TB Intensive
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Treatment of TB
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Barbara J. 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

• What’s New?
A Complete Assessment

Is Essential to Good Patient and Public Health Outcomes!

Why Did I Ask For All This?
Differentiating Between LTBI and Disease When the CXR is Abnormal

- Exclude active disease
  - Abnormal but **stable** CXR findings (>2-3 months)
    - NODULES/ FIBROTIC LESIONS OF OLD TB
    - PLEURAL THICKENING
    - CALCIFIED GRANULOMA
    - BRONCHIECTASIS
  - Sputum smear and cultures documented as negative

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: **patient is a TB suspect**
    - Start 4 drugs
  - Never start a single drug in a patient with possible active TB
Treatment Regimens for TB Disease

- **Initiation phase** of therapy
  - 8 weeks
  - INH, Rifampin and PZA +/- EMB

- **Continuation phase** of therapy
  - 16 weeks
  - INH and Rifampin
Treatment of Culture Positive Pulmonary Tuberculosis

Regimens Rated **A-1** (HIV Uninfected)

**INITIAL PHASE**
- 2 mo I,R,Z,E daily (56 doses, 8wks) **or**
- 2 mo I,R,Z,E 5x/wk (40 doses, 8wks) **then**

**CONTINUATION PHASE**
- 4 mo - I,R daily (126 doses, 18 wks) **or**
- 4 mo – I,R 5x/wk (90 doses, 18 wks) **or**
- 4 mo – I,R, 2x/wk (36 doses, 18 wks)

WHO now recommends daily therapy throughout.

Treatment of Culture Positive Pulmonary Tuberculosis

– **Regimens Rated A-II (HIV Uninfected)**
- 2 weeks – I,R,Z,E daily (14 doses) **then**
- 6 weeks – I,R,Z,E **twice** weekly (12 doses)

• PLUS (DOT only)
• 4 mo – I,R Twice weekly (36 doses, 18 weeks) **or**
Treatment of Culture Positive Pulmonary Tuberculosis

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

  • 2 weeks – I,R,Z,E 5x/week (10 doses) **then**
  • 6 weeks – I,R,Z,E twice weekly (12 doses)

  – PLUS (DOT only)
  • -4mo – I,R Twice weekly (36 doses, 18 weeks) **or**

What About Ethambutol?

- A four drug regimen is recommended until susceptibility tests are reported
  - If treatment is being initiated after drug susceptibility tests are known and the organisms are susceptible, ethambutol is not necessary if patient is given both INH and rifampin
  - Ethambutol can be stopped as soon as the lab reports an isolate susceptible to INH & rifampin.
Treatment of Culture-Positive Drug Susceptible Pulmonary TB

- General conclusions from the literature:
  - 6 mo (26 wk) is the *MINIMUM* duration of RX
  - 6 mo regimens require rifampin and INH throughout and PZA for the first 2 months
    OR
  - 6 – 9 mo regimens are effective without INH if PZA given throughout

- General conclusions from the literature:
  - Without PZA - minimum duration is 9 months
  - Without rifampin - minimum duration is 12 months (up to 18 months)
  - Streptomycin and ethambutol (EMB) are approximately equivalent in effect
    • Because of high incidence of Streptomycin resistance, EMB is preferred for initial therapy
    – Use streptomycin *only* if isolate is proven susceptible
Strategies Stressed in Guidelines

• **Identification of patients at increased risk of relapse**
  – Obtain sputum smear and culture at end of initial phase of treatment (2 months)

• **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**

• **Counting Doses**
  – Define treatment completion by number of doses taken as well as duration of treatment

Strategies Stressed in Guidelines

• **RIFABUTIN** (RBT): May be used as a primary drug for patients (especially HIV+) receiving medications having unacceptable interactions with rifampin (e.g. Protease Inhibitors, methadone)

• **Fluoroquinolones** (Levofloxacin or Moxifloxacin) may be used when first line drugs are not tolerated or the organism is resistant
Case Management – Drugs Alone Are not Enough

• Monthly clinical visit
  – check response to therapy,
  – evaluate for toxicity:
    • hepatitis, visual acuity, Ishihara Plates
  – repeat education (document!)

