Diagnosis of Tuberculosis Infection and Disease

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The Medical Evaluation for Diagnosing Tuberculosis

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

TB Control Programs
Healthcare System and Cultural Barriers
- Case identification
- Early recognition of drug resistant disease
- Availability of appropriate TB meds
- Administration of adequate TB regimens
- Treatment of co-existing medical problems
- Administrative and engineering controls to prevent TB transmission
- Isolation of contagious cases
- Quarantine for nonadherent patients
- Contact investigation/treatment of LTBI
Factors Contributing to the Increase in TB Morbidity: 1985-1992

- Deterioration of the TB public health infrastructure
- Immigration from countries where TB is common
- HIV/AIDS epidemic
- Homelessness, drug and alcohol abuse

Socioeconomic Characteristics of TB in the US

- Among non-immigrants, TB significantly associated with
  - Poverty and unemployment
  - Homelessness
  - Congregate settings
  - Incarceration
  - Alcoholism and drug abuse
- HIV infection rates also high in some of these populations

Tuberculosis and Substance Abuse in the United States, 1997-2006
Oeltmann et al Arch Int Med 2008, 169; 189

- Substance abuse is the most commonly reported behavioral risk factor among patients with TB in the U.S.
- Patients who abuse substances are more contagious and remain contagious longer because treatment failure extends periods of infectiousness
Trends in TB Cases in Foreign-born Persons, United States, 1986–2005*

No. of Cases | Percentage of Total Cases

86 87 88 89 90 91 92 93 94 95 96 97 98 99 00 01 02 03 04 05

No. of Cases

0 2,000 4,000 6,000 8,000 10,000

Percentage

60 50 40 30 20 10

*Updated as of March 29, 2006.

Estimated Migrants “Entering” U.S.

Visitors without
~ 30,000,000

Non-immigrant visas
27,907,139

Immigrants and refugees
411,266

Undocumented migrants
~ 275,000 ????

N = ~ 59,000,000


In 2005, approximately one half of the foreign-born MDR TB patients were from Mexico, the Philippines and Vietnam.
XDR TB in the United States

- Probably relatively little acquired MDR and XDR TB in the U.S.
- Major source of MDR and XDR TB patients: foreign-born patients (33% Hispanic)
- Suspicion of drug resistance paramount
- May be difficult to devise initial empiric regimens

Summary

- TB rates continue to decline in the U.S.
- Rate of decline has slowed
- Foreign-born and racial/ethnic minorities continue to be disproportionately impacted
- Unknown HIV status for almost 1/3 of TB cases
- Proportion of TB cases that are MDR remains constant

LATENT TUBERCULOSIS INFECTION (LTBI)

AJRCCM, April 2000; 161: S221-S243
Who Should be Tested for TB Infection?

- Targeted testing of high risk individuals and groups to identify those at risk of recent infection
  - Contacts of active cases
  - Foreign born who entered US in last 5 years
  - High risk populations where transmission of TB likely to have occurred (HCW, prisons, nursing homes, other congregate settings)
  - Over half of lifetime risk occurs in the first 1-2 years after infection

Who Should be Tested for TB Infection?

- Persons with medical risk factors that increase risk of progression to disease
  - HIV infection
  - Chronic renal failure
  - Immunosuppressive Rx
  - Diabetes mellitus
  - Malignancy
  - TNF Alpha blocker therapy
  - Transplant recipients
    - > 15 mg Prednisone/day
  - Silicosis

LTBI - Criteria for PPD

- 5mm cut-point

- HIV positive persons
- Recent contacts of TB cases
- Fibrotic Changes on CXR c/w old (not treated) TB
- Patients with organ transplants or other immunosuppression
- Prednisone therapy 15 mg/day > 1 month
- Patients receiving TNF-alpha blockers
Warning: Risk Of Infections
Infliximab, Etanercept, Adalimumab

