Treatment of Tuberculosis Disease

Germaine Jacquette, MD
Physician Specialist
NJMS Global Tuberculosis Institute
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Treatment of Tuberculosis
Some Highlights of Most Recent Update

• The provider has primary responsibility

• Recommendations ranked by supporting evidence and strength

• Extend treatment for those with cavitation on cx-ray and (+) sputum cultures at 2 months

• Treatment completion defined by # of doses ingested as well as duration of therapy

• Guidelines for extrapulmonary disease
  (E-P TB increasing with shift to majority non-US-born cases)

*MMWR 2003; 52(No. RR-11):1-80*
Decision to Treat
Initiation of Therapy – 1

• Treatment generally precedes definitive TB diagnosis (TB suspect)

• Treatment decision based on:
  – Epidemiologic information
  – Clinical, pathological, radiographic findings
  – Results of microscopy, culture

• Overcome unnecessary delays:
  – Improved clinical acumen in diagnosis
  – Rapid diagnostic tests – nucleic acid amplification (NAA)
  – Early empiric therapy

Archives of Internal Medicine 1994;154: 306-310
• Do **not** delay treatment waiting for smear and culture results in ill patients

• Absence of AFB on smear or granulomas on biopsy does **not** rule out TB, nor does negative TB culture (20% are culture-neg cases)

• TST is negative in 25% of active cases; IGRA test may **also** be false-negative
Case Example – 1

• 6/22/10 - 52 yo Indian male presents to ED
  US x 2 yrs
  Alcoholic

  c/o shortness of breath, cough x 3 weeks, 2 episodes of hemoptysis
  Fever, chills, night sweats
  Anorexia, wt. loss 15 lbs.

• 6/22/10 - Chest x-ray: RUL cavitary infiltrate c/w TB
Case Example – 2
Case Example – 3

- 6/24, 25, 26  Sputum AFB smear (-)
- 6/24  ↑WBC, 16% M; ESR 61 mm/hr
- 6/25  TST (+) 17 mm
- 6/28  IGRA (-)
- 6/30  Bronchoscopy AFB smear (+)  
        PCR (+)
### Estimated TB Burden

<table>
<thead>
<tr>
<th>Global figures</th>
<th>Global estimates</th>
<th>US rank – Country of origin</th>
<th># of new cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>2,000,000</td>
<td>1. Mexico</td>
<td>1,539</td>
</tr>
<tr>
<td>Philippines</td>
<td>260,000</td>
<td>2. Philippines</td>
<td>738</td>
</tr>
<tr>
<td>Vietnam</td>
<td>180,000</td>
<td>3. India</td>
<td>877</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Vietnam</td>
<td>518</td>
</tr>
</tbody>
</table>

WHO. *Global Tuberculosis Control*. WHO Report. 2010

CDC. *Trends in Tuberculosis --- United States, 2010*. MMWR 60 (11) 333-337
## Antituberculosis Agents

<table>
<thead>
<tr>
<th>First-Line Drugs</th>
<th>Second-Line Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (INH)</td>
<td>Streptomycin (SM)</td>
</tr>
<tr>
<td>Rifampin (RIF)</td>
<td>Cycloserine (CS)</td>
</tr>
<tr>
<td>Pyrazinamide PZA</td>
<td>p-Aminosalicylic acid (PAS)</td>
</tr>
<tr>
<td>Ethambutol (EMB)</td>
<td>Ethionamide (ETA)</td>
</tr>
<tr>
<td>Rifabutin* (RBT)</td>
<td>Amikacin, kanamycin*(AK,KM)</td>
</tr>
<tr>
<td>Rifapentine (RPT)</td>
<td>Capreomycin (CM)</td>
</tr>
<tr>
<td></td>
<td>Levofloxacinc* (LFX)</td>
</tr>
<tr>
<td></td>
<td>Moxifloxacinc* (MOX)</td>
</tr>
</tbody>
</table>

* Not approved by the U.S. Food and Drug Administration for use in the treatment of TB.
Ratings – Guides to almost everything in the modern world

