Financial Disclosures

• none
IS IT HARD TO DIAGNOSE AND TREAT TUBERCULOSIS IN MINNESOTA AND WISCONSIN?
Answer

• What is hard,... is to think about it – keep it in the differential diagnosis.

• If you don’t think about it you can’t purposely diagnose it.
Diagnosis by chance?
Case: Diagnosis by chance?

- 59 year old man with rheumatoid arthritis
  - On leflunomide

- Routine TB quantiferon ordered in anticipation of possible use of a TNF inhibitor
Case

• TB quantiferon positive twice
  – 1.55
  – 2.40
• Tuberculin Skin Test: 12 mm
Case

• Next step?
Case: History

- 4 months earlier had respiratory illness
- Chest x-ray two years ago was normal
- Stepfather had tuberculosis

- CXR done
Current chest x-ray. Next steps?
Case: Is this the diagnostic procedure of choice?

- Sent for interventional radiology for biopsy.
Case: biopsy results

- Biopsy: granulomatous inflammation, non-necrotizing. Negative acid fast stains, negative fungal stains
Results

- Spontaneous Sputum: AFB smear positive, few
- NAAT (nucleic acid amplified test) + MTB
- Rifampin susceptible (no mutations in rpoB gene detected)
- Culture turned positive Mycobacteria tuberculosis

- Biopsy culture: negative for Mycobacteria tuberculosis
Learning Objectives

1. Review the clinical manifestations of tuberculosis (TB)
2. Learn what tests are available to diagnose active tuberculosis
3. Review current guidelines regarding treatment of tuberculosis
4. Know common drug interactions between tuberculosis medications and other commonly used medications
5. Describe the common adverse reactions to TB medications
6. Explain how to manage adverse reactions to TB medications
Diagnosis of active tuberculosis

- History
- Physical examination
- Radiography
- Microbiologic testing
- Invasive procedures needed?
Important teaching pearl

• Using a TST (tuberculin skin test) or IGRA (interferon gamma release assay) cannot be used to exclude a diagnosis of tuberculosis
Reason why

- **Sensitivity in culture confirmed TB**
  - TST 89%
  - QFT-GIT 83%
  - T-Spot 90%

- **Specificity**
  - TST 85%
  - QFT-GIT 99%
  - T-Spot 88%

Herrera et al. CID 2011;52(8):1031
Diagnosis: tuberculin skin testing

- 10-20% PPD negative with active TB (not immunosuppressed)

Targeted Tuberculin Skin testing focuses on those at risk for TB

- **> 5 mm**
  - HIV
  - Recent TB contact
  - CXR consistent with past TB
  - Immunosuppressed patient
    - SOT
    - >15 mg prednisone, for >1 month

- **>10 mm**
  - IVDA
  - Recent immigration (< 5 years)
  - Children <4 years old
  - Residents or employees of high risk facilities
  - Medical condition associated with increased risk

- **>15 mm**
  - Everyone else
# Symptoms of TB

**Table 7.4**

Symptoms of TB Disease

<table>
<thead>
<tr>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>People who have any of the following symptoms should be evaluated for TB disease:</td>
</tr>
<tr>
<td>• Persistent cough (3 weeks or longer);</td>
</tr>
<tr>
<td>• Chest pain;</td>
</tr>
<tr>
<td>• Bloody sputum;</td>
</tr>
<tr>
<td>• Weight loss or loss of appetite;</td>
</tr>
<tr>
<td>• Fever;</td>
</tr>
<tr>
<td>• Chills;</td>
</tr>
<tr>
<td>• Night sweats;</td>
</tr>
<tr>
<td>• Malaise; or</td>
</tr>
<tr>
<td>• Fatigue</td>
</tr>
</tbody>
</table>

Diagnosis by chance!

- “early tuberculosis is asymptomatic and may be discovered by chance on a chest radiograph”

  Chapter 251, Principles and Practice of Infectious Diseases, eight edition, 2015
Case: History

• 13 year old Hmong girl
  – Dry cough for 4 months
  – coughs up blood intermittently (hemoptysis)
  – chest pain
  – No fever or chills

• CT upper lobe miliary pattern
• + PPD
CXR: Miliary pattern
CT
Case

• Positive sputum acid fast bacilli (AFB)

• Mother and 6 year old sibling, positive PPD

• 10 and 15 year old siblings, negative PPD
How common is fever?

