TB Clinical Intensive – Oakland
“Treatment of Tuberculosis”
September 30, 2015

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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

Natural History of TB

* 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 = one in $10^8$
  - INH = one in $10^6$
  - EMB = one in $10^5$

- A cavity contains billions of organisms (i.e., $10^9$ or more)
Multidrug therapy: No bacteria resistant to all 3 drugs

INH
RIF
EMB

Monotherapy: INH-resistant bacteria survive and multiply

INH

When RIF is added, INH mono-resist. mutants killed, but INH & RIF-resist. mutants multiply → MDR TB

The population of INH-resistant bacteria expands.

INH
RIF

Different levels of TB burden

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

- TB bacterial population consists of:
  - Rapidly replicating organisms → Bactericidal activity
  - Slowly replicating and semi-dormant organisms → Sterilizing activity

Simplified theory of TB chemotherapy

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

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

<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>
</tr>
<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>
</table>

Highest ++++, High ++++, Intermediate ++, Low +

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 male from Vietnam, cough x 3 weeks and a few episodes of hemoptysis. TST positive
- Smear 3+

### Case 3
- 58 yo male from India, diabetic. TST negative. He lives with his son, daughter-in-law who is pregnant and 2 yo grandson
Case 4

- 40 yo AA man, 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)
- Potential side effects
- Resources

2003
### 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

### General Principles of Therapy (2)

- 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

#### Standard Regimen

<table>
<thead>
<tr>
<th></th>
<th>Initial Phase</th>
<th>Continuation Phase</th>
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</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>0</td>
<td>1-5</td>
</tr>
<tr>
<td>Rifampin</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>3</td>
<td>6</td>
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<table>
<thead>
<tr>
<th>Months</th>
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<tbody>
<tr>
<td>0</td>
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<td>1</td>
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<td>4</td>
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<tr>
<td>5</td>
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<tr>
<td>6</td>
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</table>
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 place 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:**

**INITIAL PHASE**
8 weeks I,R,Z,E daily (56 doses)

**CONTINUATION PHASE**
18 weeks I,R daily (126 doses) or
18 weeks I,R 2x/wk (36 doses) or
18 weeks I,R 3x/wk (54 doses)
Systematic Review on Intermittent Dosing:  
\textit{Thorax}: KC Chung 2011;66:997

- Intermittent dosing can reduce the efficacy of TB treatment: higher risk of relapse or treatment failure
- Negative impact most prominent in cavitary disease
- Standard 6-mo regimen: no significant difference between daily throughout vs. daily only in initial phase

\textbf{Avoid intermittent doses, especially in initial phase and in presence of cavities (high bacillary burden)}
**WHO Guidelines (2010): Treatment of Tuberculosis**

*ATS/CDC/IDSA/ERS Guideline revision underway – expected Q4 2015*

<table>
<thead>
<tr>
<th>Intensive Phase</th>
<th>Continuation Phase</th>
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<tbody>
<tr>
<td>Daily</td>
<td>Daily</td>
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<tr>
<td>Daily</td>
<td>3x per week</td>
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**Daily vs. Intermittent Dosing**

- Daily for 6 months is the standard regimen (or “optimal”)
- How much can we deviate from the daily throughout?
  - Burden of TB disease
  - Treatment response
  - Co-morbidity
  - Adherence
  - Healthcare and public health resources

**Evolving Concept: 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, and fully sensitive cases
### Evolving Concept: 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 thrice weekly are preferred except in situations where thrice weekly is difficult to achieve and adherence to DOT is excellent.

### Relapse Prevention

A Strategy Stressed in Guidelines:
- **Identify patients at increased risk of relapse**
  - (+) sputum culture at the end of the initial phase is associated with increased risk of relapse.
- **Extend the continuation phase for those at high-risk of relapse**

### Insight into Relapse: A Study on Rifapentine-Based Continuation Phase

- CDC-sponsored TB Trials Consortium
- 1004 HIV negative patients with pulmonary TB enrolled
- Initial phase: standard 4-drug regimen
- Continuation phase: rifapentine/INH once weekly vs. rifampin/INH twice weekly

*TBTC. Lancet 2002;360:528*
Insight into Relapse: A Study on Rifapentine-Based Continuation Phase (2)

<table>
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<th>INH/Rifampin 2x/wk</th>
<th>sputum culture @ 2 mo</th>
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<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Cavity Yes</td>
<td>20.8%</td>
<td>4.7%</td>
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Insight into Relapse: A Study on Rifapentine-Based Continuation Phase (3)

(TBTC. Lancet 2002;360:528)

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Continuation Phase: Rifapentine-based Regimen

USE WITH CAUTION: only if HIV (−), smear negative at 2 months and no cavitation on CXR.

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<td></td>
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</tr>
<tr>
<td>Rifampin</td>
<td></td>
<td>Rifapentine q week</td>
</tr>
<tr>
<td>PZA</td>
<td></td>
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<tr>
<td>EMB</td>
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0 1 2 3 4 5 6

Months
**Lessons Learned From This Study**

- **Extended therapy** for patients with drug-susceptible pulmonary TB
  - Who have **cavitation** on initial CXR **AND**
  - Who have a **positive sputum culture at 2 months**

**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

**Can We Shorten The Treatment?**

*Am J Respir Crit Care Med. 2009; 180: 558–563*

- Shortening treatment in HIV-negative adults with noncavitary TB and 2-Month culture conversion:
  - RIPE x 2 mo, then IR x 2 mo →
  - After confirming 2-mo culture conversion, randomized to 2 more months of IR or d/c 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
### Which Drug Causes Serious Side Effects Most Frequently?

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<table>
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<tbody>
<tr>
<td>1.</td>
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<td>3.</td>
<td>Pyrazinamide</td>
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<td>4.</td>
<td>Ethambutol</td>
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### Serious Side Effects From First-line TB Drugs in Patients Treated for Active TB (2)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Serious Side Effects per 100 Person Months of Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>PZA</td>
<td>1.48/100</td>
</tr>
<tr>
<td>INH</td>
<td>0.49/100</td>
</tr>
<tr>
<td>RIF</td>
<td>0.43/100</td>
</tr>
<tr>
<td>EMB</td>
<td>0.07/100</td>
</tr>
</tbody>
</table>

"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
- Moxi?

### Not hepatotoxic
- Ethambutol
- Cycloserine
- Strep/Amikacin
- Capreomycin
- Levofloxacin

## 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*

### 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)

Directly Observed Therapy

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

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)
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 balance between reducing relapse rate and resource utilization