Guidelines for the
Treatment of Tuberculosis
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TB for Pulmonologist
March 13, 2015
Phoenix, AZ

Marcos Burgos, MD has the following disclosures to make:

• No conflict of interests
• No relevant financial relationships with any commercial companies pertaining to this educational activity
Objectives

- List the current recommendations for treatment of tuberculosis disease
  - Biological bases of the treatment of tuberculosis
  - TB Treatment regimens
  - Importance of the initiation phase of therapy in assuring good outcomes
  - Treatment in special situations
- Identify drug-resistant TB, when to suspect it?
  - Rapid confirmation of drug resistant TB
  - Management strategy for the drug resistant patient
  - Specific treatment regimens for the drug resistant patient
  - Expert consultation

Streptomycin

- In 1946 a small amount of streptomycin was made available in the UK and it was decided the best use would be to test its efficacy in a randomised controlled trial.
  - A landmark for tuberculosis
  - A landmark for clinical trials
The streptomycin trial – the long term results

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Total assessed 6m</th>
<th>Deaths 5 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bed rest</td>
<td>52</td>
<td>27%</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>55</td>
<td>7%</td>
</tr>
</tbody>
</table>

P = 0.01

35 of 41 streptomycin patients tested had developed resistance

Quart J. Med. 1954, 23, 347

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Selection of Naturally occurring DR mutants by Inadequate Treatment

![Graph showing the number of resistant and susceptible organisms over time](Graph.png)

Evolution and Genetic Basis of Drug Resistant tuberculosis

- Drug resistant mutations occurs spontaneously and independently in wild-type populations not previously exposed to TB-drugs
- Resistance to more than one drug is rare in wild-type populations
- Resistance to more than one drug is the product of the rates of individual drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>$1 \times 10^5-10^6$</td>
</tr>
<tr>
<td>RIF</td>
<td>$1 \times 10^7-10^8$</td>
</tr>
<tr>
<td>SM</td>
<td>$1 \times 10^5-10^6$</td>
</tr>
<tr>
<td>EMB</td>
<td>$1 \times 10^5-10^6$</td>
</tr>
<tr>
<td>PZA</td>
<td>$1 \times 10^2-10^4$</td>
</tr>
</tbody>
</table>

Mitchison DA, AJRCCM: 2005: Vol 171

**Prevention of Resistance with Association of STR & PAS**

The effect of Rifampin shortening TB treatment to 6 months

<table>
<thead>
<tr>
<th>Study</th>
<th>Place</th>
<th>Regimen*</th>
<th>No. of Patients</th>
<th>Cultures Pos. at 2 mo</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>East Africa</td>
<td>6SH</td>
<td>154</td>
<td>51</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6SHR</td>
<td>148</td>
<td>31</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>Madras</td>
<td>2SHZ/5SHZ₂</td>
<td>129</td>
<td>28</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2SHRZ/5SHZ₂</td>
<td>261</td>
<td>8</td>
<td>2.3</td>
</tr>
<tr>
<td>3</td>
<td>Madras</td>
<td>3SHZ/2SHZ₂</td>
<td>236</td>
<td>26</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3SHRZ/2SHZ₂</td>
<td></td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3SHRZ</td>
<td></td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

The control: 2STH/16TH

Definition of abbreviations: \(z\) = twice-weekly dosage; H = isoniazid; Mos. = months; No. = number; Pos. = positive; R = rifampin; S = streptomycin; Z = pyrazinamide.