–55-79% have fever*

Diagnosis in children

- Less than 50% yield + culture
- Gastric aspirates
- Spontaneous sputum
- Inducted sputum
- Nasopharyngeal aspiration
- Bronchoalveolar lavage (10-22%)
Pulmonary Radiological manifestations

• Upper lobe infiltrates
  – Cavitary
• Hilar or paratracheal adenopathy
• Miliary
• Endobronchial
• Tuberculoma
Clinical manifestations

- Pulmonary
- Extrapulmonary
- Disseminated
How does TB present

Tuberculosis Cases by Site of Disease, Minnesota, 2011-2015

- Pulmonary: 53%
- Extrapulmonary: 36%
- Both: 12%

N = 747
AIDS – pulmonary manifestations

- Lower lobe infiltrates
- Pleural effusions
- Less cavities (if CD4 count < 200 cells/mm$^3$)
- Hilar adenopathy
Clinical Manifestations: Extrapulmonary

- **Central nervous system** (meningitis, tuberculoma)
- **Bone and joint** (Pott’s disease, thoracic spine most common location)
- **Genitourinary** (prostatitis, epididymitis, orchitis, infertility in woman)
- **Disseminated** (miliary)
- **Lymphatic** (women, young children)
TB meningitis
Lymph node

30 y.o Cambodian man with Scrofula
Case

• 72 year old Native American woman
  – Growing right neck mass
  – Weight loss: 40 lbs.
  – Poor appetite
  – No pain
  – No fever or chills
  – No night sweats
  – No coughs
  – No dysphagia
Case

• PMH
  – Diabetes mellitus
  – Hypertensions
  – Atrial fibrillation

• FH: mother died of tuberculosis when she was 3 years old

• CXR: negative
Case

• Operative finding
  – Fluid filled thick walled mass
Case

• What testing would you order for the specimen?
Testing requested

– Smear and culture
– PCR (polymerase chain reaction)
– Histopathology
Diagnostic microbiology

❖ Culture
  ■ Solid media
    ■ Lowenstein-Jensen medium
    ■ Middlebrook 7H10 or 7H11
      • 6 weeks
  ■ Liquid media
    ■ BACTEC MGIT
      • 7-21 days

❖ Nucleic acid amplification
Note the “rough and buff” morphology typical of *M. tuberculosis*
Middlebrook agar 7H11

BACTEC MGIT
(mycobacterial growth indicator tube)
BACTEC MGIT 960 Culture System

MGIT - Mycobacterial Growth Indicator Tubes (Becton Dickinson)
- fluorescent indicator in bottom of tube quenched by $O_2$
- ↑ mycobacterial growth = ↓ $O_2$ and ↑ fluorescence
Diagnostic microbiology

• Liquid culture 10-14 days
• Solid media culture 3-4 weeks
• NAAT nucleic acid amplification test 1 day
  – AFB smear + sensitivity 96%, specificity 85%
  – AFB smear – sensitivity 66%, specificity 98%
  • Cannot be used alone to rule out TB
Microbiology: M. tuberculosis complex

- *M. tuberculosis*
- *M. bovis*
- *M. africanum*
- *M. microti*
Specimen sources for microbiological diagnosis:

- Sputum
- Induced sputum
- Bronchoscopy
- Gastric aspiration
Molecular diagnostics

- **Line probe assays**
  - Hybridization of amplified DNA with oligonucleotide probes
  - Can detect INH (*inhA*), rifampin (*rpoB*) resistance
- **Loop-mediated isothermal amplification**
- **Oligonucleotide microarray**
  - Can detect rifampin resistance too
- **Xpert MTB/rif**
  - Self enclosed PCR system
  - 99.7% sensitive (for smear +); 76.1% (for smear -)*
  - Specificity 98.7%*

*Cepheid.com*
Direct Detection of MTB from Patient Specimens

*Mycobacterium tuberculosis* Direct Test (MTD) (Hologic Gen-Probe)

