History of Treatment of Latent Tuberculosis Infection

For more than 4 decades, treatment of persons with latent *Mycobacterium tuberculosis* infection has been an essential component of TB control in the US.

Targeted Tuberculin Testing and Treatment of Latent TB Infection

As the rate of TB in the United States has decreased, identification and treatment of persons with latent infection who are at high risk for progressing to TB disease have become essential components of the TB elimination strategy.
Targeted testing should replace screening of low-risk persons. Benefits include:
- Identification of persons at high risk for TB who would benefit by treatment of LTBI
- Reduction of wasted resources and inappropriate treatment

Are You Ready To Test?
- Never test without a symptom and risk assessment
- Reason for testing?
- Remember a decision to test is a decision to treat
- Who will treat if positive?
- Does client have a coexisting medical condition that may influence TST results?
- Do you have client’s contact information?

Groups at Risk for TB Infection -1
Persons or groups with presumed recent MTB infection
- Close contact of person with infectious TB
- TST or IGRA conversion within 2 years
- Immigrant from endemic countries (within 5 years of arrival)
- Children <5 years with + TST or + IGRA

Groups at Risk for TB Infection -2
Clinical conditions associated with progression to TB disease
- HIV infection
- Prior, untreated TB, with fibrotic lesions on CXR
- Underweight, malnourished persons
Groups at Risk for TB Infection

Other medical conditions
- Silicosis
- Diabetes mellitus
- Chronic renal failure/hemodialysis
- Solid organ transplantation (heart, kidney)
- Carcinoma of head/neck
- Gastrectomy/jejunooilial bypass
- Immunosupression

New Risk Category in Last Decade
- Recipients of tumor necrosis factor-alpha (TNF-α) antagonists given to inhibit inflammation in diseases of autoimmune origin
  - Rheumatoid arthritis
  - Psoriatic and psoriatic arthritis
  - Crohn’s disease
- Those persons who had population risk factors but either were not screened for TB and/or did not receive TLTBI prior to TNF-α inhibitor therapy

Pulmonary TB Symptoms
- Persistent cough, productive or non-productive
- Chest pain, hemoptysis
  +/- Anorexia, weight loss
  +/- Fever, chills, night sweats

* 25% of people with active pulmonary TB are asymptomatic
*Charles Daley, MedPage Today July 27, 2007*

Diagnostic Examinations for Pulmonary TB
- Chest x-ray (PA and lateral)
- Sputum specimens (= 3 specimens obtained 8-24 hrs apart, one being an early morning specimen) for AFB microscopy and culture
  Shift from previous guideline of 3 morning specimens
- May need bronchoscopic lavage & biopsy, video-assisted thorascopic surgery (VATS), or open procedure
Treating Latent TB Infection

Treatment Regimens for LTBI

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Months of Duration</th>
<th>Interval</th>
<th>Minimum Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH 9*</td>
<td>Daily</td>
<td>2x wkly**</td>
<td>76</td>
</tr>
<tr>
<td>INH 6</td>
<td>Daily</td>
<td>180</td>
<td></td>
</tr>
<tr>
<td>RIF 4</td>
<td>Daily</td>
<td>2x wkly**</td>
<td>52</td>
</tr>
</tbody>
</table>

*Preferred  ** Intermittent treatment only with DOT
INH=isoniazid; RIF=rifampin

Treatment of LTBI - 1

- Isoniazid for 6-12 months has been the mainstay of treatment for LTBI in the United States for many years
- Effectiveness of INH “preventive therapy” for LTBI has been limited because of poor adherence related to
  - relatively long duration of treatment required
  - concerns about toxicity
- There has been interest in the development of shorter, rifampin-based regimens as alternative to isoniazid for the treatment of LTBI

Treatment of LTBI - 2

- INH administered daily for 9 months is recommended because clinical trials in HIV-negative persons indicate that 12 months of treatment is more effective than 6 months
  - maximal beneficial effect of INH is likely achieved by 9 months, and minimal additional benefit is gained by extending therapy to 12 months
- Both the 9-month and 6-month INH regimens may be given intermittently
  - only as directly observed therapy - DOT
• RIF daily for 4 months is recommended on the basis of the efficacy of a similar regimen demonstrated in clinical trials.
• In situations where rifampin cannot be used (e.g., HIV-infected persons receiving protease inhibitors), rifabutin may be substituted.

**Treatment of LTBI**

**Treating TB Disease**

**What the Guidelines Say**

Treatment of Tuberculosis (ATS/CDC/IDSA) 2003
• Responsibility for successful treatment rests with private provider or public health program, not the patient.
• Emphasis on patient-centered case management.
• Development of an adherence plan that includes directly observed therapy (DOT).

