58 - Tuberculosis in Normal and Compromised Hosts

Speaker: Susan Dorman, MD

2020 INFECTIOUS DISEASE BOARD REVIEW

Tuberculosis in Normal and Compromised Hosts

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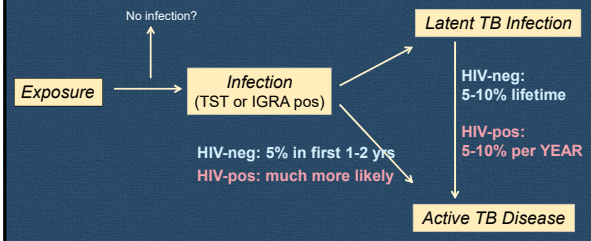
Disclosures of Financial Relationships with Relevant Commercial Interests

- Contracted Research – Sanofi-Aventis

Outline

- **Active TB disease**
  - Clinical presentations
  - Diagnosis
  - Treatment
  - Special considerations w/respect to HIV, other immunocompromising conditions
- **Drug-resistant TB**
- **Latent TB infection**
  - Diagnosis
  - Treatment
- **BCG**
  - Vaccination
  - Immunotherapy for bladder cancer and BCG-osis

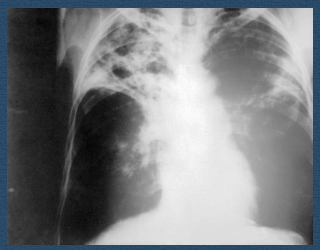
Overview of TB Epidemiology



Risk factors for TB INFECTION	Risk factors for PROGRESSION TO TB DISEASE	
Exposure to TB case	**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 in healthcare or corrections	End stage renal dz	
Injection drug use	Diabetes	
	Silicosis	

Active TB disease: clinical presentations

- Fever, sweats, wt loss
- Cough if pulmonary
- Usually 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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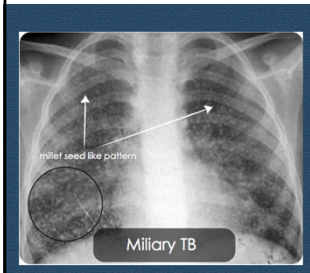

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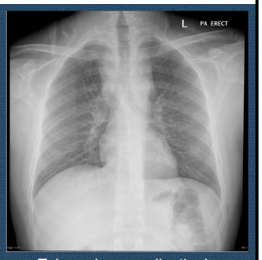

Tuberculous mediastinal lymphadenopathy

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

Active TB disease: clinical presentations

Extrapulmonary

- CNS (meningitis, focal tuberculomas)
- Lymphadenitis (cervical, thoracic, abdominal)
- Bone and joint
  - Vertebral (thoracic, lumbar, anterior wedging, +/- psoas abscess)
  - Consider TB in DDx of chronic osteomyelitis, arthritis
- Pleural
- Abdominal/pelvic
  - GU ('sterile' pyuria; obtain multiple cultures; can be associated with infertility)
  - GI (can mimic inflammatory bowel disease; obtain cultures, histopathology)

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

Disseminated

- Advanced HIV, significant iatrogenic immunosuppression
- Can present as sepsis
- Mycobacterial blood cultures, obtain respiratory specimens

Active TB disease: diagnosis

FIRST – CONSIDER TB IN THE DDx

Smear microscopy	current nucleic acid amplification tests	culture
		
LOD: 10,000 cfu/ml	100 cfu/ml	1-10 cfu/ml
Sensitivity: LOW	MEDIUM	HIGH

ADJUNCTIVE:
IGRA, TST: do not distinguish latent from active; NEG test does not rule out active TB
Chest X-ray, 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 acid fast bacilli

- * ***TAKE HOME POINT: a negative smear does <u>not</u> exclude dx of active TB*** *
- Low sensitivity: takes a lot of bacilli (10,000 cfu/ml) to make a smear positive
- Overall around 50-60% sensitive for pulmonary TB
- Much less sensitive in advanced HIV (30-50%)
- In pulmonary TB, the yield of smear microscopy increases if multiple specimens are obtained
- Not specific for M.tb (most mycobacteria look alike)
- Good PPV in TB endemic settings