- Transcription-mediated amplification of *M. tuberculosis* complex rRNA directly from respiratory specimens
- Clinical specificity: 99-100%
- Clinical sensitivity:
  - smear positive: 91-95%
  - smear negative: 83-100%
- Technically challenging
  - inhibition from specimen components a concern
  - open PCR system so false positives due to cross-contamination of specimens are possible.
  - cross-reactions occur w/ some rare mycobacteria: *M. celatum, M. terrae*-like organisms, *M. holsiatricum*
Direct Detection of MTB from Patient Specimens
Cepheid Xpert® MTB/RIF Test

- WHO-endorsed
- Runs on the Cepheid GeneXpert platform
- FDA-approved for respiratory specimens
- Detects *M. tuberculosis* complex and provides information about RIF resistance via *rpoB* gene amplification
- Results in about 2 hrs

Source: [www.finddiagnostics.org](http://www.finddiagnostics.org) [www.cepheid.com](http://www.cepheid.com)
Diagnosis: histopathology

- Granuloma formation
  - May be absent in HIV or other immunosuppressed patients
Case: microbiology and pathology results

• **Pathology Report**: lymph node reactive, no necrosis or granuloma; soft tissue abscess–granuloma present, acid fast stain negative

• **Microbiology** department: Afb smear negative on tissue

• **Culture**: + Mycobacteria tuberculosis
Factors associated with Infectiousness

Table 7.1
Infectiousness of People Known to Have or Suspected of Having TB Disease*

<table>
<thead>
<tr>
<th>Factors Associated with Noninfectiousness</th>
<th>Factors Associated with Infectiousness</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cough</td>
<td>Presence of a cough</td>
</tr>
<tr>
<td>No cavity in the lung</td>
<td>Cavity in the lung</td>
</tr>
<tr>
<td>No acid-fast bacilli on sputum smear</td>
<td>Acid-fast bacilli on sputum smear</td>
</tr>
<tr>
<td>Extrapulmonary (non-pulmonary) TB disease</td>
<td>TB disease of the lungs, airway, or larynx</td>
</tr>
<tr>
<td>Receiving adequate treatment for 2 weeks or longer</td>
<td>Not receiving adequate treatment</td>
</tr>
<tr>
<td>Not undergoing cough-inducing procedures</td>
<td>Undergoing cough-inducing procedures (e.g., bronchoscopy, sputum induction, and administration of aerosolized medications)</td>
</tr>
<tr>
<td>Negative sputum cultures</td>
<td>Positive sputum cultures</td>
</tr>
</tbody>
</table>

* Infectiousness depends on a variety of factors. Clinicians should consider all of these factors when determining whether a TB patient should be considered infectious.

Duration of isolation for pulmonary TB

- In hospital
  - Have 3 AFB smear negative
  - Clinical improvement
  - 14 days of 4 drug therapy

- If smear negative times three
  - 3-5 days of 4 drug therapy before removed from isolation
  - Show clinical improvement

http://www.health.state.mn.us/divs/idepc/diseases/tb/isolatingpat.html#i
Duration of isolation for pulmonary TB

• 2 weeks home isolation if smear negative
Yield of sputum to diagnose TB

• First AFB smear 53.8%
• Second AFB smear + 11.1%
• Third AFB smear + 2-3%

• First AM specimen is + 12% better than single spot specimen
Acid-Fast Smears Prepared from Early Morning Sputum Specimens Have Better Sensitivity

<table>
<thead>
<tr>
<th>Study</th>
<th>Spot (Random) Specimen Positive (%)</th>
<th>Early Morning Specimen Positive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abraham et al, 2012, <em>Indian J Med Res</em>, 135: 249-51 (smear is positive)</td>
<td>21/49 (43%)</td>
<td>32/49 (65%)</td>
</tr>
</tbody>
</table>
Sputum collection criteria

• Sputum volume at least 3 mL
• Optimal is 5-10 mL
Other specimen sources

- **Induced sputum** preferred over **bronchoscopy** if obtainable
- Induced sputum has **greater diagnostic yield** than bronchoscopy
- Bronchoscopy Culture Yield 50-100%
- Transbronchial biopsy: 42-63% histopathologic findings suggestive of TB
- BAL (bronchoalveolar lavage)
- Bronchoscopic brushings (9-56% smear yield)
Yield of

