Advances in the Diagnosis and Treatment of Tuberculosis
San Antonio, Texas

Clinical Predictors of TB Relapse
Robert Belknap, MD
February 22, 2012

Robert Belknap, MD has the following disclosures to make:

• No conflict of interests
• No relevant financial relationships with any commercial companies pertaining to this educational activity
Clinical Predictors of TB Relapse

Bob Belknap M.D.
Denver Public Health
February 22, 2012

What’s the chance of cure with 6-months of treatment?

- elderly male from Korea
- living in the U.S. > 30 years
- presented with cough x 6 months and 20lb weight loss
- AFB smear (+)
Overview

1. Epidemiology and timing of TB relapses

2. Role of the medication regimen and adherence

3. Risk factors / predictors of relapse

Recurrent TB – Failure, Relapse or Re-infection

Failure
- a positive culture after 4 months of treatment

Relapse
- a positive culture after documented culture conversion and treatment completion with matching genotypes

Reinfection
- original and subsequent positive cultures with non-matching genotypes
Reported TB Cases in the United States

11,182

USPHS Tuberculosis Short-Course Chemotherapy Trial 21: Effectiveness, Toxicity, and Acceptability

The Report of Final Results

Debra L. Combs, MPH; Richard J. O’Brien, MD; and Lawrence J. Geiter, MPH

- 1400 patients from 22 clinics in 13 states

<table>
<thead>
<tr>
<th></th>
<th>9m INH / Rifampin</th>
<th>2m INH/Rif/PZA + 4m INH/Rif</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse Rate at 96 weeks*</td>
<td>2.8%</td>
<td>3.5%</td>
</tr>
<tr>
<td>2 month culture conversion</td>
<td>63%</td>
<td>70%</td>
</tr>
</tbody>
</table>

15 March 1990 • *Annals of Internal Medicine* • Volume 112 • Number 6
Risk of Reinfection Based on Incidence

![Graph showing the relationship between reinfection proportion (%) and log incidence (cases/100,000 people/year of tuberculosis).](image)

Figure 2. Linear regression line for the reinfection proportion (%) and log incidence (cases/100,000 people/year of tuberculosis). Values in parentheses are the reinfection proportions. US, United States.


Relapse Rates after Short-Course TB Therapy (6-months)

- HIV-positive
  - 3/47 (6.4%) relapse
  - Median time = 125 days

- HIV-negative or unknown
  - 7/127 (5.5%)
  - Median time = 240 days

Sterling, AIDS 1999; 13: 1899
Timing of TB Relapse

90% relapsed by 12 months

Jasmer, AJRCCM 2004; 170(12): 1360
Timing of Relapse in BMRC trials

**Table 2** Summary of timing of relapse by geographical region

<table>
<thead>
<tr>
<th>Geographical region</th>
<th>Total trials</th>
<th>Total assessable</th>
<th>Relapses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n</td>
<td></td>
</tr>
<tr>
<td>East Africa</td>
<td>8</td>
<td>3817</td>
<td>394 (10)</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>4</td>
<td>2609</td>
<td>150 (6)</td>
</tr>
<tr>
<td>Singapore</td>
<td>3</td>
<td>879</td>
<td>30 (3)</td>
</tr>
<tr>
<td>Overall</td>
<td>15</td>
<td>7305</td>
<td>574 (8)</td>
</tr>
</tbody>
</table>

Nunn, IJTLD 2010; 14(2): 241

What’s the risk of relapse?

