Objectives

- Goal of this discussion:
  - Clinical Assessment of Patient with Tuberculosis
- Content:
  - Ruling out LTBI
  - Signs and symptoms
  - Medical history
  - Physical examination
  - TST result
  - Chest radiograph
  - Decision to treat based on clinical signs and symptoms
  - Culture negative TB
Most Important Objective

• Learn when to suspect TB!

• If you don’t suspect TB, you will miss the diagnosis everytime!

Examples of Patients Referred for TB Evaluation

• Asymptomatic patient with (+)TST or QFN
• Abnormal CXR, patient from high TB endemic area
• Chronic cough
• “Recurrent“ Pneumonia
• Weight Loss
• Fever of Unknown Origin
• Unilateral cervical adenopathy
• Necrotizing granulomatous inflammation on biopsy
• Combination of above
TB/LTBI Evaluation
Developed World

• Patient History
  • Symptoms
  • PMHx, comorbidities
  • FHx and patient demographics

• Physical examination

• Radiologic evaluation
  • CXR, CT

• Laboratory testing
  • TST, QFN
  • CBC, LFTs, Tissue histology, cultures

TB/LTBI Evaluation
3rd World Setting

• Limited availability
  • CXR
  • Tuberculin skin testing
    • High % positive
      • True TB infection
      • Prior BCG vaccination
  • Directly Observed Therapy (DOT)
  • Mycobacterial cultures
  • Drug susceptibility/resistance testing
  • Second Line TB drugs
A New Approach to TB Investigation: 4 Steps to Success (around the world)

1. The Host
2. The Syndrome – The Presentation
3. The Microbiology – The Bug
4. The Treatment – The Drug

1. Define the Host
Define the Host

- Risk of TB Exposure
- Age
- Underlying Health of Host
  - Comorbid medical conditions
  - Immunosuppression

Define the Host: Exposure Risk

- Exposure & Risk of TB:
  - Jail
  - Homeless Shelter
  - Health Care Worker
  - Known TB Exposure
  - Where they Live
  - Foreign Born
Define the Host: Exposure Risk


- ≤ 3.5 (year 2000 target)
- 3.6–4.2
- > 4.2 (national average)

*Cases per 100,000

Define the Host: Exposure Risk

TB Case Rates in U.S.-born vs. Foreign-born Persons
United States, 1993–2008*

*Updated as of May 20, 2009
Define the Host: Age

• Age + Untreated LTBI
  • Normal adults: 5-10% lifetime risk of active TB
    • 50% progress in the first 2-3 years
    • 50% have delayed reactivation

Define the Host: Age

• Age + Untreated LTBI
  • Children:
    • Infants: 40% progress in 1-2 years
    • 60% of all pediatric cases are < 5yrs
    • Older children: 5 -10% lifetime risk
      • 6 -12 years “favored age”
      • Teens slightly higher risk
Define the Host: Age

Reported TB Cases by Age Group, United States, 2008

Define the Host: Age

- Adult TB:
  - Reactivation TB
  - Symptomatic
    - Fevers
    - Chills
    - Cough
    - Hemoptysis
    - Night Sweats
    - Weight Loss
  - CXR Findings
    - Upper lobe infiltrates
    - Cavities
  - Cavities = Highly Contagious
Define the Host: Age

- Pediatric TB:
  - Primary TB
  - Asymptomatic
  - CXR Findings
    - Hilar Lymphadenopathy
    - Indistinct infiltrates
    - No cavities
  - Less Contagious

- Pediatric Tuberculosis
  - In U.S., up to 50% of children with pulmonary TB disease have *few or no symptoms*
    - School Age Children (80-90%)
    - Infants < 1yo (40-50%)
Define the Host: Health of Host

• Underlying Health of Host
  • Comorbid Medical Conditions
  • Immunosuppression

Comorbid Medical Conditions

• Silicosis: RR 30
  • Int. Jour. of Tub. & Lung Dis. 11(5):474-84, 2007 May
• Chronic Renal Failure/HD RR 10-25
• Diabetes: RR 4
  • Higher rates of LTBI progression and TB treatment failure
  • CID 2007;45:428-35
  • Recommendation for DM screening in LTBI and TB
Examples of Immunosuppression

