

TUBERCULOSIS

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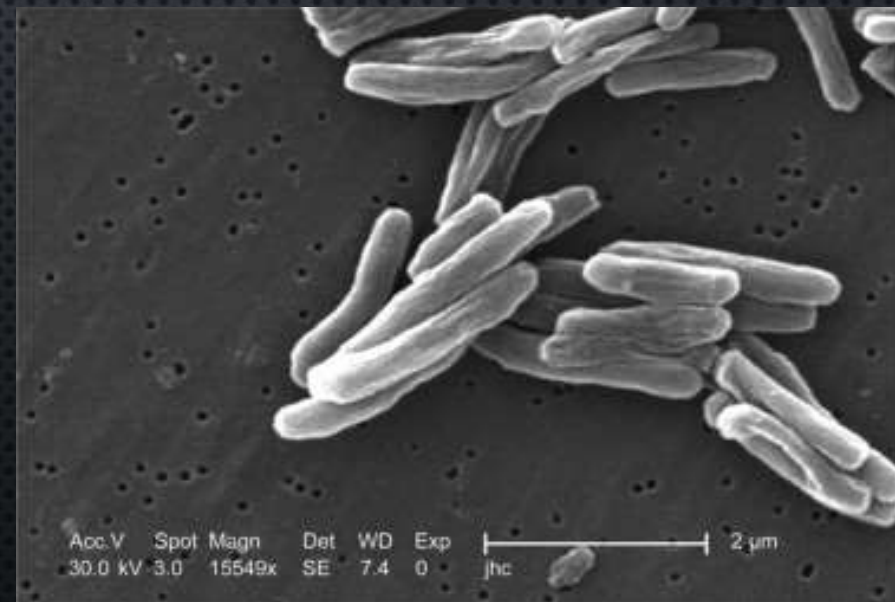
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ETIOLOGY

- *M. tuberculosis* and *M. bovis* are the cause of human tuberculosis.
- Morphology: • They are thin straight or slightly curved rods.
- They cannot be stained by simple stains due to the high lipid (mycolic acid) content of the cell wall.

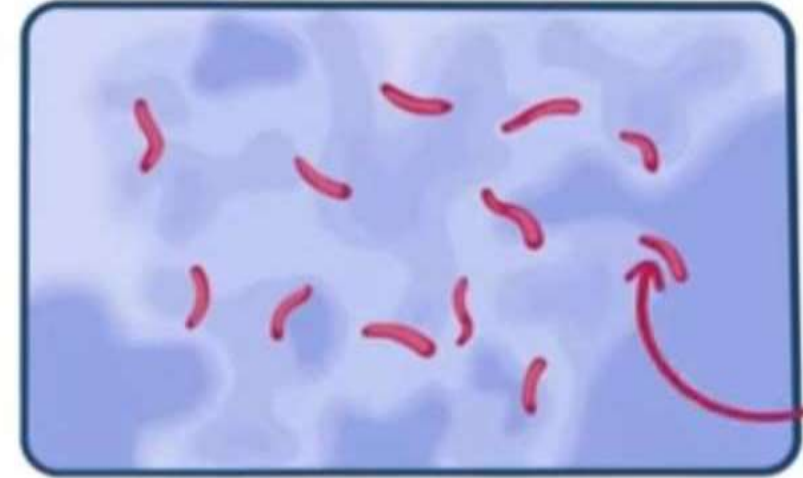


*They can be stained by *Ziehl-Neelsen stain*
Appear as thin pink rods .

* And they can stained by *Fluorochrome stains*
Apper as yellow orange bacilli in black
background by fluorescent microscopy

Difficult to stain, but once
stained, they resist
decolourization with acid or with
acid and alcohol.

ZIEHL-NEESEN STAIN



Cultural characters:

They are strictly aerobic, however it better growth occurs in presence of 5- 10% Co₂. They grow on solid media such as Lowenstein-Jensen(L-J) medium

They are slow growers ,no growth appears 2-4 weeks,incubation at 35-37c .