• Monthly laboratory to check liver enzymes, CBC

Case Management – Drugs Alone Are not Enough

• For pulmonary TB – Monthly sputum until two consecutive cultures are negative
  – 2 month sputum is crucial

  – 80% should convert by 2 months, 95% by 3 months

• Document isolate is susceptible to INH and rifampin prior to stopping ethambutol
Drug Susceptibility Tests

- Expect results by day 28
  - INH, Rifampin, Ethambutol, and PZA are recommended for each initial isolate
- If the private lab does not do susceptibilities, referral may lead to unnecessary delays
  - Positive culture should be sent for DST within 24 hrs, lab should not wait for culture to grow on solid media

Time to Culture Positive (TTP) by Extent of Disease

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Figure 2: Pre-treatment TTP (in days) and radiological extent of disease defined by Simon. There is a significant trend in TTP on the log scale (P < 0.001). Figures represent median TTP. Dots represent outliers more than 1.5 times the interquartile range beyond the upper quartile on the log scale. TTP = time to positivity.
Time to Culture Positive by Presence of Cavitary Lesions

![Graph showing time to culture positive by presence of cavitary lesions.]

When should I consider my specimen delayed?

- **Day 0**: Specimen received in the lab
- **Day 1**: At 24 hours, expect smear results
- **Day 2**: At 48 hours, expect results of NAAT or Molecular DST
- **Day 21**: At 21 days, expect a culture ID (TB or NTM)
- **Day 28**: At 28 days, expect 1st line susceptibility results, expect 2nd line 4 weeks after requested
- **Day 42-56**: At 6-8 weeks, expect the culture to be finalized if negative

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Perrin Int J TB Lung Dis, Dec 2010

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Figure 1: Pre-treatment TTP (in days) and absence or presence of single or multiple cavities. There is a significant trend in TTP on the log scale ($P < 0.001$). Figures represent median TTP. Dots represent outliers more than 1.5 times the interquartile range beyond the upper quartile on the log scale. TTP = time to positivity.
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!

Treatment Guidelines 2003

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

• Who Should We Suspect?

• What Can We Do Differently to Decrease the Risk?

TBTC STUDY 22: RATE OF FAILURE or RELAPSE, BY REGIMEN, SPUTUM CULTURE, AND CHEST RADIOGRAPH

Rate of Failure/Relapse

- Positive
- Negative
- Cavitary
- Non-Cavitary

Culture at 2 months
Chest radiograph at study entry

When (AND HOW) should treatment be extended?

The purpose of extending treatment is to prevent relapse

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*</th>
<th>SHRZ – 8mo*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=49)</td>
<td>(n=50)</td>
</tr>
<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

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

Independent of culture results

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
Does Every Patient Get The Same Treatment?

Tailoring 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
Tailoring Treatment Regimens

- **Consider** - Prolongation of continuation phase when patient:
  - Slow to clinically or radiographically respond
  - Positive 2 month culture **OR** cavitary disease?
  - End of therapy (EOT) cavity present
  - <10% ideal body weight?

Treatment Related Risk Factors for Early Relapse of TB

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

» Chang, Am J Respir Crit Care Med. 2004; 170: 1124-30
Treatment Related Risk Factors for Early Relapse-Dosing Intensity

- Review of 200 cases of relapse, 6 month RIPE treatment
- Relapse higher, especially with cavitary disease and positive 2 month cultures
  - Only 6 month daily or 6 month daily IP and 3/wk CP had relapse rates <5%

Chang Am J Respir Crit Care Med 2006; Vol 174 p 1153

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.

Treatment of TB and Optimal Dosing Schedules

Kwok Chiu Chang, Chi Chiu Leung, Jacques Grosset, Wing Wai Yew
Thorax December, 2010

Systematic Review of 17 analytic studies – 9 systematic reviews, 8 controlled studies and 2 case-control 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 Rx reduces TB treatment efficacy as shown by a higher risk of relapse or failure

- Negative impact most prominent in presence of cavities

- Review suggests with standard 6 mo Rx - no significant difference between daily throughout & 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
Medical Factors Associated With Relapse

- Cavitary TB
- Extensive disease on CXR; bilateral infiltrates
- Positive 2 month culture
- Associated medical conditions
  - Diabetes
  - HIV
- Malabsorption of TB drugs
- Tuberculous lymphadenitis
- Underweight at diagnosis and failure to gain
- Drug resistant disease
- Prior treatment for tuberculosis

Treatment Factors Associated with Relapse of Tuberculosis

- DOT
- Adherence
- Dosing intensity (Dose itself)
- Duration of therapy
  - Intensive phase
  - Continuation phase
  - Both
- Rifampin containing regimen
Length of Treatment and Relapse Risk

Risk of Relapse With a Four Month Treatment Regimen

HIV neg, 2 month culture neg, Non-Cavitary TB in Uganda.

