Tuberculosis (TB)

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Overview of TB epidemiology:

→After exposure to TB the patient will either present with an active TB or will just remain in a dormant latent phase of TB.

→Weather the patient had the infection or developed latent TB, TST or IGRA will be positive.

→The rate of progression from latent TB to active disease:

- Non-HIV patients is 5-10% lifetime.
- HIV positive patients: 5-10% per year.

Risk factors for TB infection:

1. Exposure to TB cases.
2. From TB endemic area.
3. Homelessness.
4. Incarceration.
5. Works in a healthcare or corrections.
6. Injection drug use.

Risk factors for progression to TB disease:

1. Recent infection (The most important risk factor).
2. HIV infection.
3. TNF alpha inhibitors.
4. Immunosuppression.
5. End stage renal disease.
6. Diabetes.
7. Silicosis.
8. CXR showing fibrotic lesions consistent with prior TB.
9. Intestinal bypass/ gastrectomy/ chronic malabsorption.
10. Cancer of the head or neck, Hodgkin, leukemia.

Active TB Clinical presentation:

→Fever, sweats, weight loss.

→Cough If pulmonary with hemoptysis in cases of cavitation (However the absence of hemoptysis should not exclude TB as it usually develops if there was a cavitary lesion).

→Subacute in onset (can be acute in immunocompromised patients).

Chest Imaging:

→Upper lobe/Apical cavity is typical with surrounding infiltrate +/- adenopathy.

→Miliary TB is a hematogenous spread TB.

Extrapulmonary TB:

→ TB can virtually affect any organ and any system.
→ It is reasonable to think about when patients do not respond to the typical therapy.
→ It is important to obtain clinical specimens from the site affected for mycobacteriological cultures, PCR, smears and pathology.

→ **Examples of extrapulmonary syndromes:**

1. CNS: Meningitis, focal tuberculomas.
2. Lymphadenitis (Cervical, thoracic, abdominal).
3. Bone and joint:
   - Vertebral (Thoracic- most common, lumbar, anterior wedging, +/- psoas abscess).
   - Osteomyelitis and arthritis.
4. Pleural.
5. Abdominal/ Pelvic:
   - GU: sterile pyuria, can cause infertility.
   - GI: A great mimicker for inflammatory bowel disease.

Disseminated TB:

→Can present with an acute sepsis like syndrome especially in heavily immunocompromised patients.

→Obtain mycobacterial blood cultures and respiratory specimens.

Active TB diagnosis:

→Smear microscopy:

- Has a low sensitivity overall around 50-60% sensitivity in pulmonary TB.
- In pulmonary TB the yield of test is increased with multiple specimens.
- Less sensitive in advanced HIV (30-50%).
- Needs 10,000 cfu/ml.
- A negative smear does not exclude the diagnosis of active TB.
- Not specific for MTB (Most mycobacteria look alike).
- Good PPV in TB endemic regions.

Active TB diagnosis:

→Rapid MTB PCR:

- Needs 100 cfu/ml for detection.
- A negative test does not rule out TB.
- High specificity for MTB.
- PCR based tests are designed to be specific mycobacterial TB and rifampicin resistance.
- Does not detect other mycobacteria.
- Does not predict resistance to other anti Tb medications.
- Once the rapid MTB/RIF test is reported as MTB detected RIF undetected this is by definition NOT a multidrug resistant TB.
- The test is validated to be done on sputum but can be done on non-sputum specimen (However can have false negative tests for the presence of inhibitors).

Active TB diagnosis:

→Culture:

- Has the highest sensitivity.
- Needs 1-10 cfu/ml.
- Mycobacterial culture is the most sensitive however it is a slow method (3-6 weeks).
- The median time for positivity is around 21 days.
- Once positive, additional tests need to be done to identify the species.
- Considered the gold standard:
  - Pulmonary TB 90-95% sensitive.
  - Extrapulmonary TB much less sensitive.

Active TB diagnosis:

- Histopathology:
  - Typically cause a caseating granuloma with a ZN stain for bacilli.
  - The granuloma formation requires a good immune system to form and therefore this histopathological feature may not be present in immunocompromised hosts.