- 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

LTBI - Criteria for PPD
10 mm cut-point
- Recent arrivals (<5 yrs) high prevalence countries
- IVDU
- Residents/employees - high-risk congregate facilities (health care, prisons, shelters, etc.)
- TB lab personnel
- Persons with “high-risk” medical conditions
- Children <4 yrs or exposed to adults at risk

LTBI - Criteria for PPD
15 mm cut-point
- Persons with no risk factors
- Usually shouldn’t be tested unless as part of baseline assessment for those at risk due to jobs in high risk settings
Tuberculin Skin Testing

- Requires two visits.
- Experienced personnel needed for placement and interpretation.
- Inter and intra-observer variability.
- Complex guidelines defining LTBI.
- Does not differentiate infection from disease.
- Frequently negative in high risk patients and patients with active disease.

M. TUBERCULOSIS-SPECIFIC ANTIGENS

- Sequencing the TB genome has revealed three antigens, ESAT-6 (early secreted antigenic target 6 kD protein), CFP10 (culture filtrate protein 10) and TB7.7 that are not present in BCG or in most environmental mycobacteria.
- ESAT-6, CFP-10 and TB 7.7 stimulate IFN-γ production by PBMC.

CYTOKINES PRODUCED BY M. TUBERCULOSIS-STIMULATED PBMC

- The predominant host response to M. tuberculosis infection consists of antigen-specific memory T cells releasing IFN-γ in response to previously encountered mycobacterial antigens.
- PBMC from healthy tuberculin reactors produce high concentrations of IFN-γ (with appropriate stimulation).
**PRINCIPLES FOR IFN-GAMMA BASED TB DIAGNOSTIC TESTS**

Tuberculin skin test
- Multiple (hundreds) potential antigens
- Complex immune response, multiple immune mediators

Interferon-gamma based tests
- 3 antigens (ESAT-6, CFP-10, TB7.7)
- One immune mediator

**INTERFERON GAMMA (IFN-GAMMA) BASED TESTS FOR DIAGNOSING LTBI**

**BLOOD TESTS FOR LTBI**

- Quantiferon (Cellestis)
- Quantiferon TB-GOLD (Cellestis)
- T-SPOT TB (Oxford Immunotec)
- Quantiferon TB-Gold In- Tube (Cellestis)
**Quantiferon Interpretation**

- Positive: ESAT-6 and/or CFP-10 level > 0.35 iu and 50% > placebo (negative) control
- Negative: ESAT-6 and/or CFP-10 level < 0.35 iu
- Indeterminate: low mitogen (positive) control or high placebo (negative) control
**INDETERMINATE IGRA RESULTS**

1) Poor response to mitogen that resolves with repeat assay
   - Delayed specimen processing
   - Technical errors
2) Persistent poor response to mitogen
   - Anergy from immunosuppression
   - May occur in healthy persons
3) High background
   - Often persistent, reasons unclear
   - IGRA not useful

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**Elispot Test**

- Also based on ESAT-6 and CFP-10 stimulation of primed lymphocytes.
- Does not quantitate INF\(\gamma\) in supernatants of cells.
- Assay Quantitates the number of INF\(\gamma\) producing cells.
- Currently requires separation of cells from blood (Automated system developed).

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**T-SPOT TB (ELISPOT)**

Add cells to wells coated with anti-INF\(\gamma\)-gamma antibodies

- IFN\(\gamma\)-gamma binds to antibodies

Each spot represents one IFN\(\gamma\)-gamma-producing cell

Add second antibody and substrate, which gives color change
DIAGNOSIS OF LTBI

• IGRAs more specific than TST in BCG-vaccinated
• Relative sensitivity of TST and IGRA’s unknown. IGRAs may be more sensitive than TST for recent infection, but less sensitive for remote infection
• Relative sensitivity in immune suppressed patients unknown (T-Spot may be most sensitive)
• QFT-Gold, QFT-Gold IT, T-Spot FDA Approved