Mitchison DA, AJRCCM: 2005: Vol 171
Regimens shorter than 4 months have high relapse rates

No benefit of PZA after the second month

Fox W, IJTLDD 1999;3S231

Bacteriological bases of TB treatment

1. Drug Association
2. Prolonged treatment
Treatment of Tuberculosis

Standard Regimen

<table>
<thead>
<tr>
<th>Initial Phase</th>
<th>Continuation Phase*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td></td>
</tr>
<tr>
<td>Ethambutol**</td>
<td></td>
</tr>
</tbody>
</table>

*7 months for some patients

**Streptomycin may be substituted

Antituberculosis Drugs

**First-Line Drugs**
- Isoniazid
- Rifampin
- Pyrazinamide
- Ethambutol
- Rifabutin*
- Rifapentine

**Second-Line Drugs**
- Streptomycin
- Cycloserine
- p-Aminosalicylic acid
- Ethionamide
- Amikacin or kanamycin*
- Capreomycin
- Levofoxacin
- Moxifloxacin
- Gatifloxacin
- Bedaquiline
- Delamanid
Bacteriological Activity of TB Drugs

I. Actively dividing
II. Slowly dividing
III. Semi-dormant persisters
IV. Dormant

INH
Rifampin
Rifampin
EMB
PZA

Intra & Extracellular populations of M. Tuberculosis: source of failures and relapses

No. of bacilli

10^8 extracellular bacilli
10^7
10^6
10^5
10^4
10^2
intracellular bacilli

failure
relapse

6
12
Months

J. Grosset, 1977
Intra & Extracelular populations of M. Tuberculosis: activity of primary drugs

J. Grosset, 1977

Activity of the Different anti-tuberculosis Drugs

<table>
<thead>
<tr>
<th>Activity</th>
<th>Prevention of resistance</th>
<th>Bactericidal activity</th>
<th>Sterilising activity</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Rifampicin</td>
<td>Isoniazid</td>
<td>Rifampicin</td>
<td>PAS</td>
</tr>
<tr>
<td></td>
<td>Isoniazid</td>
<td>Rifampicin</td>
<td>Pyrazinamide</td>
<td>Ethionamide</td>
</tr>
<tr>
<td></td>
<td>Ethambutol</td>
<td></td>
<td>New FQs?</td>
<td>Cycloserine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Linezolid</td>
</tr>
<tr>
<td>Moderate</td>
<td>Injectables</td>
<td>Injectable FQs</td>
<td>Injectable FQs</td>
<td>Injectable</td>
</tr>
<tr>
<td></td>
<td>FQs</td>
<td>Ethionamide</td>
<td>Ethionamide</td>
<td>Pyrazinamide</td>
</tr>
<tr>
<td></td>
<td>Cycloserine</td>
<td>Linezolid?</td>
<td>Linezolid?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PAS</td>
<td>Ethambutol</td>
<td>Isoniazid</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rifampicin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pyrazinamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>Pyrazinamide</td>
<td>Ethionamide</td>
<td>Isoniazid</td>
<td>Ethambutol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pyrazinamide</td>
<td></td>
<td>Rifampicin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Isoniazid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FQs</td>
</tr>
</tbody>
</table>
Objectives of the Treatment of Tuberculosis

- Prevent the development of drug resistance with the use of combination of drugs
- Kill rapidly replicating *M. tuberculosis* bacilli to diminish the infectiousness of the patient
  - Bactericidal drugs in the IP
- Sterilize remaining tuberculosis lesions with the most sterilizing drugs
  - Prolonged treatment in the CP
- Prolongation of treatment to avoid relapses
ATS/CDC/IDSA guidelines

Evidence-Based Rating Scale USPHS/IDSA
- 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

ATS/CDC/IDSA guidelines

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
ATS/CDC/IDSA guidelines

Duration of treatment:
- **6 months**
  - Requires INH, rifampin throughout and PZA during the initiation phase
- **9 months**
  - If PZA was not used
  - Silico-TB
  - Prolongation to decrease risk of relapse

ATS/CDC/IDSA guidelines

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)

H Isoniazid; R rifampin; Z Pyrazinamide; E Ethambutol; HRZE / RIPE
ATS/CDC/IDSA guidelines

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)

H Isoniazid; R rifampin; Z Pyrazinamide; E Ethambutol; HRZE / RIPE

ATS/CDC/IDSA guidelines

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)