• Post bronchoscopy sputum
  – 9-73% for positive AFB smears
  – 35-71% culture positive

• Miliary TB
  – Transbronchial biopsy
Case

• 59 year old man with rheumatoid arthritis
• Radiology biopsy
  – Granulomatous inflammation
  – Afb smear negative and culture negative

• But spontaneous sputum + afb
**Respirators**
- Designed to filter out droplet nuclei from being inhaled by the health-care worker and other individuals.
- Should properly fit different face sizes and features.
- Should **NOT** be worn by the patient.

**Surgical masks**
- Designed to stop droplet nuclei from being spread (exhaled) by the patient.
- Should **NOT** be worn by the health-care worker.

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**Health-care worker wearing a respirator**

**Infectious TB patient wearing a surgical mask**
Hospital room

- Negative pressure airborne isolation
- 12 Air exchanges per hour
Case

- 59 year old man with history of alcohol abuse
  - Gastrointestinal stromal tumor on imatinib (a tyrosine kinase inhibitor)
- Fever and headaches
- CSF WBC 14 13% neutrophils, 52% lymphocytes, 3% monocytes
- Total protein 118 mg/dl, Glucose 46
- Repeat CSF WBC 246, 70% neutrophils 30% lymphocytes
- Total protein 204 mg/dl, Glucose 20
TB meningitis
leptomeningeal enhancement, progression of pontine infarcts
Case

• Treated for TB
  – 4 drugs and prednisone

• Stroke signs and symptoms resolved
Other diagnostic aids

• Adenosine deaminase (ADA)
  – CSF sensitivity 79%, 91% specificity
  – Pleural fluid 89-99% sensitivity, 88-97% specificity
  – Peritoneal fluid sensitivity 100%, specificity 97%
  – Pericardial fluid sensitivity 88%, specificity 83%

• Interferon gamma (IFN-g)
  – Pleural 89%, 97%
  – Peritoneal 93%, 99%
Case

- 30 year old man HIV +, CD4 99, viral load 30K
- Not on treatment
- Foreign borne
- Cough and fever
- CXR: pleural effusion
- Sputum smear negative times 3
  - 1/3 turn +
- Pleural effusion
Case: pleural fluid

- WBC 290
  - L 72, M 28, PMN 0
- RBC 608
- LDH 520
- Culture + MTB
• What is yield of pleural fluid culture?
Extrapulmonary diagnostic yield

- **NAAT** (not FDA approved for below sources)
  - Pleural 56% sensitivity
  - CSF 62% sensitivity

- **Culture**
  - Pleural fluid 23-58%
  - Urine 80-90%
  - CSF 45-70%
  - Peritoneal 45-69%
  - Pericardial 50-65%
Treatment: Drugs

- Isoniazid (INH, H) - 1952
- Rifampin ® - 1966
- Pyrazinamide (Z) - 1952
- Ethambutol (E) - 1961
- Rifabutin - 1992
- Rifapentine - 1998
Treatment for TB disease

- 2 phases:
  - Initial intensive phase
  - Continuation phase

- DOT (Directly Observed Therapy)

- Duration:
  - 6-months (smear-positive and -negative cases)
  - 18-24 months (MDR TB)
Treatment

• Intensive phase
  – 4 drugs
  – 8 weeks
  – INH, RIF, PZA, EMB

• Pyridoxine (vitamin B6) recommended for:
  – Pregnant women
  – Breast feeding
  – HIV
  – Diabetes
  – Alcoholism
  – Malnutrition
  – Chronic renal failure
  – Advance age
## 6 month standard treatment

<table>
<thead>
<tr>
<th>Basic TB Treatment Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preferred Regimen</strong></td>
</tr>
<tr>
<td><strong>Intensive Phase</strong></td>
</tr>
<tr>
<td><strong>Continuation Phase</strong></td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
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<tr>
<td></td>
</tr>
</tbody>
</table>

*EMB can be discontinued if drug susceptibility studies demonstrate susceptibility to first-line drugs.

