Advanced Management of Patients with Tuberculosis
Little Rock, Arkansas
August 13-14, 2014

*Treatment of TB*
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Barbara Seaworth, MD has the following disclosures to make:

- No conflict of interests
- No relevant financial relationships with any commercial companies pertaining to this educational activity
Treatment of Tuberculosis

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Objectives

• Review standard regimens for treatment of drug susceptible TB

• Discuss strategies resulting in improved patient outcomes
  – Intensity of dosing
  – Prolongation of therapy
Short Course Treatment of Drug Susceptible TB

- **Initiation phase**
  - 4 drugs INH, rifampin, PZA, ethambutol
  - 8 weeks
    - Daily
    - Daily then BIW / TIW
    - TIW

- **Continuation phase**
  - 2 drugs INH, rifampin
  - 18 or 31 weeks
    - Daily
    - TIW
    - BIW
Duration of Treatment

• 6 Months
  – Requires INH, rifampin throughout and PZA during the initiation phase or
  – Rifampin, Ethambutol and PZA for entire 6 mo.

• 9 Months
  – If PZA was not used
  – TB in a person with silicosis
  – Prolongation to decrease risk of relapse

Treatment of Culture Positive Pulmonary Tuberculosis

Regimens Rated A-I (HIV Uninfected)

Initial Phase
2 mo. H,R,Z,E daily (56 doses, 8wks) or
2 mo. H,R,Z,E 5x/wk. (40 doses, 8wks) then

Continuation Phase
- 4 mo. - H,R daily (126 doses, 18 wks) or
- 4 mo. – H,R 5x/wk. (90 doses, 18 wks) or
- 4 mo. – H,R, 2x/wk. (36 doses, 18 wks)
Treatment of Culture Positive Pulmonary Tuberculosis

Regimens Rated **A-II (HIV Uninfected)**

**Initial Phase**
2 weeks H,R,Z,E daily (14 doses) *then*
6 Weeks H,R,Z,E twice weekly (12 doses) *then*

**Continuation Phase**
4 months H, R twice weekly (36 doses, 18 weeks)

Intermittent dosing by DOT only!

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Treatment of Culture Positive Pulmonary Tuberculosis

Regimens Rated **A-III (HIV Uninfected)**

**Initial Phase**
2 weeks H,R,Z,E 5x per week (10 doses) *then*
6 Weeks H,R,Z,E twice weekly (12 doses) *then*

**Continuation Phase**
4 months H, R twice weekly (36 doses, 18 weeks)

Intermittent dosing by DOT only!
Treatment of Culture Positive Pulmonary TB

– THRICE WEEKLY – “HONG KONG” REGIMEN
  » Regimen Rated BI (HIV uninfected)

**Initial Phase**

• 2mo – H,R,Z,E 3x/week (24 doses, 8 weeks)

**Continuation phase**

• 4mo – H,R 3x/wk (54 doses, 18 weeks)

Intermittent dosing by DOT only!

Newer Drugs for Treatment of TB

• Newer rifamycins
  – Rifabutin
    • HIV – TB
    • Unable to tolerate rifampin due to side effects
  – Rifapentine – long half life

• Fluoroquinolones:
  – Levofloxacin and Moxifloxacin
    • Resistance to first line agents
    • Intolerance to first line drugs
Strategies to Promote Good Outcomes

• Assess patient related risk factors for poor outcome
  – Severity of disease
    • High bacillary burden
  – Co-morbid conditions
    • Liver disease
    • HIV
    • Diabetes
    • Malignancy
  – Adherence to therapy

Populations of Mycobacteria

- Actively dividing
- Slowly dividing
- Semi-dormant persisters
- Dormant

Drugs:
- INH
- Rifampin
- EMB
- Rifampin
- PZA
Importance of the Initiation Phase

• Actively dividing bacterial subpopulation
  – INH
    • Most potent drug for killing actively dividing bacteria
    • Associated with decrease in infectiousness

Importance of the Initiation Phase

• Persisters
  – Revert back and forth to other subpopulations
  – Source of relapse
  – Rifampin is the only first line drug with activity against persisters