The growth on L-J medium is **irregular,dry and off-white.**

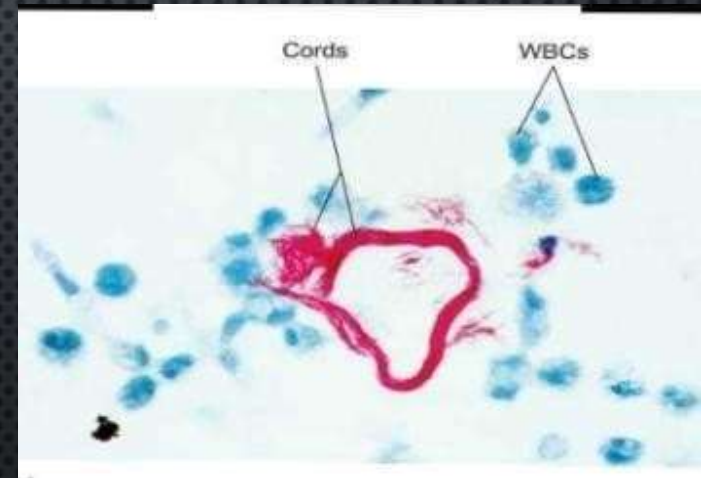
Non-motile

Non-spore forming



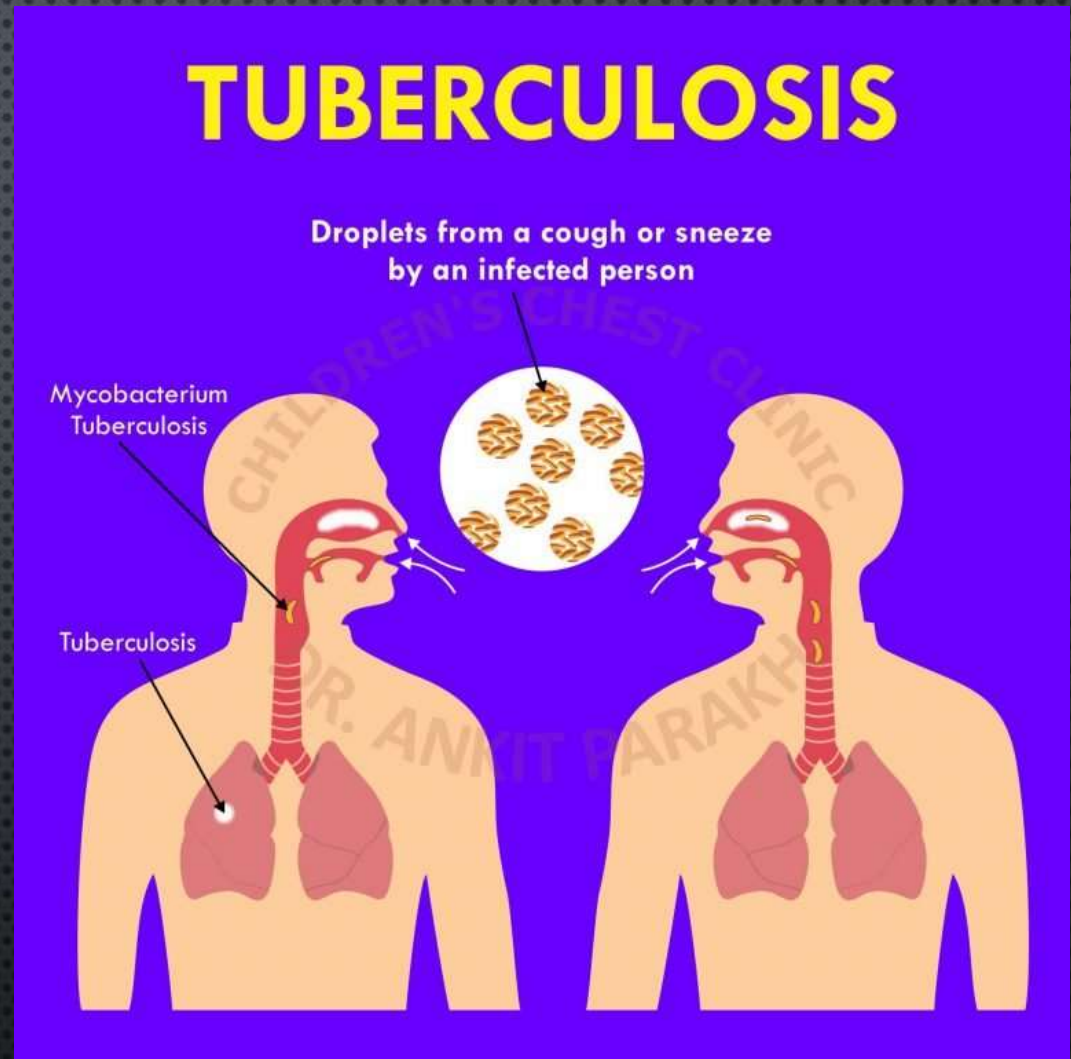
CORD FACTOR

Virulent strains grow in a characteristic serpentine cord-like pattern in fluid media due to cord factor



How does TB spread?

TB is an airborne infection, meaning that it spreads through the air

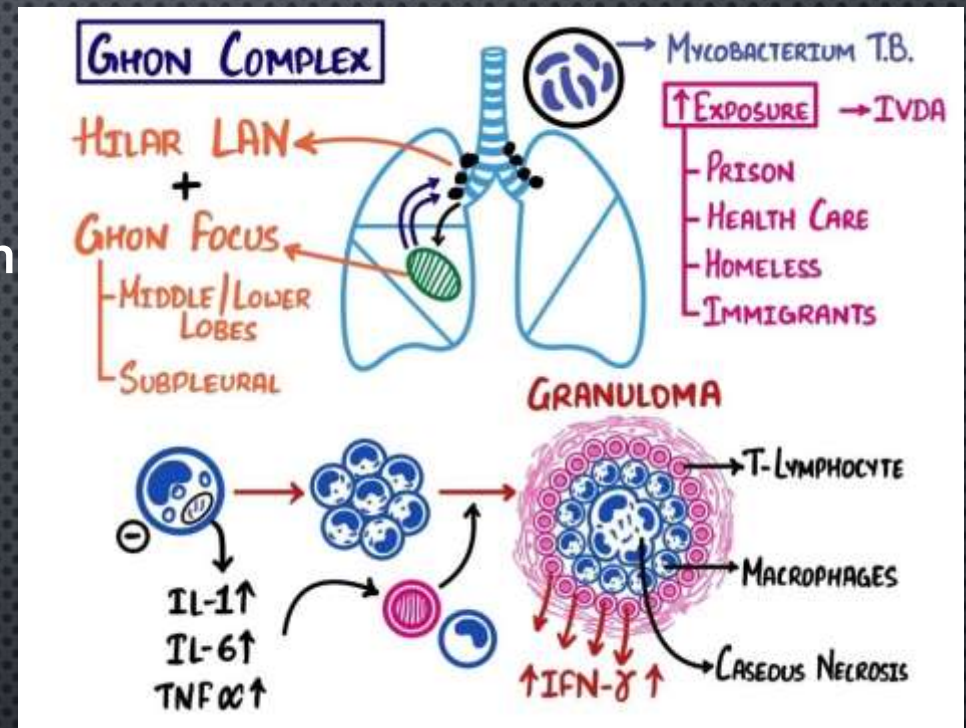


PATHOPHYSIOLOGY

- Tuberculosis is an airborne infection spread via respiratory droplets.
- Once inhaled, the organisms lodge in the alveoli and initiate the recruitment of macrophages and lymphocytes.
- Macrophages undergo transformation into epithelioid and Langhans cells, which aggregate with the lymphocytes to form the classical tuberculous granuloma.
- Clinical note : T cells in response to antigens, release cytokine called IFN gamma, which is used for diagnosis in case of BCG vaccination and in areas where exposure to non-tuberculous mycobacteria is high.