**Guidelines allow dosing 5 or 7 days-a-week; 5 days-a-week administration by DOT is an acceptable alternative to 7 days a-week administration.
Activity

- Isoniazid – rapidly potent bactericidal
- Rifampin – modest bactericidal activity, potent activity against persisters
- Pyrazinamide – activity against persisters
Treatment

• **Daily** administration recommended for **intensive phase**
Dosing of first line drugs

• **Isoniazid**  5 mg/kg; 15 mg; 300 mg daily
  – 3x/week 15 mg/kg; 900 mg
  – 2x/week 900 mg

• **Rifampin**  10 mg/kg; 600 mg daily
  – 3x/week 10 mg/kg; 600 mg
  – 2x/week 10 mg/kg; 600 mg

• **Pyrazinamide**

• **Ethambutol**
Dosing of first line drugs: PZA, EMB

### Table 10. Suggested Pyrazinamide Doses, Using Whole Tablets, for Adults Weighing 40–90 kg

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Weight, kg&lt;sup&gt;b,c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40–55</td>
</tr>
<tr>
<td>Daily (mg/kg)</td>
<td>1000 mg (18.2–25.0)</td>
</tr>
<tr>
<td>Thrice weekly (mg/kg)</td>
<td>1500 mg (27.3–37.5)</td>
</tr>
<tr>
<td>Twice weekly (mg/kg)</td>
<td>2000 mg (36.4–50.0)</td>
</tr>
</tbody>
</table>

### Table 11. Suggested Ethambutol Dosages, Using Whole Tablets, for Adults Weighing 40–90 kg

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Weight, kg&lt;sup&gt;b,c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40–55</td>
</tr>
<tr>
<td>Daily (mg/kg)</td>
<td>800 mg (14.5–20.0)</td>
</tr>
<tr>
<td>Thrice weekly (mg/kg)</td>
<td>1200 mg (21.8–30.0)</td>
</tr>
<tr>
<td>Twice weekly (mg/kg)</td>
<td>2000 mg (36.4–50.0)</td>
</tr>
</tbody>
</table>

ATS/CDC/IDSA Clinical Practice Guidelines for Drug-Susceptible TB Clin Infect Dis 2016:63 (1 October)
Treatment

- Ethambutol
  - Can stop if pansusceptible isolate
Extrapulmonary TB treatment duration

- Daily therapy recommended
- 9-12 months
  - Meningitis
- 9 months
  - Bone, joint, spine
- 6 months
  - Lymph nodes
  - Pericardial
  - Pleural
  - Genitourinary
  - Disseminated
  - Miliary
  - Abdominal
Case

• 59 year old man
  – Rheumatoid arthritis on lefluononimide
  – On twice weekly dosing INH, RIF after susceptibilities returned pan susceptible
  – Smear positive for almost 3 months
  – Culture + through week 7 treatment, then 3 consecutive negative cultures
Question

• Do these findings change duration of treatment?
Risk for relapse

• **At 2 months still culture positive and cavitation**
  – with 6 months treatment
  – 20% relapse risk if both
  – 2% relapse risk if has neither factor

• Extended for 3 more months = 9 months total treatment if **cavitation and + culture at 2 months**
Other considerations to extend therapy if positive smear at 2 months or cavitation

- Extensive disease
- Below ideal body weight
- HIV
- Diabetes
- Immunosuppressed
How to handle treatment interruptions

<table>
<thead>
<tr>
<th>Time Point of Interruption</th>
<th>Details of Interruption</th>
<th>Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>During intensive phase</td>
<td>Lapse is &lt;14 d in duration</td>
<td>Continue treatment to complete planned total number of doses (as long as all doses are completed within 3 mo)</td>
</tr>
<tr>
<td></td>
<td>Lapse is ≥14 d in duration</td>
<td>Restart treatment from the beginning</td>
</tr>
</tbody>
</table>
How to handle treatment interruptions

