RESPIRATORY PHYSIOLOGY

LUNG VOLUMES & CAPACITIES
PFT
DEAD SPACE
OBSTRUCTIVE DEFECT
RESTRICTIVE DEFECT

LUNG VOLUMES & CAPACITIES:

LUNG

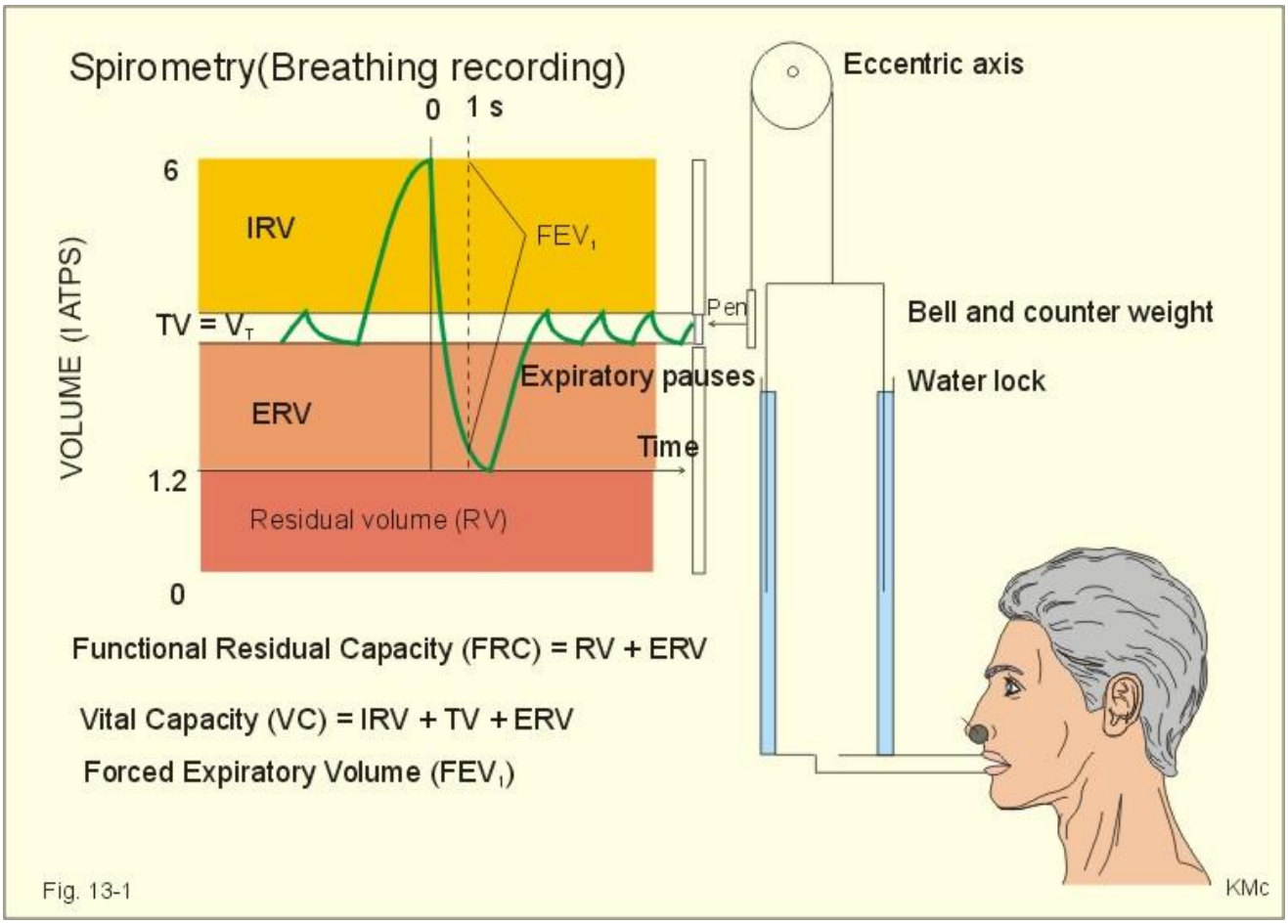
VOLUME			CAPACITIES		
Tidal volume (T.V)	500ml[Q]	Is the air that moves into the lung with each normal inspiration or the volume of air that moves out of lung with each expiration	Inspiratory capacity I C = TV+IRV	380ml	Total amount of air that can be breathed in.
Inspiratory reserve volume (IRV)	3300ml[Q]	The air inspired with a maximal inspiratory effort in excess of tidal volume	Vital capacity VC= TV+ IRV +ERV	480ml	Maximal amt. of air that can be expelled out force fully after a maximal (deep) inspiration.
Expiratory reserve volume (ERV)	1000ml[Q]	The air expelled with a maximal expiratory effort in excess of tidal volume	Functional residual capacity FRC=ERV+RV	2200ml	It is the volume of air remaining in the lung after normal expiration (after normal tidal

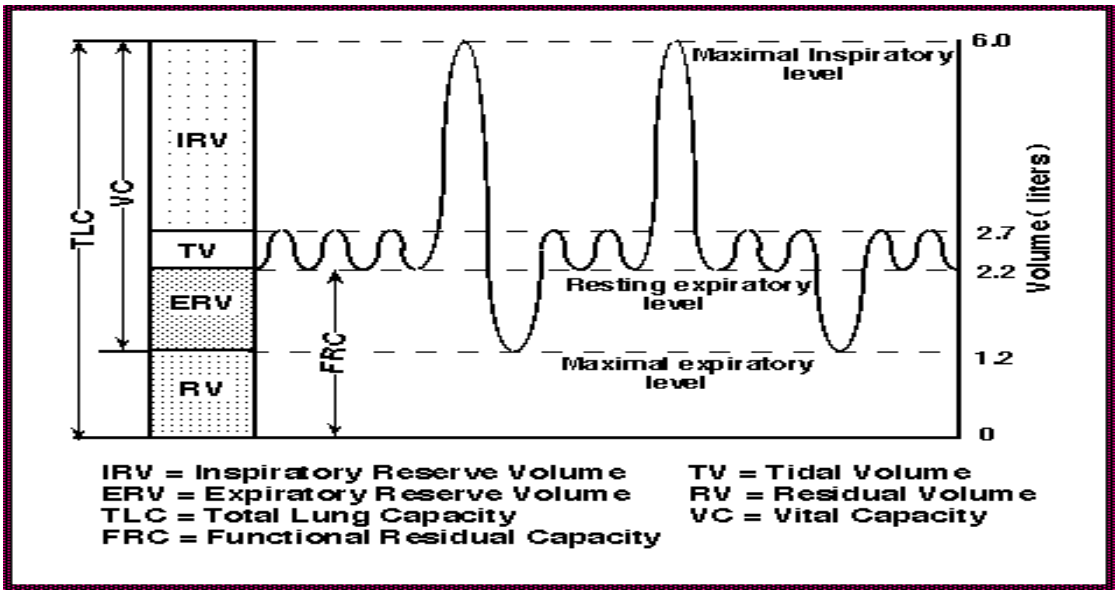
					expiration)
Residual Volume (RV)	1200ml[Q]	The amt. of air remaining in the lungs even after forced expiration	Total lung capacity TLC= TV+IRV+ER +V+RV	6000ml. (4.2-6 lit[Q])	The amount of air present in the lung after a maximal inspiration. This is the maximum volume to which the lungs can be expanded[Q]

ALSO KNOW:

Pulmonary Ventilation/Respiratory Minute Volume (RMV) **(RMV=TV x RR)**	600ml[Q] (6L) = 500x 12	The amount of air breathed in and out of lungs every minute. It is product of tidal volume (TV) and respiratory rate (RR). RMV = TVX RR
Maximal voluntary ventilation (MVV) Maximal breathing capacity	125-170L/min	The maximum amount of air which can be breathed in and out of lungs by forceful respiration in one minute.
Alveolar ventilation= (TV –Dead space volume) x RR.	4.2 liters	The amount of air utilized for gaseous exchange every minute.
Total dead space/physiological dead space = Anatomical dead space+Alveolar dead space *In normal adult Physiological dead space = Anatomical dead space[Q]	Anatomical dead space- The conducting part where gaseous exchange does not take place. It is volume of respiratory tract from nose up to terminal bronchiole. It is 150ml. Alveolar dead space – Those alveoli which are non functioning and those which do not receive adequate blood flow.	
Closing volume	The lung volume, at which, no further air can be expelled by expiratory effort.	

Alveolar ventilation: (TV-DS) x RR: The amount of air that actually participates in respiratory gas exchange


Spirometry(Breathing recording)
Eccentric axis
0
1 s
6
IRV
FEV1
TV = VT
Pen
Bell and counter weight
Expiratory pauses
Water lock
ERV
Time
1.2
Residual volume (RV)
0
VOLUME (I ATPS)
Functional Residual Capacity (FRC) = RV + ERV
Vital Capacity (VC) = IRV + TV + ERV
Forced Expiratory Volume (FEV1)
Fig. 13-1
KMc


TLC
VC
IRV
TV
ERV
RV
FRC
Maximal Inspiratory level
Resting expiratory level
Maximal expiratory level
6.0
2.7
2.2
1.2
0
Volume (liters)
IRV = Inspiratory Reserve Volume
ERV = Expiratory Reserve Volume
TLC = Total Lung Capacity
FRC = Functional Residual Capacity
TV = Tidal Volume
RV = Residual Volume
VC = Vital Capacity

Dead space: *Wasted ventilation*

- Anatomical: 1st 16 generations of airways
- Alveolar: Under-perfused alveoli
- Physiological: Anatomical + Alveolar

Volume:

1.5 to 2 ml/kg OR 30% of TV

DEAD SPACE:

Increased:	**Decreased:**
❖ Face mask, IPPV, ❖ **BE HEre TUE A3**:Bronchitis, Emphysema, Hemorrhage (pulm), Embolism (pulm), Tachypnea, Upright position, Extension (Neck), Asthma, Atropine (& other BDrs), Ageing	• **FITES**:Flexion (Neck), Intubation, Tracheostomy, Surgery (Pneumonectomy), Exercise

FEV1: (Timed VC): 83% in 1s; 97% in 3s
FEV6 (FVC): forced vital capacity

Determinants of lung volume

1. **Negativity of pleural pressure:** Negativity is maintained by opposite pull of lung & chest wall

2. Lung & chest wall compliance

3. Inspiratory muscle strength

Trans-pulmonary pressure: (Alv. pressure – Pleural pressure): Establishes a gradient between airway opening & alveoli so that gas flows into the lung

Respiratory center:

- Pneumotaxic center
- Apneustic center
- Bottzinger & Pre-Bottzinger complex

Inspiratory muscles:

- **Primary muscles**: Diaphragm, parasternal intercostals & scalene muscles
- **Accessory resp muscles:**
  -Sternocleidomastoid, trapezius, external intercostals, abdominal wall muscles

Ventilation-Perfusion ratio:

Gradients:

- Ventilation: Best at the base
- Perfusion: Best at the base

Ratio: Best at the apex

PFT

TYPE OF DISORDER	**TLC**	**RV**	**VC**	**FEV_1 / FVC**

OBSTRUCTIVE	N to ↑	↑	↓	↓
RESTRICTIVE	↓	↓	↓	N to ↑

Obstructive defect:

- COPD (chronic bronchitis, emphysema),
- Asthma,
- bronchiectasis,
- CF,
- bronchiolitis;
- *LAM(Lymphangio myomatosis)*
- *byssinosis*

Restrictive defect:

- All ILDs: (Including Sarcoidosis, IPF, Pneumoconiosis),
- long-standing bronchiectasis;
- loss of lung compliance: pneumonia, pulmonary edema

Both I & E limitation seen with: Myasthenia gravis(MG), Myotonic dystrophy(MD), GBS, Ankylosing spons(AS), Cervical spine injury

***MMFR / FEF $_{(25-75)}$ (max mid-exp flow rate / Forced exp flow):** Most *sensitive* measure of airflow obstruction in small airways
PEFR (peak exp flow rate): Most *sensitive* measure of airflow obstruction in large airways

TUBERCULOSIS

- Tuberculosis is due to bacteria belonging to the Mycobacterium tuberculosis complex: M. tuberculosis, bovis, africanum, microti, and canettii.
- One of the oldest disease known to affect the humans
- Usually affects lungs and 1/3 rd of the cases are extra pulmonary (15 % in india)
- One third of the world's population is affected by TB
- 40 percent of the world's TB cases lives in WHO's South-East Asia region
- TB kills 2-3 million people each year; nearly 1 million deaths take place in South-East Asia
- TB causes more deaths than AIDS, malaria and diarrhoea combined
- TB is the leading infectious killer of people living with HIV/AIDS

NTCP

- National Tuberculosis Control Programme was started in 1962 it could not make much of an impact on this dreaded disease.
- treatment completion rate was less than 40 per cent
- inadequate budget
- shortage of drugs
- emphasis on x-ray diagnosis (Most imp cause)
- poor quality sputum microscopy
- multiplicity of treatment regimens
- A comprehensive review in 1992 determined that the programme had not achieved the desired results

- Birth of RNTCP : **1993**

- WORLD TB DAY : **24 march** every year

RNTCP Statistics:

- *Prevalence of INFECTION: 50% of the general adult population*
- Incidence is 200/ one lakh papulation
- India accounts for more than 1/3rd of the global cases
- ***Every day, more than 20 000 people become infected with TB, more than 5000 develop TB and more than 1 000 die because of TB.***
- Every sputum-positive patient can infect 10–15 individuals in a year
- Smear positive cases are 85/ one lakh
- 100% of Indian population is covered under RNTCP
- RNTCP in Orissa is supported by the Danish Government and RNTCP in Andhra Pradesh is supported by the British Government
- RNTCP second largest such programme in the world

Goals :-
-To ensure that **70 per cent of TB** cases would be detected.
-**85 per cent** would be treated successfully
-From 2005 onwards, the whole country is covered

***Mode of infection*: Inhalation of droplet nuclei**
Risk of *Infection*: Mainly exogenous / environmental factors
1. Contact with a case
2. Degree of infectiousness of case (concentration of bacilli)
3. Duration & Intimacy of contact
4. Environment of contact

*Crowding in poorly ventilated rooms increases INTENSITY of contact
- Therefore 'prolonged intimate' contact required, as with family members.

Risk of *Disease*: Mainly endogenous / host factors
1. Most potent risk factor: HIV
2. Others: Silicosis, infection within last 1 yr, Re-infection, Age (late adolescence & early adulthood), Lung fibrosis, DM, IVDU, Immunosuppressive therapy (incl. Steroids), CRF/HDL, Jejunoileal bypass, gastrectomy, malnutrition, alcoholics.
3. NRAMP-1 gene: determines susceptibility to TB (2q)

After inhalation → 90% expelled by ciliated mucosal cells
→ 10% reach alveoli → ingested by AM's

Balance between

(a) No. & Virulence of bacilli ↔ (b) Bactericidal action of AM's

Determines Outcome
Lifetime risk of developing disease:
→ Immunocompetent individual: 10%; → HIV infection: 50%

Factors that reduce the likelihood of becoming infected:
These are factors that interrupt the chain of transmission:

1. Reducing the number of sources of infection in the community: this is most effectively achieved through ***detection and treatment of smear-positive cases*** in a community, as this "dries up" the reservoir of infection. This constitutes the ***best prevention*** against tuberculosis
2. Reducing the risk of infection among healthy individuals, by improving living conditions (reducing overcrowding, letting sun and air into dwellings) and nutrition.
3. Preventing the risk of disease in high-risk groups by BCG vaccination of noninfected children and treatment of latent tuberculous infection in individuals who have already become infected. (Treatment of latent tuberculous infection not carried out in India because of large burden of such population)

OUTCOME → Infection contained OR Disease

CLINICAL EXPRESSION OF DISEASE:

→ Progressive primary TB

→ Secondary / Post-primary / Adult-type / Re-activation TB

PATHOGENESIS OF TB

- 90% of the ingested bacilli is expelled out by the cillia and only 10 % reach the alveoli.
- These bacilli are ingested by the alveolar macrophages
- Balance between the no. and virulence of the bacteria and the bacteriacidal action of the alveolar macrophage determine the outcome.

Determinants of VIRULENCE:

- 3 genes: 1. katG → Encodes catalase
  2. rpoV → Signs factor (Initiates transcription of many enzymes)
  3. erp → Encodes a protein required for multiplication

- NRAMP-1 gene: determines susceptibility to TB

Bacilli bind to alveolar macrophage

Transferred to the regional lymph nodes and can disseminate to various organs

Two types of cells are important

– Macrophage (ingests)

– T cells (lymphokines , induce protection)

M. tb binds with Alveolar Macrophages (ALM)

Lipo-arabino-mannan (LAM) + Mannose receptor

↓ Inside ALM

Mycobacteria inhibit fusion of phagosome with lysosome

Multiply here

↓

Bacteremia; "seeding" of multiple sites: Patient asymp / mild flu-like illness

Th1 response develops in about 3 weeks

- ALM present M.tb antigen to CD4 T cells (in class II MHC restricted fashion)
- Also ALMs secrete IL-12

1. Drives differentiation of CD4 into Th1 subset
2. Stimulates production of IFNγ by T-cells

IFN γ does the following

1. Promotes fusion of phagosome with lysosome (Lysosomal enzymes degrade tubercle bacilli)
2. Stimulates iNOS → Production of reactive Nitrogen species → Degrade TB bacilli
3. Stimulates macrophages to produce TNFα → Recruits monocytes which transform into epitheloid cells

   Epitheloid cells → Granuloma formation (walls off infection) → Caseation

   The caseous focus is then extruded through a communicating bronchus leading to the formation of a cavity

Morphology of Granuloma :

1. Rounded tight collection of chronic inflammatory cells.
2. Central Caseous necrosis.
3. Active macrophages - epithelioid cells.
4. Outer layer of lymphocytes, plasma cells & fibroblasts.
5. Langhans giant cells – joined epithelioid cells.

Therefore, at the cost of tissue-destruction, the immune response attempts to remove the infected focus from the body
*Granuloma or LH giant cell is **not** pathagnomonic of TB…!*

Other conditions in which granuloma is present includes : -

- Foreign body granuloma.
- Fat necrosis.
- Fungal infections.
- Sarcoidosis.
- Crohns disease

IMMUNITY :-

- CMI confers PARTIAL immunity against M. tuberculosis.
- Two types of cells are important:
  - Macrophages: Directly phagocytize bacilli
  - CD4+ T cells: production of lymphokines (esp. IFN γ) which activate the macrophages
- Mycobacteria are resistant to the direct effect of antibodies and their products.
- Specific CD4 and CD8 lymphocytes are central to tuberculosis immunity.
- ***Primary*** tuberculous infection furnishes the individual with a certain level of immunity.
- However, the immune reaction to primary infection is insufficient to prevent the multiplication of bacilli in a focus, which can then become the site of caseating necrosis. The resulting liquefaction and evacuation of caseous material via the bronchi leads to the formation of a cavity in the lung.

- Also, this immunity is not sufficient to prevent development of the disease in cases with high numbers of bacilli
  or immune deficiency.

Cytokines produced by macrophages:
- IL1 & TNFα → pyrogenic
- TNFα → Weight loss, granuloma formation, Mycobacterial killing
- IL6 → Hyperglobulinemia

Microbiology
- Acid fastness is because of mycolic acid in the cell wall
- Other acid-fast organisms: Nocardia, Rhodococcus, Legionella micdadei, Isospora, Cryptosporidium
- LAM: facilitates survival of M. Tuberculosis within macrophages

CLINICAL DISEASE:
- Tuberculosis can involve all the organs except nail and hairs (thyroid, pancreas is known entity)
- Pulmonary TB is most frequent site of the involment , extrapulmonary is less frequent
- In advance HIV 70% of the TB is extra pulmonary
- Pulmonary tuberculosis occurs when there are large quantities of bacilli and/or when there is immune deficiency, by one of the three following *mechanisms*:
- **Infrequently, by progression of the primary focus during primary infection**
- **By endogenous reactivation** of bacilli that have remained latent after primary infection.
- **By exogenous re-infection:** the bacilli causing these cases come from a new infection in a previously infected person.
- The *mechanism* that comes into play depends on the density of the sources of infection (particularly smear-positive cases) in a community: in a country where the number of sources of infection is high, exogenous re-infection is more common; in countries where sources of infection are less frequent, endogenous reactivation is the most frequent cause of post-primary pulmonary tuberculosis.

o Tuberculosis can affect any organ / tissue in the body except hair & nails
o Pulmonary tuberculosis is the most frequent site of involvement; extra pulmonary tuberculosis is less frequent. (*
  In advanced HIV, 70% of TB is extra pulmonary)
o Only pulmonary tuberculosis is infectious.
o Patients with cavitary pulmonary tuberculosis are almost always "smear positive", and are the main source of infection in the transmission of tuberculosis. (Cavities harbor large no. of bacilli)

PRIMARY TUBERCULOSIS:
- Clinical illness directly following infection
- Usually occurs in < 4y of age
- May be severe / disseminated (hematogenous spread → military / meningeal TB)
- Usually not transmissible
- Involves lower part of upper lobe & upper part of lower lobe (M2/L2)
- 'Progressive' term is used to denote disease with cavitation

COMPLICATIONS

- Pleural effusion, LAP, hematogenous spread are common
- LAP may cause collapse / obstructive emphysema / bronchiectasis
- Ghon lesion: subpleural calcified primary lesion: the outcome of infection in the majority of patients
- Primary complex: Ghon focus + draining hilar LN

SECONDARY / POSTPRIMARY TUBERCULOSIS

- Due either to Re-activation / Re-infection
- Mostly develops within 2 y of acquiring infection
- Usually transmissible
- Involves apical & posterior segments of UL; Exceptionally, anterior segment of LL
- S/S: Fever LG, (evening rise), weight loss, night sweats, anorexia, cough with expectoration of white sputum ± blood streaking
- Frank Hemoptysis: erosion of vessel / Rasmussen aneurysm
- Physical findings: Usually none; occasionally post-tussive Inspiratory crepts
- Lab: Anemia, leukocytosis, SIADH (→ Hyponatremia)

*Sudden onset of pulmonary tuberculosis is not less frequent than insidious onset.
*The extent of the lesion does not bear a direct relation to the duration of the disease
*Cavitation is not a late occurrence: its frequency is nearly the same at all temporal stages of the disease.

***Complications* : -**

1. **Haemoptysis**

a. Cavity
b. Rasmussens aneurysm (Pulmonary artery)
c. Granulomatous inflammation of the arteries
d. Endobronchial tb
e. Bronchiectasis
f. Aspergilloma
g. Scar carcinoma (adenocarcinoma)

2. Pneumothorax
3. Bronchiectasis
4. Chronic respiratory failure may occur in patients who have previously had extensive tuberculosis, in whom large parts of the lung have been destroyed.
5. Pneumothorax may result from rupture of a bulla in association with lung scars; this type of pneumothorax does not lead to infection of the pleura
6. Aspergilloma, due to infection by Aspergillus fumigatus of a healed cavity, may present with hemoptysis and often requires surgical excision.

Clinical characteristics suggestive of <u>disseminated</u> tuberculosis

• **The tuberculin skin test** is usually negative

• **Funduscopic examination** may show the characteristic tuberculous lesions (choroidal tubercles) that signal hematogenous dissemination of the tubercle bacilli. Round, slightly raised yellow or whitish lesions of 1–3mm in diameter are clearly distinguishable from the vasculature on the retina.

<u>RADIOGRAPHY:</u>

The following features on CXR favor a diagnosis of TB:

1. UL disease
2. Patchy / nodular ds

- **Nodules** are round shadows (or "densities") with clearly defined borders; their size varies from a micro nodule (less than 3mm in diameter), to a nodule (more than 3 mm and less than 1 cm in diameter), to a round shadow (more than 1 cm in diameter);
- **Patchy shadows**, or infiltrations, have irregular borders that are not as clearly defined. They are of varying size, sometimes extending to large parts of the lungs.

3. Cavity

Cavities are the most characteristic sign of tuberculosis. A cavity is an area of lucency with a fairly thick wall (more than 1mm), in which an area of bronchial drainage, demonstrated by opaque parallel lines, may be evident at the pole closest to the hilum of the lung.

a. Features suggestive of tuberculous cavity
   i. Longer history
   ii. Surrounding infiltration (satellite nodules)
   iii. Collapse
   iv. Calcification
b. Features suggestive of non-tuberculous cavity
   i. Putrid sputum
   ii. Air-fluid level
   iii. Leukocytosis

Fate of cavities after effective chemotherapy: Usually resolve; however, non-resolution does not mean non-responsive infection

4. Calcification
5. Bilateral opacities
6. Persistent opacities (over several weeks)

▪ In films taken at least 2 weeks apart, **changes in the abnormalities** can be detected: growth of the cavities, confluence and spread of the nodules, or the formation of a cavity inside a patchy shadow. This kind of evolution of the radiographic features suggests that the tuberculosis is clinically active.

▪ However, it is impossible to be certain of a diagnosis of active tuberculosis on X-ray.

▪ No radiographic pattern is diagnostic of tuberculosis.

<u>Sputum investigation</u> :-

- The diagnostic method of choice is **sputum microscopy**
- The **gold slandered** test to diagnosis is **sputum culture**

- **AFB Microscopy** is presumptive
- Definitive diagnosis is by culture
- No of bacteria to be present to give sputum positivity is 10^4/ml
- The cell wall complex contains peptidoglycan
- Over 60% of the mycobacterial cell wall is lipid.
- The lipid fraction of MTB's cell wall consists of three major components, mycolic acids, cord factor, and wax-D.
- The high concentration of lipids in the cell wall of *Mycobacterium tuberculosis* have been associated with these properties of the bacterium:

• Impermeability to stains and dyes
• Resistance to many antibiotics
• Resistance to killing by acidic and alkaline compounds
• Resistance to osmotic lysis via complement deposition

- 3 samples are given in the lab (spot, morning spot)
- smears should be made so much thick that news paper print can be seen but not read out

Number of bacilli			Result reported
no	AFB	per 100 oil immersion fields	0
1–9	AFB	per 100 oil immersion fields	scanty (or number AFB seen)
10–99	AFB	per 100 oil immersion fields	+ (1+)
1–10	AFB	per oil immersion field	++ (2+)
> 10	AFB	per oil immersion field	+++ (3+)

Other ACID FAST ORGANISM

- Nocardia
- Isospora
- Cyptospora
- Microsporadia
- Rhodococcus
- Lenionella

Other ACID FAST STRUCTURES

- Head of human sperm
- Embryophora of T. saginata
- Hooklets of E. granulosus
- Keratin

Sputum culture :-

- **LJ medium**
- It takes a long time (6-8 WKS) to become positive, which may be late??
- However it can detect 10 AFB/ml
- This method is more sensitive and specific

Disadvantages

- Long time
- Costlier
- Doesnot corelates with infectivity

Uses of culture include
- Identify drug resistance
- Definitive diagnosis (EPTB)

Other culture medium

Solid agar based : middlebrook (3-4wks)
Liquid medium : BACTEC (8-14DAYS)
- BACTEC system contains radio-labeled palmitate as the sole carbon source (C-14)
- Septicheck – Biphasic media (solid egg + liquid broth)

PCR - AMPLICOR
- Can identify the bacilli in the specimen within 24-48 hrs
- Good specificity (98%)
- But sensitivity poor (80%) as compared to the culture

Limitations of PCR:
- Cost
- High false positivity
- Inability both to quantify mycobacteria and to distuingsh viable from nonviable bacteria.

QuantiFERON-TB Gold test :
- whole-blood test for use as an aid in diagnosing *M.tuberculosis* infection, including latent tuberculosis infection and tuberculosis disease.
- The QFT-G results are based on the amount of IFN-gamma that is released in response to the antigens

Advantages :-
- Requires a single patient visit to draw a blood sample.
- Results can be available within 24 hours.
- Is not affected by prior BCG (bacille Calmette-Guérin) vaccination

Xpert MTB/RIF is an automated, cartridge-based nucleic amplification assay for the simultaneous detection of TB and rifampicin resistance directly from sputum in under two hours. The technology is based on the GeneXpert platform and was developed as a partnership between the Foundation for Innovative New Diagnostics (FIND), Cepheid Inc. and the University of Medicine and Dentistry of New Jersey, with support from the US National Institutes of Health. WHO endorsed the technology in December 2010 and is monitoring the global roll-out of the technology to promote coordination.

