Overview: Treatment of TB

- Principles and goals of treatment
- Current drugs, recommended regimens, and duration of TB treatment
- Adverse drug reactions and monitoring
- Management of treatment failure
- End of treatment
Natural History of TB (pre-rx era)

Caution: not stable “cure”

- Cure 27%
- Chronic spreader 18%
- Death 55%

Treatment Goals

Microbiological goals of anti-TB chemotherapy

- Kill tubercle bacilli rapidly (early bactericidal effect)
- Eliminate persistent bacilli to achieve durable cure, i.e. prevent relapse (sterilizing effect)
- Prevent the emergence of drug resistance
General Principles of Therapy

- Always treat with a multiple-drug regimen
- Never add a single drug to a failing regimen
- Isoniazid, rifampin, and pyrazinamide are the basis of modern short-course chemotherapy
- Duration of treatment depends on the drugs used (the weaker the regimen, the longer the treatment)

Case 1

66 year old female from Laos seen after immigration, found to be PPD+ (13mm)

- CXR report: Left apical nodular densities consistent with prior granulomatous disease, pleural thickening
- No symptoms, otherwise healthy
- PMD treats with INH for LTBI x9 months

→ Patient returns 1 year later with 2 months of cough, significant weight loss, and CXR reveals LUL infiltrate with small cavitary lesion
Case 1

Question: All of the following statements are true EXCEPT

1. A better LTBI rx option for this patient would have been to treat her with different LTBI regimen (ex. RIF x4 mos)
2. Even if asymptomatic, sputum for AFB should have been checked here before starting LTBI rx
3. Monotherapy with INH puts her at risk for INH-resistant disease due to naturally occurring mutations

Correct answer: Best action for patient would have been to evaluate for active TB prior to any LTBI rx

True: Check sputums if CXR consistent with TB (past or present)

True: If disease was active at time of INH, resistance is a possibility
Drug resistance is conferred by genetic mutations of *M. tb*

**INH** = 1 in $10^6$

**RIF** = 1 in $10^8$

**EMB** = 1 in $10^5$

**Strep** = 1 in $10^6$

**INH + RIF** = 1 in $10^{14}$

---

**Effect of Treatment on Bacillary Population**

- **Mixed population (susceptible and resistant)**
- **INH resistant bacilli**

**Emergence of INH resistant strain because of ineffective treatment (INH monotherapy)**

**Effective multi-drug therapy**
Development of Drug Resistance

Multiple Drugs vs. Monotherapy

1

INH
RIF
PZA
EMB

2

I = INH resistant, R = RIF resistant, P = PZA resistant, E = EMB resistant

3


General Principles of Therapy

- Always treat with a multiple-drug regimen
- Never add a single drug to a failing regimen
- Isoniazid, rifampin, and pyrazinamide are the basis of modern short-course chemotherapy
- Duration of treatment depends on the drugs used (the weaker the regimen, the longer the treatment)
Development of Drug Resistance

Further acquired resistance after single drug added

I = INH resistant, R = Rif resistant, P = PZA resistant

Drug Resistant Mutants Selected by:

- Non-adherence
- Malabsorption
- Inadequate drug regimen

Remember: The higher the burden of disease, the greater the number of wild resistant mutants ("more bugs, more drugs")

Minimize Breaks in treatment, especially in the first 2 months of treatment.

Treatment of TB
Organization and Supervision

- Role of the health department
- Patient-centered care
- Case management with DOT is the preferred treatment strategy (2016 ATS/CDC/IDSA guidelines)

Outcomes of DOT studies 1966-1996

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>Impact Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enhanced DOT (n=12)</td>
<td>91.0%</td>
</tr>
<tr>
<td>DOT (n=4)</td>
<td>86.3%</td>
</tr>
<tr>
<td>Modified DOT (n=2)</td>
<td>73.6%</td>
</tr>
<tr>
<td>Non-supervised Therapy (n=0)</td>
<td>61.4%</td>
</tr>
</tbody>
</table>

% of Patients Completing Therapy for Pulmonary Tuberculosis

*DOT Consensus statement: Chaulk CP, et al. JAMA 1998;279:943*

Treatment of TB
Provider Responsibility

“...any public health program or private provider undertaking to treat a patient with TB is assuming a public health function that includes not only prescribing an appropriate regimen but also ensuring adherence to the regimen until treatment is completed.”