H Isoniazid; R rifampin; Z Pyrazinamide; E Ethambutol; HRZE / RIPE
ATS/CDC/IDSA guidelines

Treatment of Culture Positive Pulmonary Tuberculosis:
THRICE WEEKLY – REGIMEN
Regimens Rated B-I (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)

H Isoniazid; R rifampin; Z Pyrazinamide; E Ethambutol; HRZE / RIPE

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Risk factor for relapse
(n = 351, TBTC Study 22)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Univariate OR (95% CI)</th>
<th>Multiivariate OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hispanic white</td>
<td>3.3 (1.7, 6.1)</td>
<td>3.0 (1.4, 6.7)</td>
</tr>
<tr>
<td>Underweight</td>
<td>4.7 (2.6, 8.6)</td>
<td>3.7 (1.8, 7.2)</td>
</tr>
<tr>
<td>Pulmonary cavitation</td>
<td>5.0 (2.4, 10.7)</td>
<td>3.2 (1.4, 7.5)</td>
</tr>
<tr>
<td>Bilateral disease</td>
<td>2.9 (1.5-5.7)</td>
<td>1.8 (0.9, 4.0)</td>
</tr>
<tr>
<td>2-month culture positivity</td>
<td>4.7 (2.6-8.7)</td>
<td>2.4 (1.2, 4.9)</td>
</tr>
<tr>
<td>Beijing strain</td>
<td>2.1 (1.0, 4.3)</td>
<td>2.2 (1.0, 4.9)</td>
</tr>
</tbody>
</table>

Effect of cavitation, 2-month culture status on response to 6-month regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Overall recurrence</th>
<th>Cavitary +, 2-month +</th>
<th>Cavitary +, 2-month -</th>
<th>Cavitary -, 2-month +</th>
<th>Cavitary -, 2-month -</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily throughout (n = 1554)</td>
<td>1.9%</td>
<td>6.0%</td>
<td>2.2%</td>
<td>1.8%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Daily IP, twice-weekly CP (n = 506)</td>
<td>5.3%</td>
<td>15.6%</td>
<td>5.7%</td>
<td>5.4%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Thrice-weekly throughout (n = 1835)</td>
<td>3.2%</td>
<td>14.5%</td>
<td>5.3%</td>
<td>4.6%</td>
<td>1.7%</td>
</tr>
</tbody>
</table>


Effects of prolonging therapy
Treatment of Silico-Tuberculosis

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Number assessed</th>
<th>Relapse, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6SHRZ</td>
<td>45</td>
<td>9 (20%)</td>
</tr>
<tr>
<td>8SHRZ</td>
<td>44</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

Additional caveats:
- High proportions with default (13%) and changes in therapy due to side effects (23%)

Am Rev Respir Dis 1991; 143: 262-7
ATS/CDC/IDSA guidelines

<table>
<thead>
<tr>
<th>Clinical situation</th>
<th>Recommended therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cavitation + 2-month culture positivity</td>
<td>7 month continuation phase (9 months total)</td>
</tr>
<tr>
<td>Cavitation only</td>
<td>Consider prolonged therapy</td>
</tr>
<tr>
<td>2-month culture positivity only</td>
<td>Consider prolonged therapy</td>
</tr>
</tbody>
</table>

When considering prolonged therapy, evaluate for other risk factors (underweight, White race)

MMWR 2003 / 52(RR11);1-77

Dosing Frequency and Risk of Relapse

Systematic review of relapse of 6 month regimen and dosing schedule, controlling for initial cavitation and 2 month sputum culture

<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>

Duration and Intermittency of Rifampin on Outcomes

Methods:
- Systematic review and meta-analysis
- 57 trials, 312 ams and 21,472 participants

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

Menzies, PLoS Medicine, Sept 2009

Treatment of TB and Optimal Dosing Schedules

Methods:
- Systematic review of 32 articles
- 8 trials, 9 reviews, 9 PK-PD studies, 6 animal studies

Results (Non HIV related disease):
- Cavitary disease associated with failures & relapses
- Intermittent dosing specially in the IP reduces treatment efficacy

