Treatment of Tuberculosis
Elizabeth S. Guy, MD
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Elizabeth S. Guy, 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

Elizabeth S. Guy, MD
Baylor College of Medicine

No relevant financial disclosure
Objectives

• Standard treatment regimens for drug susceptible TB
  – Two phases of therapy
• Strategies associated with improved outcomes
• Delayed response and treatment failure
• Treatment in special settings
• Case studies
USPHS/IDSA Evidence-Based Rating Scale

• Strength of Recommendation
  – A = preferred
  – B = acceptable alternative
  – C = offer when unable to give A or B
  – D = should generally NOT be offered
  – E = should NEVER be offered

• Quality of Supporting Evidence
  – I – randomized clinical trial
  – II – clinical trial, not randomized
  – III – expert opinion

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
- 9 months
  - If PZA was not used
  - Silico-TB
  - Presence of risk factors for 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!
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, 8weeks)

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

Intermittent dosing by DOT only!

Strategies to promote good outcome
• Patient centered care
• DOT provided by health department
• Monthly clinical evaluation in outpatient setting
  – Early detection of side effects
  – Educate and promote adherence to therapy
  – Address comorbidities that impact treatment response
• Monthly sputum until 2 consecutive negative cultures
Strategies to promote good outcome

- Assess risk factors for poor outcome
  - Severity of disease
    • High bacillary burden
  - Co-morbid conditions
    • Liver disease
    • HIV
    • Poorly controlled DM
    • Malignancy
  - Adherence to therapy
    • Substance abuse
    • Side effects of medications

Populations of Mycobacteria

1. Actively dividing
2. Slowly dividing
3. Semi-dormant persisters
4. Dormant
Importance of the Initiation Phase

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

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

Key Goal of the Initiation Phase

• Optimizing bactericidal and sterilizing activity early will minimize overall bacterial load present during continuation phase
Significance of Persistent + 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

2 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 effective regimen

- **Treatment failure**
  - Persistent + culture after 4 months treatment

- **Relapse**
  - Symptoms or culture positive after completion of treatment

- **Development of drug resistance**
TB and alcoholism

• 50 yo male with alcoholism and 30 pack year tobacco use
  – Hemoptysis and 3 months of fatigue, fever, weight loss
  – Father obtained CXR and sent to BT
  – Cavitary and multi-lobar disease
  – Smear positive
  – LFTs normal
  – Standard therapy started

• Significant concern about adherence to treatment
  – Admission to SA chest hospital declined by patient

• Delayed culture conversion
• 9 month treatment
• No significant missed doses
• Continued to drink while on treatment
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!
Failure of treatment

- 32 yo man foreign born presented with WL, fever, malaise
- Extensive, smear + cavitary disease.
- Treatment started at community hospital
- One week later, sent ED for tachypnea, tachycardia, low BP
- Hospital day 2: massive hemoptysis with hypoxia and emergent intubation
- Bronchial and intercostal artery embolization
Failure of treatment

• Discharged to Langston Home (Homeless shelter)
• Co morbidities:
  – Daily alcohol use -> fatty liver
  – Tobacco ½ ppd
  – Malnutrition

• Failure to gain weight
• Persistent tachycardia and dyspnea
• Persistent smear positive and culture positive sputum
• Daily medications since start

Failure of treatment

• Significant muscle wasting, painful peripheral neuropathy, difficulty walking

• Admitted for additional work up
• drug levels were obtained
  – INH
  – Rifampin
Failure of treatment

- Additional drugs added including injectable
- INH and rifampin doses increased
- Nutritional supplements
Treatment Failure
Culture Positive at 4 Months

Clinical evaluation
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 antituberculosis 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” your patient relapsed so you can do it right this time!
## TBTC Study 22: Rate of Failure or 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>23.5/16.7%</td>
</tr>
<tr>
<td>Negative</td>
<td>5.6/3.8%</td>
</tr>
<tr>
<td>Cavitary</td>
<td>14.4/8.9%</td>
</tr>
<tr>
<td>Non-Cavitary</td>
<td>2.9/2.5%</td>
</tr>
</tbody>
</table>

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
Lack of Weight Gain and Relapse Risk
TBTC Study 22