*ATS/CDC/IDSA. AJRCCM 2003*
Ensuring Completion of Therapy: Patient-centered DOT

**Patient adherence**
- Single most important factor in treatment failure
- Patient-centered DOT is the international standard of care

**Elements of a successful DOT program**
- **In clinic**: supportive, welcoming atmosphere; incentives/enables such as sandwiches, food coupons, bus tokens, fast passes for transit system can help
- **In the field**: dedicated outreach workers who are “at home” and comfortable in patients’ milieu

First-line TB Drugs and regimens
General Principles of Therapy

- Always treat with a multiple-drug regimen
- Never add a single drug to a failing regimen
- Isoniazid, rifampin, and pyrazinamide are the basis of modern short-course chemotherapy
- Duration of treatment depends on the drugs used (the weaker the regimen, the longer the treatment)

Antibiotic Treatment of TB
Began Only in 1944

Home brew treatment:
- Wolf’s liver boiled in wine
- Flesh of a she-ass with broth
- Smoke of dried cow dung
- Elephant’s blood
- Woman’s milk
- Mice boiled in salt and oil
- The King’s touch
- Bleeding, purging, collapsing lung
- Healing hymns “Rigveda” (India)
Question: What was the first anti-TB drug?

1. Isoniazid
2. Rifampicin
3. Ethambutol
4. Streptomycin
5. Paraminosalicylic acid (PAS)

Timeline of TB drugs

1854: First sanatorium for “fresh air and rest”
1882: Koch discovers bacillus
1944: Streptomycin
1946: PAS
1952: INH
1961: EMB
1962: PZA
2010
1955: Cycloserine; (begin triple therapy)
1959: RIF
### Anti-TB Drugs in the United States

<table>
<thead>
<tr>
<th>First-line Drugs</th>
<th>Second-line Drugs</th>
<th>Third-line Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Linezolid**</td>
<td>(Linezolid**)</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Moxifloxacin*</td>
<td>Bedaquiline</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>Levofloxacin*</td>
<td>Clofazamine*</td>
</tr>
<tr>
<td>Rifabutin*</td>
<td>Ethionamide</td>
<td>Imipenem/cilastin*</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Cycloserine</td>
<td>Meropenem*</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>p-Aminosalicylic acid*</td>
<td>High-dose INH</td>
</tr>
<tr>
<td></td>
<td>Amikacin*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Amoxicillin/clavulanate*)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Capreomycin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Streptomycin)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not in U.S.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gatifloxacin</td>
<td>Delaminid</td>
</tr>
<tr>
<td></td>
<td>Kanamycin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prothionimide; Terizidone</td>
<td></td>
</tr>
<tr>
<td><em>Not approved by the United States FDA for use in the treatment of TB</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Linezolid currently classified as 3rd line, but used by many as 2nd line agent</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Global New TB Drug Pipeline

- **Discovery**
  - Diarylhazones
  - DprE Inhibitors
  - InhA Inhibitor
  - Macrolides
  - Mycolactone Gypc Inhibitors
  - N-Acylsulfonamides
  - Translocase 1 Inhibitors, Csp, MycolP
  - Oxazolidinones
  - Pyridines DprE, PX22, Squaramide

- **Preclinical Development**
  - CYPZ-45*
  - SATB082*
  - Spectinamidine - 1810*
  - SPR-720
  - BTZ-043*
  - TB-47*

- **Clinical Development**
  - OPC-167832*
  - TDI-357
  - TBI-166*
  - TBI-223
  - GSK-070*
  - Controzolid MRX-4/
  - MRX-1
  - Delpazolid (LCB01-0371)
  - SQ-109*
  - Delamantid* (OPC-67683)
  - Sutezolid (PNU-100480)
  - Pretomanid* (PA-824)
  - TBA-7371*

*New chemical class. Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, macrolide, minocycline, diarylquinoline, benzothiazine, imidazopyridine amide.