• Optimizing bactericidal and sterilizing activity early will minimize overall bacterial load present during continuation phase
Significance of Persistently Positive AFB Smears

- Review of lab data of 428 patients, 30 smear + at 20 weeks
  - 23/30 had a negative culture
  - 7/30 positive culture “treatment failure”

- Of those with negative cultures - none relapsed

- Most received standard therapy for 12 months
  - PZA was continued for 2-3 months

» Al-Moamary Chest 1999; 116:726-731

Prolonged Positive Smears

- 51 year old male

- Slow clinical and CXR improvement

- Prolonged conversion of cultures (10 weeks)

- Prolonged conversion of smears (7½ months)
Prolonged Positive Smears

- 12 months of RX
- Culture and smear negative 20 months after stopping TB meds
- CXR still extensive cavitary infiltrates

Two Month Culture Conversion

- Surrogate marker of sterilizing activity of drug regimen
- Used to predict likelihood of relapse
- Commonly considered to be 80% in 4 drug regimens
- More recent TBTC studies show lower rates
  - 71% Moxifloxacin vs. Ethambutol*
  - 60% Moxifloxacin vs. INH**

*Study 27 AJRCCM 2006
** Study 28 AJRCCM 2009
Adverse Outcomes

- Delayed response
  - Culture conversion after 3 months of an effective regimen
- Treatment failure
  - Persistent + culture after 4 months treatment
- Relapse
  - Symptoms or culture positive after completion of treatment
- Development of drug resistance

Delayed Response
Culture Positive at 3 Months

- TB lab should **automatically repeat** susceptibility studies on last positive culture - check to be sure

- Assess adherence

- Consider serum drug levels

- Evaluate response to therapy
  - Clinically and radiographically

**By the time you know this it is 4 months into therapy!**
Treatment Failure
Culture Positive at 4 Months

Clinical evaluation including adherence to treatment
Repeat susceptibility studies
  • On last positive culture
  • And request on a “new sputum culture” now
    – Ask for molecular detection of drug resistance
Serum drug levels if not previously done
Augment therapy
  • Add at least two and preferably three new drugs to which the isolate is likely to be susceptible
  • Even if no clinical or radiographic evidence of failure

Relapse

• Circumstance in which a patient becomes and remains culture-negative while receiving anti-tuberculosis drugs but at some point after completion of therapy, either becomes
  – culture-positive again or
  – experiences clinical and radiographic deterioration consistent with active tuberculosis
• Try to identify “WHY”
TBTC STUDY 22: RATE OF RELAPSE, BY REGIMEN, SPUTUM CULTURE, AND CHEST RADIOGRAPH

<table>
<thead>
<tr>
<th>Culture at 2 mo.</th>
<th>Chest radiograph at study entry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>16.7%</td>
</tr>
<tr>
<td>Negative</td>
<td>3.8%</td>
</tr>
<tr>
<td>Cavitary</td>
<td>8.9%</td>
</tr>
<tr>
<td>Non-Cavitary</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

Rate of Failure/Relapse

Lancet 2002; 360:528

End of Therapy (EOT) Cavity: A Risk Factor for Relapse

Figure 2. Proportion of subjects with tuberculosis relapse by findings on early and EOT CXR. EOT = end of treatment; CXR = chest radiograph.

Hamilton; Int J Tuber Lung Dis 2008
### Risk Factors for Relapse

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Rate</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cavitary and culture positive at 8 weeks</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>Cavitary</td>
<td>4.7%</td>
<td>4.7</td>
</tr>
<tr>
<td>Culture positive 8 weeks</td>
<td>5.9%</td>
<td>5</td>
</tr>
<tr>
<td>Non Hispanic White race</td>
<td>13.5</td>
<td>2.4</td>
</tr>
<tr>
<td>* &gt;10% below ideal body weight and failure to gain weight &gt; 5% at 8 weeks</td>
<td>18.4%</td>
<td>3.8</td>
</tr>
<tr>
<td>^ Beijing strain in an Asia Pacific Islander</td>
<td></td>
<td>OR:11</td>
</tr>
</tbody>
</table>