TUBERCULIN SKIN TEST
- Intra dermal skin test
- Produce a wheel of 6-10 mm
- If the bleb is less than 6 mm repeat the procedure 2.5 cm away from the site
- Induration recoded at 72 hrs
- Only tool to know the prevalence of infection in adults
- Tuberculin PPD RT 23 is used
- O.1 ml of PPD is used
- 26G short bevel needle
- at an angle of 5 to 15 degrees, almost parallel with the skin surface
- Equivalent to 5 TU

- Donot massage the site
- It does not provide proof of the tubercular disease but is used as a test to detect latent tubercular infection.
- Test can be falsely negative in 10-47% of those with active disease
- It is the result of proof of the recent infection and reflects the resulting immunity
- Tuberculin reaction becomes positive after 6-12 weeks after infection
- Test is also positive who had prior BCG vaccination, but reaction of more than 10mm is rare after the age of 5 years.
- Less than 5 mm : negative
- 5-10 mm : indeterminant
- >10mm : positive
- >20 strongly positive
- In HIV :>5 is considered positive
- It's a misconception that larger tuberculin test are more likely indicates active disease
- Less than 5 mm : no infection
- While moe than 5 mm cannot judge wheather it is active, inactive, recent or remote infection
- **False positive :** Non tubercular mycobacterial antigens & BCG vaccination
- **False negative :**
  - **Viral infections in general, including:**
    - **–Upper respiratory tract infections,**
    - **–Infectious mononucleosis**
    - **–Measles**
    - **–varicella**
    - **–Influenza**
    - **–HIV**
  - **Live viral vaccines**
  - **Sarcoidosis**
  - **Corticosteroid therapy**
  - **Immunosuppressiondue to disease or treatment including HIV infection.**
  - **Poor nutrition**
  - **Millary**

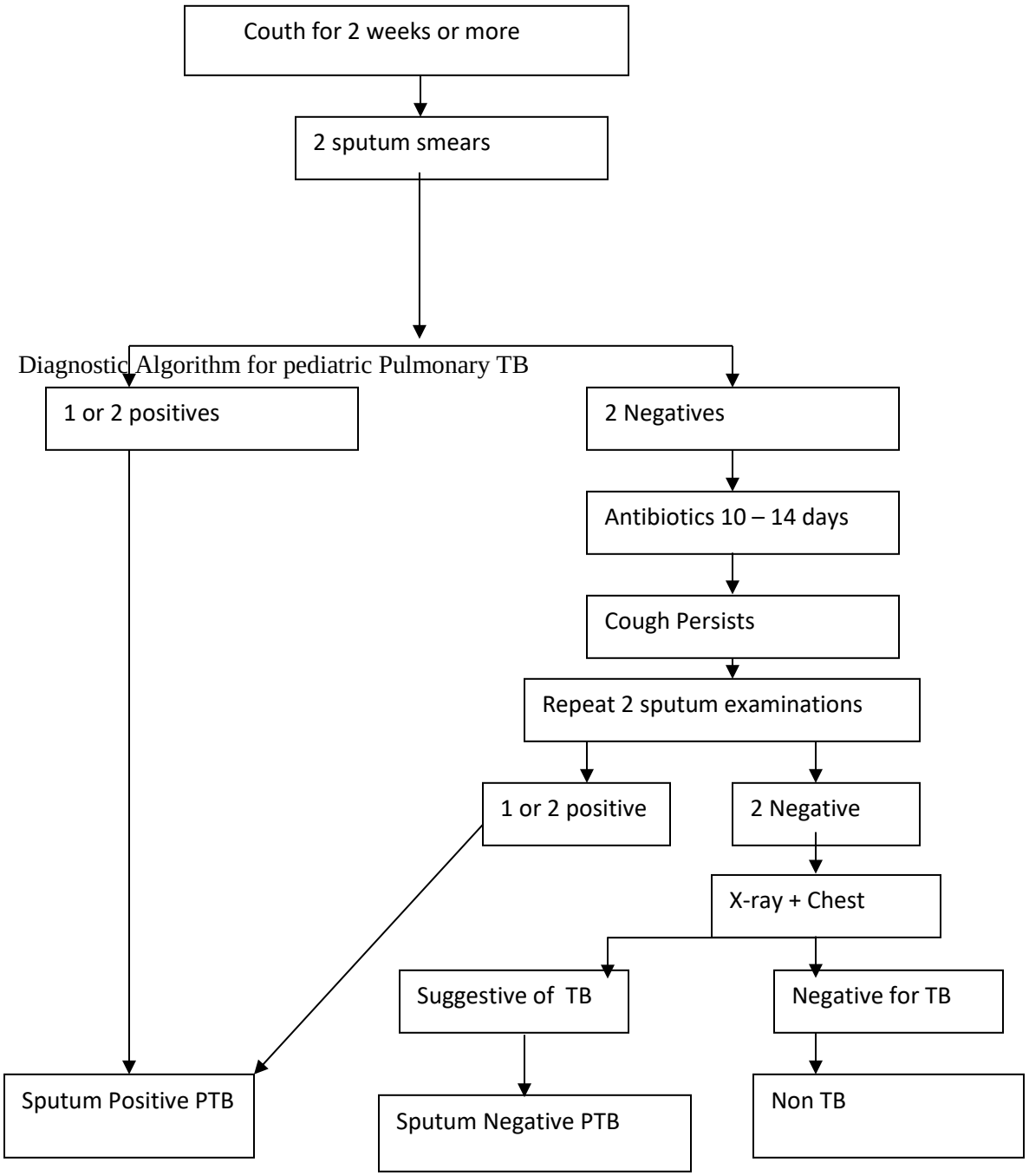
THERAPY & PROGNOSIS:

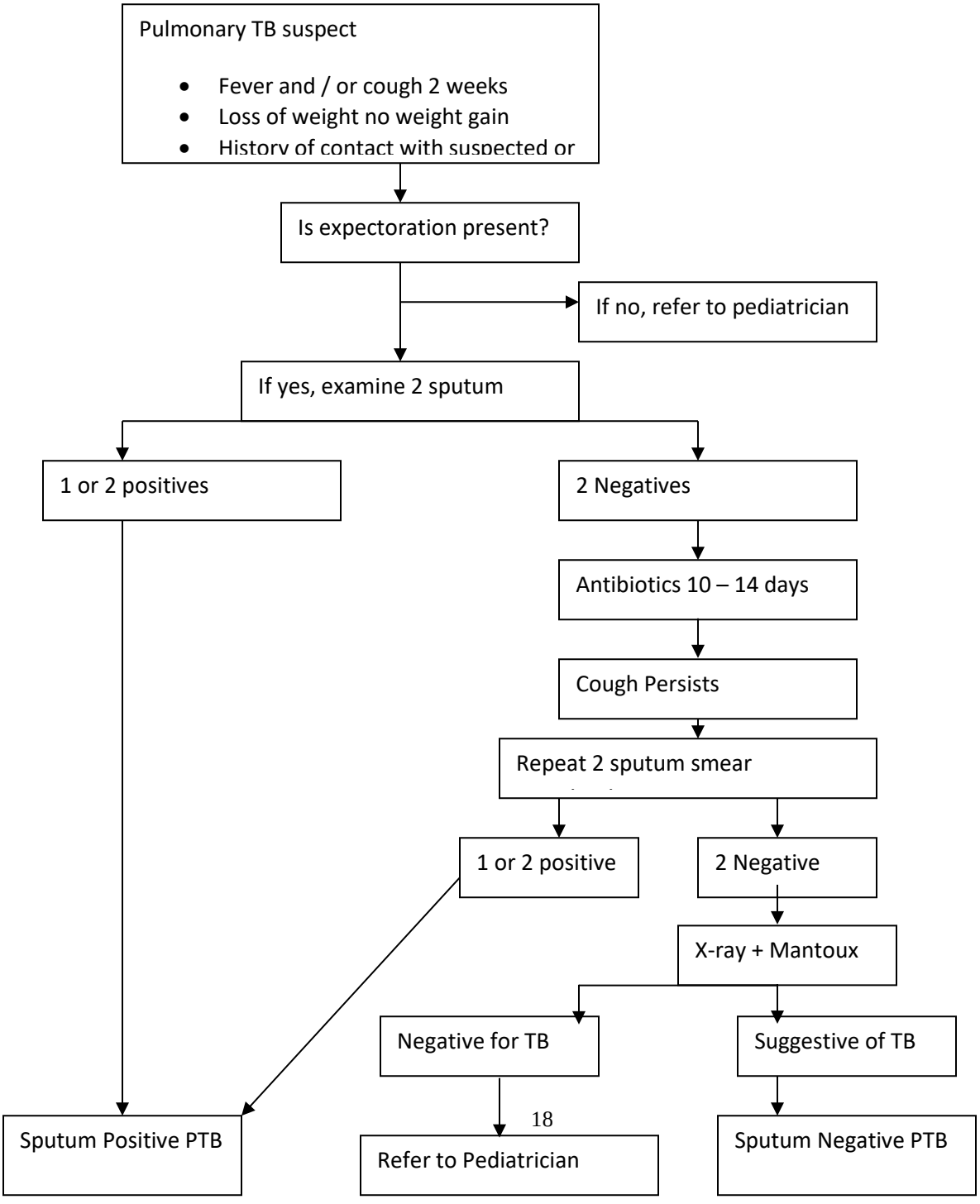
The standardized chemotherapy regimens used for treating tuberculosis are as effective among HIV-positive as among HIV-negative patients; however, the fatality rate is higher among HIV-positive patients because of AIDS-related complications.

Diagnostic Criteria for sputum smears –ve (PTB-ve) pulmonary TB.

- Atleast 2 sputum specimens negative for AFB (repeated twice)
- Radiogrophic abnormalities consistent with active TB
- No response to conrse of broad spectrum antibiotics
- Decision by a clinician to beat with a full course of ATT.

Diagnostic algorithms for pulmonary TB


Couth for 2 weeks or more
2 sputum smears
Diagnostic Algorithm for pediatric Pulmonary TB
1 or 2 positives
2 Negatives
Antibiotics 10 – 14 days
Cough Persists
Repeat 2 sputum examinations
1 or 2 positive
2 Negative
X-ray + Chest
Suggestive of TB
Negative for TB
Sputum Positive PTB
Sputum Negative PTB
Non TB


Pulmonary TB suspect
Fever and / or cough 2 weeks
Loss of weight no weight gain
History of contact with suspected or
Is expectoration present?
If no, refer to pediatrician
If yes, examine 2 sputum
1 or 2 positives
2 Negatives
Antibiotics 10 – 14 days
Cough Persists
Repeat 2 sputum smear
1 or 2 positive
2 Negative
X-ray + Mantoux
Negative for TB
Suggestive of TB
Sputum Positive PTB
Refer to Pediatrician
Sputum Negative PTB

DIFFERENTIAL DIAGNOSIS:

More than 95% of patients who present with chronic cough do not have tuberculosis.

- **Bronchiectasis**: Episodes of acute infection with abundant mucopurulent sputum. Clubbing +; Abundant chest findings +
- **Chronic bronchitis or chronic obstructive pulmonary disease**: the patient has had chronic cough and sputum production usually for many years. Seasonal exacerbations +; H/o smoking or exposure to smoke from biomass fuels.
- **Asthma** may present with chronic symptoms. **Episodic** breathlessness; Nocturnal; wheezing, chest tightness, cough; Reversible AO.

Other, less common conditions should also be considered in such cases:

- **Mitral stenosis** may present with episodes of breathlessness, accompanied by repeated light hemoptysis. Presence of the characteristic diastolic murmur can identify this condition.
- **Heart failure** with breathlessness disseminated pulmonary râles and edema in the legs.
- **Lung cancer** in men aged over 50 years with a long history of tobacco smoking presenting with cough, hemoptysis and sometimes-persistent chest pain.
- **Pneumoconiosis** in the case of long-term exposure to mineral dusts. Long duration of symptoms +
- **Aspergillus in old cavity:** chronic productive cough ± Hemoptysis; patients with chronic lung disease → TB, bronchiectasis, Sarcoidosis, histoplasmosis.

TREATMENT :

Five components of the DOTS strategy

1. Sustained political commitment.
2. Access to quality-assured sputum microscopy.
3. Standardized short-course chemotherapy for all cases of TB under proper case management conditions, including direct observation of treatment.
4. Uninterrupted supply of quality-assured drugs.
5. Recording and reporting system enabling outcome assessment of all patients and assessment of overall programme performance

Definitions

• **New**. A patient who has never had treatment for TB or who has taken antituberculosis drugs for less than 1 month.

• **Relapse**. A patient previously treated for TB who has been declared cured or treatment completed, and is diagnosed with bacteriologically positive (smear or culture) tuberculosis.

• **Failure**: sputum smear-positive after 5 months or more of treatment (or after 2 months or more of treatment if initially sputum smear-negative);
(With short-course treatment regimens of high efficacy, smears can be positive at 2–3 months because of dead bacilli in patients with negative cultures. Thus, treatment failure based on positive smear examination is not considered until the fifth month or later.)
• **Treatment after default.** A patient who returns to treatment, **positive bacteriologically**, following interruption of treatment for **2 months** or more.
• **Transfer in.** A patient who has been transferred from another TB register to continue treatment.
• **Chronic case:** a patient who is sputum-positive at the end of a re-treatment regimen.
• **Cured**: a patient who is sputum smear-negative in the last month of treatment and on at least one previous occasion during treatment;
• **Treatment completed**: a patient who completed treatment but does not meet the criteria for cure or failure (or after 2 months or more of treatment if initially sputum smear-negative);
• **Treatment success** is defined as the sum of the patients who are cured and who have completed treatment.

TARGETS OF 'DOTS'

Global targets of detecting 70% of infectious cases and curing 85% of those detected.

CATEGORIES OF DIAGNOSIS & TREATMENT

Recent changes in RNTCP(salient points):

1.Now only 2 categories are included,third one is removed.....ie.CAT I and CAT II
CAT I : New cases irrespective if their status
CAT II : Previously Treated case with Treatment Failure

New* CAT-I	**Previously treated** CAT-II**
• New sputum smear-positive, • New sputum smear-negative, • New extrapulmonary tuberculosis, • New others	• Sputum smear-positive relapse, • Sputum smear-positive failure, • Sputum smear-positive treatment after default, • others#
$2\mathbf{H}_3\mathbf{R}_3\mathbf{Z}_3\mathbf{E}_3 + 4\mathbf{H}_3\mathbf{R}_3$	$2\mathbf{H}_3\mathbf{R}_3\mathbf{Z}_3\mathbf{E}_3\mathbf{S}_3 + 1\mathbf{H}_3\mathbf{R}_3\mathbf{Z}_3\mathbf{E}_3 + 5\mathbf{H}_3\mathbf{R}_3\mathbf{E}_3$
2 months Intensive phase + 4 months continuation phase	3 months Intensive phase + 5 months continuation phase

Four drugs at Thrice-weekly Schedule for 2 months Intensive phase & Two drugs at Thrice-Weekly Schedule for remaining 4 months continuation phase.	Five drugs at Thrice-weekly Schedule for initial 2 months followed by Four drugs for next 1 month Intensive phase.Three drugs at Thrice-weekly Schedule for remaining 5 months continuation phase.

H: Isoniazid (600 mg), R: Rifampicin (450 mg), Z: Pyrazinamide (1500 mg), E: Ethambutol (1200 mg), S: Streptomycin (750 mg)

1. Patients who weigh 60kg or more receive additional Rifampicin 150mg.
2. Patients who are more than 50 years old receive Streptomycin 500mg. Patients who weigh less than 30kg receive drugs as per Pediatric weight band boxes according to body weight.

Notes:

*****New categories includes former Categories I & III

******Previously treated is former Category II

Others include patients who are Sputum Smear-Negative or who have Extra-pulmonary disease who can have recurrence or resonance.

2. Sputum samples collected are only "2"

- **If one of two samples is positive then it is sputum smear positive**

3. Change in TB Suspect Definition Among HIV-infected Individuals:
   - cough for 2 weeks alone is not a sensitive indicator of TB among HIV-infected people
   - A combination of 4 symptoms will be used for screening – "**Any cough, any fever, night sweats and weight loss**".
   - It has been decided that chest radiography may be used upfront along with sputum microscopy among chest symptomatics without having to recourse to antibiotic trial

4. Protease inhibitor (PIs)cannot be used with rifampicin-containing regimens due to hepatic enzyme inducing capacity of rifampicin rendering PI levels sub-therapeutic. Therefore NACP and RNTCP
have recommended the substitution of Rifabutin (which is equally effective but not affected by drug drug
interactions) for rifampicin for the duration

of TB treatment

5.XDR TB includes resistance to INH+Rifampicin+Injectables Amino glycosides+Flouroquinolones

DOTS-Plus refers to DOTS programmes that add components for MDR-TB diagnosis, management and treatment. These guidelines promote full integration of DOTS and DOTS-Plus activities under the RNTCP, so that patients with MDR-TB are both correctly identified and properly managed under the recommendations set out in this document

Table 7.1 Alternative method of grouping anti-TB agents

Grouping	Drugs
Group 1: First-line oral anti-TB agents	Isoniazid (H); Rifampicin (R); Ethambutol (E); Pyrazinamide (Z)
Group 2: Injectable anti-TB agents	Streptomycin (S); Kanamycin (Km); Amikacin (Am); Capreomycin (Cm); Viomycin (Vm).
Group 3: Fluoroquinolones	Ciprofloxacin (Cfx); Ofloxacin (Ofx); Levofloxacin (Lvx); Moxifloxacin (Mfx); Gatifloxacin (Gfx)
Group 4: Oral second-line anti-TB agents	Ethionamide (Eto); Prothionamide (Pto); Cycloserine (Cs); Terizadone (Trd); *para*-aminosalicylic acid (PAS)
Group 5: Agents with unclear efficacy (not recommended by WHO for routine use in MDR-TB patients)	Clofazimine (Cfz); Linezolid (Lzd); Amoxicillin/Clavulanate (Amx/Clv); thioacetazone (Thz); imipenem/cilastatin (Ipm/Cln); high-dose isoniazid (high-dose H); Clarithromycin (Clr)

7.4.1 Category IV regimen

RNTCP will be using a **Standardised Treatment Regimen** (Cat IV) for the treatment of MDR-TB cases (and those with rifampicin resistance) under the programme. Cat IV regimen comprises of 6 drugs- kanamycin, ofloxacin (levofloxacin)[†], ethionamide, pyrazinamide, ethambutol and cycloserine during 6-9 months of the Intensive Phase and 4 drugs- ofloxacin (levofloxacin), ethionamide, ethambutol and cycloserine during the 18 months of the Continuation Phase. *p*-aminosalicylic acid (PAS) is included in the regimen as a substitute drug if any bactericidal drug (K, Ofl, Z and Eto) or 2 bacteriostatic (E and Cs) drugs are not tolerated.

RNTCP CATEGORY IV REGIMEN: 6 (9) Km Ofx (Lvx) Eto Cs Z E / 18 Ofx (Lvx)Eto Cs E

Treatment regimens in special situations:

Pregnancy :-

a. The 6-month regimen based on H, R & Z should be used whenever possible.

b. **S is c/I:** can cause both oto- & nephrotoxicity

Breastfeeding :-

- A breastfeeding woman who has TB should receive a full course of TB treatment.
- The best way to prevent transmission of tubercle bacilli to the baby: Timely and properly applied chemotherapy.
- All antituberculosis drugs are compatible with breastfeeding; a woman taking them can safely continue to breastfeed.
- Mother and baby should stay together and the baby continue to be breastfed in the normal way.
- The baby should be given prophylactic isoniazid for at least 3 months beyond the time the mother is considered to be non-infectious. BCG vaccination of the newborn should be postponed until the end of isoniazid prophylaxis.

Oral contraception :-

- Rifampicin interacts with oral contraceptive medications with a risk of decreased protective efficacy against pregnancy. A woman receiving oral contraception may choose between two options while receiving treatment with rifampicin:
- The patient may use an oral contraceptive pill containing a higher dose of estrogen (50 μg).
- Alternatively, a nonhormonal method of contraception may be used throughout rifampicin treatment and for at least one month subsequently.

Liver disorders :-

✓ Isoniazid, rifampicin and pyrazinamide are all associated with hepatitis.

✓ Of the three drugs, rifampicin is least likely to cause hepatocellular damage, although it is associated with cholestatic jaundice.

✓ Of the three agents, pyrazinamide is the most hepatotoxic.

✓ Patients with the following conditions can receive the usual short-course chemotherapy regimens provided there is no clinical evidence of chronic liver disease - hepatitis virus carriage, a past history of acute hepatitis, excessive alcohol consumption.
(However, hepatotoxic reactions to antituberculosis drugs may be more common among these patients and should therefore be anticipated.)

Established chronic liver disease :-

- Patients with liver disease should not receive pyrazinamide.
- Recommended regimens are:

a) 2 SHRE/6 HR
b) 9 RE or
c) 2 SHE/10 HE.

- **Action of the various first-line anti-tuberculosis drugs :**

Anti-tuberculosis drugs act on different bacillary populations in a patient with tuberculosis:
Metabolically active bacilli that replicate constantly and rapidly. These populations are found principally inside lung cavities.

Slowly replicating (semi-dormant) bacilli, situated inside the macrophages. Their multiplication is slowed down by the lack of oxygen and the acid pH of the macrophage cytoplasm.

Dormant or persistent bacilli, which replicate in the tissues **very slowly and episodically**, are metabolically inactive. However, they are still alive, and can start to multiply once again as soon as the immune defense system weakens.

The actions of the different drugs vary depending on their bactericidal or sterilizing effect on these various bacillary populations.

- **The two most effective bactericidal drugs** are **isoniazid (H)** and **rifampicin (R)**, which act not only against the metabolically active bacteria that multiply constantly and rapidly, but also against the semi-dormant bacilli that multiply slowly in the macrophages. Another advantage of rifampicin is that it acts at a very early stage of bacillary multiplication.
- **Two other bactericidal anti-tuberculosis drugs** of medium efficacy and complementary action are **pyrazinamide (Z)**, which destroys intracellular bacteria that live in an acid environment, and **streptomycin (S)**, which is active only against extracellular bacteria as it cannot penetrate the cell membrane.
- **Two other bacteriostatic antibiotics**, which are much less effective, are **ethambutol (E)** and **thioacetazone (T).** They are used in conjunction with powerful bactericidal drugs to prevent the emergence of resistant bacilli.

  The only medications that destroy persistent bacilli and have a **sterilizing action** are **rifampicin** and **pyrazinamide**. These medications are always used in short-course chemotherapy.

Drug	**Route**	**Dose in mg/kg *(Maximum Dose)***						**Adverse Reactions**	**Monitoring**	**Monitoring Comments**
		Daily		**2 Times/Week***		**3 Times/Week***				
		Children	**Adults**	**Children**	**Adults**	**Children**	**Adults**			
INH	**PO or IM**	**10 - 20** ***(300 mg)***	**5** ***(300 mg)***	**20 - 40** ***(900 mg)***	**15** ***(900 mg)***	**20 - 40** ***(900 mg)***	**15** ***(900 mg)***	**Rash Hepatic enzyme elevation Hepatitis Peripheral neuropathy Mild CNS effects Drug interactions resulting**	**Baseline measurements of hepatic enzymes for adults Repeat measurements if - baseline results are abnorma**	**Hepatitis risk increases with age and alcohol consumption Pyridoxine (Vitamin B6) may prevent peripheral**

								in increased phenytoin (Dilantin) or disulfiram (Antabuse) levels	**l - patient is at high risk for adverse reactions - patient has symptoms of adverse reactions**	**neuropathy and CNS effects 10-15 mg/kg should be used for children when treating for latent TB infection**
R I F	**PO or IV**	**10 - 20** ***(600 mg)***	**10** ***(600 mg)***	**10 - 20** ***(600 mg)***	**10** ***(600 mg)***	**10 - 20** ***(600 mg)***	**10** ***(600 mg)***	**GI upset Drug interactions Hepatitis Bleeding problems Flu-like symptoms Rash Renal failure Fever**	**Baseline measurements of CBC, platelets, and hepatic enzymes Repeat measurements if - baseline results are abnormal - patient has symptoms of adverse reactions**	**Significant interactions with methadone, birth control hormones, and many other drugs Contraindicated or should be used with caution when administered with PIs and NNRTIs Colors body fluids orange May permane**

										ntly discolor soft contact lenses
R F B †	**PO or IV**	**10-20 *(300 mg)* or *(150 mg)* § or *(450 mg)***	**5 *(300 mg)* or *(150 mg)*§ or *(450 mg)***	**10 - 20 *(300 mg)* or 10 - 20 *(300 mg)* or *(450 mg)***	**5 *(300 mg)* or 5§ (300 mg) or *(450 mg)***	**Not Known Not Known Not Known**	**Not Known Not Known Not Known**	**Rash Hepatitis Fever Thrombocytopenia With increased levels of RFB: - Severe arthralgias - Uveitis - Leukopenia**	**Baseline measurements of CBC, platelets, and hepatic enzymes Repeat measurements if - baseline results are abnormal - patient has symptoms of adverse reactions Use adjusted daily dose of RFB§, and monitor for decreased antiretroviral activity and for RFB toxicity if RFB taken concurre**	**Reduces levels of many drugs (e.g., PIs, NNRTIs, methadone, dapsone, ketoconazole, hormonal contraceptives, etc.) Colors body fluids orange May permanently discolor soft contact lenses**

									ntly with PIs or NNRTIs	
P Z A	**PO**	**15 - 20 *(2 g)***	**15 - 30 *(2 g)***	**50 - 70 *(4 g)***	**50 - 70 *(4 g)***	**50 - 70 *(3 g)***	**50 - 70 *(3 g)***	**Hepatitis Rash GI upset Joint aches Hyperuricemia Gout (rare)**	**Baseline measurements of uric acid and hepatic enzymes Repeat measurements if - baseline results are abnormal - patient has symptoms of adverse reactions**	**Treat hyperuricemia only if patient has symptoms May make glucose control more difficult in diabetics**
E M B #	**PO**	**15 - 25**	**15 - 25**	**50**	**50**	**25 - 30**	**25 - 30**	**Optic neuritis Rash**	**Baseline and monthly tests of visual acuity and color vision**	**Not recommended for children too young to be monitored for changes in vision unless TB is drug resistant Optic neuritis may be unilateral, check each eye**

										separately
SM	**IM or IV**	**20 - 40 *(1 g)***	**15 *(1 g)***	**25 - 30 *(1.5 g)***	**25 - 30 *(1 .5 g)***	**25 - 30 *(1 .5 g)***	**25 - 30 *(1.5 g)***	**Ototoxicity (hearing loss or vestibular dysfunction) Renal toxicity**	**Baseline and repeat as needed of hearing and renal function tests**	**Ultrasound and warm compresses to injection site may reduce pain Avoid or reduce dose in adults 60 years old**

INH - isoniazid, RIF - rifampin, RFB - rifabutin, PZA - pyrazinamide, EMB - ethambutol, SM - streptomycin, PIs - Protease Inhibitors, NNRTIs - nonnucleoside reverse transcriptase inhibitors
PO - by mouth, IM - intramuscular, IV - intravenous, CNS - central nervous system
Notes: Consult product insert for detailed information.
Children 12 years old.
Adjust weight-based dosages as weight changes.

INDIVIDUAL DRUGS

LAND MARK YEARS

- STREPTOMYCIN : 1947
- INH : 1952
- ETHAMBUTAMOL : 1961
- RCIN : 1962

1. INH:

- MOA: Inhibition of mycolic acid cell wall synthesis via O_2 dependent pathways e.g. Catalase-peroxidase reaction
- Bactericidal against rapidly multiplying & bacteriostatic against resting bacilli
- Active against both extracellular & intracellular organisms
- Mech. of resistance: Mutation in katG or inhA
- No cross-resistance with other drugs
- Resistance occurs spontaneously in 1 in 10^5 bacilli
- Excreted in urine: Decrease dose if CCr < 30 ml/min
- Slow vs. Rapid Acetylators ($t_{1/2}$)
- ADVERSE EFFECTS:

1.Peripheral Neuropathy: commoner in slow acetylators, diabetics, alcoholics, malnourished patients;

- Prevention: Pyridoxine 10 mg/d
- Indications: Patients at risk of peripheral neuropathy, (malnutrition, chronic alcohol dependence or diabetes), should additionally receive pyridoxine, 10 mg daily.

- *Where the standard of health in the community is low, this should be offered routinely.*
- T/t: 100 mg/d
- Convulsions: IV pyridoxine 100 mg
- *Other TB-related drugs that cause PNP: Pyridoxine, E, and Cycloserine

2.Hepatitis:

- Idiosyncratic reaction (10% develop LEE; 1% develop hepatitis)
  - A sharp rise in serum concentrations of hepatic transaminases at the outset of treatment is not of clinical significance, and usually resolves spontaneously during continuation of treatment.
- Due to ACETYLHYDRAZINE
- Increased risk: Age > 35y, alcohol abuse, co-administration of R/Z, HIV infection, chronic Hepatitis B, pregnant females, immediate postpartum (3 mo.)

3.Others: SLE, acne, rash, anemia, psychosis, memory impairment, optic neuritis (→atrophy)

** Isoniazid alone is occasionally used to prevent:*

- Transmission to close contacts at high risk of disease;
- Progression of infection to primary complex in recently infected, asymptomatic individuals;
- Development of active TB in immunodeficient individuals.

2. <u>RIFAMPICIN</u>

- (Derived from Streptomyces mediterranei)
- MOA: Inhibition of β-subunit of DNA-dependent RNA polymerase → inhibit RNA synth
- Bactericidal against both extracellular & intracellular organisms
- Mech. of resistance: Mutation that alters the β-subunit of DNA-dependent RNA polymerase gene (rpoV)
- No cross-resistance with other drugs except with Rifapentine

<u>**Rifabutin*</u>: Active against rifampicin-resistant M. tuberculosis; more active than R'cin against NTM; longer $t_{1/2}$; extent of absorption unchanged with food; recommended instead of R'cin in patients on PIs

<u>**Rifapentine*</u>: Higher likelihood of relapse, but lower risk of A/E's & less frequent administration than with R'cin

-<u>ADVERSE EFFECTS:</u>

1. MC: gastrointestinal reactions
2. Most serious: Hepatitis

- Dose-related

3. Rash
4. Poisoning 'RED MAN' syndrome
5. Immunological reactions: Thrombocytopenic purpura, shock, renal failure (azotemia)

- WITHDRAW & NEVER RE-CHALLENGE

6. Pseudomembranous colitis (esp. Rifabutin)
7. 'Flu' syndrome
8. Exfoliative dermatitis is more frequent in HIV-positive TB patients.
9. Adverse effects more common with intermittent administration:

- Influenza-like syndrome, skin rashes, thrombocytopenia, temporary oliguria, dyspnea and hemolytic anemia. These reactions usually subside if the regimen is changed to one with daily dosage.