*New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at [http://www.newtbdrugs.org/pipeline/clinical](http://www.newtbdrugs.org/pipeline/clinical)

Ongoing projects without a lead compound series identified can be viewed at [http://www.newtbdrugs.org/pipeline/discovery](http://www.newtbdrugs.org/pipeline/discovery)

*Updated: September 2017*
Fixed-Dose Combination Preparations in U.S.

- **Rifamate**
  - Isoniazid (150 mg) + rifampin (300 mg)

- **Rifater**
  - Isoniazid (50 mg) + rifampin (120 mg) + pyrazinamide (300 mg)

- Prevents patients from taking some but not all their medications
- May reduce the likelihood of acquiring drug-resistance

---

Case 2

50 year old male from the Philippines recently diagnosed with cough and night sweats x3 weeks

- No prior TB rx, no known contact with active case
- AFB smear+

➤ What drugs will you start?
ATS/CDC/IDSA Treatment Guidelines
August 2016 (last version 2003!)

Nahid et al, CID 2016


Nahid et al, CID 2016

Treatment of TB
Standard Regimen: 6 month short course

But what does each drug contribute to combination?
Case 2

50 year old male from the Philippines recently diagnosed with smear+ TB

- Started on INH/RIF/PZA/EMB
- Diffuse rash developed by day 7 and all drugs held. Rash resolves after 3 days
- Start serial rechallenge

Case 2

Which drug would you start first and why?

1. INH because it is the best early bactericidal
2. Rifampin due to its excellent sterilizing
3. PZA to help shorten the course of rx
4. EMB as least likely to cause a rash
Treatment of TB
Action of Anti-TB Agents

High

INH (RIF, SM, EMB)

Continuous growth

Speed of bacteria growth

Low

INH (RIF, SM, EMB)

Dormant

RIF

Spurs of growth

Acid inhibition

PZA

Mitchison DA. Int J Tuberc Lung Dis 1998;2:10

Clinical correlation

• **Bactericidal effect:** (INH/FQ>>RIF/SM>E)
  Reverse disease process and stop transmission

• **Sterilizing effect:** (RIF/PZA)
  Prevent relapse
Activities of Antituberculosis Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Early bactericidal activity</th>
<th>Preventing drug resistance</th>
<th>Sterilizing activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>++++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>++</td>
<td>+++</td>
<td>++++</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>++ - +++</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

PZA: minimal impact on prevention of drug resistance

- Drug resistance is more likely to occur when the large burden of organisms are rapidly replicating (i.e. cavitation)
- Activity of PZA is limited to special environments (e.g. acidic environment)
- Therefore, PZA as companion drug to protect against development of resistance is limited (avoid use if only two-drug combo)
Recommended Regimens
ATS/CDC/IDSA CID 2016

<table>
<thead>
<tr>
<th>Initial</th>
<th>Continuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reg</td>
<td>Drugs</td>
</tr>
<tr>
<td>1</td>
<td>INH</td>
</tr>
<tr>
<td></td>
<td>RIF</td>
</tr>
<tr>
<td></td>
<td>EMB</td>
</tr>
<tr>
<td></td>
<td>PZA</td>
</tr>
</tbody>
</table>

Preferred regimen for patients with newly diagnosed pulmonary TB

5 vs. 7 daily doses:
- When DOT is used, drugs may be given 5 days per week and the necessary number of doses adjusted accordingly.
- Although no studies compare 5 with 7 daily doses, extensive experience indicates this would be an effective practice. DOT should be used when drugs are administered <7 days per week.

