TB Clinical Intensive – Seattle
“Treatment of Tuberculosis”

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Outline

- Unique features of TB treatment
- Decision to initiate TB treatment
- Regimens
- Intermittent dosing
- Relapse and its prevention
- Side effects
- (DOT: crucial, but will not be discussed in detail during this session)
Natural History of TB

Caution: not stable "cure"
Unique Features of TB Treatment

- Multiple drugs
  - Prevent development of drug resistance
  - Result in frequent side effects

- Long duration of treatment
  - Two phases of TB treatment
  - Relapse: 2-3% even when the best regimens are used
Why do we use multiple drugs for active TB?

- Drug resistance is conferred by genetic mutations of *M. tuberculosis*:
  - RIF resistance: one in $10^8$
  - INH resistance: one in $10^6$
  - EMB resistance: one in $10^5$
- A typical cavity contains billions of organisms (i.e., $10^9$ or more)
Drug-resistant mutants pre-exist in a large bacterial population
Multidrug therapy: No bacteria resistant to all 3 drugs

Monotherapy: INH-resistant bacteria survive and multiply
1. The population of INH-resistant bacteria expands.

2. When RIF is added, INH mono-resistant bacteria killed, but INH & RIF-resistant mutants multiply → MDR TB
Different levels of TB burden

- Latent TB infection
- Pauci-bacillary disease
- Asymptomatic immigrants
- Disseminated disease in HIV
- Cavitary, high-burden disease
Lengthy Treatment: Background

- TB bacterial population consists of:
  - **Rapidly replicating organisms** → antibiotics with bactericidal activity
  - **Slowly replicating and semi-dormant organisms** → antibiotics with sterilizing activity

An ideal TB drug has both properties.
Simplified theory of TB chemotherapy

- Extracellular areas: caseum (high oxygen tension $\rightarrow M.tb$ grows rapidly):
  - INH/FQ $>>$ RIF/SM $>$ EMB
    - PZA has little impact
- Slowly multiplying (acidic intracellular):
  - PZA $>>$ RIF $>$ INH (FQ)
- Sporadic growth:
  - RIF $>$ INH (FQ)
Clinical correlation

- **Bactericidal effect**: Reverse disease process and stop transmission

- **Sterilizing effect**: Prevent relapse
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 intra-cellular environment)
- Therefore, **PZA’s protection against development of resistance of a companion drug is limited**
# 1st Line TB Drugs: Activities of 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>Rifampin</td>
<td>++</td>
<td>+++</td>
<td>++++</td>
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<tr>
<td>Pyrazinamide</td>
<td>+</td>
<td>+</td>
<td>+++</td>
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<tr>
<td>Streptomycin</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>+/+</td>
<td>++</td>
<td>+</td>
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</tbody>
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Highest ++++, High ++++, Intermediate ++, Low +
Summary: Treatment Goals

1. Decrease the bacillary burden rapidly to reduce severity of the disease, prevent death and halt transmission of TB
2. Eradicate persisting bacilli to prevent relapse after completion of therapy
3. Protect against development of drug resistance during therapy
Decision to Initiate TB Treatment
Case 1

- 40 yo homeless man, originally from Ethiopia, has fever and cough x 4 weeks and lost 15 lb
- AFB smears: 4+
Case 2

- 30 yo man from Vietnam, cough x 3 weeks and a few episodes of hemoptysis. TST positive
- Smear 3+
Case 3

- 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 infeccion.
Case 4

- 40 yo AA woman, HIV infected. CD4 100
- Cough x 2 weeks. No history of TB exposure
- AFB smear negative
Factors Influencing Initiation of Empirical TB Treatment

- Likelihood of TB diagnosis: epidemiologic info (TB exposure), CXR, labs, alternate diagnosis
- Severity of illness
- Risk of disease progression (e.g., immunosuppression, children)
- Pulmonary vs. extrapulmonary
- Community risk (environment where the patient spends his/her time)
- Increased concern for side effects
- Resources
The update being published this year (the GRADE methodology was used)
General Principles of Therapy

- Always use a multiple-drug regimen
- Never add a single drug to a failing regimen
- Duration of treatment depends on:
  - Drugs that are used (the weaker the regimen, the longer the treatment)
  - Co-morbidity
  - Response to treatment
  - Severity of disease
Isoniazid, rifampin, and pyrazinamide are the basis of the modern short-course chemotherapy. Ethambutol became a part of the standard regimen, because the prevalence of INH resistance is > 5% in many areas.
## Treatment of Tuberculosis
### the Standard Regimen

<table>
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<tr>
<th>Medication</th>
<th>Initial Phase</th>
<th>Continuation Phase</th>
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<tbody>
<tr>
<td>Isoniazid</td>
<td>2 months</td>
<td>6 months</td>
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- **Isoniazid**: 2 months initial phase, 6 months continuation phase.
- **Rifampin**: 2 months initial phase, 6 months continuation phase.
- **Pyrazinamide**: 2 months initial phase, 6 months continuation phase.
- **Ethambutol**: 2 months initial phase, 6 months continuation phase.