*Peculiar s/e's of Clarithromycin + Rifabutin combination: (used for NTM)

- Anterior uveitis
- Hyperpigmentation
- Polymyalgia / Arthralgia

*Potent inducer of Cyt P450 system

- OCPs, Digoxin, corticosteroids, oral hypoglycemic agents, oral anticoagulants, phenytoin, cimetidine, cyclosporine and digitalis glycosides

*Vitamin K should be administered at birth to the infant of a mother taking rifampicin because of the risk of postnatal hemorrhage.

3. PYRAZINAMIDE:

- MOA: *fasI* gene (inhibition of mycolic acid - cell wall – synthesis)
- Bactericidal to slowly metabolizing bacilli in phagosome / granuloma
- Most effective in acidic pH (<6.0)
- Prodrug: converted to active form, pyrazinoic acid, by……..
- Mech of resistance: Mutation in pncA gene → loss of pyrazinamidase activity

1. All strains of M. bovis are inherently resistant to Z
2. Z & H are active only against M. tuberculosis

-ADVERSE EFFECTS:

i.Hepatotoxicity: RARE: DO NOT RE-CHALLENGE

ii.Arthralgias

Polyarthralgias (esp. shoulders) are common; Hyperuricemia is common; Arthralgias are not related to the serum uric acid level; Development of new-onset gout is rare, but pre-existing gout may be exacerbated; Both Arthralgias and Hyperuricemia resolve with intermittent admin.

4. ETHAMBUTOL

-MOA: Inhibits

Arabinose (arabinosyltransferase) → Arabinogalactone Polymerization

-Bacteriostatic

-Excreted in urine (Dose reduction required for patients with CCr < 50 ml/min)

-No cross-resistance with other drugs

-ADVERSE EFFECTS:

i.Retrobulbar neuritis

- Dose-dependent (5% with 25 mg/kg; 1% with 15 mg/kg)
- Usually occurs after many months of t/t
- Involves papillo-macular bundle
- Manifests with: reduced visual acuity, central scotoma, disturbance of red-green discrimination (loss of ability to see green)
- OA & permanent blindness occur if E not discontinued
- Avoid in young children

ii.Others: Hyperuricemia, peripheral sensory neuropathy (esp. LL)

5. STREPTOMYCIN:

-(Derived from Streptomyces griseus)

-MOA:

-Bactericidal

-ADVERSE EFFECTS:

i.Ototoxicity

a. Vestibular damage

b. Deafness

* Dosage should be reduced if headache, vomiting, vertigo and tinnitus occur.
* Avoid in young children

ii. Renal damage (Non oliguric renal failure)

*Dosage must be reduced by half immediately if urinary output falls, if albuminuria occurs or if tubular casts are detected in the urine.

iii. Potentiate NM block (C/I in MG)

iv. Anaphylaxis: rare

v. Others: Hemolytic anemia, aplastic anemia, agranulocytosis, thrombocytopenia and lupoid reactions are rare adverse effects.

- DRUG INTERACTIONS

Do not co-administer other aminoglycosides, amphotericin B, cephalosporins, ethacrynic acid, cyclosporine, cisplatin, furosemide and vancomycin.

SECOND LINE ANTITUBERCULOUS DRUGS

Drug	**Route**	**Daily Dose**** ***(Maximum Dose)***	**Adverse reactions**	**Monitoring**	**Comments**
Capreomycin	IM or IV	15 - 30 mg/kg *(1 g)*	Toxicity - auditory - vestibular - renal	Assess vestibular function and hearing function prior to initiation of therapy and at regular intervals during treatment Measure blood urea nitrogen and creatinine throughout treatment	After bacteriologic conversion, dosage may be reduced to 2 -3 times per week Safety and effectiveness in children have not been established
Kanamycin	IM or IV	15 - 30 mg/kg *(1 g)*	Toxicity - auditory - vestibular - renal	Assess vestibular function and hearing function prior to	After bacteriologic conversion, dosage may be reduced to 2 -3 times per week

				initiation of therapy and at regular intervals during treatment Measure blood urea nitrogen and creatinine throughout treatment	Not approved by FDA for TB treatment
Amikacin	IM or IV	15 - 30 mg/kg *(1 g)*	Toxicity - auditory - vestibular - renal Chemical imbalance Dizziness	Assess vestibular function and hearing function prior to initiation of therapy and at regular intervals during treatment Measure renal function and serum drug levels	After bacteriologic conversion, dosage may be reduced to 2 -3 times per week Not approved by FDA for TB treatment
Ethionamide	PO	15 - 20 mg/kg *(1 g)*	GI upset Hepatotoxicity Hypersensitivity Metallic taste	Measure hepatic enzymes	Start with low dosage and increase as tolerated May cause hypothyroid condition, especially if used with PAS
Para-aminosalicylic acid (PAS)	PO	150 mg/kg (16 g)	GI upset Hypersensitivity Hepatotoxicity Sodium load	Measure hepatic enzymes Assess volume	Start with low dosage and increase as tolerated Monitor

				status	cardiac patients for sodium load May cause hypothyroid condition, especially if used with ethionamide
Cycloserine	PO	15 - 20 mg/kg (1 g)	Psychosis Convulsions Depression Headaches Rash Drug interactions	Assess mental status Measure serum drug levels	Start with low dosage and increase as tolerated Pyridoxine may decrease CNS effects
Ciprofloxacin	PO	750 - 1500 mg/day	GI upset Dizziness Hypersensitivity Drug interactions Headaches Restlessness	Drug interactions	Not approved by the FDA for TB treatment Should not be used in children Avoid coadministration within 2 hours of: - antacids - iron - zinc - sucralfate
Ofloxacin	PO	600 - 800 mg/day	GI upset Dizziness Hypersensitivity Drug interactions Headaches Restlessness	Drug interactions	Not approved by the FDA for TB treatment Should not be used in children Avoid coadministration within 2 hours of: - antacids - iron - zinc - sucralfate
Levofloxacin	PO	500 mg/day	GI upset Dizziness Hypersensitivity	Drug interactions	Not approved by the FDA for TB treatment Should not be

			Drug interactions Headaches Restlessness		used in children Avoid coadministration within 2 hours of: - antacids - iron - zinc - sucralfate

Fluoroquinolones :-

- Ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin and gatifloxacin are active against M. tuberculosis, even those resistant to other drugs. They are given orally or IV. They are useful in treating infections resistant to standard drugs and in cases with relapse.

Ethionamide :-

- Ethionamide is structurally related to INH and acts by inhibiting the mycolic acid synthesis. It is effective against bacilli resistant to other drugs and has proved effective in infections due to atypical mycobacteria. It is effective against intracellular as well as extracellular organisms.

Capreomycin :-

- It is bactericidal. Its mechanism of action, pharmacokinetics and adverse reactions are similar to those of streptomycin. It should be administered with caution in presence of renal impairment.

Kanamycin and Amikacin :-

- They are bactericidal and are active against bacilli resistant to streptomycin. INH and cycloserine.

Cycloserine :-

- The drug is mainly bacteriostatic. It is effective against bacilli resistant to INH or streptomycin and against atypical mycobacteria, although antitubercular activity is less than that of these two drugs. It acts by inhibiting the synthesis of the bacterial cell wall.

Macrolides :-

- Newer macrolides azithromycin and clarithromycin also have action against tubercular bacilli. They are used to treat atypical mycobacterial infection and cases with relapse.

Managing side effects of ATT

SIDE-EFFECT	DRUG RESPONSIBLE	MANAGEMENT
Pain in the joints	Pyrazinamide	Aspirin
Burning sensations in the feet	Isoniazid	Pyridoxine 100mg/day
Anorexia, nausea, abdominal pain	Rifampicin	Take with food
Itching, skin reaction	Thioacetazone or Streptomycin	Stop and do not give again (replace by ethambutol)

Itching, skin reaction	Rifampicin or isoniazid	Stop, then reintroduce with desensitization
Deafness or dizziness	Streptomycin	Stop and do not give again (replace by ethambutol)
Jaundice	Isoniazid, rifampicin, pyrazinamide	Stop until the jaundice disappears
Visual impairment	Ethambutol	Stop and do not give again
Purpura, shock, acute kidney failure	Rifampicin	Stop and do not give again

DRUG THERAPY

- ✓ The most powerful bactericidal drugs: H, R
- ✓ The most potent sterilizing drug: R
- ✓ Pyrazinamide is active only in an acid environment.
- ✓ Streptomycin is bactericidal against rapidly multiplying TB bacilli.

⏵ Infectious patients quickly become noninfectious (within approximately two weeks of therapy).

⏵ Most patients with sputum smear-positive TB become smear-negative within two months.

⏵ During the continuation phase, the sterilizing effect of the drugs eliminates the remaining bacilli and prevents subsequent relapse.

Intermittent use

Isoniazid, rifampicin, pyrazinamide and streptomycin are all as efficacious when given three times weekly as when given daily. Thioacetazone is the only antituberculosis drug that is ineffective when given intermittently. Ethambutol can be used intermittently only when Rifampicin is also being used.

SENSITIVITY TESTING :-

There are two types of susceptibility testing:

• **Indirect susceptibility testing** performed after obtaining colonies in culture before testing; the results are available only 2 to 3 months after sampling.

• **Direct susceptibility testing**, performed directly on the sample if it is rich in bacilli (i.e. if the smear made from the sample is strongly positive). In this case the results are available in 4–6 weeks.

TREATMENT OF MDR & CHRONIC CASES

- Definitions: MDR-TB bacilli are resistant to at least both of INH and rifampicin
- Chronic cases and MDR-TB cases are not synonymous.
- Chronic patients probably have MDR-TB because they have previously received at least two full courses of
  treatment with essential antituberculosis drugs.
- MDR-TB can rarely be observed in new cases; it is more frequent in re-treatment cases, especially in failure cases.
- *MDR-TB is a man-made phenomenon*
  - deficient or deteriorating TB control programmes resulting in inadequate administration of effective treatment

- poor case holding, administration of sub-standard drugs, inadequate or irregular drug supply and lack of supervision
- ignorance of health care workers in epidemiology, treatment and control
- improper prescription of regimens
- interruption of chemotherapy due to side effects
- non-adherence of patients to the prescribed drug therapy

- *XDR TB* : Resistance to atleast INH & RCIN + resistance to any fluoroquine & anyone of the 2nd line injectable (amika / kana / capreomycin).
- DOTS PLUS : administration of Second line drugs through RNTCP programme
- GREEN light committee
  - Concessiuonal 2nd line drugs from various pharma companies
- Full implementation of DOTS is the best prevention against chronic disease and extension of MDR-TB.
- Principles of treatment: by DOTS plus: Given daily
  - ***Intensive treatment***
    - ***Six months***
    - ***Min of five drugs***
    - ***One injectible necessary***
  - ***Continuation treatment***
    - ***18 months***
    - ***Four drugs***
    - ***All oral***

PREVENTION

- The BEST method of prevention: Identification & treatment of open cases
- ***BCG vaccination***

BCG vaccination confers partial immunity, essentially against the consequences of primary infection, and particularly against the acute forms of tuberculosis in children (disseminated tuberculosis and meningitis).

Indications for treatment with steroids :

- TB meningitis (decreased consciousness, neurological defects, or spinal block).
- TB pericarditis (with effusion or constriction).
- TB pleural effusion (when large with severe symptoms).
- Hypoadrenalism (TB of adrenal glands).
- TB laryngitis (with life-threatening airway obstruction).
- Severe hypersensitivity reactions to anti-TB drugs.
- Renal tract TB (to prevent ureteric scarring).
- Massive lymph node enlargement with pressure effects.

TB & HIV

IMPACT OF HIV ON TB :-

➢ HIV is the most powerful risk factor for progression from TB infection to TB disease. HIV infected persons who become newly infected by M. tuberculosis **rapidly progress** to active TB.

➢ ↑ predisposition to TB: An HIV positive person infected with M. tuberculosis has a 50% lifetime risk of developing TB whereas an HIV negative person infected with M. tuberculosis has only a 10% risk of developing TB.

➢ Unusual forms of TB common

IMPACT OF TB ON HIV:-

- TB shortens the survival of patients with HIV infection.
- TB may accelerate the progression of HIV, as observed by a six- to seven- fold increase in HIV viral load in TB patients.
- TB is the cause of death for one out of every three people with AIDS worldwide.

EARLY DISEASE (high CD4 count)	LATE DISEASE (low CD4 count)
1. Pulmonary disease more common	1. Extra pulmonary disease commoner than pulm.
2. Upper lobe	2. Lower lobe
3. Cavitation +	3. Cavitation -
4. Mediastinal LNs -	4. Mediastinal LNs +
5. Sputum positivity rate higher	5. Sputum usually negative

TREATMENT OF TB IN HIV POSITIVE PATIENTS:-

In general, anti-TB treatment is the same for HIV-infected and HIV-negative TB patients, with the exception of the use of **thiacetazone**. Thiacetazone causes severe cutaneous reactions. Exfoliative Dermatitis or Steven Johnson syndrome may occur and can be fatal.

➢ In place of TZN, use EMB in HIV +ve persons.

➢ HIV-infected smear-negative pulmonary TB patients may have a worse prognosis than HIV-positive patients with smear-positive pulmonary TB. Delays in the diagnosis of TB have been associated with worse outcomes

- **NARTIs can be safely co-administered with ATT.**
- **Rifampicin + PI → C/I**
- **Rifampicin + NNRTI → C/I**
- Rifamycins induce Cytochrome P-450 and may substantially decrease blood levels of the antiretroviral drugs resulting in the potential development of resistance. Rifabutin is a less potent Cytochrome-450 inducer than rifampicin and thus can be used concurrently with the NNRTIs (eg nevirapine, efavirenz) or with certain protease inhibitors (eg indinavir, nelfinavir).
- If protease inhibitor or non-nucleoside reverse transcriptase inhibitor is to be started after giving Rifampicin, then at least two weeks should elapse after the last dose of Rifampicin. This time gap is necessary for reduction of the enzyme inducing activity of Rifampicin prior to commencing of antiretroviral drugs.

- IRIS – Immune reconstitution inflammatory syndrome – Paradoxical reaction. On starting HAART, there is increase in sign & symptoms of tuberculosis. This is due to improving immune function.

Recent WHO Recommendations:

1. CD4 > 350 : give ATT first then srtart ART
2. CD4 350-200 : Start ART after initial phase of ATT
3. CD4 < 200 : Start ART as soon as ATT tolerated
4. Except for Ritonavir, PIs are not recommended during TB treatment with rifampicin due to their interactions with the latter drug.

Pleural tuberculosis :-

- MC form of EPTB in the developed world
- Due to rupture of subpleural caseous focus
- Gradually / rapidly progressive DOE
  - Usu. manifests in < 1 month (longer in HIV pts)
- Pleuritic chest pain, F/B nonproductive cough
- Constitutional s/s +, but not as prominent as in PTB; Commoner in HIV pts
- Occurs within the first months after primary infection,
- Not usu. accompanied by active pulmonary (parenchymal) tuberculosis: Coexisting Parenchymal disease in 20%

*If with parenchymal disease, a pleural effusion is present → INVARIABLY indicates ACTIVE disease

- The effusion is usually unilateral, more often on the right than on the left.
- A straw-colored / amber (yellow) liquid, an exudate showing a lymphocytosis (80–100% lymphocytes).

DIAGNOSIS of TB pleuritis :-

- Because the number of bacilli present is relatively small, acid-fast bacilli are usually not seen on microscopy of centrifuged specimens of pleural fluid

*Tubercular *empyema* is usually rich in AFB

- However, culture may be positive:
  - Pleural fluid culture +ve in 33%
  - Pleural biopsy culture +ve in 70%
- Fluid:
  - Exudative lymphocytosis
  - Mesothelial cells < 5%
  - High protein (>5 gm/dl)
  - ADA ↑ (>70)
    - ADA-2 more specific than ADA-1
    - ADA also raised in Rheumatoid pleuritis, Empyema, malignancy
  - IFNγ ↑ (>140)
  - Lysozyme levels ↑ (also raised in malignant pl eff)

***Tuberculous lymphadenitis* :-**

- Most frequently affects the lymph nodes in the neck.
- Occurs relatively early after primary infection
- Often affects young people in countries with a high prevalence of tuberculosis.
- Jones & Campbell staging
    - Stage 1: Discrete, mobile nodes
    - Stage 2: Matted LNs
    - Stage 3: Slightly fluctuant (Caseation in centre)
    - Stage 4: Collar-stud abscess
    - Stage 5: Sinus tract

- Systemic symptoms limited to HIV +ve patients
- MC form of EPTB in immunocompetent individuals & also in HIV infection
- Scrofuloderma: Tuberculous LN that tracks percutaneously by a fistulous tract
- The tuberculin skin test is usually significant.
- Diagnosis may be confirmed by aspiration or biopsy of the most enlarged lymph node.
- ***Granulomas are usually absent in HIV patients.***

PNEUMONIA

- Pathological definition: infection of the alveoli, distal airway, interstitium of the lung. Characterized by increased wt, replacement of the normal sponginess by the consolidation Alveoli filled by the WBC, RBC & fibrin

- Clinical definition– constellation of symptoms & signs (fever, chills, cough, pleural chest pain, sputum, BBS, egophony, crackles, wheeze, pleural friction rub) with at least one opacity on CXR PA view.

CLASSIFICATION of pneumonias

- CAP / HAP: Clinically most useful classification
- Bronchopneumonia / Lobar pneumonia
- Typical / Atypical pneumonias
- Infective/ Non infective pneumonia

Non-infective pneumonias:

1. LIPOID PNEUMONIA:

- Aspiration of fatty / oily material into lungs
- Decreasing order of severity of manifestations: Mineral oil > Animal oil > Vegetable oil
    - (b/c veg, & to some extent, animal oils can be hydrolyzed in the body)
- Liquid paraffin causes the most cases of lipoid pneumonia
    - Chronic persistence of the oil in the lung can produce fibrosis / paraffinomas (paraffin granulomas)

2. RADIATION PNEUMONITIS

- *Dose > 25 Gy*
- Risk ∞ 1. Radiation dose
  2. Volume of lung irradiated

- Early phase: cough, fever, CXR infiltrate
- Late phase: (3-6 weeks): Dyspnea
- Lung Fibrosis: with excessive dose / large lung volume irradiation
- Treatment: Glucocorticoids → improve symptoms, but have no ultimate effect on the development of fibrosis

***Recall pneumonitis**: Pneumonitis due to chemotherapy, within the distribution of a previous radiotherapy field (the radiation sensitizes the lung tissue to the toxic effects of chemotherapy)

3. CHEMICAL PNEUMONITIS

- If Aspirated fluid: pH < 2.5 & volume > 0.3 ml/kg → Chemical pneumonia → ARDS / secondary bacterial infection
- If Gastric pH alkaline: colonization of gastric mucosa by EGNB → pneumonitis
- Poor oro-dental hygiene with gross aspiration → Lung abscess

Pathogenesis

MC mechanism by which pathogenic organisms reach the LRT: Micro-aspiration
Others: hematogenous / inhalation (droplet nuclei / aerosols) / contiguous spread

ATYPICAL PNEUMONIAS

- Causes: L. pneumophila, C. pneumoniae, C. psittaci, M. pneumoniae, C. burnettii, viruses (influenza, adeno, RSV, measles, VZV, CMV)
- Evolve much more slowly than bacterial pneumonias
- SYMPTOMS>>SIGNS
    - DRY cough
    - Chest examination → very few signs (Signs of pulmonary consolidation usually lacking)
    - Well-defined radiographic infiltrate +
        - Radio infiltrate: Atypical → interstitial; Typical → Alveolar
    - Prominence of extra-pulmonary symptoms
    - No leukocytosis

S/S of pneumonia:

1. Cough & sputum production: reflect bacterial proliferation & resulting inflammatory response in the alveoli
2. Fever
3. Infiltrate on CXR
4. Physical findings:
    - Tachypnea
    - Cyanosis ±
        - ➢ Hypoxemia is because of R→L shunt
    - Dullness to percussion
    - ↑ TVF
    - Auscultatory signs: WP, Bronchophony, BBS; Inspiratory crackles

Mortality Rate: Max for Pseudomonas (50%) > Kleb = E.coli = Staph = Acinetobacter (30%)

CXR patterns:

1. Lobar pneumonia: Pneumococcal, Klebsiella, Legionella

2. Bronchopneumonia: 'SHIPS': Staph, H. influenzae, Pseudomonas, Streptococcus
3. Miliary pneumonia: (1-2 mm shadows): TB, Histoplasma, Coccidiodomycosis, Herpes, CMV, VZV

Non-infective causes: Pneumoconiosis / Pulmonary hemosiderosis / Histiocytosis X / Primary Amyloidosis

4. Interstitial infiltrate: PCP, TB, Mycoplasma, Viral pneumonias (Most atypical pneumonias)
5. Non-resolving pneumonia: Immune deficiency, Inappropriate antibiotic, Legionella, Neoplasm

(Pneumonia with a slow resolution of radiographic infiltrate or clinical symptoms despite adequate antibiotic

treatment (generally 10 to 14 days) due to defects in immune defense mechanisms or the presence of unusual

organisms, resistant bacteria, or diseases that mimic pneumonia)

6. Cavitating pneumonia:
   A) Infective: Anaerobes, Staph, Kleb, EGNB, Type 3 Pneumococcus, Pseudomonas, TB, Histoplasma, Blastomycosis, Coccidiodomycosis
   B) Non-infective: Wegener's, Infarction, Neoplasms

Pneumonia patient outcome research team criteria

- Criteria for Admission
- < 70 → OPD; 71-90 → Observe & Individualize; > 90 → IPD

Single most useful clinical sign of severity of pneumonia: **Respiratory rate**

Table 1. Pneumonia severity index (PSI) scoring

Patient Characteristics	Points
Demographics	
Age(years): Male: age	—
Female: age	—
Nursing home resident	+10
Co-morbidities	
Neoplastic disease	+30
Liver disease	+20
Congestive heart failure	+10
Cerebrovascular disease	+10
Renal disease	+10
Examination findings	
Altered mental status	+20
Respiratory rate ³30/minute	+20
Systolic blood pressure <90 mmHg	+20
Temperature <35°C or ³40°C	+15
Pulse ³125/minute	+10
Laboratory findings	
pH <7.35 (do ABG only if hypoxic or COPD)	+30
BUN >10.7 mmol/ L	+20
Sodium <130 mEq/L	+20
Glucose ³13.9 mmol/L	+10
Hematocrit <0.30	+10
PaO_2 <60mmHg or oxygen saturation <90%	+10
Pleural effusion	+30

Risk	Class	Score
Low	I	<51
Low	II	51 - 70
Low	III	71 - 90
Medium	IV	90 - 130
High	V	>130

Hospitalisation is recommended for class IV and V. Class III is based on clinical judgement

Other predictors of severe pneumonia:
'Severe' pneumonia: pneumonia requiring admission to ICU
BTS scale:

Table 2. CURB-65 criteria scoring

Confusion
Blood urea >7 mmol/L at the time of admission.
Respiratory Rate of ≥30/minute
Systolic BP ≤90 mmHg or diastolic BP ≤60mmHg
Age ≥65 years

A score of 1 is given for presence of each of the variables
BP=Blood pressure

ATS: Need for mechanical ventilation, PaO_2 / FiO_2 ratio < 250, multilobar disease, need for vasopressor therapy > 4 hours

PFT

- Restrictive defect
- Greater volume loss with bronchopneumonia (compared to lobar pneumonia)

PNEUMOCOCCAL PNEUMONIA

- Streptococcus pneumoniae, Diplococcus pneumoniae
- MC cause of CAP, Serotype III is most virulent
  **Top 4 causes of CAP: Pneumococcus, H. influenzae, C. pneumoniae, L. pneumophila
  **Strongest independent risk factor for CAP: Alcoholism

Microbiology: GPC, pairs / chains, catalase –ve, α hemolytic, optochin sensitive, bile soluble

***Risk Factors for Penumococcal pneumonia* :**

- Extremes of age
- Influenza / other respiratory viral infection } Mucosal edema & ↓ ciliary action
- Allergies, air pollution, cigarette smoking, COPD
- HIV infection; Alcoholism; Malnutrition
- Multiple Myeloma, IgG deficiency disorders (lack of anti-capsular antibodies)
- Splenectomy (whether iatrogenic / asplenia / sickle cell disease)
  - Disease has the most fulminating course in these patients

Immunity to pneumococci: Humoral (ANTICAPSULAR ANTIBODY)
Strongest independent risk factor for invasive pneumococcal disease: Cigarette smoking

- Other risk factors for invasive pneumococcal disease: Passive smoking, Male gender, chronic illness

Clinical Features: Indistinguishable from other pneumonias. Rusty brown sputum
- Herpes labialis is common
CXR: MC pattern – multilobar disease ± air bronchogram

MC complication: Empyema, Pleural effusion, lung abscess, DIC.
DOC - β lactam or Macrolide
ALCOHOLISM & PNEUMONIAS

- Alcoholism predisposes to pneumonia because of ↑ risk of aspiration and ↓ mucociliary clearance
- Organisms: Pneumococci, Anaerobes, Kleb, EGNB
- ALPS: Alcoholism, Leucopenia, Pneumococcal sepsis; mortality rate 80%
- Independent risk factor for ARDS
- Higher rate of empyema
- Longer courses of parenteral antibiotics

LEGIONELLOSIS

- Pontiac fever: Acute self-limiting febrile illness
- Legionnaire's disease: Pneumonia
- MC species causing human infections: L. pneumophila
- MC serogroup causing CAP: 1
- MC serogroup causing nosocomial pneumonia: 6
- Aerobic, Gram –ve; BCYE medium
- Source: Water (esp. potable water), AC plants
- Risk factors: smoking, chronic lung disease, **advanced age**, immunosuppression, surgery, **organ transplant**, alcoholism, **HIV**
  ***Neutropenic patients are not predisposed*
- Immunity to Legionellosis: CMI (intracellular)

Clinical Features:

- minimally productive cough
- chest pain
- ***abdominal complaints: pain, nausea, vomiting, diarrhea***
- ***Confusion***
- High fever
- ***Hyponatremia*; hematuria, SIADH**
- ***Relative brodycardia***

CXR: Not diagnostic; lobar / multilobar infiltrate; Incomplete & delayed clearing; persistent fibrosis ±

DIAGNOSIS:
Culture: Definitive method; requires 3-5 days; most sensitive method
Gram stain: Many PMN's, No organisms → SUGGESTIVE (usual picture with all atypical pneumonias)
*False +ve AFB stain: L. micdadei: aka Pittsburgh pneumonia agent

- DFA (direct fluorescent antibody) test: both sensitive & specific
  - Antibody: 4-fold rise in titer from acute to convalescent stage is diagnostic;

- Serology has only epidemiologic significance
- Urinary antigen: 2nd to culture in terms of both sensitivity and specificity

TREATMENT:

Drugs of choice are –

1. Macrolide + Rifampicin
2. Azithromycin: initial DOC for uncomplicated diseases
3. Quinolones: Faster response & fewer side-effects
   Esp. useful for transplant patients & HIV positive pts

MYCOPLASMA

- Smallest free-living organism
- Aka Eaton agent / PPLO
- Neither virus (able to grow & multiply extracellularly)
- Nor bacteria {Lack cell wall (resistant to penicillins, cephalosporins& all other cell-wall active agents)}
- Maximum cases in 5-20 y olds (most commonly causes URI, tracheobronchitis; less commonly causes pneumonia)
- Infections are more serious in older children & adults
- Cases evolve slowly (Slower than viral / bacterial pneumonias)
- Clinical features of atypical pneumonias
- Infection is severe in Sickle cell disease and other HbS-related hemoglobinopathies (functional asplenia)

- esp. prone to digital necrosis in patients with high titre of cold ab's

EXTRAPULMONARY COMPLICATIONS:

1. Ear pain → BULLOUS MYRINGITIS
2. EM: target / iris lesion, Erythema multiforme → SJ Syndrome
3. Digital necrosis (esp. in patients with sickle cell disease)
4. Neuro: Encephalitis, Cerebellar ataxia, GBS, Transverse myelitis, peripheral neuropathy
5. Hemat: hemolytic anemia & coagulopathy

- M. pneumoniae evoke IgM antibodies which agglutinate human RBC's at 4°C

Extra pulmonary complications have an autoimmune

CXR: Reticulonodular / interstitial shadows in LL

DIAGNOSIS:

1. Gram stain: Not useful because no cell wall & too small to be seen under the LM
2. Cold Agglutinin test:
   - Non-specific
   - Becomes +ve in 7-10 days of illness
   - Therefore +ve by the time patient presents
   - A titer ≥ 1:32 is supportive
3. Culture / Serology (antibodies): Give results too late, so not useful

TREATMENT: DOC is Macrolide

1. Clarithromycin / Azithromycin / Fluoroquinolone
2. Doxycycline / Erythromycin

H. influenzae

- Serotypes a to f: possess polysaccharide capsule: type b is MC → causes infections in children
- Non-typable H. influenzae → Lacks polysaccharide capsule: Causes CAP in adults, esp. patients with COAD/AIDS and hypogammaglobulinemia.

