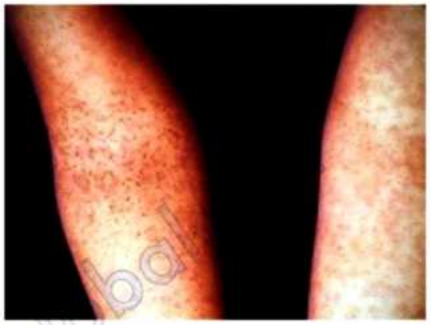
- Person Living or traveling in endemic areas.



Diagnosis

Fever and any 2/ 6 features present

- Retro orbital pain or myalgia or Break bone fever
- Protracted Nausea or vomiting: Dehydration.
- Rash (during illness): Initially it's pale.
- Warning Signs: any 1
- Positive Tourniquet Test: > 20 Petechiae/ sq. inch.
  - BP cuff in the arm of the patient.
  - Inflate the BP cuff between the systolic and diastolic blood pressure (mean arterial pressure)
  - Keep the cuff inflated for 5 minutes.
  - > 20 petechiae in a one-inch square indicates capillary fragility.



- Leucopenia (TLC reduced)

During Defervescence

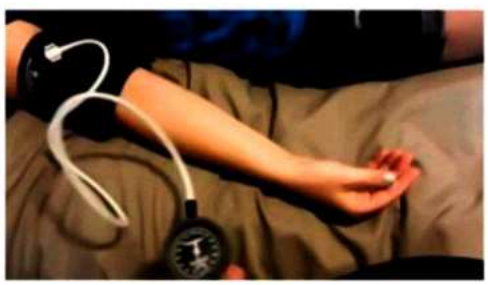
- When the Fever comes down that is after 2-7 days.
- It is a critical period.

Look for

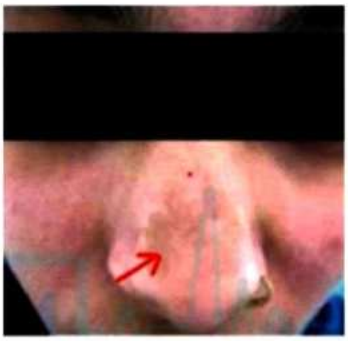
- Dengue shock syndrome: Hematocrit increased by more than 20% over the admission value.
- Dengue hemorrhagic fever: Platelet decreases.

Differential diagnosis

- Also, inpatient,
  - Undergone massive blood transfusion.
  - Post thyroid surgery.
  - Which would contribute to cytotoxicity → Tetanus
- Trousseau Sign:
  - Inflation of the BP cuff above the 20 mm Hg of SBP
  - Wait for 3 minutes.
  - Results in carpopedal spasm
  - No petechiae



- If History of fever and joint pain
  - Recovery 2 weeks: hyperpigmentation (Melasma)
  - Diagnosis: Chikungunya



Severe Dengue 00:22:13

1. Plasma leakage or fluid loss: pleural effusion and ascites
   - Decrease in BP
   - Hypotensive Shock
2. Bleeding
3. Organ malfunction
   - Obtundation
   - SGPT increases.
     → Compensated: Thready pulse, BP decreases
     → Hypotensive: Pulse may not be felt, and BP is unrecordable. (Requires ICU admission)

- Dengue without warning symptoms: Group A, treated on an OPD basis
- Dengue with warning symptoms: Group B, admitted in IPD
  - OR with Risk factors (Infants, > 65 years, DM, CKD)
- Dengue with plasma leakage or organ malfunction: Group C, ICU/IPD

Don'ts 00:31:37

- Don't use corticosteroids. They are not indicated and can increase the risk of GI bleeding, hyperglycemia, and immunosuppression.
- Don't give platelet transfusions for a low platelet count. Platelet transfusion does not decrease the risk of severe bleeding and may instead lead to fluid overload and prolonged hospitalization.
- Don't give half normal (0.45%) saline. Half-normal saline should not be given, even as a maintenance fluid, because it leaks into third spaces and may lead to a worsening of ascites and pleural effusions.
- Don't assume that IV fluids are necessary. First, check if the patient can take it orally. Use only the minimum amount of IV fluid to keep the patient well perfusion. Decrease IV fluid rate as hemodynamic status improves or urine output increase.

Management 00:35:38

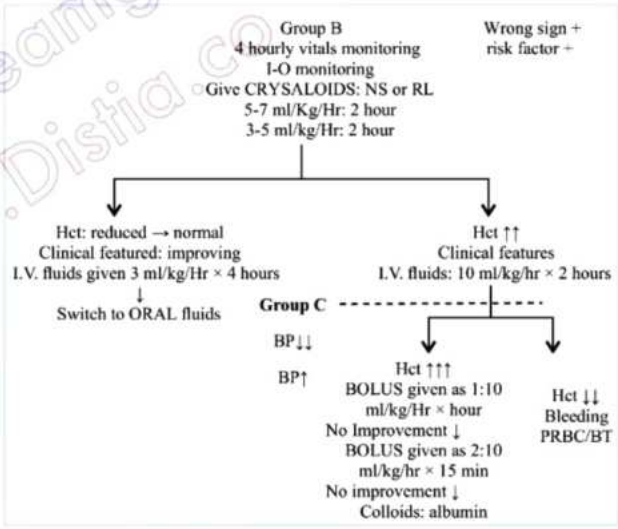
Group A: Dengue Fever

- Awareness of critical period
- Dehydration: Sunken eyeballs, dry oral mucosa, cold clammy extremities, decrease urine output.
- Fever: Paracetamol 6 hourly Tepid sponging
- Cox 1 inhibitors are Contraindicated as they interfere with the function of platelets
- Insect repellent on patient

On arrival monitor the patient's CCTV-R

- **C - C**olor of the patient: PALLOR
- **C - C**apillary refill time ((n) <3 sec)
- **T - T**emperature (cold clammy limbs)
- **V - V**olume of pulse
- **R - R**ate of pulse
  - Would help to decide if the patient requires aggressive fluid Resuscitation or not

Group B: Dengue with warning signs (not in shock): Inpatient fluid management



Refer Table 73.1

Work Up 00:44:15

1. IgM Dengue Virus: 4x ↑↑
2. NAAT
3. NS-1 Antigen (IgG).

Discharge 00:47:00

- Patients who are resuscitated from shock rapidly recover. Patients with dengue haemorrhagic fever or dengue shock syndrome may be discharged from the hospital when they meet the following criteria.

1. Afebrile for 24 hours without antipyretics
2. Good appetite, clinically improved condition
3. Adequate urine output
4. Stable hematocrit level
5. At least 48 hours since recovery from shock
6. No respiratory distress
7. Platelet count greater than 50,000 cell/μL

Vaccine

00:49:28

Dengvaxia

- CYD-TDV is a tetravalent, live attenuated, chimeric dengue vaccine 17D backbone developed by Sanofi Pasteur. The schedule that has been evaluated in Phase III clinical trials includes 3 doses of vaccine (at 0, 6 and 12 month)

Table 73.1

Component	Volume, mL	Content	Clinical response
PRBC	250-300 (including additive solution)	RBCs with variable leukocyte content and small amount of plasma	Increase hemoglobin 10 g/L and hematocrit 3%
Platelets (from whole blood)	50-70/RD unit pool of 4 to 6 RD unit	5.5×10^{10} /RD unit	Increase platelet count 5000-10,000 /L/ RD unit
Platelets (from apheresis)	200-400	2×10^{11} /SDAP product	For pooled RD and SDAP: CCI 10×10^{9} /L within 1 h and 7.5×10^{9} /L within 24 h posttransfusion
FFP	200-250	Plasma proteins-coagulation	Increases coagulation factors about 2%

74 NIPAH VIRUS AND ZIKA VIRUS

Nipah Virus

00:00:11

- Family: Paramyxovirus, single stranded RNA virus
- Genus: Henipa virus or Hendra virus (Hev)
- Naturally occurs in bats or pigs or horses or dogs.
- Death rate: 40-70%
- Incubation period is 4 – 14 days
- 1st case was reported in Malaysia, mainly in people who worked in Pig farms.
- Incidence: Initial report of Nipah virus from a village in Malaysia and then spreading to other parts of the World, India, Bangladesh, etc.
- Source: Fruits contaminated with dropping or saliva of Pteropus/ Flying Fox (BAT)
- It negative single-stranded RNA virus

Modes of Transmission

- Pigs: farm workers
- Saliva-contaminated fruits: Pteropus
- Man-to-man transmission via body fluids.
- It is a Category C Bioterrorism agent

Refer Image74.1

Clinical manifestation

00:06:05

1. Fever
2. Headache
3. Dizziness
4. Altered sensorium are Initial symptoms seen on day 1 of illness.
5. Progression is very fast (4 days)
6. Other symptoms reported: Altered sensorium, Coma: GCS<8
   - Myoclonic jerk
   - Seizures
   - Hallucinations
7. Respiratory symptoms: Respiratory distress
   - Cough
   - ARDS

Work Up

00:10:13

1. Serum IgM capture E.I.A from Nipah virus or Hendra virus,
   - IgG indirect E.I.A for Nipah virus/ Hendra virus
2. Lumbar puncture: CSF Reverse Transcriptase PCR
3. MRI head: Punctuate hyperdensities (Vasculitis is a manifestation of disease and leads to microinfarction in brain.)

Management

1. No vaccine
2. No treatment
3. Some improvement in patients with the usage of
   - Ribavirin
   - M 102.4: currently in Phase 1 trial
     → Monoclonal Ab against Henipa virus G protein: used to prevent further damage to brain by blocking the receptor engagement.