- Pansusceptible TB
- 8 weeks with I/R/Z/E and 18 weeks with INH/Rpt
Duration and Intermittency of Rifampin on Outcomes

**Methods**
- Systematic review and meta-analysis
- 57 trials, 312 arms, and 21,472 participants

**Results**
- Increased risk of failure, relapse, and resistance in regimens using 1-2 m Rifampin resistance
- No difference between daily and intermittent regimens

Menzies, PLoS Medicine, Sept 2009

Dosing Schedules and Risk of Relapse

- Systematic review of published clinical trials
- Stratified by cavitation, 2-month culture and regimen dosing frequency

**Modeled relapse risk vs. daily therapy**
- 1.6 for daily initial and 3x/week continuation
- 2.8 for daily initial and 2x/week continuation
- 2.8 for 3x/week throughout
- 5.0 for daily initial plus 1x/week continuation
- 7.1 for 3x/week initial plus 1x/week continuation

Chang, AJRCCM 2006; 174: 1153
Effect of DOT on Relapse

Methods
- Retrospective study in Tarrant County, Texas
- Jan 1980 – Oct 1986 treatment by SAT

Results
- ↓ relapse from 20.9% to 5.5%
- ↓ primary resistance 13.0% to 6.7%
- ↓ acquired resistance 14.0% to 2.1%

Weis, NEJM 1994; 330: 1179

First Priority – Treatment Completion

Chaulk, JAMA 1998; 279(12): 943
Nested Case-Control of Risk Factors for Relapse

**Methods**
- Computerized registry of all pulmonary TB patients diagnosed Jan 1998 to Dec 2000
- Followed through the territory-wide reporting system for 30 months after starting therapy
- 113 relapse cases and 226 controls
- Matched by age, gender, year of diagnosis, chest clinic, and pretreatment sputum culture

Chang, AJRCCM 2006; 174: 1153

Nested Case-Control of Risk Factors for Relapse

**Results**
- Risk factors
  - Extrapulmonary disease other than pleuritis
  - More extensive disease than RUL
  - Cavitation
  - Thrice-weekly therapy throughout
- Protective
  - Extended treatment in both the initial and continuation phases

Chang, AJRCCM 2004; 170: 1124
Predictors of Relapse – TBTC Study

Methods
- > 1,000 HIV-negative adult patients with drug-susceptible TB
- Randomized at 2 months to once weekly INH/Rifapentine vs twice weekly INH/Rif
- Follow-up for 24 months after treatment

Burman, Lancet 2002; 360: 528

<table>
<thead>
<tr>
<th>Cavity</th>
<th>Culture-positive at 2 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Yes</td>
<td>20.8 (48) ‡</td>
</tr>
<tr>
<td>No</td>
<td>5.9 (17)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cavity</th>
<th>Culture-positive at 2 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Yes</td>
<td>22.2 (72)</td>
</tr>
<tr>
<td>No</td>
<td>11.8 (17)</td>
</tr>
</tbody>
</table>

Burman, Lancet 2002; 360: 528
Lack of Weight Gain and Relapse Risk

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;= 5% weight gain*</td>
<td>2.4 (1.1–5.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Cavity and sputum culture + after 2 mo of treatment†</td>
<td>7.9 (2.2–28.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>Cavity or sputum culture + after 2 mo of treatment†</td>
<td>3.5 (1.0–12.1)</td>
<td>0.05</td>
</tr>
<tr>
<td>Rifapentine treatment arm</td>
<td>2.0 (0.9–4.4)</td>
<td>0.10</td>
</tr>
<tr>
<td>White race</td>
<td>2.9 (1.3–6.7)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Underweight at diagnosis (≥ 10% below IBW) with cavitation and (+) culture at 2 months:

- Stratified by weight gain
  - ≤ 5% → 50% relapse
  - > 5% → 19% relapse

Khan, AJRCCM 2006; 174(3): 344

What’s the risk of relapse?

- 8 weeks with I/R/Z/E and 18 weeks with INH/Rpt
- Smear and culture negative at 6 weeks
- Chest CT @ dx with emphysema but no cavitation
- Weight change – 109 lbs to 116 lbs (BMI 19.9 to 21.3)
Impact of Diabetes on TB Treatment

Background
- DM is a risk for progression to active TB
- Prevalence of DM is increasing

Methods
- Systematic review and meta-analysis
- 742 papers reviewed
- 33 studies included
- 5 studies reported relapse