STAPHYLOCOCCAL PNEUMONIA

- Usually because of S. aureus
- Usually nosocomial. MC organism causing HAP
- Fulminating course: any case of severe pneumonia to be considered as being Staph

Risk Factors for Staphylococcal pneumonia:

- Prolonged iv cannulation, Chronic hemodialysis, IVDU, Intubated patients, Diabetics, Trauma patients
- Causes of ↑ risk of infections in diabetics:
    - Abnormal CMI / Abnormal phagocytic fn / ↓ vascularity / Poor glycemic ctrl → favors colonization with Candida / other fungi; ↑ rate of colonization of skin & external nares with Staph

CXR: Consolidation with PNEUMATOCELES
Gram stain of sputum: GPC in grape-like clusters
TREATMENT:

- MSSA: Extended spectrum / SPRPs:
- MRSA: Vancomycin
- VISA: Quinupristin/Dalfopristin; Linezolid

COMPLICATIONS:
1. TSS → Manifestations are due to excessive multiplication and activation of T-lymphocytes
- Menstrual: TSST1
- Non-menstrual: Enterotoxin

✓ Cutaneous exfoliation, mucosal involvement and multisystem involvement are common
✓ Desquamation includes palms & soles
✓ Usually occurs in the absence of overt infection (i.e., usu. Occurs in the presence of only COLONIZATION with S. aureus)

2. SSSS
- Neonates and children
- Nikolsky sign +

KLEBSIELLA

- Friedlander's pneumonia
- Non-motile, Enteric GNB
- 2nd MC organism causing nosocomial pneumonia & CAP due to GNB

- ***Risk Factors for Kleb pneumonia: Alcoholics, diabetics, Intubated patients, chronic lung ds.***

Clinical Features:
- Red currant jelly / brown sputum

CXR: UL pneumonia

Bulging fissure: However, most patients earlier than the development of this sign.

TREATMENT:
- Intrinsically resistant to ampicillin and other aminopenicillins
- ESBLs: confer resistance to cephalosporins, aminoglycosides and aztreonam
- ESBL-producing strains remain susceptible to carbapenems.

PSEUDOMONAS

- Occasionally *COLONIZES* skin, external ear, skin, resp tract, bowel of *HEALTHY* humans
- Potential reservoirs of infection in the hospital: Respiratory equipment, cleaning solutions, disinfectants, sinks, vegetables, flowers, endoscopes. (Most reservoirs are assoc with moisture)
- Nosocomial outbreaks / Major route of patient-to-patient transmission: hands & fingernails of HCWs
- Does not cause CAP in healthy persons but is highly virulent for:
    - *Disruption of cutaneous / mucosal barriers*: burns, CF, dermatitis, penetrating trauma, surgery, ET intubation, indwelling central venous cath, UB cath, IDU
    - *Immunosuppression:* Neutropenia, hypogammaglobulinemia, defective CMI, extremes of age, DM, steroid therapy, cancer, AIDS
    - *Disruption of normal bacterial flora:* Broad spectrum antibiotic therapy (in the last 1 month), exposure to hosp environment

Primary / Nonbacteremic pneumonia

- Due to aspiration of URT secretions
- Signs of severe systemic toxicity: fever, chills, severe dyspnea, cyanosis, productive cough, confusion, apprehension
- Fulminant, life-threatening illness
- CXR: B/L bronchopneumonia; pleural eff common, empyema is rare; Cavities common in AIDS

Bacteremic pneumonia
- Begins as respiratory infection
- Differences from primary pneumonia: Assoc with neutropenia, bacteremia, metastatic spread to other viscera
- CXR: pulmonary vascular congestion → interstitial edema → Necrotizing pneumonia
- Pathognomonic skin lesions: Ecthyma gangrenosum (minority)
- Death in 3-4 days

Chronic infection of LRT

- Mucoid strains that produce alginate
- CF, (Bronchiectasis, AIDS)

Pseudomonas & AIDS

- CD4 < 100
- *CAP*
- Cavities commoner

SARS

- Corona virus (SARS CoV) – ssRNA virus
- Usually causes common cold
- Transmission: Aerosol, feco-oral (?drinking water / sewage)
- HCWs are at ↑↑ risk during outbreak
- SARS epidemic began in Nov 2002 in Guangdong, China; 90% cases in China & HK
- Original source of infection: Palm civet / Dog raccoon
- Case fatality rate: 11%
- Pulmonary path: Hyaline membrane formation, pneumocyte desquamation, interstitial infiltrates (lymphocytes, mononuclear cells)
- Incubation period: 2-7 days
- Begins with systemic features: fever, myalgias, headache → after 1-2 days → dry cough + dyspnea
- Severe cases: ARDS + MODS (2^{nd} week)
- Risk factors for severe disease: Age > 50 (milder in children), pregnancy, DM, Hepatitis B, CVS disease
- Diagnosis: Lymphopenia (esp CD4), thrombocytopenia; may be grown in Vero E6 (African green monkey kidney) cells; RT-PCR (+ in 30%)
- Treatment: supportive

AVIAN INFLUENZA

- Causative agent: Avian influenza viruses
- Most pathogenic species: H5N1
- Spread: Birds → Human
- Secretions / excretions / feathers / etc
- Properly cooked poultry / eggs: harmless
- No human to human spread documented
- Treatment: Zanamivir / Oseltamivir

SWINE FLU

- Also known as swine influenza, hog flu, or pig flu.
- Pandemic of 2009, caused by new strain of H influenzae A subtype H1N1.
- Origin was in Mexico as a result of genetic reassortment of 4 strains of human influenza Virus A- Human, bird & 2 swine.
- Transmission is from person to person. Pigs to human is not common. Not a zoonotic disease.
- Primarily Airborne through droplet. Can also be transmitted by body secretions.
- People predisposed are 1) who handle poultry | pigs

2) Vets | meat processing unit.

- Clinical Features
  - Pig – Fever, cough, SOB, Chills, weight loss, lethargy, abortion. Weight loss upto 12 pounds in 1 month.
  - Humans - Fever, chills, flu like illness, cough, cold rough throat, loose motions, Nausea, Vomiting, SOB.
- Out of 1000 infected – 40 require admission – 1 dies.
- Nasal | Throat swab
  Serology, RTPCR
- Complications – Pneumonia, myocarditis, Pericarditis, myositis, rhabdomyolysis.

Generally seen in patients with chronic debility or with predisposed to diseases.

- Emergency signs – Dyspnea, Cyanosis, pneumonia, sepsis, RF, ARDS, Dehydration
- Treatment – Clinical judgement.
  - Patient has less morbidity and mortality if treated early.
  - High risk patients are: < 5m infant, child less than 2yrs age,
    - Elderly patient >65 years
    - Pregnant patient
    - Patients having chronic debility like COPD | CLD | CRF | Malignancy
    - Diabetic | immunocompromised patient.
  - Symptomatic treatment
  - Oseltamavir 75mg BD X 5d
    Zanamavir 2 puff 5mg BD

Prevention:-

Pig to human – In swine farms, use of masks, swine vaccines & no smoking, Handle with care.

Humans to humans:

- Standard care techniques
- Hand washing is most important
- Quarantine of patients
  Social distancing – Avoid meetings, parties, gathering.

NOSOCOMIAL PNEUMONIAS (incl. VAP – Venti assoc pneumonia)

- MC nosocomial infection: UTI
- Nosocomial infection causing the most mortality: Pneumonia
- **HAP** is defined as pneumonia that occurs 48 hours or more after admission, which was not incubating at the time of admission.
- **VAP** refers to pneumonia that arises more than 48–72 hours after endotracheal intubation.

- MC mechanism of nosocomial pneumonia: Aspiration
- MC organism: Staph. Aureus
- The most common resistant organism causing HAP: Staph. Aureus
- The most common MDR GNB causing HAP/VAP: *P. aeruginosa*,

- **Early-onset HAP and VAP**: occurring within the first 4 days of hospitalization, usually carry a better prognosis, and are more likely to be caused by antibiotic sensitive bacteria.

- **Late-onset HAP and VAP** (5 days or more) are more likely to be caused by multidrug-resistant (MDR) pathogens, and are associated with increased patient mortality and morbidity.

- EARLY ONSET: (within 4 days of hosp): Staph aureus, EGNB, S. pneumoniae & H. influenzae
- LATE ONSET: S. aureus, Pseudomonas, Enterobacter, Klebsiella, Acinetobacter
- Risk factors: Nasogastric tube (lesser risk with orogastric tube), endotracheal tube, decreased level of consciousness, prior AMA use, decreased gastric acidity, contaminated ventilator tubings, upper abd surgery, COPD, old age
- Increased risk of VAP: Re-intubation, Supine positioning, Enteral nutrition (Post-pyloric feeding ↓ risk; early EN > PN: reduces the risk of complications related to central intravenous catheters and to prevent reflux villous atrophy of the intestinal mucosa that may increase the risk of bacterial translocation), Heavy sedation, Paralytic agents, H2 antagonists and antacids (Decreased risk seen with sucralfate, but GI bleeding more common)

CRITERIA:

- At least two of three clinical features (fever greater than 38˚C, leukocytosis or leucopenia, and purulent secretions), a positive culture of sputum or tracheal aspirate, and a new lung infiltrate.
- When fever, leukocytosis, purulent sputum, and a positive culture of a sputum or tracheal aspirate are present without a new lung infiltrate, the diagnosis of **nosocomial tracheobronchitis** should be considered.

ALSO KNOW:

Clinical Pulmonary Infection Score (CPIS)	
Criterion	**Score**
Fever (°C)	
38.5 but 38.9	1
>39 or <36	2
Leukocytosis	
<4000 or >11,000/ L	1
Bands >50%	1 (additional)
Oxygenation (mmHg)	
Pa_{O2}/F_{IO2} <250 and no ARDS	2
Chest radiograph	
Localized infiltrate	2

Patchy or diffuse infiltrate	1
Progression of infiltrate (no ARDS or CHF)	2
Tracheal aspirate	
Moderate or heavy growth	1
Same morphology on Gram's stain	1 (additional)
Maximal score[a]	12

[a]At the time of the original diagnosis, the progression of the infiltrate is not known and tracheal aspirate culture results are often unavailable; thus, the maximal score is initially 8–10.

Abbreviations: ARDS, acute respiratory distress syndrome; CHF, congestive heart failure

LUNG ABSCESS

- Less than 2 cm diameter: Necrotizing pneumonia
- MC mechanism: Aspiration
  - Therefore commoner in alcoholics, head injury, post-GA, CVA, seizures, mechanically ventilated patients
  - Periodontal disease & poor dental hygiene are common
    - Uncommon in edentulous individuals

MC site

- Supine: Posterior segment of right upper lobe > Apical segment of right lower lobe
- Lateral decubitus: Lateral segment of RML / lateral segment of LUL

Clinical features: Indolent, sub acute course with fever, weight loss, putrid sputum, clubbing.

MC organisms:

- Anaerobes: Prevotella > Bacteroides > Peptostreptococcus
- Polymicrobial growth commoner in hospital acquired lung abscess
- MC gram negative bacillus causing lung abscess: KLEBSIELLA

- **SPUTUM CULTURE – not useful**
- Hallmark CXR finding: Air-fluid level

TREATMENT

- Parenteral antibiotic till complete radiologic resolution
- DOC is clindamycin for 4 – 6 weeks.

ALSO KNOW SUMMARY OF CAUSATIVE ORGANISMS:

Epidemiologic Factors Suggesting Possible Causes of Community-Acquired Pneumonia

Factor	**Possible Pathogen(s)**
Alcoholism	*Streptococcus pneumoniae,* oral anaerobes, *Klebsiella pneumoniae, Acinetobacter* spp., *Mycobacterium tuberculosis*
COPD and/or smoking	*Haemophilus influenzae, Pseudomonas aeruginosa, Legionella* spp., *S. pneumoniae, Moraxella catarrhalis, Chlamydia pneumoniae*
Structural lung disease (e.g., bronchiectasis)	*P. aeruginosa*, *Burkholderia cepacia*, *Staphylococcus aureus*
Dementia, stroke, decreased level of consciousness	Oral anaerobes, gram-negative enteric bacteria
Lung abscess	CA-MRSA, oral anaerobes, endemic fungi, *M. tuberculosis*, atypical mycobacteria
Travel to Ohio or St. Lawrence river valleys	*Histoplasma capsulatum*
Travel to southwestern United States	Hantavirus, *Coccidioides* spp.
Travel to Southeast Asia	*Burkholderia pseudomallei,* avian influenza virus
Stay in hotel or on cruise ship in previous 2 weeks	*Legionella* spp.
Local influenza activity	Influenza virus, *S. pneumoniae, S. aureus*
Exposure to bats or birds	*H. capsulatum*
Exposure to birds	*Chlamydia psittaci*
Exposure to rabbits	*Francisella tularensis*
Exposure to sheep, goats, parturient cats	*Coxiella burnetii*

-

PLEURAL DISEASE

Physiology of Pleural Space

- Pleural pressure is the pressure at the outer surfaces of the lung and heart; and at the inner surface of the chest wall.
- The lung, chest wall and heart are all DISTENSIBLE structures.
- The volume of a distensible object depends on:

1. Pressure difference between the inside and the outside
2. Compliance of the object

Therefore pleural pressure plays an important role in determining the volume of these 3 vital structures.

- At FRC, the opposing elastic forces of the chest wall (outwards) and lung (inwards) produce a negative pressure between the visceral & parietal pleurae → pleural pressure → this is the PRIMARY determinant of lung volume.
- Pleural pressure gradient: most negative at apex
- Alveolar pressure gradient: none, i.e., intra-alveolar pressure is constant from lung apex to base

PNEUMOTHORAX

Pathophysiology :-

Because pleural pressure is –ve & both atmospheric and intra-alveolar pressure are > pleural pressure, whenever there is a communication between,

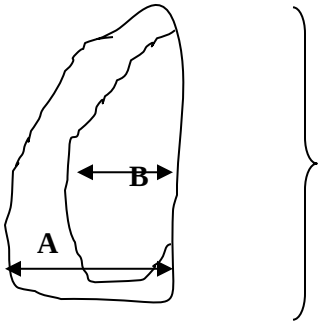
Either: - ATM → pleura
OR
Alveoli → pleura

} Air flows from high pressure → low pressure until equalization of pressures OR until the communication is sealed

Physiologic Consequences

↓ VC: Lung volumes are decreased, work of breathing increases; ↓ PaO_2; ↑ A-aDO_2

Calculating the volume of a pneumothorax



$$\frac{A^3 - B^3}{A^3} \times 100$$

TYPES OF PNEUMOTHORAX:-

1. Spontaneous
   a. Primary
   b. Secondary
2. Traumatic
   Iatrogenic / Non-iatrogenic
3. Tension PTX

1. Spontaneous pneumothorax occurs without any trauma to the thorax

a) Primary spontaneous pneumothorax

- Exclusively in smokers (Subclinical disease)
- Tall, thin patients; most in their early 20's
- MC occurs at rest. Due to rupture of subpleural blebs.
- Chest pain on the affected side; Dyspnea
- 50% recur
- Treatment: 1st: Observation
  2nd: Aspiration
  3rd: ICD

Lung does not expand / Recurrence
→ Thoracoscopy with stapling of blebs & pleural abrasion

b) <u>Secondary spontaneous pneumothorax</u>

- MC cause: COPD (Emphysema predominant) . MC pneumonia – staph aureus.
- Other causes: TB, PCP in AIDS, Sarcoidosis
- More life-threatening than primary spontaneous pneumothorax
  - Lack of pulmonary reserve
- Dyspnea out of proportion to size of pneumothorax
- Treatment: Tube Thoracotomy for ALL

↓ If after 3 days lung unexpanded / persistent air leak OR recurrence

Thoracoscopy + pleural abrasion

⇒ IMPORTANT DIFFERENTIAL DIAGNOSIS TO BE RULED OUT BEFORE INSERTING CHEST TUBE:
Primary collapse

2. <u>TRAUMATIC PNEUMOTHORAX</u> ;-

- Can be due to both: penetrating & non-penetrating chest trauma
- Treatment: Tube Thoracotomy
- If hemopneumothorax: single tube – 5th ic space, mid-axillary line

<u>Hemothorax</u>:

- Criteria: Hematocrit of pleural fluid > 50% of that of peripheral blood
- Treatment: ICD
  - Quantification

<u>IATROGENIC PNEUMOTHORAX</u> :-

- MC cause: TTNA
- Other causes: Thoracentesis, Central venous line insertion
- Treatment:
  - Etiology → Mechanical ventilation: Urgent tube Thoracotomy
    → Other: < 40% → Observe ± O_2
    > 40% → Aspirate
    ↓ Unsuccessful
    Tube Thoracotomy

3. *TENSION PNEUMOTHORAX*
   - MC with Mechanical Ventilation; also with CPCR
   - Pleural space pressure is positive throughout the respiratory cycle
   - "Valve" mechanism: Open in inspiration & closed during expiration → air accumulates
   - Positive pressure is conveyed to
     1. Lungs: Collapse → ↓ Ventilation → Life threatening hypoxemia
     2. Mediastinum: ↓ venous return → ↓ CO
   - MC cause of death:
   - 'Clue' to diagnosis: High peak inspiratory pressure during mech. ventilation OR difficulty in AMBU ventilation during CPCR

CXR:
1. Bulla Vs. Pneumothorax
2. Recognizing pneumothorax in a patient on Mech Vent:
   - Most superior part of chest in supine position:

Physical findings (of any pneumothorax): Enlarged hemithorax, Absent breath sounds, Absent TVF,
- Hyper-resonant percussion note, Shift of trachea → opp side
- SUSPECT TENSION PNEUMOTHORAX: HR > 140, hypotension, cyanosis, electromechanical dissociation

TREATMENT
- Do not wait for CXR
- Large bore needle through 2nd anterior intercostals space → gush of air confirms diagnosis
- Leave needle in space until tube Thoracotomy is done (URGENT BASIS)
- Start high concentration of supplemental O_2

ICD indication :-

- Primary pnuemothorax
- Secondary pnuemothorax
- Hydropnuemothorax
- Pyopnuemothorax
- Complicated pleural effusion
- Hemothorax
- Malignant pleural effusion

????Chylothorax (never indicated)

- Pleurodesis indications
  - Recurrent 1° pneumothorax
  - First episode of 2° pneumonorax
  - If patient is treated by chest tube
  - Malignant pleural effusion.

PLEURAL EFFUSION

Light's Criteria:

Exudate if any of:
1. PF / serum protein > 0.5
2. PF / serum LDH > 0.6
3. PF-LDH > 2/3 of normal upper limit (in serum)
   *SPFAG (Serum-Pleural Fluid Albumin Gradient) >1.2 → Transudate

Transudative Effusions:
CHF, cirrhosis, nephrotic syndrome, Peritoneal dialysis, SVCO, myxedema, urinothorax, PE

Exudative Effusions: Bacterial & viral pneumonias, PE, Neoplasm – mesothelioma / mets (e.g. bronchogenic), esophageal perf, pancreatitis, CTDs (RA, SLE, drug-induced lupus, Sjogren's, Wegener's, Churg Strauss), Sarcoidosis (<5%), Asbestosis, Post-CABG, Renal failure, Meig's syndrome, Chylothorax,
Drugs: Nitrofurantoin, Dantrolene, Methysergide, Amiodarone, Bromocriptine, and Procarbazine

- 1st accumulates → Sub-pulmonically
- Next, spills → Posterior CP angle
- For blunting of the lateral CP angle (on PA view) → 175 ml

✓ Any amount of pleural fluid is abnormal
✓ For pleural effusion seen on an erect film, OBTAIN BILATERAL DECUBITUS FILMS

Physical findings
1. Trachea: opp side, if free moderate to large sized effusion
2. Movements: Reduced on the affected side
3. IC spaces: Unaffected in uncomplicated effusion; in empyema – overlying skin is shiny & bulging
4. TVF: Decreased to absent
5. Breath sounds: Reduced intensity to absent

- Mesothelioma, Lymphoma / other mediastinal tumor, Primary ipsilateral atelectasis
- MC cause of pleural effusion: CHF
- PF with ↑ amylase: Pancreatitis, Esophageal rupture, malignant effusion

Effusion due to Heart failure R > L
Diagnostic Thoracentesis indicated if: u/l, disproportionate, fever, pleuritic chest pain, persists despite therapy for HF
Effusion secondary to ascites
Mech: Direct movement of peritoneal fluid, through small holes in the diaphragm, into the pleural space
MC right-sided

Effusion after CABG:-
1st 2 weeks: hemorrhagic; eosinophils +; left-sided; no recurrence after Thoracentesis
After 2 weeks: yellow, lymphocytosis, recurrent

Effusion with PE :-
Usually Exudative
PE with pulmonary infarction: hemorrhagic

Effusion in AIDS:
- Uncommon
- MC cause: parapneumonic eff (f/b TB)
- Also: KS, Cryptococcosis, body cavity lymphomas
- Very uncommon with PCP

Parapneumonic / synpneumonic effusion
- MC cause of Exudative effusion: parapneumonic
- MC cause of massive exudative effusion: TB
- Empyema: Gross pus in pleural cavity

Indication of Diagnostic thoracocentesis:
- Fluid > 10 mm on lateral decubitus film

Indication of Tube Thoracotomy:
- In increasing order of importance → "LPGOP"
- Loculation, pH < 7.2, Glucose < 40, Organism (on gram stain / culture), Pus
- *Indications of Intrapleural thrombolysis*
- Loculation (without pus)

However, STK / UK should be given within 3 days of onset of effusion (i.e., before fibrosis sets in)
- If pus →
  - Single loculus: Chest tube (Under US guidance)
  - Multiple loculi: Decortication procedure

Chylothorax :-
- MC cause: traumatic disruption of thoracic duct
- Others: mediastinal tumors
- Milky fluid with high triglyceride content (> 110 mg %)
- T/t: Pleuroperitoneal shunt is a temporizing measure; Definitive treatment is repair of thoracic duct
- Prolonged tube Thoracotomy: C/I

Hemothorax :-
- If hematocrit of pleural fluid > 50% of that of peripheral blood
- T/t: Tube Thoracotomy
- Thoracotomy indicated if drainage > 200ml/h OR if upon initial insertion of chest tube, ≥ 1.5 L is drained

OBSTRUCTIVE_DISEASES

COPD

Definition: Airflow limitation that is not fully reversible & is progressive.

- c.f. Asthma (Reversible airflow limitation)

✓ **Chronic bronchitis**, defined as the presence of cough and sputum production for at least 3 months in each of 2 consecutive years, is not necessarily associated with airflow limitation.

✓ **Emphysema,** defined as destruction of the alveoli, is a pathological term that is sometimes (incorrectly) used clinically.

✓ Abnormal inflammatory response to noxious particles e.g. SO_2, SPM

RISK FACTORS

- The most important **risk factor** for COPD is **cigarette smoking**.
  - Other types of tobacco smoking popular in many countries are also risk factors for COPD.
- Also, indoor air pollution from BIOMASS FUEL (for cooking / heating) in poorly ventilated dwellings
- Coal mining, gold mining, cotton textile dust, cadmium fumes, So_2
- **Gender: More common in men. M:F ratio is 5:2.7 (in India)**

Note: SO_2 causes COPD (and not Asthma)
NO_2 causes asthma (and not COPD)

AAT Deficiency associated emphysema :-

- AR with co-dominant expression
- Genotypes: PiMM / PiSS / PiZZ / Null allele
- Normal function of α_1 antitrypsin:
- Early onset COPD → *PANACINAR emphysema*; SMOKING → centriacinar emphysema
- Testing indicated in patients with emphysema ≤ 50 years, non-smokers, predominantly basilar disease, family history of COPD
- COPD develops in 80% of patients with PiZZ
- AAT defi also predisposes to neonatal hepatitis, cholestasis, chronic hepatitis, cirrhosis in about 10% patients; HCC develops in 2-3%

Suspect AAT :-

- Presentation less than 50 years
- Family history
- Those with minimal smoking
- Prominent basilar disease
- Concominant liver cirhosis

Emphysema

3 morphologic patterns
-Centriacinar emphysema
-Panacinar emphysema
-Distal acinar emphysema or paraseptal emphysema

centriacinar emphysema

- Focal destruction limited to the respiratory bronchioles and the central portions of acinus associated with cigarette smoking and is most severe in the upper lobes and superior segments of the lower lobes
- It is **focal**

panacinar emphysema

- Involves the entire alveolus distal to the terminal bronchiole
- The panacinar type is most severe in the lower lung zones
  patients with homozygous alpha1-antitrypsin (AAT) deficiency

distalacinar emphysema

- Also called as paraseptal emphysema
- Involves distal airway structures, alveolar ducts, and sacs
- Least common form
- This form of emphysema is localized to fibrous septa or to the pleura and leads to formation of bullae.
- The apical bullae may cause pneumothorax
- Paraseptal emphysema is not associated with airflow obstruction.

Blue bloaters

- Chronic bronchitis
- Patients may be obese.
- Frequent cough and expectoration are typical.

Pink puffers

- Emphysema
- Patients may be very thin with a barrel chest.
- They typically have little cough or expectoration when compared with bb.

Symptoms of COPD include:

- Cough
- Sputum production, Increased in amount, thickness or purulence signify injection.
- Dyspnea on exertion.

Grading of respiratory breathlessness

- **MRC grading**
  - 1.Breathlessness on strernous exercise
  - 2.Breathlessnesson walking up hill or hurring on a level
  - 3. Walks slower than people of same age group
  - 4.Stops for breath after 100meter
  - 5. At rest

SIGNS: Evidence of hyperinflation: (Clinical & Radiological)

Causes of Acute exacerbations of COPD:

MC → Chest infection & Air pollution – Viral and not bacterial.

Others: Pneumothorax, LV failure, pulmonary embolism, lung cancer
Exacerbations result in worsening lung function and therefore worsening resp failure

PFT
↓ FEV_1& FEV_1/FVC &**DLCo**
↑ FRC, RV
TLC: N to ↑
Best guide to progression of COPD over time: Change in FEV_1
- *HOWEVER, MEASUREMENTS MUST BE AT LEAST 12 MONTHS APART*

GOLD Staging of COPD
Stage 0: Normal PFT; Chronic cough & sputum production; "At risk for COPD"
Stage I: Mild: FEV_1/FVC < 70%; FEV1 ≥ 80% predicted
Stage II: Moderate: FEV_1 50-80%
Stage III: Severe: FEV_1 30-50%
Stage IV: Very severe: < 30%
- Normal FEV1/FVC: 0.75 to 0.80
- Repeated exacerbations complicate the course of *SEVERE* disease
- Chronic respiratory failure supervenes in *VERY SEVERE* disease

ABG
Hypoxemia &Hypercapnia :
- paO_2 remains near normal until FEV_1 decreases to ≈50%
- The predominant mechanism of hypoxemia is V/Q mismatch
- Hypercapnia occurs when FEV_1 decreases to ≈25%
- PHT (→corpulmonale& RV failure) occurs when FEV_1 decreases to ≈25% along with the presence of chronic hypoxemia (paO_2< 55 mmHg)

MANAGEMENT
1. **Cessation of smoking:** is the *single most effective intervention* to decrease risk of developing
   COPD & slow its progression – Nicotine patches, gums and bupropion can be used.
2. **Bronchodilators**
   a. β2 agonists: BD^{r}of choice for acute exacerbation
   b. Anticholinergics: *BD^{r}of choice in COPD*
   c. Methylxanthines
3. **Corticosteroids**
   Indications for long term inhaled steroids: FEV_1< 50% predicted & repeated exacerbations
4. Treatment of Infection (antibiotics)
5. Prevention of infection
   INFLUENZA vaccine is recommended for all COPD patients
6. Nutrition
7. LTOT / Domiciliary O_2 therapy – O_2 decreases mortality when given >15 hrs /d (When spo2 <88%)
   Indications:
   i. Resting paO_2 (room air) <55 mmHg
   ii. Resting paO_2 55-59 with
      (a) Evidence of RHF → edema / p-pulmonale

(b) Pulmonary HT
(c) Polycythemia (hematocrit > 56%)

8. LVRS: patients with UL emphysema & low exercise capacity
9. Lung transplantation: Criteria for referral for lung transplantation include FEV1 <35% predicted,

PaO2 <7.3–8.0 kPa (55–60 mm Hg), PaCO2>6.7 kPa (50 mm Hg), and secondary pulmonary hypertension

ASTHMA

Definition: Chronic inflammatory disease of airways due to hyper-responsiveness of tracheobronchial tree to several stimuli

Asthma is characterized by:

1. Paroxysmal & / or persistent symptom
2. Variable airway obstruction
3. Airway hyper responsiveness to variety of inhalational stimuli.

In 30 -50% of the patient second wave of broncho constriction called as late reaction develops 6 to 10 hours later.

