TB Diagnosis

“The first rule of TB diagnosis: is to think TB....”
Diagnosis of Pulmonary TB
(80-85% of TB Cases)

- **Chest x-ray**
  - Standard PA and lateral films; apical lordotic views may be helpful
  - Infiltrates, nodular densities, cavities, +/- hilar adenopathy
  - Abnormalities may be subtle in immunocompromised patients
  - Previous x-rays for comparison may be useful

- **CT scans**
  - Often obtained
  - Nice to have but rarely critical to diagnosis
  - Expensive
Diagnosis of Pulmonary TB

- **TST**
  - Positive supports but does not make diagnosis
  - Negative does not exclude TB as possible diagnosis

- **Quantiferon**
  - Screening test only, not diagnostic
Diagnosis of Pulmonary TB

- Mycobacteriology laboratory tests
  - AFB smear
  - MTD – NAA
  - Preliminary results
    - Beware!
  - Culture
  - ID of isolate – confirm *M. tb*
  - Antimicrobial susceptibility testing
Diagnosis of Pulmonary TB

- Coughed sputum
  - Best specimen when available
  - Early AM best, supervise collection
  - AFB smear best available tool for assessing infectiousness
  - Most likely to yield positive culture
  - Multiple specimens recommended to maximize chances for +AFB/culture
Induced sputum (% yield)

<table>
<thead>
<tr>
<th>specimen</th>
<th>one</th>
<th>two</th>
<th>three</th>
<th>four</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFB smear</td>
<td>64</td>
<td>81</td>
<td>91</td>
<td>98</td>
</tr>
<tr>
<td>AFB culture</td>
<td>70</td>
<td>91</td>
<td>99</td>
<td>100</td>
</tr>
</tbody>
</table>

Treatment of Pulmonary vs. Extra-Pulmonary TB

- Same drugs, same doses, duration of treatment may vary
- Prospects for survival, cure similar; permanent damage depends on location of infection
- Guidelines for monitoring (drug side effects/toxicity) similar
- Guidelines for supervision of treatment (DOT) similar – less strict for extra-pulmonary because usually not infectious
Treatment of TB Disease

- The “enough” rules
  - Enough drugs
  - Enough medication
  - Long enough

- Generally two types of errors
  - Failure to prescribe correct regimen
  - Failure of patient to adhere to regimen

- Appropriate case management and DOT can lessen risk of developing drug resistance
Treatment Pearls

- Ethambutol can be discontinued once susceptibility to INH and RIF demonstrated
- PZA must be continued for full recommended course to qualify for short-course treatment
- DOT standard of care for all – extremely important for co-infected
- Sputum collection at end of first 2 months of treatment essential
Antituberculosis Drugs Currently in Use in the US

- **First-line Drugs**
  - Isoniazid
  - Rifampin
  - Rifapentine
  - Rifabutin
  - Ethambutol
  - Pyrazinamide

- **Second-line Drugs**
  - Cycloserine
  - Ethionamide
  - Levofloxacin
  - Moxifloxacin
  - Gatifloxacin
  - *P*-Aminosalicylic acid
  - Streptomycin
  - Amikacin/kanamycin
  - Capreomycin
  - Linezolid
Drug Regimens for Culture-Positive TB with Drug Susceptible Organisms

Regimen 1

○ Initial phase
  - INH/RIF/PZA/EMB
    ○ 7 d/wk for 56 doses (8 weeks)
    ○ Option – 5 d/wk for 40 doses (8 weeks)

○ Continuation phase
  - INH/RIF
    ○ 7 d/wk for 126 doses (18 weeks)
    ○ 5 d/wk for 90 doses (18 weeks)
    ○ Twice weekly for 36 doses (18 weeks)*
  - INH/RPT
    ○ Once weekly for 18 doses (18 weeks)*
Drug Regimens for Culture-Positive TB with Drug Susceptible Organisms

Regimen 2

- **Initial phase**
  - INH/RIF/PZA/EMB
    - 7 d/wk for 14 doses (2 weeks)
    - Then twice weekly for 12 doses (6 weeks) *
  - OR
  - 5 d/wk for 10 doses (2 weeks)
    - Then twice weekly for 12 doses (6 weeks) *