**Months**

0 1 2 3 4 5 6
Role of Ethambutol (EMB)

- **Prevention of drug resistance development**
- The four-drug regimen until the susceptibility test results are reported
- EMB can be stopped when:
  1. the isolate is susceptible to INH & RIF, AND
  2. the patient is on at least INH & RIF.
- EMB may not be necessary if:
  1. the isolate is known to be susceptible to INH & RIF at the treatment initiation, AND
  2. the patient will be placed on at least INH & RIF.
When EMB is not an option

- Consider using:
  - A third- or fourth- generation fluoroquinolone (i.e., levofloxacin, moxifloxacin)
  - An injectable agent (i.e., streptomycin, amikacin, capreomycin)
Treatment of Culture-Positive Pulmonary TB Caused by Drug-Susceptible Organisms

The Standard Regimen:

**INTENSIVE PHASE**
8 weeks I,R,Z,E daily

**CONTINUATION PHASE**
18 weeks I,R daily or
18 weeks I,R three times weekly
Treatment of Culture-Positive Pulmonary TB

Conditional: If non-HIV, drug-susceptible, non-cavitary, smear negative

**INTENSIVE PHASE**
- 2 weeks  I,R,Z,E daily  *then*
- 6 weeks  I,R,Z,E three times weekly

*Or*
- 8 weeks  I,R,Z,E three times weekly

**CONTINUATION PHASE**
- 18 weeks  I,R  three times weekly
Treatment of Culture-Positive Pulmonary TB

Exceptional conditions:
If non-HIV, drug-susceptible, non-cavitary, smear negative, excellent adherence, limited resources

**INTENSIVE PHASE**
2 weeks  I,R,Z,E daily  then
6 weeks  I,R,Z,E twice weekly

**CONTINUATION PHASE**
18 weeks  I,R  twice weekly
Daily vs. Intermittent Dosing

- Daily for 6 months is the standard regimen (or “optimal”, “preferred”)
- How much can we deviate from the 6-month daily regimen?
  - Burden of TB disease
  - Treatment response
  - Co-morbidity
  - Adherence
  - Healthcare and public health resources
Recent Literature Review on Intermittent Dosing

- Avoid twice weekly during the intensive phase
- Three times weekly during the intensive phase may be acceptable if daily is difficult in HIV-negative, non-cavitary, smear negative, and fully sensitive cases
Recent Literature Review on Intermittent Dosing (2)

- **Continuation phase**: Daily and three times weekly are equally acceptable options.
- Twice weekly is reported to show equal efficacy in randomized trials.
- Daily and three times weekly are preferred except in situations where the patient's adherence to DOT is excellent but three times weekly is difficult to achieve.
Risk of relapse

- Cavitation on initial CXR AND a positive sputum culture at 2 months → ~20% risk of relapse

- Extend treatment (9 months total)
Relapse Prevention

- **Identify patients at increased risk of relapse**
  - Sputum culture positivity at the end of intensive phase
  - Cavitation on chest radiograph
  - Underweight
  - Bilateral pulmonary involvement

- **Extend the continuation phase for those at high-risk of relapse**
Relapse Prevention: Extension of Continuation Phase

- If non-cavitary but culture remains positive beyond 2 months (~5% of relapse)
  - Some experts extend continuation phase at least 4 months beyond culture conversion

- Cavitary but culture conversion occurs within 2 months (~5% of relapse)
  - May consider other risk factors
    - HIV, > 10% underweight at diagnosis, extensive disease on CXR
Shortening treatment in HIV-negative adults with noncavitary TB and 2-Month culture conversion:

- RIPE x 2 mo, then INH/RIF x 2 mo →
- After confirming 2-mo culture conversion, randomized to 2 more months of INH/RIF or discontinuation of treatment.
- Relapse: 1.6% in 6 mo vs. 7% in 4 mo
Alternative Regimens