Zika Virus

00:14:45

- It is a single stranded RNA virus.
- Family: Flavivirus
- Cases reported first in 2016, It was reported In Rio (Brazil) children born in 2016 had microcephaly which is neurological sequelae where the mother developed Zika Virus infection in pregnancy.

- Increase incidence of GBS in people exposed to zika virus infection.
- Incubation period is 3-12 days.
- Fever lasts between 2-7 days.
- Transmission
  - Aedes Aegypti (present at more than 2000 m altitude)
  - Sexual transmission (man to man)

Clinical features 00:17:26

1. Fever or Retro orbital pain or arthralgia (mainly small joints of hands)
2. Rash (Palms, chest, trunk) throughout the fever
3. Conjunctivitis
4. It is a self-limiting illness.

Clinical features in infant

1. Microcephaly: Head circumference < -3 SD
2. Abnormal foveal reflex
3. Macular atrophy
4. Hypoplasia of optic nerve head
5. Incidence of GBS increases

Extra Mile:

Brighton Criteria for diagnosis of GBS 00:20:19

- Ascending flaccid symmetric Paralysis
- Distal Areflexia (Knee and Ankle jerk will disappear)
- 12 hour – 28day: progression
- Electro diagnostic test: Nerve conduction velocity (F- reflex latency increased)
- Lumbar puncture: albumino-cytological dissociation

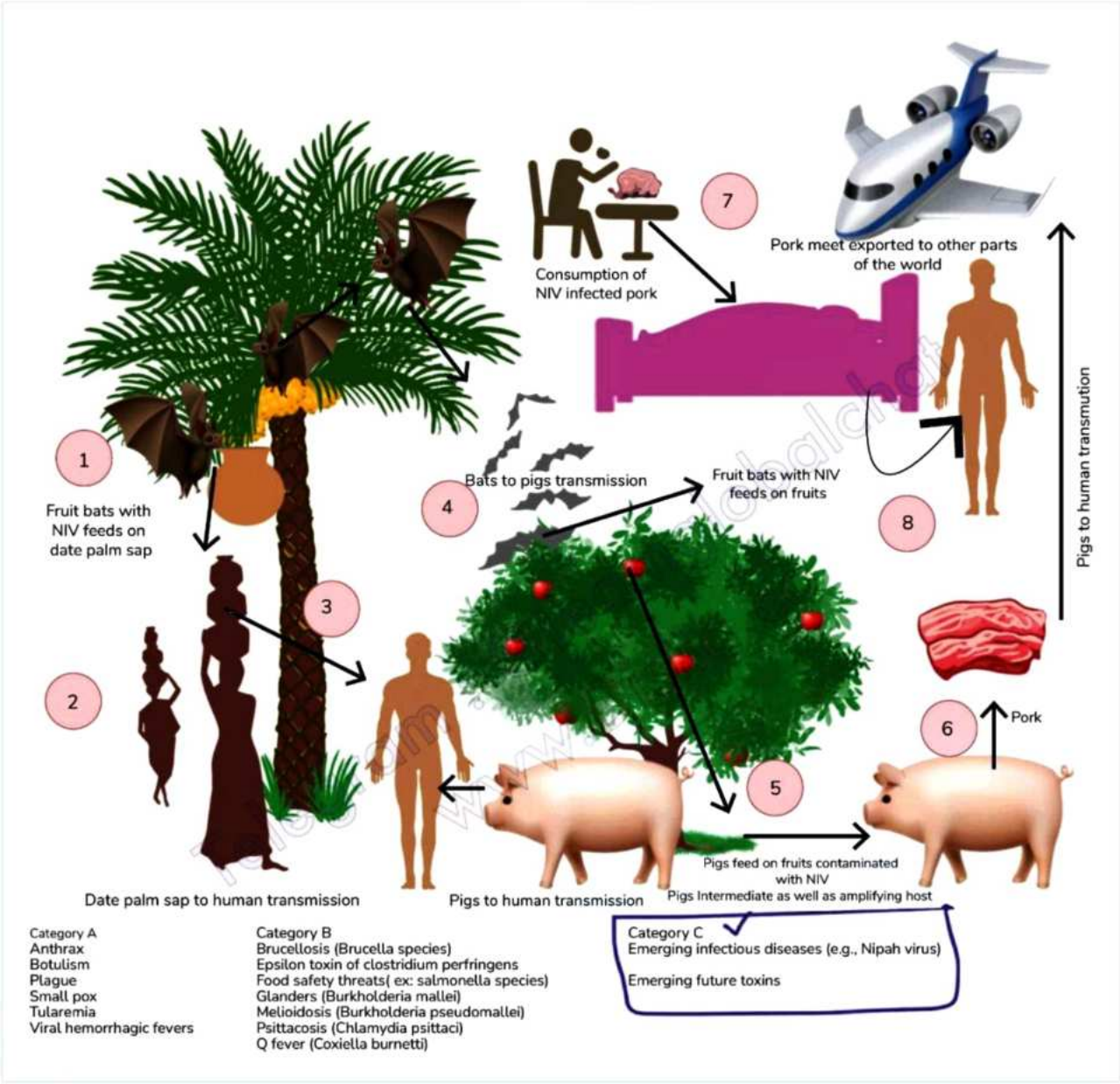
Work-up 00:22:05

1. Investigation of choice: Urine Assay: Urine Triplex PCR (rRT – PCR) (Combination of Real-time and Reverse Transcriptase PCR)
2. Blood sample: RT – PCR
3. ELISA IgM Zika (demonstrated only if > 7 days)
4. Pregnant Female
   - Serial USG: microcephaly
   - Amniocentesis

Treatment

- No definite management.
- No Vaccine

Image74.1



75 PNEUMOCYSTIS JIROVECI

Cause of Pneumocystis Jiroveci

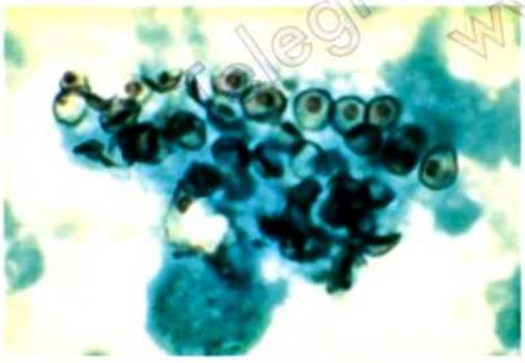
00:00:24

- Common opportunistic organism causing infection in:
  1. AIDS/ HIV+ patient
  2. Any immunocompromised patient on steroids
  3. A child with nephrotic syndrome on steroids
  4. Ankylosing spondylitis patient on infliximab
  5. A person who has undergone kidney or bone marrow transplantation (Hemopoietic stem cell transplant)
- This organism has a tropism for lungs.
- Route of transmission is person to person via respiratory droplets infection or due to reactivation of latent infection.
- It is an important cause of pneumonia in AIDS patients.
- Overall Leading cause of pneumonia in AIDS-positive patients: Pneumococcus Auscultatory Finding of Bronchial breathing is heard.
- In AIDS-positive patients with CD_4 count less than 200 with perihilar infiltrates, nonproductive cough: Pneumocystis jiroveci
- Prophylaxis of P. Jiroveci infection: Cotrimoxazole

Clinical Features & Diagnosis

00:07:28

1. Shortness of breath
2. Dyspnea
3. Fever
4. Nonproductive cough



- Image shows Gomori methenamine stain (with multiple) Black color-cysts seen of P. Jiroveci.

Workup

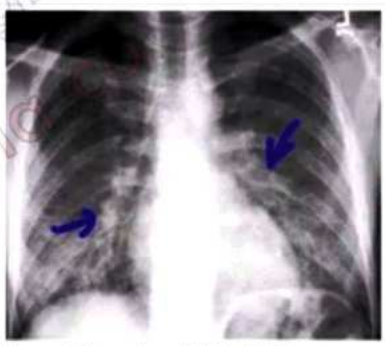
1. CXR chest: Initially Normal, in the later part of illness: Perihilar diffuse infiltrate
2. HRCT: Ground glass opacities might have cysts present in them so pneumothorax can also develop in these patients which may cause sudden deterioration.
3. Open lung biopsy done earlier.
4. β 1,3 Glucan test: Used for invasive fungal infection

Important Information

- β 1,3 glucan test can also Diagnosis
  - Candida
  - Aspergillus
  - Can't identify mucormycosis in DM patients.

- Real-time PCR: Can't distinguish colonization of airways.
- So, it cannot be established whether it is infection or colonization.

5. Investigation of choice is Broncho Alveolar Lavage (BAL)
   - Then the specimen is stained with Giemsa or Gomori methenamine stain.



CXR Shows bilateral peri hilar infiltrates present.

HRCT: Ground Glass Opacities With Cysts

Diagnosis: Non-Invasive Tests

6. IFA: can be done with BAL specimen to identify the infection
7. LDH is elevated, increased A-a gradient in PFT [(n) 5-15 mmHg] SpO_2 reduced.

- PCR can't distinguish between colonization and infection.