Lancet 2002; 360:528  
*AJRCCM 2006; 174:344  
^Emerging Infect Dis 2009; 15:1061

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### Lack of Weight Gain and Relapse Risk, TBTC Study 22

- Relapse risk high in those underweight at diagnosis  
  19.1% versus 4.8%

- Among patients underweight at diagnosis, if weight gain ≤ 5% after 2 months of treatment:  
  - Relapse risk 18.4%  
  - If cavitary disease and positive 2 month culture: 50.5%

Case Study

- 47 yr old male, recurrence of TB
  - Weight at Diagnosis 117 pounds (<10% IBW)
  - Two months, 114 pounds
  - Three months, 114 pounds
  - Four months, 115 pounds

- Extensive cavitary disease on CXR

- Sputum smear + 5 ½ months

- Sputum culture + 3 ½ months
Treatment Related Risk Factors for Early Relapse of TB

- Evaluation of 113 cases of relapsed TB, matched with case controls

  - **Non-cavitary TB relapse rate:**
    - 3 x per week x 6 month - 1.1%

  - **Cavitary TB relapse rates:**
    - Thrice weekly x 6 month - 7.8%
    - Daily x 6 month - 3.3%
    - Extended thrice weekly - 0.5%
    - Extended daily - 0.4%
    - Either intensive phase or CP beneficial

  Am J Respir Crit Care Med. 2004; 170: 1124-30

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Treatment Related Risk Factors for Early Relapse-Dosing Intensity

- In cavitary disease (regardless of 2 month culture), risk of relapse of 6 month regimen > 5% except,
  - Daily IP, CP
  - Daily IP, thrice weekly CP

- In cavitary disease and 2 month culture +, risk of relapse is 6% in 6 month regimen
  - Daily IP, CP
  - Daily IP, thrice weekly CP

  Am J Respir Crit Care Med 2006; 174: 1153
Treatment of TB and Optimal Dosing Schedules

Kwok Chiu Chang, Chi Chiu Leung, Jacques Grosset, Wing Wai Yew
Thorax 2011 66:997-1007

Systematic Review of 32 articles – 9 systematic reviews, 8 controlled studies, 9 PK-PD studies, and 6 animal studies.

Levels of evidence and grades of recommendations assigned according to clinical evidence with reference to Scottish Intercollegiate Guidelines

Non HIV related TB (11 studies)

• Suggests that intermittent dosing reduces TB treatment efficacy shown by a higher risk of relapse or failure

• Negative impact most prominent in presence of cavities

• Standard 6 mo. regimen - no significant difference between daily throughout and daily in initial phase

Level of evidence: 1+
Grade of recommendation: “A”
• Avoid intermittent doses, especially in initial phase and in presence of cavities
TB With INH Resistance (2 studies)

- Suggests that dosing intermittency reduces TB treatment efficacy as shown by:
  - Higher risk of treatment failure, relapse or acquired drug resistance

Level of evidence 1+
Grade of evidence: “A”
- Avoid dosing intermittency, especially in the initial phase in the presence of INH resistance

HIV Related TB (3 studies)

- Suggests intermittent Rx, especially in initial phase reduces treatment efficacy as shown by
  - a higher risk of treatment failure, relapse, or acquired Rifampin resistance

Level of evidence 1+
Grade of recommendation “A”
- Avoid intermittency, especially in the initial phase in HIV TB
Prolongation of Continuation Phase

Continuation phase increased to 7 mo if initial CXR is cavitary & culture is positive at 2 mo

Treatment of Tuberculosis MMWR 2003

- Rational for Extending Therapy
  - Continuation of PZA for an additional 2 months was not helpful in drug susceptible disease
  - Prolongation of continuation phase by 2 months decreased relapses in silico-tuberculosis from 20% to 2%

Effect of Prolonging Therapy on Treatment Failure or Relapse

Treatment of Silico-tuberculosis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>SHRZ - 6mo* (n=49)</th>
<th>SHRZ – 8mo* (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse</td>
<td>20%</td>
<td>2%</td>
</tr>
</tbody>
</table>

