Diagnosis of Tuberculosis Infection and Disease

David E. Griffith, M.D.
Assistant Medical Director
Heartland National TB Center

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

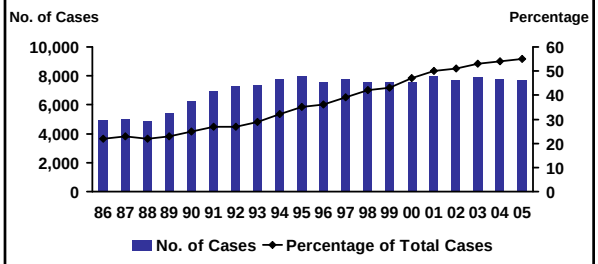
- **Among non-immigrants, TB significantly associated with**
  - **Poverty and unemployment**
  - **Homelessness**
  - **Congregate settings**
  - **Incarceration**
  - **Alcoholism and drug abuse**
- **HIV infection rates also high in some of these populations**

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*



*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 ????

679,305

N= ~ 59,000,000

Source: U.S. Department of Homeland Security, 2003 (2002 data)

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 continues 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, Adalimuamab

- 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

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

– 3antigens (ESAT-6, CFP-10, TB7.7)

– One immune mediator

INTERFERON GAMMA (IFN-GAMMA)

BASED TESTS FOR DIAGNOSING

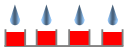
LTBI

BLOOD TESTS FOR LTBI

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

QuantiFERON-TB Gold (ELISA)

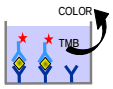
Obtain blood



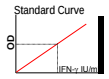
Transfer blood to wells and add antigens

Culture overnight. TB-infected individuals secrete IFN-γ

Harvest supernatants and perform ELISA



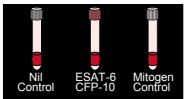
Wash, add substrate, incubate 30 min



Measure OD and determine IFN-γ levels

QuantiFERON-TB Gold In Tube

Stage One – Blood Incubation and Harvesting



1. Collect blood. Incubate at 37°C for 16-24 hrs.

2. Centrifuge tubes for 5 minutes.

IFN-γ stable refrigerated for at least 8 weeks.

Stage Two – Human IFN-γ ELISA

3. Add plasma and conjugate to ELISA plate. Incubate for 120 mins.

4. Wash and add substrate. Read absorbance after 30 min.

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

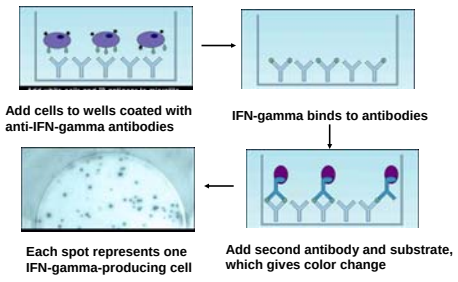
INDETERMINATE IGRA RESULTS

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

Elispot Test

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

T-SPOT TB (ELISPOT)



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

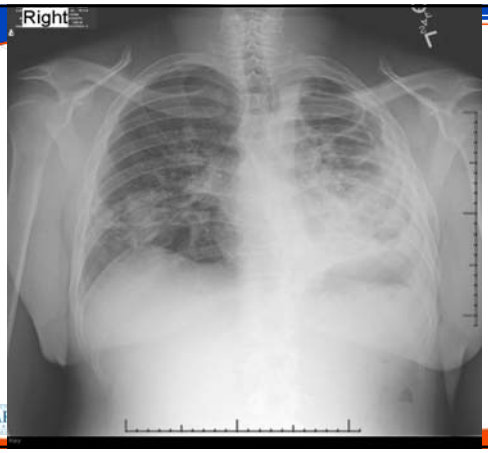
- **Iatrogenic immunosuppression (dialysis, organ transplantation, anti-TNF-alpha).**
- **Young children, HIV infected.**
- **Evaluate risk of progression to TB disease in patients with (+) IFN-gamma tests.**
- **Head to head evaluation of ELLISPOT vs. QFN-TB-Gold.**
- **Short and longterm variability**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