Treatment of TB and Optimal Dosing Schedules

Methods:

- Systematic review of 32 articles
- 8 trials, 9 reviews, 9 PK-PD studies, 6 animal studies

Results (HIV related disease - 3 studies):

- Intermittent dosing specially in the IP reduces treatment efficacy
- Higher risk of treatment failure, relapse and acquired rifampin resistance

Risk of TB relapse for DM patients with TB compared to non-DM patients with TB

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Population with DM Relapse/Total</th>
<th>Population without DM Relapse/Total</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wada, 2000</td>
<td>Japan (11%)</td>
<td>7/61 (11%)</td>
<td>4/284 (1%)</td>
<td>8.15 (2.46, 26.97)</td>
</tr>
<tr>
<td>Moussaia, 2003</td>
<td>Congo (68%)</td>
<td>6/17 (35%)</td>
<td>9/77 (12%)</td>
<td>3.02 (1.34, 7.35)</td>
</tr>
<tr>
<td>Singla, 2006</td>
<td>Saudi Arabia (2%)</td>
<td>2/130 (1%)</td>
<td>3/367 (1%)</td>
<td>1.88 (0.32, 11.14)</td>
</tr>
<tr>
<td>Maalej, 2009</td>
<td>Tunisia (7%)</td>
<td>4/55 (7%)</td>
<td>1/82 (1%)</td>
<td>5.96 (0.68, 51.95)</td>
</tr>
<tr>
<td>Zhang, 2009</td>
<td>China (20%)</td>
<td>33/165 (20%)</td>
<td>9/170 (5%)</td>
<td>3.78 (1.87, 7.65)</td>
</tr>
<tr>
<td>Summary</td>
<td></td>
<td></td>
<td></td>
<td>3.89 (2.43, 6.23)</td>
</tr>
</tbody>
</table>

Heterogeneity: I-squared = 0%

*Weights are from random effects analysis*

Bark, BMC Medicine 2011; 9:81

Pharmacokinetics of Rifampin in Peruvian Tuberculosis Patients with and without Comorbid Diabetes or HIV

- 67% slow absorption
- Serum drug level for RIF was low 1,6 mg/L a 3,2mg/L.
- Only 10-16% of patients had adequate Cmax.
Summary of patient related factors associated with failure/ relapse

- Suboptimal adherence
- Extent of pulmonary disease, esp. cavitation
- Pulmonary silicosis
- Baseline mycobacterial burden
- Low body-mass index
- HIV infection (immunodeficiency)
- Low drug levels
- Diabetes

WHO Treatment of TB Guidelines 2010

**Strong / High grade evidence:**

- Optimal dosing frequency for PTB daily throughout treatment
- Recommended against BIW dosing

**Conditional/High & moderate grade evidence:**

- Daily intensive phase followed by TIW in continuation phase
- Three times weekly dosing throughout – by DOT only in non HIV patients
Management considerations:

- Prolongation of treatment in delayed responders
- Increase frequency of dosing at least three times a week
- Evaluation and management of delayed response
- Serum drug level monitoring

Treatment in Special Situations
Treatment Failure

- Defined as positive cultures after 4 months of treatment in patients for whom medication ingestion was ensured
- Single new drug should never be added to a failing regimen; it may lead to acquired resistance to the added drug
- Add at least three new drugs (e.g., fluoroquinolone, ethionamide, and an injectable drug: SM, amikacin, kanamycin, or capreomycin) to the existing regimen because of the possibility of drug resistance

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

- **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)

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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
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
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

Treatment of Tuberculosis

Outcome of Pulmonary Tuberculosis

- 50% No Chemotherapy
- 32% Poor Chemotherapy
- 18% Sputum positive
- 64% Poor Chemotherapy
- 20% Sputum positive
- 98% Good Chemotherapy
- 1.2% Dead
- 0.8% Sputum negative

