Treatment of Tuberculosis

ATS/CDC/IDSA Joint Statement
2003

Outline
2015

• Principles of treatment of tuberculosis
• Recommended treatment regimens
• Case management and monitoring
• Special circumstances

Fundamental Responsibility and Approach

• The *provider* (or *program*) is responsible for prescribing an appropriate regimen AND ensuring that treatment is completed successfully

• *Direct observation of treatment* (DOT) with individualized *case-management* is the approach of choice

Treatment of Tuberculosis

• Emphasis on *provider/program responsibility*
• Focus on individual case management with DOT
• Tailoring treatment regimens to circumstances
• Importance of evaluating response
• Monitoring for adverse events
• Increasingly complicated patients

Effects of Anti-tuberculosis Chemotherapy

• Rapid killing of tubercle bacilli
• Minimize potential for organisms to develop drug resistance: Combination chemotherapy
• Sterilize host tissues: Sufficient length of treatment
• Result: Patient is cured with very small likelihood of relapse
Initiation of Therapy

- Often is based on high index of suspicion
  - Do not delay treatment waiting for smear and culture results, especially in ill patients
  - Absence of AFB on smear or granulomas on biopsy does not rule out tuberculosis, nor does negative TB culture
  - A positive TST is only supportive, may be negative in 25% of cases

Drugs in Current Use

<table>
<thead>
<tr>
<th>First-line</th>
<th>Second-line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (INH)</td>
<td>Cycloserine</td>
</tr>
<tr>
<td>Ethambutol (EMB)</td>
<td>Levofloxacin*</td>
</tr>
<tr>
<td>Rifampin (RIF)</td>
<td>Ethionamide</td>
</tr>
<tr>
<td>Rifabutin* (RBT)</td>
<td>Moxifloxacin*</td>
</tr>
<tr>
<td>Rifapentine (RPT)</td>
<td>p-Aminosalicylic acid (PAS)</td>
</tr>
<tr>
<td>Pyrazinamide (PZA)</td>
<td>Gatifloxacin*</td>
</tr>
<tr>
<td>Rifampin (RIF)</td>
<td>Amikacin/Kanamycin*</td>
</tr>
<tr>
<td>Rifabutin* (RBT)</td>
<td>Capreomycin</td>
</tr>
<tr>
<td>Rifapentine (RPT)</td>
<td>Streptomycin (SM)</td>
</tr>
</tbody>
</table>

*Not approved by FDA for use in tuberculosis

Roles of “Newer” Agents

- **Rifabutin**: May be used as a primary drug for patients receiving medications having unacceptable interactions with rifampin, especially for patients with HIV infection

- **Rifapentine**: May be used as a primary drug by DOT in a twice-weekly initial phase (FDA 2010) and once-weekly continuation phase for highly-selected (HIV-neg) patients; prevention (FDA 2015)

- **Levofloxacin, Moxifloxacin (Gatifloxacin – not in US)**: Oral agents that can be used when first line drugs are not tolerated or the organism is resistant

Bedaquiline (TMC 207)

- Accelerated FDA approval, November 2012
  - 2 studies involving a total of 440 patients with MDR-TB: time to culture conversion
  - Safety concerns

  - Unique mechanism
    - ATP synthase proton pump inhibitor

  - Indication
    - as part of combination therapy for the treatment of MDR pulmonary TB in adults

  - Phase 3 trial planned for 2013
    - double-blind study: 9 months bedaquiline versus placebo, with background regimen

  Sirtrino’ Janssen Therapeutics

Treatment of Culture-positive Pulmonary Tuberculosis

**General Conclusions from the Literature**

- 6 months (26 wks) is the minimum duration of treatment
- 6 month regimens require a rifamycin throughout and PZA for the first 2 months
- 6 month regimens are effective without INH

**General Conclusions from the Literature**

- Without PZA minimum duration is 9 months (39 wks)
- Without RIF, minimum duration is 12 months (up to 18+ mos)
- SM and EMB are approximately equivalent in effect
Multiple Drugs?