Active TB disease: diagnosis

Nucleic Acid Amplification Tests

- E.g. 'Xpert MTB/RIF'
- Sensitivity of currently available NAATs 'in between' that of smear and culture
- A negative test does not rule out TB
- High specificity for *M. tuberculosis* (by design)
- Xpert MTB/RIF detects *M. tuberculosis* and also 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 of amplification rxn

Active TB disease: diagnosis

Mycobacterial Culture

- **The most sensitive method**
- SLOW (3-6 weeks)
- Once growth observed, the lab performs additional tests to identify species (e.g. *M. tuberculosis*)
- Considered the gold standard, but not 100% sensitive
  - Pulmonary TB around 90-95% sensitive
  - Extrapulmonary TB much less sensitive

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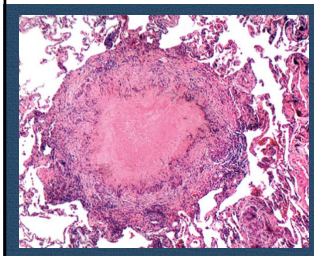
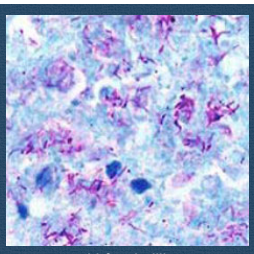


Caseating granuloma



acid-fast bailli on
Ziehl Neelsen smear micrscopy

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

Question 1

38 y/o M physician, previously healthy, with periodic travel to South Africa for medical research work. Reports a positive TST six years ago, and admits poor adherence with a course of isoniazid preventive therapy at that time. Now with 5 weeks of fever, chills, night sweats, 10-lb wt loss, productive cough. CXR shows RUL cavitary lesion. Sputum GeneXpert MTB/RIF test result is "MTB detected" and "Rifampin resistance not detected" (culture results pending), HIV test is negative, liver chemistries are 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 and cx pos at end of tx month 2 (9 months total)
- CNS TB (usually 9-12 months total duration)
- Bone and joint TB (6-9 months total duration)

Corticosteroids indicated for TB meningitis

- Pericardial TB: previously universally recommended BUT recent placebo controlled randomized trial showed no difference in outcomes overall

Active TB disease: treatment durations

months	1	2	3	4	5	6	7	8	9	10	11	12
Pulmonary (including pleural)	Rifampin INH PZA EMB		Rifampin + INH									
Pulmonary that is cavitary plus cultures still pos at completion of 2 months of tx			Rifampin + INH									
Bone and Joint (6 to 9 months)			Rifampin + INH				Consider extending to 9 mos					
CNS (9 to 12)			Rifampin + INH							Consider extending to 12 months		

Question 2

The 38 y/o M physician is started on rifampin, isoniazid, PZA, ethambutol (plus pyridoxine) for presumed pulmonary TB. About 3 weeks later the culture grows *M. tuberculosis*, susceptible to those drugs. About 4 weeks into TB treatment the patient reports several days of progressive nausea, anorexia, abdominal discomfort. Liver function testing shows 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

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Active TB disease: treatment

Drug adverse effects

- **Hepatotoxicity: isoniazid, PZA, rifampin**
- **Peripheral neuropathy: isoniazid (use pyridoxine)**
- **Retrobulbar neuritis: ethambutol (color vision 1st affected)**
- Arthralgias: PZA
- Vestibular/ototoxicity: streptomycin > amikacin, kanamycin
- Nephrotoxicity: amikacin, kanamycin > streptomycin

Active TB disease: treatment

Drug-drug interactions: RIFAMPIN

- Potent inducer of hepatic cytochromes and uridine diphosphate gluconyltransferase; this results in increased metabolism (and decreased serum levels, potential decreased efficacy, potential need for increased doses) of other drugs metabolized by those enzymes
- Warfarin, hormonal contraceptives, methadone, corticosteroids, fluconazole, HIV PIs, HIV NNRTIs, HIV INSTIs, HIV CCR5 inhibitors, TAF*