* Three times weekly therapy

Am Rev Respir Dis 1991;143:262-267
Factors Associated with Relapse of Tuberculosis

<table>
<thead>
<tr>
<th>Disease related</th>
<th>Treatment related</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cavitation</td>
<td>• DOT</td>
</tr>
<tr>
<td>• Bilateral disease</td>
<td>• Adherence</td>
</tr>
<tr>
<td>• Sputum culture at 2 months</td>
<td>• Dosing intensity</td>
</tr>
<tr>
<td>• Low body weight</td>
<td>• Duration of therapy</td>
</tr>
<tr>
<td>• Lack of weight gain</td>
<td>• Use of rifamycin</td>
</tr>
<tr>
<td>• Drug resistance</td>
<td></td>
</tr>
<tr>
<td>• ?Beijing strain in Pacific Islander</td>
<td></td>
</tr>
<tr>
<td>• Other comorbidities</td>
<td></td>
</tr>
<tr>
<td>– DM, HIV, malabsorption</td>
<td></td>
</tr>
<tr>
<td>• Prior TB treatment</td>
<td></td>
</tr>
</tbody>
</table>

Tailoring Treatment Regimens

- **Prolong** continuation phase when:
  - Positive 2 month culture with cavitary disease
  - Extra-pulmonary disease
    - Meningitis
    - Disseminated disease in children
  - HIV TB in children and adolescents

ATS, CDC, IDSA: Treatment of Tuberculosis 2003
Tailoring Treatment Regimens

• Consider - Prolongation of continuation phase:
  – Slow clinical or radiological response
  – Positive 2 month culture **OR** cavitary disease?
  – End of therapy (EOT) cavity present
  – >10% below ideal body weight?

ATS, CDC, IDSA: Treatment of Tuberculosis 2003

Tailoring Treatment Regimens

• Daily Intensive Phase
  – cavitary disease
  – HIV TB
  – INH resistance
Tuberculosis Drug Serum Level Monitoring Recommended

- Delayed response to therapy
- Advanced AIDS with evidence of malabsorption
- Seriously ill patient to maximize therapy
- ? Diabetics
- Toxicity evaluation
- Use of second line drugs
- Acquired drug resistance
- Relapse
- Potential for drug-drug interactions
- Renal and hepatic insufficiency

In the Treatment of TB, You Get What You Pay For...

- "A consistent theme has begun to appear: more extensive disease requires more treatment, and the fewer total doses, the higher the risk that treatment will prove inadequate"

  - What should we conclude?
    - First: More treatment means more cures
    - Second: Programs need to consider some individualization of therapy
    - Third: Should not deter us from intermittent therapy but should remind us of need for sophisticated management based on case-specific circumstances
      - Should not be surprised that individuals differ in their response.

WHO 2010 Guidelines

• Whenever feasible, the optimal dosing frequency for new patients with pulmonary TB is daily throughout the course of therapy (Strong / High grade evidence)

• Alternatives (Conditional/High and moderate grade evidence)
  – Daily intensive phase followed by TIW in continuation phase
  – Three times weekly dosing throughout – by DOT only and non HIV patients

• Recommended against BIW dosing (Strong / High grade evidence)
Treatment in Special Situations
Relapsed Tuberculosis Management Strategies

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

- Microbiological Confirmation of Relapse Should be Pursued Vigorously
  - Confirm relapse bacteriologically
  - Identify drug susceptibility pattern of isolate
  - Use DNA fingerprinting to identify new infection causing the disease versus relapse

ATS, CDC, IDSA: Treatment of Tuberculosis 2003

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Relapsed Tuberculosis Management Strategies

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

Treat with standard RIPE regimen

ATS, CDC, IDSA: Treatment of Tuberculosis 2003
Relapsed Tuberculosis Management Strategies