Bark, BMC Medicine 2011; 9:81

Impact of Diabetes on TB Relapse

Bark, BMC Medicine 2011; 9:81
TB Strain and Relapse Risk

Beijing Genotype

- Singapore
  - 32/45 (71%) of relapses vs 148/290 (51%) of non-relapses
    Sun Epid & Infect 2006; 134 (2): 329

- TBTC Study 22
  - 14/56 (25%) relapse vs 42/296 (14%) controls, OR 2.0, p=0.04
    Burman Emerging ID 2009 15(7): 1061

Follow-up 6 months after treatment

- Feels well, chronic non-productive cough, No fever, stable weight (121 lbs)
- AFB (-) x 3
Clinical Symptoms at Relapse

Methods
- 394 pulmonary TB patients in a multicenter clinical trial
- 16 patients with relapse

Results
- Symptoms at Relapse vs non-Relapsers
  - Fever – 31% vs 5.1%
  - Cough – 75% vs 12%
  - Chest Pain – 25% vs 7.6%

Follow-up 6 months after
- Restarted on I/R/Z/E
- Random Glucose 248 (previously normal)
- Cultures negative x 3
Time to Detection on Liquid Culture as a Predictive Tool

**Table 5** Cox regression analysis for baseline predictors of tuberculosis recurrence at 24 months following completion of treatment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazard ratio</th>
<th>95%CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTD ≤3 days</td>
<td>3.74</td>
<td>1.04–13.41</td>
<td>0.043</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.79</td>
<td>0.47–1.35</td>
<td>0.399</td>
</tr>
<tr>
<td>Body mass index ≤18 kg/m²</td>
<td>3.80</td>
<td>1.07–13.55</td>
<td>0.039</td>
</tr>
<tr>
<td>Extensive disease</td>
<td>0.89</td>
<td>0.43–1.85</td>
<td>0.755</td>
</tr>
</tbody>
</table>

* Only cases with favourable outcome (according to international recommendations) at month 6 and TTD available at diagnosis were included (171 patients without recurrence and in 19 patients with recurrence).
* Radiological extent of parenchymal disease > RUL or > 1 lung,
  CI = confidence interval; TTD = time to culture detection in days; RUL = right upper lobe.

Hesseling, IJLTD 2010; 14(5): 560

Treatment Recommendations to Minimize Relapses

**Table 3. Recommendations for treating pulmonary tuberculosis stratified by initial cavitation and 2-month sputum culture**

<table>
<thead>
<tr>
<th>Disease Category</th>
<th>Recommended Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cav+, C2m+</td>
<td>2-mo daily IP + 7-mo thrice-weekly CP</td>
</tr>
<tr>
<td>Cav+, C2m−</td>
<td>2-mo daily IP + 4-mo thrice-weekly CP</td>
</tr>
<tr>
<td>Cav−, C2m+</td>
<td>Extend 6-mo regimens by three months if CP contains 600mg rifampin once weekly, or 600mg rifampin twice weekly</td>
</tr>
<tr>
<td>Cav−, C2m−</td>
<td>Any 6-mo regimen</td>
</tr>
</tbody>
</table>

Chang, AJRCCM 2006; 174: 1153
Summary

- Relapse occurs in ≈ 3-10% of TB cases
- Most relapses are in ≤ 6 months and nearly all by 12 months
- Include a Rifamycin throughout treatment (when susceptible)
- More drugs are better but not at the expense of DOT
- Early relapse may not be symptomatic

Summary

- Definite Risks for Relapse
  - Cavitation on chest x-ray
  - Delayed culture conversion (positive cx at 2 months)
  - Being underweight (< 10% IBW) and failing to regain at least 5% by 2 months

- Possible / Probable Risks
  - TB genotype
  - Diabetes
  - HIV (particularly patients with a lower CD4)
The Best Laid Plans ...  

1. 4m I/R/Z in Mexico
2. 2m R/Z/E/Levo + 4m R/E/Levo
3. 3m R/Z/Strep + 6m R/E
4. 2m R/Z/E + 9m R/E (pregnant)
5. 2.5m R/E/Levo/Strep + 15.5m R/E/Levo

INH-R Pulmonary TB