**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*

Drug-resistant TB

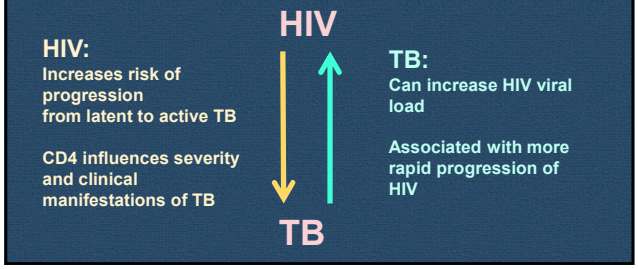
- Risk factors for:
  - Contact with drug-resistant TB case
  - From (or prolonged travel to) eastern Europe, former Soviet Union
  - Prior h/o TB treatment, esp if non-adherent with tx
- **MDR=resistance to isoniazid plus rifampin**
- **XDR=MDR plus resistance to fluoroquinolones plus at least one of the injectable 2nd line drugs (amikacin, kanamycin, capreomycin)**
- Treat with multiple agents against which the isolate is susceptible
- Never add a single drug to a failing regimen
- Bedaquiline (Sirturo™): novel drug, novel target (Mtb ATP synthase), FDA-approved for pulm drug-R TB when effective tx cannot otherwise be provided; QT prolongation; half-life 4 months; restricted access

Question 3

24 y/o M from Zambia, in U.S. for community college, recently tested HIV-positive with CD4 400, not yet on ART. He has a prominent anterior cervical lymph node but is otherwise well-appearing with normal BMI, normal liver and renal chemistries, and mild anemia. Lymph node biopsy grows *M. tuberculosis* in culture. What is the best course of action with respect to the timing of TB therapy and HIV therapy?

A. Start ART immediately, defer TB tx
B. Start TB tx immediately, defer ART until after completion of 6 months of 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



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
  - Extrapulm TB (with or WITHOUT pulm dz)
  - CNS TB
  - Widely disseminated TB/mycobacteremia

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Active TB disease: Special considerations w/ respect to HIV

Drug-drug interactions

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

- **RIFAMPIN**
  - 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
    - Do not use rifampin with PI-based regimens
- **RIFABUTIN**
  - Weaker enzyme inducer than rifampin
  - A CYP450 substrate (rifabutin metabolism affected by NNRTIs and PIs)
  - 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 4

30y/o F with HIV, CD4=25, viral load 480,000 copies/mL, with microbiologically confirmed pulmonary TB. She was not on ART at the time of TB diagnosis. At the time of TB dx, treatment with rifampin/INH/PZA/ethambutol (plus pyridoxine) was started immediately. She tolerated TB treatment well, and efavirenz-based ART was started 12 days later. Four weeks after ART was started she reports new headaches, as well as R-sided weakness that is confirmed on physical exam. 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 tx; unmasking TB when ART started in setting of not-yet-recognized 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: Special considerations: transplant recipients

- **Transplantation-associated immunosuppression increases the risk of active TB disease if the person is infected**
- '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
- DDI between **rifampin** and 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: Special considerations: 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)

Question 5

24 y/o U.S. born M whose wife (with whom he lives) was recently diagnosed with smear-positive pulmonary TB. During a contact investigation, the 24 y/o M had a strongly positive IGRA assay, and is referred to you. He has no other known TB contact, and reports a negative TST years ago. What is the most appropriate next course of action?