- **Without PZA**
  - 9 months of INH/RIF with initial use of EMB (Rating C-I)

- **Without INH**
  - 6 months of RIF/EMB/PZA (Rating B-I)
  - 12 months of RIF/EMB with PZA for the first two months (Rating B-II)

- **Without RIF**
  - 12-18 months of INH/EMB/FQN with PZA for at least two months (plus 2-3 months of an injectable for advanced disease or to shorten the duration) (Rating B-III)
Side Effects
Serious Side Effects From First-line TB Drugs in Patients Treated for Active TB

- 37 of 430 patients had major side-effects: 9 had a second major adverse event (46 total events)
  - Rash/drug fever: 21
  - Hepatitis: 12
  - Severe GI upset: 11
  - Visual Toxicity: 1
  - Arthralgia: 1

- Associated with Female sex, age >60, Birthplace in Asia and HIV infection

Yee, AJRCCM 2003; 167: 1472

(ARS on next slide)
ARS: Which Drug Causes Serious Side Effects Most Frequently?

1. INH
2. Rifampin
3. Pyrazinamide
4. Ethambutol
PZA: 1.48/100 person months of exposure
INH: 0.49/100 person months of exposure
RIF: 0.43/100 person months of exposure
EMB: 0.07/100 person months of exposure

“The drug most likely responsible for hepatitis or rash during therapy for active TB is PZA”

Yee, AJRCCM 2003; 167: 1472
Recommended Baseline Tests

- HIV
- LFT, creatinine, platelet count
- Visual acuity and red-green color discrimination
Routine Follow-up Labs

- Routine measurements of LFT, Cr, and platelet count are not recommended.
- Consider monthly LFT for those with:
  - Abnormal baseline
  - Underlying liver disease, heavy alcohol
  - HIV
  - Pregnant/post-partum
  - Persistent GI intolerance
  - Advanced age
### Hepatotoxicity

#### Hepatotoxic
- INH
- Rifampin/Rifabutin
- PZA
- Ethionamide
- PAS
- Linezolid
- Bedaquiline
- Moxifloxacin?

#### Not hepatotoxic
- Ethambutol
- Streptomycin
- Amikacin
- Capreomycin
- Levofloxacacin
- Cycloserine
Drug Induced Liver Injury (DILI)

- Threshold: Transaminase levels elevated
  - $\geq 3X$ upper limit of normal (ULN) with symptoms
  - $\geq 5X$ ULN without symptoms:
- If DILI is suspected,
  - 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
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
Special Situations

- Smear-negative, culture-negative case (clinical and radiographic improvement):
  - RIPE x 2 months, then INH/RIF for 2 months (4 months total)

- Smear-negative, culture-negative with stable radiographic findings (old healed TB) = LTBI
  - RIPE x 2 months
A Few More Principles

- Use the drugs based on susceptibility test results
  - If any doubt, don’t count it as an effective drug (e.g., low-level INH resistance)
  - Carefully interpret conflicting lab results.
- Once daily dosing:
  - A single daily dose of 400mg of INH was more effective than the same total dose given in two divided doses
    *(Bull World Health Organ 1960;23:535)*
Management of Relapsed TB

- Most relapses occur within the first 6 – 12 months after stopping therapy but some occur 5 or more years later.

- Nearly all drug susceptible patients who were treated with a rifamycin and received DOT will relapse with drug susceptible organisms.

Initiate standard RIPE regimen.
Management of Relapsed TB

- **Suspect drug resistance if:**
  - Treatment was self-administered previously
  - The patient was poorly adherent
  - Clinical or radiographic worsening during initial weeks of treatment for relapsed TB

- **Request molecular testing** for drug resistance
- Consider **expanded regimen**, especially if immunosuppressed
  - Add at least two drugs previously not used (e.g., fluoroquinolone, an injectable)
Summary

- The higher the TB burden is, the more intense regimen should be used (the more bugs, the more drugs for longer duration)
- Careful consideration on reducing relapse rate, addressing risk of side effects, and utilizing limited resources
Additional slides
Directly Observed Therapy

- DOT is the preferred treatment strategy.
- “Enhanced DOT” consists of “supervised swallowing” plus social supports, incentives, and enablers.

Chaulk CP, et al. JAMA 1998;279:943
DOT Improves Treatment Completion Rate

- At least one third of patients on self-administered treatment do not adhere to Rx.
- Difficult to predict which patients will/will not take medicines (exception: mental health, substance abuse)