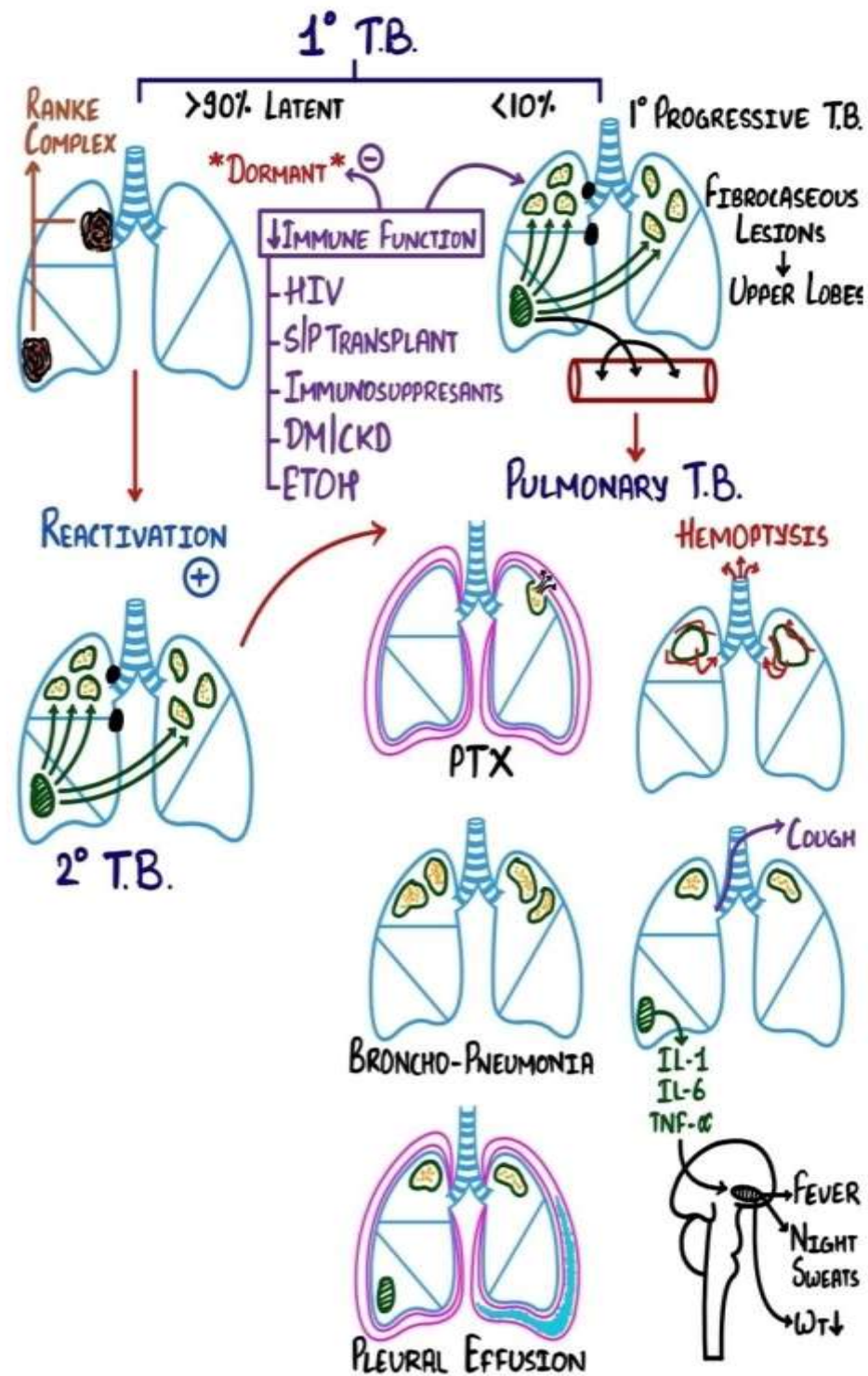
CONT

- Numerous granulomas aggregate to form a primary lesion or 'Ghon focus'.
- On a chest X-ray, the Ghon focus is evident as a small calcified nodule often within the upper parts of the lower lobes or the lower parts of the upper lobes, seen in the mid-zone.
- focus can also develop within the regional draining lymph node (primary complex of Ranke).



PRIMARY TUBERCULOSIS

- It refers to the infection of a previously uninfected (tuberculin-negative) individual.
- Initial containment complex (Ghon focus of infection and hilar node) within granuloma: Granulomatous Latent TB infection.
- In some cases, when the infected PT has low immunity as in AIDS or malnutrition, a primary progressive disease can occur.
- Primary progressive is when the immune response fails to control multiplication of the tubercle bacilli after first exposure.



FACTORS INCREASING THE RISK OF TB :

1 19.52 Factors increasing the risk of TB
Patient-related
• Age (children > young adults < elderly) <i>→ at extreme of ages.</i> • First-generation immigrants from high-prevalence countries • Close contacts of patients with smear-positive pulmonary TB • Overcrowding (prisons, collective dormitories); homelessness (doss houses and hostels) • Chest X-ray evidence of self-healed TB • Primary infection < 1 yr previously • Smoking: cigarettes and bidis (Indian cigarettes made of tobacco wrapped in temburini leaves)
Associated diseases
• Immunosuppression: HIV, anti-tumour necrosis factor (TNF) therapy, high-dose corticosteroids, cytotoxic agents • Malignancy (especially lymphoma and leukaemia) • Diabetes mellitus • Chronic kidney disease • Silicosis • Gastrointestinal disease associated with malnutrition (gastrectomy, jejunio-ileal bypass, cancer of the pancreas, malabsorption) • Deficiency of vitamin D or A • Recent measles in children

Clinical features

CLINICAL FEATURES: PULMONARY DISEASE

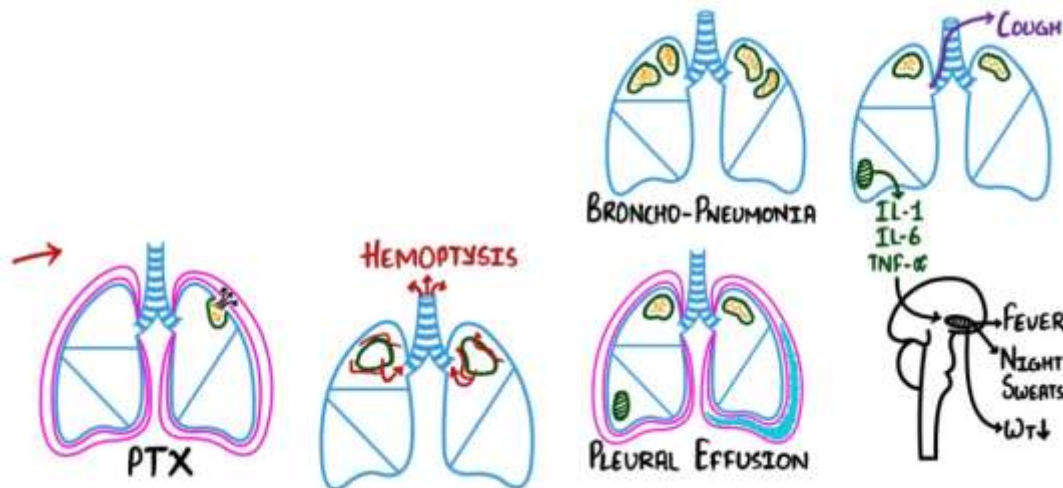
1-Primary pulmonary TB

-Often times primary TB patients are asymptomatic Sometimes even in secondary TB

-If they do present with symptoms, it's usually in
1-Secondary reactivation TB. 2-Primary progressive TB

-Pulmonary complication due to fibrocaseous lesions, consolidations, Ghon complex, hilar lymphadenopathy .

