Tuberculosis in Immunocompetent & Immunosuppressed Hosts

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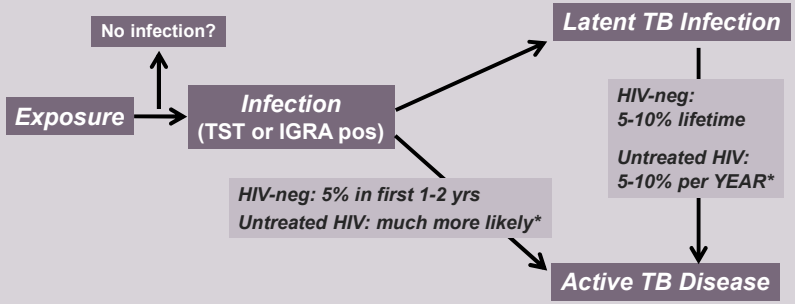
Disclosures of Financial Relationships with Relevant Commercial Interests

- 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



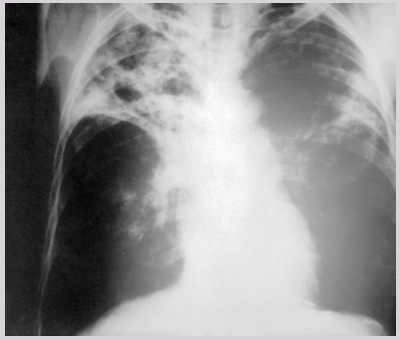
*risk increases as immunosuppression increases

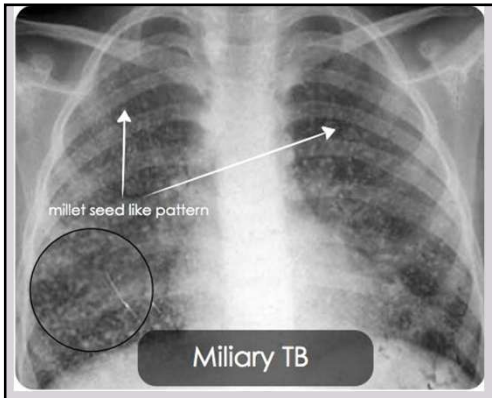
Risk Factors for TB Disease

Epi Risk Factors for TB INFECTION	Medical Risk Factors for PROGRESSION to TB DISEASE	
Exposure to person w/ active TB	Recent TB infection	End stage renal dz
From TB endemic area	HIV infection	CXR fibrotic lesions c/w prior TB
Homelessness	TNF-alpha inhibitors	Intestinal bypass, gastrectomy, chronic malabsorption
Incarceration	Immunosuppression	
Works healthcare, corrections	Diabetes	CA head or neck, Hodgkins, leukemia
Injection drug use	Silicosis	

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





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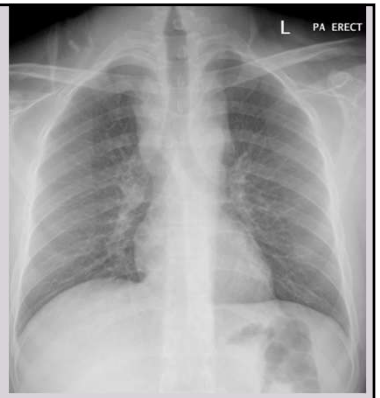

Tuberculous Mediastinal Lymphadenopathy

http://images.radiopaedia.org/images/5440907/ba7efaf8df7333e5eef8f4a964dd8e_jumbo.jpg

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 IFNγ/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

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Speaker: Susan Dorman, MD

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

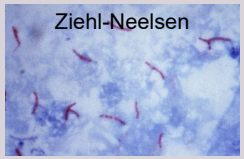


Image credits:
1. CDC/Dr. George P. Kubica
2. https://laboratoryinfo.com/auramine-rhodamine-staining-for-afb-principle-procedure-reporting-and-limitations/

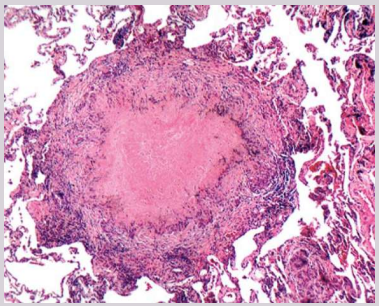
Active TB Disease Diagnosis

- 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://pathhsw5m54.ucsf.edu/overview/tb.html

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 cavitary 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

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Active TB Disease Treatment

1st Line tx = RIPE

- Rifampin, Isoniazid, PZA, Ethambutol x 2 months then
- Rifampin plus isoniazid x 4 more months (continuation phase)
- Use pyridoxine (vitamin B6) to prevent neuro toxicity of INH

Always start with daily treatment

- Daily more efficacious than intermittent
- In HIV-pos, intermittent tx associated with emergence of RIF resistance

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

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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
Hormonal contraceptives
Methadone
Corticosteroids
Fluconazole
HIV PIs
HIV NNRTIs
HIV INSTIs
HIV CCR5 inhibitors
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

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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: BPaL(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

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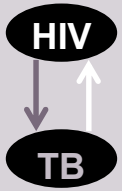
Active TB Disease
Special Considerations for PLWH

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

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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**

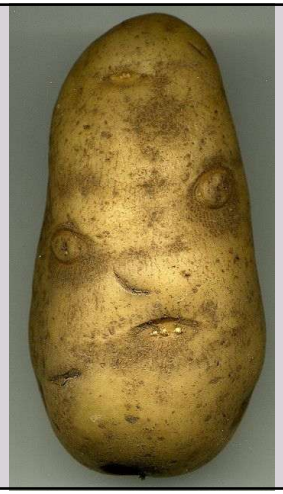
Active TB Disease
Transplant Recipients

- **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
TNFα 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 **Tuber**culosis

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

Signs & Symptoms + **CXR**

Latent TB Infection Treatment

OK with DTG 50 mg qd

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

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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