**Outline**

- TB treatment principles
- Decision to initiate TB treatment
- Regimens
- Intermittent dosing
- Relapse and its prevention
- Side effects
- DOT

**Natural History of TB**

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

*Not stable "cure"*
TB Control Principles

Treatment of infectious TB cases is the most crucial element in controlling TB in a community
- Cuts the line of transmission
- Decreases morbidity and mortality

Key Steps:
- Diagnosing infectious TB cases early
- Knowing when to start treatment when a person is suspected of having active TB

Unique Features of TB Treatment

- Multiple drugs
  - 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 To Treat Active TB?

- Drug resistance is conferred by spontaneous genetic mutations of *M. tuberculosis*
  - RIF = one in $10^8$
  - INH, SM = one in $10^6$
  - EMB = one in $10^4$
- A 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 proliferate

INH resistant bacteria multiply to large numbers

INH mono-resist. mutants killed, but RIF-resist. mutants proliferate → MDR TB
### INH Resistance After 2 months of INH Monotherapy

- Retrospective analysis from INH treatment trial in 1952
- All isolates were drug-susceptible before starting.

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Cavities</th>
<th>% Cult +</th>
<th>% Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>0</td>
<td>40%</td>
<td>22%</td>
</tr>
<tr>
<td>57</td>
<td>1+</td>
<td>44%</td>
<td>40%</td>
</tr>
<tr>
<td>89</td>
<td>2+</td>
<td>70%</td>
<td>61%</td>
</tr>
<tr>
<td>43</td>
<td>3+</td>
<td>88%</td>
<td>87%</td>
</tr>
</tbody>
</table>

The higher the burden of TB disease is, the higher likelihood of developing drug-resistance

*Fox W, Sutherland I. Thorax 1955;10:85-98*

---

### Continuum of TB

- Latent TB infection
- Pauci-bacillary disease
- Cavitary, high-burden disease

- Disseminated disease in HIV
- Asymptomatic immigrants

---

### Lengthy Treatment

- TB bacterial population consists of:
  - Rapidly replicating organisms
  - Slowly replicating and semi-dormant
  - Dormant
- Bactericidal activity (ability to kill rapidly replicating organisms)
- Sterilizing activity (ability to kill semi-dormant organisms) : prevention of relapse → lengthy treatment
Theory of Bactericidal Activities

- Extracellular areas: caseum (high oxygen tension → *M. tb* grows rapidly):
  - INH >> SM > RIF > EMB
  (*PZA has little activities)
- Slowly multiplying (acidic, intracellular):
  - PZA >> RIF > INH
- Sporadic growth: RIF > INH

PZA: little impact on development of drug resistance

- Drug resistance is more likely to occur when the large burden of organisms are rapidly replicating (i.e., cavitation)
- PZA works best in acidic intra-cellular environment, but not with high oxygen tension
- Therefore, its 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>
</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>

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

Initiation of Empirical TB Treatment
- Consider:
  - Likelihood of TB diagnosis (epidemiologic info, symptoms, CXR, labs)
  - Severity of illness
  - Pulmonary vs. extrapulmonary
  - Community risk (environment where the patient spends his/her time)
  - Potential side effects
  - Resources
General Principles of Therapy

- Always use a multiple-drug regimen
- Never add a single drug to a failing regimen
- Duration of treatment depends on the drugs that are used (the weaker the regimen, the longer the treatment)

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>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Ethambutol</td>
<td></td>
<td></td>
</tr>
</tbody>
</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 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)
Recommended Treatment Regimens
IDSA/USPHS Rating System

- Strength of recommendation
  A. Preferred; should be offered
  B. Alternative; acceptable to offer
  C. Offer when above cannot be given
  D. Should generally not be offered
  E. Should never be offered

- Quality of Evidence
  I. At least one randomized trial
  II. Other clinical trials
  III. Expert opinion

Gross PA, et al. CID 1994;18:421

Treatment of Culture-Positive Pulmonary TB Caused by Drug-Susceptible Organisms

Regimens Rated A-I (HIV negative) and A-II (HIV positive) → 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)

Treatment of Culture-Positive Pulmonary TB Caused by Drug-Susceptible Organisms (2)

