CLINICAL DIAGNOSIS AND MANAGEMENT OF TB DISEASE

Annie Kizilbash MD, MPH
September 22, 2015

TB Nurse Case Management
September 22-24, 2015
San Antonio. TX

Annie Kizilbash MD, MPH has the following disclosures to make:

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

• Utilize diagnostic tools to identify TB disease
• Identify standard regimens for treatment of drug susceptible TB
• Discuss strategies resulting in improved patient outcomes
  – Intensity of dosing
  – Prolongation of therapy
• Recognize those at risk of poor outcomes
<table>
<thead>
<tr>
<th>Purpose</th>
<th>1</th>
<th>5. Recommended Treatment Regimens</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>What’s New In this Document</td>
<td>1</td>
<td>CONTENTS OF</td>
<td>6. Practical Aspects of Treatment</td>
</tr>
<tr>
<td>Summary</td>
<td>1</td>
<td>THE 80-Page</td>
<td>7. Drug Interactions</td>
</tr>
<tr>
<td>1. Introduction and Background</td>
<td>13</td>
<td>Document</td>
<td>8. Treatment in Special Situations</td>
</tr>
<tr>
<td>3. Drugs in Current Use</td>
<td>19</td>
<td>10. Treatment of Tuberculosis in Low-Income Countries: Recommendations and Guidelines of the WHO and the IUATLD</td>
<td>72</td>
</tr>
</tbody>
</table>

## Clinical Diagnosis
Assessing the Possible Risk

- EXPOSED
- LATENT TB INFECTION (LTBI)
- TB DISEASE
  - Primary
  - Post Primary-Reactivation

Pathogenesis of TB Progression to Disease

Exposure (LTBI)

- 5% First Year
- 2-3% Second Year
- ~0.1% per year thereafter

No Disease (90%)

Disease
Primary Tuberculosis

• TB is divided into primary and post-primary (or reactivation)

• Most primary TB resolves spontaneously, but reactivation may occur without treatment

Primary Tuberculosis

• Most are asymptomatic; fever and nonproductive cough may occur

• Opacities are in middle and lower lungs
  – Commonly unilateral

• Lymph node enlargement often occurs, and may cause bronchial compression
Primary Tuberculosis

• Pleural Effusion: Seen in up to 25% of those with primary TB.

• Often is the only manifestation.
  – It is seen 3 to 7 months after initial exposure

• May leave residual pleural thickening and calcification
Primary Tuberculosis

- The natural history of TB pleuritis is spontaneous resolution over 2 to 4 months
- If not treated
  - High risk of reactivation
  - Rapid development of devastating disease in infants and immunocompromised persons
Primary Tuberculosis

• Miliary disease:
  – more commonly seen in the elderly, infants, and immuno-compromised host.
  – Usually seen within 6 months of the initial exposure
• Evenly distributed diffuse small 2-3 mm nodules, with a slight lower lobe predominance

Miliary Tuberculosis
Post primary or reactivation tuberculosis

- Post Primary TB is progressive
- Upper lobes predilection, cavitation and absence of lymphadenopathy
- Fibrosis and calcification are seen after healing

Reactivation Tuberculosis
Standard Components of TB Evaluation

• Patient History
  – Symptoms
  – History, co morbidities, demographics, family history
  – Hospital Discharge Information

• Physical examination

• Laboratory testing
  – Tuberculin Skin Test or Interferon Gamma Release Assays
    QTF Gold In Tube, TSpot TB
  – CBC, LFTs, sputum smears/cultures, Tissue histology

• Radiologic evaluation
  – CXR, (CT, MRI)

Why Did I Ask For All This?
Populations at High Risk for TB

• Contacts of infectious persons
• HIV-infected persons
• Foreign-born persons
• Homeless persons
• Those in congregate living situations
• Persons who inject illicit drugs
• Detainees and prisoners

