



Tuberculosis in Immunocompetent & Immunosuppressed Hosts

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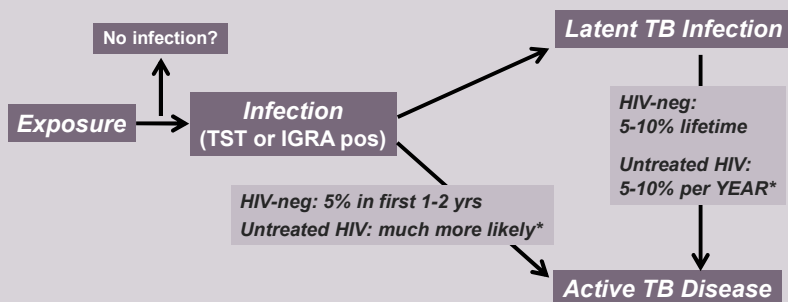
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- I receive salary support from grants from NIH and CDC for my work on several clinical trials of novel TB regimens and novel TB diagnostics.

Natural History of *M. tuberculosis* Infection



Risk Factors for TB Disease

Epi Risk Factors for TB INFECTION

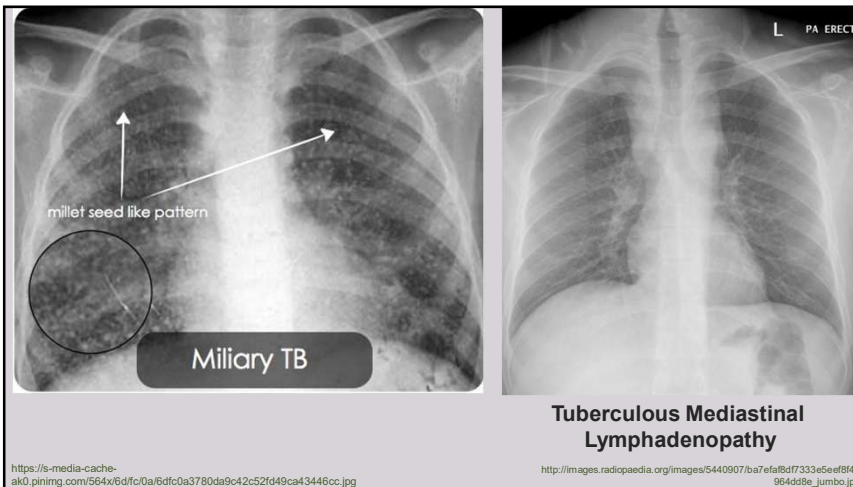
Exposure to person w/ active TB
From TB endemic area
Homelessness
Incarceration
Works healthcare, corrections
Injection drug use

Medical Risk Factors for PROGRESSION to TB DISEASE

Recent TB infection
HIV infection
TNF-alpha inhibitors
Immunosuppression
Diabetes
Silicosis
End stage renal dz
CXR fibrotic lesions c/w prior TB
Intestinal bypass, gastrectomy,
chronic malabsorption
CA head or neck, Hodgkins,
leukemia

Active TB Disease Clinical Presentations

- Fever, sweats, weight loss
- Cough if pulmonary
- Subacute to chronic (weeks to months)
 - Can be acute in immunocompromised
- Upper lobe/apical cavity is 'typical'
 - With surrounding infiltrate
 - + / - adenopathy



Active TB Disease Extrapulmonary

Disease Site	Comments
CNS	• Meningitis (esp basilar and associated with CN palsies, hydrocephalus, obliterative vasculitis with strokes); focal tuberculomas
Lymphadenitis	
Bone & Joint	• Vertebral (thoracic, lumbar; anterior wedging; +/- psoas abscess) • Consider TB in ddx of chronic osteomyelitis, arthritis
Pleural	• Exudative lymphocytic effusion; low bacillary burden; obtain pleural biopsy
Pericardial	• Exudative lymphocytic effusion; low bacillary burden; obtain biopsy
Abdominal / pelvic	• GU: sterile pyuria; obtain multiple urine cultures; can cause infertility • GI: can mimic inflammatory bowel disease
Disseminated	• Advanced HIV, iatrogenic immunosuppression, d/o of IFN-γ/IL12/TNFα axis • Can present as sepsis • Mycobacterial blood cultures, get respiratory specimens, other tissue specimens