Treatment 00:16:28

1. Drug of choice: IV Trimethoprim-Sulfamethoxazole
   - Also used for prophylaxis
   - Given for 21 days.
   - Mode of action: It inhibits folate metabolism.
2. For prophylaxis as well as management
   - IV pentamidine (also given as a nebulizer for prevention)
   - Clindamycin
   - Primaquine
   - Atovaquone
   - Steroids are also useful here (Cytokines are produced on the destruction of organisms, so steroids will help reduce symptoms of inflammation when organisms die) Reduced cytokine mediated damage.
     → Indication $Pa0_2 < 70mmHg$
     → A-a gradient > 35mmHg

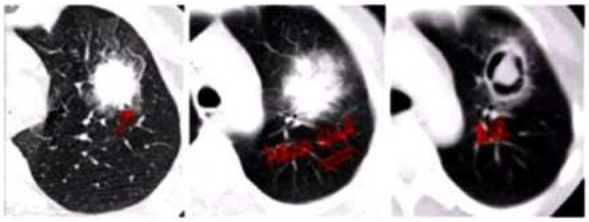
Q. Beta 1,3 glucan test is positive in all except? (AIIMS NOV 2019)

A. Aspergillus
B. Candida
C. Mucormycosis
D. Pneumocystis jiroveci

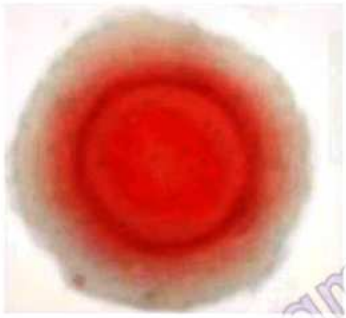
76 ASPERGILLOSIS

Features Seen in Aspergillosis 00:00:39

- Aspergillosis has many subtypes like Niger, fumigatus, Flavus, etc.
- Aspergillosis on CT chest shows characteristic "Halo sign"



CT chest shows: Halo sign and Air Crescent sign



- Holo sign seen on CSF sample taken in case of CSF rhinorrhea with relation to anterior Cranial fossa fracture
- As Aspergillosis progresses destruction of lung parenchyma shows another characteristic "Air crescent sign" (that is the air around the actual fungal lesion)

Subtypes 00:02:58

1. **A. fumigatus**: causes ABPA (Allergic Broncho Pulmonary Aspergilloma)
   - Associated with Asthma and Cystic fibrosis.
2. **Thermophilic Actinomycetes**: seen in Bagassosis
3. **A. Niger**: Causes Angio invasive infection in diabetic patients which results in cavity formation and can also contribute to massive hemoptysis.
4. **A. flavus**:
   - It Causes Sinusitis
   - Produces Aflatoxin leading to Hepatocellular cancer.

Risk Factors 00:06:28

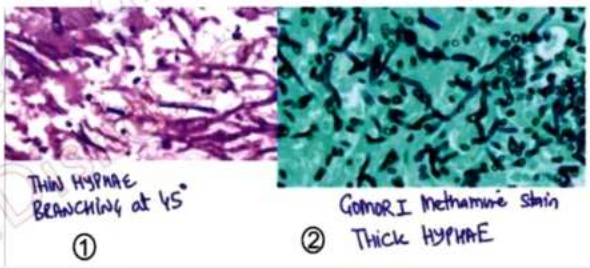
1. Neutropenia
2. Leukemia
3. Hematopoietic stem cell transplant
4. AIDS
5. Steroids
6. COPD
7. Cystic fibrosis and Asthma are conditions with a higher risk of developing **ABPA.**
   - **Invasive Aspergillosis:** 100% mortality
   - **Chronic Aspergillosis:** 50% mortality
   - **Allergic Aspergilloma:** < 1% mortality

Etiology

- Inhalation of dust consisting of conidia of this fungus by the severely immunocompromised patient.

Diagnosis

- **By lung Biopsy: Histopathological examination**

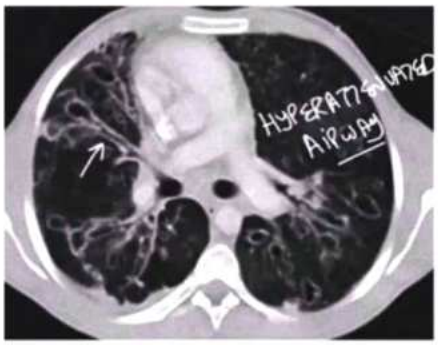


1. Thin Hyphae branching at 45° of aspergillus
2. Gomori Methenamine Stain: Seen in Mucorales. of
   → Hyphae is thicker; ribbon-like hyphae branching occurs at a right angle (90°)

Acute pulmonary aspergilloma	Chronic pulmonary aspergilloma
• Post HSCT, Respiratory distress present, Haemoptysis, Fever • Antigen detection: Galactomannan • Beta-1, 3 D Glucan test: • HRCT: Halo sign & air crescent sign due to hemorrhagic pneumonitis. • BAL: Hyphae branch at 45° **Management:** Voriconazole • **Primary prophylaxis**: Posaconazole	• Cavitation usually misdiagnosed as TB, Sarcoidosis, atypical mycobacterial infection, and Rheumatoid nodules • Fungal balls may be seen in the cavity (coughed out sometimes)

ABPA (Allergic Bronchopulmonary Aspergilloma)

00:16:36



- Associated with A. fumigatus
- Mostly seen in Asthma or Cystic fibrosis (mucoviscidosis): autosomal recessive with a mutation in the CFTR gene

Clinical features

1. Coughing bouts: episodes of bronchial obstruction with the mucus plug.
2. Thick tenacious sputum or casts
3. Shortness of breath

Allergic Fungal Sinusitis

- Presentation: Chronic sinusitis unresponsive to antibiotics
  1. Nasal polyps
  2. Congested mucosa
  3. Eosinophilia
  4. Secretions of mucoid material
  5. Charcot laden crystals

Work up

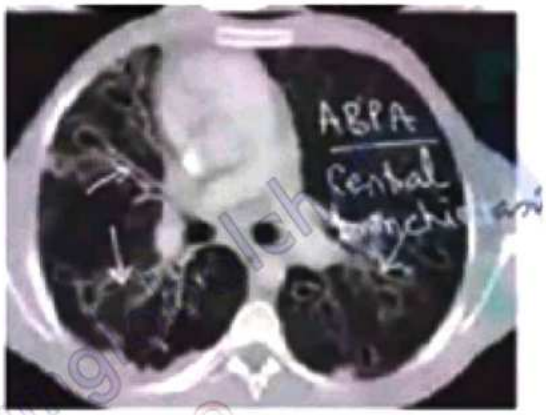
1. Eosinophilia
2. HRCT: Central Bronchiectasis (Hyper attenuated airways)
3. IgE for Aspergillus Fumigatus
4. Total IgE > 1000 ng/mL
5. Positive skin prick test

} Cardinal diagnostic Tests for ABPA

- If the above criteria are not met, then the diagnosis is Severe Asthma with Fungal Sensitization (SAFS) ABPA
- Fungal asthma or SAFS
  - Hypersensitivity reaction to the fungus occurring in lung.

Management

- Itraconazole



On CT

00:19:12

- HALO SIGN
- Air crescent sign

Management of Aspergillosis

00:23:27

1. Acute exacerbation ABPA: Steroids (as it is a hypersensitivity reaction)
2. ABPA: Itraconazole
3. Invasive pulmonary aspergilloma acute or chronic: Voriconazole
4. 1° prophylaxis: Posaconazole

Diagnostic Criteria Used Earlier

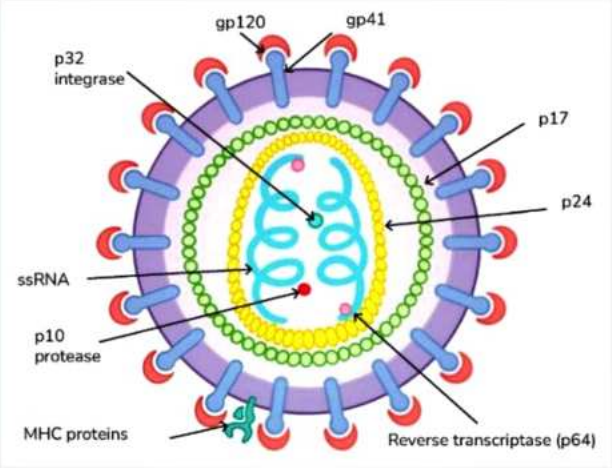
00:27:29

- The Rosenberg – Patterson criteria: Major criteria

A – **A**sthma
R – **R**adiographic fleeting pulmonary opacities (Not used as it can be seen with drugs, parasites, fat embolisms, tropical pulmonary eosinophilia.)
T – Skin test positive for aspergillus (Type, HSN management immediate cutaneous HSN)
E – **E**osinophilia
P – **P**recipitating antibodies (IgG) in Serum
I – **I**gE in Serum elevated (1000 IU/MI)
C – **C**entral bronchiectasis
S – **S**erum A fumigatus specific IgG & Ig E (> twice the value of pooled serum sample from patient with asthma who have aspergillus HSN by skin test.

77 AIDS

Acquired Immunodeficiency Syndrome 00:00:16



- Individual having HIV Serology positive and CD_4 Count < 200 cells/cu. mm or CD_4 count <14%
  - Normal CD4 count: 800-1200 / cu.mm.
- It belongs to the lentivirus genus and it's a retrovirus.
- Enveloped and it's a single standard RNA virus.
- It has an enzyme called Reverse transcriptase, which converts RNA to DNA, and an enzyme called Integrase. Which helps to integrate with the host genome.
- The HIV or AIDS epidemic in India began in 1986-1987 with the detection of the first HIV infection in Chennai and the first AIDS case was detected in Mumbai.