<table>
<thead>
<tr>
<th>During continuation phase</th>
<th>Received $\geq 80%$ of doses and sputum was AFB smear negative on initial testing</th>
<th>Further therapy may not be necessary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Received $\geq 80%$ of doses and sputum was AFB smear positive on initial testing</td>
<td>Continue therapy until all doses are completed</td>
</tr>
</tbody>
</table>
|                           | Received $< 80\%$ of doses and accumulative lapse is $< 3$ mo in duration        | Continue therapy until all doses are completed (full course), unless consecutive lapse is $>2$ mo  
If treatment cannot be completed within recommended time frame for regimen, restart therapy from the beginning (ie, restart intensive phase, to be followed by continuation phase) |
|                           | Received $< 80\%$ of doses and lapse is $\geq 3$ mo in duration                 | Restart therapy from the beginning, new intensive and continuation phases (ie, restart intensive phase, to be followed by continuation phase) |
Goal for treatment completion

Intensive phase complete all doses in 3 months

Continuation phase complete all doses in 6 months
Case

• 30 year old South Asian
• AIDS
• CD4 99, viral load 29,900 copies
• Not on HAART (highly active antiretroviral therapy)
• Cough and fever
Case: Diagnostic findings

- Pleural fluid
  - WBC 290
    - Lymphocytes 72%
    - Monocytes 28%
    - Neutrophils 0%
  - LDH 530
  - pH 7.5
Case

• AFB sputum negative times 3
HIV and TB medications

• Daily treatment not intermittent
• Pulmonary tuberculosis
• Duration: 6 months if on HAART
  – 9 months if not on HAART
• Intermittent therapy risk for rifamycin resistance and relapse
**HIV**

- **TB**
  - Start HAART within the first 2 weeks of start TB treatment if CD4 < 50
  - 8-12 weeks if CD4 count > 50 cell/ul

- **TB meningitis**
  - Delay start of HAART for 8 weeks
  - Reason: IRIS (immune reconstitution inflammatory syndrome)
Immune Reconstitution Inflammatory Syndrome (IRIS)

- Higher risk when HAART started earlier or start with low CD4
  - Fever
  - Worsening respiratory symptoms
  - Increased size of lymph nodes
  - Worsening brain lesions
  - Worsening pulmonary infiltrates
  - Pleural effusions
IRIS treatment

• Anti-inflammatories
• Prednisone 1.25 mg/kg/d 50-80 mg a day for 2-4 weeks
  – Taper over 6-12 weeks
TB pericarditis

• Corticosteroids no longer routinely recommended
TB meningitis

- Duration 9-12 months
- Adjunctive corticosteroids tapered over 6-8 weeks
Culture negative pulmonary tuberculosis

• 4 months if smear and culture negative
  – Clinical response at 2 month mark
  – 2 month intensive phase
  – 2 months continuation phase
Frequency of medications

• Intermittent therapy thrice weekly preferred over twice weekly
  – Factors:
    • Hiv negative
    • Noncavitary
    • Smear negative at diagnosis
    • Drug susceptible
Risk for relapse

- HIV
- Cavitary
- Culture + at 2 months
- Baseline drug resistance
Not recommended

• Once weekly regimens
• Once weekly INH and rifapentine for continuation phase
Moxifloxacin

• Not to be used to replace RIF or PZA!
• If Isoniazid or ethambutol can’t be used
• **6 months duration**
• If INH not used:
  – MOXI/RIF/PZA/EMB 2 months daily followed by
  – 4 months RFT 1200 mg + MOXI 400 mg weekly
• 4 month regimen of using moxifloxacin as substitute of INH or EMB; was inferior to the standard 6 month regimen (2 month INH/RIF/PZA/EMB, 4month INH/RIF) due to relapses (clinical or bacteriological)


Treatment failure

• Culture positive at 4 months into treatment
Persistent smear positive, but culture negative

- Cavitary disease

- Not a sign of treatment failure
When to test for drug resistance

- Prior therapy
- Contact with patient with known MDR TB
- HIV +
- Resistance to rifampin or unable to tolerate rifampin
- Foreign born or lived in country with prevalence of TB (≥20 per 100,000)
- Positive cultures after 3 months of treatment
Rapid molecular Drug Susceptibility Testing