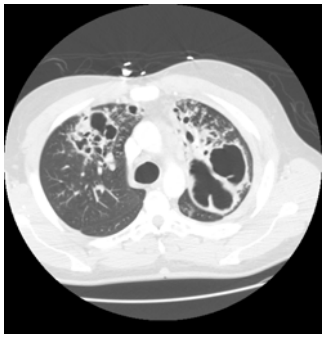
IFN-gamma Based Diagnostic Tests for TB

- 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

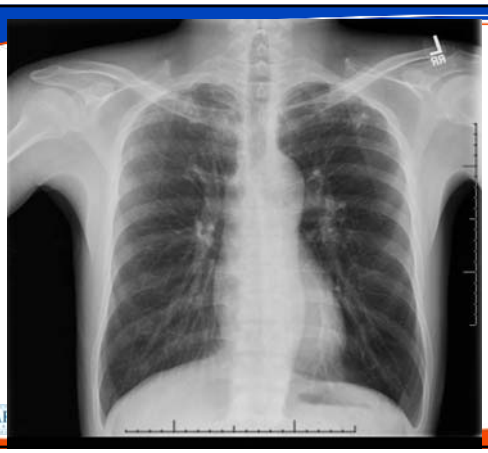
- **Prevent progression of infection to disease**
- **Aid in the diagnosis of TB disease**
- **Interrupt transmission of disease**
  - **The next step that must be taken to move toward TB elimination in the US**





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 (+)

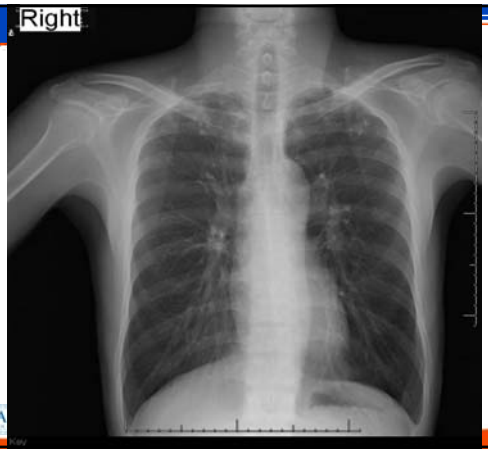


Managing patients with abnormal CXR's and (+) PPD's

- 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

Diagnosis of Tuberculosis

- 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
  - CXR: if suggestive of TB collect 3 sputum specimens for AFB and culture
- 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

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 >7days
- 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

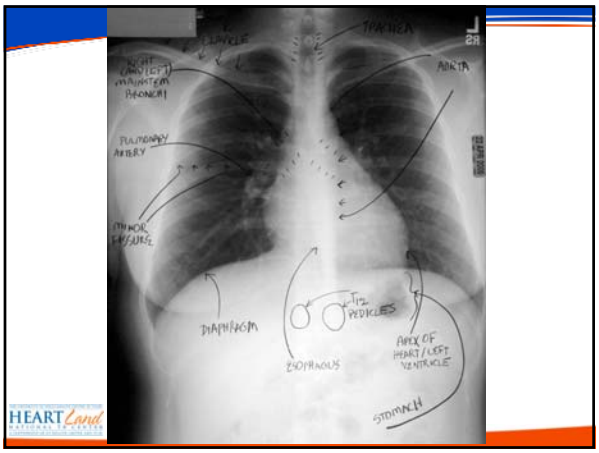
Controlling TB in U.S. MMWR: Nov 2005

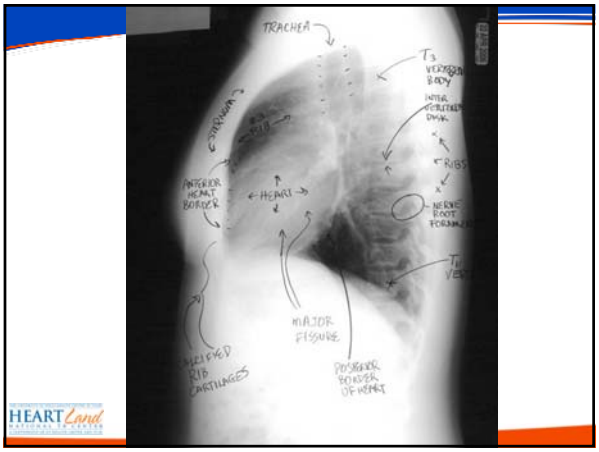
Postprimary (Reactivation) TB:Radiographic Findings