- Resistance mutations occur spontaneously within a replicating population of bacteria with a predictable frequency ($f$)
  - $f$ Rif-R mutation $10^{-8}$; INH-R $10^{-6}$
- Mutations appear independently of each other
- Among a population of $10^9$ AFB (e.g., intracavitary), 10 bacteria will be Rif-resistant; 1,000 will be INH-resistant
  - These resistant populations will be mutually exclusive
  - Therefore 2 drugs will cover the entire population

"Evidence-based" Guidelines* for the Treatment of Tuberculosis

Strength of the recommendation
A. Preferred; should generally be offered
B. Alternative; acceptable to offer
C. Offer when A or B regimens cannot be given
D. Should generally not be offered
E. Should never be offered

Quality of evidence supporting the recommendation
I. At least 1 randomized trial with clinical endpoints
II. Clinical trials that were not randomized or were performed in other populations
III. Expert opinion

Regimens for Culture-Positive TB

Treatment of Culture-positive Pulmonary Tuberculosis

Regimens Rated A-I (HIV Uninfected)

2 mos - I, R, Z, E daily (56 doses, 8 wks) then
4 mos - I, R daily (126 doses, 18 wks) or
4 mos - I, R 2X / wk (36 doses, 18 wks)

Continuation phase increased to 7 months if initial film shows cavities and sputum is culture-positive at completion of 2 months of treatment.

Tailoring Tuberculosis Treatment Regimens

Rationale for Extending Treatment by 3 Mos

- Continuation of PZA for additional 2 months does not improve outcome
- Prolongation of continuation phase by 2 months decreased relapses in silicotuberculosis from 20% to 3%

Risk Factors for Relapse: Study 22

<table>
<thead>
<tr>
<th>Continuation Phase, Control (I/R Twice weekly)</th>
<th>Cavity</th>
<th>Culture Positive at 2 Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>Yes, No</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>21.8%, 6.2%</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>5.0%, 2.1%</td>
</tr>
</tbody>
</table>

Tuberculosis Trials Consortium. Lancet. 2002; 360: 528
Sputum Monitoring

*Simply Stated*

- Obtain sputum every month until culture-negative for at least 2 consecutive months
- For those with *either* delayed culture conversion (beyond 2 months) or cavitation on plain CXR, clinicians may extend treatment to 9 months, although 6 mos is acceptable
- For those with *both* cavitation and delayed culture conversion, 9 months is recommended
- Patients with sputum cultures that remain positive at 3 months require further investigation

Preventing Complications:

*Drug Selection and Dosing*

- Select individual treatment regimen based on individual risk factors for toxicity, clinical, and life conditions
  - Understand specific toxicities of TB medications
    - *e.g.*, Avoid hepatotoxic medications in patients with active hepatitis
    - Tailor regimen to accommodate lifestyle of patient
    - Case management-DOT → SAT?
- Adjust doses of specific drugs as necessary
  - Use weight-based dosing
  - Reduce doses of specific drugs if metabolism is impaired
  - *e.g.*, Increase dosing interval of EMB in renal failure (3x/wk, with dialysis)
  - Consider drug level testing/monitoring in specific circumstances
    - Malabsorption?

Treatment of Culture-positive Pulmonary Tuberculosis

*Rifapentine Regimen (Once Weekly) Rating B-I*

2 mos - I, R, Z, E daily (56 doses, 8 wks) or
0.5 mos - I, R, Z, E daily (14 doses, 2 wks) then
1.5 mos - I, R, Z, E 3X / wk (12 doses, 6 wks) then
4 mos - I, RPT once weekly (18 doses, 18 wks)