A. Start preventive therapy immediately using daily isoniazid
B. Start preventive therapy immediately using weekly isoniazid plus rifapentine
C. Repeat the IGRA assay
D. Start INH/RIF/PZA/EMB immediately for active TB
E. Obtain medical history, perform TB symptom review and CXR

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:
  - 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
Recent TB contact	Injection drug use	
CXR with fibrotic changes	Residents & employees of high-risk settings (HWC, corrections, homeless shelters)	
Organ transplantation	Mycobacteriology lab staff	
Prednisone ≥ 15 mg/d x 1 month or more	Children < 5 years old	
TNF alpha antagonists	Medical conditions: diabetes, silicosis, end-stage renal dz, gastrectomy or small bowel bypass, solid organ transplant, CA head and neck	

Latent TB infection (LTBI): diagnosis

Interferon gamma release assays

- 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* and *M. marinum* can cause false pos IGRA)
- Sensitivity is approx same as that of TST
- Can be negative in immunosuppressed
- As for TST, adjunctive in diagnostic eval for active TB
- Lots of 'issues' around performance in clinical care; not fodder for board Q's

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

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Latent TB infection (LTBI): 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

Latent TB infection (LTBI): treatment

- Perform LFTs prior to tx in adults with risks for hepatotoxicity (etoh, risk for viral hepatitis, other hepatotoxic meds)
- Monthly ROS for adverse effects
  - Peripheral neuropathy (numbness/tingling extrems) if on INH (use Vitamin B6=pyridoxine)
  - Hepatotoxicity (N/V, abd discomfort, jaundice)
  - LFT monitoring as clinically indicated

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

Susan Dorman [DORMAN@MUSC.EDU]

TB Summary: *Active TB Disease*

- Standard tx for pulmonary TB
  - 2 months RIF/INH/PZA/EMB then 4 months INH/RIF
  - Always start with daily treatment
- Hepatotoxicity: PZA, INH, RIF
- Rifampin has drug-drug interactions that can reduce effectiveness of other drugs (warfarin, OCPs, methadone, steroids, fluconazole, PIs, NNRTIs, INSTIs)
- Rifabutin is an alternative to rifampin, esp in HIV
- A negative smear does not exclude TB
- TST and IGRAs do not distinguish active from latent TB

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TB Summary: *TB in HIV*

- Cavitary dz with preserved CD4; o/w usually noncavitary pulmonary and/or extrapulmonary; disseminated with very low CD4
- Timing of ART start (for those not already on):
  - If CD4<50, start ART within 2 weeks; otherwise within 8 weeks
- IRIS (unmasking of TB or paradoxical worsening):
  - Look for other causes (other OI's, malignancy, unrecognized drug-resistant TB)
  - Continue TB tx and ART, relieve symptoms (NSAIDS, steroids if needed)
  - Can have emergencies (i.e. CNS inflammation, SVC syndrome, etc)
- Rifampin has drug-drug interactions with PI's, most NNRTIs, INSTIs

TB Summary: *Latent TB Infection*

- IGRAs have approx same sensitivity as TST
- BCG does NOT cause false-pos IGRA
- No age cut-off for treatment (targeted testing of those at risk for TB)
  - At risk for having been exposed
  - At risk for progression to active TB once exposed
- Preferred: 3HP, 3HR, 4R (6H or 9H as alternatives)
- Exclude active TB (ROS, CXR) prior to LTBI tx

Supplemental Question I

28 y/o F from Honduras with 4 weeks of fever, cough with scant sputum, mild dyspnea. She is HIV-positive, CD4 250, and not on ART. A PPD was positive at her last visit with you, but she did not return for f/u. Chest X-ray shows increased interstitial markings. O2 saturation is 95%. Sputum PCP is negative, and AFB smear negative x 2, with mycobacterial cultures incubating (results pending). What additional tests should you perform?

A. None, since the negative AFB smears rule out TB
B. Sputum GeneXpert MTB/RIF nucleic acid amplification test
D. Urine lipoarabinomannan (LAM) test
E. Sputum adenosine deaminase test

Supplemental Question II

In which individual would 6 mm induration in response to TST be considered positive?

A. 6 mm induration is never considered positive
B. 6 mm induration is always considered positive
C. A 30 y/o M with HIV-infection
D. A 30 y/o M who is healthy with no risk factors for TB exposure or progression
E. A 30 y/o M who is a healthy healthcare worker without known TB exposure