**Treatment of TB**

• RIF, INH, PZA, EMB ("RIPE") standard regimen.
• 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.
Random Mutation Probabilities for TB Drugs

- Rifampin 1 in 100,000,000 \( (10^{-8}) \)
- Isoniazid 1 in 1,000,000 \( (10^{-6}) \)
- Pyrazinamide 1 in 1,000,000 \( (10^{-6}) \)
- Ethambutol 1 in 10,000 \( (10^{-4}) \)
- Streptomycin 1 in 1,000,000 \( (10^{-6}) \)

The likelihood of an organism spontaneously resistant to 2 antibiotics is the product of their probabilities (i.e., for Isoniazid & Rifampin 1 in \( 10^{-14} \))

Routine Examinations at Start of Treatment

- Weight (doses calculated on mg/kg basis)
- HIV test and counseling
- Baseline lab tests:
  - Liver function tests (AST, ALT, alk phos and bilirubin)
  - Creatinine
  - Platelets

Drug Susceptibility Testing

- Routine drug susceptibility testing for INH, RIF, and EMB on initial positive culture
- Repeat susceptibility testing if culture positive after 3 months of treatment

Antituberculosis Agents

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

Second-Line Drugs
- Streptomycin (SM)
- Cycloserine (CS)
- p-Aminosalicylic acid (PAS)
- Ethionamide (ETA)
- Amikacin, kanamycin* (AK, KM)
- Capreomycin (CM)
- Levofloxacin* (LFX)
- Moxifloxacin* (MOX)

* Not approved by the U.S. Food and Drug Administration for use in the treatment of TB.
**Initiation Phase**

- Preferred Regimen – 4 antituberculosis drugs x 2 months
- Daily INH, RIF, PZA, and EMB
- 56 doses (8 weeks)

**Continuation Phase**

- INH, RIF for an additional 4-7 months
- Daily INH and RIF for 126 doses (18 weeks) or Twice-weekly INH and RIF for 36 doses (18 weeks)

**When to Extend the Continuation Phase**

- Cavitary pulmonary disease and positive sputum cultures at completion of initial phase
- Initial phase excluded PZA
- HIV-infected with positive sputum culture at the end of initial phase
  - Treat with once-weekly INH and rifapentine
Rationale for Extending Continuation Phase

- Cavitary disease and positive sputum culture at 2 months associated with increased relapse in clinical trials
- Relapse rates after 6 months of treatment
  - Non-cavitary disease, culture (-) at 2 mo. - 2% relapse
  - Cavitary disease AND culture (+) at 2 mo. - 22% relapse

Note: 5-6% relapse if either present

Monitoring During Treatment - 1

- Monthly face-to-face evaluation to review symptoms, assess adherence and identify adverse reactions
- Sputum smears
  - Weekly to assess early response to therapy
  - Monthly after sustained conversion to negative
- Sputum cultures
  - Monthly until consistently negative
  - Duration of therapy determined by time to culture conversion

Monitoring During Treatment – 2

- Repeat chest x-ray at completion of initial phase
- Renal function, AST, ALT, bilirubin, and platelet count if abnormalities were detected at onset of treatment
- Monthly testing of visual acuity and color vision if EMB used > 2 months or doses > 15-20 mg/kg

Monitoring for Medication Side Effects

Instruct patient to report signs or symptoms of adverse drug reactions
- Rash
- Anorexia, nausea, vomiting, pain in right upper quadrant of abdomen
- Fatigue or weakness
- Dark urine
- Persistent numbness in hands or feet
Addressing Side Effects

• Administer medications with food if not tolerated on empty stomach
  – This is preferred to splitting doses or changing to second-line medication
• Consider switching from Rifampin to Rifabutin if GI intolerance occurs
• Antihistamines for itching
• Repeat LFTs if symptomatic or other indications for routine monitoring

Managing Treatment Interruptions

Rx Interruption - Example

• 12/20 19 yo ♀ dx TB meningitis in California
• 1/02 Discharged with 7d supply RIFE & steroids
• 1/07 Did not keep clinic appointment
• 1/16 Admitted to a NJ hospital, altered mental status
  Q – Continue treating? Restart?

Significance of Tx Interruption

• 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
Completion of Therapy Defined – 1

• Completion of treatment can be defined by calculating number of doses ingested within specified time frame.
• It is not based solely on duration of therapy.
• For example:
  • 6-month daily regimen (7 days/wk) = at least 182 doses of INH and RIF, and 56 doses of PZA.
  • 6-month daily regimen (5 days/wk) = at least 130 doses.

Completion of Therapy Defined – 2

• In cases of drug toxicity or non-adherence, all 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.

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).

Definitions of Drug Resistance

Acquired Drug Resistance
Is that which is found in a patient who has received at least 1 month of prior anti-TB drug treatment.

Primary Drug Resistance
Is the presence of resistant strains of *M. tuberculosis* in a patient with no history of prior treatment.

Multi-drug Resistance (MDR)
Is defined as resistance to at least INH and RMP, the two most potent drugs and the mainstay of anti-TB treatment.

Extensive Drug Resistance (XDR)
Is defined as resistance to at least Isoniazid, Rifampin, any Fluoroquinolone, and at least one 2nd line injectable drug (Kanamycin, Amikacin, or Capreomycin).
Drug Resistance

- Drug resistance is only established by DST
- Treatment of drug-resistant TB should be done in close consultation with an expert

Management Strategies

- Case management
- **Enablers** to assist in completion of therapy (transportation, convenient clinic hours, bilingual staff)
- **Incentives** meaningful to the patient (movie passes, gift cards, meal vouchers, clothing)
- Care plan for completion: DOT is central

Impact of DOT on Completion Rates

- Non-supervised therapy: 61%
- Modified DOT: 79%
- DOT: 86%
- Enhanced DOT: 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

Responsibility for Successful Treatment

- Successful treatment benefits the individual patient and the community
  - Cures the individual patient
  - Minimizes transmission of M. tb
- Responsibility lies with health care provider, not only for prescribing appropriate regimen, but for ensuring successful completion of therapy
Successful Treatment

• Depends on more than just the science of chemotherapy
• Treatment must be provided in a clinical and social framework based on the individual patient’s circumstances