Obtain specimen(s) from affected site(s)

Active TB Disease Diagnosis

Smear Microscopy



LOD: 10,000 cfu/ml
Sensitivity: LOW

Nucleic Acid Amplification Tests



100 cfu/ml
Sensitivity: MEDIUM
(currently)

Culture



1-10 cfu/ml
Sensitivity: HIGH

ADJUNCTIVE:

- **IGRA, TST:** do not distinguish latent from active; NEG test does not rule out active TB
- **CXR, other radiology:** can be suggestive of active TB; not specific
- **Histopathology:** can be suggestive of active TB; not specific

Active TB Disease Diagnosis

Smear microscopy for AFB

• **NEG SMEARS DO NOT EXCLUDE A DX OF ACTIVE TB**

- Low sensitivity
- Overall 50-60% sensitive for pulmonary TB
- Less sensitive in advanced HIV (30-50%)
- In pulmonary TB: yield of smear microscopy increases if multiple specimens obtained
- Not specific for MTB (mycobacteria look alike)
- Good PPV in TB endemic settings



Image credits:
1. CDC/Dr. George P. Kubacka
2. <https://laboratoryinfo.com/auramine-rhodamine-staining-for-afb-principle-procedure-reporting-and-limitations/>

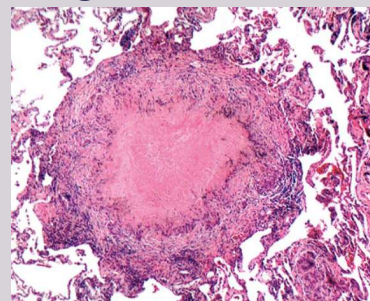
Active TB Disease Diagnosis

- Nucleic Acid Amplification Tests
- E.g., 'Xpert MTB/RIF'
- Sensitivity of available NAATs 'in between' that of smear and culture
- **A negative NAAT does not rule out TB**
- **High specificity for *M. tuberculosis* (by design)**
- Xpert MTB/RIF detects MTB & rifampin resistance (NO info about INH)
- Procedures designed for, validated for sputum
 - Can use for other specimens but test can be falsely negative due to inhibitors

Active TB Disease Diagnosis

- Mycobacterial Culture
- The **most sensitive method** but SLOW (3-6 weeks)
- Once growth observed, lab performs additional tests:
 - Species identification
 - Growth-based DST
- Considered the gold standard, but not 100% sensitive
 - Pulmonary TB around 90-95% sensitive
 - Extrapulmonary TB much less sensitive

Active TB Disease Diagnosis



Typical Caseating Granuloma

Immunodeficient Patients:
(e.g., advanced HIV; use of TNF- α inhibitors)

- Caseation may not be apparent
- Granulomas may lack structure

Image credit: <http://pathhs.w5m54.ucsf.edu/overview/tb.html>

31 Tuberculosis in Immunocompetent and Immunosuppressed Hosts

Speaker: Susan Dorman, MD

Question #1

- 38-year-old healthy physician; periodic travel to South Africa for work.
- 6 years ago: pos TST; poor adherence with isoniazid preventive therapy
- Now 5 weeks of fever, chills, night sweats, 10-lb wt loss, productive cough.
- CXR: small RUL cavitory lesion with surrounding infiltrate. HIV negative, LFTs normal. Sputum smears x 3: negative for AFB
- Sputum Xpert MTB/RIF: "MTB detected" & "Rifampin resistance not detected"

What is the best course of action?

- A. Prescribe 9 months of isoniazid for presumed latent TB infection
- B. Do nothing pending culture results
- C. Start TB treatment with rifampin, isoniazid, PZA, ethambutol
- D. Start TB treatment with rifampin, isoniazid, PZA
- E. Start TB treatment with a regimen for multidrug-resistant TB

Active TB Disease Treatment

Extend continuation phase therapy for

- Pulmonary dz if cavitation & cx pos at end of tx month 2 (9 months total)
- CNS TB (9-12 months total duration)
- Bone and joint TB (6-9 months total duration)

Corticosteroids: indicated for TB meningitis

- Pericardial TB: probably reduce the risk of constrictive pericarditis
 - Most experts use for patients at high risk for inflammatory complications, e.g.,
 - Large effusion, high levels of inflammatory cells in fluid, early constriction

Question #2

- The 38-year-old physician is started on rifampin, isoniazid, PZA, ethambutol (plus pyridoxine) for presumed pulmonary TB
- 3 weeks later the culture grows *M. tuberculosis*, susceptible to those drugs
- 4 weeks into TB treatment develops nausea, anorexia, abdominal pain
- ALT 380, AST 270. He reports no alcohol consumption or acetaminophen

Which drug is least likely to be associated with liver toxicity?