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

• Among pts underweight at diagnosis, if weight gain ≤ 5% after 2 months of treatment:
  – Relapse risk 18.4% vs. 10.3%
  – If also cavitary disease: 18.9%
  – If cavitary and + 2 month culture: 50.5%


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 8 weeks</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>Cavitary</td>
<td></td>
<td>4.7</td>
</tr>
<tr>
<td>Culture positive 8 weeks</td>
<td></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 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
Treatment Related Risk Factors for Early Relapse of TB

• Evaluation of 113 cases of relapsed TB, matched with case controls
  – Non-cavitary TB, thrice weekly, 6 mo relapse rate: 1.1%
  – Cavitary TB relapse rates:
    • Thrice weekly, 6 mo 7.8%
    • Daily, 6 mo 3.3%
    • Extended thrice weekly 0.5%
    • Extended daily 0.4%
      – Either intensive phase or CP was beneficial

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

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily IP, thrice weekly CP</td>
<td>1.6 (0.6 – 4.1)</td>
</tr>
<tr>
<td>Daily IP, twice weekly CP</td>
<td>2.8 (1.3 - 6.1)</td>
</tr>
<tr>
<td>Thrice weekly IP, CP</td>
<td>2.8 (1.4 – 5.7)</td>
</tr>
<tr>
<td>Daily IP, weekly rifapentine</td>
<td>5.0 (3.3-15.3)</td>
</tr>
</tbody>
</table>

Am J Respir Crit Care Med 2006; 174: 1153
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 Options to Prevent Poor Outcome

• Increase frequency of dosing
• Prolongation of treatment in delayed responders
• Evaluation and management of delayed response
• Serum drug level monitoring
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

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

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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

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

Factors Associated with Relapse / Failure of Tuberculosis Treatment

<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>
Personalized Treatment Regimens

• **Prolong** continuation phase when:
  
  – Positive 2 month culture with cavitary disease
  
  – Extrapulmonary disease
    • Meningitis
    • Disseminated disease in children
  
  – HIV TB in children and adolescents

ATS, CDC, IDSA: Treatment of Tuberculosis 2003

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Personalized 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
Personalized Treatment Regimens

• Daily IP
  – cavitary disease
  – HIV TB
  – INH resistance

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

• 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)
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

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

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

• Suspected drug resistance
  – 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
    - 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: presumptive TB
    - Start 4 drugs
  - Never start a single drug in a patient with possible active TB

### Culture Negative TB

- Suspicion for TB and 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 identified by all TB labs or PCR
- Similar to other members 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

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**Treatment completion / interruption**

- Treatment completion
  - Total number of doses taken within a specified period, using an effective regimen and dosing schedule
  - 6 months (26 weeks) completed within 9 months
- Treatment interruption
  - Formalized algorithm accounting for bacillary burden (smear +)
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.

ATS, CDC, IDSA: Treatment of Tuberculosis 2003

TB Research

Impact on Future TB Treatment
• Rifapentine and isoniazid once a week versus rifampicin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients: a randomised clinical trial. Lancet 2002 TBTC
• Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection. NEJM Dec 2011 TBTC
• Substitution of Rifapentine for Rifampin During Intensive Phase Treatment of Pulmonary Tuberculosis: Study 29 of the TBTC, JID 2012

• Four-Month Moxifloxacin-Based Regimens for Drug-Sensitive Tuberculosis SH Gillespie, et al. NEJM 2014
• A Four-Month Gatifloxacin-Containing Regimen for Treating Tuberculosis CS Merle, et al NEJM 2014
• High-Dose Rifapentine with Moxifloxacin for Pulmonary Tuberculosis A Jindani, et al. NEJM 2014
• USPHS – US public health service
• TBTC – tuberculosis trials consortium
• ACTG – AIDS clinical trials group
• TBnet – tuberculosis network European study group
• TB Alliance – global alliance for TB drug development
• EDCTP - European and Developing Countries Clinical Trials Partnership

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
Summary

• Treatment of TB is evolving and requires inclusion of risk factors for poor outcome
• Individualization of therapy may be necessary
• Increase dosing intensity especially in IP
• Therapeutic drug monitoring
• Patient centered care
• Actively address co morbidities that portend poor outcome