Case Load 00:03:45

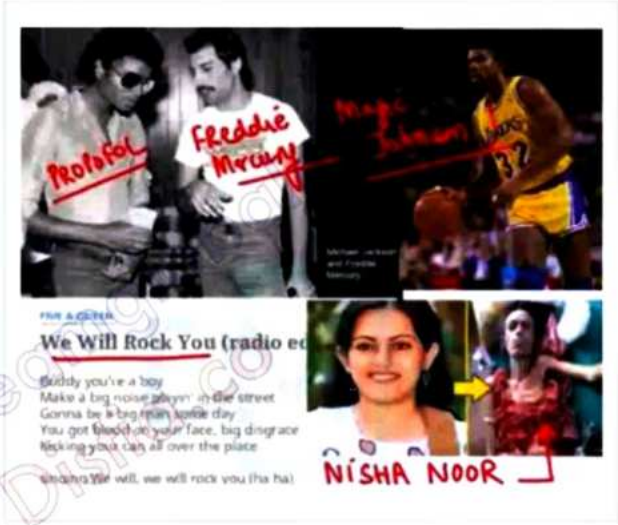
- 37 million people living with HIV in the world.
- Maximum prevalence: 27% in Swaziland
- 2.4 million in India

High Prevalence State

- Mizoram has a higher prevalence than Manipur.
- 4 states with maximum numbers of 55% of cases
  - Maharashtra
  - Andhra Pradesh
  - Tamil Nadu
  - Karnataka
- 83% of total cases: 15-49 years of age
- 39% of total cases: Female
- HIV-1 takes 10 years to get converted to AIDS.
- HIV-2 takes 15-20 years to get converted to AIDS.
  - HIV-2 is common in Africa.
- HIV-1 group M-Subtype C is common in India.

90-90-90 approach

- 90% of the patient should be aware of their HIV-positive status.
- 90% who are aware of their status should be on combination antiretroviral therapy (CART).
- 90% who are on CART should have sustained viral remission. (<40 copies of viral RNA/ml on PCR)



Route of Transmission 00:11:50

- Sexual Contact is more common than Blood transfusion.
- Heterosexual
- Unprotected Receptive Anal Intercourse (URAI): 1:30
- Unprotected Vaginal Intercourse: 1:10,000
- Insertive Anal act: 1:1000
- Fellatio with ejaculation: 1:1000
- Needle Stick Injury: 1:300
- Needle Sharing: 1:150
- Blood transfusion-infected blood: 95% chance.

Transmission Incidence

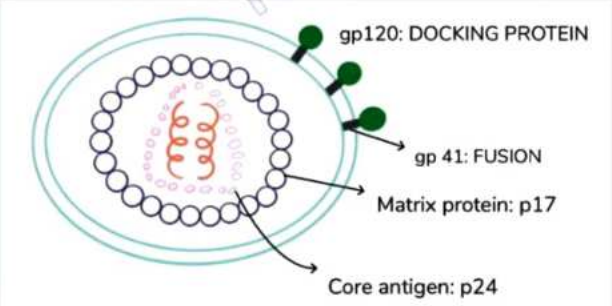
- Hepatitis B: 1:300,000
- HIV-1,2: 0.1–1:1,000,000
- Highest incidence of transmission: HBV > HCV > HIV
- Leading cause of transfusion association Hepatitis: HBV
- Blood transfusion can be associated with the transmission of
  - Dengue
  - Zika Virus
  - West Nile virus
  - Parvo virus B19
  - Trypanosoma

- Ehrlichia
- Syphilis
- HHV 8

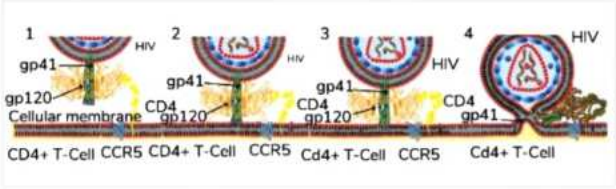
Pathology 00:19:23

- Dendritic cells (Antigen-presenting cells) present in the Anal Mucosa or Vaginal Mucosa are the first cells to be affected.
- CD4 Counts reduced (both infected and non-infected cells are dying)
  - Apoptosis increased.
  - Pyroptosis increased.
- Older than 6 years of age or adults
  - Stage I: CD4 count < 500 cells / > 26%
  - Stage II: CD4 count 200-499 cells / 14-25%
  - Stage III: CD4 count < 200 cells / <14%
- <1 year of age
  - Stage I: CD4 count < 1500 cells / < 34%
  - Stage II: CD4 count 750-1499 cells / 26-33%
  - Stage III: CD4 count < 750 cells / <26%
- AIDS Defining Malignancies:
  - Kaposi Sarcoma
  - Non-Hodgkin's Lymphoma
  - Invasive Cervical Cancer
- Autoimmunity increased: Lymphocytic Interstitial Pneumonitis (LIP)
  - This is a rare disorder.
  - There is a B cell dysregulation antibody that causes damage to the lung parenchyma.
  - Rate of incidence of idiopathic thrombocytopenia (ITP) is increased.

Viral Structure 00:27:00



- gp 120: Docking protein: by which CD_4 cells attach to its CD_4 receptors.
- gp 41: Fusion
- p 17: Matrix Protein
- p 24: Core antigen
- Vertical Transmission is 30%
- Best test to identify vertical transmission: HIV PCR DNA > p24 antigen assay



Docking

- GP 120 is attaching to CD_4 receptors on the cell.
- Co receptor
  - CCR_5 } present on CD_4 cells.
  - $CXCR_4$ }
  - They contribute to Conformational change.
  - The Virus comes closer to the cell wall of CD_4 which will further help in the fusion.

Fusion

- Virus ready to inject RNA into the cell.
  - RNA Converted to double Standard DNA
  - Double standard DNA with help of Integrase gets integrated into the host domain.

- CCR_5 delta 32 mutation: Patient will not express CCR_5
  - The virus will be present in the blood but does not attack the target cells Called Hampering the infiltrative ability of the virus.

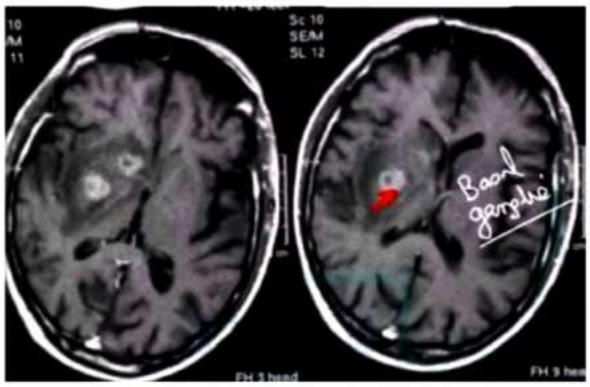
CDC AIDS Definition with or Without HIV Serology (11 - 6C 2P HKM)

- **C**andida: involving the esophagus, trachea, bronchus
- **C**ryptococcus neoformans meningitis (extrapulmonary cryptococcus)
- **C**ryptosporidium parvum: causes chronic diarrhea for more than 1 month.
- **C**MV colitis or esophagitis (serpiginous ulcers)
- **C**erebral toxoplasmosis: Seizure present in AIDS patients
- Primary **C**NS lymphoma
- **P**neumocystis jiroveci: CD_4 < 200.
- **P**rogressive multifocal leuco-encephalopathy (JC virus) causes subcortical white matter damage.
  - Hyperintense lesion will be seen on CT.
- **H**SV esophagitis, mucocutaneous ulcer > 1 month (painful)
- **K**aposi Sarcoma: present in < 60 years of age.
- **M**ycobacterium Avium Intercellular (MAI): CD4 < 50

Cd_4	< 500	TB
	< 200	P. jiroveci
	< 100	Cerebral Toxoplasmosis
	< 50	CMV Retinitis or MAI

Cerebral Toxoplasmosis

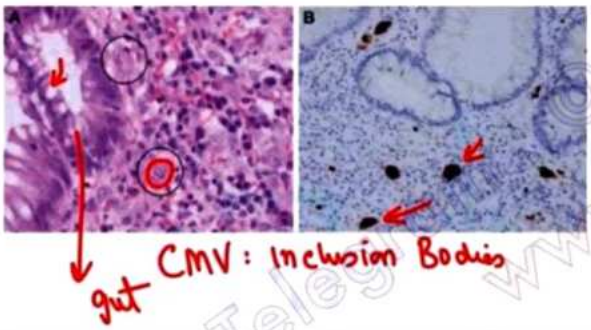
00:40:06



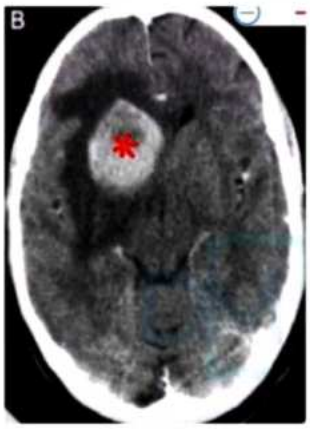
- Eccentric dot Sign or Ring enhancing Sign.
- Multiple lesions can be seen.
- Mostly basal ganglia area is involved.

CMV (Cytomegalovirus)

- Basophilic intracytoplasmic, Intranuclear inclusion bodies is seen



Primary CNS Lymphoma



- In this NCCT, Single lesion with extensive cerebral edema: Seizures can occur.