EPISODIC disease: No morbidity between episodes / exacerbations

Age:

> 50% cases → < 10y
> 80% cases → < 40y

Sex: M: F = 2:1 in childhood; 1:1 by 30 years of age

Risk Factors:

- Single *largest* risk factor: ATOPY (defn: genetically determined predisposition to develop localized / systemic anaphylaxis to inhaled / ingested allergen)
- Personal / family history of allergic disease e.g. rhinitis, urticaria, eczema

Various stimuli which precipitate asthma:

1. Allergens
2. Pharmacological stimuli – aspirin, β blockers
3. Environmental pollution – O_3, NO_2
4. Occupational factors
5. Infection – virus
6. Exercise
7. Emotional stress

Types of asthma

Allergic/atopic/extrinsic :

- Early in life
- Family history +
- Rhinitis, urticaria,eczema.
- + wheal& flare response to Ag
- IncIgE

Idiosyncratic / intrinsic

- Late in life
- Family history –ve
- No allergic features
- Negative skin test
- Normal IgE

Pathogenesis

Cells playing important role in asthma

- Mast cells
- Macrophage
- Eosinophils
- T lymphocytes
- Epithelial cells
- Fibroblast
- Neutrophills

Bronchocostriction

- histamine, PAF, PGD2,LTC4,LTD4

Vasodilation

- NO, PGE2, 5HT

Inflammation

- Cytokines(IL 8, GMCSF)

Fibrosis/ smooth muscle hyperplasia

- EGF, IGF,PDGF

Cytokines:

- Secreted esp. by T lymphocytes; also → epithelial cells, airway smooth muscle cells, alveolar macrophages
- IL-3: ↑ mast cell survival
- IL-4: B-lymphocytes switch to IgE production (from IgG / IgM)
- IL-5: ↑ Eosinophil survival

Pathophysiology: ↓ airway diameter → ↑ airway resistance, hyperinflation → **↑ work of breathing**

CLINICAL FEATURES

MC precipitant of acute exacerbation of asthma: Respiratory infection

- Adults: Rhinovirus, Influenza
- Children: RSV, Para-influenza virus

- Triad of dyspnea, cough & wheeze
- Also, chest tightness
- Cough: initially non-productive; later, sputum +
  - Occasionally, Curschmann's spirals: thick mucus that takes the form of casts of distal airways (microscopic finding)
- Prolonged expiration; Tachypnea, tachycardia, mild systolic hypertension
- ↑ AP diameter of thorax, Accessory muscles active
- Cyanosis: very late, therefore unreliable

- Circadian rhythm in degree of AO +: most severe between 2am&4am → nocturnal awakening with dyspnea / wheeze

- **OMINOUS SIGNS:**
  1. SOB at rest / $pO_2 < 60$
  2. Normo- / hypercapnia ($CO_2 \geq 42$)
  3. 'Silent' chest
  4. Speech in monosyllables / mute
  5. Shallow breathing
  6. paradoxical pulse / thoraco-abdominal paradox
  7. PEFR < 100 l/min

With long-standing, severe disease: PAH, RVH

Lung volumes:
- FEV_1 (30%), FVC, MMFR ↓
- RV ↑ (400%)
- An attack ends clinically when FEV_1 50%; RV 200%

ABG:
- MC: Respiratory alkalosis
- Hypoxemia / Normocapnia imply severe obstruction

Differential diagnosis:
1. Upper airway obstruction: (e.g. tumor): Stridor; no wheeze
2. Lower airway obstruction: (FB aspiration / endobronchial neoplasm / bronchial stenosis) → localized wheeze ± cough
3. ALVF: Moist basilar râles, S_3 gallop, orthopnea, blood-tinged sputum
4. Recurrent episodes of bronchospasm also seen in: Carcinoid tumors, recurrent pulmonary emboli, chronic bronchitis
5. Systemic vasculitis: e.g. Churg Strauss syndrome

DIAGNOSIS:
- Reversible AO: ≥ 12%↑ or 200 ml in FEV_1 after 2 puffs of a short-acting β_2-agonist / 14 days of 30 mg prednisolone per day
- ≥ 12% ↓ in FEV_1 after running for 6 minutes
- ≥ 20% diurnal variation in PEFR

Monitoring response to therapy: PEFR

Role of skin tests: Not used for diagnosis (however, may have therapeutic benefit)

Role of provocation tests: If the PFTs do not yield a diagnosis → histamine / methacholine

TREATMENT:

CATEGORY	**SYMPTOMS**	**PEFR**	**TREATMENT (Long term ctrl)**
Intermittent asthma	< 2 DAYS / WEEK; < 2 NIGHTS / MONTH	> 80%	**SOS**: Inhaled β_2 agonist; (No regular t/t)

Mild persistent	> 2 DAYS / WEEK; > 2 NIGHTS / MONTH	> 80%	INHALED CORTICOSTEROIDS
Moderate persistent	DAILY; > 1 NIGHT / WEEK	50-80%	INHALED CORTICOSTEROIDS + β2 AGONIST
Severe persistent	CONTINUAL, FREQUENT SYMPTOMS	< 50%	ORAL & INHALED CORTICOSTEROIDS + 'L-A' β2 AGONIST

1. **Drug of choice for chronic asthma: Inhaled Corticosteroids& LABA**
2. **Drug of choice for acute, severe asthma: Inhaled short acting β2 agonist + steroids (systemic)**
3. Anti-cholinergic: Ipratropium
4. Mast Cell Stabilizers: Cromolyn / Nedocromil
5. LT receptor blockers / Lipoxygenase inhibitor: montelukast / Zafirlukast / zileuton
6. Adrenaline
7. $MgSO_4$ (i.v.)
8. Theophylline, Aminophylline
9. OMALIZUMAB: IgE-associated monoclonal antibody

SPECIAL CATEGORIES

EXERCISE INDUCED ASTHMA

Mechanism: Thermally produced hyperemia of bronchial mucosa; *not because of bronchoconstriction*

Exercise produces symptoms in *ALL* patients with asthma; degree of exertion at which symptoms occur vary from 1 person to another)

T/t: inhaled short-acting β2 agonist (Estd attack)

Prophylaxis: Inhaled long-acting β2 agonist / LT receptor blocker

DRUG INDUCED ASTHMA

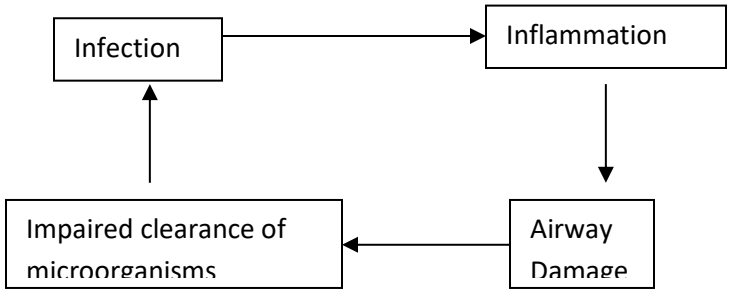
- 10% of asthma patients are aspirin-sensitive
- MC due to Aspirin; also with ibuprofen, indomethacin, naproxen, phenylbutazone, mefenamic acid
- Other drugs that can cause bronchospasm: Adenosine, prostaglandin analogues, BBs, cholinergic drugs, streptomycin, pentazocine, penicillin
- Non-pharmaceutical agents: tartrazine (coloring agent), sulfating agents (preservatives in food / medicines)

SAFE NSAIDs: Acetaminophen, sodium salicylate, choline salicylate, salicylamide; Propoxyphene also safe

- *Mech: Over-secretion of cysteinyl LTs*
- *Associations: Nasal polyps, vasomotor rhinitis, hyperplastic rhino sinusitis*

BRONCHIECTASIS

- Abnormal & permanent dilatation of bronchi
  → Clinical consequence: Recurrent / Chronic infection (pooled secretions)
- Path
  - Involves medium sized airways (segmental &subsegmental bronchi)
  - Cartilage, muscle, elastic tissue of bronchial wall destroyed



CAUSES:

1. Infections: Adenovirus, Influenza, Bacterial pneumonias (esp. Staph, Klebsiella& anaerobes); TB
2. Primary ciliary disorders e.g. Kartagener's syndrome
3. CF
4. AAT deficiency (usu. → panacinaremphysema; occ. → Bronchiectasis)
5. Yellow nail syndrome (Triad of lymphedema, pleural eff, yellow nails)
6. ABPA
7. Associations: UC, RA, Sjogren's

CLINICAL FEATURES:

Recurrent / persistent cough with purulent sputum production

Exacerbations:

- COPIOUS amounts of purulent sputum
- Hemoptysis (bleeding from hypertrophied BRONCHIAL arteries)
- Fever
- Clubbing (chronic suppurative chest infection ± chronic hypoxemia)
  Ultimately, the chronic hypoxemia → PHT &corpulmonale

CXR: Tram-track / Ring shadows (dilated airways with thick walls)

Diagnostic modality of choice: HRCT

**Nodular bronchiectasis: MAC infection

PFT: Obstructive & Restrictive defects

TREATMENT

1. Antibiotics (for infection)
2. Chest physiotherapy / positioning (improved drainage of pooled secretions)
3. Bronchodilators (improve AO & help clear secretions)
4. Surgery: Indicated when bronchiectasis is localized & morbidity is substantial despite adequate medical therapy

*Mucolytics have no role

CYSTIC FIBROSIS

- Multisystem disorder because of abnormal ion transport function → inability to adequately hydrate mucus
- Genetics: AR; mutation in gene on chromosome 7; non-uniform geographic distribution (most prevalent in North & Central Europe);
- Large number of mutations may cause CF;
- MC mutation: 3-bp DELETION → Δ F_{508} of CFTR

Pathogenesis:

- Types of epithelia:
  - Volume absorbing epithelia: Airways & Distal intestinal
  - Salt absorbing: Sweat duct
  - Volume secretory: Proximal intestine & Pancreas
- CFTR protein: Normally present in epithelia; functions as cAMP-regulated Cl^- channel & as inhibitor of Na^+ channels; mutation → intracellular degradation of CFTR
- Membranes of CF epithelial cells are unable to secrete Cl^- in response to cAMP mediated signals
- Normal airway epithelia absorb Na^+ from & secrete Cl^- into the airway lumen
- Na^+&Cl^- transport can be varied to adjust the VOLUME of liquid on the airway surfaces for efficient mucus clearance
- In CF → ↑ Na^+ absorption & ↓ Cl^- secretion → ↓ volume of periciliary fluid → Thickening of mucus → Adhesion & Failure to clear mucus
- Mucus stasis & mucus hypoxia → ↑ Pseudomonas growth
- PANCREAS: Failure of Cl^- - HCO_3^- exchanger to secrete Na^+, HCO_3^- and water → Enzymes retained → Steatorrhea, Azotorrhea& Pancreatic destruction
- INTESTINE: ↓ bicarbonate secretion
  - Low pH in duodenum
  - Thick intestinal mucus → predisposition to obstruction
- Hepatobiliary system: Retention of biliary secretion, Focal biliary cirrhosis, Bile duct proliferation, chronic cholecystitis, cholelithiasis

- Sweat Gland: Normally secrete sweat, but unable to absorb NaCl as sweat moves through the duct

CLINICAL FEATURES:

- Most patients present in infancy
- Earliest presentation: meconium ileus
- Pancreatic & intestinal manifestations occur early
- Pulmonary manifestations occur late
    - After the neonatal period, maximum morbidity & mortality is because of pulmonary disease
- RESPIRATORY TRACT:
    - Earliest functional abnormality → Small airways disease
    - Earliest symptom → Cough
    - Earliest CXR manifestation: Hyperinflation
    - FINAL EXPRESSION: BRONCHIECTASIS
    - PFT: Obstructive pattern with partial bronchodilator response
    - Earliest & most severe changes in RUL
    - URT: chronic sinusitis, rhinorrhea, nasal polyps
    - Persistent cough → viscous, purulent sputum
    - Intermittent exacerbations → increased cough, increased sputum volume, decrements in pulmonary function, weight loss
    - As exacerbations become more frequent, lung function deteriorates → Eventually, respiratory failure
    - Pathogens in newly diagnosed patients: H. influenzae, S. aureus
    - In established disease: Ps. aeruginosa (mucoid form)
    - Burkholderiacepacia: infection portends rapid decline in lung fn& poor prognosis
    - ABPA, NTM each seen in 10% patients; M. tuberculosis is rare
    - Complications: Pneumothorax, hemoptysis, clubbing, respiratory failure, corpulmonale
- GIT:
    - Exocrine pancreatic insufficiency: Steatorrhea, Azotorrhea → consequent malnutrition
        - MC *presenting* feature
        - Recognized only when secretion of amylase & lipase falls below 90%
    - Endocrine pancreatic insufficiency occurs in 10%, much later
    - Others: Intestinal obstruction, appendicitis, recurring acute- or chronic pancreatitis
    - Increased incidence of GI malignancy
- GUT:
    - Late onset of puberty in both males & females
    - 95% azoospermic
    - 20% women infertile
    - 90% completed pregnancies produce viable infants; breast feeding normal
- Retardation of bone age
- Heat stroke

DIAGNOSIS

- One or more characteristic clinical features + Abnormal sweat Cl^- OR Nasal bio-electrical response (nasal
  TEPD – trans-epithelial potential difference)
- Other disorders with **raised sweat Cl^-**: Ectodermal dysplasia, Glycogen storage ds I, Adrenal insufficiency,
  Mucopolysaccharidoses, Acute respiratory disorders (croup, epiglottitis, viral pneumonias), Chronic respiratory
  disorders (AAT deficiency, Bronchopulmonary dysplasia)
- Pilocarpineiontophoresis:
  - *Sweat Cl^- > 70 mEq/L DISTINGUISHES*
- Nasal TEPD ↑ed
  - Amiloride application → loss of this PD
  - β-agonist → No response
- DNA testing (for mutation) not useful because > 1000 mutations exist

TREATMENT

1. Lung disease
   a) Clear secretions: Breathing exercises, flutter valves, chest percussion, recombinant human DNAse
   b) Infection: long courses of C/S-guided antibiotic therapy; higher doses required (↑ V_D); oral / iv / aerosolized
   c) Inhaled β-agonists / anticholinergics: short-term benefit +
   d) Long term high dose NSAID (some patients)
   e) The only effective therapy for respiratory failure in CF: LT
      - O_2 and medical management are temporary measures
2. GIT
   a) Pancreatic enzyme replacement (microsphere formulation)
   b) Replacement of fat-soluble vitamins
   c) T/t of acute obstruction: Enema of hypertonic radio-contrast material (megalodiatrizoate)
3. Assisted reproductive technology

INTERSTITIAL LUNG DISEASE / Diffuse Parenchymal Lung Disease

"includes a heterogonous group of disorders of both known and unknown causes that share a common finding – inflammation of the pulmonary interstitium (i.e. the alveolar walls and perialveolar tissues) – but differ in the type of inflammatory response and the degree of progression to interstitial fibrosis.
ILD have similar **clinical, radiological, physiological & pathological** manifestations.

Classification

1. *Alveolitis, inflammation and fibrosis*
   IPF, CTD-associated ILDs, Good-pasture syndrome, Radiation pneumonitis, Aspiration pneumonitis, Asbestosis, Interstitial pneumonias, PAP, Eosinophilic pneumonias, ARDS residuum, Drugs

2. *Granulomatous reaction*
   HP, PLCH, Sarcoidosis, Wegener's, Churg Strauss, Be, Si

History
- Acute : EP, HP, AIP
- Sub acute: Sarcoidosis, Alveolar hemorrhage (e.g. GPS), Drugs, CTD-associated
- Chronic: MC presentation: IPF, PLCH, Pneumoconiosis
- Episodic: EP, HP

Age
- IPF > 50;
- Connective Tissue diseases, Sarcoidosis, LAM, PLCH: 20-40
- Gender

LAM, pulmonary inv in TS: EXCLUSIVELY in premenopausal females
Pneumoconiosis & RA-associated ILD: males
Family History
Familial lung fibrosis: Mutation in surfactant protein C gene
AR TS, NF, NPD, Gaucher's, HermanskyPudlak syndrome
Smoking History
DIP is seen exclusively in smokers.
PLCH, GPS, RB-ILD, IPF
ILDs commoner in non-smokers (than smokers): Sarcoidosis, HP
HIV Association
BOOP, LIP, NIP, Diffuse alveolar hemorrhage
DRUGS
Amiodarone, gold, Alkylating agents (incl. bleomycin*), methysergide, methotrexate, acyclovir, azathioprine, sulfonamides
**Bleomycin-induced lung fibrosis*
- After *cumulative* dose of 300 U
- Progresses despite withdrawing bleomycin
- Administration of high FiO_2: Risk factor for fibrosis

Drug-induced pulmonary disease
1. *Pulmonary edema*: contrast media, hydrochlorothiazide, heroin, methadone, propoxyphene, IL-2, ritodrine
2. *Bronchospasm*: BBs, anticholinergics, adenosine, dipyridamole, prostaglandins, streptomycin, pentazocine, penicillins, NSAIDs, tartrazine
3. *Respiratory depression*: sedatives (eg barbiturates, opiates, benzodiazepines), aminoglycosides, trimethaphan, polymyxin
*Diseases in which ILD is an uncommon / non-dominant feature: HermanskyPudlak syndrome, TS, NF, Gaucher's
*GI associations with ILD: Crohn's, Ulcerative colitis, PBC, Chronic active hepatitis

Clinical features
Symptoms / signs may not correlate with extent of disease in the lungs
- *Progressive* Dyspnea: Initially on exertion; later at rest (as Alveolitis / fibrosis progress)
  - *Exceptions:* Sarcoid, PLCH, lymphangitiscarcinomatosis, HP, silicosis, lipoid pneumonia→ can have extensive ILD (on CXR) without dyspnea
- Cough: nonproductive
- Weight loss & Fatigue: all ILDs

Physical findings

- Initially, only Tachypnea
- Velcro, end-inspiratory, bi-basilar crepts: Seen with inflammation; less common with granulomatous disorders
- Clubbing, Cyanosis, evidence of PHT → Advanced disease

Inspiratory 'squeaks': Respiratory Bronchiolitis
ILDs that predispose to pneumothorax: PLCH, LAM, TS, NF
Uncommon manifestations of ILDs

- Wheeze: EP
- Chest pain: Sarcoidosis
- Hemoptysis: Alveolar hemorrhage syndromes

LAB

- *Non-specific*
  - ↑ LDH
  - +ve ANA / RA factor (even in patients without any CTD)

CXR

Correlates Poorly with clinical / histopathologic stage of disease;
MC: Bibasilar, Reticular opacities} MOST ILDs
± Alveolar opacities
ILDs with predilection for UL: Si, Be, Sarcoidosis, AS, RA, PLCH, Chronic HP
'Honeycombing': due to cystic spaces and fibrosis; occurs late; indicates a poor prognosis
HRCT: Imaging modality of choice for ILD
'Ground glass opacities' suggest Alveolitis

PFT:

1. Restrictive defect } Poor correlation with disease stage
2. ↓ DLCo }

*ILD's with OBSTRUCTIVE defect: TS, LAM

ABG

Normal / hypoxemia / Respiratory alkalosis
*CO2 retention RARE (Except in END-STAGE disease)
If resting ABG is normal → Exercise testing
On exercise →
1. Arterial O2 desaturation
2. Excessive tachypnea w/o corresponding ↑in TV
Serial assessment of resting / exercise ABG → METHOD OF CHOICE for assessing
1. Disease activity 2. Response to t/t

BAL:

Helpful in diagnosis:

- Establishes presence of alveolitis (esp in the absence of Lung Biopsy)
- Neutrophil-rich: IPF
- Lymphocyte-rich
  - *CD4: Sarcoidosis*
  - *CD8: HP*
- Eosinophil-rich: Eosinophilic pneumonias

No specific role in assessment of activity

The 3 investigations that do not bear good correlation with disease stage / activity: CXR, PFT, BAL

LUNG BIOPSY:

- Diagnostic investigation of choice
- Provides CONFIRMATORY evidence
- Preferably done before initiating therapy
- Initial procedure of choice: FOB+TBLB → VATS / Thoracotomy

TREATMENT

Glucocorticoids ± Azathioprine

- Steroids are mainstay of suppression for alveolitis
- Recommended for IPF, COP, EP, CTD, Sarcoidosis, Acute inorganic dust exposure, HP, acute radiation pneumonitis, Diffuse alveolar hemorrhage, drug-induced lung disease
- Additional Immunosuppressive agent added if patient continues to decline on steroid alone
- Supplemental O2

BrochiolitisObliterans Organizing Pneumonia (BOOP)/ Cryptogenic Organizing Pneumonia

- Idiopathic; $D_{5/6}$
- Fever, cough, weight loss
- CXR: B/L Alveolar opacities in lung periphery & lower zones,
    - WITH NORMAL LUNG VOLUME

❖ ***"BOOP pattern" seen in: Wegener's, EP (Eosinophilic pneumonias), HP, HIV, Lymphoma, Cryptococcosis***

❖ ***T/t: Steroids***

❖ ***GOOD PROGNOSIS***

Pulmonary Alveolar Proteinosis

- Autoimmune disease with IgG*auto-antibodies against* ***GM-CSF***
- Defect in macrophage function: ↓ surfactant clearance
- ***Accumulation of PAS +ve material in alveoli***
- Minimal inflammation
- Lung architecture preserved
- Associations: Hemat malignancies, Immunodeficiency disorders, & Acute Silicosis
- ↑ Serum levels of surfactant proteins A & D
- CXR: Centrally located opacities in mid- & lower zones → 'Batwing' pattern

Diffuse Alveolar Hemorrhage

- *Hemoptysis* ±
- Decreasing Hb / Decreasing Hematocrit + hemorrhagic BAL fluid
- Diffuse alveolar opacities on CXR
- Recurrent episodes of DAH → pulmonary fibrosis
- Associations: FSG ± Crescentric GN
- ***DLCo*** ↑

- ❖ ***Immunofluorescence of lung / kidney tissue →***
    1. Absent immune complexes: Wegener's, Microscopic PAN
    2. Granular pattern: SLE, HSP
       *HSP: granules containIgA-containing immune deposits
    3. Linear pattern: Good pasture syndrome
- - T/t: Intravenous methylprednisolone

GOODPASTURE SYNDROME

- Example of Type II hypersensitivity
- Anti-GBM antibodies; M>F; M:F = 6: 1 2nd /3rd decade; Smoking history
- Second peak in the 6th decade: M=F; Pulm hemorrhage uncommon
- Target antigen: α_3 chain of NCI of type I collagen
- Linear immunofluorescence on renal biopsy.
    - Alport's: α_5 chain
- GN + pulmonary hemorrhage
- Assoc with influenza A infection, hydrocarbon exposure, HLA B7 and DR2
- Penicillamine can lead to GPS
- Onset preceded by URI in 10%
- The kidney disease is a DPGN
- ↑ DLCo
-
- T/t:
    - Mainstay: Intravenous methylprednisolone
    - Adjunctive: Plasmapharesis

IPF

- MC type of idiopathic interstitial disease
- Smoking >75%
- Males
- Age >50
- bronchietasis
- poor prognosis and no proven effective treatment

Acute interstitial pnuemonia

- **HAMMAN RICH SYNDROME**
- **Age > 40 yrs**
- **Max mortality rate > 60% in 6 months**
- **Clinically similar to ARDS**

LAM

- **Perimenopausal females**
- **Suspect in young females with pnuemothorax/ emphysema**

- **Pathologically proliferation of pulmonary interstitial smooth muscle proliferation**
- **Hemoptysis is common**
- **Association with meningioma, renal angiomyolipoma and tuberous sclerosis**
- **PFT shows obstructive / mixed pattern.**
- **Treatment includes**
  - **Oopherectomy**
  - **Progestrome**
  - **tamoxifen**

PLCH

- Smoking related
- Men of 20 -40 years of age
- Pnuemothorax in 25% of the patient, Diabetes inipidus is rarely associated.
- HRCT s/o thin walled cyst and nodules
- Histology s/o birbek granules

HYPERSENSITIVITY PNEUMONITIS

- Inflammatory disorder of the lung involving alveolar wall caused byrepeated inhalation of a variety of organic agents by a susesptible host
- Delayed hypersenstivity reaction
- *Aka Extrinsic allergic alveolitis*
- Involves TERMINAL airways and alveolar walls
- Due to repeated inhalation of ORGANIC agents, by a SUSCEPTIBLE host
- Effect of **smoking: Chronic** (rather than acute HP)

ETIOLOGY

1. Bird Fancier's lung: proteins in feathers / droppings
2. Farmer's lung: thermophilicactinomycetes
3. Bagassosis: (sugarcane): thermophilicactinomycetes
4. Cephalosporium HP – contaminated sewage
5. Chemical lungs : isocynates : antihapten antibodies

** Thermophilicactinomycetes also cause: potato riddler's lung, mushroom worker's lung

Pathogenesis: Th-1 mediated immune response to antigen; (delayed hypersensitivity reaction), **(No eosinophilia)**

Clinical presentation:

*Acute:*6-8 hours after exposure – fever with chills, cough, dyspnoea, and malaise – clear in few days if no further exposure.

*Sub acute:*insidious onset of symptoms over weeks.

*Chronic:*evolution into pulmonary fibrosis in patients with continued antigen exposure. (These patients present with long-standing DOE, clubbing, evidence of PHT, respiratory failure)

TEMPORAL relation to exposure +, i.e., symptoms may decrease/disappear after patient leaves the site of exposure for few days; reappear on returning.
DISEASE SEVERITY CORRELATES WITH INHALED ANTIGEN LOAD.

Investigation:

Patient Shows:

CXR: normal / reticulonodular infiltrate; apical sparing; eventually honeycombing
HRCT: GGO in LL, patchy emphysema > interstitial fibrosis; No LNs
PFT: Restrictive defect
With antigen avoidance in early disease, PFT abnormalities reverse.
BAL: lymphocytic alveolitis with inverse CD4/CD8 ratio
Biopsy: Usually not required; mononuclear bronchiolitis, interstitial infiltrate of lymphocytes & plasma cells, single non-necrotizing parenchymal granulomas without vascular involvement.
TREATMENT: Discontinuation of ag exposure / Resp equipment / Steroids

EOSINOPHILIC PNEUMONIAS

- ✓ Associated with asthma & peripheral eosinophilia → *both of which do not occur in HP*
- ✓ *Fleeting / migrating* pulmonary infiltrates
- ✓ Invariable response to steroids & Absence of recurrences

Important types of EP

ABPA

- MC cause is: A. fumigatus
- Diagnostic criteria:
  - Asthma
  - Infiltrates (pulm)
  - Eosinophilia>1000/ml
  - Raised serum IgE
  - Type I hypersensitivity to A. fumigatus
  - Serum precipitins to A. fumigatus
  - Central bronchiectasis
- T/t: Long term use of steroids
- Prophylaxis: Itraconazole

Tropical Pulmonary Eosinophilia

- MC due to filarial infection (W. bancrofti, malayi)
- Also: Ascaris, Ancylostoma, Toxocara, Strongyloides
- T/t: DEC / Ivermectin / etc.

Drugs:***Nitrofurantoin*, sulfonamides**, penicillins, thiazides, chlorpropamide, tricyclic anti-depressants, **hydralazine**, gold, **INH**, PAS, indomethacin, **anti-TNFα monoclonal antibodies**

Loeffler's syndrome

Unknown cause; migratinginfiltrates on CXR; *minimal clinical manifestations*

Churg-Strauss syndrome

- Small vessel granulomatous vasculitis
- Triad of EP; peripheral neuropathy; mild GN in 20-30%; Allergic rhinitis
- Myocardial inv is the MC cause of death
- Zafirlukast therapy might unmask CSS
- Treatment: Steroid + Cyclophosphamide

Hyper-eosinophilic syndrome

- Peripheral eosinophilia >1500/mm^3 ≥ 6 months, Bone marrow eosinophilia +.
- No parasitic / allergic / other known cause
- Cardiac manifestations: TV abnormality, endomyocardial fibrosis, RCMP
- Other organ systems affected: lungs, liver, skin, spleen, nervous system
- T/t: Glucocorticoids / hydroxyurea / Imatinib

ENVIRONMENTAL LUNG DISEASES

Particle size

- 10-15 μm: 'Fugitive' dusts
- 2.5-10 μm: High tracheobronchial tree
- <2.5 μm: Alveoli
- <0.1 μm: Airstream

ASBESTOSIS

- 2 geometric forms of asbestos
  - i. Serpentine (curled, flexible)
  - ii. Amphibole (straight, stiff)
- MC type of asbestos used in industry: Chrysotile (serpentine)
- *Although both are fibrogenic, amphiboles more pathogenic than Chrysotile*
  1. Chrysotile deposited in upper airway → cleared
  2. Chrysotile more soluble → gradually leached from tissues
  3. Amphiboles align better with the inhaled stream of air (straight) → deposited in alveoli → penetrate epithelium (stiff) → reach interstitium
  4. *Only amphibole exposure causes mesothelioma*
- Fibers > 8 mm long &< 0.5 mm thick are more injurious

Diseases due to Asbestos exposure:

1. Pleural fibrosis
2. Interstitial fibrosis
3. Pleural effusion
4. Bronchogenic carcinoma
5. Mesothelioma (usu. pleural; occasionally, peritoneal)
6. Laryngeal & colon cancer

At risk: Asbestos miners, Fabrication workers, Insulation material exposure

*Family workers of asbestos workers are also at ↑ risk

- Disease occurrence is ∞ Duration & Intensity of exposure
- Manifestations usually occur 10-20 years *after* exposure
- Exposure *for* 10 years is usually required for disease causation

Clinical features are those of ILD, i.e., progressive exertional dyspnea, minimally productive cough; (hypoxemia, dyspnea at rest, evidence of RHF: occur very late in the course)

PFT's:

- Early sign: ↓ DLCo
- Eventually → Restrictive pattern on spirometry

CXR: Pleural plaques (diaphragmaticparietal pleura, esp. lower lobes)

- MC manifestation of asbestos exposure
- Imply exposure, not pulmonary impairment
- Asbestosis: Irregular / linear opacities → 1st in lower lobes; later spreads to middle & upper zones; 'ground glass' appearance in some patients

T/t: No specific t/t; Supportive management, as for other causes of pulmonary fibrosis

SILICOSIS

Is the MC chronic occupational disease in the world?

Mining, stone cutting, packing of silica flons, quarrying (granite), sand blasting, tunneling through rock are few occupations which lead to siticosis.

2 forms of silica:

A. Crystalline: includes Quartz (MC cause), crystobalite, tridymite
B. Amorphous

- More fibrogenic form: Quartz
- Quartz, if mixed with other minerals, is less fibrogenic than pure quartz

Pathogenesis: Inhaled SiOH (hydrates of silica) → form bonds with cell membrane PLs & proteins → cell membrane damage → Activation & release of inflammatory mediators by alveolar macrophages

- Disease occurrence is ∞ Duration & Intensity of exposure
- Manifestations usually occur 10-20 years *after* exposure
- Disease progresses even after cessation of exposure
- Presents with features of pulmonary fibrosis
- ↑ risk of TB & NTM – Silicotuberculosis.

