Welcome

TB Nurse Case Management
San Antonio, Texas
October 14-16, 2014

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

CLINICAL DIAGNOSIS AND MANAGEMENT OF TB DISEASE

Annie Kizilbash MD, MPH
Assistant Professor
University of Texas Health Center Northeast
Staff Physician, Texas Center for Infectious Diseases
Annie Kizilbash 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
Clinical Diagnosis

Assessing the Possible Risk

• EXPOSED

• LATENT TB INFECTION (LTBI)

• TB DISEASE
  – Primary
  – Postprimary-Reactivation
Pathogenesis of TB
Progression to Disease

Exposure (LTBI)

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

Disease

No Disease (90%)

Primary Tuberculosis

- TB is divided into primary and post-primary (or reactivation)
- Most resolve spontaneously, but reactivation may occur without treatment
- Smears are positive in < 20%
- Cultures are positive in ~ 50%

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 – Ghon’s Complex

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 – Pleural effusion

Primary Tuberculosis

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

Primary Tuberculosis - Miliary
Post primary or reactivation tuberculosis
• Postprimary 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
  – 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
- 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)

Evaluation: Sputum Collection

• Each patient should have at least one specimen sent for nucleic acid amplification testing (NAAT)
  – Even if smear negative
  – > 60% of smear negative persons with active TB will be NAAT positive
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 control activities.”

Why Use A NAAT?

• Confirms AFB + case as M TB

• If AFB + case is NAAT negative on 2 specimens
  – Suspect this is not 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
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

- Exclude active disease
  - Abnormal but stable CXR findings (>2-3 mo)
    - NODULES/FIBROTIC LESIONS OF OLD TB
    - PLEURAL THICKENING
    - CALCIFIED GRANULOMA
    - BRONCHIECTASIS
  - Sputum smear and cultures documented as negative

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: patient is a TB suspect
    - Start 4 drugs
  - Never start a single drug in a patient with possible active TB
Management of TB Disease

Strategies Stressed in Guidelines

• **Counting Doses**
  – Define treatment completion by number of doses taken as well as duration of treatment

• **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**

Treatment of Culture-Positive Drug Susceptible Pulmonary TB - Duration

• **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**!
Treatment of Culture-Positive Drug Susceptible Pulmonary TB - Duration

- General conclusions from the literature:
  - Without PZA - minimum duration is 9 months
  - Without rifampin - minimum duration is 12 months (up to 18 months)
  - Streptomycin and ethambutol (EMB) are approximately equivalent in effect
    - Because of high incidence of Streptomycin resistance ethambutol is preferred for initial therapy
      - Use streptomycin only if isolate is proven susceptible

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

What About 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 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-I (HIV Uninfected)

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

CONTINUATION PHASE
- 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)

Regimens Rated A-II (HIV Uninfected)

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

CONTINUATION PHASE
PLUS (DOT only)
4mo – I,R twice weekly (36 doses, 18 weeks)

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.

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 Should We Suspect?
- 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
- Rifampin 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

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
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 (adalimubab)
  - Cimzia (certolizumab)

Warning: Risk Of Infections
Infliximab – PDR 2004

• 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.

TB Presentation in Dialysis Patient

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

- 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 in Dialysis Patient

- 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**

- TB suspect 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 MTB complex which is what is identified by all TB labs or PCR

- Similar to other members but is resistant to PZA

- Is associated with increased extra pulmonary disease and higher mortality

- Is common in children (> 1 year) along U.S. Mexico border
  - Non-pasteurized milk and cheese – a food borne disease as well as respiratory

**Management of Treatment Interruptions**

- **Initial phase of therapy**
  - <14 days missed – complete standard # of doses
  - >14 days missed – 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?

• Previously thought not to affect treatment outcomes

• Four more recent studies from Baltimore, Texas, Taiwan and Indonesia reveal:
  – Delayed culture conversion
  – Higher mortality
    – Dooly, 2009; Restrepo 2008; Wang 2008; Alisahlanda, 2007

Does Diabetes Impact TB Treatment Outcomes?

• Relapse may be more frequent
  –Recent Shanghai study - 203 diabetics with TB followed for 2 years after standard treatment
    • 20% relapse rate in patients with DM (most Type 2)
    • 5% relapse rate in patients without DM

Zhang et al. Jpn J Infect Dis, 2009

A Complete Assessment

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

Thank you!