Medical Conditions Which Increase Risk for Progression to Active TB

- HIV infection
- Chronic renal failure
- Diabetes mellitus
- Malignancy
- Silicosis
- Immunosuppressive Rx
- TNF Alpha blocker therapy
- > 15 mg Prednisone/day
- Transplant recipients
Evaluation: Sputum Collection

• Collect sputum specimens if:
  – Abnormal CXR consistent with TB
  – Presence of respiratory symptoms even if normal CXR

Mycobacterial Cultures

• Three initial sputum cultures within 24 hours
  – At least one first morning
  – At least one observed

• Cultures should be obtained monthly until negative on two consecutive months
  – Determine length of therapy
  – Identify delayed response (+ > 2 to 3 months)
  – Identify treatment failure (+ at 4 months)
CDC Recommendations for NAAT

• “NAAT should be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a
• (1) diagnosis of TB is being considered but has not yet been established, and for whom the test
• (2) result would alter case management or TB care and prevention activities.”

Why Use A NAAT?

• Confirms AFB + patient as M TB
• If AFB + patient is NAAT negative on 2 specimens
  – Less likely to have M TB
    • Suspend Contact investigation and
    • Hold TB treatment unless TB strongly suspected.
• If patient is not strongly suspected as M TB and is NAAT negative x 2,
  – Remove from isolation.
When should I consider my specimen delayed?

- **Specimen received in the lab**
- **Day**: 0 1 2 3
  - At 24 hours, expect smear results
  - At 48 hours, expect results of NAAT or Molecular DST
  - At 72 hours, expect results of IGRA
  - At 21 days, expect a culture ID (TB or NTM)
  - At 28 days, expect 1st line susceptibility results, expect 2nd line 4 weeks after requested
- **Day**: 21 28 42-56
  - At 6-8 weeks, expect the culture to be finalized if negative

Clinical Evaluation: CXR

- **Obtain a CXR in**
  - Every person with a newly positive TST or IGRA
  - Any person at risk of TB who has symptoms and no other obvious diagnosis
  - May be indicated in some asymptomatic, TST/IGRA negative contacts at increased risk
    - Children 4 years and younger
    - HIV infected
    - Immunosuppressed
Differentiating Between LTBI and Disease when the CXR is abnormal

Abnormal CXR findings which could be consistent with latent TB
- Nodules/ Fibrotic lesions of old TB
- Pleural thickening
- Calcified granuloma
- Bronchiectasis

Management of TST + Persons With an Abnormal CXR and – AFB Smear

- Isolated CXR with nodules and/or fibrotic lesions:
  - If no symptoms - wait
    - Collect sputum culture
    - Evaluate for symptoms
    - Repeat CXR
  - If CXR stable at 2 – 3 months and cultures are negative, treat as LTBI

- Isolated CXR with nodules and/or fibrotic lesions:
  - If patient has any signs or symptoms of TB disease: This person may have tuberculosis
    - Start 4 drugs
  - Never start a single drug in a patient with possible active TB
Management of TB Disease

Strategies Stressed in Guidelines

• **Identification of patients at increased risk of relapse**
  – Obtain sputum smear and culture at end of initial phase of treatment (2 months)

• **Extended therapy** for patients with drug-susceptible pulmonary TB
  – Who have **cavitation** on initial CXR
  – Who have a **positive sputum culture at 2 months**

• **Counting Doses**
  – Define treatment completion by number of doses taken as well as duration of treatment
Treatment Regimens for TB Disease

• **Initiation phase** of therapy
  – 8 weeks
  – INH, Rifampin and PZA +/- EMB

• **Continuation phase** of therapy
  – 16 weeks
  – INH and Rifampin

Treatment of Culture-Positive Drug Susceptible Pulmonary TB

• **General conclusions from the literature**
  – 6 mo (26 wk) is the *minimum* duration of RX
  – 6 mo regimens require rifampin and INH throughout and PZA for the first 2 months
  – 6 – 9 mo regimens are effective without INH if PZA given throughout
  – Intermittent regimens (2-3x/wk): DOT ONLY!
    • Drug susceptible isolate
## Treatment of Culture-Positive Drug Susceptible Pulmonary TB