-Progressive primary disease may appear during the course of the initial illness or after a latent period of weeks or months.



CLINICAL FEATURES

(1) Pneumothorax

- **Fibrocavitary lesion of the upper lobe—> May extend into parenchyma and pleura—>“Eating up” the lung tissues**
- **Cavity opens up into pleural space—> Opportunity for air to leak into the pleural cavity**

(2) Bronchopneumonia

- **Fibrocaseous necrosis leads to pathogens not easily cleared So, the patient may develop bronchopneumonia**

(3) Pleural effusion (TB pleurisy)

- **Remember Ghon complex is in the lower/middle lobe and subpleural—> Massive amount of inflammatory cytokines—>
Causes increased capillary permeability—>vasodilation—> Proteins and fluid leak out**

(4) Hemoptysis

- **Fibrocavitary lesions that are forming, “eating up” the lung tissues ,There are bronchial blood vessels near these lung tissues, If they “eat” the bronchial blood vessel—> Cough up blood due to cavitation → hemoptysis**

(5) Productive cough

- **Fibrocavitary lesion compresses nearby bronchial system —>End up with inflammation of the airway
Cough receptors and sensory receptors → pick up information and trigger cough reflex**

Clinical features

(6) Fever

- Cytokines released from granuloma and fibrocaseous necrosis (IL-1, IL-6, TNF- α)—> These affect the hypothalamus

-Remember hypothalamus controls our eating and temperature

—> Dysregulation of the hypothalamus leads to

1. Fever.
2. Night sweats.
3. Weight loss

-Features of primary tuberculosis

- Infection (4-8 weeks) Influenza-like illness Primary complex

Skin test conversion

- Hypersensitivity Erythema nodosum, Dactylitis, Phlyctenular, conjunctivitis

Dactylitis



Clinical features

2-MILIARY

Blood-borne gives rise to miliary TB, which may present acutely but more frequently is characterised by 2-3 weeks of fever, night sweats, anorexia, weight loss and a dry cough.

Hepatosplenomegaly may develop and the presence of a headache may indicate coexistent tuberculous meningitis.

Anaemia and leucopenia reflect bone marrow involvement

3-Post-primary pulmonary TB

Post-primary disease refers to exogenous ('new' infection) or endogenous (reactivation of a dormant primary lesion) infection in a person who has been sensitised by earlier exposure.

It is most frequently pulmonary and characteristically occurs in the apex of an upper lobe, where the oxygen tension favours survival of the strictly aerobic organism.

The onset is usually insidious, developing slowly over several weeks.

Clinical features

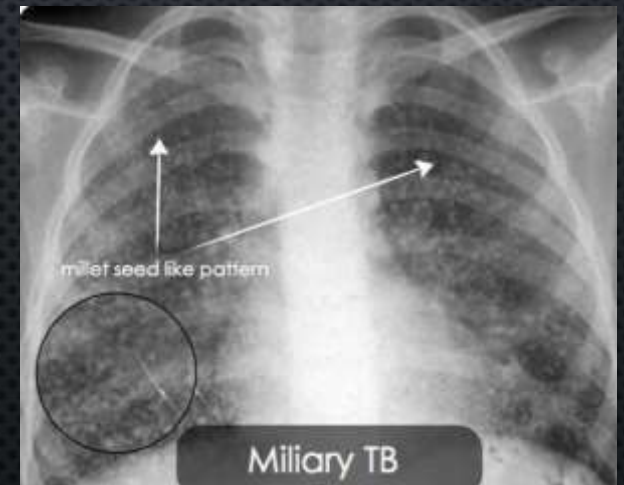
PHYSICAL FINDINGS IN MILITARY TB

- **Auscultation** of the chest is frequently normal but in more advanced disease widespread crackles are evident.
- **Fundoscopy** may show choroidal tubercles.
- **chest X-ray**
1-2 mm lesions “millet seed” distributed throughout the lung fields, although occasionally the appearances are coarser.