Intermittent dosing
ATS/CDC/IDSA CID 2016

- Preferred once daily for intensive and continuation phases (*Strong recommendation; moderate certainty in the evidence*)
- Alternate regimens acceptable in certain program/public health situations (require DOT)
  - Non-HIV, non-cavitary, low-risk for relapse: can consider 3x wk dosing
  - Some public health programs successfully use 2x wk dosing – new guidelines suggest caution – one missed dose is equivalent to 1 per wk dosing (shown inferior)
Relapse risk with intermittent 6 mo. dosing:
200 events in 5,208 patients (32 studies), Chang, AJRCCM 2006

- Daily IP & CP relapse rate 1.9%,
  - 6% for Cav+, C2m+
  - 0.6% for Cav-, C2m-
- Relapse relative risk (RR) with intermittent dose
  - Daily IP, 3x CP: 1.6-fold
  - Daily IP, 2x CP: 2.8-fold
  - Daily IP, 1x CP: 7.1

Recommended Regimens
ATS/CDC/IDSA CID 2016

<table>
<thead>
<tr>
<th>Initial</th>
<th>Continuation</th>
<th>Effective-ness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reg.</td>
<td>Drugs</td>
<td>Interval/Dose</td>
</tr>
<tr>
<td>2</td>
<td>INH, RIF, EMB, PZA</td>
<td>7 days/wk for 56 doses (8 wk) or 5 days/wk for 40 doses (8 wk)</td>
</tr>
<tr>
<td>3</td>
<td>INH, RIF, EMB, PZA</td>
<td>3X wkly for 24 doses (8 wk)</td>
</tr>
<tr>
<td>4</td>
<td>INH, RIF, EMB, PZA</td>
<td>7 days/wk for 14 doses then twice weekly for 12 doses</td>
</tr>
</tbody>
</table>
General Principles of Therapy

- Always treat with a multiple-drug regimen
- Never add a single drug to a failing regimen
- Isoniazid, rifampin, and pyrazinamide are the basis of modern short-course chemotherapy
- Duration of treatment depends on the drugs used (the weaker the regimen, the longer the treatment)

Treatment of Tuberculosis

Optimum Duration

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>Relapse Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTA, 1982</td>
<td>2I/7R</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>2I/4R</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>2I/4R</td>
<td>2.5</td>
</tr>
<tr>
<td>USPHS 21, 1990</td>
<td>2I/4R</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>9I/4R</td>
<td>2.8</td>
</tr>
<tr>
<td>Denver, 1990</td>
<td>0.5I/2R, 2Z/2S/2R/2I</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Treatment of Tuberculosis
Increased Risk of Relapse

- **2-month culture positive status**
  - 7 BMRC trials
  - USPHS trial in Poland
  - TBTC Study 22 (2002)

- **Cavitary disease**
  - TBTC Study 22 (2002)
  - Hong Kong (2004)

---

**TBTC. Lancet 2002;360:528**

---

### Treatment of Tuberculosis
Study 22 – Risk of Relapse

<table>
<thead>
<tr>
<th>Continuation of INH/RIF twice wkly</th>
<th>Culture + at 2 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cavity</td>
<td>Yes</td>
</tr>
<tr>
<td>Yes</td>
<td>20.8%</td>
</tr>
<tr>
<td>No</td>
<td>5.9%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Continuation of INH/RPT once wkly</th>
<th>Culture + at 2 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cavity</td>
<td>Yes</td>
</tr>
<tr>
<td>Yes</td>
<td>22.2%</td>
</tr>
<tr>
<td>No</td>
<td>11.8%</td>
</tr>
</tbody>
</table>

1004 HIV-negative patients, standard 4 drug initiation; *TBTC. Lancet 2002*
Treatment of Tuberculosis

Extending Therapy – 9 mo total duration

*If cavitary disease and culture (+) at 2 mos., extend continuation phase from 4 to 7 mos.