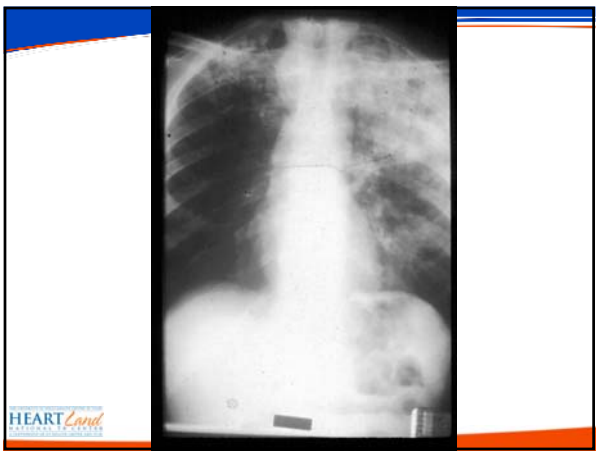
- Primarily apical/posterior segments of the upper lobes, superior segments of lower lobes (90%)
- Prediliction for Reactivation TB to involve the upper lung zones
  - Relatively higher oxygen tension in the upper lung zones
  - Impaired lymphatic drainage in the upper lung zones

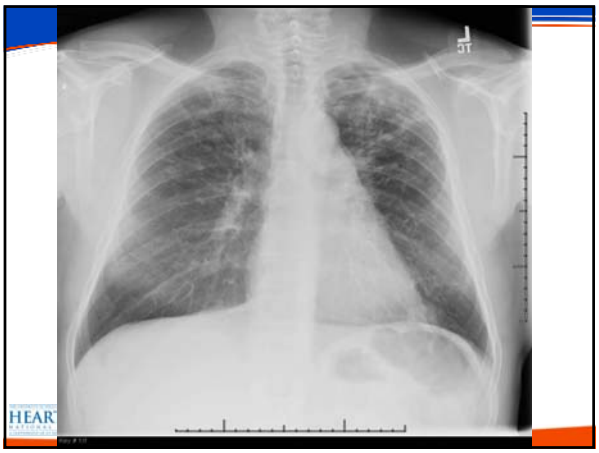
Post Primary (Reactivation) TB: Radiographic findings

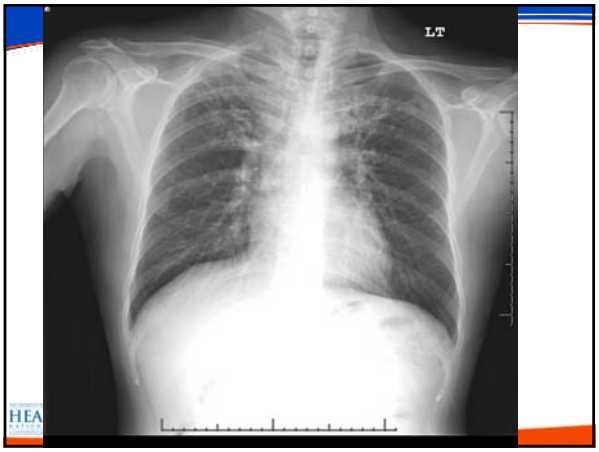
- Patchy consolidation with streaky opacities (100%)
- Cavitation 45%
- Bronchogenic spread of disease with ill-defined nodules (20-25%)
- Fibrosis (30%)
- Pleural effusion (20%)


TRACHEA
AORTA
PULMONARY ARTERY
DIAPHRAGM
T12 PEDICLES
APEX OF HEART / LEFT VENTRICLE
ESOPHAGUS
STOMACH
HEART Land


TRACHEA
T3 VERTEBRAL BODY
RIBS
HEART
MAJOR FISSURE
HEART Land


HEART Land

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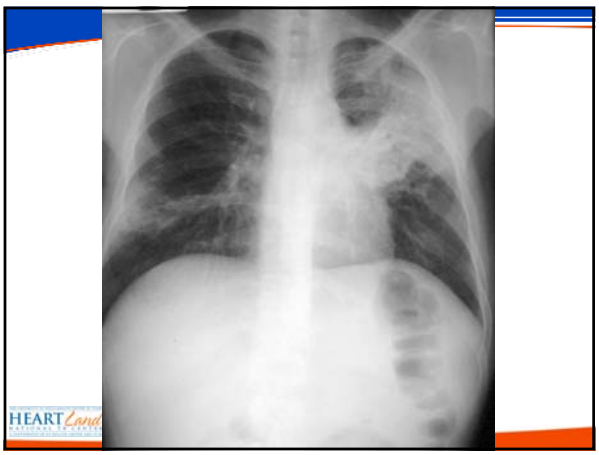
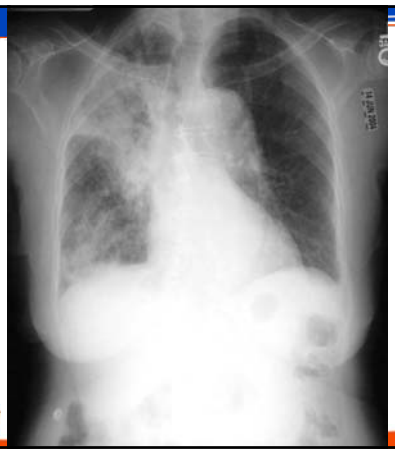