- **Continuation phase**
  - INH/RIF
    - Twice weekly for 36 doses (18 weeks) *
  - INH/RPT
    - Weekly for 18 doses *
Drug Regimens for Culture-Positive TB with Drug Susceptible Organisms

Regimen 3

- **Initial phase**
  - INH/RIF/PZA/EMB
    - Three times weekly for 24 doses (8 weeks)

- **Continuation phase**
  - INH/RIF
    - Three times weekly for 54 doses (18 weeks)
Regimen 4

- Initial phase
  - INH/RIF/EMB
    - 7 d/wk for 56 doses (8 weeks)
    - or
    - 5 d/wk for 40 doses (8 weeks)

- Continuation phase
  - INH/RIF
    - 7 d/wk for
When to Extend Continuation Phase of Treatment

- (from 2 drugs x 4 months to 2 drugs x 7 months)
- Recommended for patients with cavitary pulmonary disease and positive 2-month sputum culture
  - Extension may be considered if either factor is present
- Initial phase did not include PZA
Treatment Monitoring (1)

- Periodic (minimum monthly) clinical evaluation to assess adherence and identify adverse reactions
- Bacteriologic monitoring
  - Sputum smears every 2 weeks to assess early response until smear negative
  - After converted to smear negative, monthly sputum clusters until culture negative
Treatment Monitoring (3)

- Visual acuity and color vision monthly if EMB used
# Common Adverse Reactions to Drug Treatment (1)

<table>
<thead>
<tr>
<th>Caused by</th>
<th>Adverse Reaction</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any drug</td>
<td>Allergy</td>
<td>Skin rash</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Eye damage</td>
<td>Blurred or changed vision</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Changed color vision</td>
</tr>
<tr>
<td>Isoniazid, Pyrazinamide, or Rifampin</td>
<td>Hepatitis</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abnormal liver function test results</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lack of appetite</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nausea / Vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yellowish skin or eyes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dark urine</td>
</tr>
</tbody>
</table>
## Common Adverse Reactions to Drug Treatment (2)

<table>
<thead>
<tr>
<th>Caused by</th>
<th>Adverse Reaction</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Peripheral neuropathy</td>
<td>Tingling sensation in hands and feet</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Gastrointestinal intolerance</td>
<td>Upset stomach, vomiting, lack of appetite</td>
</tr>
<tr>
<td></td>
<td>Arthralgia</td>
<td>Joint aches</td>
</tr>
<tr>
<td></td>
<td>Arthritis</td>
<td>Gout (rare)</td>
</tr>
<tr>
<td>Injectibles</td>
<td>Ear damage</td>
<td>Balance problems</td>
</tr>
<tr>
<td></td>
<td>Kidney damage</td>
<td>Hearing loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ringing in the ears</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abnormal kidney function test results</td>
</tr>
</tbody>
</table>
## Common Adverse Reactions to Drug Treatment (3)

<table>
<thead>
<tr>
<th>Caused by</th>
<th>Adverse Reaction</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifamycins</td>
<td>Thrombocytopenia</td>
<td>Easy bruising</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Gastrointestinal intolerance</td>
<td>Slow blood clotting</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>Drug interactions</td>
<td>Upset stomach</td>
</tr>
<tr>
<td>Rifampin</td>
<td></td>
<td>Interferes with certain medications, such as birth control pills, birth control implants, and methadone treatment</td>
</tr>
</tbody>
</table>
Drug Interactions

- Some drug interactions change concentrations of antituberculosis drugs
- Antituberculosis drugs can change concentrations of other drugs
  - Rifamycins can decrease serum concentrations of some drugs used in treatment of HIV
  - Isoniazid increases concentrations of some drugs (e.g., phenytoin) to toxic levels
- Complete drug history of all prescription, OTC, and herbals essential part of treatment process
Drug Resistance (1)

- Established only by drug-susceptibility testing
- DOT is mandatory for all patients with drug resistant disease
- Treatment for drug resistant TB disease is dependent on susceptibility patterns of the specific organism
Special Treatment Situations
Extrapulmonary TB

- Similar treatment regimen for pulmonary TB*
- 6- to 9-month regimens that include INH and RIF are effective
- Corticosteroids sometimes used for patients with TB meningitis and pericarditis
- If PZA cannot be used in the initial phase, continuation phase must be increased to $\geq 7$ months

Except for central nervous system (CNS) TB, including meningitis; length of therapy is 9-12 months
Renal insufficiency complicates management of TB because some antituberculosis medications are cleared by the kidneys.