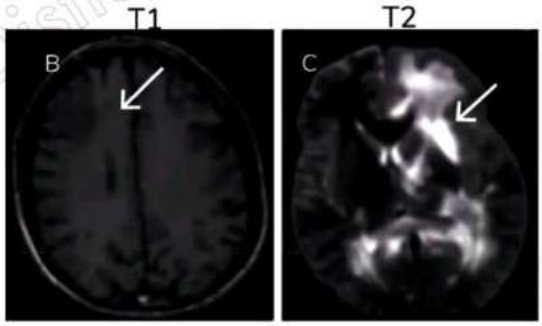
Cerebral Toxoplasmosis	Primary CNS Lymphoma
• Multiple lesions present mostly in basal ganglia. o Eccentric dot sign o Ring enhancing sign	• Single lesion present • Cerebral edema present Which causes seizures

Pneumocystis Jiroveci

- AIDS patient with a history of cough for 2 weeks and O_2 saturation of patient is disproportionately low
- In this X-ray Perihilar Shadows are present bilaterally
- Broncho alveolar lavage (BAL) positive stained with Gomori methenamine silver stain shows black cysts indicating Pneumocystis jiroveci

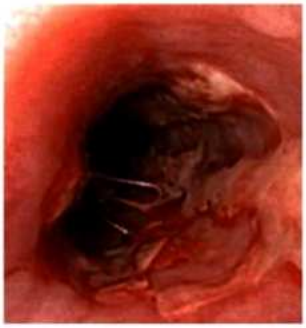
Progressive Multifocal Leuco-Encephalopathy

00:43:39



- In MRI: Subcortical hyperintense white matter lesions present, mostly in the parietal or temporal lobe of the brain present

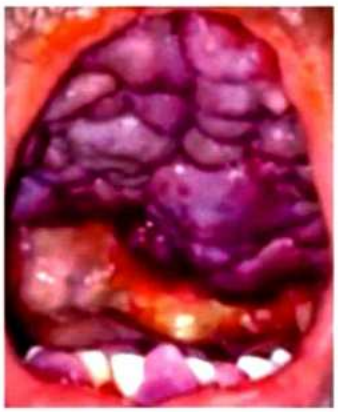
HSV Esophagitis



- Solitary large ulcer in the esophagus or punched out ulcer can also be seen sometimes cause odynophagia

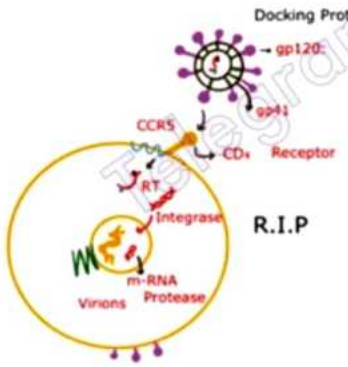
Kaposi Sarcoma

- Vascular tumor in the oral cavity or elsewhere in the body.
- < 60 years of age included in AIDS criteria.
- Differential diagnosis: Bacillary angiomatosis caused by Bartonella henslae
- Reddish brown lesion present all over the body which may bleed on touch.



Life Cycle of HIV

00:46:08



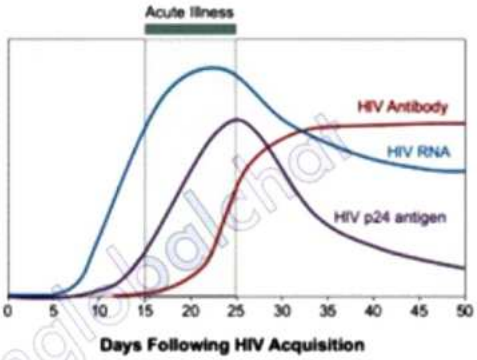
- Whenever docking occurs conformational change in receptor and co-receptor occurs.
- Integration of virus with CD_4 cell.
- Single-stranded RNA comes inside the CD_4 cells.
- Reverse transcriptase converts the single-stranded RNA into double-standard DNA.
- Integrase splice up host DNA and HIV virus DNA integrated into it.
- It Produces messenger RNA which utilizes the host's rough Endoplasmic Reticulum
- Protease breaks down the long-chain molecule into small ones and forms new virions.

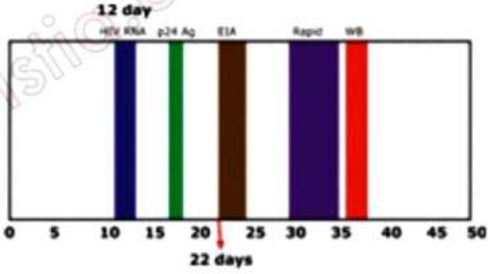
Diagnosis

- To diagnose AIDS
  - Histoplasmosis with HIV serology positive
  - Coccidioidomycosis with HIV serology positive
  - HIV wasting with HIV serology positive.
  - HIV Encephalopathy with HIV serology positive
  - TB or Extrapulmonary TB with HIV serology positive

Laboratory Diagnosis of HIV

00:51:31





- 4th generation Enzyme immunoassay (EIA)
  - It can identify:
    - → Antibody against HIV – 1
    - → Antibody against HIV – 2
    - → Antibody against p24 antigen
  - Sensitivity is 99.5%.
  - Helps to diagnose in the early days of infection.
- 3rd generation EIA: Turns positive by day 22 after unprotected intercourse with an HIV patient.
  - Window period for HIV infection: 3 weeks (50%)- 6 weeks (80%)
- For early diagnosis: HIV–RNA starts appearing in blood as early as in 1st week of infection.
- Best test for early diagnosis: Nucleic Acid Amplification Technology (NAAT)
- HIV RNA will be positive by day 12 after exposure.

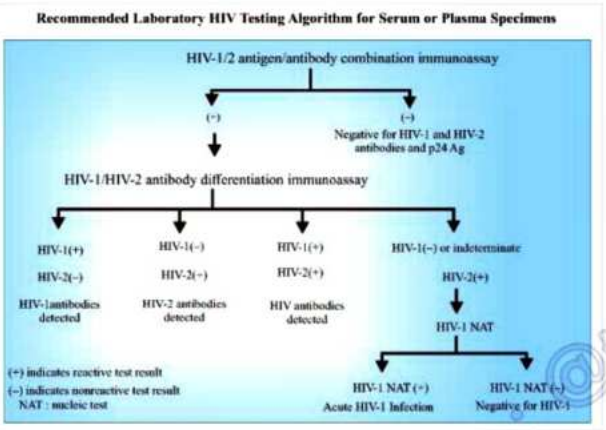
- P24 antigen will be positive between 15 to 20 days.
- Other tests include EIA on day 22.
- Western blot will start turning positive in around 30 days.

False (+) ELISA HIV Conditions

- Pregnancy
- Influenza
- Vaccination
- Blood transfusion
- Autoimmune disorders like SLE, scleroderma
- Liver disease

CDC Protocol

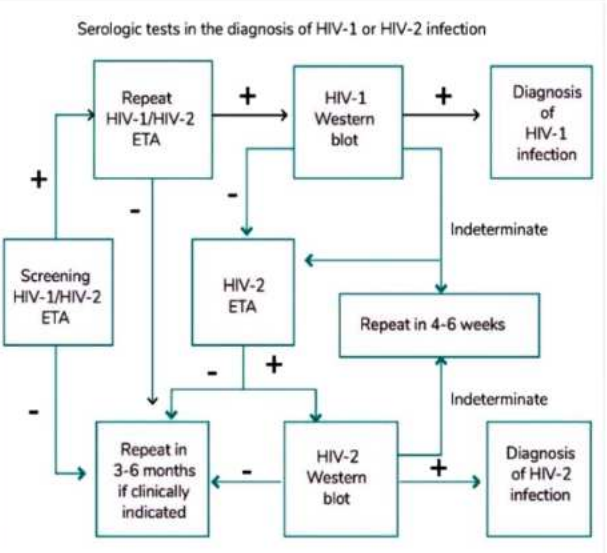
00:56:44

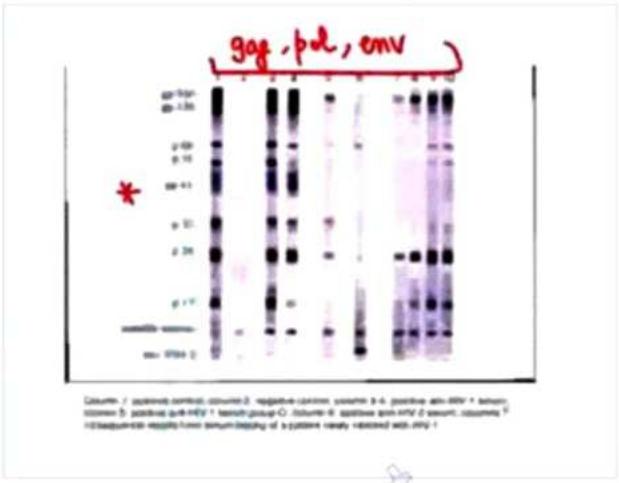


Tests

- E.I.A 4th generation combined immunoassay
- Differentiation Immunoassay
- If both Indeterminate N.A.T or PCR

According to NACO or the Government of India





- Most sensitive test: EIA
- Most specific test: Western Blot
  - Picks up antibodies against all these antigens-group 160,120, p17, p24, which are encoded by 3 gene gag, pol, env.

Other Tests

- CD_4 count: use as a diagnostic test.
- Liver function test: Most drugs can affect the liver.
- Lipid profile: because of Cardiovascular complications.
- HIV RNA: Talks about viral load
- HIV DNA: Vertical Transmission of HIV
- VDRL: Coinfection-positive inpatient
  - Hepatitis B/C/D/G
  - With Hepatitis G: progression of HIV is slower
- Purified Protein Derivative (PPD): for LTB
- Anti-Toxoplasma Antibody: IgG.
- MMSE (Mini Mental Score Examination): to check the cognitive decline in the patient.
- ORAQUICK: New test for HIV done with saliva or blood at home.