choroidal
tubercles

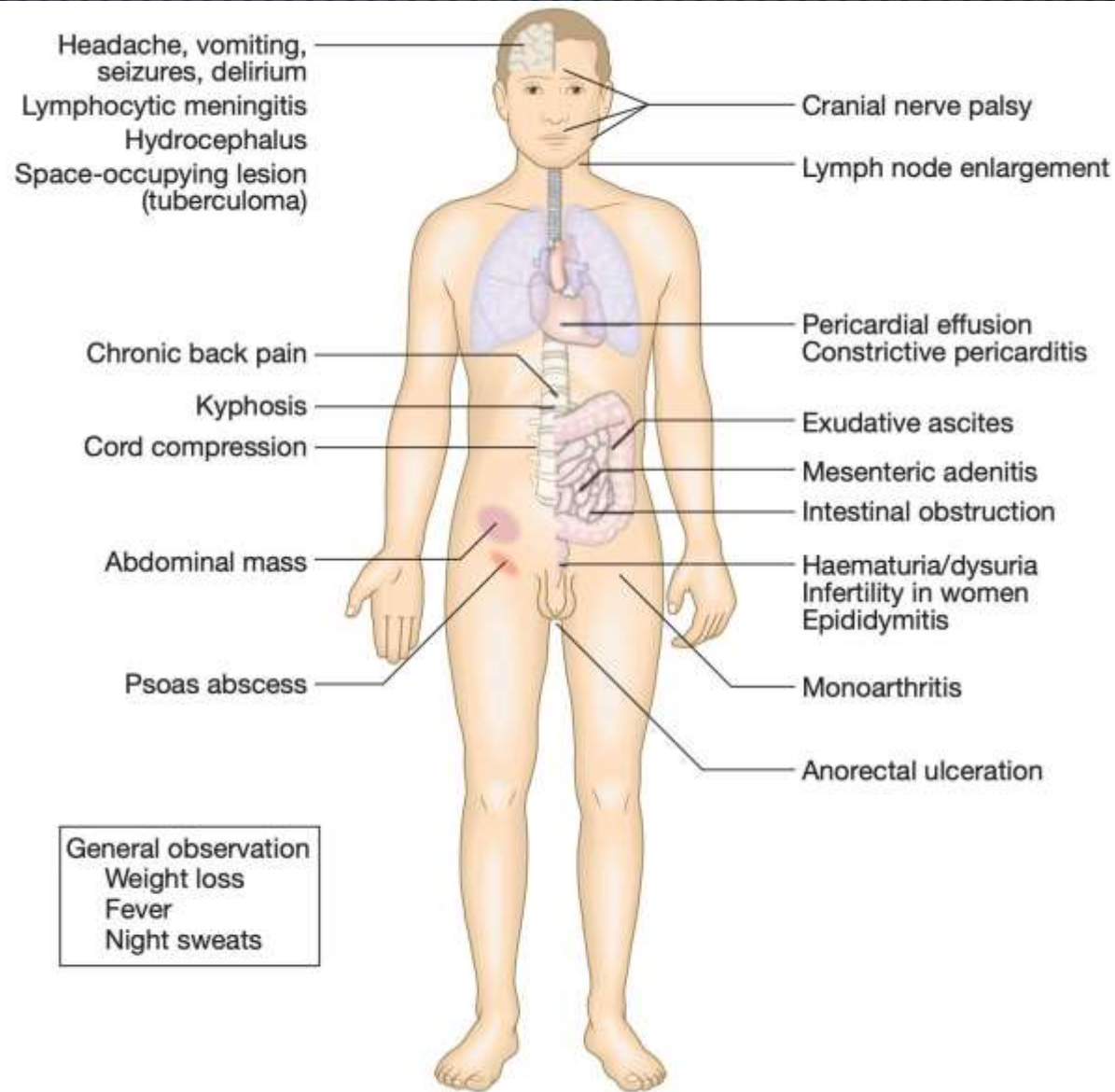


millet seed
appearance



EXTRAPULMONARY DISEASE

- Extrapulmonary TB accounts for 20% of cases in those who are HIV- negative but is more common in HIV-positive patients.



TUBERCULOUS LYMPHADENITIS

- the most common extrapulmonary site of disease (Cervical and mediastinal glands)
- Supraclavicular lymphadenopathy is often the result of spread from mediastinal disease
- Caseation -> may discharge through the skin -> “collar-stud” abscess
- tuberculin test ++
- During or after treatment, paradoxical enlargement

SCROFULA (CERVICAL LYMPHADENITIS)

- Swelling of the cervical lymph node



GASTROINTESTINAL TUBERCULOSIS:

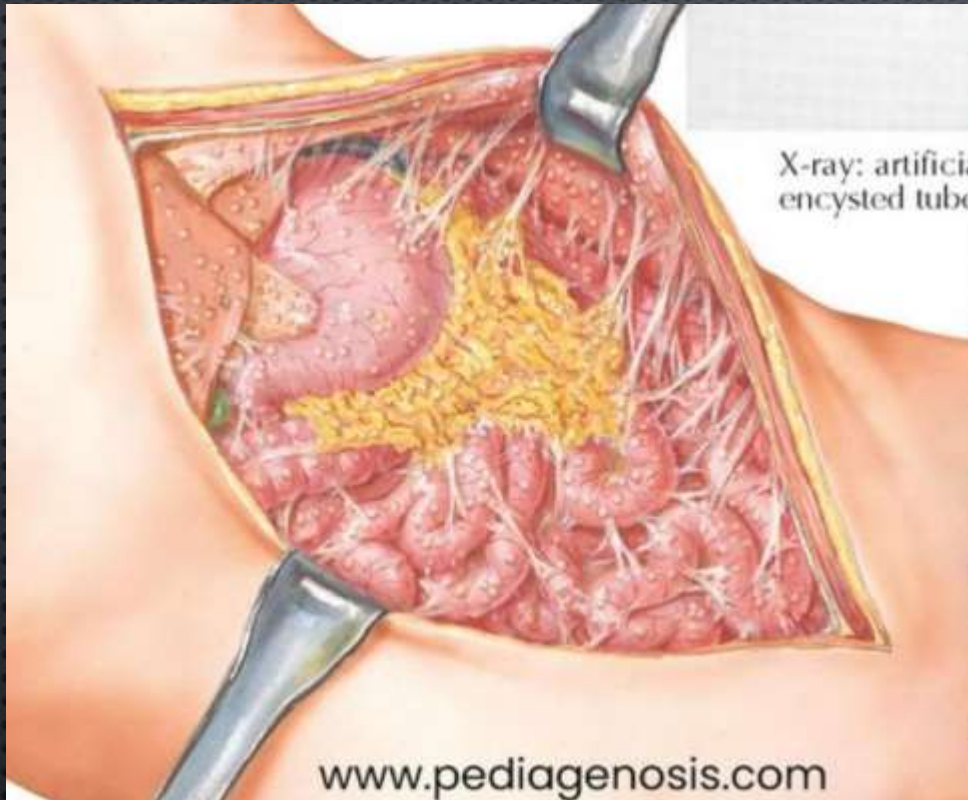
Ileocecal disease

- accounts for approximately half of abdominal TB cases
- Fever, night sweats, anorexia and weight loss
- thickened bowel wall on ultrasound & CT
 - abdominal lymphadenopathy, mesenteric thickening or ascites
- narrowing, shortening and distortion of the bowel, with caecal involvement predominating.
- abdominal distension, pain and constitutional symptoms
- The ascitic fluid is exudative and cellular, with a predominance of lymphocytes
- multiple white 'tubercles' over the peritoneal and omental surfaces