*Regimen is limited to HIV-negative adults (>12y/o)*

CDC 2003

Clinical Case Management

Reportable to state DPH (suspects and cases)
1-888-MASS MTB

Massachusetts’ Nursing Case Management Model

*Principles:*

- Relationship between patient and nurse is built upon trust - with a common understanding of issues of culture, lifestyle, and language
- Patients have the right to exercise *choice* in their treatment plan
- Nurse is responsible for *identifying behaviors* that predict nonadherence and for *developing strategies* that address these behaviors and assure treatment completion

Baseline Evaluations

- Collect appropriate specimens for microscopy and culture
  - 3 sputum samples, 8-24 hr apart
  - Sputum induction or bronchoscopy
- Perform susceptibility testing for INH, Rif, EMB on an initial positive culture (each site of disease)
- Perform HIV counseling and testing for all patients/suspects
  - CD4, viral load if HIV-positive
Monitoring for Drug Toxicity

• At baseline
  – ALT, bilirubin, alkaline phosphatase, serum creatinine, and platelet count
  – Eye examination (V	extsubscript{a}, color*) for all patients receiving EMB
  – Education
  – Education!

• At least MONTHLY
  – Clinical evaluations usually are sufficient, unless abnormal baseline values are found or other risk factors for toxicity exist
    • e.g., Risk factors for hepatitis: chronic hepatitis (hep. C), use of hepatotoxic drugs (including acetaminophen, EtOH, lipid lowering drugs), age (>35), postpartum, young black or Hispanic women
  – Eye examinations (EMB) – monthly testing of V	extsubscript{a} and color* is recommended for patients receiving EMB >15-20 mg/kg/d and if on drug for >2 mos.

• For second and third-line medications, seek expert consultation

* Ishihara Color Testing plates

Response to Treatment

• May be rapid (days)
  – Signs/symptoms

• Expect > 90% sputum culture conversion by 3 months
  – If slow conversion – evaluate and consider longer treatment

• Allow return to home/work environment based on individual considerations
  – Infectiousness of case
    look for clinical response, declining organisms on smear
  – Risk of others becoming infected (contacts)

Follow-up Evaluations

• For pulmonary TB
  – Sputum smear/culture monthly until 2 consecutive samples are culture negative
    • Repeat drug susceptibility testing, other investigations, if culture-positive still at 3 months
  – If initial culture positive - consider repeat CXR at 2 mos, and get CXR at completion of therapy
  – If initial culture negative – perform 2 mos CXR to assess response; CXR at completion of therapy

• For extrapulmonary TB
  – Frequency and types of evaluations depend on site

Clinical Hepatitis in Persons Taking INH and Rif

<table>
<thead>
<tr>
<th>Drug</th>
<th>Studies</th>
<th>Patients</th>
<th>% Clinical Hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>6</td>
<td>38,257</td>
<td>0.6</td>
</tr>
<tr>
<td>INH + other drugs</td>
<td>10</td>
<td>2,053</td>
<td>1.6</td>
</tr>
<tr>
<td>(NOT Rif)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INH + Rif</td>
<td>19</td>
<td>6,155</td>
<td>2.7</td>
</tr>
<tr>
<td>Rif + other drugs</td>
<td>5</td>
<td>1,264</td>
<td>1.1</td>
</tr>
<tr>
<td>(NOT INH)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Serum Drug Level Monitoring

• Useful in selected circumstances
  – e.g., inadequate response to treatment, severe disease where malabsorption is questioned

• Helps determine therapeutic concentrations
  – Allows adjustments for variable drug absorptions

• Documents adherence to treatment

• May reduce toxicities

Serum Drug Level Monitoring

• Aminoglycosides
  – To reduce toxicity, achieve therapeutic levels
  – In-house (Amikacin) vs send-out (Kanamycin)

• Ethambutol
  – May be useful in renal insufficiency to reduce toxicity

• Rifampin
  – To determine malabsorption (e.g. in severe HIV)