IFN-G-BASED BLOOD TESTS

ADVANTAGES

• Lack of inter-individual variability in test administration.
• More objective read-out (? reproducibility).
• Requires one visit (no return visit unless test is positive).
• More specific and (?) equally sensitive compared with TST.
• Guidelines for Using the QuantiFERON-TB Gold test for detecting MTB infection, U.S. MMWR 2005; 54 (No. RR-15, 49-55)

IFN-gamma Based Diagnostic Tests for TB-Future Study

• Iatrogenic immunosuppression (dialysis, organ transplantation, anti-TNF-alpha).
• Young children, HIV infected.
• Evaluate risk of progression to TB disease in patients with (+) IFN-gamma tests.
• Head to head evaluation of ELLISPOT vs. QFN-TB-Gold.
• Short and longterm variability
• Boosting after TST
IFN-gamma Based Diagnostic Tests for TB

• Be familiar with the cutoffs for a positive test
• USE ONE TEST, IGRA or TST (except under unusual circumstances): *disparate results are still hard to interpret*
• The gold standard is still elusive, but we have made some progress

Rationale for Treatment of LTBI

• Prevent progression of infection to disease
• Aid in the diagnosis of TB disease
• Interrupt transmission of disease
  – The next step that must be taken to move toward TB elimination in the US
Abnormal CXR and (+) TST

- 50 yo physician from China who entered the U.S. as a post-doctoral fellow
- Known abnormal CXR with negative sputum smears
- Asymptomatic, history of partial TB treatment in China
- QFT-TB Gold (+)
Managing patients with abnormal CXR’s and (+) PPD’s

• Option #1:
  – Collect sputum for AFB analysis
  – Begin multidrug tuberculosis Rx
  – Reevaluate at 2 months: if (+) cultures or radiographic improvement treat as active case
  – If cultures (-) and no radiographic change treat as LTBI
• Advantages: Minimizes public health risk, 2 mos of 4 drug Rx adequate for LTBI
• Disadvantages: Possible medication toxicity

Managing patients with abnormal CXR’s and (+) PPD’s

• Option #2:
  – Collect sputum for AFB analysis
  – Reevaluate at 2 months: if (+) cultures or radiographic progression treat as active case, if (-) cultures and radiographic stability treat as LTBI
• Disadvantages: Unavoidably involves at least some public health risk
• Advantages: Avoids risk of medication toxicity
Diagnosis of Tuberculosis

Symptoms

Radiologic Findings

Microbiologic Findings

• Clinical suspicion is the single most important factor in the timely diagnosis of tuberculosis.
• The greatest risk for nosocomial transmission of tuberculosis is exposure to an undiagnosed case of TB.
• There is no diagnostic substitute for thinking about the diagnosis.

Good Outcomes Depend on Complete Evaluation and a Correct Diagnosis

• Medical Evaluation
  – Signs and symptoms
  – History of risk factors and/or exposures
  – Physical exam
• Chest X-ray
• Bacteriology
  – Cultures of suspected site
  – Susceptibility testing of positive isolate
  – Rapid diagnostic tests (HPLC, NAA)
Where Are Patients Diagnosed With TB?

- California, 18 counties with highest TB morbidity
  - Hospital inpatient evaluation 45%
  - Outpatient clinic evaluation 32%
  - TB clinic 12%
- Seattle, Washington
  - Outpatient evaluation 48%
  - Hospital evaluation 32%
  - TB clinic 2%

Symptoms of Tuberculosis

- Cough
- Fever
- Nite Sweats
- Weight Loss
- Hemoptysis

- Chronicity is the key

Guidelines for Evaluation of Pulmonary TB in Adults

- Any cough ≥ 2-3 wks plus at least one additional symptom: fever, night sweats, weight loss or hemoptysis
- Any high risk for TB; unexplained illness including respiratory symptoms ≥ 2-3 wks
  - CXR: if suggestive of TB collect 3 sputum specimens for AFB and culture
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Controlling TB in U.S. MMWR: Nov 2005
Guidelines for Evaluation of Pulmonary TB in Adults