HEPATITIS

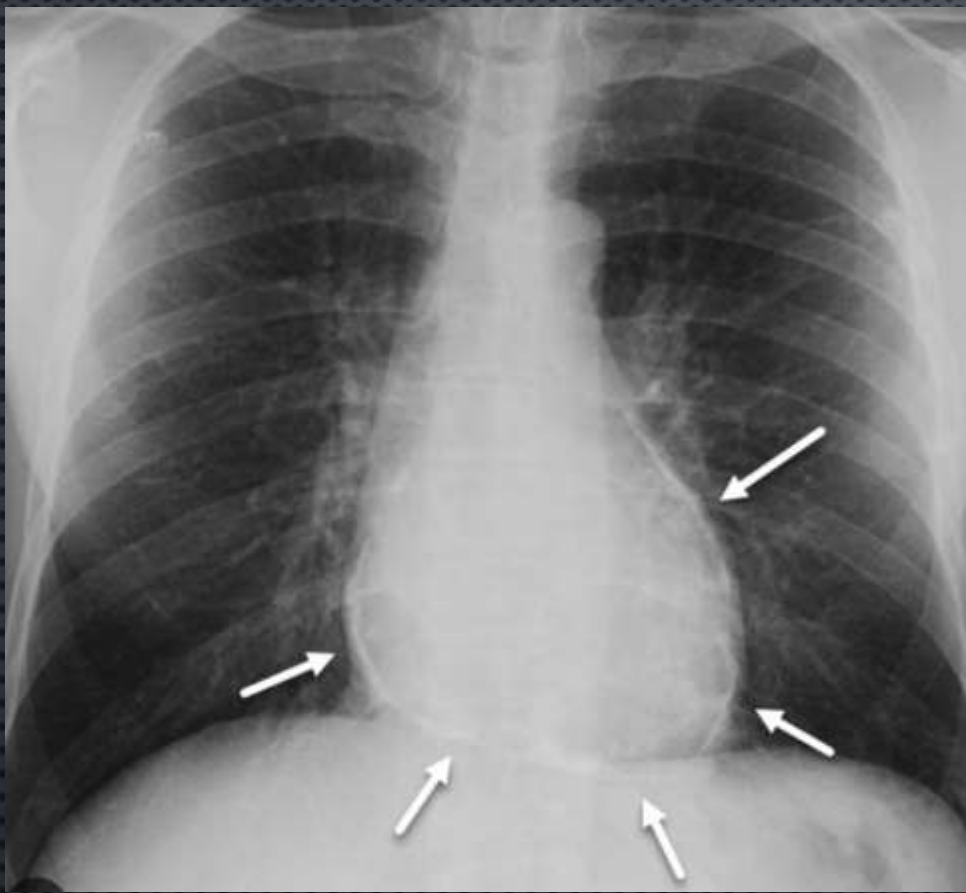
- Liver injury
- Inflamed liver causes AST and ALT to bump up in the blood
- Look for hepatitis
 - Abdominal pain (right upper quadrant)
 - Hepatomegaly
 - Increased LFT

MULTIPLE WHITE 'TUBERCLES'



PERICARDIAL DISEASE

- Disease occurs in two forms: pericardial effusion and constrictive pericarditis
- usually insidious, with breathlessness and abdominal swelling
- Coexistent pulmonary disease is very rare, with the exception of pleural effusion
 - Diastolic heart failure signs
 - increased pericardial dullness (pericardial effusion)
 - globular enlarged heart on chest X-ray (pericardial effusion)
 - pericardial calcification occurs in around 25% of cases
 - S3 sound (constrictive pericarditis)
 - The effusion is frequently blood-stained



Pericardial Calcification

Central nervous system disease

- Meningeal TB is the most important (uncommon)
- mortality rates of 30%
- Headache
- Vomiting
- Low-grade fever
- Oculomotor palsies
- Papilloedema

GENITOURINARY DISEASE

- Haematuria, frequency and dysuria are often present, with sterile pyuria
- In women, infertility from endometritis, pelvic pain and swelling from salpingitis or a tubo-ovarian abscess occurs
- In men, epididymitis or prostatitis

BONE AND JOINT DISEASE

- The spine is the most common site for bony TB (Pott's disease)
- chronic back pain (T&L)
- Paravertebral and psoas abscess
- kyphosis
- (cold) abscess in the inguinal region.
- TB can affect any joint but most frequently involves the hip or knee
- Radiological changes are often non-specific



DIAGNOSIS

- ◆ History
- ◆ Physical Examination
- ◆ Investigations (Laboratory, Imaging)

HISTORY

Typical symptoms for TB patient include:

- General: fever, lethargy, anorexia, weight loss, enlarged and tender lymph nodes.
- Pulmonary: cough (usually chronic), sputum (initially dry, then purulent or blood-stained), breathlessness, pleuritic chest pain.
- Extra-pulmonary: genitourinary (urinary symptoms), musculoskeletal (joint pain), neurological (headache, reduced GCS, focal neurology), cardiac (chest pain), gastrointestinal (abdominal pain, bloating), rash.

Other aspects we should cover with history:

- Past medical history: HIV or other immunosuppressive condition, chronic conditions such as diabetes
- Drug history: immunosuppressive medications including steroids
- Social history: occupation, alcohol or drug dependence, homelessness, country of birth and travel history
- TB contacts: nature and duration of contact

PHYSICAL EXAMINATION

Findings for the patient with TB:

- • Sputum pots with purulent or blood-stained sputum
- ENLARGED, TENDER LYMPH NODES
- • Crackles or bronchial breathing over consolidation
- • Dullness to percussion and decreased fremitus over pleural effusions



BLOOD STAINED
SPUTUM

Enlarged
lymph node



INVESTIGATIONS

LABORATORY:

- Basic blood tests: looking for raised inflammatory markers, renal and liver profile to guide the use of drug treatment
- Viral screen: HIV, hepatitis B and C which can increase the risk of TB
- Sputum microscopy, culture and sensitivities: three samples (a least one early morning) prior to starting antimicrobial treatment. Bronchoscopy with lavage or bronchial washings can be considered if there is no spontaneous sputum production.
- Rapid diagnostic tests for TB are used in some cases.
- Extra-pulmonary sites: early morning urine or lymph node biopsies can be cultured for TB.
- Tuberculin Skin Tests

IMAGINING:

Chest X-ray is the most useful initial imaging, and pulmonary TB can have various appearances on X-ray.

- Patchy or lobar consolidation
- Linear and nodular opacities
- Miliary TB (small, uniformly distributed nodules)
- Cavitating lesions (more likely in post-primary TB)
- Tuberculoma (a caseating granuloma)
- Calcified tuberculoma (known as a Ghon focus) or lymph nodes
- Lymphadenopathy
- Pleural effusion



**Chest X-ray
showing patchy
opacification of
pulmonary TB**

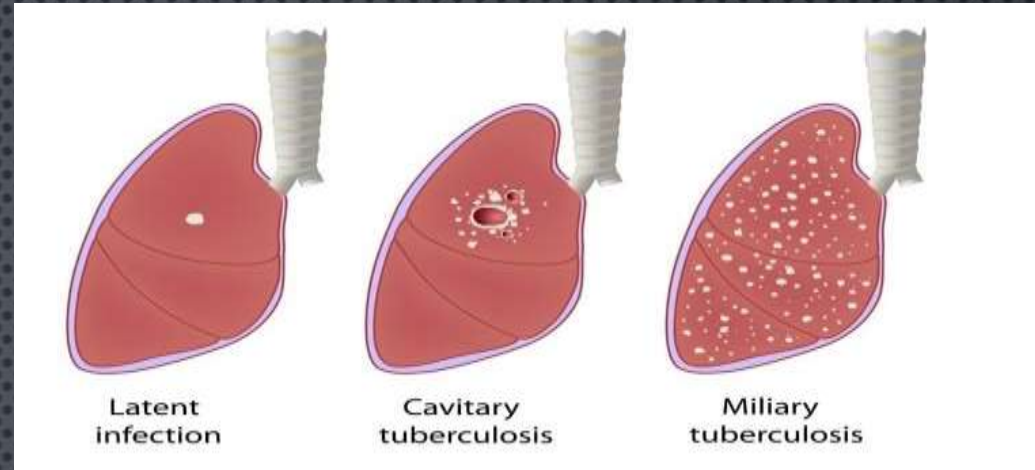


**Chest X-ray
showing the
appearance
of miliary TB**



**Section of a
chest X-ray
showing a
Ghon focus**

MANAGEMENT OF TB



- **Firstly:** the goal of treatment The treatment of TB is based on the principle of an initial intensive phase to reduce the bacterial population rapidly , followed by a continuation phase to destroy any remaining bacteria
- **Secondly:** identify category that need treatment
- Treatment should be commenced immediately in any patient who is smear-positive ,and in those who are smear-negative but with typical chest X-ray changes and no response to standard antibiotics