<table>
<thead>
<tr>
<th>General conclusions from the literature:</th>
</tr>
</thead>
<tbody>
<tr>
<td>– <strong>Without PZA</strong> - minimum duration is <strong>9 months</strong></td>
</tr>
<tr>
<td>– <strong>Without rifampin</strong> - minimum duration is <strong>12 months (up to 18 months)</strong></td>
</tr>
<tr>
<td>– Streptomycin and ethambutol (EMB) are approximately equivalent in effect</td>
</tr>
<tr>
<td>• Because of <strong>high incidence of Streptomycin resistance</strong> ethambutol is preferred for initial therapy</td>
</tr>
<tr>
<td>– Use streptomycin only if isolate is proven susceptible</td>
</tr>
</tbody>
</table>

## Why Give Ethambutol?

- A four drug regimen is recommended until susceptibility tests are reported
- If treatment is being initiated after drug susceptibility tests are known and the organisms are susceptible, ethambutol is not necessary if the patient is given both INH and rifampin
- Ethambutol can be stopped as soon as the lab reports an isolate susceptible to INH & rifampin.
Treatment of Culture Positive Pulmonary Tuberculosis

Regimens Rated **A-1 (HIV Uninfected)**

- 2 mo I,R,Z,E daily (56 doses, 8wks) or
- 2 mo I,R,Z,E 5x/wk (40 doses, 8wks) then

4 mo - I,R daily (126 doses, 18 wks) or
4 mo – I,R 5x/wk (90 doses, 18 wks) or
4 mo – I,R, 2x/wk (36 doses, 18 wks)

Initial phase

continuation phase

---

Regimens Rated **A-2 (HIV Uninfected)**

- 2 weeks – I,R,Z,E daily (14 doses) then
- 6 weeks – I,R,Z,E twice weekly (12 doses)

4 mo – I,R Twice weekly (36 doses, 18 weeks)

Initial phase

continuation phase

- PLUS (DOT only)
In the Treatment of TB, You Get What You Pay For…

• “A consistent theme has begun to appear: more extensive disease requires more treatment, and the fewer total doses, the higher the risk that treatment will prove inadequate”
  – What should we conclude?

- First: More treatment means more cures
- Second: Programs need to consider some individualization of therapy
- Third: Should not deter us from intermittent therapy but should remind us of need for sophisticated management based on case-specific circumstances
  – Should not be surprised that individuals differ in their response.

Relapse

• Circumstance in which a patient becomes and remains culture-negative while receiving antituberculosis drugs but at some point after completion of therapy, either becomes culture-positive again or experiences clinical and radiographic deterioration consistent with active tuberculosis
Patients at Risk of Relapse

• Who is more likely to have Relapse?

• What Can We Do Differently to Decrease the Risk?

Medical Factors Associated With Relapse

• Cavitary TB
• Extensive disease on CXR; bilateral infiltrates
• Positive 2 month culture
• Associated medical conditions
  – Diabetes
  – HIV
  – Malabsorption of TB drugs
• Tuberculous lymphadenitis
• Underweight at diagnosis and failure to gain
• Drug resistant disease
• Prior treatment for tuberculosis
Treatment Factors Associated with Relapse of Tuberculosis

- DOT
- Adherence
- Dosing intensity (Dose itself)
- Duration of therapy
  - Intensive phase
  - Continuation phase
  - Both
- Rifamycin containing regimen

Tailoring Treatment Regimens

- **Prolong** continuation phase when:
  - Positive 2 month culture with cavitary disease
  - Extrapulmonary disease
    - Meningitis
    - Disseminated disease in children
  - HIV TB in children and adolescents