→ PPD and IGRA:
  - Do not distinguish latent from active TB.
  - Negative test does not rule out active disease.

Active TB treatment:

→ **First line treatment:**

→ Induction phase:

- Rifampicin, Isoniazid (Use B6 to prevent neurotoxicity of INH) Ethambutol, Pyrazinamide for two months.
- Continuation phase: Rifampicin + INH for four more months.
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→ Extend the continuation phase in the following situations:

- Pulmonary disease if cavitation and culture positive at the end of the second month of treatment (9 months total).
- CNS TB (usually 9-12 months total duration).
- Bone and joint TB (6-9 months total duration).

Active TB treatment

→ **Corticosteroids indicated in:**

- TB meningitis: improved morbidity and mortality.
- TB pericarditis: Previously recommended but recent trials showed no difference in outcome. Can be considered in cases of inflammatory fluid analysis.

→ **General rules:**

- Daily regimen is mor efficacious than intermittent (2 or 3 times a week).
- IN HIV positive, intermittent treatment is associated with Rifampin resistance.

ATT side effects:

→ Hepatotoxicity:
- Main ATT: INH, Rif, PYZ.
- INH and pyrazinamide are more hepatotoxic than rifampicin. Ethambutol is the least hepatotoxic of all 4 anti TB.
- Rifampicin mostly causes cholestatic liver derangement.

→ Ethambutol:
- retrobulbar neuritis (Color vision is the first affected, visual acuity will later be affected, unlikely to occur with the doses and duration of therapy given in TB).

→ Rifampicin:
- A potent enzyme inducer and decreases the level of other drugs of particular importance warfarin ART (Integrase inhibitor, PI, NNRTI) hormonal contraceptives, corticosteroids.
- Of the four anti TB drugs Rifampicin is the most important and if it was dropped for side effect or intolerance short course (6 months therapy) can no longer be used.

→ PYZ:
- Arthralgias.

→ Aminoglycosides:
- Ototoxicity, vestibular toxicity, nephrotoxicity.

→ Bedaquiline:
- A novel drug with a novel mechanism of action targeting (MTB ATP synthase).
- Approved for pulmonary drug resistant TB when effective therapy cannot be provided.
- QT prolongation is a serious adverse effect of the medication.
- Has a long half-life 4 months.

Summary of ATT mechanism of action/resistant/ common side effec

Drug	Mechanism of action	Mechanism of resistance	Dose	Side effect
Isoniazid	Inhibits mycolic acid synthesis. Penetrates well even to the brain.	Loss of katG overexpression. Alteration in inhA encoded reductase.	5 mg/kg/day Maximum dose: 300	Hepatotoxicity. Peripheral neuropathy.
Rifampin	Inhibits DNA dependent RNA polymerase, blocking RNA transcript	rpoB (RNA polymerase subunit beta) mutation.	10 mg/kg/day Maximum dose: 600.	Rash. Hepatoxicity. Thrmobocytopenia Potent enzyme inducer.
Ethambutol	Inhibits arabinosyl transferase enzyme which will inhibit cell wall arabinogalactan and lipoarabinomannan.	embB gene mutation causing enzymatic alteration in ethambutol binding site.	15 mg/kg/day	Optic neuritis. Peripheral neuritis. Hepatotoxicity.
Pyrazinamide	Unknown. Pyrizinoic acid lowers the PH below the level necessary for mycobacterial growth.	pncA gene mutation. M. Bovis and M. Leprae are intrinsically resistant.	20 mg/kg/day	Hepatotoxicity. Asymptomatic hyperuricemia. Polyarthralgia.
Bedaquiline	Inhibits ATP synthetase by binding to subunit c. Prevents mycobacterium from ATP synthesis and eventually lead to cell death.	Point mutation in the atpE gene, efflux pump. mmpR mutation.	400 mg daily for 14 days followed by 200 mg thrice weekly to complete 24 weeks.	QTc prolongation.

Resistance

- Risk factors for drug resistant TB:

→ Contact with a known case of drug resistant TB.
→ Previous history of treatment especially if the patient was non adherent.
→ Travel to an area known to have drug resistant TB (Eastern Europe).