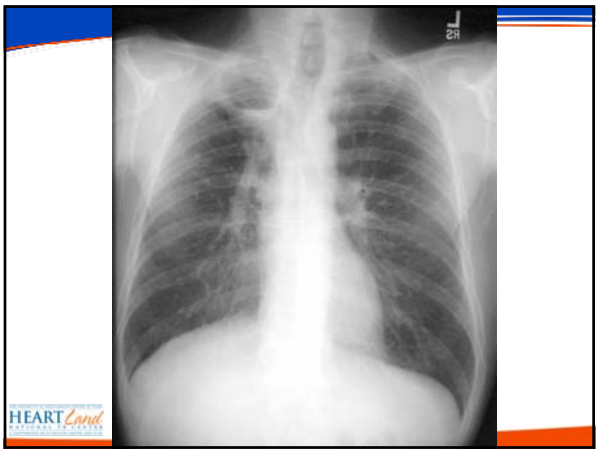


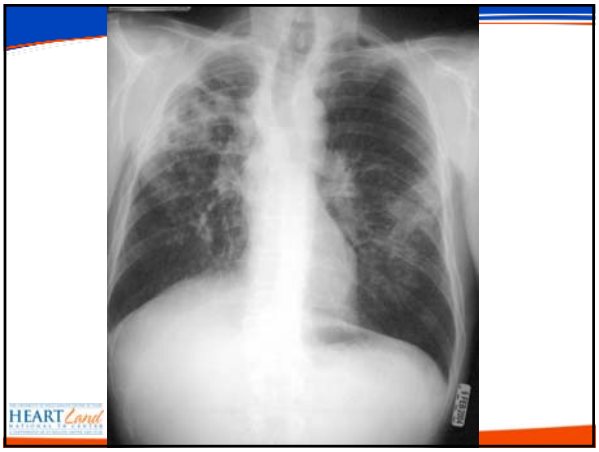
Postprimary (Reactivation) TB Cavities

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

Primary TB: Progressive Primary TB

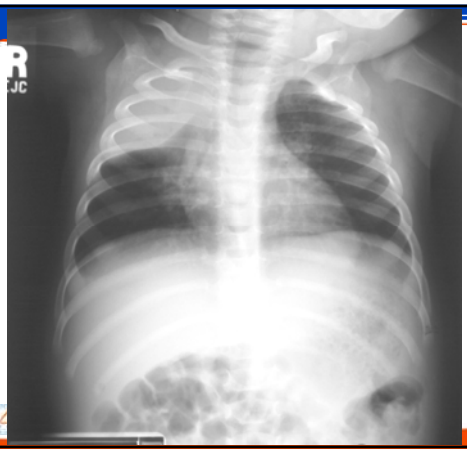
- in 5-10% the infection is poorly controlled, resulting in progressive primary tuberculosis.
- The most common form of pulmonary tuberculosis in infants and children.
- 23-34% of all adult cases of tuberculosis (primarily HIV-associated)

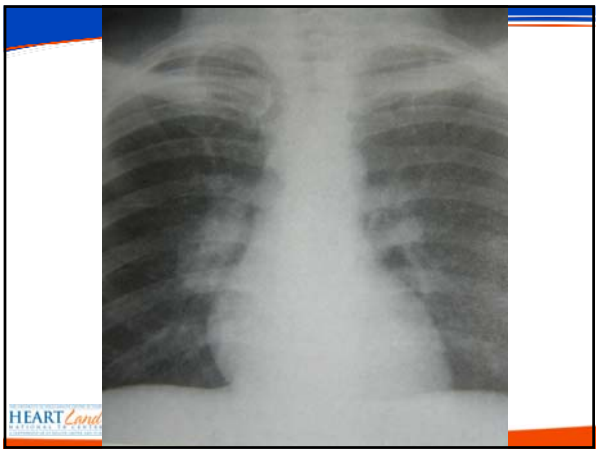
Progressive Primary TB: Radiographic Findings