- HIV infection / AIDS
- Tumor necrosis factor (TNF-α) inhibitors
  - Rheumatoid arthritis, inflammatory bowel disease
- Lymphomas and hematologic malignancies
- Bone marrow transplant
- Solid organ transplant
- Long term steroid use
- Congenital immunodeficiency syndromes

Define the Host: HIV/AIDS

- HIV infected adults + LTBI:
  - **Risk of Active TB is 7-10% per year!**
  - Higher rates of primary TB disease
  - More atypical pulmonary findings
  - Higher rates of extrapulmonary disease
  - Higher rates of dissemination (60%)
  - More atypical presentations:
    - Diarrhea
    - Hepatosplenomegaly
    - Lymphadenopathy
Define the Host: HIV/AIDS

- “Primary Complex pattern” common with HIV/AIDS
  - Hilar adenopathy
  - Lower / mid lung infiltrates, unilateral
  - Pleural effusions
- Atypical CXR findings
  - Confluent pneumonia
  - Lower zone infiltrates
  - Hilar / paratracheal adenopathy
  - Risk for Miliary spread

Define the Host: HIV/AIDS

- Reactivity of TST decreases as CD4 count decreases:
  - 15-25% false (-) in normal host with active TB
  - 50-90% false (-) in pts. with early HIV (no other OI's)
  - 80-100% false (-) in pts. with advanced HIV
- In USA/UK, consider preventative INH therapy for HIV & immunosupp. pts regardless of TST if a close contact to “infectious” cases
Define the Host: HIV/AIDS

• Sputum smear and culture somewhat less sensitive in HIV (+) pts
  • May be 2° to decrease tendency for cavitary disease (less organism load)
  • May need to collect additional sputum samples; consider gastric and urine samples
  • Consider MTB Gen-probes on smear negative sputum samples

As CD4 cell counts decrease:

• Increased (+) yield from LN aspirates and pleural / pericardial fluid
• Increased (+) yield from mycobacterial blood cultures
• Histology - Less well-formed granulomas
2. Define the Syndrome

Define the Syndrome

- Pulmonary TB
  - Primary
  - Reactivation/Cavitary
- Extrapulmonary TB
  - Lymph Nodes (42%)
  - Pleural (18%)
  - Bone & Joint (11%)
  - Meningeal (6%)
  - GU (5%)
  - Peritoneal (5%)
  - Others (11%)
- HIV & IRIS
Primary TB Without Progression

- Ghon focus: Isolated small fibrocalcific lesions
  - Site of primary pulmonary infection
  - No increased risk of reactivation
- Ranke’s complex:
  - Dense calcified hilar LN with ipsilateral Ghon lesion (calcified)
  - No increased risk of reactivation
- Simon Foci: Apical/bi-apical fibronodular shadowing
  - Higher risk for reactivation or postprimary-type TB
- Other findings - No increased risk of reactivation
  - Thickening of apical pleura
  - Blunting of costophrenic sulcus
Primary TB with Progression

- Hilar Lymphadenopathy
- Indistinct infiltrates
- Pleural Effusions
- No cavities

Miliary Tuberculosis

Granulomas from Mycobacterium tuberculosis
Reactivation Pulmonary TB

- Classic Adult TB:
  - Reactivation TB
  - Symptomatic
    - Fevers
    - Chills
    - Cough
    - Hemoptysis
    - Night Sweats
    - Weight Loss
  - CXR Findings
    - Upper lobe infiltrates
    - Cavities
    - Cavities = Highly Contagious

Reactivation Pulmonary TB

- Location: Upper Lobe Predominant
  - Apical and/or posterior segment of RUL; apicoposterior segment of LUL or superior segment of either lower lobe
- Infiltrates:
  - Fibronodular, irregular with variable coalescence
  - Cavities: Thick, moderately irregular walls
  - Volume loss: progressive, can be rapid