Dosage should not be decreased because peak serum concentrations may be too low; smaller doses may decrease drug efficacy.
Special Treatment Situations: Renal Insufficiency and End-Stage Renal Disease

- Dosing interval of antituberculosis drugs should be increased
- Most drugs can be given 3 times weekly after hemodialysis; for some drugs, dose must be adjusted
Special Treatment Situations
Hepatic Disease (1)

- May need to consider regimens with fewer hepatotoxic agents for patients with liver disease
- **Recommended regimens:**
  1) Treatment without PZA
     - Initial phase (2 months): INH, RIF, and EMB
     - Continuation phase (7 months): INH and RIF
  2) Treatment without INH
     - Initial phase (2 months): RIF, PZA, and EMB
     - Continuation phase (4 months): RIF, EMB, and PZA
Special Treatment Situations
Hepatic Disease (2)

- **Recommended regimens:** (continued)
  3) Regimens with only one potentially hepatotoxic drug
     - RIF should be retained
     - Duration of treatment is 12-18 months
  4) Regimens with no potentially hepatotoxic drugs
     - Duration of treatment is 18-24 months
TB & HIV Infection

- Risk factor of greatest significance for progression to active disease
- AIDS defining diagnosis
- Progression is preventable !!
Treatment for HIV-positive patients same as for HIV-negative patients, except

1) Once-weekly INH-rifapentine in continuation phase is contraindicated in HIV-positive patients

2) Twice-weekly INH-RIF or INH-rifabutin should not be used in patients with CD4+ T-lymphocyte counts less than 100/\(l\)

Every effort should be made to use a rifamycin-based regimen for the entire course of therapy
Effect of HIV on TB Infection

- HIV infection increases risk of TB disease by 100 fold
- Detection may be difficult in some patients
- Non-classical CXR presentation
- TB & anti- HIV therapies can interact negatively and cancel each other out
Effect of TB on HIV

- Increases HIV replications – higher viral load
- Decreases CD4 counts
- Higher risk of opportunistic infections & death
- Exacerbates weight loss & wasting
- Complicates treatment regimens
Challenge of Co-infection with HIV & TB

- Absorption of anti-TB drugs
- HAART & TB drug interactions
Treatment in special populations: Children

- Children
  - Same as adults
  - Doses based on weight
  - Fewer problems with toxicity
  - Harder to administer
  - Harder to monitor
  - Pills (crushed) vs. liquid preparations
  - Some clinicians reluctant to use ethambutol
Untreated TB represents greater hazard to a woman and her child than treatment of disease.

Treatment of pregnant woman with suspected TB should be started if probability of TB is moderate to high.
Treatment in Special Populations: Pregnancy

- Initial phase treatment regimen should consist of INH, RIF, and EMB
- PZA not generally recommended for pregnant women in the United States
- SM should not be substituted for EMB because of possible teratogenic effects
Other Medication Issues

- Difficulty swallowing pills
  - Patient may not tell you
  - Crushed pills, administered in small amt food ok

- GI side effects (IREZ)
  - Nausea, anorexia common - usually can continue treatment – can be sign/symptom of hepatitis
  - Diarrhea less common but potentially important – can be marker for malabsorption, low blood/tissue drug levels
Side Effects vs. Toxicity

- Read (and re-read) drug sections of Treatment Guidelines (CDC/IDSA guidelines and Curry Center guidelines for drug resistant TB)
  - Section on each drug
  - Drug-drug interactions (table of rifamycin interactions w/ other drugs)
  - Make patient and family aware of side-effects
  - Consider copying info on drugs
Side Effects vs. Toxicity

- Observe and question patient, and document findings at each encounter
- Obtain LFTs and other screening tests at recommended intervals
- ORW, PHNs, HCPs should review case prn new symptoms and/or abnormal lab results, and at regular intervals
QUESTIONS?