- Definitions:

→ MDR TB: Resistance to ***both*** Rifampicin ***and*** INH.
→ XDR TB: MDR plus resistance to fluroquinolones plus at least one of the injectable 2nd line drugs (Amikacin, kanamycin, capreomycin).

HIV and TB considerations:

→ HIV increases the risk of progression from latent to active TB.
→ CD4 influences the severity and clinical manifestations of TB.
→ TB can increase HIV viral load.
→ TB is associated with more rapid progression of HIV.
→ In HIV patients it is less likely to see a cavitary lung disease.
→ With advancing immunosuppression there is increased risk for:
  - Smear negative pulmonary TB.
  - Extrapulmonary TB +/- Pulmonary disease.
  - CNS TB.
  - Widely disseminated TB/ Mycobacteremia.
→ A negative CXR and a negative smear does not exclude TB.

- Extrapulmonary TB, CNS TB and widely disseminated TB are the usual forms in advanced HIV.

HIV- TB treatment:

→ Despite the drug-drug interaction rifampicin cause, a rifamycin based therapy is still the preferred regimen.
→ ART guidelines recommend efavirenz based combination with higher doses of integrase inhibitors.
→ Rifampin:
- Accelerate clearance of PI, NNRTI, INSTI, CCR5 inhibitors.
- Integrase inhibitor: Need to give BID dosing.
- TAF: If used need to closely monitor HIV viral load while on therapy.
- Should not combine PI with Rifampin.

→ Rifabutin:
- Weaker enzyme inducer than rifampin.
- A CYP450 substrate (Rifabutin metabolism affected by NNRTI and PIs).
- If a PI based ART will be used decrease the Rifabutin dose to 150 mg daily or 300 mg every other day.

→ When to start ART:
- CD4< 50: Within 2 weeks of starting TB treatment.
- CD4> 50: Within 8 weeks of starting TB treatment.
- HIV infected pregnant women with active TB should be started on ART as soon as feasible (For maternal health and Prevention of mother to child transmission).
- In TB meningitis ART should not be given until after 8 weeks of anti TB medications.

Immune reconstitution inflammatory syndrome (IRIS):

- **Two forms:**
  - Paradoxical worsening of TB when ART is started after TB treatment.
  - Unmasking TB when ART started in setting of not yet recognized TB.
- Typically occurs 2 weeks to 3 months after starting ART.

- **Risk Factors:**

1. CD4< 50.
2. High pre-ART viral load.
3. Severe TB.
4. Short interval between initiation of TB treatment and ART.

- **Protean manifestation:**

- Fever, new lesion, extension of prior lesions.

- **Management approach in IRIS:**

- Deal promptly with any limited space issue: CNS inflammation, obstructing adenopathy), corticosteroid, surgery if needed.
- Consider other differential diagnosis:
- Give NSAID in mild cases.
- Give corticosteroids in more severe and refractory cases: Prednisone 1.5 mg/kg/day for two weeks then 0.75 mg/kg/day for two weeks.
- Continue both TB plus ART.

TB in transplant recipients:

→ Transplant associated immunosuppression increases the risk of active TB disease if the person is infected.

→ Presents atypically and therefore diagnosis is delayed:

- One third to half is disseminated or extrapulmonary.
- The ability of granuloma formation is lost by immunosuppression and therefore patients are unable to contain the infection and they rapidly progress and disseminate.
- 4% are thought to be donor derived.

→ Can rapidly progress and carry high mortality.

→ Small proportion are donor derived.

→ There is a drug-drug interaction with:

- MTOR inhibitors (Sirolimus/everolimus).
- Calcineurin inhibitors (Cyclosporin, tacrolimus).
- Frequent drug levels of calcineurin and MTORs is advised.
- Corticosteroid and hence they are at risk for graft rejection.

→ Rifabutin based regimen is preferred to minimize interaction.