ATS, CDC, IDSA: Treatment of Tuberculosis 2003
Relapsed Tuberculosis Management Strategies

• Most relapses occur within the first 6 – 12 months after stopping therapy but some occur 5 or more years later

• 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

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)
Treatment in Special Situations

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

“Delayed Response”
Culture Positive at 3 Months

- TB lab should automatically repeat susceptibility studies on last positive culture - check to be sure

- Assess adherence

- Consider serum drug levels

- Evaluate response to therapy
  - Clinically and radiographically

By the time you know this it is 4 months into therapy!
“Treatment Failure”
Culture Positive at 4 Months

Repeat susceptibility studies
• On last positive culture
• And request on a “new sputum culture” now
  – Ask for molecular detection of drug resistance
  – Serum drug levels if not previously done
  – Clinical evaluation

Augment therapy
• Add at least two and preferably three new drugs to which the isolate is likely to be susceptible
• Even if no clinical or radiographic evidence of failure

MMWR Treatment of Tuberculosis 2003; 52

TNF alpha Antagonists

• Block TNF alpha activity which is required for granuloma formation and control of M TB infection
• Used for rheumatoid arthritis, Crohn’s disease, psoriasis and a variety of other immune mediated diseases
• Remicaid (inflixamab)
• Embril (entanercept)
• Humira (adalimumab)
• Cimzia (certolizumab)
Warning: Risk Of Infections
Infliximab

- Tuberculosis (frequently disseminated or extrapulmonary at clinical presentation), ...and other opportunistic infections have been observed in patients receiving Remicade some of these infections have been fatal.
- Patients should be evaluated for LTBI with a TST.
- Treatment of LTBI should be initiated prior to therapy with Remicade.
- SEE WARNINGS

PDR 2004

TB Presentation in Dialysis Patient

- Pulmonary - Atypical presentation
  - Fever – most common sign!
    - Low or high grade
  - Weight Loss
  - Anorexia
  - Cough (may not be present)
- TB Disease considered in ANY patient with
  - recurrent pneumonia
  - pneumonia not improved within 2 weeks of antibiotics
TB Presentation in Dialysis patients

- Extra pulmonary TB
  - More common in dialysis patients
    - Pleural and lymph node – most common
    - Peritoneal/Abdominal
      » Can be indistinguishable from typical bacterial peritonitis
      » Peritoneal BX may show caseating granulomas
  - Any site – (Bone, Brain, Pericardium, etc.)
  - Don’t forget to do SPUTUMS!!

Treatment Regimen: Active TB

- Initial Phase (first two months):
  - INH 300mg po daily or 900 mg thrice weekly
  - Rifampin 600mg po daily or thrice weekly
  - Ethambutol 15-25mg/kg po Thrice weekly
  - PZA 25-35mg/kg po thrice weekly
  - Vitamin B6 50mg thrice weekly
  - All doses should be given AFTER DIALYSIS
Culture Negative TB

• A person who could have TB 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
**Mycobacterium bovis**

- A member of the M TB complex
- Is common in children (>1 year) along U.S. Mexico border
  - Non-pasteurized milk and cheese – a food borne disease as well as respiratory
- Is associated with extra pulmonary disease and increased mortality
- Similar to other members but is resistant to PZA

---

**Management of Treatment Interruptions**

- Initial phase of therapy
  - <14 days –complete standard # of doses
  - >14 days – restart from the beginning
- Continuation phase
  - >80% doses by DOT – if initial smear–, may stop
  - < 80% doses by DOT and/or initial smear +
    - Repeat culture
      - Management based on clinical and bacteriological factors.
Does Diabetes Impact TB Treatment Outcomes?

- A link between diabetes and TB has been recognized for centuries
- Diabetics have increased risk of progression to disease, failure of therapy, relapse and mortality from TB


In Summary: A Complete Assessment

...Is Essential to Good Patient and Public Health Outcomes

Thank you!
Questions