• Cycloserine
  – To determine therapeutic levels
Discharge Planning
- Start when TB diagnosed or suspected:
  - Clinical/laboratory evidence or patient on TB drugs
- Pre-discharge conference required:
  - Include local health department nursing case manager, providers, discharge planners
- Home assessment by local health department nursing case manager necessary to:
  - Prevent putting potentially vulnerable household members at risk - especially children
  - Coordinate community follow-up for continuation and completion of therapy

Regulation 105 CMR 365.600, MGL

Involuntary Hospitalization: the Massachusetts Menace Law
- In Massachusetts, a patient who is a danger to the public health can be hospitalized against his/her will until that threat no longer exists
  - Includes due process
  - Is rarely used
- TBTU at Lemuel Shattuck Hospital (MDPH)
  - “Locked” unit: New England referral site
  - Behavioral milieu

Completion of Therapy
- 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

Completion of Therapy
- 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 is not administered within the targeted time period, patient is considered to have interrupted therapy

Therapy Deviations
- Treatment interruptions: Significance varies with
  - Bacillary load at time of interruption
  - Time in course when interruption occurred (initial or continuation phase)
  - Duration and intermittency of interruption
- Split dosing of first line agents
  - Lowers peak serum concentrations – may encourage emergence of resistance

Special Treatment Situations
- Pregnancy & breastfeeding
- Renal disease
- HIV-AIDS
- Indiscreet use of Fluoroquinolones
TB in Pregnancy

- Treatment for TB is ok
  - HRE + B₉ usual (PZA not used in US) → 9 mos reqd
  - Avoid aminoglycosides (SM, KM, AK), Capreomycin
    - May be assoc w fetal deafness
- Consider possible transplacental spread to infant
  - Prepare for examination of placenta post-delivery for pathology, AFB stains/cultures
  - Alert pediatrician to observe infant for signs of congenital TB
- Separation of mom from infant?

TB after Pregnancy

- Pediatrician evaluates baby, considers treatment (individualized) for potential transplacental contact if mother not on Rx prenatally: review placenta data later
- Baby gets “window treatment plus” (6 months) if non-protected exposure to a case took place after delivery

Breastfeeding

- Breastfeeding ok, except in women taking fluoroquinolone
- INH given to mother is not adequate as preventive therapy in breastfeeding infant
  - Infant receives drug, may exhibit side effects
  - TB-exposed infant needs own INH, Vit B₉

Renal Disease

- Consider increasing dosing interval of renally excreted anti-TB drugs (rather than lower dose) if Creatinine clearance decreased (<30ml/min)
  - EMB, PZA, Fqn, aminoglycosides, Capreo, CS
- Consult experts for dosing of patients on dialysis
  - No adjustment for INH & RIF
  - Lengthen interval for EMB & PZA (generally 3x/wk, following dialysis)

Fluoroquinolones and Drug-Resistant TB

- Use of a fluoroquinolone-class drug alone in patients with unsuspected tuberculosis has been shown to delay diagnosis and induce resistance to this class of drug (Wang, Thorax, 2006; Ginsberg, NEJM, 2003; Ginsberg, CID, 2003)
  - Potential contribution to XDR
- Up to 1/3 of patients with pulmonary TB will have “atypical” radiographic presentations
- TB risk history should be performed before empiric use of these drugs is initiated for CAP
  - Persons at-risk for TB should not be treated with fluoroquinolone empirically
  - EDUCATE YOUR COLLEAGUES !!!!
**IDSA / ATS: Empirical Antibiotics for Community Acquired Pneumonia**

- **Outpatients**
  - Previously healthy and no use of antimicrobials within the previous 3 months
  - A macrolide (strong recommendation; level I evidence)
  - Doxycycline (weak recommendation; level III evidence)
- 2. Presence of comorbidities such as chronic heart, lung or renal disease, diabetes mellitus, alcoholism; malignancies; immunosuppressive conditions or use of immunosuppressing drugs, or use of antimicrobials within the previous 3 months (in which case an alternative from a different class should be selected)
  - A respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin [750 mg] [strong recommendation; level I evidence])
  - A β-lactam plus a macrolide (strong recommendation; level I evidence)
- **Inpatients, non-ICU**
  - A respiratory fluoroquinolone (strong recommendation; level I evidence)
- **Inpatients, ICU**
  - β-lactam + azithromycin or respiratory fluoroquinolone