• Electronics (energy saver)
• Films (PG, PG-13, R)
• Animal friendly ("No Animals Were Harmed”®)
• ~1994: Infectious Disease/USPHS guidelines using ratings to help guide choices of therapies
Rating System – TB Regimens
Part 1 (of 2)

Strength of the recommendation

A. Preferred, should generally be offered
B. Alternative; acceptable to offer
C. Offer when preferred or alternative cannot be offered
D. Should generally not be offered
E. Should never be offered
Quality of supporting evidence

I. At least one properly randomized trial with clinical end points

II. Clinical trials that were either not randomized or were conducted in other populations

III. Expert opinion
Initial Regimens: Principles

- 4 currently recommended; similar outline
  - Initial phase of 2 months
  - Continuation phase of 4 or 7 months

- 9 months total for
  - Pulmonary cases with cavitation and culture (+) at 2 months (continuation phase, 7 mos.)
  - Persons unable to take PZA in initial phase

- Caveats for HIV-infected persons
  - RPT-containing regimens not advised
  - Thrice weekly RIF/RBT-containing regimens for patients with <100 CD4+ cells (not 2x/wk)
Anticipate Drug-Drug Interactions

• Rifabutin/Rifampin considerations
  – Patients on drugs with potential for reduced activity
    • Patients on high dose methadone (withdrawal)
    • Corticosteroids, oral contraceptives, beta-blockers
  – Dosage of Rifabutin (300 mg) = Rifampin 600 mg
    • RBT may cause less gastritis, hepatotoxicity

• INH/RIF interactions with psychiatric drugs
  – Valproic acid (Depakoate®), oxcarbazepine (Trileptal®)
Case Example: Rifamycin – steroid interaction – 1

- 50 yo Haitian female identified as a contact of case (spouse) with pan-sensitive TB
- h/o diagnosis of vasculitic renal disease, with renal failure 2009: treated with methylphenalate (Cell-Cept®) and Prednisone; currently on steroid taper
- (+) TST, abnormal chest x-ray
- Asymptomatic
Case Example: Rifamycin – steroid interaction – 2

- RIPE begun; observe for steroid withdrawal
- Rifampin changed to Rifabutin to decrease interaction with steroid
- 10 days later, severe headache, nausea, muscle aches, dizziness
- LFTs normal
- RBT d/c: symptoms resolved
Initial Regimen: 4 drugs

• RIF, INH, PZA, EMB ("RIPE") standard regimen

• PZA omitted in most pregnant females in USA, in persons with gout, severe liver disease (some experts advise caution with elderly)

• Combination of drugs needed over sufficient time
  – To kill the TB bacilli rapidly (INH>EMB>RIF)
  – To prevent the emergence of drug resistance
  – To eliminate persistent bacilli to prevent relapse or failure
Routine Examinations at Start of Treatment

• Weight (doses calculated on mg/kg basis)
  – Rifampin 450 mg for weight < 50 kg (110 lbs.)

• HIV testing

• Baseline lab tests, at a minimum:
  – Liver function tests (AST, ALT, alk phos and bilirubin)
  – Creatinine
  – Platelets
Regimens for Culture (+) TB

(refer to table in handout)
Adjunctive Therapy – 1
Corticosteroids

• Used for suppression of inflammatory phenomena
  – When negative effects of inflammation operative, such as fluid expansion into closed space
  – May involve hypersensitivity to tuberculoprotein

• “...it is the final judgment of treating physician to decide indications, duration and dosages”\(^1\) .... (of corticosteroids)

Monitoring during TB Treatment

Monthly visits should include a brief physical exam and a review for:

- Adherence
- Adverse drug reactions
- Use of alcohol and other potential hepatotoxins
- Follow up testing (sputum, LFTs, renal function, platelet count, visual acuity/color, x-rays)
- Drug susceptibility testing if culture (+) 3-4 months
DOT Impact on Completion Rates

- Non-supervised therapy (n=9) 61%
- Modified DOT (n=2) 79%
- DOT (n=4) 86%
- Enhanced DOT (n=12) 91%

DOT = Directly Observed Therapy
Modified DOT = DOT given only for a portion of the treatment period, often while the patient was hospitalized
Enhanced DOT = Individualized incentives & enablers were provided in addition to DOT

JAMA 1998;279:943-948
DOT: 7 days vs. 5 days per week?

