29 – Tuberculosis in Immunocompetent and Immunosuppressed Hosts

Speaker: Susan Dorman, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

Tuberculosis in Immunocompetent and Immunosuppressed Hosts

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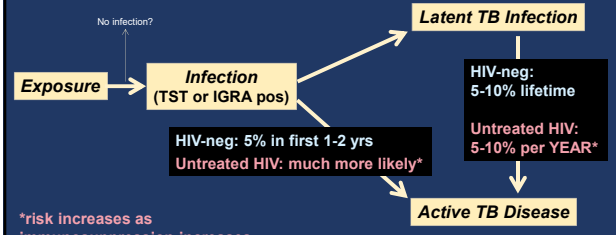
- **Disclosures of Financial Relationships with Relevant Commercial Interests**
  - **None**

Overview of TB Epidemiology



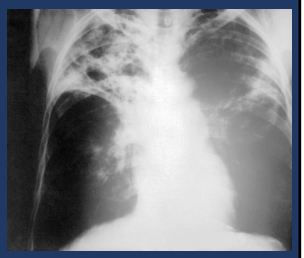
*risk increases as immunosuppression increases

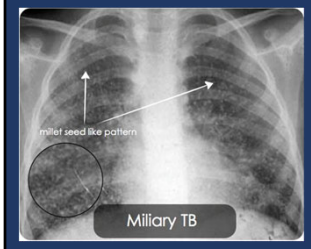
Risk Factors for Active TB Disease

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

Active TB disease: clinical presentations

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





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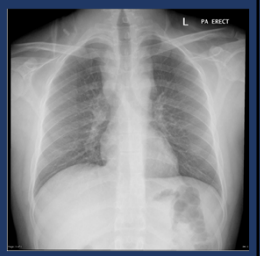

Tuberculous mediastinal lymphadenopathy

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

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Active TB disease: clinical presentations

Extrapulmonary

- **CNS** (meningitis, focal tuberculomas)
- **Lymphadenitis**
- **Bone and joint**
  - Vertebral (thoracic, lumbar, anterior wedging, +/- psoas abscess)
  - Consider TB in DDx of chronic osteomyelitis, arthritis
- **Pleural** (lymphocytic effusion, low bacillary burden, obtain pleural bx)
- **Pericardial** (lymphocytic effusion, low bacillary burden, obtain pericardial bx)
- **Abdominal/pelvic**
  - GU ('sterile' pyuria; obtain multiple cultures; can be associated with infertility)
  - GI (can mimic inflammatory bowel disease; obtain cultures/PCR, histopathology)

Obtain specimens from affected sites:
AFB smear
Mycobacterial culture
NAAT/PCR
Histopathology

Disseminated

- Advanced HIV, significant iatrogenic immunosuppression, d/o of IFN-gamma/IL-12/TNF axis
- Can present as sepsis
- Mycobacterial blood cultures, obtain respiratory specimens, other tissue specimens

Active TB disease: diagnosis

Smear microscopy	nucleic acid amplification tests	culture
		
LOD: 10,000 cfu/ml	100 cfu/ml	1-10 cfu/ml
Sensitivity: LOW	MEDIUM (currently)	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: takes 10,000 cfu/ml bacilli to make a smear pos
- Overall 50-60% sensitive for pulmonary TB
- Less sensitive in advanced HIV (30-50%)
- In pulmonary TB, the yield of smear microscopy increases if multiple specimens obtained
- Not specific for MTB (mycobacteria look alike)
- Good PPV in TB endemic settings

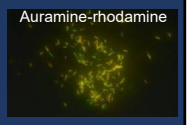


Image credits:
1. CDC/Dr. George P. Kubica
2. https://laboratoryinfo.com/auramine-rhodamine-staining-for-afb-principle-procedure-reporting-and-limitations/

Active TB disease: diagnosis

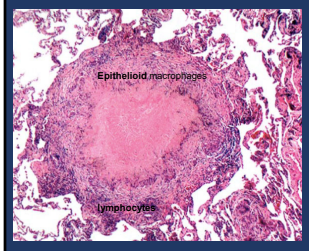
Nucleic Acid Amplification Tests

- 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



Typical caseating granuloma

Immunodeficient patients:
(e.g. advanced HIV; use of TNF alpha inhibitors)

- Caseation may not be apparent
- Granulomas may lack structure

Image credit: http://pathhsw5m54.ucsf.edu/overview/tb.html

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Question 1

PREVIEW QUESTION

38 y/o 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 RUL cavitary lesion.
Sputum Xpert MTB/RIF: "MTB detected" & "Rifampin resistance not detected".
HIV negative, LFTs normal. 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

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

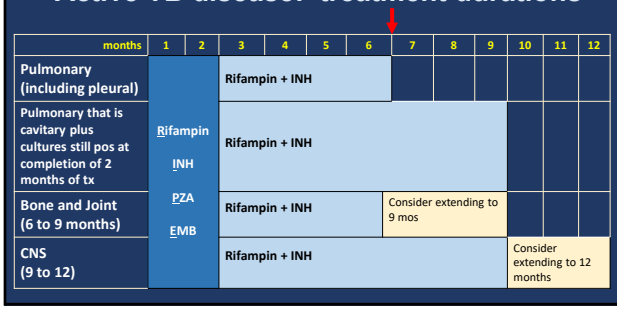
Extend continuation phase therapy for

- 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

Active TB disease: treatment durations



Question 2

The 38 y/o 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 acetominophen.
Which drug is **least** likely to be associated with liver toxicity?