- A. Rifampin
- B. Isoniazid
- C. PZA
- D. Ethambutol

TB Drug Adverse Effects

Drug	Key Adverse Effects
INH	• Hepatotoxicity • Peripheral neuropathy (use pyridoxine = vitamin B6)
Rifampin	• Hepatotoxicity (cholestasis usually prominent) • Drug-drug interactions • Red discoloration of urine, sweat, etc.
PZA	• Hepatotoxicity • Arthralgias
Ethambutol	• Retrobulbar neuritis (color vision, acuity)

Hepatotoxicity: INH = PZA > Rifampin

Rifampin Chews Up Some Other Drugs*

Oral anticoagulants	HIV PIs
Hormonal contraceptives	HIV NNRTIs
Methadone	HIV INSTIs
Corticosteroids	HIV CCR5 inhibitors
Fluconazole	TAF



*Induces hepatic cytochromes & uridine diphosphate gluconyltransferase, resulting in increased metabolism (and decreased serum levels, potential decreased efficacy, potential need for increased doses) of other drugs metabolized by those enzymes

Question #3

53-year-old female recently arrived in US from Ukraine. Reports 3 months of cough. CXR with RUL cavity. Sputum Xpert result "MTB detected" and "Rifampin resistance detected". Additional molecular testing shows mutation in *katG* associated with high-level INH resistance. No mutations in *gyrA* or *gyrB* (i.e., no molecular evidence of FQ resistance).

What is the best treatment approach?

- A. Start RIPE plus moxifloxacin, plus amikacin given daily
- B. Start RIPE plus moxifloxacin, plus amikacin given 3x/week
- C. Start moxifloxacin, amikacin, cycloserine, linezolid, ethionamide
- D. Start bedaquiline, pretomanid, linezolid, moxifloxacin

Drug-resistant TB

- Risk factors for:
 - Contact with drug-resistant TB case
 - Prior h/o TB treatment, esp if non-adherent
- **MDR=resistance to isoniazid plus rifampin**
- **XDR=MDR plus resistance to fluoroquinolones plus at least one of bedaquiline or linezolid**
- Treat with multiple agents against which the isolate is susceptible
- Do not add single drug to a failing regimen
- WHO/FDA: BPoL(M) = Bedaquiline + Pretomanid + linezolid (+/- moxifloxacin)
- **Bedaquiline (Sirturo™): novel drug, novel target (MTB ATP synthase); QT prolongation; half-life 4 months**
- **Pretomanid: inhibits mycolic acid synthesis; elevated LFTs**

Question #4

24-year-old M from Zambia, in U.S. for community college, recently tested HIV-positive, CD4 400, not yet on ART.

Prominent anterior cervical lymph node but well-appearing, normal BMI, normal liver and renal chemistries, mild anemia.

Lymph node biopsy grows *M. tuberculosis* in culture.

What is the best course of action regarding timing of TB therapy and HIV therapy?

- A. Start ART immediately, defer TB tx
- B. Start TB tx immediately, defer ART until completes 6 months TB tx
- C. Start TB tx immediately, and start ART within 8 weeks
- D. Start both TB tx AND ART immediately

Active TB Disease Special Considerations for PLWH

HIV:

Increases risk of progression from latent to active TB

CD4 influences TB severity & clinical manifestations



TB:

Can increase HIV viral load

Associated with more rapid progression of HIV



Advanced immunosuppression associated with:

- Increased risk for extrapulmonary (including CNS) & disseminated TB
- Absence of lung cavitation resulting in low bacillary load **in airways**

Active TB Disease: Special Considerations for PLWH

Drug-drug Interactions

• RIFAMPIN (RIF)