  - Diagnostic accuracy
    → Saliva: 98%
    → Blood: 99%

Prophylactic Drugs for HIV Patients To increase Longevity Of Life Span

Guidelines for primary opportunistic infection in AIDS positive

P. jiroveci	Cotrimoxazole (Drug of choice and Prevention)
Toxoplasma	Cotrimoxazole Prevention)
Toxoplasmosis with encephalitis	Pyrimethamine with Sulfadiazine with Leucovorin
MTB + PPD > 5 mm (in 48 to 72hrs) or IGRA (Interferon Gamma Release Assay) (+) or Contact with an active case of TB (Latent TB infection (LTBI))	Isoniazid (INH) + Pyridoxine x 9 months
Mycobacterium Avium Intercellular (MAI)	Clarithromycin + Ethambutol may be added Rifabutin
HIV (+) patient exposed to chicken pox pt	Varicella zoster immunoglobulin (VZIg)
Cryptococcus Coccidioides	Fluconazole
Histoplasmosis	Itraconazole
Salmonella	Ciprofloxacin
Bartonella henselae	Doxycycline
CMV	Valcyclovir or acyclovir

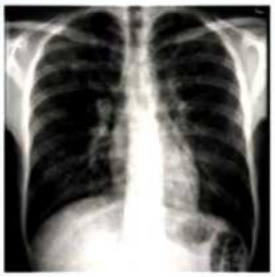
- If TB diagnosed in HIV patients
  - Treat TB 1st to decrease bacterial load in the body
  - Chances of high risk that is Immune reconstitution inflammatory syndrome will be less.
  - Then HIV treatment should be given.

Vaccines for HIV Positive Patients 01:15:00

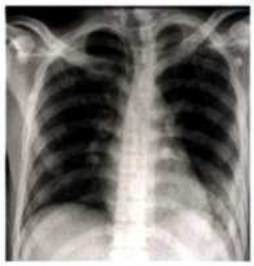
- HAV, HBV, PCV 13 (pneumococcus), HPV vaccine.

Respiratory Diseases in AIDS Patients 01:16:15

- Incidence of Pneumococcal pneumonia > TB > P. jiroveci
- Pneumococcal pneumonia: Consolidation or patch in one lobe of lungs



P. Jiroveci: Bilateral perihilar opacities



Multiple spots present in both lung fields suggestive of Miliary TB

- History was given by patients of p. Jiroveci
  - Fever
  - Shortness of breath
  - Chest pain
  - Weight loss
- Chest X-ray can be normal at early stages in all the above 3 conditions.
- Perihilar opacities present in P. Jiroveci
- LDH values are elevated.
- β 1, 3 glucan test is positive
- Diffusion capacity of lungs for carbon monoxide (DLCO) is reduced.
- BAL: Wright Giemsa
  - Methenamine Silver
- Management
  - Co-trimoxazole
  - IV Pentamidine if allergic to cotrimoxazole
  - Steroids are given if:
    → $paO_2 < 70$ mm Hg
    → A – a gradient > 35 mm hg (Normal: 15mmHg)
- Extrapulmonary Manifestations
  - Otic mass on the external meatus
  - Lymph nodes enlargement
  - Hepatosplenomegaly
  - Lesion in the choroid

Mycobacterium TB 01:23:21

- MTB with HIV-positive patients have Cavity size relatively smaller and dissemination chances are more.
- Treatment: Before giving CART give anti tubercular therapy for 2 weeks ATT CART
  - Time gap between the ATT and CART is 2 weeks.

- LTBI (latent TB infection): based on Mantoux test >5mm.
  - Management: Isoniazid with Vitamin B_6 for 9 months.
- **MAI**: CD4 < 50 cells/ cu.mm incidence increases
  - Entry: Lungs or GIT
  - On chest X-ray: Bilateral infiltrates
  - Investigation of choice: Culture BAL or Bone Marrow biopsy or Blood
  - Treatment: Clarithromycin with Ethambutol may or may not Rifabutin added.

Lymphocytic Interstitial Pneumonitis (LIP)

- Antibody-mediated damage to lungs.
- Hazy Bilateral lung field, but no organism has been isolated.
- Due to B cell dysregulation in HIV positive patients.

Important Information

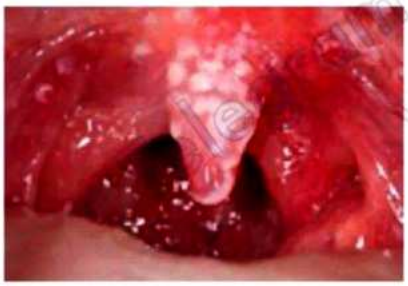
- Invasive Aspergillosis is Not seen in AIDS positive patients (Common in Asthmatics & Cystic Fibrosis)

Cardiovascular Association in HIV Patients 01:28:44

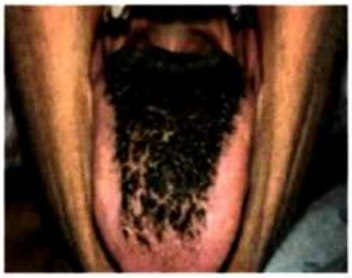
- MI
- Cardiomyopathy

GIT Disease in AIDS

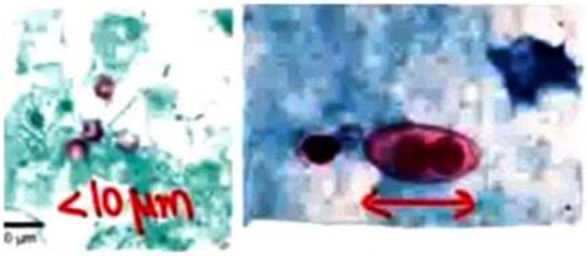
- Oropharyngeal Candida or Oral thrush



  - Clinical presentation: HIV positive truck driver presents with odynophagia.
  - Diagnosis: Esophageal candida
  - Management: I.V. Fluconazole
- Black hairy tongue: EBV



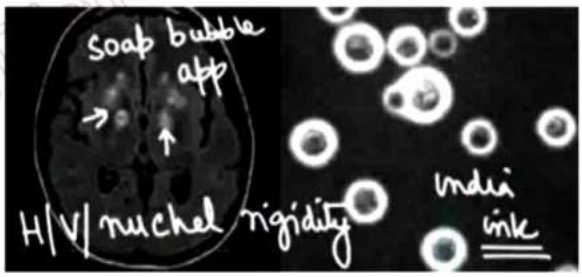
  - Enlargement of filiform papillae of tongue
- Chronic diarrhea in AIDS positive patient
  - On ZN staining:
    → If cyst <10µm: Cryptosporidium
    → If size is bigger: Isospora belli



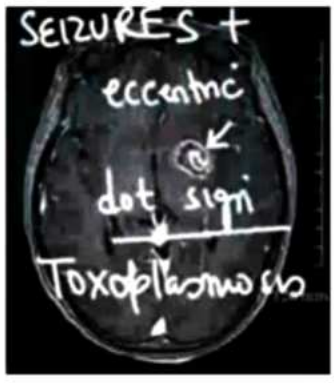
Cryptosporidium Isospora belli

- Management
  - Drug of choice for Cryptosporidium diarrhea is Nitazoxanide
  - Drug of choice for Isospora belli diarrhea is Cotrimoxazole.
  - Cotrimoxazole uses: P. jiroveci, Toxoplasmosis and Isospora belli

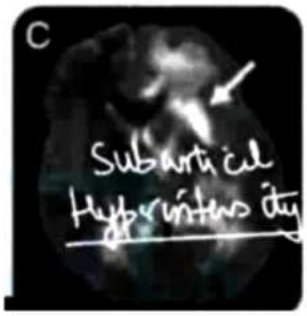
CNS Manifestations in AIDS Positive Patients 01:33:11



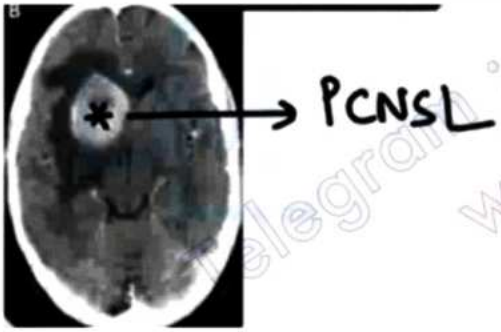
- Patient presents with headache, projectile vomiting with nuchal rigidity.
- MRI shows soap bubble appearance (anywhere in the brain).
- Diagnosis: Cryptococcal meningitis



- AIDS positive rickshaw puller with recurrent episodes of seizure and MRI shows Eccentric dot sign in basal ganglia.
- Diagnosis: Cerebral toxoplasmosis
- If test for Abs against toxoplasma is positive:
  - Management: Pyrimethamine
    → Sulfadiazine
- In T2 image



  - Subcortical hyperintensity
  - Seen with JC virus.
  - Diagnosis: Progressive Multifocal Leukoencephalopathy
- PCNSL: Primary CNS Lymphoma



  - Single large lesion association with perilesional edema
- Soap bubble appearance anywhere in the body: Cryptococcus
- Eccentric dot sign especially in basal ganglia: Toxoplasmosis
- Cryptococcal Meningitis Best test: CSF ELISA for Cryptococcal antigen
  - Management
    → First-line treatment: Liposomal Amphotericin B with 5 Flucytosine for 2 weeks
    → Oral Fluconazole for 8 weeks
- Seizures: cause is HIV Dementia > Cerebral Toxoplasmosis
  - Tests: IgG anti toxoplasmosis
  - Eccentric dot sign on MRI mostly in basal ganglia
- Management: Pyrimethamine with Sulfadiazine with Leucovorin
- Progressive multifocal leukoencephalopathy Tests
  - PCR CSF for JC virus
  - MRI: subcortical hyperintensity in T2 images
- Primary CNS lymphoma:
  - Tests: Stereotactic or guided biopsy

Cart Regimens

- Start trail: Early initiation of treatment decrease mortality to 50%
- Acute opportunistic infection present: start CART simultaneously.