• If culture & susceptibility studies (those treated in other countries) were not done but treatment given by DOT
  – Usual treatment with RIPE
    • Watch carefully for clinical deterioration -
  – Consider an expanded regimen if immune suppressed, significantly ill, or extensive disease
    • Use at least 2 drugs to expand the regimen
    • (Molecular detection of drug resistance MDDR)

ATS, CDC, IDSA: Treatment of Tuberculosis 2003

Relapsed Tuberculosis Management Strategies

• Suspect drug resistance if:
  – Patients treated with self administered therapy
  – Patient was poorly adherent
  – Patient deteriorates clinically or radiographically during initial weeks of treatment

• Do molecular testing for drug resistance
  • Consider expanded regimen, especially if immune suppressed
  • Add at least 2 (fluoroquinolone and an injectable)
Active TB During Pregnancy

• Diagnosis may be difficult
  – Respiratory symptoms common in late pregnancy
  – Reluctance to do a CXR
  – Extra-pulmonary disease is even more difficult

• Outcomes for BOTH mom and baby are improved with treatment during pregnancy

• Infection control is important at time of delivery if mom is still infectious

Active TB During Pregnancy

• Treatment:
  – INH, Rifampin, Ethambutol x 9 months
    • Stop ethambutol if susceptible to INH and rifampin
  – PZA only if drug resistance is present
    • PZA regarded as safe by most countries in world

• Follow carefully for hepatotoxicity- risk is increased
  – During pregnancy
  – Three months postpartum
Management of TST + Persons With an Abnormal CXR and – AFB Smear

- Isolated CXR with nodules and/or fibrotic lesions:
  - If no symptoms - wait
    - Collect sputum culture
    - Do NAAT or PCR (Xpert)
    - Evaluate for symptoms
    - Repeat CXR
  - If CXR stable at 2 – 3 months and cultures are negative, treat as LTBI

- Isolated CXR with nodules and/or fibrotic lesions:
  - If patient has any signs or symptoms of TB disease: patient is a TB suspect
    - Start 4 drugs
  - Never start a single drug in a patient with possible active TB

Culture Negative TB

- TB suspect with positive TST or IGRA
  - Risk factors for TB
  - Abnormal CXR
  - Usually – clinical symptoms
- All cultures are negative
- Classify based on clinical and/or radiograph response to treatment at 2 months
  - Clinical or CXR improvement – Culture Negative TB
  - Treat for 4 months (children and HIV + 6 months)
  - RIPE for 2 months, then RIE +/- PZA dependent on INH resistance
**Mycobacterium bovis**

- A member of the M TB complex which is what is identified by all TB labs or PCR
- Similar to other members of complex but is resistant to PZA
- Is associated with extra pulmonary disease and increased mortality
- Is common in children (> 1 year) along U.S. Mexico border
  - Non-pasturized milk and cheese – a food borne disease as well as respiratory

**Management of Treatment Interruptions**

- **Initial phase** of therapy
  - <14 days – complete standard # of doses
  - >14 days – restart from the beginning

- **Continuation phase**
  - >80% doses by DOT – if initial smear–, may stop
  - < 80% doses by DOT and/or initial smear +
    - Repeat culture
    - Management based on clinical and bacteriological factors.
TB Research

Impact on Future TB Treatment

Length of Treatment and Relapse Risk

Figure 2: Risk of Relapse With a Four Month Treatment Regimen

HIV neg, 2 mo culture neg, Non-Cavitary TB in Uganda.
Rifampin Dose - High is Better

• Higher peak serum concentrations were linked to
  – Improved killing of MTB,
  – Suppression of resistance
  – Post antibiotic effect

• Short half life not important but peak concentration was

Gumbo; Antimicrob Agents Chemother, 2007

TBTC Study 27
Moxifloxin Substituted for Ethambutol

Per cent with negative sputum culture

Weeks of treatment

Moxifloxacin
Ethambutol

Burman; Am J Resp Crit Care Med 2006
Where to Get More Information

• HEARTLAND NATIONAL TB CENTER
  – 1-800-TEX LUNG: Medical Consultation and Technical Assistance Line
  – Future training courses

• CDC

• TB Educate

• TBresources.com