Tuberculosis
Epidemiology, Pathogenesis & Diagnosis

TB/NTM lectures - housekeeping

- "Know This!!" markers - indicate key lecture points.
- All epi figures are incident (new case) numbers.
- To print slides, use "Black and White" or "Grey Scale" settings.
- Questions about lecture content can be emailed
- Dr. Sabzwari's email = rabeeya.sabzwari@va.gov

- Fellowship - Infectious Diseases at University of Illinois
- Infectious Diseases attending - IU health system for 2+ years
- Antimicrobial Stewardship Director at Hines VA 2013 ......
- Assistant Professor of Medicine - Division of Infectious Ds.
- Weekly mycobacterial diseases clinic at Loyola
Global TB Perspective

- 1/3 world infected
- 22.4 million - extra, world incidence
- Approx. 1.4 million deaths globally

Incident (new) cases of TB disease

TB - History in the U.S.

In the early 1900’s, TB was the most common cause of death in the U.S.

New England 1800’s: MORTALITY = 1,600/100,000

Translated to Chicago today -- >100,000 deaths/year

TB - Incidence in the U.S.

Reported Tuberculosis (TB) Cases
United States, 1982-2016*

*As of June 21, 2017.
National TB Perspective

- ~10 million Americans are infected (positive skin tests)

DISTINCTION BETWEEN INFECTION AND DISEASE

- Only 7-10% infected people develop disease in their lifetimes — the remainder have latent infections.

- AIDS patients — of those who are infected with TB, 10% per year will develop active disease.
Persons who are more likely to be infected with TB

- Close contacts of an active case
- Foreign-born persons from areas where TB is common
- Medically underserved, low income populations
- Residents of long-term care facilities
- Persons who inject drugs
- Migrant farm workers and homeless persons
- Occupationally exposed persons - e.g., health care workers

Persons who are more likely to progress to disease

- HIV infection
- Recently infected with TB (within the past 2 years)
- Certain medical conditions - silicosis, gastrectomy, jejunoo-ileal bypass, weight of 10% of more below ideal body weight, chronic renal failure, diabetes mellitus, chronic immunosuppressive therapy (e.g., prolonged, high-dose corticosteroids), leukemia, lymphoma, and other malignancies
- Injection drug use
- History of inadequately treated TB

TB Transmission

- Almost exclusively airborne
- Close contacts are at greatest risk (approx. 20%)
- AIDS - the only OI transmitted to normal people
- Nosocomial - (in health care setting)
- Extrapulmonary TB is rarely contagious
- Transmission by ingestion - very rare now
TB Pathogenesis

- "Droplet nucleus" - alveolar macrophage access
- Regional lymph node and blood-borne spread
- "Ghon focus" - primary site of lung infection
- "Ranke complex" - calcified Ghon complex = Ghon focus + mediastinal lymph nodes
- Immunopathogenesis - TB antigens → lymphoproliferation, cytokine production, granuloma formation, tissue destruction; positive PPD skin test and Quantiferon assay

TB Pathogenesis

- "Primary" (initial) TB infection - results in either:
  - Latent TB infection (LTBI) > 90% initial infections
  - Primary progression to active TB (mostly HIV/AIDS)
- "Secondary" disease (reactivation) < 10% infections
  - Usually (80-90% of 2nd disease) - upper lung infiltrate/cavitation
  - Less commonly (10-15% of 2nd disease) - "extrapulmonary" sites of reactivation from initial blood borne spread of infection (e.g., brain [meninges], heart [pericardium], bone, GU)
**TB - Lung Granuloma**

- Pathologic endothelial cells
- Multinucleated giant cells

**Central necrosis**

- Amorphous necrotic material

**TB - Ghon Complex**

When these lesions become calcified, they are called the Ranke Complex.