CXR: UL (esp. posterior part) NODULAR opacities (c.f. diffuse interstitial opacities in asbestosis)

- Nodules coalesce with progression
- > 1 cm → PMF
- Eggshell calcification of hilar LNs

PFT: *Both Restrictive & Obstructive components*

(*Also with bronchiectasis)

Coal Workers' Pneumoconiosis

- Anthracite > Bituminous
- 70% in anthracite miners, 12% in all miners.
- Additive effect on smoking for the development of COPD
- "Simple" CWP:
  - Reticular opacities (small irregular)
  - Prolonged exposure: Nodular (Regular rounded 1 – 5 mm)
  - Calcification not seen
- "Complicated" CWP:
  - Form of PMF
  - Coalescent nodules from 1 cm – entire lobe
  - *Upper lobes*
- Caplan syndrome

BERYLLIOSIS

Ceramics & fluorescent light industry
2-15 years of exposure required for disease

- Chronic granulomatous disease*

BYSSINOSIS

- 'Monday chest tightness': Symptoms at the end of the 1st day of the workweek
- As disease progresses, symptoms start occurring everyday
- **PFT:***Obstructive pattern*
- Additive effect of cotton dust & cigarette smoking
  T/t: ↓ exposure; Bronchodilators & Antihistamines reduce chest tightness symptoms

PULMONARY THROMBOEMBOLISM

Risk Factors for development of DVT:
Long distance air travel, obesity, smoking, OCP (incl. HRT), Surgery, Trauma, APLS, Cancer, HT, COPD, Factor V Leiden mutation, Prothrombin gene mutation.
Pathophysio:

- **Thrombi dislodge from site of formation → embolize to PA**
- **(Or paradoxically to arterial circulation through PFO/ASD)**

Pathophysiologic effects of PE:

1. **↑ PVR (vasc obs + serotonin secretion)**
2. **Hypoxemia (↑ in dead space; Alveolar hypoventilation relative to perfusion in the normal non obstructed lung; R→L shunt; ↓DLCo)**
3. **↑ airway resistance (Because of constriction of airway distal to bronchi)**
4. **Tachypnea**
5. **↓ pulmonary compliance**

MC source of pulmonary emboli: Pelvic veins / leg veins proximal to knees (Ileofemoral veins)
MC source of paradoxical emboli: Calf veins

Non-thrombotic PE: Fat / tumor / amniotic fluid / air etc
MC cause of death: Right Heart Failure
Scoring system to assess likelihood of PE: 'WELLS'

- **Includes: s/s of DVT, HR>100, surgery/immobilization > 3 days in last 4 weeks, previous DVT/PE, Hemoptysis, malignancy**
- **Carries more NPV than PPV**

Clinical features:
MC symptom: Dyspnea
MC sign: Tachypnea
Massive PE: Dyspnea, Cyanosis, Hypotension, Syncope
Small to Moderate PE: Chest pain (infarction)
DIAGNOSIS :-

1. D-dimer ELISA: ↑↑

- **Non-specific, Highly sensitive (>95%)**
- **Acute phase reactant (↑ in MI, fulminant sepsis, other systemic illness, Cancer, Pregnancy – IIIrd trimester)**
- **NPV**

2. ABG

- **No diagnostic utility**
- **↓ PO_2 & ↓ PCO_2**

3. ECG

- **MC ECG abnormality: RV strain**
- **Sinus tachycardia**
- **$S_1Q_3T_3$**

4. CXR

- **MC: NORMAL CXR *(A normal CXR is suggestive of PE)***
- **Westermark sign: Focal oligemia (s/o massive PE)**
- **Hampton's hump: peripheral wedge shaped opacity above diaphragm (s/o small PE)**
- **Palla's sign: Enlarged right descending PA**

5. Venous Doppler for DVT

- **Loss of vein compressibility → implies DVT**
- **Adequate 'surrogate' for PE**
- **Absent in 50% patients: absence does not r/o PE**
- **PPV only**

6. CECT Chest

- ***Initial imaging modality of choice in suspected PE***
- **Embolus visible as 'filling defect' in pulm vasculature**

7. V/Q Scan

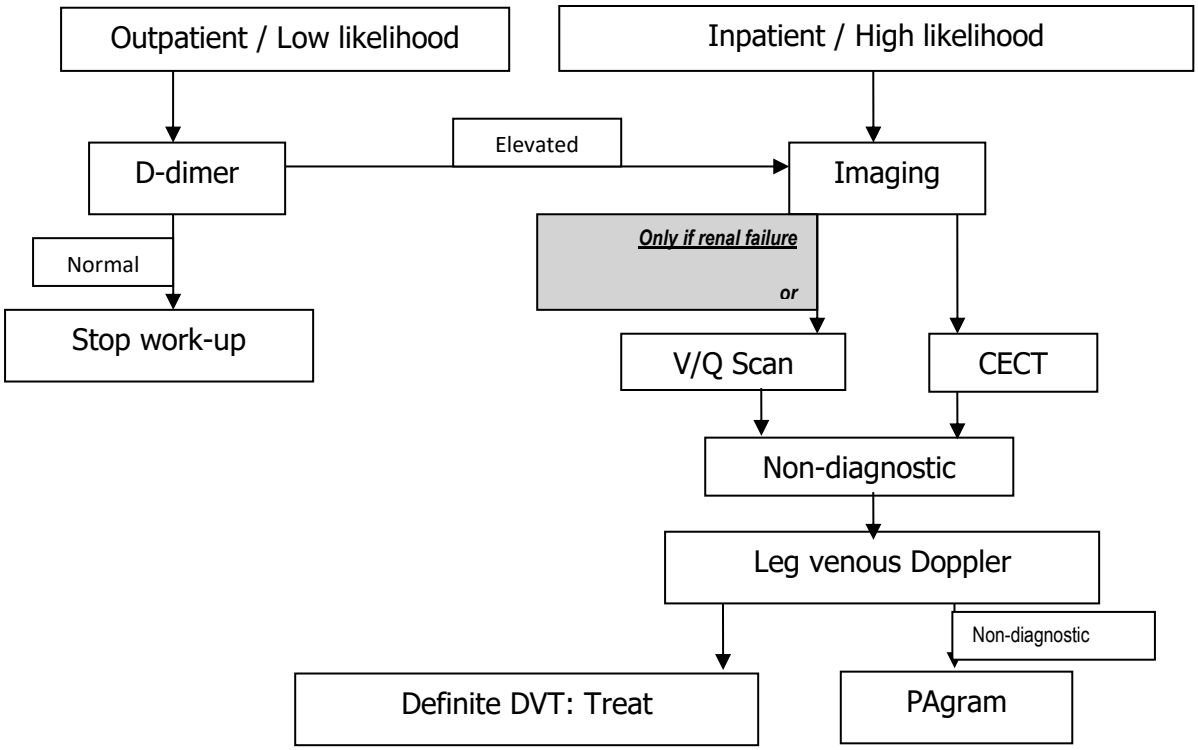
- **Reserved for patients with renal failure or contrast allergy**
- **V Scan: Xenon / Krypton gas**
- **Q scan: Radiolabelled Albumin**
- **High Probability scan for PE:**
    - **2 / more segmental perfusion defects with normal ventilation**
  - ✓ ***Usually V/Q scan is non-diagnostic***
  - ✓ ***V/Q is never diagnostic***
  - ✓ ***A normal scan reliably excludes PE***

Imaging modality of choice for diagnosis of PE in

8. Pulmonary Angiogram
- **Gold standard**
- **Most specific**
- **Reserved for**
    1. **Non-diagnostic CT / VQ scan**
    2. **Patients who are to undergo embolectomy**

9. Echocardiography
- **Helpful for**
    1. **D/D: (MI / tamponade / dissection)**
    2. **Assessment of degree of RV dysfunction**
- **McConnell's sign: RV free wall hypokinesis with normal RV apical motion**

APPROACH TO SUSPECTED PULMONARY EMBOLISM



TREATMENT

PRIMARY THERAPY:

- **Thrombolysis / Embolectomy**
  - **(Preferred thrombolytic agent is tPA)**
- Indications of primary therapy:

1. **Hypotension**
2. **RV dysfunction**
3. **↑ troponin levels → (evidence of RV ischemia)**

SECONDARY PREVENTION:

- **Anticoagulation / IVC filter**
- **Anticoagulation with heparin / warfarin**
  - ***Duration:* 6 months / Indefinite**
- ***Indications of IVC filter*: Active bleeding / Recurrent PE despite anticoagulation**

PREVENTION OF DVT

(e.g. Surgical patients)

1. **Graduated compression stockings**
2. **Pneumatic devices**
3. **Anticoagulation with heparin (Occasionally, Long term warfarin: THR / TKR / Cancer surgery)**

PULMONARY HYPERTENSION

- Mechanism of pulmonary vasoconstriction: Inhibition of K^+ channels & ↑ Ca^{2+} entry in vascular smooth muscle cells
  - Cor pulmonale: RV enlargement / dilatation
  - RV failure: Raised RVEDP
  - MC cause of cor pulmonale: PHT

CAUSES & DISEASE ASSOCIATIONS: MC cause of PHT worldwide → schistosomiasis; Collagen vascular diseases (esp. CREST), CHD, fenfluramine, Aminorex, Jamaican bush tea, HIV, Pulmonary VOD, portal HT (occasionally), pulmonary capillary hemangiomatosis

PULMONARY VENOUS HT: PHT due to ↑ resistance to pulmonary venous drainage
Because of either → LV diastolic dysfunction: HHD, CAD, ↓ LV compliance secondary to old age / DM
OR Mitral Valve disease → MS / MR

FAMILIAL PPH: AD inheritance, gene on chromosome 2 (PPH I gene)

PRIMARY PULMONARY HYPERTENSION

- Mutation in BMPR2 protein
- Strong female preponderance
- Usually presents with advanced disease (4^{th} – 5^{th} decade)

CLINICAL FEATURES:
- MC symptom: DOE
- Also: angina, syncope, peripheral edema, Raised JVP, palpable RV lift (LPSH), loud P2, TR, [Clubbing is not a feature of PPH → seen in PHT associated with CHD / ILD]

CXR: Enlarged central PA
ECG: RAD, RVH
Echo: RA & RV enlargement; TR
↓ PaO_2 & ↓ DLCo
Cardiac catheterization: Diagnostic modality of choice

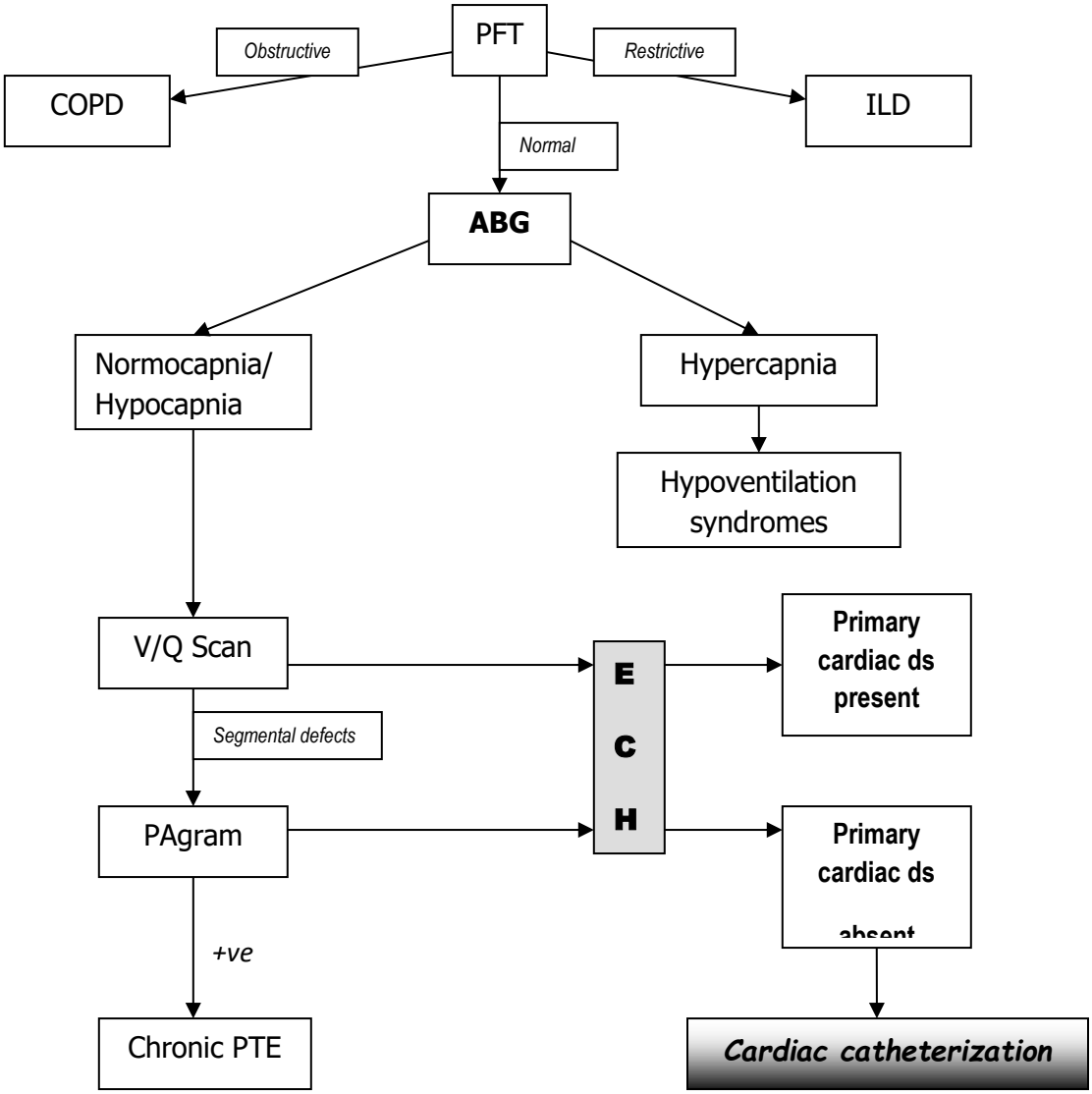
PROGNOSIS:
Life Expectancy → CHD > PPH > Scleroderma-associated PPH

TREATMENT :-

Anticoagulation & Diuretics → indicated for all patients

1. CCB
2. PGI_2 analogue
3. Inhaled NO
4. Bosentan
5. Sildenafil: response similar to inhaled NO
6. Lung transplantation: indicated for patients on epoprostenol who continue to have RHF

APPROACH TO UNEXPLAINED PULM HYPERTENSION


PFT
Obstructive
Restrictive
COPD
ILD
Normal
ABG
Normocapnia/
Hypocapnia
Hypercapnia
Hypoventilation
syndromes
V/Q Scan
Segmental defects
PAgram
+ve
Chronic PTE
E
C
H
Primary
cardiac ds
present
Primary
cardiac ds
absent
Cardiac catheterization

ABG

Steps of taking ABG

- 1. with patient palm up, wrist is extended, and radial artery is palpated
- 2. the skin is cleaned with spirit, with 1% xylocaine is injected
- Both needle and syringe is rinsed with heparin
- Artery is entered with needle as much parallel to the vessel as it decreses the scraping of the periosteum and decreases the pain.
- Blood will enter the syringe (glass) as soon it enters the artery, 5 ml of the blood is taken usually . Suction is not applied by pulling the plunger.
- Air bubbles are removed
- Rubber stopper is applied
- Immersed in bag of slush
- Superficial artery is preferred
- The radial artery is the preferred site for cannulation
- it is superficial at the wrist if there is any thrombus formed due to injury ulner artery can form collateral circulation to the hand. Allen test.
- Dorsalis pedis, femoral, brachial and posterior tibial artery are the alternative sites.
- Glass syringes should be used for the most accurate results as diffusion of po2 can occur through the plastic tube
- For adequate equilibration of gases, 25 min may be required after starting or stopping supplemental oxygen prior to drawing the ABG blood sample

Components of ABG

- pH : 7.35-7.45
- PaCO2 : 35-45 mm Hg
- PaO2 : 70-100 mm Hg
- HCO3- : 22-26 mEq/L
- SaO2 : 93-98%
- %MetHb : <2.0%
- %COHb : <3.0%
- Base excess : -2.0 to 2.0 mEq/L

pH

- Indicates whether the person is in a normal, acidotic or alkalotic state
- Concentration of hydrogen ions expressed as a negative logarithm
- Normal value: 7.35 – 7.45

PO2

- Partial pressure of oxygen dissolved in the blood
- Must have sufficient partial pressure in order to bind to Hb for transport to tissues
- Normal: 80 – 100 mmH
- **Effect of age:** pO2 = 104.2 – (0.27 x age)

PCO2

- Partial pressure of CO**2** being carried in the blood to lungs for excretion
- Represents RESPIRATORY component
- Normal: 35 – 45 mmHg

HCO3

- Represents the amount of bicarbonate present in the blood
- Represent METABOLIC component
- Renal tubules regulate balance of hydrogen ions and bicarbonate ions
- Acidosis – excrete hydrogen, reabsorb bicarb
- Alkalosis – retain hydrogen, excrete bicarb
- Kidneys generate additional bicarbonate when needed
- Normal: 22 – 26 mEq/L

Base Excess

- Includes the total of bases (alkalis) such as bicarb, Hgb, plasma proteins
- Excess metabolic acids cause bicarb level to drop, creating a NEGATIVE BE (sometimes called base deficit)
- May be used to guide bicarbonate administration
- Normal: between -2 and +2

How to treat metabolic acidosis

- HCO3 therapy is given in metabolic acidosis when either ph is <7.2 or BE >-15.
- Amount of HCO3 to be given in merabolic acidosis is calculated as ½ x body weight (in kg) x base deficit
- Half is given usually in first half an hour while rest is given in normal saline in two hours.

STEPWISE APPROACH TO EVALUATION OF ACID-BASE DISORDERS

- **Determine acid/base balance**
- **Determine cause of pH change**
- **Compensated or uncompensated**
- **Determine oxygen status**
- **If the pH is low (acidotic)**
- **The cause is respiratory if the CO2 is elevated**
- **The cause is metabolic if the HCO3- is low**
- **If the pH is high (alkalotic)**
- **The cause is respiratory if the CO2 is low**
- **The cause is metabolic if the HCO3- is elevated**

Compensation

- **Respiratory compensation is rapid minutes**
- **Metabolic compensation is slow hours to days**
- **Partial compensation**
  - **Opposing parameter abnormal, but pH remains abnormal**
- **Full or Complete compensation**
  - **Opposing parameter abnormal, and pH is normal**

****pH – pCO_2 relationship *(Applies only to acute respiratory disorders)***

If pCO_2 ↑ 20, pH ↓ 0.10 units

If pCO_2 ↓ 10, pH ↑ 0.10 units

1. Check if HCO_3^- (metabolic status) is compatible with findings from Step 2
   - Compensation for respiratory acidosis & resp alkalosis:
     - "14-24"
   - Respiratory acidosis
     - Acute: For every 10 rise in CO_2 there is **1** rise in HCO_3^-
     - Chronic: For every 10 rise in CO_2, there is **4** rise in HCO_3^-
   - Respiratory alkalosis
     - Acute: For every 10 fall in CO_2, there is **2** fall in HCO_3^-
     - Chronic: For every 10 fall in CO_2, there is **4** fall in HCO_3^-
   - Metabolic Acidosis
     - Winter's formula: $pCO_2 = [(1.5 \times HCO_3^-) + 8] \pm 2$
     - If pCO_2 is outside this range, there is a co-existing respiratory disorder
     - Respiratory compensation for met acidosis is prompt (compensation may or may not be complete)
   - Metabolic Alkalosis
     - Respiratory response
       1. Non-linear ↑ in pCO_2 (with ↑ in HCO_3^-)
          - pCO_2 ↑ 0.75 mmHg per 1 mmol/l ↑ in HCO_3^-
          - pCO_2 ↑ 6 mmHg per 10 mmol/l ↑ in HCO_3^-
       2. pCO_2 is never more than 55
       3. Resp compensation is never complete, i.e., pH will always be > 7.45
2. For metabolic acidosis, determine **ANION GAP**
   - Normal AG = 10-12 mEq/L
     - Normal AG or Non-anion gap acidosis → AG ≤ 12
   - Reflects unmeasured anions and cations in the serum
   - Unmeasured anions: Proteins, phosphates, sulphates, organic acids
     - Serum ALBUMIN accounts for 11 mmol of AG
     - When acid anions e.g. lactate / acetoacetate accumulate in ecf → AG↑
   - Unmeasured cations: K, Mg, Cl
   - $AG = Na^+ - (Cl^- + HCO_3^-)$
     - Cl^- = 98 – 106 m Eq/L

   - ***Causes of High AG met acidosis: "MULEPAK"***
     - **Methanol poisoning, Uremia, Lactic acidosis, Ethylene glycol, Paraldehyde, Aspirin, ketoacidosis**
   - <u>Causes of HAG in absence of met acidosis (unusual)</u>
     - Mild increase in AG (12 – 14) with respiratory / metabolic alkalosis
     - ↓ Unmeasured cations - Severe hypocalcemia/ hypokalemia

<u>Decreased Anion gap</u>

a) Hypoalbuminamia eg. Nephrotic syndrome, Severe hemodilution, Hyponatremia, IgG myeloma; Increase in non major cations: Lithium toxicity, Bromide, & iodine toxicity, Hypercalcemia, Hypermagnesemia

METABOLIC ACIDOSIS

- Association with hyperkalemia: pH ↓ by 0.10 → Serum K^+ ↑ by ≈0.6mmol/l
- Hyperkalemia occurs because: kidney compensates by excreting more H^+ ions, in exchange for K^+
- Exceptions: DKA, Renal failure-associated acidosis, diarrhea, types I and II RTA
- ***Physiologic effects***

    - Kussmaul's resp: Rapid, deep breathing (↑ in TV)
    - Acidosis depresses cardiac contractility but also stimulates CA release → inotropic fn may be normal or ↓
    - Peripheral arterial VD
    - Central & pulm VC
    - CNS depressed → headache / lethargy / stupor
    - Glucose intolerance may occur

CAUSES

Increased Anion Gap	Normal Anion Gap
a) Ketoacidosis: Diabetic, Alcoholic, starvation b) Lactic acidosis: Shock, mesentric, ischemia, gen. seizures, severe asthma, hypothermic shivering c) Renal failure (Uremia) d) Methanol poisoning e) Ethylene glycol Poisoning f) Paraldehydc poisoning g) Salicylate intoxication	1. Normal or hyperkalemia a) Early renal failure b) Tubulointerstial diseases c) Adrenal insufficiency d) Type IV renal tubular acidosis (RTA) e) Addition of acid (eg. HCl, Arg HCl, TPN) 2. Hypokalemia a) Diarrhea b) Entero cutaneous fistula c) Pancreatic drainage d) Biliary drainage e) Villous adenoma f) Ureteral diversions g) RTA Type I , Type II h) Carbonic acid anhydrase inhibitors (Acetazolamide) i) Post-hypocapnia j) Dilutional acidosis (N/S) k) Some cases of DKA

NAGMA

- Primary abnormality is low HCO_3
- NAGMA is hyperchloremic b/c Cl replaces HCO_3
- The ↑ in Cl above normal (98-106) ≅ ↓ in HCO_3 below normal (22-26)
    - Absence of such a relationship suggests a mixed disorder

HAGMA

↓ HCO_3 & ↑ AG; Also ↓ Cl

If added disorder is present e.g. resp acidosis/ met alkalosis, the HCO_3 may be normal / ↑, but HAG will persist

☛ HAGMA + Resp alkalosis → Salicylate ingestion

LACTIC ACIDOSIS

Clinical indicator of tissue hypoxia

- Type A: Poor tissue perfusion: shock, severe anemia, CO / CN poisoning
- Type B: Aerobic disorders: Renal / hepatic failure, Ethanol, Methanol, INH, ZDV, Metformin, Severe cholera, malaria, malignancy
- D-lactic acidosis: (↑ AG, hyperchloremia): Due to formation of D-lactate by gut bacteria;
  - Causes: Jejuno-ileal bypass, intestinal obstruction
- Vasopressor therapy in circulatory failure worsens lactic acidosis
- TREATMENT: Alkali ($NaHCO_3$); if pH < 7.15 (to prevent arrhythmias)
  - $NaHCO_3$ may itself paradoxically ↑ lactic acid production (HCO_3 stimulates PFK) → worsens acidosis → further depresses cardiac fn
  - Other complications (of therapy): Fluid overload, HT
  - Therefore therapy should to ↑ pH to ≯ 7.2, over 30-40 minutes

*****ASSESSMENT OF METABOLIC ALKALOSIS*****

Based upon 4 parameters: ECFV, Serum K^+, Blood pressure & RAA axis status

1. ECFV contraction, Hypokalemia, Normotension, Secondary Hyperreninemic hyperaldosteronism
   (A) GI Causes: Excessive vomiting, NG aspiration
   (B) Renal Causes: Diuretic use, Penicillin, Bartter syndrome, Gitelman syndrome

2. ECFV expansion, hypokalemia, Hypertension, Hyperaldosteronism
   (A) High Rennin: Renal artery stenosis, Accelerated hypertension, Estrogen therapy, Rennin secreting tumor
   (B) Low Rennin: Primary aldosteronism (Hyperplasia / Adenoma / Carcinoma), Cushing's syndrome, 11β- or 17α- hydroxylase defects, Carbenoxolone / Licorice intake

3. ECFV expansion, hypokalemia, Hypertension, Hyporeninemic hypoaldosteronism
   Liddle's syndrome

METABOLIC ALKALOSIS

I. Chloride responsive	**II. Chloride resistant**
Gastrointestinal causes 1. Vomiting 2. Nasogastric suction 3. Villous adenoma 4. Congenital cholridorrhoea Renal causes 1. Diuretic induced (thiazide or loop) 2. Carbenicillin , Penicillin 3. Sulfates, phosphates 4. Post-hypercapnia Exogenous alkali 1. Bicarbonate therapy 2. Acid salts eg. Acetate 3. Blood transfusions - ↑ citrate load 4. Antacid therapy a) Absorbable antacids b) Nonabsorbable + ion resins 5. Milk – alkali syndrome	A. Normotensive variants 1. Bartter's syndrome 2. Gitelman's syndrome 3. Profound potassium depletion 4. Refeeding alkalosis 5. Hypercalcemia 6. Hyperparathynoidism 7. Severe Mg^{++} depletion B. Hypertensive variants a) Endogenous variants 1. Primary aldosteronism 2. Cushings syndrome 3. Hypereninism (secondary aldosteronism, renal artery stenosis, malignant hypertension) 4. 11 or 17 – hydroxylase deficiency 5. Liddle's syndrome b) Exogenous mineralocorticoid 1. Steroid therapy 2. Carbenoxolone 3. Glyrrhizic acid (licorice)

RESPIRATORY ACIDOSIS (ALVEOLAR – HYPOVENTILATION)

↓ CNS drive: Sedative overdose, brainstem injury, CSA, hypothyroidism
↓ strength: MG, GBS, ALS, phrenic n. injury, resp. ms. Fatigue
↑ load: Airway obstruction

RESPIRATORY ALKALOSIS (ALVEOLAR HYPERVENTILATION)

(A) CNS stimulation: Anxiety / hysteria, Fever, Pain, Psychosis, CVA, meningitis, encephalitis, tumor trauma
(B) Hypoxemia or tissue hypoxia: high altitude, pneumonia, pulmonary edema, aspiration, severe anemia
(C) Drugs / hormones: pregnancy, progesterone, salicylates, nikethamide
(D) Stimulation of chest receptors: hemothorax, flail chest, cardiac failure, pulmonary embolism
(E) Miscellaneous: Septicemia, hepatic failure, mechanical hyperventilation, heat exposure, recovery from metabolic acidosis

RESPIRATORY FAILURE

- Definition: **inability of the lung to meet the metabolic demands of the body. This can be from failure of tissue oxygenation and/or failure of CO2 homeostasis.**

- In practice, respiratory failure is defined as a PaO2 value of less than 60 mm Hg while breathing room air or a PaCO2 of more than 50 mm Hg.

- **Acute respiratory failure is characterized by life-threatening derangements in arterial blood gases and acid-base status. eg . Rupture of bulla causing pnuemothorax in COPD patient etc.**

- **Chronic respiratory failure are less dramatic and may not be as readily apparent**

Normal respiration requires the integrated function of 5 components:

1. **Nervous system: Medulla + Cerebral cortex → determine the rate & effort**
   - **Dysfunction: Causes CENTRAL APNEA**
   - **Evidence: RR < 12 with hypoxia / hypercarbia**
2. **Musculature (Pump)**
   - **Normal individual: Inspiration active; Expiration passive**
   - **Respiratory failure: Even expiration requires the action of accessory resp muscles**
     - **Evidence of dysfn: Thoraco-abd paradox (specific for RM fatigue)**
3. **Airways**
   - **Conduit for delivery of gases**
   - **Dysfn in COAD / asthma / bronchiectasis**
   - **Evidence of dysfn: wheezing / stridor (Upper large airway obstruction)**
4. **Alveolar units**
   - **Functions:**
     i. **Respiratory gas exchange**
     ii. **Elastic recoil**
   - **Dysfn in pneumonia / collapse / ARDS**
   - **Evidence: BBS, WP, BP, insp crackles, dull percussion note**
5. **Vasculature (Pulm capillaries)**
   - **Evidence of dysfn: e/o PE / PHT**

DYSFUNCTION OF 1 / MORE OF THE ABOVE 5 → RESP FAILURE

Types of resp failure

Type 1: Hypoxemic RF

Type 2: Hypercapnic RF: Alveolar hypoventilation → ↓ CNS drive, impaired NM function, ↑ load on RS

Type 3: Peri-operative respiratory failure (because of atelectasis: ↓ FRC after GA → collapse)

Type 4: Hypoperfusion of respiratory muscles in shock

Type 1: MC type of RF.

