The Medical Evaluation for Diagnosing Tuberculosis
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**Objectives**

- 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

Details covered in other lectures during course

Goal of this discussion:
- Outline a *Medical Management Approach* to the evaluation of LTBI and active Tuberculosis

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**Variety of Patient Referrals for TB/LTBI Evaluations – Examples:**

- Asymptomatic patient with reactive TST or (+) serum QFN
- Abnormal CXR in patient living in / from high TB endemic area
- Chronic adverse respiratory symptoms
- Unilateral cervical adenopathy
- Necrotizing granulomatous inflammation on tissue histology
- Combination of above
Standard Components of TB/TLBI Evaluation

- **Patient History**
  - Symptoms
  - PMHx, comorbidities
  - FHx and patient demographics

- **Physical examination**

- **Radiologic evaluation**
  - CXR, CT

- **Laboratory testing**
  - TST, QFN
  - If available: CBC, LFTs, Tissue histology, cultures

A New Approach to TB Investigation: 4 Steps to Success:

Defining / characterizing:

1. The **Host**
2. The **Syndrome**
3. The **Microbiology**
4. The **Treatment**
Defining the Host

- **Immunocompetent vs. Immunosuppressed**
  - Immunosuppression:
    - Higher rates of primary TB disease
    - More atypical pulmonary findings
    - Increase rates of extrapulmonary disease
    - Higher rates of dissemination

- **Other medical comorbidities**: Silicosis

- **Living status**: community vs. nursing home, hospital, jail, shelter etc.
  - Other cases of TB reported, pattern of spread?
Examples of Immunosuppression

- **HIV infection / AIDS
- Tumor necrosis factor (TNF-α) inhibitors
  - Rheumatoid arthritis, inflammatory bowel disease
- Many types of lymphomas and other hematologic malignancies
- Bone marrow and solid organ transplantation
- Long term / higher dose steroid usage
- Select congenital immunodeficiencies and other CMI suppressant causes

Presentation of TB can be different in Immunosuppressed Pts

TB in an immunosuppressed patient
- Can be more of a “Systemic” illness
- More extrapulmonary involvement - up to 60% cases in HIV (+) pts:
- More atypical presentations:
  - Diarrhea
  - Hepatosplenomegaly
  - Lymphadenopathy
**Pulmonary TB with immunosuppression**

- CXR findings - advanced HIV/AIDS (↑ variable):
  - Confluent pneumonia
  - Lower zone infiltrates
  - Hilar / paratracheal adenopathy
  - Pleural shadows
  - Miliary shadowing

- **“Primary Complex pattern”** of TB common with AIDS
  - Hilar adenopathy
  - Lower / mid lung infiltrates, unilateral
  - Pleural effusions

**Tuberculin skin testing & HIV infection**

- Reactivity of TST decreases as CD4 count decreases:
  - 15-25% false-neg. (-) in normal host with pulmonary TB (disease)
  - 50-90% false-neg. (-) in pts. with early HIV (no other OI’s)
  - 80-100% false-neg. (-) in pts. with advanced HIV

- Consider preventative INH therapy for HIV & immunosup. pts regardless of PPD for:
  - Close contacts to “infectious” cases
Other Comorbidities

• Higher rates of LTBI progression and TB treatment failure with Diabetes
  - CID 2007;45:428-35
  - Recommendation for DB screening in LTBI and TB

• Silica dust exposure and pulmonary silicosis associated with increased risk of TB development
  - Int. Jour. of Tub. & Lung Dis. 11(5):474-84, 2007 May

Clinical Presentations of Pediatric TB is NOT the same as with Adult TB

Distinction between TB infection and disease more clear in adult than in children / infants

• Adult: disease usually follows reactivation of previously dormant organisms and almost always have
  • significant symptoms and CXR abnormalities.

• Infants & children: disease more often complicates initial infection
  • LTBI & active disease are less distinct on presentation
  • CXR findings can be subtle and symptoms are lacking in up to 50% children.

Children with pulmonary TB are rarely (if ever) contagious

• Relatively sparse load of MTB bacilli in typical intrathoracic lesion
• Cavities are rare
Pediatric Tuberculosis

In U.S., up to 50% children with pulmonary TB disease have few or No symptoms

- Young infants are more likely than older children to have a symptomatic presentation.
- Asymptomatic presentation more common among school-age children (80-90%) than among infants <1yo (40-50%)
- Note – Erythema nodosum may be present

Must search for index case – will help to:
1. Confirm the child’s diagnosis of MTB
2. Establish drug susceptibility pattern

2nd - Define the Syndrome the “-itis”
**Define the Syndrome – the “itis”**

- Pneumonitis – clinical sx’s or via CXR?
- Lymphadenitis, meningitis / cerebritis, pericarditis, hepatitis, peritonitis, pyelonephritis, etc.

Is the syndrome consistent with TB?
Is this new vs. recurrent TB?
Is drug-resistant TB possible? Prev trx?