THIRDLY: TREATMENT PLAN

1

19.60 Main adverse reactions of first-line antituberculous drugs

	Isoniazid	Rifampicin	Pyrazinamide	Streptomycin	Ethambutol
Mode of action	Cell wall synthesis	DNA transcription	Unknown	Protein synthesis	Cell wall synthesis
Major adverse reactions	Peripheral neuropathy ¹ Hepatitis ² Rash	Febrile reactions Hepatitis Rash Gastrointestinal disturbance	Hepatitis Gastrointestinal disturbance Hyperuricaemia	8th nerve damage Rash	Retrobulbar neuritis ³ Arthralgia
Less common adverse reactions	Lupoid reactions Seizures Psychoses	Interstitial nephritis Thrombocytopenia Haemolytic anaemia	Rash Photosensitisation Gout	Nephrotoxicity Agranulocytosis	Peripheral neuropathy Rash

¹The risk may be reduced by prescribing pyridoxine. ²More common in patients with a slow acetylator status and in alcoholics. ³Reduced visual acuity and colour vision may be reported with higher doses and are usually reversible.

- Standard treatment involves 6 months treatment with >> isoniazid and rifampicin, supplemented in the first 2 months with pyrazinamide and ethambutol.

➤ **6 months regimen is appropriate for all patients with new-onset pulmonary TB and most cases of extrapulmonary TB**

- But TB with CNS involvement need 12 months treatment. (*TB meningitis*)
- Also, involvement of CNS , CVS (pericardial disease) and children with endobronchial disease need to add Glucocorticoids to reduce inflammation and limit tissue damage.

1

19.59 Treatment of new TB patients (World Health Organization recommendations)

Intensive phase	Continuation phase	Comments
Standard regimen		
2 mths of HRZE	4 mths of HR	Applies only in countries with high levels of isoniazid resistance in new TB patients, and where isoniazid drug susceptibility testing in new patients is not done (or results are unavailable) before the continuation phase begins
2 mths of HRZE	4 mths of HRE	
Dosing frequency		
Daily*	Daily	Optimal
Daily*	3 times/wk	Acceptable alternative for any new patient receiving directly observed therapy
3 times/wk	3 times/wk	Acceptable alternative, provided that the patient is receiving directly observed therapy and is NOT living with HIV or living in an HIV-prevalent setting

*Daily (rather than 3 times weekly) intensive-phase dosing may help to prevent acquired drug resistance in TB patients starting treatment with isoniazid resistance. (H = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol) Adapted from WHO Treatment of Tuberculosis Guidelines, 4th edn.

ADVERSE EFFECTS OF ANTI-TB DRUGS

- **Isoniazid** can cause a polyneuropathy due to B6 deficiency (*as it interacts with pyridoxal phosphate so pyridoxine 10–25 mg daily, should be prescribed concomitantly to prevent this.*), allergic reaction as skin rash, hepatitis occurs in less than 1% of cases. so, monitor liver function is ordered
- **Rifampicin** stains body secretions red/pink so get color change in urine, tears and sweat. Also, rifampicin induces liver enzymes, means patient's therapy will need to be undertaken, particularly with antidepressants, anticoagulants and antiepileptics. In addition to oral contraception will not be effective, so alternative birth-controlled methods should be used.
- **Pyrazinamide** may cause hepatic toxicity, itching, rash and arthralgia. & reduces renal excretion of urate and may lead to hyperuricemic gout.
- **Ethambutol** can cause a dose-related optic retrobulbar neuritis.

TREATMENT RECAP

LATENT  CXR/CT ⊖ + No Sxs	[I] INH + B₆ × 9 MONTHS [II] RIFAMPIN × 4 MONTHS
ACTIVE  CXR/CT ⊕ + Sxs	[I] RIFAMPIN + INH + PYRAZINAMIDE + ETHAMBUTOL OR STREPTOMYCIN × 2 MONTHS ↓↓↓ [II] RIFAMPIN + INH × 4 MONTHS

RIFAMPIN	INH	PYRAZINAMIDE	ETHAMBUTOL	STREPTOMYCIN
 RED/ORANGE ↓ LFT's CYP450 INH ↓ [ACTIVE DRUG]	 B₆ ↓ NEUROPATHY ↓ LFT's	 GOUT ↑ URIC ACID ↓ LFT's	 OPTIC NEURITIS	

- Most patients can be treated at home.
- Admission to a hospital unit with appropriate isolation facilities should be considered in these situations: 1)intolerance of medication,
- 2)questionable treatment adherence,
- 3) adverse social conditions or a significant risk of multidrug-resistant TB after 2 months on treatment
- 4) contact with known multidrug-resistant TB.

- ***effectiveness of treatment*** : Effectiveness of therapy for pulmonary TB is assessed by further sputum smear
at 2 months and at 5 months.
- Treatment failure is defined as:
 - *a positive sputum smear or culture after 5 months
 - * any patient with a multidrug-resistant strain, regardless of whether they are smear-positive or negative.
 - ***If treatment failure occurs, the case should be referred to a regional center to deal with it.***