- Any HIV infected with unexplained cough and fever
- Any at high risk for TB with dx CAP & not improved >7 days
- Any at high risk for TB with incidental findings on CXR of TB even minimal/no sx
- CXR and collect 3 sputum for AFB smear and culture
- CXR and 3 sputum for AFB smear and culture
- Review prior CXR if available, 3 sputum for AFB smear and culture

Controlling TB in U.S. MMWR: Nov 2005

Postprimary (Reactivation) TB: Radiographic Findings

- Primarily apical/posterior segments of the upper lobes, superior segments of lower lobes (90%)
- Predilection for Reactivation TB to involve the upper lung zones
  - Relatively higher oxygen tension in the upper lung zones
  - Impaired lymphatic drainage in the upper lung zones
- Patchy consolidation with streaky opacities (100%)
- Cavitation 45%
- Bronchogenic spread of disease with ill-defined nodules (20-25%)
- Fibrosis (30%)
- Pleural effusion (20%)
Postprimary ( Reactivation) TB Cavities

- Sites of cavitary disease
  - 83%-85% apical/posterior segments upper lobes
  - 11%-14% superior segments lower lobes
- Usually involves more than one segment

Postprimary ( Reactivation) TB Cavities

- Cavities usually multiple with thin and smooth to thick and irregular walls
- Air-fluid levels in cavities unusual (9-20%)
- Anterior segment of upper lobes or basilar segments of lower lobes without typical pattern of involvement-5%
Atypical Presentation of TB

- HIV infection, chronic renal disease, diabetes, immunosuppression may alter presentation
  - CXR may be atypical; lower lobe infiltrate, adenopathy or completely normal
  - Negative TST or QFT Gold
  - Negative smear in up to 50%
  - Atypical clinical presentation
Radiographic Assessment of Disease Activity

- Normal CXR: high negative predictive value, but false negatives occur 1% in immunocompetent, 7%-15% HIV seropositive
- Lack of radiographic change over a 4 to 6 month interval generally indicates inactive disease (radiographically stable).

Postprimary ( Reactivation) TB CT Findings

- Lobular (airspace) consolidation (41%)
- Cavity (51%)
- Poorly defined nodule (endobronchial spread) (61%)
- Bronchial wall thickening (73%)
- Nodule or branching linear structure (95%)
- Hematogenous spread with small diffuse nodules

Resolution: disappearance of lobular consolidation, poorly defined nodules, and cetrilobular nodules or branching linear lesions (in that order)

Primary TB: Progressive Primary TB

- in 5-10% the infection is poorly controlled, resulting in progressive primary tuberculosis.
- The most common form of pulmonary tuberculosis in infants and children.
- 23-34% of all adult cases of tuberculosis (primarily HIV-associated)
Progressive Primary TB:
Radiographic Findings

• Parenchymal disease: areas of greatest ventilation-lower and middle lobes
• Lymphadenopathy
• Pleural effusion
• Miliary tuberculosis
• Obstructive atelectasis due to lymphadenopathy
• Normal chest radiograph

Progressive Primary TB:
Lymphadenopathy

• 83%-96% of pediatric cases
• Prevalence of lymphadenopathy decreases with increasing age
• Right paratracheal, hilar nodes most common, bilateral 15%
• Lymphadenopathy may result in lobar atelectasis due to bronchial compression.
• By CT: central areas of low attenuation with peripheral rim enhancement
Miliary TB

- Normal radiographic findings in the early stages, 25%-40% at initial presentation, can occur with progressive primary or reactivation disease
- Characterized by innumerable, 1-3mm noncalcified nodules in both lungs with mild basilar predominance
- 30% with associated TB findings including consolidation, cavitation, lymphadenopathy
- ARDS-rare
TB and AIDS: Radiographic Appearance

- The radiographic manifestations of HIV-associated pulmonary TB are dependent on the level of immuno-suppression.
  - Relatively intact cellular immune function (CD4 > 200): radiographic findings similar to non-HIV infected individuals (upper lobe, cavitary disease)
  - Severe immunosuppression (CD4 < 200): findings c/w primary disease or normal chest radiographs or dissemination with miliary pattern or extrapulmonary disease
TB and AIDS: Radiographic Appearance