(see demonstration)
Special Treatment Situations

• Special issues in E-P disease
• Paradoxical reaction (IRIS)
• Pregnancy
• Renal and hepatic disease
• Diabetes
• TNF-alpha inhibitors

(Other lectures to follow on drug toxicities, adherence, children, HIV, MDR-TB)
Extrapulmonary (EP) TB

- Of 11,545 cases (US, 2009)
  - 69 % pulmonary only
  - 21 % EP only
  - 9 % pulmonary & EP

<table>
<thead>
<tr>
<th>Site of disease</th>
<th>% cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphatic</td>
<td>45%</td>
</tr>
<tr>
<td>Pleural</td>
<td>19%</td>
</tr>
<tr>
<td>Bone &amp; Joint</td>
<td>10%</td>
</tr>
<tr>
<td>Peritoneal</td>
<td>6%</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>6%</td>
</tr>
<tr>
<td>Meningeal</td>
<td>6%</td>
</tr>
<tr>
<td>Other</td>
<td>8%</td>
</tr>
</tbody>
</table>

Management of Extrapulmonary TB cases

• Consult textbooks, guidelines, and experts\(^1\)

• Do thorough literature review

• Interventions may be life-saving, especially in
  – Central nervous system TB
  – Pericardial TB
  – Miliary TB, septic form

\(^1\)Regional Training and Medical Consultation Centers (RTMCCs); National Jewish Medical Research Center; State medical consultants, other experts
Central Nervous System TB: TB Meningitis – 1
• Need CSF penetrating agents
  – Good: INH, PZA
  – Less good: RIF, EMB
  – Consider available parenteral forms

• Follow up imaging; prefer MRI (more sensitive)
  – Ventricular enlargement may require shunting
  – Watch for development of tuberculomas on Rx
• Adjunctive steroids
  – Limitations of studies (no large randomized controlled studies containing RIF); expert opinion
    – Dexamethasone 12 mg/day x 3 weeks, followed by taper over 3 weeks
  – Rifampin/steroid drug-drug interactions
TB Meningitis – 4
Ventricular Shunting for Hydrocephalus
CNS Tuberculoma
Central Nervous System TB: Tuberculoma

• Additional barrier for drugs to penetrate

• Maximize drug and steroid therapy

• Decisions:
  – Surgical option?
  – Length of therapy?
Lymphatic TB

- Mass effect may be great if multiple nodes
- Excisional biopsy preferable
- Nodes often increase in size (IRIS) while on therapy, while biopsies culture-negative (not a failure)
- Longer treatment sometimes necessary
  - Subset of patients with complicated courses
  - Evidence of LN response lagging TB at other sites
Paradoxical Reaction – 1

• Temporary exacerbation of symptoms, signs, or radiographic manifestations of TB after beginning anti-TB treatment
  – High fevers
  – Esp. increase in size of lymph nodes/new lymph nodes
  – Worsening of infiltrates or pleural effusions
  – Expanding central nervous system lesions

• Can occur in apparently immunocompetent persons, but more common among HIV-infected on highly active anti-retroviral therapy (HAART)
Paradoxical Reaction – 2
Enlargement of TB Lymph Nodes
Paradoxical Reaction – 3
Treatment

• Evaluate if other cause or Rx failure

• Mild – moderate:
  – No change in anti-TB therapy
  – Symptomatic treatment: non-steroidal anti-inflammatory drugs (NSAIDs)

• Severe
  – May include airway compromise, sepsis syndrome
  – Prednisone 1 mg/kg, with taper after few weeks
Bone & Joint TB