Relapsed TB - Management Strategies

• 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

  – Treat with standard RIPE regimen

ATS, CDC, IDSA: Treatment of Tuberculosis 2003
Relapsed TB - 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
  - Patient from area with high incidence of drug resistance

• **Do molecular testing for drug resistance (MDDR)**
  - Consider expanded regimen, especially if immune suppressed
  - Add at least 2 (fluoroquinolone and an injectable)

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Relapsed Tuberculosis - Case Study
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

What is problem?

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%

Treatment in Special Situations

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

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

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
  – Clinical evaluation

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

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

MMWR Treatment of Tuberculosis 2003; 52
Culture Negative TB

- Classify based on **clinical and/or radiograph response** to treatment at 2 months
  - Clinical or CXR improvement – Culture Negative TB
  - All cultures are negative

- TB suspect with positive TST or IGRA and TB risk factors
  - Usually these persons have clinical symptoms
  - CXR abnormal

- Treat for 4 months (children and HIV + 6 months)
  - RIPE for 2 months, then RIE +/- PZA dependent on risk of INH resistance

TB in Chronic Renal Failure Patients

- Pulmonary findings often atypical, especially in dialysis patients
  - Fever – most common symptom
  - Weight Loss/Anorexia
  - Cough (may be present)

- Abdominal disease common in persons on dialysis

- Treatment must be adjusted if Cr Cl < 40

- Treat after dialysis
Prolonged Positive Smears

- 51 year old male
- Slow clinical and CXR improvement
- Prolonged conversion of cultures (10 weeks)
- Prolonged conversion of smears (7½ months)
Significance of Persistent + AFB Smears

• Review of lab: 428 patients, 30 with smear persistently positive for more than 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

• 12 months of RX

• Culture and smear negative 20 months after stopping TB meds

• CXR still shows extensive cavitary infiltrates
Culture Result if Smear Positive at 2 Months

- Review of 2 month smear and culture
  - All treated with **daily treatment throughout**
  - 6.7% (60/812) remained smear +, half culture positive

- Clinical factors which predict positive culture if smear positive at 2 months
  - High smear grade at diagnosis
  - No radiographic improvement
  - Incomplete remission of symptoms
  - Treatment interruption, especially INH  

  Wang, Eur Resp J

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**Mycobacterium bovis**

- Included in the designation of “MTB complex”
  - Report given out by all TB labs for both culture results or by rapid molecular screening (PCR, Gene Xpert, NAAT)

- **M bovis** is:
  - Always resistant to PZA
  - Associated with extra pulmonary disease and increased mortality
  - Common in children (> 1 year) along U.S. Mexico border
  - Spread by both person to person and animal to person airborne transmission
  - Spread by consumption of non-pasteurized milk and cheese – a food borne disease as well as respiratory
M. bovis & Genotyping - Texas

All M. bovis are resistant to PZA and need treatment for 9 months with INH and Rifampin +/- EMB.

Raw (unpasteurized) Milk – think M. bovis in most places!
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**
**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

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**How Easy Can It Get?**

Abstract presented 2013

Trial treatment = Standard RIPE7 x 2, IR7 x4

- Daily RIF, MOXI, EMB, PZA x 2 months
- Once weekly Rifapentine 1200mg and Moxi 400mg x 6 months

- Adverse events similar
- But failure in 14% of each arm.
What is the Right Dose of Rifampin?

- Maximum dose for Rifampin never identified
  - Cost
  - Toxicity of higher intermittent doses
  - Standard dose is rifampin 600mg (10mg/kg)

- Abstract CROI 2013
  - Highest fall in of log colony-forming units of MTB was with 35mg/kg dose.
  - After 14 days 8/14 patients had negative cultures as did 6/15 given 20mg/kg
  - Higher doses safe, well tolerated

TB Trial Consortium Study 29

- Part I compare standard therapy (rifampin 10mg/kg) to daily rifapentine 10mg/kg
  - Rifapentine safe but not more active than rifampin.
    - Dorman et al JID July 2012

- Part II
  - Higher daily rifampin doses (? 20mg/kg)
  - Higher daily or three times/week Rifapentine (? 15 – 20mg/kg)
TBTC Study 27
Moxifloxin Substituted for Ethambutol

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

Burman; Am J Resp Crit Care Med 2006