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Initial</th>
<th>Continuation Phase*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethambutol</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

0 1 2* 3 4 5 6 7 8 9 months

Treatment of TB

Decreasing the Risk of Relapse:

- **Hong Kong silicotuberculosis trial**
  - Extending the continuation phase from 4 to 6 months decreased relapse rate from 22 to 7% (p<0.025)

- **Hong Kong PZA trial**
  - Extending the duration of PZA (2, 4, 6 mo) had no significant effect on relapse
    - 6IR4S + 2Z: 3% relapsed
    - 6IR4S + 4Z: 5% relapsed
    - 6IR4S + 6Z: 3% relapsed
### TBTC Study 22: Proportion (%) relapse: Low Ideal Body Weight (IBW) at dx combined with cavitation and/or positive 2-mo culture

*Khan, AJRCCM 2006*

<table>
<thead>
<tr>
<th>&lt; 90% IBW</th>
<th>Neither</th>
<th>One</th>
<th>Two</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>4/71</td>
<td>16/109</td>
<td>17/51</td>
<td>37/231</td>
</tr>
<tr>
<td></td>
<td>5.6%</td>
<td>15%</td>
<td>33%</td>
<td>16%</td>
</tr>
<tr>
<td>No</td>
<td>3/251</td>
<td>8/212</td>
<td>11/60</td>
<td>22/523</td>
</tr>
<tr>
<td></td>
<td>1.2%</td>
<td>3.8%</td>
<td>18%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Total</td>
<td>7/322</td>
<td>24/321</td>
<td>28/111</td>
<td>59/754</td>
</tr>
<tr>
<td></td>
<td>2.2%</td>
<td>7.5%</td>
<td>25%</td>
<td>7.8%</td>
</tr>
</tbody>
</table>

### Treatment of TB

**Extending Therapy**

- Consider *extending the continuation phase* with cavitation or delayed culture conversion

  **plus:**
  - HIV infection, particularly if advanced
  - Other form of immunosuppression, diabetes, or significant tobacco hx
  - Underweight (< 90% of IBW)
  - High burden: extensive radiographic disease
Case 3

40 yo homeless man, originally from Ethiopia, has fever and cough x 4 weeks and lost 15 lb

- AFB smears: 4+
Overview: Treatment of TB

- Principles and goals of treatment
- Current drugs used, recommended regimens, and duration of TB treatment
- Adverse drug reactions and monitoring
- Management of treatment failure
- End of treatment

Adverse Reactions

- Between 8-18% have drug regimens modified
- Most common side effects:
  - Rash
  - Gastrointestinal intolerance
  - Liver toxicity
  - Peripheral neuropathy (INH)
  - Optic neuritis (EMB)—dose and duration dependent
  - Gout, arthropathy (PZA)
### Isoniazid (INH)

**Adverse Effects**

- Asymptomatic transaminitis
  - Up to 5X upper limit normal in 10-20%
- Clinical hepatitis
  - With INH alone approximately 0.6%; 2.7% with RIF
- Peripheral neurotoxicity
  - Less than 0.2% unless predisposing factors
- Central nervous system effects
  - Not well quantified
- Lupus-like reaction
  - Approximately 20% develop positive ANA; Lupus in less than 1%

### Rifampin (RIF)

**Adverse Effects**

- Cutaneous reactions
  - Pruritus with or without rash in up to 6%
- Gastrointestinal reactions
  - Variable incidence but usually mild
- Flu-like syndrome
  - Occurs in 0.4-0.7% receiving 600 mg twice weekly
- Hepatotoxicity
  - Transient asymptomatic hyperbilirubinemia in 0.6%
  - Clinical hepatitis uncommon, usually cholestatic
- Immunological reactions
  - <0.1% develop ↓plts, anemia, renal failure
Ethambutol (EMB)
Adverse Effects

- Retrobulbar neuritis
  - Less than 1% with dose of 15 mg/kg
  - 18% with more than 30 mg/kg/day
- Peripheral neuritis
  - Rare
- Cutaneous reactions
  - Approximately 0.2-0.7% require discontinuation of drug