(A) Represents failure of oxygenation

(B) PaO2 : low < 60mmhg
(C) PaCO2: Normal or low (< 49 mmhg)
(D) P(A-a) O2 : Increased
P(A-a) O2 Gradient

- **Used to evaluate the cause of decrease in Pao2, it is extremely helpful to know the difference between the alveolar and arterial PO2**

- **PAO2 = 150 – PaCO2/ 0.8**
- **The normal P(A-a) O2 Gradient is 5-10 mmhg**
- **At any age P(A-a) O2 Gradient greater than 20mmhg should be considered abnormal is suggestive of pulmonary parenchyma dysfunction**

Causes of type I RF

- **Parenchyma diseases**
- **Diseases of vasculature**

Type 2:

- **Represents a defect in ventilation (hypoventilation)**
- **PaO2 : low < 60mmhg**
- **PaCO2: Increased (> 49 mmhg)**
- **P(A-a) O2 : normal**

Causes of type II RF

- **Obstructive lung diseases**
- **Foreign body**
- **Decreased central respiratory drive e.g. CNS disorders, brain injury, meningitis**
- **Weakness of the respiratory muscle**
- **Disorder of spine e.g. kyphoscoliosis**

Type III respiratory failure

- **Also called as perioperative respiratory failure.**
- **Occurs as a result of atelactasis in the perioperative period**
- **Due to decrease in the FRC leading to collapse of dependent lung unit after general anesthesia.**

- TREATMENT
  - **Frequent change in position**
  - **Chest physiotherapy**
  - **Upright positioning**
  - **Aggressive control of pain**
  - **NIPPV can also be used**

Type IV respiratory failure

- **Occurs because of hypo perfusion of respiratory muscles in patients of shock.**
- **Lactic acidosis and pulmonary edema can occur in these patient**
- **Intubations and mechanical ventilation is required in these patients till shock recovers**

Clinical and Laboratory Manifestation of respiratory failure

- **Cyanosis - Bluish color of mucous membranes/skin indicate hypoxemia**
  - Unoxygenated hemoglobin 4 gm/dL
  -Meth HB >1.5mg/dl
  - Sulph hb >0.5mg/dl
  - Cyanosis appear when SO2 <88%

Psuedocyanosis

- **Organic nitrites/nitrates**
  - **Nitroglycerin**
  - **Nitroprusside**
  - **TNT**

- **Others**
  - **Local anesthetics - Benzocaine, lidocaine, prilocaine,**
  - **Antimalarials - Primaquine, chloroquine**
  - **Antineoplastic agents - Cyclophosphamide, ifosfamide,**
  - **Analgesics/antipyretics - Acetaminophen, acetanilid,**
  - **Phenacetin, celecoxib**
  - **Antibiotics - Sulfonamides, nitrofurans, P-amino-salicylic acid, dapsone**
  - **Industrial/household agents - Aniline dyes, nitrobenzene, naphthalene (moth balls), aminophenol, nitroethane (nail polish remover)**

ASSESSMENT OF PATIENT

- **Careful history**
- **Physical Examination**
- **ABG analysis**
  - **-Classify RF and help with cause**

    1) **PaCO2**
    2) **P(A-a)02**

- **Lung function**
- **Chest Radiograph**
- **ECG MC finding is sinus tachycardia, next most common is p pulmonale**

Pulse oximetry

- **Estimates arterial saturation not PaO2 using absorption of two different wavelengths of infrared light.**

- **Sources of error**
  - **Poor peripheral perfusion**
  - **Dark skin (oximeter over-reads slightly)**
  - **False nails or nail varnish**
  - **Lipaemia**
    - **Hyperlipidaemia**
    - **Lipid infusion for TPN**
    - **Propofol infusion**
  - **Bright ambient light**
  - **Poorly adherent probe**
  - **Excessive motion**
  - **Carboxyhaemoglobin**

TREATMENT OF RESPIRATORY FAILURE :-

Oxygen Therapy

- **Supplemental O2 therapy essential titration based on SaO2, PaO2 levels and PaCO2**

- **Goal is to prevent tissue hypoxia**

- **Tissue hypoxia occurs (normal Hb & C.O.) occours when arterial PaO2 < 38 mmHg or SaO2 < 70%**

- **Increase arterial PaO2 > 60 mmHg (SaO2 > 90%)**

O2 TOXICITY

- **FiO2 35 to 40% can be safely tolerated indefinitely**
- **Very high levels(>1000 mmHg) CNS toxicity and seizures**
- **Lower levels (FiO2 > 60%) and longer exposure: - capillary damage, leak and pulmonary fibrosis**
- **PaO2 >150 can cause retrolental fibroplasia**

TYPES OF MECHANICAL VENTILATION
INVASIVE AND NON INVASIVE

INDICATIONS OF MECHANICAL VENTILATION

- **Apnea with respiratory arrest**
- **Acute lung injury**
- **Respiratory rate >35breaths per minute**
- **Vital capacity <15 mL/kg**

- **Po2<60 at FIO2 0.6**
- **Respiratory muscle fatigue**
- **Obtundation or coma**
- **bradypnea**
- **(PCO2) of >50 mm Hg with pH <7.25**

General principals of ventilation

- **The endotracheal tube should be inserted to an average depth of 23 cm in men and 21 cm in women (measured at the incisor)**
- **The pressure in the cuff generally should not exceed 25 mm Hg.**
- **Tracheostomy should be done if we are anticipating ventilatory setting for more than 3 days.**
- **Routine suctioning is not recommended because suctioning may be associated with a variety of complications, including desaturation, arrhythmias, bronchospasm, severe coughing, and introduction of secretions into the lower respiratory tract.**

Modes of ventilatory support

- **CMV**
- **ACMV**
- **SIMV**
- **CPAP/PEEP (positive end-expiratory pressure)**

CMV

- **Controlled mode ventilation**
  - **Used for initiation of the ventilation**
  - **No patient contribution**
  - **All variables are independent**
    - **FIo2**
    - **TV**
    - **RR**
    - **I/E**

ACMV

- **Assist control mode ventilation**
- **Inspiratory cycle is initiated either by the patient or**
- **If no patient effort is present then by a timer signal within the ventilator.**
- **Also commonly used for initiation**
- **Synchronization of ventilatory cycle with patients inspiratory effort.**
- **Respiratory alkalosis**
    - **Myoclonus**
    - **Seizures**

SIMV

- **Synchronized intermittent mandatory ventilation**
- **Patient is allowed to breathe spontaneously without ventilator assist in between the ventilator breaths**
- **Ventilatory breath are delivered in synchrony**
- **Mandatory are the number of preset breaths**
- **Intermediate mode**
- **Helpful in weaning**
- **Respiratory muscle training**

CPAP

- **Continuous positive airway pressure**
- **Not a true mode of ventilation**
- **All ventilation occurs because of patients spontaneous efforts Ventilator just gives fresh gas to the breathing circuit with operator depended positive pressure.**
- **Used to access the extubation potential in the patient who require very little ventilatory support or in patient with intact respiratory system function who require an ET tube for airway protection.**

- SIMV/ PSV : extended period

- T piece/ CPAP : brief period ventilation
  - Spontaneous trial for 5-10min/hr with one hour rest and with daily incremented

Advantages:

1. **Guaranteeing minute ventilation**
2. **Reducing O_2 & energy consumption of respiratory muscles.**

Disadvantages:

1. **Quiet, sedated paralyzed patient**
2. **Ventilator disconnection can be fatal**
3. **Protonged use can lead to atrophy of respiratory**
4. **CMV is unresponsive to minute volumes requirements and hence lead to alkalosis.**

Weaning :

- **Arterial Ph : 7.35 – 7.40**
- **So2 >90% with FI02 0.5**
- **PEEP < 5mmhg**
- **Intact cough reflex (assessed during suctioning)**
- **Weaning index RR/TV < 105**

Failed weaning :

- **RR>35 > 5 MIN**
- **Sao2 <90%**
- **>140**
- **SBP<90/>180mmhg**
- **Diaphoresis**

Complications of ventilation :

- **Pulmonary**
  - **Baro trauma (>50 mmhg)**
  - **Interstitail emphysema**
  - **Puemomediastinum**
  - **Subcutaneous emphysema**
  - **Pnuemothorax**
  - **VAP**
  - **Tracheal stenosis**

- **Hypotension**
  - **Resulting from elevated intrathoracic pressure and decreased venous return**
  - **Responsive to volume repletion**
- **Gastrointestinal**
  - **Stress ulcers and cholestasis**

ARDS

- **Acute respiratory distress syndrome**
- **The mortality rate for ARDS is approximately 40%.**
- **ALI less severe and generally precursor of ARDS.**
- **ARDS : Po2/FiO2 <200**
- **ALI : Po2/FiO2 <300**
- ***Increased alveolar permeability due to direct neutrophil-mediated injury to the alveolar epithelium***
- **Baby Lungs : FRC can be reduced by 80% or more in ARDS**
- **Clinical terms synonymous with ARDS**
  - **acute respiratory failure**
  - **Capillary leak syndrome**
  - **Da Nang Lung**
  - **Shock Lung**
  - **Traumatic wet Lung**
  - **Adult hyaline membrane disease**

CAUSES :

Clinical Disorders Commonly Associated with ARDS

Direct Lung Injury	**Indirect Lung Injury**
Pneumonia	Sepsis
Aspiration of gastric contents	Severe trauma
Pulmonary contusion	Multiple bone fractures
Near-drowning	Flail chest
Toxic inhalation injury	Head trauma
	Burns
	Multiple transfusions
	Drug overdose
	Pancreatitis
	Postcardiopulmonary bypass

MC cause: Sepsis

CRITERIA :

Diagnostic Criteria for ALI and ARDS			
Oxygenation	**Onset**	**Chest Radiograph**	**Absence of Left Atrial Hypertension**
ALI: PaO_2/FIO^2 ≤300 mmHg	Acute	Bilateral alveolar or interstitial infiltrates	PCWP ≤18 mmHg *or* no clinical evidence of increased left atrialpressure
ARDS: PaO_2/FIO_2 ≤200 mmHg			

PATHOPHYSIOLOGY & CLINICAL FEATURES

1. **Exudative phase:**

- **First 7 days**
- **Injury to alveolar capillary endothelial & epithelial cells, which leads to loss of tight alveolar barrier and hence edema.**
- **Edema fluid rich in protein & PMNs**
- **Edema esp. in dependent portions of lung**
- **Lung compliance decreased**
- **Plasma proteins & dysfunctional surfactant aggregate to form 'hyaline membrane whorls'**
- **Hypoxemia because of intrapulmonary shunting & atelectasis**
- **Usually presents within 12 to 36 hours of inciting cause**

- **Dyspnea, Tachypnea, fatigue, failure**

2. **Proliferative phase:**

- **Days 7 to 21**
- **Shift from PMN to Lymphocyte-predominant pulmonary infiltrate**
- **Lung shows signs of resolution with lung repair, organization of alveolar exudates, proliferation of type II pneumocytes & production of new surfactant.**
- ***Most patients recover during this phase***
- **Type III procollagen: predictor of fibrosis & ↑ mortality from ARDS.**

3. **Fibrotic phase:**

- **3 to 4 weeks onwards**
- **Few patients**
- **Alveolar, interstitial & pulmonary vascular fibrosis.**
- **Consequences: Respiratory failure, Pneumothorax, Pulmonary HT**

RADIOLOGICAL IMAGING :-

Differences from HF:

- **Absence of pleural effusions, cardiomegaly, pulmonary vascular re-distribution**
- **Perihilar sparing**
-

TREATMENT :-

- **Treat underlying cause**
- **Ventilation**
  - **Low tidal volume**
  - **High PEEP**
  - **Prone position**
  - **Inverse I/E ratio (>1:1)**

SLEEP APNEA

Definition: Intermittent cessation of airflow at the nose and mouth during sleep Conventiolly at least 10 sec, but may be upto 2-3 min.

Apnea Hypopnea Index (AHI)

- **Normal: less than 5 events per hour**
- **Mild: 5 - 15 events per hour**
- **Moderate: 16 - 30 events per hour**
- **Moderately severe: 31 - 39 events per hour**
- **Severe: over 40 events per hour**

Prevalence: 2% of middle-aged women & 4% of middle-aged men

Factors: BMI > 30, Short mandible, maxilla.

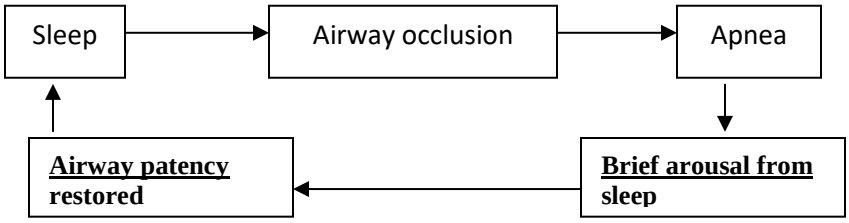
Hypothyroidism, acromegaly, myotonic dystrophy, Ehlers danlos syndrome, smoking.

In child, presence of enlarged tonsils or adenoids.

Types:

1. OSA

- **Definitive event: Oropharyngeal occlusion**



- **Apneas of at least 10 seconds duration are considered significant**
- **Sleep plays a *permissive role***
- **Obesity and alcohol intake are *cofactors***
- **Clinical features**
    - **Males, 30-60 y**
    - **Excessive daytime somnolence, intellectual deterioration, personality changes, behavioral disorders, ↑ accidents and depression.**
    - **Pulmonary HT, RHF**
    - **Systemic HT**
    - **Sudden death**
    - **Left heart failure**

- **Diagnosis:**
    - **Definitive: Polysomnography**
        - **Includes: EEG, EOG, EMG; Ventilatory variables; pulse oximetry; heart rate**
        - **Key diagnostic finding: Airflow cessation / reduction at mouth**
          despite continuing respiratory effort

- **Management: Nasal CPAP (Pressure of 5 – 20 cm Hg)**
    - **CPAP is also preferred therapy for patients of IHD / CHF with OSA**
    - **UPPP for patients who cannot tolerate CPAP**
    - **Medication is usually ineffective for OSA, except patients with REM sleep-related events: Protriptyline / Fluoxetine / Modaginil.**
      ALSO KNOW:

Epworth Sleepiness Score
How often are you likely to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose the *most appropriate number* for each situation:
0 = would *never* doze

1 = *slight* chance of dozing	
2 = *moderate* chance of dozing	
3 = *high* chance of dozing	
Sitting and reading	.....
Watching TV	.....
Sitting, inactive in a public place (e.g., a theater or a meeting)	.....
As a passenger in a car for an hour without a break	.....
Lying down to rest in the afternoon when circumstances permit	.....
Sitting and talking to someone	.....
Sitting quietly after lunch without alcohol	.....
In a car, while stopped for a few minutes in traffic	.....
TOTAL	

2. CSA

- **Definitive event: Transient abolition of central drive to respiratory muscles**
- **Two mechanisms:**
    1. **Defects in the metabolic respiratory control system (Hypoventilation syndromes: in which the hypoventilation further increases with sleep)**
    2. **Transient instabilities in respiratory control**
        - **Pathophysiology: Chronic hyperventilation during wakefulness**
- **Obesity and hypertension are less prominent in CSA than OSA**

- **Diagnosis:**
    - **Definitive: Polysomnography**
        - **Key diagnostic finding: Apneas not accompanied by respiratory effort**
        - **Transcutaneous pCO_2 → Raised in patients with disorder of resp ctrl / NM function; ↓ in instability of respiratory control**

Management: For primary hypoventilation syndromes → treatment of the hypovent syndrome

- **For patients with instability of respiratory drive → Supplemental O_2 (for patients with hypoxemia)**
  Nasal CPAP may be beneficial (esp for pts with CHF & CSA)
- **Patients with idiopathic CSA: Variable efficacy with:**
    1. **Respiratory stimulation with acetazolamide**
    2. **Triazolam sedation**

Lung Transplantation:

Indications:

- The most common indications in the last few years have been chronic obstructive pulmonary disease (COPD), ~30%; idiopathic pulmonary fibrosis (IPF), ~30%; cystic fibrosis (CF), ~15%; alpha$_1$-antitrypsin deficiency emphysema, ~3%; and idiopathic pulmonary arterial hypertension (IPAH), ~2%.
- Recipient Selection

Disease-specific consensus guidelines for referring patients for evaluation and for proceeding with transplantation are summarized in **Table**and are linked to clinical, physiologic, radiographic, and pathologic features that influence the prognosis of the respective diseases

- The upper age limit is ~65–70 years at most centers

Disease-Specific Guidelines for Referral and Transplantation
Chronic Obstructive Pulmonary Disease
Referral BODE index >5
Transplantation BODE index 7–10 *or* any of the following criteria: Hospitalization for exacerbation, with $PaCO_2$ >50 mmHg Pulmonary hypertension or cor pulmonale despite oxygen therapy FEV_1<20% with either DLCO <20% or diffuse emphysema

Cystic Fibrosis/Bronchiectasis
Referral FEV_1<30% or rapidly declining FEV_1 Hospitalization in ICU for exacerbation Increasing frequency of exacerbations Refractory or recurrent pneumothorax Recurrent hemoptysis not controlled by bronchial artery embolization
Transplantation Oxygen-dependent respiratory failure Hypercapnia Pulmonary hypertension
Idiopathic Pulmonary Fibrosis
Referral Pathologic or radiographic evidence of UIP regardless of vital capacity
Transplantation Pathologic or radiographic evidence of UIP *and* any of the following criteria DLCO <39% Decrement in FVC 10% during 6 months of follow-up Decrease in SpO_2 below 88% during a 6-min walk test Honeycombing on HRCT (fibrosis score >2)
Idiopathic Pulmonary Arterial Hypertension

Referral NYHA functional class III or IV regardless of therapy Rapidly progressive disease
Transplantation Failing therapy with intravenous epoprostenol (or equivalent drug) Persistent NYHA functional class III or IV on maximal medical therapy Low (<350 m) or declining 6-min walk test Cardiac index <2 L/min/m^2 Right atrial pressure >15 mmHg

Abbreviations: BODE, body-mass index (B), airflow obstruction (O), dyspnea (D), exercise capacity (E); FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; DLCO, diffusing capacity for carbon monoxide; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; SpO_2, arterial oxygen saturation by pulse oximetry; ICU, intensive care unit; UIP, usual interstitial pneumonitis; HRCT, high-resolution computed tomography; NYHA, New York Heart Association.

HIGH-YIELD ESSENTIALS

1. Lung volumes and capacities: definitions (spirometer graph)
2. Dead space: increased in("BE HEre TUE A3" ,)Bronchitis, Emphysema, Hemorrhage (pulm), Embolism (pulm), Tachypnea, Upright position, Extension (Neck), Asthma, Atropine (& other BDrs), Ageing +face mask, IPPV;
   decreased in FITES: Flexion (Neck), Intubation, Tracheostomy, Surgery (Pneumonectomy), Exercise
3. ET Intubation: Decreases dead space, increases work of breathing, muco-ciliary transport in upper airway lost, cough reflex ineffective
4. Gradients of ventilation and perfusion in the lung: Both individually best at the base, but ratio best at the apex
5. FRC: resting state / equilibrium state of the resp system
6. *MMFR / $FEF_{(25-75)}$ (max mid-exp flow rate / Forced exp flow): Most *sensitive* measure of airflow obstruction in small airways

PEFR (peak exp flow rate): Most *sensitive* measure of airflow obstruction in large airways

7. Drug-induced pulm ds: chapter 5
8. DPLD (ILD)
    a. MC presentation: Chronic progressive exertional dyspnea (with dry cough, clubbing)
    b. Fine, end-insp, bi-basilar (Velcro) crepitations
    c. Cyanosis, PHT: late
    d. Initial investigation: CXR: bi-basilar reticular opacities
    e. Upper Lobe ILDs: Sarcoidosis, Si, Be
    f. ABG: Type I Resp failure
        - *The only mechanism of hypercapnia: HYPOVENTILATION*
    g. PFT: Earliest is decreased DLCo, f/b loss of volumes
    h. HRCT: GGOs suggest alveolitis (Active disease)
    i. Investigation of choice: Lung biopsy
    j. ILD that can be diagnosed on BAL: PAP (t/t is also whole lung lavage)
9. HP (Bagassosis, Farmer's lung)
    a. Environmental dust ds due to organic agent inhalation, in a susceptible host
    b. Inflammatory of peripheral airways
    c. Type IV hypersens (No eosinophilia / bronchospasm)
    d. Best therapy is avoidance of ag exposure
10. **ABPA**: AIEE 1 PB
11. Churg Strauss syndrome: Small vessel granulomatous vasculitis: skin manifestations, mononeuritis multiplex, triad of EP; treat with steroid and cyclophosphamide
12. Hypereosinophilic syndrome: multisystem disease with most clinically significant involvement of CVS: biventricular RCMP is mc cause of death; monoclonal eosinophilia; treat with steroids, hydroxyurea, imatinib
13. Drugs that cause PIE (pulm infiltrates with eosinophilia): Nitrofurantoin, hydralazine, INH, sulfonamides, TNF-alpha blockers
14. COPD
    a. Incompletely reversible AO
    b. Monitor with FEV1
    c. Most effective therapy: stop smoking
    d. BDr of choice: anticholinergic (e.g. Ipratropium, Tiotropium)
    e. LTOT / Domicilairy oxygen for >15 hrs per day
    f. Influenza vaccine annually & pneumococcal vaccine every 5 yrs
15. Asthma
    a. Fully reversible AO (>12% increase in FEV1……..)
    b. Ominous signs: Ventilate
    c. Treatment differs for acute attack versus long-term control (table on page 12)
    d. **Exercise-induced asthma**: treat with inhaled SABA; prophylaxis with inhaled LABA
    e. **Drug-induced asthma:** list of safe NSAIDs (page 12); URT manifestations

16. Pneumonia :

- Lipoid pneumonia: liquid paraffin, oily nasal drops

- Radiation pneumonitis: 25 Gy, steroids provide symptomatic benefit
- Chemical pneumonitis: pH < 2.5 and volume > 0.3 ml/kg; leads to ARDS
- Atypical pneumonias: "LCMV" ; no airspace exudation hence clinical & radiological profile are different from typical bacterial pneumonias

- ***Miliary shadows: THC, SZC, PHAX***
- ***Cavities: SPEAK THCB***
- PORT score: criteria for admission
- Severe pneumonia: CURB; need for MV, PaO_2 / FiO_2 ratio < 250, multilobar disease
- Single drug of choice for treatment of CAP: Respiratory quinolone
- Treatment for nosocomial pneumonia: Cover at least both of Staph and Pseudomonas (plus t/t acc to local prevalence / specific risk factors)

Lung abscess: diagnostic hallmark – air-fluid level; MC in post segment of RUL; bronchoscopic procedure reqd for recovering causative organism; parenteral antibiotics till complete radiologic recovery (4 to 8 weeks)

BRONCHIECTASIS: TB, NTM (nodular), ABPA (central), CF, hypogammaglobulinemia; Diagnostic inv is HRCT; presents with copious sputum, hemoptysis, clubbing; CXR may show tram-track & ring shadows; PFT shows both obs& restrictive patterns; only mandatory indication for bilateral lung transplant

CF: Earliest presentation: Meconium ileus; MC presentation: steatorrhea / azotorrhea; Max morbidity / mortality due to pulm disease (severe gen BXSIS); earliest and most severe inv: RUL; early infections are with Staph; in late stages – pseudomonas; B. cepaciainfns are common and ominous; ABPA and NTM each in 10%; male > female infertiliy; GI malignancy in few; diagnosis by sweat Cl or raised nasal TEPD with one characteristic c/f; human DNAse-B as mucolytic

Pneumothorax

TYPE	Symptoms / size	Treatment
Primary spontaneous	Asymp – mild symp or < 15%	Observe
	Significant dyspnea	Needle aspiration (if unsuccessful – ICD)
Secondary spontaneous	NA	ICD
Non-iatrogenic trauma	NA	ICD
Iatrogenic trauma	MV / CPCR	ICD
	Other causes – asymp / < 40%	Observe / Oxygen inhalation
	Other causes – symp / > 40%	Needle aspiration (if unsuccessful – ICD)

Hemothorax: always treat with ICD

Tension PTX: Clinical diagnosis (ptx with evidence of severe pulm / cardiovascular compromise) – Urgent decompression with wide-bore needle f/b urgent ICD

Pleural effusion

- MC cause: CHF; MC cause of inflammatory fluid: Synpneumonic

- Light's criteria: Fluid rich in protein / LDH: Exudate
- Causes of transudates: CHF, Cirrhosis, nephrotic syndrome, PD, SVCO, myxedema, urinothorax (occ PE)
- Drugs that cause pleural ds (usually assoc with eosinophils in PF): "ProMet BAND"
- Indications of tube thoracostomy for synpneumonic effusion: "LPGOP"

Lung cancer

- MC tumor of lung is primary malignant tumor (carcinoma)
- MC benign tumor of lung is hamartoma (chondroadenoma)
- "POPCORN CALCIFICATION" is pathognomonic findings of pulmonary hamartomas
- Clubbing of Hypertrophic osteoarthropathy does not occur in benign tumor of the lung except in fibrous – mesotheliomas
- Marble like feel of the tumor is characteristic of pulmonary hamartoma
- MC cause of recurrent hemoptysis is BRONCHIAL ADENOMA
- TOC of benign tumor of lung is conservative surgery in the form of either enclueation or wedge excision
- Pulmonary hamartomas are located peripherally and contain normal pulmonary tissue component

Carcinoma Lung :-

- MC cause of cancer death in both men and women
- MC cancer of lung is ADENOCARCINOMA
- MC cancer of lung in India is SQ. CELL CARCINOMA.
- MC risk factor responsible for lung cancer is SMOKING
- MC lung cancer found in nonsmoker is ADNOCARCINOMA
- MC environmental pollutants of natural origin responsible for lung cancer is RADAN GAS

- Type of Lung carcinoma:

○ Non Small Cell carcinoma : ✓ Sq. cell carcinoma (Epidermoid CA) ✓ Adenocarcinoma ✓ Large cell carcinoma	○ Small cell carcinoma	○ Mixed Type

Features of individual types:

Sq. cell carcinoma :

- ✓ More common in Male
- ✓ Located centrally, near the hilum (MC site – proximal segmental bronchi)
- ✓ Strongest association with smoking
- ✓ Cavity formation & obstructive pneumonitis is common
- ✓ MC cause of PANCOAST TUMOR
- ✓ Have best prognosis
- ✓ MC associated paraneoplastic syndrome is hypercalcemia and hypophosphatemia
- ✓ Have highest resectibility rate

- ✓ MC molecular genetic abnormality is over expression of epidermal growth factor receptor (EGFR)

Adenocarcinoma:

- ✓ MC type of lung cancer
- ✓ More common in Female
- ✓ Located peripherally
- ✓ MC cancer arises from a PULMONARY SCAR (especially, Bronchoalveolar type)
- ✓ MC cancer that may be spread by AEROSOL TRANSMISSION (especially, Bronchoalveolar type)
- ✓ Common type found in non – smokers.
- ✓ May present as a FLUFFY INFILTRATE (especially, Bronchoalveolar type)
- ✓ Bronchoalveolartype arise from type II pnumatocytes.
- ✓ Bronchoalveolar type can spread TRANSBRONCHIALLY
- ✓ MC associated with paraneoplastic syndrome is HEMATOLOGICAL SYNDROME comprising
- Migratory venous thrombophlebitis (TROUSSEU'S – SYNDROME)
- Marantic (nonbacterial) endocarditis
- DIC
- Anemia, polycythemia, nonspecific leucocytosis, fibrinolyticpurpura
- ✓ MC associated skeletal – connective tissue syndrome is Hypertrophic pulmonary osteoarthropathy
- ✓ Pleural involvement is common
- ✓ MC molecular genetic abnormality is mutation of K-ras oncogene.