• The presence of intrathoracic adenopathy in a patient with AIDS and poor immune function (very low CD4 count), without an explanation, should be considered TB until proven otherwise.
Role of CT in the Diagnosis of TB

- CT is not the primary radiologic diagnostic test for TB (CT is overused)
- Usually don’t need CT for cavitary consolidation
- If TB is a possible diagnosis, sputum for AFB should be obtained prior to CT
- In most instances, CT should be reserved for patients in whom the diagnosis is unclear

Role of CT in the Diagnosis of TB

- Reveals occult lung disease in patients with pleural effusion, pericarditis, etc.
- Reveals intrathoracic lymphadenopathy (children, HIV co-infected)
- Can suggest miliary disease
- Reveals alternative diagnoses (lung cancer)

Diagnosis of Tuberculosis: Microbiology

AFB Smears
AFB Cultures
Rapid Diagnostic Techniques: HPLC, Nucleic Acid Amplification Studies
Diagnosis of TB

AFB Smears

- Most rapid diagnostic test
- Need $10^3$ organisms/ml sputum for (+)
- Sensitivity and Specificity poor
- (+) in only about 70% of active TB cases
- (+) in patients with non-tuberculous mycobacterial disease
- Necessary for determining contagiousness

AFB Cultures

- Remains the "gold standard" for diagnosis
- Processing kills up to 90% of AFB
- More sensitive than smear ($10^1$ organisms/ml)
- Liquid media culture the standard technique
- (+) in > 90% of patients with cavitary disease, < 70% of patients with non-cavitary disease.
- Necessary for in-vitro susceptibility testing
- Lengthy: 1-3 weeks for liquid media (2-6 solid)

AFB Cultures

- More sensitive than smear ($10^1$ organisms/ml sputum)
- Required for drug susceptibilities
- Requires a quality specimen
- Processing kills up to 90% of AFB
- Positive for only ~ 80% active disease
- Lengthy:
  - 1-3 weeks for liquid media
  - 2-6 weeks by solid media
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

Diagnosis of Tuberculosis:
Rapid Diagnostic Techniques

- High Performance Liquid Chromatography (HPLC) : State of Texas Mycobacteriology Laboratory-routinely done for AFB smear (+) sputum specimens (> 90% sensitivity and specificity if smear (+))

Rapid Diagnostic Techniques:
Nucleic Acid Amplification (NAA) Tests

- Mycobacterium tuberculosis Direct Test (E-MTD, Gen-Probe)
  - Approved for AFB smear (+) and (-)
  - >95% sensitivity smear (+), 75-90% smear (-)
- Amplicor Mycobacterium tuberculosis test
  - > 95% sensitivity smear (+), 60-70% smear (-)
- >95% specificity for both tests
- Neither approved for non-respiratory specimens
Nucleic Acid Amplification (NAA) Tests

- “NAAT should be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a diagnosis of TB is being considered but has not yet been established, and for whom the test result would alter case management or TB control activities”
  – MMWR, January 2009, 58:7-10

Increasing Complexity of TB Control Efforts

- Foreign born
- Drug Resistant
- TB recipients of TNF alpha blockers
- TB in transplants
- TB in dialysis and chronic renal failure
- HIV TB
- MDR TB/XDR TB
- Decreasing clinical experience
- Loss of traditional experienced workers
- Providers may see only one case in a lifetime of practice
- TB care is more specialized

When to Ask for Consultation

- HIV TB
- Renal Disease
- Drug resistance
- Slow to convert
- Treatment relapse
- Treatment failure
- Toxicity
- Management of treatment interruptions
- When you have a question you need answered
Tuberculosis Consultation

• Center for Pulmonary and Infectious Disease Control (CPIDC): 1-800-428-7432

• Heartland National Tuberculosis Center: 1-800-TEX-LUNG