Gryzbowski S. BIUAT1978
Dynamics of pulmonary TB in Peru 1980-2000

DOTS 1990

PTB falling at 6%/yr

Pulmonary TB cases/100,000


100 120 140 160 180 200 220

case finding
Association between treatment supervision and outcomes (San Francisco)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>DOT (n = 149)</th>
<th>SAT (n = 223)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cure</td>
<td>134 (98%)</td>
<td>171 (89%)</td>
<td>&lt; 0.002</td>
</tr>
<tr>
<td>Failure, relapse, or death</td>
<td>1 (1%)</td>
<td>19 (9%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>1 (1%)</td>
<td>4 (2%)</td>
<td>0.39</td>
</tr>
<tr>
<td>Relapse</td>
<td>0</td>
<td>3 (2%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Death due to TB</td>
<td>0</td>
<td>12 (6%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Acquired drug resistance</td>
<td>0</td>
<td>2 (1%)</td>
<td>0.52</td>
</tr>
</tbody>
</table>


Strategies to promote good outcome

- 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
- Patient centered care
Patient-centered care

- If we are to improve TB treatment completion rates we need patient-centered care management strategy to maximize the likelihood of completion of therapy
- Each patient’s management plan should be individualized to incorporate measures that facilitate adherence to treatment
  - social service support,
  - treatment incentives and enablers,
  - housing assistance
  - referral for treatment of substance abuse,
  - comanagement of comorbidities with other providers

Drug-resistant TB

- When to suspect DR
- Rapid confirmation of drug resistant TB
- Management strategy for the drug resistant patient
- Specific treatment regimens for the drug resistant patient
- Expert consultation
Individuals at Increased Risk for Drug Resistance

- History of treatment with TB drugs
- Contacts of persons with drug-resistant TB
- Smears or cultures remain positive despite 2 months of TB treatment
- Received inadequate treatment regimens for >2 weeks

Individuals at Increased Risk for Drug Resistance

- Lack of adherence/intermittent or interrupted therapy
- Malabsorption
- Inappropriate regimens
- Sub-therapeutic dosing
- Expired or substandard drugs
Example of Management Errors Resulting in Acquired Drug Resistance

- 35 MDR TB cases referred to US TB specialty hospital
- Average 3.9 errors per patient
  - Inadequate primary regimen
  - Addition of single drug to failing regimen
  - Failure to address non-adherence
- Isoniazid alone to treat active TB misdiagnosed as LTBI

Mahmoudi A, Iseman MD. JAMA 1993;270:65-68

Drug-Resistant TB Definitions

<table>
<thead>
<tr>
<th>Primary Resistance</th>
<th>Caused by person-to-person transmission of drug-resistant organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary Resistance</td>
<td>Develops during TB treatment:</td>
</tr>
<tr>
<td></td>
<td>• Patient was not given appropriate treatment regimen OR</td>
</tr>
<tr>
<td></td>
<td>• Patient did not follow treatment regimen as prescribed</td>
</tr>
</tbody>
</table>
Drug-Resistant TB Definitions

<table>
<thead>
<tr>
<th>Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mono-resistant</td>
<td>Resistant to any one TB treatment drug</td>
</tr>
<tr>
<td>Poly-resistant</td>
<td>Resistant to at least any 2 TB drugs (but not both isoniazid and rifampin)</td>
</tr>
<tr>
<td>Multidrug resistant (MDR TB)</td>
<td>Resistant to at least isoniazid and rifampin, the 2 best first-line TB treatment drugs</td>
</tr>
<tr>
<td>Extensively drug resistant (XDR TB)</td>
<td>Resistant to isoniazid and rifampin, PLUS resistant to any fluoroquinolone AND at least 1 of the 3 injectable second-line drugs (e.g., amikacin, kanamycin, or capreomycin)</td>
</tr>
</tbody>
</table>