CONTROL AND PREVENTION

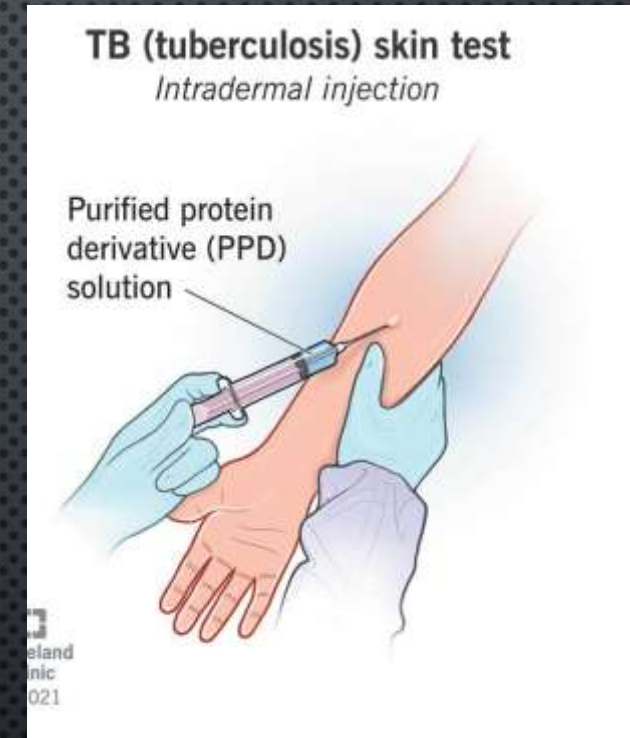
- Approximately 10-20% of close contacts of patient with smear- positive pulmonary TB and 2- 5% of those with smear-negative, culture-positive disease have evidence of TB infection.

- *Test to screen for M.Tuberculosis:*

- Tuberculin skin testing is the most common method used to screen for latent M tuberculosis (*positive tuberculin skin test indicates tuberculous infection, with or without disease , without differentiating if its Active or Latent*).

- Due to poor adherence to therapy is a major factor in prolonged illness, there's high risk of relapse, and the emergence of drug resistance,

So, DOT (Directly observed therapy) has become important control strategy in resource-poor nations. By supervised administration of therapy 3 times weekly to improve adherence.



BCG VACCINE

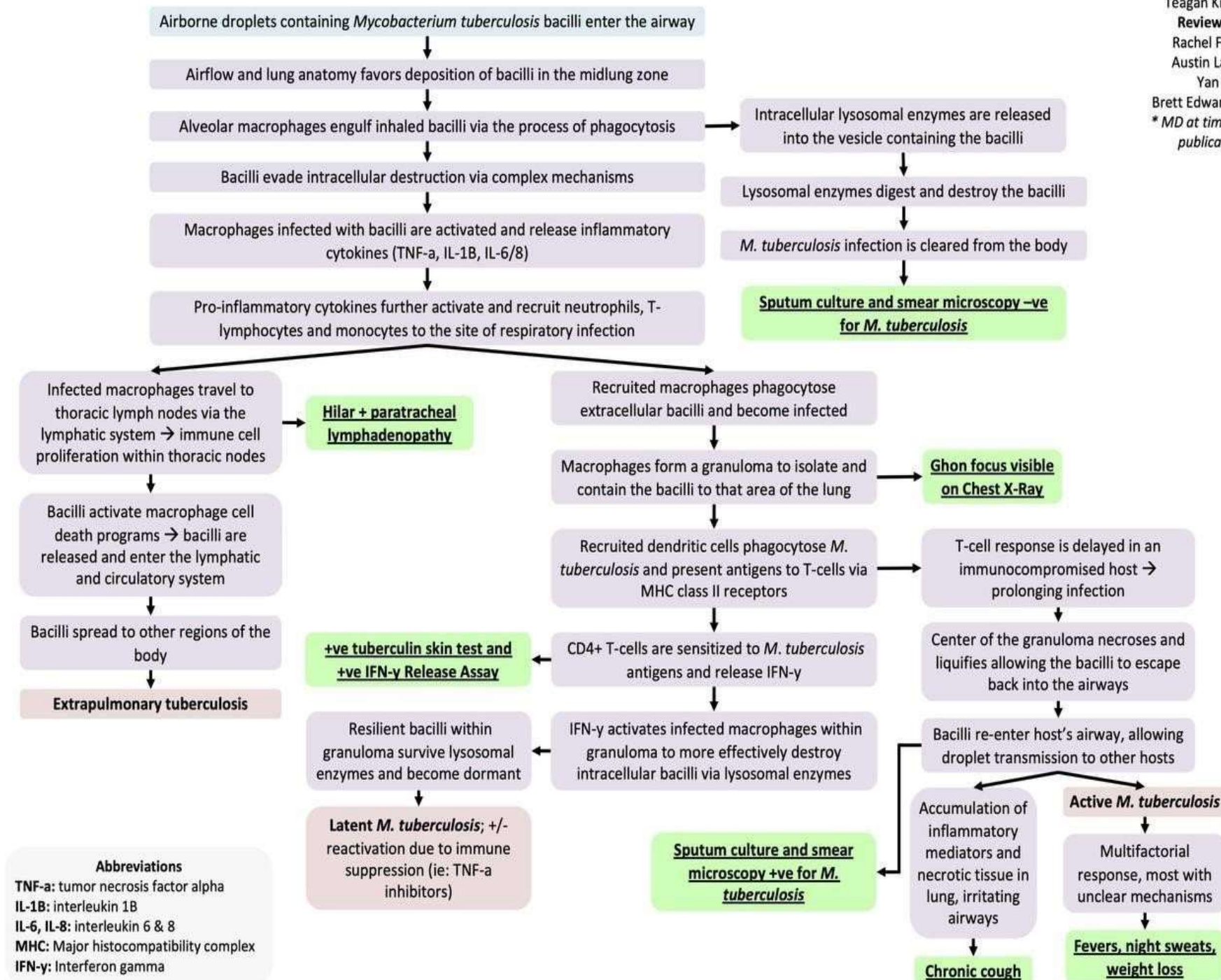
- A live attenuated vaccine derived from *M. bovis*, is the most established TB vaccine. administered by intradermal injection. BCG appears to be effective in preventing disseminated disease, including tuberculous meningitis in children.
- BCG is very safe, with the occasional complication of local abscess formation. It should not be administered to those who are immunocompromised (e.g. by HIV) or pregnant.
- **In Jordan, the vaccine is listed as part of the national vaccination program and is given to children at birth**

Prognosis

Following successful completion of chemotherapy, cure should be anticipated in the majority of patients. Most relapses occur within 5 months & usually have the same drug susceptibility. In the absence of treatment, a patient with smear-positive TB will remain infectious for an average of 2 years; in 1 year, 25% of untreated cases will die. Death is more likely in those who are smear-positive and those who smoke, HIV positive pts. Have higher mortality rates and increased risk of relapse

Mycobacterium Tuberculosis: Pathogenesis and clinical findings

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Legend:

Pathophysiology

Mechanism

Sign/Symptom/Lab Finding

Complications

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THANK YOU