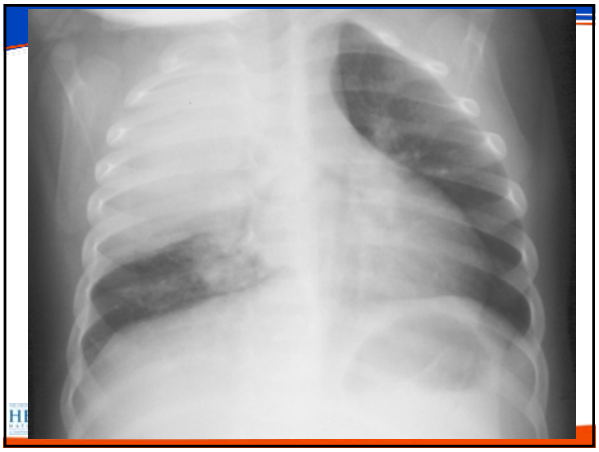
- Parenchymal disease: areas of greatest ventialtion-lower and middle lobes
- Lymphadenopathy
- Pleural effusion
- Miliary tuberculosis
- Obstructive atelectasis due to lymphadenopathy
- Normal chest radiograph

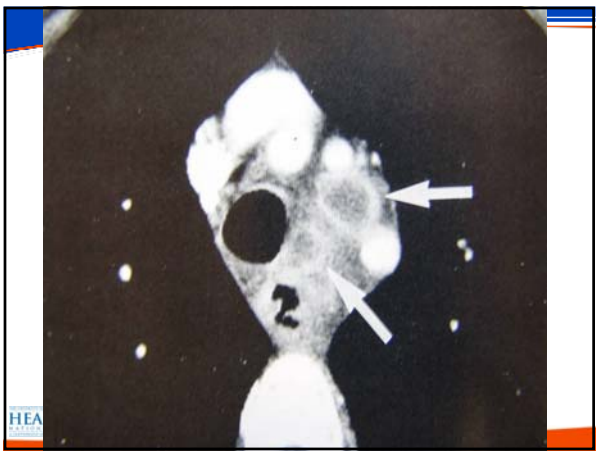
Progressive Primary TB: Lymphadenopathy

- 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



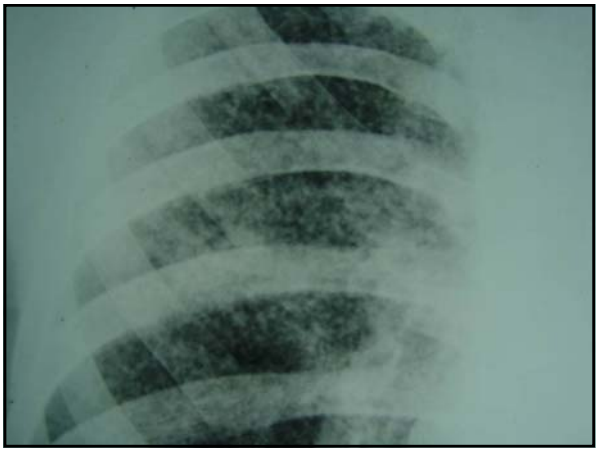


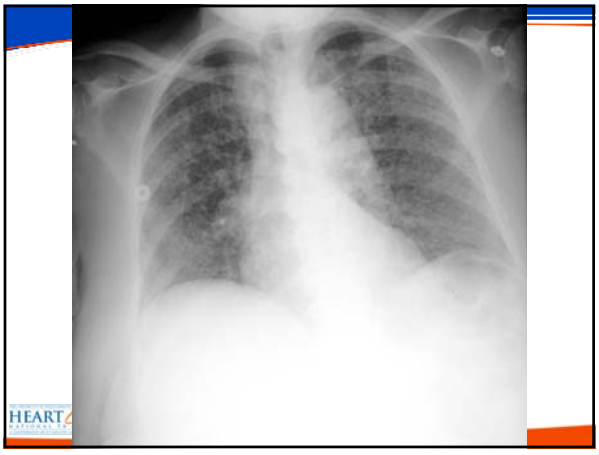


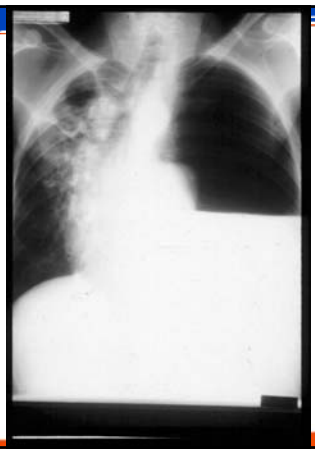


Miliary TB

- 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

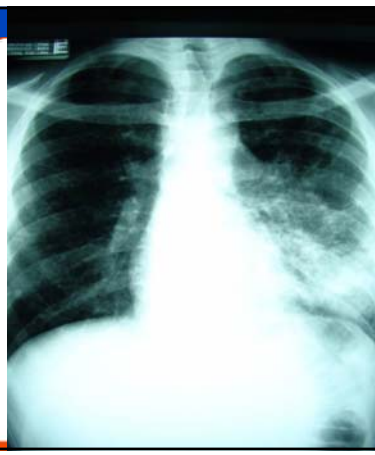


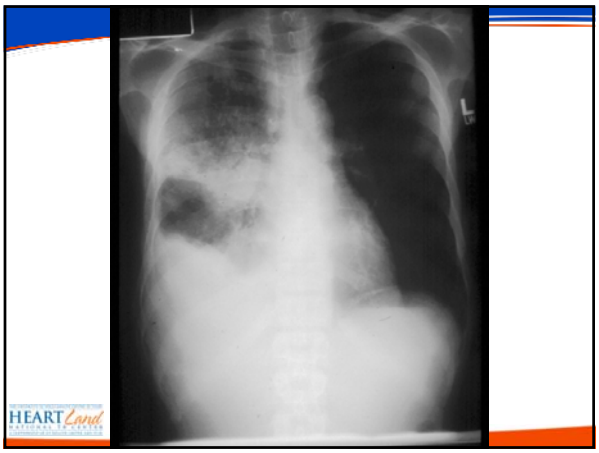


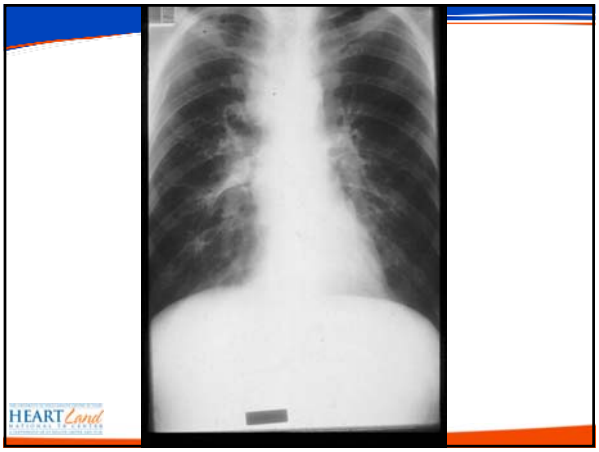