Molecular Drug Resistant Testing

- Useful for testing isolates and respiratory specimens directly
- The sensitivity and specificity of molecular DR tests for RIF are sufficiently high (97%) to use for management decisions
- Molecular DR testing is not sufficient to exclude INH resistance based on a negative test
- Molecular DR testing do not replace culture or standard susceptibility testing
- Earlier detection of DR TB cases should lead to earlier testing for susceptibility to other first and second line anti-TB drugs
- Failure of molecular DR test can be caused by inhibitors
**GeneXpert MTB/RIF Test**

1. Sputum liquefaction and extraction with ZI sample reagent
2. Sample automatically filtered and washed
3. Transfer of 2 ml of material into test cartridge
4. Cartridge inserted into 970 MTB test platform
5. Ultrasensitive amplification of DNA
6. DNA is melted with dry PCR reagents
7. Sensitized real-time amplification and detection is integrated

Time to result, 1 hour 45 minutes

---

**GeneXpert MTB/RIF Performance Characteristics**

<table>
<thead>
<tr>
<th>No. Sputums Tested</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Sputum Samples</td>
<td></td>
</tr>
<tr>
<td>Sensitivity, all</td>
<td>97.4%</td>
</tr>
<tr>
<td>Smear-positive</td>
<td>99.8%</td>
</tr>
<tr>
<td>Smear-negative</td>
<td>90.2%</td>
</tr>
<tr>
<td>1 Sputum Sample</td>
<td></td>
</tr>
<tr>
<td>Sensitivity, all</td>
<td>92.2%</td>
</tr>
<tr>
<td>Smear-positive</td>
<td>98.2%</td>
</tr>
<tr>
<td>Smear-negative</td>
<td>72.5%</td>
</tr>
</tbody>
</table>

- Sensitivity HIV+ → 93.9%
- Sensitivity HIV- → 98.4%

Specificity 98.1 – 99.2%
Sensitivity for RIF-resistance 99.1%

Early identification and prompt treatment of DR-TB

- Prevents the spread of disease
- Helps stop amplification of further resistance
- Results in higher cure rates
- Reduces morbidity and mortality

Management of Drug-Resistant TB

- Patient-centered measures, including observation of treatment, are required to ensure adherence
- Expert consultation should be obtained with a provider experienced in treatment of patients with DR, or MDR/XDR tuberculosis
Antituberculosis Drugs

**First-Line Drugs**
- Isoniazid
- Rifampin
- Pyrazinamide
- Ethambutol
- Rifabutin*
- Rifapentine

**Second-Line Drugs**
- Streptomycin
- Cycloserine
- p-Aminosalicylic acid
- Ethionamide
- Amikacin or kanamycin*
- Capreomycin
- Levofoxacin
- Moxifloxacin
- Gatifloxacin
- Bedaquiline
- Delamanid

Activity of the Different antituberculosis Drugs

<table>
<thead>
<tr>
<th>Activity</th>
<th>Prevention of resistance</th>
<th>Bactericidal activity</th>
<th>Sterilising activity</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Rifampicin Isoniazid Ethambutol</td>
<td>Isoniazid Rifampicin</td>
<td>Rifampicin Pyrazinamide New FQs?</td>
<td>PAS Ethionamid Cycloserine Linezolid</td>
</tr>
<tr>
<td>Moderate</td>
<td>Injectables FQs Ethionamide Cycloserine PAS Linezolid?</td>
<td>Injectables FQs Linezolid?</td>
<td>FQs Injectables Isoniazid Linezolid?</td>
<td>Injectables Pyrazinamide</td>
</tr>
<tr>
<td>Low</td>
<td>Pyrazinamide Ethionamide Pyrazinamide</td>
<td></td>
<td>Isoniazid Ethambutol Rifampicin Isoniazid FQs</td>
<td></td>
</tr>
</tbody>
</table>

