Diagnosis and Medical Management of TB Disease

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CLINICAL DIAGNOSIS AND MANAGEMENT OF TB DISEASE

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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
  - Post Primary-Reactivation
Pathogenesis of TB Progression to Disease

Exposure (LTBI)

No Disease (90%)

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

Disease

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

• 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
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)

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**
- **At 24 hours**, expect smear results
- **At 48 hours**, expect results of NAAT or Molecular DST
- **At 21 days**, expect a culture ID (TB or NTM)
- **At 72 hours**, expect results of IGRA
- **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

• **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
  **and**
  – 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

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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

• 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

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-1 (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)

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Regimens Rated A-II (HIV Uninfected)

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

- 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
      – 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 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

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 (adalimubab)
- 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 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
  – Don’t forget to do SPUTUMS!!
    • 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.)

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

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

- Similar to other members but is resistant to PZA

- Is associated with extra pulmonary disease and increased 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

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**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?

- Previously thought not to affect treatment outcomes

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

Response to Treatment

- Relapse may be more frequent
  - 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!