Important Information

- TB patients with HIV Start ATT first then after 2 weeks CART.
- If CART gave 1st: Immune Reconstitution Inflammatory Syndrome (IRIS)
- IRIS leads to the production of cytokines which reset the thermostat of the hypothalamus so the patient will have a fever after medication. So, dropout rate will be higher due to worsening of symptoms

- 3 medications should be given from 2 classes.
- Check HIV PCR RNA level to know the viral load : which should decrease with treatment
- Resistance testing (K103N): NNRTI
  - Same kind of mutation present in CML: T315L
  - Management: Ponatinib

Nucleoside Reverse Transcriptase Inhibitors (NRTI) 01:46:20

- Didanosine: Peripheral Neuropathy, pancreatitis, hepatitis, or Fulminant hepatic failure
- Stavudine: Peripheral Neuropathy, pancreatitis, hepatitis, Lipoatrophy.
- Zidovudine or AZT: Anemia and neutropenia
- Abacavir: HLA B5701 testing is necessary as it can cause rash, anaphylaxis
- Emtricitabine, Lamivudine: Safe, It can be used in patient who have coinfection with HBV.

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

- Delavirdine: Rarely used due to Inconvenient dosing :
  - Side effects elevated transaminase.
- Efavirenz: Neuropsychiatric symptoms, suicidality
- Etavirine: Second-generation NNRTI can be used in case if resistance present.
- Nevirapine: On long term use: Rash, Hepatotoxicity (decrease vertical transmission of HIV)
- Rilpivirine

Nucleotide Reverse transcriptase inhibitors

- Tenofovir Alafenamide (TAF)
- Tenofovir Disoproxil Fumarate (TDF)
- Side effects: Kidney damage, Bone matrix damage
- Advantage: Effective against HBV

Protease Inhibitors

- Atazanavir or Cobicistat: Side effect is liver damage, jaundice and rash
- Darunavir or Ritonavir: side effects is liver damage, jaundice and rash.
- Indinavir: Side effects is Kidney stones
- Fosamprenavir
- Lopinavir
- Nelfinavir
- Saquinavir

  } GIT complaints
- Lipodystrophy is a common Side effects for all the protease inhibitors

Entry Inhibitors

- Enfuvirtide is given subcutaneously twice a day.
- Maraviroc is CCR5 co receptor is affected

Integrase inhibitors

- Elvitegravir
- Raltegravir
- Dolutegravir

Once a day pill: AIDS 01:56:50

- Dolutegravir + Abacavir + lamivudine: integrase inhibitor + nucleotide reverse transcriptase inhibitor
- Dolutegravir + Emtricitabine + TAF
- Elvitegravir + Emtricitabine + TAF
- Raltegravir (twice a day) + emtricitabine + TAF (If patient cannot take integrase inhibitor)

↓

- [Efavirenz + Emtricitabine + TDF] – Atripla with longest clinical experience.

Accidental Needle stick injury 02:00:42

- Incidence of infection up to 0.3%
- Post exposure prophylaxis: PEP should be administered ideally within 2 hours (but certainly within the first 72 hours) of exposure and the risk evaluated as soon as possible.
- According to NACO guidelines: Tenofovir (TDF) 300 mg + Lamivudine (3TC) 300 mg. (mostly 3 drugs are preferred)
- According to CMDT: Tenofovir 300 mg + Emtricitabine 200 mg daily with Raltegravir 400 mg twice a day.

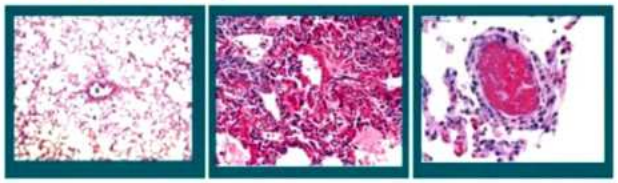
78 COVID - 19

Introduction

00:00:13

- Single Stranded positive sense RNA virus with one of largest RNA genomes of 30 kb
- Eclipse period (time to make intracellular virions): 10h
- Incubation period (IP): 4-5 days
- Median Incubation period (in 97.5% population): 11.5 days
- Virus detectable upto 3 weeks up to 1 month.
- Not culturable after 8 to 9 days.
- Aerosolization of the virus plays a definite role in its spread.

Virus Impact on Lungs



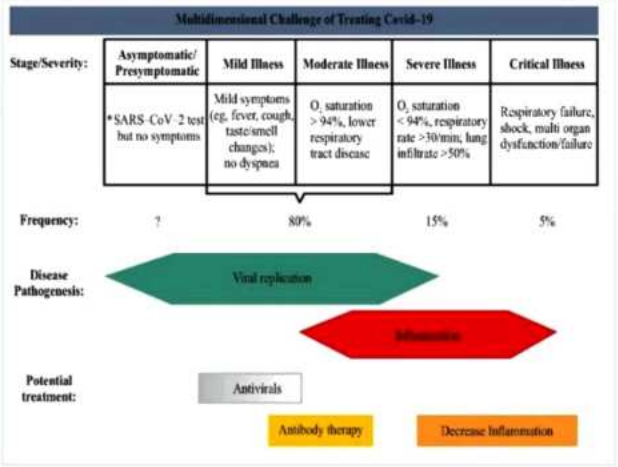
Normal Alveoli

- Thickened Alveolar septa due to alveolar edema and inflammation.
- Leads to impaired gas exchange damage resultant endothelitis leads to non-cardiogenic pulmonary edema

- Inhibition of Factor H: Uncontrolled complement-mediated damage.
- Release of Tissue factor leads to micro–Thrombi formation in Lung vessels

Clinical Features

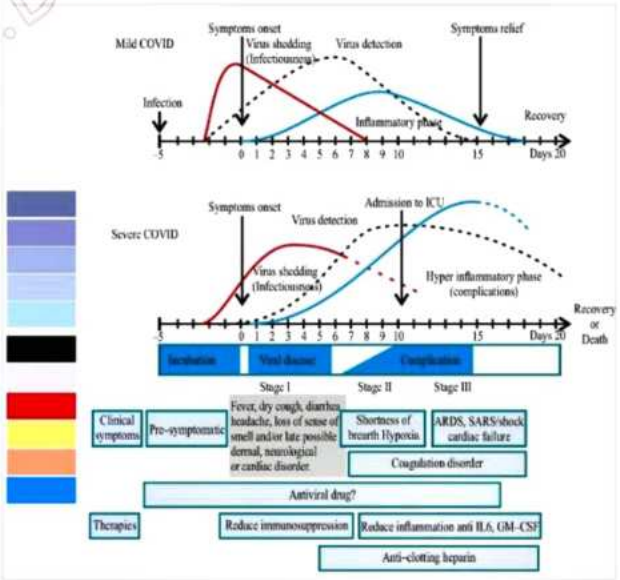
00:11:13



- Stage I (Early infection)
  - Anosmia +/-
  - Mild cough
  - Fever
  - Diarrhea
- Stage II (Pulmonary phase)
  - Shortness of breath
    → RR (more than 24)
    → SPO_2 (less than 93%)
  - Happy Hypoxia
    → Day 6-10
- Stage III (Hyper inflammatory Phase)
  - ARDS (acute respiratory distress syndrome)
  - Sepsis
  - MODS (multi-organ disease)
  - CS (cardiogenic shock)
  - Steroids play a big role in stage III.
- In the pulmonary phase we have to start with heparin. Because this is the phase from where the coagulation starts occurring.

Timeline

00:19:42



- STAGE I
  - Early infection
- STAGE II
  - Pulmonary phase
- STAGE III
  - Hyperinflammation

Work Up 00:21:22

Investigation of choice: RT-PCR for SARS-COV-2

- Sample was taken from nasopharyngeal swabs and oropharyngeal swabs.
- Distance between nostril and posterior wall of nasopharynx is 8-10 cm in adults.
- Wooden shaft or calcium alginate swab should not be used.

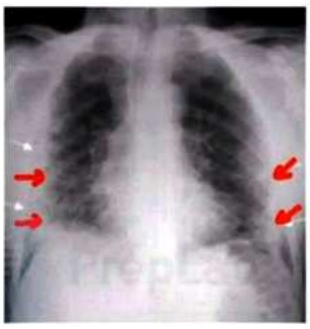
- Cycle Threshold value is inversely related to viral load.
  - low CT value means high viral load.
- Rapid Antigen tests help in increasing testing on a wider scale.
- Any of the two is sufficient for diagnosis.

Labs

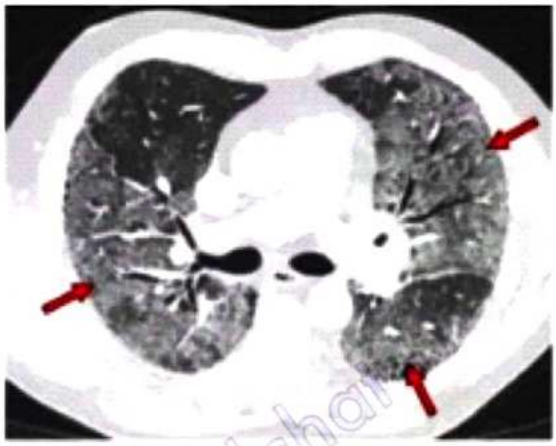
- TLC Lymphopenia
- Neutrophil-Lymphocyte ratio > 6
  - Higher the value poorer the prognosis.
  - >17 is having a poor prognosis.
- D – Dimer assay: values increased.
- CRP, LDH, IL-6, Ferritin } Alarm markers
- Troponin I, Pro BNP

Imaging

- Chest X-ray shows multiple opacities in mid and lower-long zones.