- Accelerates clearance of PIs, NNRTIs, INSTIs, CCR5 inhibitors
 - INSTIs: rifampin + (DTG 50 mg **BID** or RAL **800 BID**) OK for selected patients
- TAF: intracellular TFV-DP levels higher with TAF+RIF than with TDF alone but clinical outcomes not well-studied. If TAF+RIF used, monitor HIV VL
- Good virologic, immunologic, clinical outcomes with rifampin + standard dose EFV regimens
- PI-based regimens: Do not use rifampin
- Cabotegravir and cabotegravir/rilpivirine: do not use rifampin

Active TB Disease: Special Considerations for PLWH

Drug-drug Interactions

• RIFABUTIN (RBT)

- Weaker enzyme inducer than rifampin
- A CYP450 substrate (rifabutin metabolism affected by NNRTIs and PIs)
- OK with DTG, RAL at standard doses
- OK with cabotegravir but not with rilpivirine
- PI-based ART: decrease rifabutin to 150 mg daily, or 300 mg every other day

Active TB Disease: Special Considerations for PLWH

When to start ART

- **CD4 < 50:** **ASAP within 2 weeks of starting TB tx**
- **CD4 ≥ 50:** **within 8 weeks of starting TB tx**
- HIV-infected pregnant women with active TB should be started on ART as soon as feasible (for maternal health and PMTCT)
- **TB meningitis: be cautious** (high rates of AEs and death in RCT); start ART when TBM is under control and patient has had at least 2 weeks of TB tx

Question #5

30-year-old F with HIV, CD4=20, viral load >1 million copies/mL (new dx). Microbiologically confirmed pulmonary TB (new dx). RIPE TB treatment started immediately. 12 days later starts DTG-based ART with appropriate bid dosing of DTG. Four weeks after ART started, she reports new headaches, RUE paralysis.

Which is most appropriate?

- A. Stop TB tx immediately since this is likely a side effect of a TB drug
- B. Obtain a brain MRI immediately
- C. Perform a lumbar puncture immediately
- D. Change TB treatment to cover drug-resistant TB
- E. Stop ART immediately

Active TB Disease Special Considerations for PLWH

Immune reconstitution inflammatory syndromes (IRIS)

**PARADOXICAL
WORSENING of TB
when ART started after
TB treatment initiated**



**UNMASKING of TB
when ART started in setting
of not-yet-recognized active
TB**

- Typically 2 weeks to 3 months after starting ART
- Risk factors: CD4<50, high pre-ART VL, severe TB, short interval between initiation of TB treatment and ART
- Protean manifestations (fever, new lesions, extension of prior lesions)

Active TB Disease Special Considerations for PLWH

Immune reconstitution inflammatory syndromes (IRIS)

- Deal promptly with any 'limited space' issues (CNS inflammation, obstructing adenopathy, etc.): corticosteroids; surgery if indicated
- Consider in DDx: malignancy, other OI, wrong original dx of TB, drug-resistant TB; clinical eval is patient-specific
- NSAIDs if mild; corticosteroids if more severe/refractory signs/sx (prednisone 1.5 mg/kg/d x 2 wks then 0.75 mg/kg/d x 2 wks - Meintjes et al AIDS 2010;24:2381)
- **Continue TB treatment plus ART**

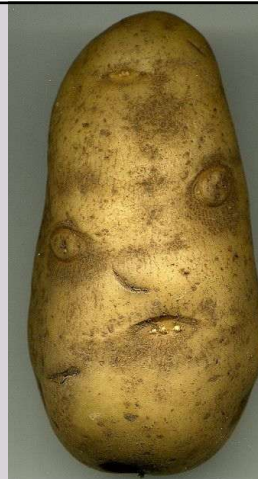
Active TB Disease Transplant Recipients

- **Increased risk of active TB disease (if infected with MTB)**
- **'Atypical' presentations leading to delayed dx**
 - 1/3 to 1/2 is disseminated or extrapulmonary
 - 4% of cases thought to be donor derived
- High mortality
- **RIFAMPIN DDI** with calcineurin inhibitors (cyclosporine, tacrolimus), mammalian target of rapamycin inhibitors (sirolimus, everolimus), corticosteroids...**at risk for graft rejection**
 - Monitor drug levels of immunosuppressants
 - Use rifabutin instead of rifampin

