Treatment of Tuberculosis

ATS/CDC/IDSA Joint Statement
2003

Outline, 2012

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

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

ATS/IDSA/CDC 2003 Treatment Guidelines
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.

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

**First-line**
- Isoniazid (INH)
- Ethambutol (EMB)
- Rifampin (RIF)
- Rifabutin* (RBT)
- Rifapentine (RPT)
- Pyrazinamide (PZA)

**Second-line**
- Cycloserine
- Levoﬂoxacin*
- Ethionamide
- Moxifloxacin*
- p-Aminosalicylic acid (PAS)
- Gatifloxacin*
- Amikacin/Kanamycin*
- Capreomycin
- Streptomycin (SM)

*Not approved by FDA for use in tuberculosis* 2012
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 and once-weekly continuation phase for highly-selected (HIV-neg) patients.

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

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.

Treatment of Culture-positive Pulmonary Tuberculosis

**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

* IDSA/USPHS

Regimens for Culture-Positive TB

<table>
<thead>
<tr>
<th>Drug regimens for culture-positive pulmonary tuberculosis caused by drug-susceptible organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial phase</td>
</tr>
<tr>
<td>---------------</td>
</tr>
</tbody>
</table>

CDC/IDSA/ATS Treatment of Tuberculosis, 2003

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>Cavity</th>
<th>Culture Positive at 2 Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes 21.8% No 6.2%</td>
</tr>
<tr>
<td>No</td>
<td>Yes 5.0% No 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)
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_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_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

CDC/ATS/IDSA. MMWR 6/03
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
- Indiscrete use of Fluoroquinolones

TB in Pregnancy

- Treatment for TB is ok
  - HRE + B₆ 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 in 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 B₆

Renal Disease

- Consider increasing dosing interval of renally excreted anti-TB drugs (rather than 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)

Tuberculosis and HIV*

- Stay tuned…

* WHO, 2011

CDC: Treatment of Tuberculosis, 2003 Table 15
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

- Outpatient
  - 1. Previously healthy and no use of antibiotics within 3 months
     - A macrolide (strong recommendation; level I evidence)
     - Doxycycline (weak recommendation; level III evidence)
  - 2. Presence of comorbidities such as chronic heart, lung, liver or renal disease; diabetes mellitus; alcoholism; malignancies; exposure; immunosuppressing conditions or use of immunosuppressing drugs, or use of antimicrobials within 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 b-lactam plus a macrolide (strong recommendation; level I evidence)

- Inpatients, non-ICU
  - A respiratory fluoroquinolone (strong recommendation; level I evidence)

- Inpatients, ICU
  - b-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 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