6/18/2015
Categories of Anti-tuberculosis Drugs

- **Group 1 – First-line drugs:** Isoniazid, rifampicin, ethambutol, pyrazinamide
- **Group 2 - Injectable agents:** Kanamycin, amikacin, capreomycin, streptomycin
- **Group 3 - Fluoroquinolones:** Levofloxacin, moxifloxacin, ofloxacin
- **Group 4 - Oral bacteriostatic agents:** Ethionamide, cycloserine, para-aminosalicylic acid (PAS), prothionamide, terizadone
- **Group 5 – Unclear role:** Clofazamine, linezolid, Bedaquiline, Delamanid, amoxicillin/clavulanate, Imipenem/cilastatin, thioacetazone, high-dose isoniazid, clarithromycin,

*Adapted from WHO Guidelines 2011 Update; Caminero JA. Lancet Inf Dis 2010; 10; 621-629*

Designing an MDR/XDR Treatment Regimen

**General Principles:**

- Use of at least four drugs highly likely to be effective
- Do not use drugs for which there is cross-resistance
- Eliminate drugs that are unsafe for the patient
- Include drugs from groups 1-5 in a hierarchical order based on potency
- Be prepared to prevent, monitor and manage adverse effects from the drugs selected

*WHO Guidelines Management of Drug-Resistant TB, Update 2011*
Additional Important Principles

- Use direct observation of treatment (DOT) with a patient-centered approach to care
- Use daily, not intermittent, administration
- Treatment duration of a minimum of 18-24 months after culture conversion
- When possible, continue injectable for minimum six months (at least 4 months post-culture conversion)
- Continue at least three oral drugs for full treatment duration

Cross-Resistance

- All rifamycins: high level cross-resistance
- Fluoroquinolones: variable, but probably should be assumed to be cross-resistant
- Amikacin and kanamycin: generally highly cross-resistant, but both should be tested
- Capreomycin and aminoglycosides: occasional cross-resistance, susceptibilities should be tested

Treatment Regimens for the management of mono- resistant and poly- resistant TB


Treatment Regimens for MDR-TB

<table>
<thead>
<tr>
<th>Resistance Pattern</th>
<th>Empiric Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH, RIF</td>
<td>Fluoroquinolone, PZA, EMB, Injectable</td>
</tr>
<tr>
<td>INH, RIF, EMB</td>
<td>Fluoroquinolone, PZA, Injectable, CS, + PAS or ETH</td>
</tr>
<tr>
<td>INH, RIF, PZA</td>
<td>Fluoroquinolone, EMB, Injectable, CS, + PAS or ETH</td>
</tr>
<tr>
<td>INH, RIF, PZA, EMB</td>
<td>Fluoroquinolone, Injectable, CS, PAS or ETH, + one more drug</td>
</tr>
</tbody>
</table>

INH = Isoniazid, RIF = Rifampicin, EMB = Ethambutol, PZA = Pyrazinamide, CS = Cycloserine, PAS = P-aminosalicylic acid, ETH = Ethionamide

Successful ‘9-month Bangladesh regimen’ for multidrug-resistant tuberculosis among over 500 consecutive patients


- Bangladesh regimen: (4 Kn-Pth-H-Gx-Cfz-E-Z / 5 Gx-Cfz-E-Z)
- The 4-month intensive phase was extended until sputum smear conversion
- Of the 515 patients (enrolled from 2005 to 2011) → 84.4% had a bacteriologically favorable outcome.
- Only half of the patients completed treatment within 9 months → however, 95% complete treatment within 12 months.
- Eleven patients failed or relapsed, and 93.1% of the 435 patients who were successfully treated completed at least 12 months follow-up.

Summary

- Patients with cavitation and 2-month culture-positivity have relapses > 5% with 6-month regimens
- Details of short-course therapy not adequately evaluated, especially in high-risk patients
- New guidelines from CDC for drug susceptible disease will probably reflect more recent WHO guidelines
- BIW dosing in the IP and CP should be avoided, specially in patients at risk for relapse
- We are at the cusp of a new management strategy for the treatment of drug resistant disease
Resources

- American Thoracic Society: www.thoracic.org
- Core Curriculum on Tuberculosis: what the clinician should know, 6th edition 2013