- Increasing in frequency: ~ 3-4% of all TB cases
- Serious forms affect mobility
- Vertebral most common
  - Lumbar > thoracic; cervical rare; difficult to diagnose
  - Paraspinal abscesses common (Pott’s disease)
  - Immediate and ongoing evaluation for neurologic deficits
Vertebral TB with Paraspinal Abscess
**Extrapulmonary TB**

**Other examples**

<table>
<thead>
<tr>
<th>Location</th>
<th>Management and Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pericardial</td>
<td>Corticosteroids indicated; monitoring, ECHO to r/o constriction; may require pericardiectomy</td>
</tr>
<tr>
<td>Peritoneal</td>
<td>May get false (+) CA-125: repeat test on or after TB Rx; steroid role unclear;</td>
</tr>
<tr>
<td>Pleural</td>
<td>Collect sputum even when no parenchymal infiltrate; yield high</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Urology consult; image entire GU tract during Rx; monitor bladder symptoms</td>
</tr>
<tr>
<td>(male)</td>
<td></td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Major cause of infertility in women from high prevalence countries; do bx</td>
</tr>
<tr>
<td>(female)</td>
<td></td>
</tr>
</tbody>
</table>
Liver disease and TB – 1

- Alcoholism most frequent underlying cause; chronic Hepatitis B or C; autoimmune

- Consider liver-sparing agents: EMB, FQN\(^1\), injectables, cycloserine (therapy duration extended)

\(^1\) occasionally hepatotoxic
Liver Disease and TB – 2

- Tolerate enzyme elevations to 5x upper limit of normal (ULN) if no GI symptoms
- Alcohol program often needed post hospital discharge
- Question arises for DOT worker of whether to give doses of TB meds if patient acutely intoxicated?
TB in Pregnancy

• Treatment for TB is compatible with pregnancy

• If TB suspected pre-natally
  – Expedite mother’s diagnosis
  – Immediate treatment if active disease
  – Make preparations for examination of placenta after delivery for: pathology, AFB stains/cultures
  – Alert pediatrician to consider possible transplacental spread to infant

• Watch for post-partum hepatotoxicity
Diabetes and TB – 1

- Diabetes control more difficult with active TB, may improve as TB treated
- Low Rifampin in Type 2 diabetics; consider levels\(^1\)
- Use insulin if necessary\(^2\)
- Do not use Pioglitazone (Actos\(^{®}\)) if ALT >2.5x nl\(^3\)

\(^1\) Clin Inf Dis. 2006; 43:848-854

\(^2\) Tuberculosis and Diabetes. Frances J. Curry National Tuberculosis Center. Webinar, Dec 10, 2009. (internet access next slide)

\(^3\) City Health Information. NYCDOHMH, May/June 2010, p. 21 (access via nyc.gov, DOHMH, diabetes)
Diabetes and TB – 2

• Summary of recent data in diabetics with TB\textsuperscript{1}:
  – delayed sputum conversion
  – higher incidence of relapse
  – greater mortality rate

• Consider extending treatment to 9 months

Renal Disease

• Adjustment for creatinine clearance < 30 ml/min
  – ↑dosing interval of renally excreted drugs (or those with renally-excreted metabolites) rather than dosage
  – No adjustment for INH & RIF
  – Lengthen interval for EMB & PZA (generally TIW)
  – If on dialysis, dose at completion of session

• Anti-rejection agent/rifampin interactions in renal transplant patients;
  – Cyclosporine (do levels); tacrolimus
  – Prefer rifabutin for less drug-drug interaction
Creatinine Clearance ($\text{Cl}_{\text{cr}}$) Formula

$$\frac{(140 - \text{age}) \times \text{weight in kg}}{\text{serum creatinine} \times 72}$$

Note: for females, multiply result by 0.85
TB in Patients on TNF-a Antagonists

• Infliximab (Remicade®), Etanercept (Enbrel®), Adalimumab (Humira®), etc. used in rheumatoid arthritis, Crohn’s disease, psoriasis, other conditions

• Inhibit or reverse granuloma formation
  – Resultant TB often fulminant, disseminated
  – Early empiric therapy may be life-saving

• Collaborate with rheumatologist on management
  – Choice of alternate therapies
  – Re-introduction of TNF-a inhibitor?
Rationale for Extending Continuation Phase:

Relapse Rates – 6 months Rx

Cavitary disease AND culture (+) at 2 mos
- 22% relapse

Non-cavitary disease, culture (-) at 2 months
- 2% relapse

Note

5-6% relapse if either present
Algorithm to Guide Treatment of Culture-Negative TB

At-risk patient with +/-
- Abnormal chest x-ray
- Clinical symptoms
- No other diagnosis
- Positive TST or IGRA

Patient placed on initial phase regimen: INH, RIF, EMB, PZA for 2 mos.