TB and AIDS: Radiographic Appearance

- 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

Diagnosis of TB:
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)

Diagnosis of TB:
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 Diagnositic 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

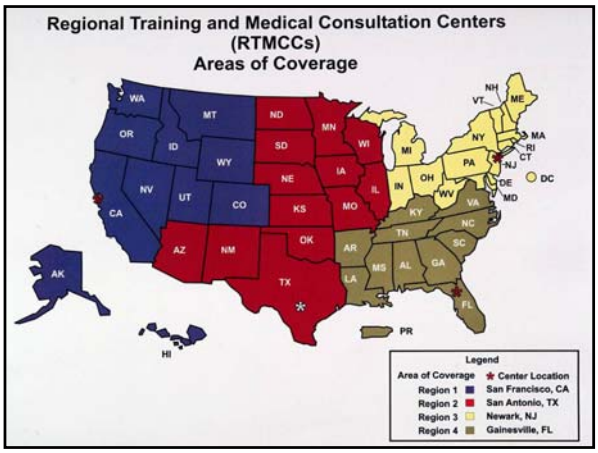
- "NAAT should be performed on at least one respiratory speciemen from each patient with signs and symptoms of pulmonary TB for whom a diagnosis of TB is being considered but has not yet been established, and for whom the test result would alter case management or TB control activities"
  - MMWR, January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