Active TB Disease TNF α Inhibitors

- ***TNF- α inhibitors markedly increase risk of active TB if infected***
 - Atypical presentations (non-cavitary pulm dz, extrapulm, disseminated)
 - Increased TB morbidity, mortality
 - Full monoclonal IgG1 mabs most potent (infliximab, adalimumab, golimumab)
- ***Test for latent TB infection (TST or IGRA) before starting anti-TNF tx***
 - If LTBI, then initiate LTBI tx prior to starting anti-TNF agent
 - Limited data on optimal duration of delay between initiating LTBI treatment and initiating anti-TNF treatment (some say 2-8 weeks)

Why
Was The
POTATO
Unhappy?



Because
It Had
Tuberculosis

Latent TB Infection Diagnosis

Interferon gamma release assays (IGRAs)

- QuantiFERON-TB tests; T-SPOT.TB
- Blood-based; in vitro stimulation of WBC with protein antigens specific for *M. tuberculosis*
- **No cross-reactivity with BCG**
 - *M. kansasii*, *M. marinum*, *M. szulgai* can cause false pos IGRA
- Sensitivity approx same as that of TST
 - Can be negative in immunosuppressed
- As for TST, adjunctive in diagnostic eval for active TB
- 'Issues' around performance in clinical care; not fodder for board Q's

Latent TB Infection Diagnosis

Tuberculin skin test

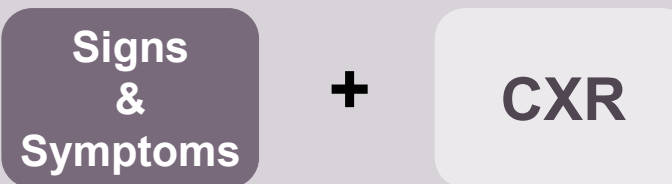
- A mix of antigens; can have 'false-pos' test due to prior BCG vaccination, NTM
- Intradermal inoc, measure induration at 48-72 hours (pos rxn lasts a few days)
- Cut-offs based on likelihood of true exposure, risk of progression to active TB if infected (5 mm; 10 mm; 15 mm)
- Adjunctive in diagnostic eval for active TB
- Booster effect (recall of waned CMI):
 - Some people infected with MTB may have neg rxn to a TST if many years have passed since Mtb infection. However, the TST PPD stimulates immune response to Mtb antigens, and a subsequent TST can be positive.
 - "Booster effect" can be mistaken for TST conversion
 - Use 2-step TST for individuals who may be tested periodically (e.g. HCW)

Classification of TST Induration Diameters

≥ 5 mm is POS	≥ 10 mm is POS	≥ 15 mm is POS
- HIV-infected - Recent TB contact - CXR with fibrotic changes - Transplantation - Prednisone ≥ 15 mg/d x 1 month or more - TNF-α 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 resection, CA head & neck	Persons with no known risk factors for TB infx or progression

Latent TB Infection Diagnosis

Excluding active TB is a key component of the diagnosis of latent TB infection



Latent TB Infection Treatment

Preferred

- Isoniazid plus rifapentine once weekly x 12 doses (3HP)
- Rifampin daily for 4 months (4R)
- Isoniazid plus rifampin daily for 3 months (3HR)

Alternative

- Isoniazid daily for 6 months (or 9 months)

Notes:

- Rifampin + PZA NOT recommended (hepatotoxicity)
- No age cut-off for LTBI treatment

OK with DTG 50 mg qd

Bacille Calmette-Guerin (BCG) Vaccine

- Attenuated live vaccine (from *M. bovis*)
- Neonatal vaccination**
 - Decreases incidence of severe forms of childhood TB
 - No/very limited impact on adult TB
 - Regional lymphadenitis can occur after vaccination; typically, no treatment needed
 - Disseminated infection can occur in immunocompromised (treatment indicated)

Bacille Calmette-Guerin (BCG) Preparation

Immunotherapy for Bladder Cancer

- Intravesicular administration
- Complications
 - Granulomatous prostatitis or hepatitis, epididymo-orchitis, spondylitis, psoas abscess, miliary pulmonary, disseminated
 - Contemporaneous with BCG tx or up to years later
- Treatment
 - Inherent resistance to PZA
 - Treat with rifampin + INH + ethambutol

Thank You & Good Luck!

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