- Typical HRCT chest findings: Peripheral Ground glass opacities consolidation
  - Crazy pavement
  - Reverse Halo sign



- Findings less consistent with COVID-19: Pleural effusion lymphadenopathy

Treatment For Mild Cases 00:32:51

Symptomatic home care

Treatment For Moderate Case 00:38:17

Pneumonia with no signs of severe disease RR ≥ 24 /min OR
SpO_2 < 90-93% on room air

↓

Admit in ward

↓

1. Target SpO_2: 92 - 96% (88-92% in patients with COPD)
2. Preferred device for oxygenation: Non-rebreathing face mask
3. Awake proning for 30-120 minutes may be used in patients who continue to have hypoxemia despite oxygen >4L/min if no contraindications.

Anticoagulation

4. Prophylactic dose of LMWH/UFH, if no contraindications (e.g. enoxaparin 40 mg daily SC)3

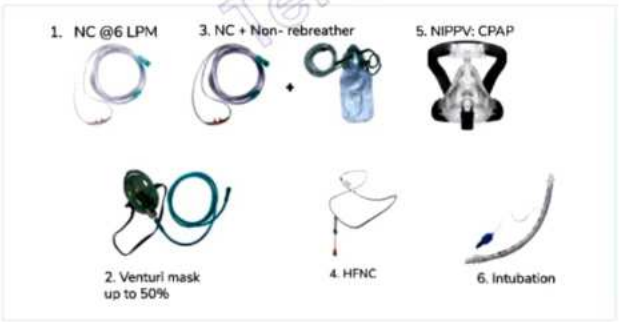
Corticosteroids

5. IV methylprednisolone 0.5 – 1 mg/kg or Dexamethasone 0.1 -0.2 mg/kg for 5 days

- Step up oxygen
  - (Preferred) Non-rebreathing face mask with flow Rates up to 15L/min HFNO system.

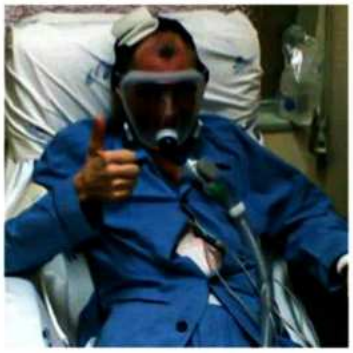
- High-flow nasal cannula can have flow rates up to 60 L/min. It reduces dead space and work of breathing

In resource-limited settings you can escalate O_2 delivery as follows:



- Nasal Cannula
- Venti Mask

1. Non-rebreather mask
2. HFNC
3. NiV
4. Intubation/ Tracheostomy
   - Trial of NiV if cannot tolerate or work of breathing is high, intubate



Treatment For Severe Case 00:48:20

RR ≥ 30/min OR SpO2 < 90% on room air

↓

Admit to ICU

- High–risk patients for severe disease include:
  - Age: 60 years or more
  - Hypertension, DM (diabetes mellitus), and Other immune-compromised states.
  - Cerebrovascular disease and obesity (BMI > 25kg/m^2)
  - Chronic lung or kidney or liver disease
- Interventions for a severe case

1. NIV with Tight fitting face mask or helmet interface
2. HFNC (high-flow nasal cannula)
3. Intubate using Lung protective strategy
   → Patient has to be kept Prone: P/F < 150, FiO_2 > 0.6, PEEP> 5cm H_20
   → Low tidal volume
   → High PEEP
   → NM blockage

4. Anticoagulation

- High dose prophylactic UFH or LMWH (e.g. enoxaparin 40 mg or0.5 mg/kg BD SC) if not a high risk of bleeding

5. Corticosteroids

- If sepsis / septic shock: Manage as per existing protocol & local antibiogram use sedation and nutrition therapy as per existing guidelines
- IV methylprednisolone 1-2 mg /kg or dexamethasone 0.2 – 0.4 mg/kg for 5 – 7days

ARDS

- Use Low Tidal volume Ventilation, high PEEP, NM Blockade, Proning
- If pO2 / FiO2 < 80 : E.C.M.O

AIIMS/ICMR–COVID–19 National Task Force/Joint Monitoring Group (Dte.GHS)
Ministry of Health & Family Welfare, Government of India
Clinical Guidance For Management of Adult COVID–19 Patients

Covid–19 Patient

Mild disease

Upper respiratory tract symptoms (&/or fever) Without shortness of breath or hypoxia

Home Isolation & care

MUST DOs
- Physical distancing, indoor mask use, strict hand hygiene.
- Symptomatic management (hydration, anti-pyretics, antitussive, multivitamins).
- Stay in contact with treating physician.
- Monitor temperature and oxygen saturation (by applying a SpO_2 probe to fingers).

Seek immediate medical attention if:
- Difficulty in breathing
- High grade fever/severe cough, particularly if lasting for >5 days
- A low threshold to be kept for those with any of the high-risk features*

*High-risk for severe disease or mortality
- Age >60 years
- Cardiovascular disease, hypertension, and CAD
- DM (Diabetes mellitus) and other immuno compromised states
- Chronic lung/kidney/liver disease
- Cerebrovascular disease
- Obesity

Moderate disease

Any one of:
1. Respiratory rate ≥ 24 /min, breathlessness
2. SpO_2: 90 % to ≤ 93 % on room air

ADMIT IN WARD

Oxygen Support:
- Target SpO_2: 92-96 % (88-92% in patients with COPD).
- Preferred devices for oxygenation: non-rebreathing face mask.
- Awake proning encouraged in all patients requiring supplemental oxygen therapy (sequential position changes every 2 hours).

Anti-inflammatory or immunomodulatory Therapy
- Inj. Methylprednisolone 0.5 to 1 mg/kg in 2 divided doses (or an equivalent dose of dexamethasone) usually for a duration of 5 to 10 days.
- Patients may be initiated or switched to oral route if stable and/or improving.

Anticoagulation
- Conventional dose prophylactic unfractionated heparin or Low Molecular Weight Heparin (weight based e.g., enoxaparin 0.5 mg/kg per day SC). There should be no contraindication or high risk of bleeding.

Monitoring
- Clinical Monitoring: Work of breathing, Hemodynamic instability, Change in oxygen requirement.
- Serial CXR; HRCT chest to be done ONLY If there is worsening.
- Lab monitoring: CRP and D-dimer 48 to 72 hrly; CBC, KFT, LFT 24 to 48 hrly; Il-6 levels to be done if deteriorating (subject to availability).

Severe disease

Any one of:
1. Respiratory rate >30 /min, breathlessness
2. SpO_2<90 on room air

ADMIT IN ICU

Respiratory support:
- Consider use of NIV (Helmet or face mask interface depending on availability) in patients with increasing oxygen requirement, if work of breathing is LOW.
- Consider use of HFNC in patients with increasing oxygen requirement.
- Intubation should be prioritized in patients with high work of breathing /if NIV is not tolerated.
- Use conventional ARD5net protocol for ventilatory management.

Anti-inflammatory or immunomodulatory therapy
- Inj Methylprednisolone 1 to 2 mg/kg IV in 2 divided doses (or an equivalent dose of dexamethasone) usually for a duration 5 to 10 days.

Anticoagulation
- Weight based intermediate dose prophylactic unfractionated heparin or Low Molecular Weight Heparin (e.Ev. Enaxaparin 0.5mg/kg per dose 5C BD). There should be no contraindication or high risk of bleeding-

Supportive measures
- Maintain euvolemia (if unavailable, use dynamic measures for assesing fluid responsiveness).
- If sepsis/septic shock: manage as per existing protocol and local antibiogram.

Monitoring
- Serial CXR; HRCT chest to be done ONLY If there is worsening.
- Lab monitoring, CRP and D-dimer 24-48 hourly; CBC, KFT, LFT daily; IL.-6 to be done If deteriorating (subject to availability).

After clinical improvement, discharge as per revised discharge criteria.

EUA/Off label use (based on limited available evidence and only in specific circumstances):
- Remdesivir (EUA) may be considered ONLY in patients with
  - Moderate to severe disease (requiring SUPPLEMENTAL OXYGEN), AND
  - No renal or hepatic dysfunction (eGFR <30 ml/min/m^2; ST/ALT>5 times ULN (Not an absolute contradiction), AND
  - Who are within 10 days of onset of symptom/s.
    → Recommended dose: 200 mg IV on day 1 f/b 100 mg IV OD for next 4 days.
  - Not to be used in patients who are NOT on oxygen support or in home settings
- Tocilizumab (Off-label) may be considered when ALL OF THE BELOW CRITERIA ARE MET
  - Presence of severe disease (preferably within 24 to 48 hours of onset of severe disease/ICU admission).
  - Significantly raised inflammatory markers (CRP &/or IL-6).
  - Not improving despite use of steroids.
  - No active bacterial/fungal/tubercular infection.
    → Recommended single dose: 4 to 6 mg/kg (400 mg in 60kg adult) in 100 ml NS over 1 hour.
- Convalescent plasma (Off label) may be considered ONLY WHEN FOLLOWING CRITERIA ARE MET
  - Early moderate disease (preferably within 7 days of symptom onset, no use after 7 days).
  - Availability of high titre donor plasma (Signal to cut-off ratio (S/0) ≥ 3.5 or equivalent