*From Table 7: CID, 44 (suppl. 2), 2007*

**Summary**

- Patient-centered case management is standard of care
- When prescribing treatment:
  - Use preferred regimens
  - Extend treatment for cavitation and/or positive sputum cultures at 2 mos
  - Calculate # doses within prescribed time frame
  - Use DOT as a tool to ensure treatment adherence
- Special situations
  - Be mindful of additional guidelines for pregnant or breastfeeding women, HIV (+) persons, patients with renal or liver disease

---

**Heliotherapy (sun therapy)**

Valley Echo, April, 1927

---

**Isoniazid**

- **Dose:** 5 mg/kg/d (to 300mg)
- **Route:** Oral, parenteral
- **Major Toxicities:**
  - Fatigue
  - Rash
  - Nausea
  - Neuropathy
  - Hepatitis
- **Drug Interactions**
  - Phenytoin (competes at CYP 450 sites)

---

**Rifampicin**

- **Dose:** 10 mg/kg/d (to 600mg)
- **Route:** Oral, parenteral
- **Major Toxicities:**
  - Nausea
  - Rash
  - Hepatitis
  - Thrombocytopenia
- **Also:**
  - Orange coloration of urine, secretions
  - False positive urine tests for opiates
  - Inactivates hormonal contraceptives, warfarin, many other drug interactions (induces CYP 450)

---

**Pyrazinamide**

- **Dose:** 15 - 30 mg/kg/d
- **Route:** Oral
- **Major Toxicities:**
  - Nausea
  - Rash
  - Hepatitis
  - Hyperuricemia
- **No fetal safety data (avoided during preg)**
**Ethambutol**

- Dose: 15 - 25 mg/kg/d
- Route: Oral
- Poor CSF penetration
- Major Toxicities:
  - Optic neuritis
  - Rash
- Renal and fecal excretion

**Streptomycin**

- Dose: 15 mg/kg/d (to 1000mg)
- Route: Parenteral
- Major Toxicities:
  - Ototoxicity
  - Nephrotoxicity
- Do not use in pregnancy

### Management of Hepatotoxicity

**Defined:** Hepatotoxicity = AST $\geq$ 3x-uln with sx, or $\geq$ 5x-uln without sx
- AST <5x = mild; 5 – 10x = mod.; >10x = severe
- If hepatotoxicity occurs, stop Rx immediately
  - Also evaluate promptly if significant rise in Bili and/or alkaline phosphatase
- Question patient about prior hepatobiliary disease, use of alcohol or other hepatotoxic drugs
  - Stop these drugs, if possible

**Management of Hepatotoxicity (cont’d)**

*Individualize approach:*
- Start $\geq$ 3 non-hepatotoxic drugs until specific cause is determined; or
- After AST returns to $< 2x$-uln, restart suspect drugs one at a time
  - Restart Rif (± EMB) first, then after 1 wk add INH, then after another wk add PZA; check AST at each step
- If sx recur, or AST increases, the last drug used should be stopped
- If Rif and INH are tolerated and hepatitis was severe, assume PZA was responsible
  - Stop PZA, and consider extending treatment to 9 mos.