Pyrazinamide (PZA)
Adverse Effects

- Hepatotoxicity
  - About 1% develop clinical hepatitis, can be severe
- Gastrointestinal symptoms
  - Mild anorexia and nausea are common
- Non-gouty polyarthralgia
  - Up to 40% receiving daily PZA, not serious
- Hyperuricemia
  - Asymptomatic - expected effect
  - Acute gouty arthritis - rare except if pre-existing gout
- Cutaneous reactions
  - Transient morbilliform rash, self-limited
  - Photosensitive dermatitis
GI Intolerance

- Discern between transient vs. persistent
- Transient: pill burden, indigestion – BIW=>TIW=>daily dosing
- Persistent: anorexia, nausea, and fatigue may signify liver toxicity
- If hepatotoxicity suspected, hold meds and obtain liver function tests (LFTs)
- If LFTs are normal, restart meds and reassure

Liver toxicity

- Most feared adverse reaction
- INH, rifampin, and PZA can all cause liver injury
- Warn patients to seek immediate attention if anorexia, nausea, emesis, abdominal discomfort, fatigue, (or jaundice develops – but this is late!)
- 4-5 fold increased risk with hepatitis C
- **Prevention:** avoidance of alcohol and monitoring LFTs if other drugs with potential liver toxicity are used
Drug Induced Liver Injury (DILI)

- Transaminase levels elevated
  - ≥ 3X ULN with symptoms
  - ≥ 5X ULN without symptoms:

- Response to DILI
  - Stop hepatotoxic medications.
  - Evaluate for viral hepatitis, biliary disease, alcohol, other hepatotoxic drugs
  - Consider “liver sparing” regimen if interruption would be detrimental (EMB/FQN/Injectable)

*AJRCCM 2006; 174: 935-952*

Drug Induced Liver Injury (DILI)

- After ALT <2X ULN: restart RIF ± EMB (or add RIF to liver sparing regimen)

- After 3-7 days: check LFT and restart INH
  - If hepatitis recurs: stop the last drug added

- If RIF and INH tolerated: consider not using PZA
  - Disadvantages: 9 month regimen
  - Continue careful monitoring

*AJRCCM 2006; 174: 935-952*
Liver Toxicity: Order of Re-challenge Depends on Circumstances

Patterns of hepatitis

- Hepatocellular (increased transaminases): can be caused by all three 1st line agents
- Cholestasis (high Alk phos and bilirubin) is usually due to rifampin
- INH hepatitis: often age-dependent
- PZA hepatitis: often age & dose-dependent

Case 4

58 yo man from India, diabetic. TST negative. He lives with his son, daughter-in-law who is pregnant and 2 yo grandson

- He drinks heavily and has hepatitis C infection.
- Cough x 6 wks, seen by PMD (failed trial abx)
Drug-Induced Peripheral Neurotoxicity

- Drugs: INH, ethionamide, cycloserine, linezolid, (EMB)
  More common in patients with
  - Diabetes
  - Alcoholism
  - HIV infection
  - Pregnancy
  Usually symmetrical - tingling, prickling, burning

- Pyridoxine to prevent: 25-50 mg daily (if baseline neuropathy, some experts use 100 mg; caution as B6 alone can cause neuropathy as dose increases)

Monitoring: Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>PZA, INH, RIF, EMB</td>
</tr>
<tr>
<td>Gastrointestinal intolerance</td>
<td>PZA, RIF</td>
</tr>
<tr>
<td>Liver toxicity</td>
<td>PZA, INH, RIF</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>INH, (EMB)</td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>EMB</td>
</tr>
<tr>
<td>Gout</td>
<td>PZA</td>
</tr>
</tbody>
</table>

- Drugs are listed in order of relative likelihood of causing adverse reaction.
- INH/RIF and RIF/PZA appear to have synergistic effects in causing hepatitis.
Case 5
33 y.o. man with LTBI & DM

- TST 16 mm 7 yrs ago
- Developed diabetes mellitus
- Started on INH with 25 mg pyridoxine
- Had a seizure at home after 2 weeks
- PCP thought cause was hypoglycemia
- Repeat seizure 3 weeks later

Case: Randall Reves

Case 5
33 y.o. with seizure x2
Case 5
33 y.o. on INH with brain mass

- Seizures controlled with phenytoin
- Tuberculoma removed at craniotomy
- AFB stains negative
- HRZE started post-op
- Are there drug interactions to consider?