Treatment approaches based the syndrome – not all the same

**Considerations Depending upon the Type of Tuberculosis – “The Syndrome”**

- **Infectiousness** to others – more of a concern with pulmonary disease
- Role of **Steroids** – meningeal and pericardial disease
- **Extensions** in duration of therapy – e.g. bone/joint (vertebral), CNS TB
- Presentations of **IRIS**
CXR Residuals of Primary Infection

- Apical / bi apical fibronodular shadowing ("Simon foci")
  - high risk for reactivation or postprimary type TB
- Ghon focus = isolated small fibrocalkistic lesions (usually > 1 yr.)
  - 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
- Other findings: no increased risk of reactivation
  - thickening of apical pleura
  - blunting of costophrenic sulcus
Reactivation Pulmonary TB

More common presentation in immunocompetent, non HIV adults

Typical Symptoms  
- **nonspecific:**
  - Dry, NP cough
  - Hemoptysis
  - Hoarseness
  - Chest pain, pleurisy
  - Dyspnea
  - Constitutional symptoms: (malaise, feverish, sweats, weight loss)

Predilection for **upper lung zones** - possible reasons:
- Impaired lymphatic clearance in lung apices
- Less macrophage activity in oxygen rich environment of apices
  - high O₂ tension decreases macrophages ability to kill bacilli

CXR of Pulmonary TB Disease - Reactivation

- **Location:** apical and/or posterior segment of RUL; apicoposterior segment of LUL or superior segment of either lower lobe
- **Infiltrate:** fibronodular, irregular with variable coalescence and cavitation
- **Cavities:** thick, moderately irregular walls
- **Volume loss:** progressive, can be rapid

Notes:
- “Atypical” lung findings in approx. 1/3 patients
- Infiltrates can appear anywhere!!
Pulmonary Tuberculosis in Children and HIV (+) Adults

- CXR more variable – hallmark findings: Hilar adenopathy and segmental pulmonary lesions
  - Hilar, mediastinal or subcarinal adenitis
  - Large adenopathy may produce airway obstruction, segmental atelectasis or consolidation

- Chronic pulmonary TB or “adult-type” TB (reactivating) is rare in children.
  - Asymptomatic and progressive primary pulmonary TB is much more common in pediatric population

Immunologic Reconstitution Syndrome (IRIS) “Paradoxical Reactions”

- Increased immune response to MTB bacilli
  - Reaction to both live and dead bacilli

- Best described in HIV (+) patients after starting HAART
  - Reactions begin median of 15 days after starting HAART
  - HAART should not be withheld in HIV pts on MTB therapy
  - Consider delay HAART 2wks - 2 months after starting MTB therapy

- IRIS may occur in HIV (-) patients
Immunologic Reconstitution Syndrome (IRIS) Presentation depends upon location of TB infection

- Most common reactions: Dependent upon location of MTB infection:
  - Fever
  - Increased adenopathy
  - Increase pulmonary infiltrates (worsening CXR), cough, CP

- IRIS becomes a “diagnosis of exclusion”
  - Must rule out TB progression (e.g. drug resistance), co-infection with another pathogen or other process (acute MI, PE, CVA, etc.)

3rd - Define the Microbiology

Either confirmed or suspected
Defining the Microbiology

Questions to consider:

1. Is it Infection vs. Non-infection-driven inflammation?
   If infection present:

2. Is the Infection mycobacterial, bacterial, fungal, viral, protozoan, helminthic?
   - AFB staining, KOH, Gram staining on sputum smear or tissue?
   - Easily done in most laboratories; rapid results

3. Is the infection caused by *M. tuberculosis* vs. NTM?
   - MTD direct probe → rapid test (more sensitive when AFB (+))

4. Drug susceptible vs. resistance (single drug, MDR, XDR-TB)
   - >1-2 weeks to determine

** Note: MTB may not be confirmed when starting therapy
Diagnostic Considerations in HIV (+) pts with MTB Disease

• 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 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
4th - Define the Treatment

Defining the Treatment

- Select combination therapy for “induction phase”
  - Based on suspected or confirmed drug susceptibilities
- Selection of drugs for Re-treatment of TB (relapse or reinfection)
- Re-selection of drug(s) during therapy in setting of drug intolerance or toxicity
- Approach to Culture-Negative TB
Patients at Increased Risk for Drug Resistant MTB Infection

- Prior history of treatment with MTB medications
- Contacts of a person with documented drug-resistant MTB
- Foreign-born persons from areas where prevalence of drug-resistant MTB is high
- Residents of areas in U.S. where prevalence of INH-resistant MTB is $\geq 4\%$
- Persons whose smears or cultures remain positive after 2 months of MTB therapy

Culture Negative (-) TB

- 10-15% of pulmonary cases
- 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 treatment for active disease
- 6 mo of 4 drugs OR 2 mo INH/RFP/PZA/EMB + 2 mo INH/RFP
The Medical Evaluation for Diagnosing Tuberculosis

1. The Host
2. The Syndrome
3. The Microbiology
4. The Treatment

Traditional Approach
- Patient History
- Physical examination
- Radiologic evaluation
- Laboratory testing

A New Approach – Define:
1. The Host
2. The Syndrome
3. The Microbiology
4. The Treatment
THE END
Thank you for your attention