### Common Adverse Drug Problems

- GI intolerance: Administer meds with food if not tolerated on empty stomach
  - Preferred over splitting doses or changing to 2nd-line drugs
  - Consider switching from Rifampin to Rifabutin
    - But no dairy: impairs absorption of rifamycins
- Itching: Antihistamines

**Tuberculosis and HIV**

- 1.1 million (est.) new HIV-positive TB patients globally
- Number of new TB cases has tripled in High-HIV-prevalence countries in the last 20yr
- 350,000 people died of HIV-associated TB in 2010
  - TB is the leading cause of death in HIV patients in Africa
- The Reservoir: 1/3 of the 34 million people with HIV are TB-infected
  - are 21-34 times more likely to develop TB
- Active TB accelerates progression of AIDS
- The 3 “I”s” – to control the crisis:
  - Intensified case finding
  - Infection control
  - INH preventive therapy
- Populations at-risk: IDU; heterosexual

* Looming Threat of Drug-Resistant TB
- 440,000 emergent MDR-TB cases in 2010

*WHO, 2011*
**Treatment of TB in HIV**

- Drugs work
  - Treatment - with usual TB drugs – cures
- But –
  - Presentation may be atypical (esp with CD4<200)
  - Case management
    - Unique issues in TB
    - Drug interactions?
    - Secondary drug resistance?
    - Timing of HIV treatment?

**HIV-Related Tuberculosis: Issues in TB Treatment**

- Treatment is similar to non-HIV Tuberculosis
- Rifamycin drug interactions via Cytochrome P450 system
  - Protease Inhibitors (PI) and Nonnucleoside Reverse Transcriptase Inhibitors (NNRTI)
  - Rifamycins induce the activity of CYP3A4 and thereby may decrease serum concentrations of PI's and NNRTI's
  - Rifampin most potent, Rifabutin least potent inducer
  - Rifabutin can be safely used with most protease inhibitors and NNRTI's, except saquinavir and delavirdine
  - However, PI's can increase Rifabutin concentrations (toxic)
- Rifapentine is not recommended for tx in HIV-TB
  - Associated with acquired rifamycin resistance
- Seek expert consultation*

---

**Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis**

CDC; December, 2007


**Other Issues in the Treatment of Active TB and HIV**

- Coincident, other opportunistic infections
  - May have multiple infections; Hepatitis B and/or C
- Drug absorption
  - Monitor drug levels?
- Social, economic and logistical issues
- Timing of AIDS treatment
  - IRIS: Paradoxical worsening of TB following initiation of HAART for AIDS

**Antiretroviral Therapy in TB**

- ART should be started in all HIV-infected TB patients
  - Irrespective of CD4 counts (strong recommendation, low quality of evidence).
- Antituberculosis tx should be started first, followed by ART asap
  - Start within the first 8 wks treatment (strong recommendation, moderate-quality of evidence).
- HIV-infected TB patients with profound immunosuppression (CD4 <50/mm³) should start ART immediately - within the first 2 wk of starting TB treatment**.
- Efavirenz should be used as the preferred non-nucleoside reverse transcriptase inhibitor in patients starting ART while on anti-TB treatment (strong recommendation, high quality of evidence).

* WHO, 2011
** ACTG - NEJM, 2011

**Multidrug Resistance (MDR)**

- Definition:
  - Resistance to at least INH and Rifampin
- 1% of US cases (2012)
- Usually occurs following inappropriate treatment (secondary drug resistance)
- Usually requires specialized management
Extensively Drug Resistant (XDR) Tuberculosis

- Defined (WHO, 10/14/06): Resistance to INH + Rifampin (MDR), plus any fluoroquinolone and at least 1 of 3 injectable second-line drugs
  - Capreomycin, kanamycin, amikacin
- Worldwide: 20% MDR, 2% XDR (est.)*
  - Latvia: 19% (115/605) of MDR cases XDR (2000 – 2002)
  - South Korea: 15% of MDR cases XDR (2000 – 2002)
- Increasing XDR/MDR in E. Europe, Africa
  - KwaZulu-Natal, 2006: 544 Cult + / 221 MDR / 53 XDR / 52 died
  - XDR/MDR: 17/381 (4.5%)
- XDR versus MDR
  - More likely to die or experience treatment failure