PLEASE NOTE:
- "Atypical" lung findings in approx. 1/3 patients
- "Infiltrates can appear anywhere!!"
Pleural TB

Pleural TB - Calcified
Lymphatic TB (Scrofula)

Bone/Spine TB
Bone/Spine TB

- Pott’s Disease
- Pain
- Neurologic Findings
  - Motor Deficits
  - Abnormal Reflexes
  - Bowel/Bladder Incontinence
  - Long Term Neuropathic Pain
  - Paralysis

Meningeal TB
Meningeal TB

• A – Clinical
  • Mandatory – Fever & HA > 14 days
  • Optional – Vomiting, AMS or focal deficit

• B - Cerebrospinal Fluid
  • Pleocytosis > 20 cells
  • 60% lymphocytes
  • Protein > 100
  • Sugars < 60% of serum
  • Negative India ink study
  • Negative cytology study

• C - Radiological – Head CT with 2 or more:
  • Exudates in basal cisterns or Sylvian fissures
  • Hydrocephalus
  • Infarcts
  • Gyral enhancement

• D - Extra Neural Tuberculosis
  – Active TB of:
  • Lungs
  • GI
  • GU
  • Lymph nodes
  • Skeletal
  • Skin

Ahuja GK. Tubercle and Lung Disease. 1994; 75:149-152.

Meningeal TB

• Stage 1: Good Prognosis
  • No confusion
  • No focal neurologic signs
  • No hydrocephalus

• Stage 2:
  • Confusion or
  • Focal neurologic signs

• Stage 3: 50% die or permanent neurologic sequelae
  • Stuporous or
  • Dense hemiplegia or paraplegia

Genitourinary TB

- Classic: Sterile Pyuria
  - Prostatitis
    - Acute Urinary Obstruction
    - Renal Abscesses
- Rarely the only TB presentation
Pericardial TB

Cutaneous TB
TB & HIV & IRIS

- Immunologic Reconstitution Inflammatory Syndrome
  - Rapid increase in CD4 after initiation of HAART
  - Reactions begin median of 15 days after starting HAART
    - Fever
    - Increased, suppurative lymphadenopathy
    - Increase pulmonary infiltrates (worsening CXR)
    - Cough
  - IRIS is a diagnosis of exclusion!
- Therapy
  - Delay HAART 2 wks - 2 months after starting MTB therapy
  - NSAIDS
  - Steroids

3. Define the Microbiology
Define the Microbiology

- Is the presentation caused by an Infection or Non-Infectious process?
  - Not all Cavitary Lung Lesions are Infectious
  - Examples:
    - Squamous Cell Lung Cancer
    - Wegener’s Granulomatosis

Define the Microbiology

- If infectious, what is the organism?
  - What Infections cause cavitary lung lesions?
    - TB
    - NTM: *M. kansasii*, MAC
    - Fungi: Coccidioidomycosis
    - Bacteria:
      - *S. aureus*
      - *Klebsiella* spp.
      - Rhodococcus
      - *Nocardia* spp.
      - Actinomycetes
      - Anaerobes
Define the Microbiology

• Full Microbiology evaluation needed
  • Stains and cultures for
    • Bacteria
    • Mycobacteria
    • Fungi
  • All types of Specimens Possible
    • Sputum
    • Tissue
    • Urine
    • BAL
    • Etc.
  • Easily done in most US laboratories with rapid results

Define the Microbiology

• Is the infection caused by TB or NTM?
  • MTB direct probe → rapid test
  • Other Rapid probes:
    • MAC
    • M. kansasii
    • M. gordonae
  • Cultures may take up to 6 weeks
Define the Microbiology

• Drug susceptible vs. Drug resistant
  • Laboratory methods are slow:
    • > 3-4 weeks to confirm

Define the Microbiology

• Types of Drug Resistance
  • Single Drug Resistance
  • Multi Drug Resistant TB (MDRTB)
    • At least INH and Rifampin Resistant
  • Extensively Drug Resistant TB (XDRTB)
    • MDRTB plus
    • Any Fluoroquinolone Resistance and
      • Ciprofloxacin, Ofloxacin, Levofloxacin or Moxifloxacin
    • Any Second Line injectable Resistance
      • Kanamycin, Amikacin or Capreomycin
Define the Microbiology