Isoniazid
Drug Interactions

- Isoniazid - Relatively potent inhibitor of several cytochrome P450 isozymes, but not CYP3A
- Inhibitory activity of INH increases the serum concentrations of phenytoin (Dilantin®), carbamazepine (Tegretol®), and diazepam
- Rifampin has opposite effect and outweighs inhibitory effect of INH
- INH may increase toxicity to acetaminophen, valproate, serotonergic antidepressants, disulfiram, warfarin, and theophylline
Rifamycins
Drug Interactions

- Rifamycins - Induce various isozymes of the cytochrome P450 system resulting in a decrease in serum concentration of many drugs
- Enzyme induction: Rifampin > rifapentine > rifabutin
- Ex. Corticosteroids, oral contraceptives, oral hypoglycemic agents, oral anticoagulants, phenytoin, cimetidine, digitalis, antiretroviral agents, immunosuppressants
- Ask patients to bring in all concurrent medications
- Communicate with the primary care provider

Case 5
33 y.o. on INH tuberculoma

- Anticipated reduction in phenytoin levels discussed with Neurology
- Levetiracetam (Keppra) started
- Phenytoin stopped
- No further seizures during treatment
Case 6

30 yo woman moved to US from India 4 yrs ago
- Needs clearance to work in school
- TST 12 mm
- No symptoms

What would you do next?

1. Collect three sputum for AFB/ culture?
2. Begin treatment for LTBI with INH?
3. Repeat the skin test?
4. Repeat the CXR in 6 months?

Anything else?
Case 6
After two months of INH/RIF/PZA/EMB:
Sputum smears/cultures for AFB are negative
What would you do next?

1. Obtain a CT scan
2. Repeat CXR
3. FNA the nodule
4. Bronchoscopy for better samples

Now what?
Approach to the Patient:
Culture Negative TB

**CDC clinical diagnosis criteria (all required)**
- Clinical presentation consistent with TB
- Clinical or radiographic response to anti-TB therapy in the absence of another diagnosis
- Positive TB skin test

**Provider diagnosis**
- Selected cases reported without all 3 criteria above (e.g., TST negative)
- 18% of cases in U.S. are culture negative (CDC 2005)

*Again, clinical acumen and index of suspicion remain key*

## Treatment of Culture-negative TB

- **Low suspect**
  - No rx
  - CXR unchanged = TB4
  - (INH)/RIF x 4 mo
- **TB suspect/PPD+**
  - Abnormal CXR
  - Smear neg x3
  - CXR unchanged = TB4
  - INH x 9 mo
- **High suspect**
  - Rx: I/R/P/E
  - CXR / sx improved = Culture neg. case TB
  - INH/RIF x 2 more mo**
  - CXR unchanged = TB4 ➔ Treatment done

**Guidelines, but ....**

At 2 mo the cultures are negative
Case 7

25 year asymptomatic Chinese woman who came to SF to attend college

- PMH - unremarkable
- Habits - 5 pack-year smoker
- Meds - None
- TST - “positive”
- What would you do next?
Case 7

- Three sputum specimens were collected and noted to be AFB smear negative
- A CT was performed:

![CT images]

Case 7

- Based on the mass-like lesion on the CT, a bronchoscopy was performed.
- Bronchoalveolar lavage was AFB smear negative, cytology negative
- What would you do now?