Regimens Rated A-II (HIV negative) and B-II (HIV positive with CD4 ≥ 100)

INITIAL PHASE
2 weeks I,R,Z,E daily (14 doses) then
6 weeks I,R,Z,E twice weekly (12 doses)

CONTINUATION PHASE
18 weeks I,R twice weekly (36 doses)
Regimens Rated A-III (HIV negative)

INITIAL PHASE
- 8 weeks I, R, Z, E 5x/week (40 doses) OR
- 2 weeks I, R, Z, E 5x/week (10 doses) then
- 6 weeks I, R, Z, E twice weekly (12 doses)

CONTINUATION PHASE
- 18 weeks I, R twice weekly (36 doses)

Regimens Rated B-I (HIV negative)

INITIAL PHASE
- 8 weeks I, R, Z, E 3x/week (24 doses)

CONTINUATION PHASE
- 18 weeks I, R 3x/week (54 doses)

Treatment of Culture-Positive Pulmonary TB
Caused by Drug-Susceptible Organisms (3)

Treatment of Culture-Positive Pulmonary TB
Caused by Drug-Susceptible Organisms (4)

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)
Evolving Concern: Daily vs. Intermittent Dosing

- Biological and practical rationales for intermittent dosing.
- Systematic Review of 17 analytic studies
  - 9 systematic reviews, 8 controlled studies and 2 case-control studies.


Intermittent Dosing: TB Treatment Among HIV-Negative

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

Level of evidence 1+, Grade of recommendation “A”
Avoid intermittent doses, especially in initial phase and in presence of cavities

WHO Guidelines for Treatment of Tuberculosis in Resource Limited Settings

<table>
<thead>
<tr>
<th>Duration</th>
<th>Intensive phase</th>
<th>Continuation phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 months of INH</td>
<td>4 months of RIF, PZA, EMB</td>
<td></td>
</tr>
<tr>
<td>2 months of INH</td>
<td>1 month of RMP</td>
<td></td>
</tr>
</tbody>
</table>

ATS/CDC/IDSA/ERS
Guideline revision underway – expected Q4 2015
Daily vs. Intermittent Dosing

- Daily for 6 months is the standard regimen (or “optimal” per WHO)
- How much can we deviate from the daily through-out?
  - Burden of TB disease
  - 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

Rational for Extending Therapy Decreasing the Risk of Relapse: Example of Silicosis

- Hong Kong silicotuberculosis trial (Am Rev Resp Dis 1991;143:262)
  - Extended the continuation phase from 4 to 6 months
  - Decreased relapse rate to 7% from 22%

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>
<thead>
<tr>
<th>INH/Rifampin 2x/wk</th>
<th>sputum culture @ 2 mo</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cavity</td>
<td>Yes</td>
<td>20.8%</td>
<td>4.7%</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>5.9%</td>
<td>1.7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INH/Rifapentine once/wk</th>
<th>sputum culture @ 2 mo</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cavity</td>
<td>Yes</td>
<td>22.2%</td>
<td>9.1%</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>11.8%</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

Insight into Relapse: A Study on Rifapentine-Based Continuation Phase (3)

<table>
<thead>
<tr>
<th>INH/Rifampin 2x/wk</th>
<th>sputum culture @ 2 mo</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cavity</td>
<td>Yes</td>
<td>20.8%</td>
<td>4.7%</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>5.9%</td>
<td>1.7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INH/Rifapentine once/wk</th>
<th>sputum culture @ 2 mo</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cavity</td>
<td>Yes</td>
<td>22.2%</td>
<td>9.1%</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>11.8%</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

Continuation Phase: Rifapentine-based Regimen

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

<table>
<thead>
<tr>
<th>Initial Phase</th>
<th>Continuation Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid q week</td>
<td>Rifapentine q week</td>
</tr>
<tr>
<td>Rifampin</td>
<td></td>
</tr>
<tr>
<td>PZA</td>
<td></td>
</tr>
<tr>
<td>EMB</td>
<td></td>
</tr>
</tbody>
</table>
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
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

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
  - Age advanced

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)

(2)

- 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