• Rifampin
  – Sensitivity 97%
  – Specificity 97%

• Isoniazid
  – Sensitivity 90%
  – Specificity 99%
DRUG INTERACTIONS
Drug interactions

- **Inhibitors of CYP3A** (e.g. ritonavir) increase Rifabutin (therefore, decrease to 150 mg a day)
  - Leukopenia
  - Arthralgia
  - Anterior uveitis
  - Skin discoloration

- **Inducer of CYP3A** (e.g. efavirenz, phenytoin) decrease rifabutin levels (therefore, increase to 600 mg a day)
  - Treatment failure
  - Drug resistance
rifamycin

- Inducer of cytochrome P450 (CYP) system
Isoniazid is an inhibitor of CYP isoenzymes

- Increases levels of:
  - Phenytoin
  - Carbamazepine
  - Benzodiazepine – diazepam, triazolam
  - Warfarin
  - Theophylline
  - Serotonergic antidepressants
Protease inhibitors

- Lopinavir-ritonavir
- Darunavir-ritonavir
- Atazanavir-ritonavir

- Use Rifabutin 150 mg daily
Moxifloxacin

• Avoid divalent cations: calcium, zinc, iron
  – Because it reduces absorption
NNRTI (nonnucleoside reverse transcriptase inhibitors)

- Efavirenz  
  ok to use with rifampin  
  rifabutin $\uparrow$ 600 mg a day

- Nevirapine  
  rifabutin ok

- Rilpivirine  
  avoid rifampin  
  with rifabutin, rilvipirine $\uparrow$ 50 mg a day

- Etravirine  
  avoid rifampin  
  Rifabutin ok
Integrase inhibitors

• **Raltegravir** double dose to 800 mg 2 times a day with rifampin

• **Dolutegravir** double to 50 mg 2 times a day with rifampin

• **Elvitegravir** – do not use with rifampin

• Rifabutin can be used with dolutegravir and raltegravir;
  – not elvitegravir since comes in combo tablet Stribild (elvitegarvir/cobicistat/tenofovir/emtricibatine)

https://aidsinfo.nih.gov/guidelines
http://www.hiv-druginteractions.org/
Second line TB drugs available

- Cycloserine
- Ethionamide
- Aminoglycosides: Streptomycin, Amikacin, kanamycin
- Capreomycin
- Para-amino salicylic acid
- Fluoroquinolone: Levofloxacin, Moxifloxacin
- Linezolid
- Delamanid
- Bedaquiline
Multidrug-Resistant Tuberculosis (MDR TB) and Possible Effective Treatments
XDR TB

- Extensively drug-resistant tuberculosis
  - Resistant to isoniazid, rifampin, fluoroquinolone
  - Resistant to at least one second line injectable drug
    - Amikacin, capreomycin, kanamycin

- 83 XDR TB cases in the United States between 1993-2007.*
Extensively Drug-Resistant Tuberculosis (XDR TB)
Diminishing Options for Treatment

- Isoniazid
- Rifampin
- Fluoroquinolones
- Injectable Second-Line Drugs:
  - Kanamycin
  - Capreomycin
  - Amikacin

Bacteria are resistant to this drug
Possibly Effective
- Ethambutol
- Pyrazinamide
- Thioamides
- Cycloserine
- PAS
- Streptomycin

Resistant to at least one of the three
Management of patients with drug-resistant TB disease is based on the following guidelines:

• A single new drug should never be added to a failing regimen;

• four to six drugs that are new to the patient and to which the isolate shows in vitro susceptibility

• Patients with multidrug-resistant organisms should receive the highest priority for DOT

• Do not use drugs with demonstrated in vitro resistance

• Resistance to RIF is associated in nearly all instances with cross-resistance to rifabutin and rifapentine (RPT)

• There is no cross-resistance between SM and the other injectable agents, amikacin, kanamycin, and capreomycin

• Resistance to PZA is uncommon in the absence of resistance to other first-line drugs; if monoresistance to PZA is observed, consideration must be given to the possibility that the disease is caused by M. bovis, not M. tuberculosis

• Intermittent therapy should not be used in treating MDR TB disease, except perhaps for injectable agents after the initiation phase (usually 2 to 3 months) of daily therapy.
THANK YOU.