**Ghon Focus, Complex / Ranke Complex**
TB - Cavitary Lung Disease

TB Diagnosis

- **Medical history** - nonspecific symptom complex
- **Physical examination** - nonspecific or NO findings
- **Radiographic examination** - upper lung field infiltrates, cavities, ± lesions in other organs (extrapulmonary TB)

Extrapulmonary TB (XPTB)

- **Mechanism and incidence:**
  - Sites that progress from original, bacteremic phase: brain, epiphyses of long bones, kidneys, vertebral bodies, lymph nodes
  - Many XPTB pts have co-existing pulm TB
  - Immunocompetent pts: ~65% pulm, ~15% only XPTB
  - AIDS pts: ~1/3 pulm TB, ~1/3 only XPTB, ~1/3 both (i.e., increased XPTB)

- **Sites of infection** (think TB w/ lymphocyte-predominant fluids)
  - CNS TB - peak incidence in children, 0-4 yr of age
  - TB Pericarditis - more common in older pts (>50-55 yr old)
  - Osteomyelitis of spine: "Pott's disease": lower thoracic, upper lumbar
  - TB Peritonitis
  - GU/Gyne - local symptoms; genitul TB - female > male
TB - Differential Diagnosis

- **Medical history** - TB exposure; risk groups
- **Physical examination** - nothing specific to help
- **Other chronic granulomatous infections:**
  - Nontuberculous mycobacterial infections
  - Fungal infections

**TB Diagnosis - Tuberculin (PPD) Skin Test**

**Interferon Gamma Production Assays In the Diagnosis of Tuberculosis**

Lancet Infect Dis 4:761, 2004
TB Diagnosis - Microbiology

- Sputum "AFB" smears; cultures from otherwise sterile sites
- Sputum - nucleic acid amplification testing (NAAT)
- Multiple culture techniques:
  - Solid media --> colony morphology
  - Liquid media --> rapid detection
- HPLC - mycolic acids --> speciation
- Molecular diagnostics --> Genetic probes; PCR
- Antibiotic susceptibility testing

TB Diagnosis - Sputum AFB Stain and Molecular Diagnostics

"Acid Fast" Auramine-Rhodamine Fluorescence

TB Diagnosis - Culture

Growth on agar

Principles of the BACTEC System:
1. ^14C substrate utilization → ^14CO₂
2. Quantity of ^14CO₂ → Growth Index (GI)
Nontuberculous Mycobacteria
environmental pathogens that affect predisposed hosts


Nontuberculous Mycobacteria (NTM)

TB
M. tuberculosis

Nontuberculous Mycobacteria (Runyon Classification)

Group I (Photochromogens)
M. kansasi
M. marinum
M. xenopi

Group II (Scotochromogens)
M. szulgai
M. scrofulaceum
M. tuberculoideum

Group III (Nonphotochromogens)
M. abscessus
M. chelonae
M. fortuitum

Group IV (Rapid Growers)

Pathogenic Mycobacteria

Environmental Sources of NTM

- **Bioaerosols**
- **Water** - fresh, salt, domestic, hot tubs, swimming pools
- **Soil** - 80% of soil samples (especially, SE U.S.)
- **Nosocomial sources**
  - Rapid growers - most common pathogens identified
  - Slow growers - MAC, M. xenopi - hospital water supplies
Predisposing Conditions for NTM Lung Disease

- Pre-existing, underlying lung abnormalities:
  - COPD - emphysema
  - Bronchiectasis - dilated, scarred airways (↑ AFB colonization)
  - Previous chest radiotherapy (e.g., for breast Ca → lung fibrosis)
  - Interstitial pulmonary fibrosis (IPF/ILD)
  - Congenital cystic abnormalities
  - Previous pulmonary emboli/infarction
  - Recurrent aspiration pneumonia (source of bronchiectasis)

Common theme: structural lung abnormality = predisposing factor

Contrast of NTM Infections with TB

- NTM = environmental in origin (not human-to-human transmission)
- NTM infections "require" an underlying predisposition to cause dis.
- NTM infections do not have a prolonged latent phase.
- NTM infections do not disseminate outside the lung (XC in AIDS!!).
- Skin testing and Quantiferon testing are not available for NTM.
- Radiographic presentations of NTM lung disease may differ from TB.

Older male smoker with emphysema and cavitary MAI disease
Female nonsmoker with mid-lung bronchiectasis and NTM disease

Think TB!

But most patients you see who look like they have TB will turn out to have NTM disease