• When to Suspect Drug Resistant TB
  • Prior Therapy for TB
  • Lack of Clinical/Microbiologic Improvement by 3 months
  • Country of origin can increase suspicion
    • Single Drug:
      • Rifampin Resistance/HIV
      • Mexico high rate of INH and/or Streptomycin resistance
    • MDRTB/XDRTB
      • China
      • Russia
      • Former Soviet Block Countries

Burden of MDRTB

MDR-TB Survey Findings:
- Worldwide Average: MDR-TB is 5.3% of TB cases
- MDR-TB rates greater than 6%:
  1. Azerbaijan, Baku City (22.3%)
  2. Moldova (19.4%)
  3. Ukraine, Donetsk (16%)
  4. Russia, Tomsk (15%)
  5. Uzbekistan, Tashkent (14.8%)
  6. Estonia (13.3%)
  7. Russia, Mary El (12.5%)
  8. Latvia (10.8%)
  9. Lithuania (9.8%)
 10. Armenia (9.4%)
 11. Russia, Orel (8.8%)
 12. China, Inner Mongolia (7.3%)
 13. China, Heilongjiang (7.2%)
 14. Georgia (6.8%)

WHO Feb 2008
Burden of XDRTB

XDR-TB Survey Findings:

- 45 countries with at least one case confirmed
- In former Soviet Union countries, proportions of XDR-TB among MDR-TB range from 4% in Armenia, to almost 24% in Estonia

WHO Feb 2008

4. Define the Treatment
Define the Treatment

- Drug Selection
- Duration of Therapy
- Adjunctive Therapy
- DOT: Directly Observed Therapy

Define the Treatment

- Drug Selection
  - RIPE + B6 x 2 months
  - Followed by Rifampin and INH for 4 months
  - But not all patients are that easy!
Define the Treatment

• Drug Selection: Drug Toxicities
  • Liver
    • Elevated Transaminases
    • Elevated Bilirubin
  • Kidney: Renal failure
  • Skin: Rash
  • Bone Marrow:
    • Neutropenia
    • Anemia
    • Thrombocytopenia
  • Eyes:
    • Visual impairment
    • Color Blindness
    • Uveitis
  • Plus many more…

Define the Treatment

• Drug Selection: Drug Resistance
  • One Drug
  • MDRTB
  • XDRTB
Define the Treatment

• Drug Selection: Culture Negative TB
  • 10-15% of pulmonary cases
  • RIPE + B6 x 6 months
  • Re-evaluation of patient after 2 months of treatment
    • Repeat CXR (or CT chest if done)
    • Clinical status
    • Sputum cultures
  • If there is any clinical OR radiographic improvement while on treatment during the first 2 months → tuberculosis clinically diagnosed and continue empiric treatment for active disease

Define the Treatment

• Duration of Therapy
  • 6 Months:
    • Uncomplicated Pulmonary TB
  • 7 Months:
    • Cavitary Pulmonary TB
  • 9 Months:
    • Delayed Sputum Conversion
    • Lack of PZA in TB induction
  • 12 Months:
    • Bone and Joint TB
    • Meningeal TB
    • Widely Disseminated TB
  • 24 Months:
    • MDRTB
    • XDRTB
Define the Treatment

• Adjunctive Therapy: Steroids
  • Steroids should only be used as an adjunct to effective TB therapy
  • When to use:
    • Meningeal TB
    • Pericardial TB
    • Skeletal TB with Spinal Cord Compression
    • Ocular TB
    • Severe Pulmonary TB

Define the Treatment

• DOT: Directly Observed Therapy
  • At least 183 countries have some form of DOT program
  • WHO Goal is 70% treated by DOT
    • In 2005 60% were treated by DOT
Summary

1. Define the Host
2. Define the Syndrome - The Presentation
3. Define the Microbiology – The Bug
4. Define the Treatment - The Drugs

You will never diagnose Tuberculosis if you don’t suspect it!
Questions?