Is the initial culture Positive?

- Yes
  - Continue treatment for culture-positive TB

- No
  - Was there symptomatic or CXR improvement after 2 mos. of treatment?
    - No
      - Discontinue treatment
      - Patient presumed to have LTBI
      - Treatment completed
    - Yes
      - Give continuation-phase treatment of INH/RIF daily or 2X weekly for 2 mos.
Therapy Deviations

- Avoid split dosing of first-line agents

- Analyze treatment interruptions
  - Timing in course
  - Duration of interruption
  - Bacillary load at time of interruption (smear status)
Therapy Deviations

• Modify for drug toxicities
  – Follow regimens for drug-resistance\textsuperscript{1}
  – May affect duration of therapy
  – Examples:
    • Loss of INH: 6-9 months; consider addition of FQN
    • Loss of RIF: add FQN; 12-18 months; consider injectable if extensive disease

\textsuperscript{1}Francis J. Curry National Tuberculosis Center. \textit{Drug Resistant Tuberculosis: A Survival Guide for Clinicians}. 2\textsuperscript{nd} ed. 2008, p.34.
Completion of Therapy Defined – 1

- Completion of treatment primarily defined by number of ingested doses within specified time frame (not solely on duration of therapy)

- For example:
  1. 6-month daily regimen (7 days/wk) = at least 182 doses of INH and RIF, and 56 doses of PZA
  2. 6-month daily regimen (5 days/wk) = at least 130 doses
• In cases of drug toxicity or non-adherence to regimen, all specified number of doses must be administered within:
  – 3 months for initial phase
  – 6 months for 4-month continuation phase

• If the specified number of doses are not administered within the targeted time period, patient is considered to have interrupted therapy
Continuation Phase
Treatment Interruptions

• If patient has received ≥80% of total doses:
  – Consider bacillary load at time of interruption to decide if additional treatment needed (smear + or smear - ?)

• If patient has received <80% of total doses:
  – Consider duration of lapse and ability to complete full four months of Rx within 6 months time
Rx Interruption Example – 1

12/20 19 yo dx TB meningitis in California

1/02 Discharged with 7d supply RIPE & steroids

1/07 No show clinic appointment

1/16 Adm. to NJ hospital, altered mental status

Q – Continue treating? Restart?
Rx Interruption Example – 2

• Time of interruption: initial phase (first 2 mos)

• Duration of interruption: (~8 days? - ~15 days?)

• Guidelines:
  – If lapse >14 days, restart from beginning
  – If lapse <14 days, continue treatment to complete total doses warranted (if it can be completed within 3 months)

• In this case, consequence of interruption can be serious; restart treatment
Relapse & Treatment Failure

- Relapse is defined as clinical deterioration or reversion to positive culture after treatment completion.

- Treatment failure is defined as positive cultures after 4 months of treatment in patients for whom medication ingestion was ensured (by DOT).
Role for Vitamin D?

• Background:
  – Vitamin D used to treat TB in pre-antibiotic era
  – Studies in humans showed enhanced macrophage microbicidal activity in vitro\(^1\)

• Contacts, Pakistan (n=128)
  – low vitamin D levels associated with 5-fold risk to TB progression\(^2\)

• Vitamin D supplementation during treatment controversial
  – Studies with conflicting results

\(^2\) Vitamin D deficiency and Tuberculosis Progression. Emerging Infectious Diseases. 2010; 16.
Reminder: treat a patient with TB, not just the disease