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

Active TB disease: treatment

Drug adverse effects

- **Hepatotoxicity: isoniazid = PZA > rifampin**
- **Peripheral neuropathy: isoniazid (use pyridoxine = Vit B6)**
- **Retrobulbar neuritis: ethambutol (acuity, color vision)**
- Arthralgias: PZA

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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

*intracellular TFV-DP levels higher with TAF+RIF c/w TDF alone, but clinical outcomes not well-studied – if TAF+RIF used then monitor HIV VL

Question 3

53F 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* (ie 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 with tx
- **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

PREVIEW QUESTION

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

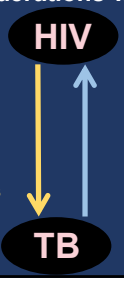
Prominent anterior cervical lymph node but well-appearing, normal BMI, normal liver and renal chemistries, mild anemia.

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

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 about 8 weeks
D. Start both TB tx AND ART immediately

Active TB disease: Special considerations w/ respect to HIV



HIV:
Increases risk of progression from latent to active TB

CD4 influences severity & clinical manifestations of TB

TB:
Can increase HIV viral load

Associated with more rapid progression of HIV

Active TB disease: Special considerations w/ respect to HIV

Clinical Presentation

- Lung cavitation may be absent in advanced immunosuppression
- Negative CXR does not exclude TB
- With advancing immunosuppression, risk for
  - 'Smear-negative' pulmonary TB
  - Extrapulmonary TB (with or without pulmonary involvement)
  - CNS TB
  - Widely disseminated TB including mycobacteremia

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Active TB disease: Special considerations w/ respect to HIV

A rifamycin-based TB regimen is recommended despite drug-drug interactions

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 then 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
- **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 w/ respect to HIV

When to start ART

- **CD4 < 50: 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); guidelines recommend not starting ART within first 8 weeks

Question 5

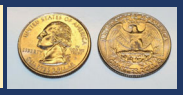
30y/o F with HIV, CD4=20, viral load >1 million copies/mL (new dx).
Microbiologically confirmed pulmonary TB (new dx).
RIPE TB treatment started immediately; tolerated well.
12 days later starts DTG-based ART with appropriate bid dosing of DTG.
Four weeks after ART started she reports new headaches, 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 w/ respect to HIV

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 tx and ART
- Protean manifestations (fever, new lesions, extension of prior lesions)

Active TB disease: Special considerations w/ respect to HIV

Immune reconstitution inflammatory syndromes (IRIS)

- General clinical approach
  - 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

- **Transplantation-associated immunosuppression increases risk of active TB disease if the person is 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 (e.g. cyclosporine, tacrolimus), mammalian target of rapamycin inhibitors (e.g. sirolimus/everolimus), corticosteroids…….at risk for graft rejection
  - Monitor drug levels of calcineurin inhibitors, mTORs
  - Use rifabutin instead of rifampin

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Active TB disease: People on TNF-alpha inhibitors

- ***TNF-alpha inhibitors markedly increase the risk of active TB if infected***
  - Can present with atypical TB (e.g. non-cavitary pulm dz, extrapulmonary, disseminated)
  - Increased TB morbidity, mortality
  - Full monoclonal IgG1 mabs most potent (ie infliximab, adalimumab, golimumab)
- ***Test for latent TB infection (TST or IGRA) prior to starting anti-TNF agents***
  - If LTBI, then initiate LTBI tx prior to starting anti-TNF
  - Limited data on optimal duration of delay between initiating LTBI treatment and initiating anti-TNF treatment (some say 2-8 weeks)

Latent TB infection (LTBI): 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 (LTBI): 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)

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 arrival (w/in 5 years) from TB high prevalence area	Persons with no known risk factors for TB infx or progression
Recent TB contact	Injection drug use	
CXR with fibrotic changes	Residents & employees of high-risk settings (HWC, corrections, homeless shelters)	
Transplantation	Mycobacteriology lab staff	
Prednisone ≥ 15 mg/d x 1 month or more	Children < 5 years old	
TNF-α antagonists	Medical conditions: diabetes, silicosis, end-stage renal dz, gastrectomy or small bowel resection, CA head & neck	

Latent TB infection (LTBI): diagnosis

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

- **ROS** (fever, wt loss, cough, night sweats, focal signs/sx that could be assoc with extrapulmonary TB)
- **Chest X-ray** to exclude occult pulmonary TB

Latent TB infection (LTBI): treatment

Preferred

- Isoniazid plus rifapentine once weekly x 12 doses (3HP) — OK with DTG 50 mg qd
- 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

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Bacille Calmette-Guerin (BCG)

- 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)

Immunotherapy for bladder cancer

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

Thank YOU & Good luck!

Susan Dorman [DORMAN@MUSC.EDU]