Large cell carcinoma:

- ✓ Also called Anaplastic carcinoma
- ✓ Located peripherally
- ✓ Pleural involvement is common (like adenocarcinoma)
- ✓ CNS involvement is most common in this variety
- ✓ MC associated paraneoplastic syndrome includes:
  - ➢ Tender gynecomastia
  - ➢ Ectopic gonadotropin secretion
  - ➢ Ectopic growth hormone secretion
- ✓ Least common type of lung carcinoma
- ✓ Cavity formation (like sq. cell CA)

Small cell carcinoma:

- ✓ Strong association with smoking (like Sq. cell CA)
- ✓ More common in male
- ✓ Also called as OAT – CELL CARCINOMA (due to presence of LYMPHOCYTE – LIKE oat cells)
- ✓ Most rapidly growing tumor
- ✓ WORST PROGNOSIS
- ✓ Located centrally
- ✓ Most early & widely metastasizing tumor
- ✓ Most resistant to combined – modality treatment
- ✓ Have least respectability
- ✓ MC molecular genetic abnormalities are :

- Ampification of the myc – oncogene family
- Mutation of raf – gene
- Delation of short arm of chromosome 3 (3p)

✓ MC type of lung cancer associated with paraneoplastic and skeletal connective tissue syndromes
✓ MC lung carcinoma having extrathoracic metastases.
✓ Appears primarily as HILAR MASSES
✓ Cells exhibit salt & pepper distribution of chromatin
✓ Specific paraneoplastic syndrome associated with small cell lung carcinoma includes:

- Hyponatremia with SIADH (syndrome of inappropriate secretion of antidiuretic – hormone) leading to DIABETES INSIPIDUS.
- Ectopic secretion of ACTH leading to HYPOKALEMIA (not the changes in body habitus seen in Cushing secretion)
- Ectopic growth hormone – releasing hormone secretion
- Ectopic secretion of placental lactogen
- Ectopic secretion of Bombesin – like gastrin releasing peptides
- Ectopic secretion of VIP, gastrin, somatostatin, calcitonin and chromogrannin – A

Specific Neurologic – myopathic syndrome associated with small cell lung cancer includes:

- Myasthenic EATON – LAMBERT SYNDROME
- Retinal blindness
- Subacute cortical cerebellar degeneration
- Brainstem & limbic encephalitis
- Necrotizing myelopathy
- Necrotizing myopathy

- Other paraneoplastic& related syndromes which are related to all types of lung carcinoma include :
  - ✓ Clubbing on finger (usually non – small cell carcinomas)
  - ✓ Peripheral – myoclonus
  - ✓ Necrotizing myopathy
  - ✓ Polymositis
  - ✓ Dermatomyositis
  - ✓ Acanthosisnigrans - Cutaneous manifestations
  - ✓ Scleroderma
  - ✓ Superior venacaval syndrome
- The main pathology in Eaton – Lambert syndrome is development of ANTIVOLTAGE – GATED CALCIUM – CHANNEL ANTIBODIES
- MC nerves involved in Pancoast Syndrome is $C_8T_{1,2}$
- MC structure destroyed in Pancoast syndrome is First and second ribs
- MC symptom of lung cancer is COUGH
- Lung carcinoma may also be linked with the development of chronic obstructive pulmonary disease (COPD)
- MC site of distant metastasis is LIVER (second MC site – Bone)
- The best screening test for distant metastasis is HISTORY and PHYSICAL EXAMIANTION

- After history & physical examination, next best screening test is SERUM ALKALINE PHOSPHATASE estimation
- Investigation of choice for mediastinal involvement is CT- SCAN.
- MC source of metastatic lung carcinoma is colon carcinoma
- TOC is localized non – small cell lung cancer (stage I & II) is PULMONARY RESECTION
- MC type of pulmonary resection utilized for conservative surgical resection is LOBECTOMY
- TOC in non – small cell lung cancer is Radiotherapy in cases of :
    - ✓ Stage III disease
    - ✓ Stage I & II disease, who refuses surgery
    - ✓ Not medically fit for surgical resection
- TOC in occult and stage – O carcinoma (CA – in – situ) includes :
    - ✓ Conservative surgical resection
    - ✓ Photodynamic therapy using Hematoporphyrin
- TOC of the carcinoma of superior pul. Sulcus producing Pancoast's syndrome is Radiotherapy + Surgery
- MC anticancer drug used for treatment of non – small cell lung carcinoma is ETOPOSDE + CISPLATIN
- Treatment of Disseminated non – small cell lung cancer includes :
    - ✓ Radiotherapy to the primary tumor
    - ✓ Thoracocentasis for small amount of pleural effusion
    - ✓ Pleurodesis for recurrent small pleural effusion
    - ✓ Drainage under video – associated thoracoscopy in case of large pleural effusion
    - ✓ Nd- YAG laser therapy for recurrent symptomatic intrabronchial lesions
    - ✓ Immunotherapy (using BGC, Levamisol, IL – 2 etc)
- Small cell lung cancers are usually UNRESECTABLE
- TOC in small cell lung cancer includes :
    - ✓ Chemotherapy with or without Radiotherapy OR Surgery
    - ✓ High dose radiotherapy to whole brain for metastatic deposits
- Signs of Inoperability (Contraindications of surgical resection):
    - ✓ Malignant (bloody) pleural effusion
    - ✓ Horner's syndrome
    - ✓ Vocal cord paralysis
    - ✓ Phrenic nerve paralysis
    - ✓ Superior venacava syndrome
    - ✓ Extrathoracic distant metastases
    - ✓ Cardiac temponade
    - ✓ Tumor within 2 cm of carcinoma (curable by radiotherapy)
    - ✓ Metastases to contralateral lung
    - ✓ Bilateral endobronchial tumor (curable by radiotherapy)
    - ✓ Metastases to supraclavicular lymph node
    - ✓ Lymph node metastases to contralateral mediastinum (curable by radiotherapy)
    - ✓ Involvement of the main stem pulmonary artery
    - ✓ Myocardial infarction within past 3 months

- ✓ Uncontrolled major arrhythmias
- ✓ Maximum breathing capacity of less than 40% predicted
- ✓ FEV_1 of less than 1L.
- ✓ CO2 retention (more serious than hypoxemia)
- ✓ Severe pulmonary hypertension
- ✓ Severe emphysema
- ✓ PO2 < 50 mmHg or a PCO2 > 45 mmHg
- ✓ Exercise O2 consumption (MVO2) < 10 mL/kg/minute

- o Contraindications of Radiation Therapy:
  - ✓ Extrathoracic distant metastases
  - ✓ Positive supraclavicular nodes
  - ✓ Malignant pleural effusion
  - ✓ Cardiac involvement
- o Prognosis:

✓ Asymptomatic patients have the Best prognosis
✓ Highest risk of lung cancer is related to smoking + Asbestous exposure
✓ Once lung cancer is diagnosed
Or Mean survival is Less than 1 Year
Unresectable non – small cell cancer having undergone primary radiotherapy
✓ Two – Year survival rates after surgical resection of non – small cell lung tumor are, Stage – I – 60%, Stage II – 40%, Stage III - < 10%
✓ Best Serum Marker for patient with small – cell lung cancer having greatest sensitivity & specificity is Neuron – specific ENOLASE (NSE)

Lung metastases:

- o Second MC site of visceral metastases in the body (MC site liver)
- o MC symptom = Cough & hemoptysis
- o MC source of secondaries = Colon CA
- o Calcified metastasis in lung is seen in cases of :
  - ✓ Osteosarcoma, Chondrosarcoma& Synovial sarcoma
  - ✓ Mucinous GIT tumors
  - ✓ Breast ovary & thyroid CA
  - ✓ Post chemotherapy
  - ✓ Post radiotherapy
- o Cavitatory metastasis in lung is seen in cases of :
  - ✓ Sq. cell CA of head & neck
  - ✓ Sarcomas
  - ✓ Testicular CA
- o Lymphangiticcarcinomatosis is seen in cases of :
  - ✓ Lung, gastric & breast CA
  - ✓ Pancreatic & prostate CA
- o Endobronchial metastasis is seen in cases of :
  - ✓ CA breast
  - ✓ Colon CA
  - ✓ Kidney & pancreatitis CA

- Primary tumors whose pulmonary metastasis have been successfully resected for cure include :
    - ✓ Osteosarcoma (most dramatic result)
    - ✓ Soft tissue sarcoma
    - ✓ Colorectal CA
    - ✓ Cervix & uterine carcinomas
    - ✓ Head & neck and salivary gland cancers
    - ✓ Breast, tests, kidney, & bladder cancers
    - ✓ M. melanoma

Solitary Pulmonary Nodule:

- Also known as 'COIN LESIONS'
- Are peripheral circumscribed pulmonary lesions
- Are due either to -
    - ✓ Granulomatous disease, or
    - ✓ Neoplasm - Primary ,Secondary
- Diagnosis is by Radiology
- The overall incidence of cancer is solitary nodular lesion seen on X-ray is about 5 – 10%
- More common in Male than Female
- Cancer in solitary nodule is two times greater in male than female
- Lesions less than or upto 1 cm in diameter are probably granulomatous
- Lesions more than 1 cm in diameter have significant probability and 4 cm or more in diameter, very high probability of being malignant
- Symptoms are usually ABSENT in solitary nodule
- Hypertrophic osteoarthropathy signifies an 80% or more probability of cancer
- The most valuable radiological evidence of benignity are

✓ Calcification as

- ✓ Calcification tends to favor granulomas
- ✓ Conventric or laminated calcification denotes benign character
- ✓ Calcification of the 'TARGET' or 'POPCORN' or 'BULL's – EYE' variety are very unlikely to be malignant
- ✓ Lesions that are completely or heavily calcified are most likely benign
- ✓ Multiple punctuate foci of calcification favours benignity
- ✓ Documented absence of growth over a period greater than 2 years
- ✓ Malignant lesions with calcification are most often SQUAMOUS CELL CARCINOMAS
- ✓ Calcification in malignant lesions generally consists of small flecks located eccentrically at the periphery of the nodule.
- ✓ Heavy dense lesions on X-ray less than 3 cm in diameter are often malignant
- ✓ Diagnosis of solitary nodule according to shape

- Irregular shape – Inflammatory lesions
- Benign lung tumors
- White rounded lesion WITH UMBLICATION – Cancers
- Indistinct margin – Cancers
- Distinct margin – Benign tumor :

- ✓ Presence of SATELLITE DENSITIES favors a diagnosis of granuloma
- ✓ Percutaneous needle biopsy should not be done in potentially curable candidates for surgery because of possible intrathoracic dissemination of the tumor

Treatment of solitary nodules :

- Excisional biopsy, for :
  - ✓ Surgical diagnosis of peripheral lesions
  - ✓ Definitive therapy for benign lesions, and solitary metastasis
  - ✓ Definitive treatment for primary cancer in poor – risk patients
- Lobectomy for :
  - ✓ Centrally placed lesions
  - ✓ Lesion suspected of being coccidoidomycosis
- Lobectomy + Regional Node Dissection,: For
  - ✓ Primary cancers in good – risk patients.

Multiple Choice Questions

1. Which of the following causes decreases in both VC and TLC?
   A) Sarcoidosis
   B) Cystis fibrosis
   C) Bronchial asthma
   D) Bronchiectasis
2. A 12 year old girl presents with acute rheumatic carditis with mitral insufficiency. She is likely to have
   A) Increased peak expiratory flow
   B) Increased TLC
   C) Increased RV
   D) Decreased FRC
3. All the following are true of polymyositis (PM) except
   A) 20% of patients with polymyositis develop ILD
   B) ILD in PM is related to the presence of anti-Jo 1 antibodies
   C) The commonest cause of death in PM is cardiomyopathy
   D) Patients with PM are at increased risk for aspiration
4. All the following increase work of breathing except
   A) ET intubation
   B) Exercise
   C) Acute left ventricular failure
   D) Tracheostomy
5. Which of the following statements is correct?
   A) Negativity of pleural pressure is maximum at the base of the lung
   B) Pulmonary capillary pO2 (at venous end) is maximum at the base of the lung
   C) Ventilation is best at the apex of the lung
   D) Intra-alveolar pressure of apical alveoli is more than that of basal alveoli
6. Pulmonary compliance is decreased in all the following conditions except
   A) Pulmonary fibrosis
   B) ARDS
   C) Pleural effusion
   D) Kyphoscoliosis
   E) COPD
7. Vital capacity (Vc) is the maximum volume exhaled after a maximal inspiration. It is the sum of three lung volumes viz
   A) RV, V_T, IRV
   B) FRC, V_T, IRV
   C) ERV, V_T, IRV
   D) ERV, V_T, IC
8. In a normal person, PaO_2 is slightly less than PAO_2 primarily because of

A) Shunted blood
B) Significant diffusion gradients
C) Reaction time of O_2 with hemoglobin
D) Unloading of CO_2
E) None of the above

9. Which of the following investigation is ideal for measuring total lung capacity (TLC)?
   A) Spirometry
   B) PFT
   C) Helium dilution technique
   D) Body plethysmography
10. The Functional Residual Capacity (FRC) is defined as the combination of
   A) Tidal volume and residual volume
   B) Tidal volume and expiratory reverse volume
   C) Inspiratory reserve volume and tidal volume
   D) Residual volume and expiratory reserve volume
11. Restrictive pulmonary disease is characterized by all of the following except:
   A) Hypoxemia aggravated by exercise
   B) Increased functional residual capacity
   C) Reduced compliance
   D) Hypocapnia
12. ANCA positive diseases are all of the following except
   A) Microscopic polyangitis
   B) Henoch Schonlein purpura
   C) Churgs Straus syndrome
   D) Wegeners Granulomatosis
13. True about restrictive lung disease
   A) ↑ FRC, compliance of lung tissue
   B) ↑ FEV_1 / FVC, ↓ compliance of lung tissue
   C) ↓ FEV_1, FVC, ↓ compliance of lung tissue
   D) TLC ↑, RV ↓
14. The following alteration in ventilatory function takes place in restrictive lung disease EXCEPT
   A) ↑ FEV_1/FEV, ↓ compliance
   B) ↓ FEV_1/FVC, ↑ compliance
   C) Normal FEV1/FVC, ↓ compliance
   D) ↑ FEV_1/FVC, ↓ compliance
15. A young male develops serous otitis media of the left ear with cough, occasional hemoptysis, hematuria and epistaxis for 2 months. Hb is 7.5 g% with heavy proteinuria, BP 170/100 mmHg, RA –ve and ANCA +ve. The most probable diagnosis is
   A) Wegener's granulomatosis
   B) Rapidly proliferative glomerulonephritis
   C) Rheumatoid arthritis
   D) Goodpasture's syndrome
16. Extra-parenchymal restrictive lung disease occurs in all the following EXCEPT
   A) Sarcoidosis
   B) Myasthenia gravis
   C) Ankylosing spondylitis
   D) Kyphoscoliosis
17. Functional residual capacity comprise
   A) Residual volume
   B) Dead space volume
   C) Volume of air present after normal expiration
   D) Volume of air present after forceful expiration
18. Pulmonary function changes seen in emphysema are
   A) ↑TLC
   B) ↓ RV
   C) ↑ FEV_1
   D) ↑ VC
19. Total lung capacity depends upon
   A) Size of the airway
   B) Closing tidal volume
   C) Lung compliance
   D) Residual volume
20. Maximum mid-expiratory flow rate indicates obstruction in
   A) Large airway
   B) Small airway
   C) Trachea
   D) Trachea and bronchi
21. Increased radiolucency of one-sided hemithorax may be caused by all the following EXCEPT
   A) Obstructive emphysema
   B) Pneumothorax
   C) Expiratory film

D) Rotation of the patient

22. A patient presented with hemoptysis and persistent cough. The chest X-ray is normal. The next best investigation is?
    A) Montoux test
    B) High – resolution CT
    C) Bronchoscopy
    D) Angiography
23. The abnormal pre-operative PFT in a patient with severe kyphoscoliosis includes
    a) Increased RV/TLC
    b) Reduced FEV1/FVC
    c) Reduced FEF (25-75%)
    d) Increased FRC
24. On sectioning of an organ at the time of autopsy, a focal, wedge – shaped firm area is seen accompanied by extensive hemorrhage, with a red appearance. The lesion has a base on the surface of the organ. This finding is typically of
    A) Lung with pulmonary thromboembolism
    B) Heart with coronary thrombosis
    C) Liver with hypovolemic shock
    D) Kidney with septic embolus

Answer Key

1. A
2. D
3. C
4. D
5. B
6. E
7. C
8. A
9. D
10. D
11. B
12. B
13. B
14. B
15. A
16. A
17. C
18. A
19. C
20. B
21. C
22. B
23. D
24. A

Multiple Choice Questions

1. All of the following are risk factors for the development of TB disease except
    a) Cystic fibrosis
    b) Cigarette smoking
    c) Infliximab therapy
    d) Poorly controlled diabetes
2. An HIV-positive patient presents with fever, cough and dyspnea for 10 days. His sputum reveals M. avium and Pneumocystis. Which of the following is the next best step?
    a) Do a BAL for definitive diagnosis
    b) Treat the patient for both infections
    c) Treat only with clarithromycin, ethambutol & rifabutin since Pneumocystis is a frequent pulmonary commensal in HIV +ve patients
    d) Treat only with cotrimoxazole since M. avium is a frequent pulmonary commensal in HIV +ve patients
3. All the following are features of TB in a patient with advanced HIV except
    a) Multifocal lymphadenopathy
    b) Sputum negativity
    c) Tuberculin negativity
    d) High tubercle bacillary load
    e) Poorer response to ATT compared to HIV negative patients
4. All the following are true except
    a) For identification of tubercle bacilli, fluorescent microscopy is faster than light microscopy
    b) The chances of getting a positive result are greater with fluorescent microscopy than with LM
    c) ZN staining is required for both fluorescent & light microscopy
    d) Fluorescent microscopy is costlier than light microscopy
5. Which of the following is the method of choice for evaluating an HIV positive patient who presents to you with symptoms suggestive of TB?
    a) Sputum smear examination
    b) Sputum culture
    c) Chest X-ray
    d) A 1 week course of broad spectrum antibiotics
6. The highest priority of the national tuberculosis program is
    a) Prevent emergence of MDR-TB
    b) Identification and cure of smear positive PTB
    c) Implementation of Directly Observed Therapy
    d) Identification and cure of smear negative PTB
7. The most potent antituberculosis drug is
    a) H
    b) R
    c) E
    d) Z
8. The most potent antituberculosis drug is
    a) H
    b) S
    c) E
    d) Z
9. The first symptom of ototoxicity due to Streptomycin is
    a) Decreased hearing
    b) Tinnitus
    c) Vertigo
    d) Otalgia
10. Pyrazinamide is converted to its active form, pyrazinoic acid, by the
    a) Liver
    b) Vascular endothelium
    c) Gut epithelium
    d) Tubercle bacillus
11. A 22 year old man presents with h/o fever, weight loss & intermittent diarrhea. He gives h/o regular consumption of unpasteurized cow milk. His BaMFT shows a 'pulled-up' caecum. Which of the following drugs should not be given to this patient?
    a) H
    b) R
    c) Z
    d) E
12. Which of the following is the least potent?
    a) E
    b) S
    c) Z

d) H

13. All the following are true with respect to pyrazinamide therapy except:
    a) Hyperuricemia occurs commonly
    b) Polyarthralgias occur commonly, but are not related to the serum level of uric acid
    c) Gout is rare
    d) The occurrence of hyperuricemia increases with concurrent rifampicin therapy
14. All the following can cause peripheral neuropathy except:
    a) H
    b) E
    c) Pyridoxine
    d) Streptomycin
15. All the following can cause neuropathy except:
    a) E
    b) Streptomycin
    c) Z
    d) H
16. All the following are true except:
    a) Rifabutin is more potent than rifampicin than for t/t of disease due to NTM
    b) The absorption of both rifampicin & rifabutin is decreased when co-administered with food
    c) The $t_{1/2}$ of rifampicin is shorter than that of rifabutin
    d) Rifabutin may be co-administered with Pis, while rifampicin may not
    e) Strains of Mycobacterium tuberculosis that are resistant to rifampicin are susceptible to rifabutin
17. All the following are derivatives of isonicotinic acid except:
    a) Isonicotinic acid hydrazide
    b) Z
    c) Ethionamide
    d) Para-amino salicylic acid
18. Which of the following drugs causes hypothyroidism?
    a) H
    b) Z
    c) Ethionamide
    d) Cycloserine
19. All the following are true except:
    a) Incidence of TB in the industrialized nations has decreased over the past few years, despite an increase in the number of HIV infections
    b) Risk of acquiring Mycobacterium tuberculosis infection is determined mainly by endogenous / host factors
    c) Immunosuppression, whether acquired or iatrogenic, increases risk of developing disease
    d) All forms of EPTB are non-infectious
20. HIV infection predisposes to all the following except:
    a) PTB
    b) JC virus infection
    c) Vulvo-vaginal candidiasis
    d) KS
21. MC manifestation of genital TB in males is:
    a) Orchitis
    b) Prostatitis
    c) Epididymitis
    d) Urethritis
22. All the following are true of genito-urinary TB except:
    a) It is usually due to hematogenous spread
    b) Local symptoms are commoner than constitutional symptoms
    c) Urinalysis reveals hematuria
    d) Culture for AFB is only rarely diagnostic
23. All the following are benefits of steroid therapy in TB pericarditis except:
    a) Decreases effusion
    b) Facilitates recovery from tamponade
    c) Decreases mortality

d) Prevents development of Chronic constrictive pericarditis

24. All the following are true of TST except:
    a) Does not differentiate between infection and active disease
    b) Severe cases may manifest a strongly positive reaction
    c) PPD +ve persons are less susceptible to developing disease
    d) PPD +ve persons are less susceptible to acquiring new infection
25. Which of then following therapies would be safest in a patient with abnormal liver function:
    a) S + H
    b) E + H
    c) R + H
    d) S + E
26. Not a feature of miliary tuberculosis:
    a) Mantoux is usually negative
    b) Common in children
    c) Meningitis is common
    d) Dyspnea commonest presentation
27. Positive tuberculin test indicates:
    a) Susceptibility
    b) Present & past infection
    c) Vaccination with BCG
    d) Is highly specific
28. Acid fast bacilli seen in the stools of HIV patients commonly are
    a) M. tuberculosis
    b) M. leprae
    c) M. avium intracellular
    d) Actinomycosis
29. Which vitamin is added for INH toxicity?
    a) B_1
    b) B_2
    c) B_6
    d) B_{12}
30. Which of the following are bacteriostatic drugs:
    a) INH
    b) Rifampicin
    c) Ethambutol
    d) Ciprofloxacin
31. The second line antitubercular drug is:
    a) Pyrazinamide
    b) Ethambutol
    c) Thiacetazone
    d) Ciprofloxacin
32. Antitubercular drug, which cannot cross blood brain barrier, is?
    a) Streptomycin
    b) INH
    c) Pyrazinamide
    d) Rifampicin
33. Antitubercular drug used in intermittent therapy are all the following except:
    a) Ethambutol
    b) Thiacetazone
    c) INH
    d) Streptomycin
34. In Tuberculosis in an AIDS patient, which of the following radiological manifestations is most likely?
    a) Miliary shadow
    b) Cavity
    c) Fibrosis
    d) Collapse
35. A patient with pulmonary tuberculosis is infective:
    a) Till sputum AFB is negative
    b) Till culture negativity is confirmed
    c) Till radiological cavity disappears
    d) In the initial few weeks after optimal exposure of drugs
36. Not seen in Rifampicin therapy:
    a) Hepatic damage
    b) Renal damage
    c) Porphyria
    d) Oral pills failure
37. Not a side effect of pyrazinamide:
    a) Peripheral neuritis
    b) Raised bilirubin levels
    c) Elevated transaminases
    d) Increased uric acid
38. The best single laboratory aid in diagnosis of tuberculosis
    a) Skin test
    b) Chest X – ray
    c) Sputum examination
    d) Histology
    e) CT chest

39. Following exposure to the tubercle bacillus the amount of time necessary by the tuberculin skin test to become positive is:
    a) 2-4 days
    b) 4-6 days
    c) 2 – 4 weeks
    d) 4 – 6 weeks
    e) 3 months
40. Essential steps in the management of massive life threatening hemoptysis include all of the following except:
    a) Emergency bronchoscopy to localize the site of bleeding
    b) Notification of thoracic surgeon
    c) Maintaining the affected lung in non- dependant position
    d) Immediate chest radiography
41. In the treatment of tuberculosis, corticosteroid therapy is indicated in all of the following EXCEPT
    a) Progressive primary pulmonary tuberculosis
    b) Miliary tuberculosis
    c) Tubercular pericardial effusion
    d) Tubercular meningitis
42. False – negative tuberculin test is seen in ALL EXCEPT
    a) After 4-6 weeks of measles attack
    b) Immuno deficiency state
    c) Miliary tuberculosis
    d) Atypical Mycobacterial infection
43. Tuberculosis pleural effusion is characterized by all the following EXCEPT
    a) Hemorrhagic
    b) LDH more than 60%
    c) Protein is increased
    d) ↑ Mesothelial cells
44. If the creatinine clearance is < 30 ml/min, which of the following drugs does NOT need dose reduction
    a) INH
    b) Ethambutol
    c) Rifampicin
    d) Kanamycin
45. A 24-year-old person is diagnosed to have AIDS. He develops pulmonary tuberculosis. Which of the following statements is FALSE?
    a) Extra thoracic manifestations are common
    b) Poor sensitivity to tuberculin test
    c) Cavities in lung are uncommon
    d) High AFB content in sputum
46. In hemoptysis, blood usually comes from
    a) Bronchial veins
    b) Pulmonary veins
    c) Bronchial arteries
    d) Pulmonary arteries
47. A patient of renal transplant receiving cyclosporine developed tuberculosis. Which of the following regimen will be advised to the patient?
    a) 2 HRZE/4HR
    b) $2\ H_3R_3Z_3E_3\ /\ 4H_3R_3$
    c) $2S_3H_3R_3Z_3E_3/H_3R_3Z_3E_3/5H_3R_3E_3$
    d) 2 HZE / 10 HE
48. What drug should be avoided in the case of HIV patient, who is receiving zalcitabine, indinavir & lomivudine:
    a) INH
    b) Rifampicin
    c) Pyrazinamide
    d) Ethambutol
49. According to newer TB control program, a case should be monitored (while continuing medication) at?
    a) 1,5,6 months
    b) 2,4,6 months
    c) 1,3,6 months
    d) 2,5,6 months
50. Babu a HIV positive patient presents with c/o mild fever, non-productive cough on & off for 3 weeks. He has B/L hilar lymphadenopathy. All other X-ray findings are normal. Most likely condition is?
    a) Pneumonia
    b) TB
    c) PCP
    d) Legionella
51. Babu a HIV positive patient presents with c/o mild fever, non-productive cough, pleuritic chest pain & dyspnea

for 10 days. He has B/L hilar lymphadenopathy. All other X-ray findings are normal. Most likely condition is?

a) Pneumonia
b) TB
c) PCP
d) Legionella

52. An adult male patient presented in the OPD with complaints of cough and fever for 3 months and hemoptysis off and on. On probing it was found that he had already received treatment with RHZE for 3 weeks from a nearby hospital and discontinued. How will you categorize and manage the patient?
    a) Category III, start $2(RHZ)_3$
    b) Category II, start $2(RHZE_3$
    c) Category I, start $2(RHZE)_3$
    d) Category II, start $2(RHZES)_3$

53. A patient, who had undergone renal allograft transplantation 6 months back, on treatment with azathioprine and prednisolone, comes to the hospital with a history of fever, night sweats, cough and breathlessness. On X-ray, a cavity is seen in the right apical region along with calcification. Auramine-rhodamine staining of sputum shows tubercle bacilli and serum creatinine level 1.2 mg%. The treatment given is
    a) INH, rifampicin, pyrazinamide
    b) INH, rifampicin, pyrazinamide, ethambutol
    c) INH, pyrazinamide, ethambutol, streptomycin
    d) Rifampicin, pyrazinamide, ethambutol

54. A 25-year-old female has been diagnosed to be suffering from tuberculosis categorized as category II (sputum +ve relapse). The treatment regimen recommended under DOTS is
    a) $2\ (HRZE)_3 + 5\ (HR)_3$
    b) $2\ (HRSZE)_3 + 1(HRZE)_3 + 5\ (HR)_3$
    c) $3\ (HRZE)_3 + 2\ (HRE)_3 + 4\ (HR)_3$
    d) $3\ (HRSZE)_3 + 1\ (HRZE)_3 + 6\ (HRE)_3$

55. A 25-year-old man presented with fever and cough for two months. CT chest showed bilateral upper lobe fibrosis and mediastinal enlarged necrotic nodes with peripheral rim enhancement. What is the most likely diagnosis
    a) Sarcoidosis
    b) Tuberculosis
    c) Lymphoma
    d) Silicosis

56. Which one of the following statement is true regarding pathogenecity of Mycobacteria species?
    a) *M.tuberculosis* is more pathogenic than *M.bovis* to the humans
    b) *M.Kansasii* can cause a disease indistinguishable from tuberculosis
    c) *M.africanum* infection is acquired from the environmental source
    d) *M.marinum* is responsible for tubercular lymphadenopathy

57. At what period does tuberculosis flare up most commonly in a pregnant patient?
    a) First trimester
    b) Second trimester
    c) Third trimester
    d) Puerperium

58. If the objective of the investigator is to assess the prevalence of tuberculosis infection in a community, the most appropriate methodology would be to:
    a) Identify all individuals with positive tuberculin test.
    b) Perform sputum examination of chest symptomatics.
    c) Identify new converters to tuberculin test.
    d) Screen all under-five children with Tuberculin test.

59. All of the following are true about therapy for tuberculosis except:

a) "Flu like syndrome" is usually seen in people taking rifampicin on daily basis
b) Ethambutol accumulates in renal failure.
c) Hyperuricemia is a recognized side effect of pyrazinamide
d) Red-green color impairment is an early sign of ethambutol induced optic neuritis

60. Memory impairment is seen with which of the following drugs?
    a) Isoniazid
    b) Ethionamide
    c) Ethambutol
    d) Streptomycin

Answer Key

1.	A
2.	B
3.	E
4.	A
5.	B
6.	B
7.	B
8.	A
9.	C
10.	D
11.	C
12.	A
13.	D
14.	D
15.	B
16.	B
17.	D
18.	C
19.	A
20.	C
21.	C
22.	C
23.	C
24.	C
25.	D
26.	D
27.	B
28.	C
29.	C
30.	C
31.	D
32.	A
33.	B
34.	A
35.	B
36.	C
37.	A
38.	C
39.	D
40.	C
41.	A
42.	D
43.	D
44.	C
45.	D
46.	C
47.	D
48.	B
49.	D
50.	B
51.	B
52.	C
53.	C
54.	B
55.	B
56.	A
57.	C
58.	A
59.	A
60.	A