She grew *M. tuberculosis* from one of her sputum specimens!
Approach to the Patient: The Case for Presumptive Treatment

- Earlier treatment may prevent the progression of disease and limit transmission
- Presumptive treatment with standard RIPE x2 mo would fulfill current recommendation for LTBI (if turns out to not be active TB)
- Adverse reaction in <10% of patients without active TB who were presumptively treated
- Use rapid diagnostic tests to assist decision-making

Treatment of Tuberculosis Special Situations

- Pregnancy
- Liver Disease
- Renal Disease
- HIV/Immunosuppressed
- Pediatrics
- Drug Resistant Disease
- Extrapulmonary
  To be discussed by others
Routine Monitoring and Frequency

<table>
<thead>
<tr>
<th>Signs and symptoms</th>
<th>Monitoring</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum conversion</td>
<td>Baseline,</td>
<td>monthly till negative</td>
</tr>
<tr>
<td>Weight</td>
<td></td>
<td>Monthly</td>
</tr>
<tr>
<td>LFTs</td>
<td>Baseline,</td>
<td>1 month and prn</td>
</tr>
<tr>
<td>Side effects</td>
<td></td>
<td>Monthly: include visual acuity, and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>red/green discrimination; (Ask</td>
</tr>
<tr>
<td></td>
<td></td>
<td>routinely with DOT: GI complaints,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>joints/arthralgias, rash, neuropathy)</td>
</tr>
<tr>
<td>Adherence and</td>
<td></td>
<td>Weekly for DOT patients</td>
</tr>
<tr>
<td>psychosocial issues affecting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MD evaluations</td>
<td>Minimum at</td>
<td>baseline, 3 months and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>end of therapy</td>
</tr>
</tbody>
</table>

Management of Relapse, Treatment Failure

- 90-95% of patients treated for pulmonary TB will have negative sputum cultures by 3 months
- If still culture positive after 3 months of therapy:
  - Re-check drug susceptibility tests
  - Assess adherence
  - Consider malabsorption of drugs
Management of Relapse, Treatment Failure (2)

**Treatment failure:** Culture positive after 4 months of therapy

- Obtain rapid molecular DST
- If the patient is seriously ill or sputum AFB smear +, an empiric expanded regimen should be started with at least two new drugs
- If the patient is not seriously ill, consider waiting for the results of drug susceptibility testing
- If malabsorption suspected, consider IV therapy (INH, rifampin, moxifloxacin) and check therapeutic drug levels

**Case 2 (continued saga)**

50 year old male from the Philippines recently diagnosed with smear+ TB

- Rash after 7 days
  - INH/RIF/PZA/EMB
- Serial restart (q2-3 days) points to INH as source of rash

➤ What would you treat with?
Alternate Regimens
Drug Resistance (or intolerance)

- **Without INH**
  - 6-9 month regimen of RIF, PZA, and EMB (+/-FQ)
  - 9-12 months RIF, EMB, FQ

- **Without Rifampin**
  - 12-18 month regimen of INH, EMB, and FQ (with PZA x2 mo)
  - 18 month regimen of INH, EMB, PZA
  - If cavitary/extensive – or to support shorter 12 mo. duration, can add injectable for at least first 2 mo

- **Without PZA**
  - 9 months of INH/RIF (initial use of EMB while await DST)

---

**Case 2 (continued saga)**

50 year old male from the Philippines recently diagnosed with smear+ TB

- Rash after 7 days INH/RIF/PZA/EMB
- Serial restart points to INH as source of rash
- What if rash was due to RIF and he was INH resistant, is PZA/EMB a good idea?

No, PZA poor at preventing resistance
Treatment of TB
Completion of Therapy

- Initial phase: all of the specified doses should be delivered within 3 months
- Continuation phase: all of the specified doses should be administered within 6 months
- Thus, a 6-month regimen should be completed within 9 months

End of Therapy

- Determined by number of doses completed and not number of months
- **Duration of treatment** is a clinical decision based on the following factors:
  - Extent of disease
  - Time to sputum culture conversion
  - Complexity of the case and site of disease
  - Presence of drug resistance
- **End of treatment evaluation:** chest x-ray (CXR) and sputum (especially if adherence questionable or drug resistance found)
Summary

Treatment and its completion is the single most important factor in controlling TB in a population

- Cuts the line of transmission
- Decreases morbidity and mortality
- Prevents acquired drug resistance

Success requires provider knowledge, a patient-centered approach, and a meaningful relationship between the patient and provider.

Use an expert when encountering problems!

The End