TB and TNF alpha inhibitor inhibits:

→ TNF alpha inhibitors markedly increase the risk of active TB if infected.
→ Can present with atypical TB (e.g., non-cavitary pulmonary disease, extrapulmonary disseminated).
→ Increased TB morbidity and mortality.
→ Full monoclonal IgG1 monoclonal antibody most potent (i.e., infliximab, adalimumab, golimumab).
→ It is recommended to do a PPD or IGRA prior to starting anti TNF:
- If any is positive, patient should be started on latent TB management before starting therapy (2-8 weeks).

Latent TB:

→ Tuberculin skin test:
→ A mix of antigens.
→ It is a delayed type IV hypersensitivity reaction.
→ Intradermal inoculation, measure induration at 48-72 hours (positive reaction lasts a few days).
→ Adjunctive in the diagnosis of TB.
→ False positive results may be seen with NTM or prior BCV vaccine or NTM.
→ A booster effect can be mistaken for positive PPD test:
  - TST maybe initially negative if there is a remote history of infection. However, TST stimulates immune response to MTB antigens and a subsequent TST can be positive and mistaken for seroconversion.
  - For that a 2 step TST for individuals who may be tested periodically (e.g., HCW).

- Cutoffs are based on likelihood of true exposure, risk of progression to active TB if infected (5 mm; 10 mm; 15 mm)

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Latent TB infection (LTBI): classification of tuberculin skin test results

≥ 5 mm is POS	≥ 10 mm is POS	≥ 15 mm is POS
HIV-infected Recent TB contact CXR with fibrotic changes Organ transplantation Prednisone ≥ 15 mg/d x 1 month or more TNF alpha antagonists	Recent arrival (w/in 5 years) from TB high prevalence area Injection drug use Residents & employees of high-risk settings (HWC, corrections, homeless shelters) Mycobacteriology lab staff Children < 5 years old Medical conditions: diabetes, silicosis, end-stage renal dz, gastrectomy or small bowel bypass, solid organ transplant, CA head and neck	Persons with no known risk factors for TB

Interferon gamma release assays- IGRA:

→ Two tests are currently available: QuantiFERON-TB; T-SPOT.TB.
→ Blood based, in vitro stimulation of WBC with protein antigens specific for M. TB.
→ The advantage of IGRA over PPD is that there is no cross reactivity with BCG vaccine.
→ IGRA is as sensitive as PPD but more specific.
→ M. Kansasii and M. Marinum can cause a false positive IGRA.
→ It might be negative in immunocompromised.

Management of latent TB:

→ Excluding active TB is a key component of the diagnosis of latent TB infection:
- Review of system: Fever, weight loss, cough, night sweats, focal signs/symptoms that could be associated with extrapulmonary TB).
- Chest X-ray to exclude occult pulmonary TB.

→ **Regimens for latent TB include:**
- Preferred:

1. INH + Rifapentine once weekly for 12 doses.
2. Rifampin daily for 4 months.
3. INH+ Rifampin daily for 3 months.

- Alternative:
  - INH daily for 6 or 9 months.

- Rifampin + PYZ is NO longer used because of the risk of hepatotoxicity.
- Perform LFTs prior to treatment in adults with risks for hepatotoxicity (Ethanol, risk for viral hepatitis, other hepatotoxic medications).
- Monthly review of systems for adverse effects:
  - Peripheral neuropathy if on INH (Can be avoided by B6 supplements).
  - Hepatotoxicity (Nausea/vomiting, abdominal discomfort, jaundice).

BCG vaccine:

→ Live attenuated vaccine (from M. Bovis).

→ Neonatal vaccination:

- Decreases the incidence of severe forms of childhood TB.
- No very limited impact on adult TB.
- Regional lymphadenitis can occur after vaccination, typically no treatment is indicated.
- Disseminated infection can occur in immunocompromised (Treatment is needed).

→ Immunotherapy for bladder cancer:

- Intravesicular administration.
- Complications:
  - Granulomatous prostatitis or hepatitis, epididymitis-orchitis, spondylitis, psoas abscess, military pulmonary, disseminated/sepsis.
  - Contemporaneous with BCG treatment or up to years later.
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- Treatment:
  - Inherent resistance to PZA.
  - Treat with rifampin+ INH + Ethambutol.