Emphasis on:

• Tuberculosis
• Leprosy
Mycobacterium leprae
• There are several other Mycobacteria
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## Classification of Mycobacteria Pathogenic for Humans

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Mycobacteria

- obligate aerobe
- acid-fast rods
Why acid-fast?

Lipid-rich cell wall

(60% of the cell wall is lipid, i.e. mycolic acids, glycolipids, LAM)
High Lipid Content of Cell Wall

- Resistance to Disinfectants
- Resistance to commonly-used antibiotics
Acid-fast stain (AFB)
Ziehl-Neelsen Stain with carbolfuchsin
Mycobacterium tuberculosis
Mycobacteria tuberculosis
M. Avium intracellulare
Fluorochrome Stain

Auramine

Auramine - Rhodamine
Mycobacteria: species identification

- morphologic properties
- biochemical reactions
- analysis of cell wall lipids
- nucleic acid probes
- nucleic acid sequencing
Tuberculosis

- A third of the world’s population is infected with Mycobacterium tuberculosis
- A total of 8.8 million new cases each year
- 2 million deaths every year
- About 10% of infected normal people will develop disease at some time
- Disease most common in Southeast Asia, Subsaharan Africa and East Europe
- Major opportunistic infection among HIV/AIDS patients
- Humans are the only natural reservoir
- Person to person spread by aerosol
Tuberculosis (TB, consumption)

- *M. tuberculosis*
- major human disease
  - healthy people
- problems
  - association with AIDS
  - multiple drug-resistance
Tuberculosis: Transmission

*M. tuberculosis*: person to person through inhalation

*M. Bovis*: ingestion of contaminated milk

*M. Avium intracellulare*: mainly by ingestion of contaminated food or water, but may be also by inhalation

*M. Leprae*: person to person via inhalation or skin contact
Transmission and Pathogenesis
Symptoms of Pulmonary TB

- Productive, prolonged cough (duration of ~3 weeks)
- Chest pain
- Hemoptyisis
Systemic Symptoms of TB

- Fever
- Chills
- Night sweats
- Appetite loss
- Weight loss
- Easy fatigability
Tuberculosis: Clinical Features

Primary
Secondary (reactivation)
Extrapulmonary TB (GI, Menenges, Bone, etc.)
Miliary (Dessiminated TB)
Common Sites of TB Disease

- Lungs
- Pleura
- Central nervous system
- Lymphatic system
- Genitourinary systems
- Bones and joints
- Disseminated (miliary TB)
Pathogenesis of tuberculosis

- infects lung

- distributed within macrophages

- facultative intracellular pathogen
  - inhibits phagosome-lysosome fusion
  - resists lysosomal enzymes
Cell-mediated immunity - tuberculosis

- **infiltration**
  - macrophages
  - lymphocytes

- **granulomas**

- **tubercules**
Mycobacterium tuberculosis in lung
Diagnosis of Mycobacterial Disease

**X-ray**

**Skin Test** (Tuberculin, PPD, Mantoux)

**Microscopy:** Z-N Stain, Fluorochrome Stain

**Culture:** Solid Media (Lowenstein Jensen)

Automated Liquid Media (Bactec)

**DNA Amplification:** PCR, LCR (ligase chain reaction)
Chest Radiograph

- Abnormalities often seen in apical or posterior segments of upper lobe or superior segments of lower lobe

- May have unusual appearance in HIV-positive persons

- Cannot confirm diagnosis of TB
Skin Testing

- delayed hypersensitivity
  - tuberculin
  - protein purified derivative, PPD
Tuberculosis: Laboratory Diagnosis

**Sputum:** most common specimen

**Microscopy:** Z-N Stain, Fluorochrome Stain

**Culture:** Solid Media (Lowenstein Jensen)

Automated Liquid Media (Bactec)

**DNA Amplification:** PCR, LCR (ligase chain reaction)
Specimen Collection

- Obtain 3 sputum specimens for smear examination and culture
- Persons unable to cough up sputum, induce sputum, bronchoscopy or gastric aspiration
- Follow infection control precautions during specimen collection
Laboratory diagnosis

*M. tuberculosis* (culture)

- grows very slowly
  - several weeks
  - non-pigmented colonies
  - niacin production

*differentiates from other mycobacteria*
Tuberculosis

• polymerase chain amplification
  – rapid diagnosis
Testing for TB Disease and Infection
Administering the Tuberculin Skin Test

• Inject intradermally 0.1 ml of 5 TU PPD tuberculin

• Produce wheal 6 mm to 10 mm in diameter

• Do not recap, bend, or break needles, or remove needles from syringes

• Follow universal precautions for infection control
Reading the Tuberculin Skin Test

- Read reaction 48-72 hours after injection
- Measure only induration
- Record reaction in millimeters
Positive skin test - tuberculosis

- indicates exposure to organism
- does not indicate active disease
Treatment

- Multiple antimycobacterial agents required (e.g. isoniazid (INH), + rifampicin + pyrazinamide + ethambutol)
- The problem of multiple drug resistance
- The importance of sensitivity testing
Treatment of TB for HIV-Negative Persons

- Include four drugs in initial regimen
  - Isoniazid (INH)
  - Rifampin (RIF)
  - Pyrazinamide (PZA)
  - Ethambutol (EMB) or streptomycin (SM)

- Adjust regimen when drug susceptibility results are known
Antibiotic treatment - tuberculosis

- extensive time periods (e.g. 9 months)
- organism grows slowly, or dormant
- Three to four antibiotics
  - resistance minimized
Treatment of TB Disease
Adherence

- Nonadherence is a major problem in TB control
- Use case management and directly observed therapy (DOT) to ensure patients complete treatment
Multidrug-Resistant TB (MDR TB)

- Presents difficult treatment problems
- Treatment must be individualized
- Clinicians unfamiliar with treatment of MDR TB should seek expert consultation
- Always use DOT to ensure adherence
Prevention

- Vaccination with BCG (bacillus Calmette-Guerin)
- Chemoprophylaxis: with NIH
- Isolation of sputum-positive patients
- General measures to improve nutrition and hygiene
BCG Vaccination
Infection Control in Health Care Settings
Vaccination

- **BCG vaccine**
  - an attenuated strain of *M. bovis*
  - not effective

- **in US,**
  - incidence is low
  - vaccination not practiced
  - immunization interferes with diagnosis
M. bovis

• spread from cattle

• infected cattle are culled
  – positive skin test

• rarely seen in US
Mycobacterium avium and AIDS
M. avium- M. intracellulare complex (M. avium)

- non-AIDS
  - infection almost never
- AIDS
  - major bacterial opportunist
- multiple drug-resistance
Other mycobacteria

- Atypical
Atypicals - mycobacteria
(other than *M. tuberculosis* and *M. leprae*)

- infect compromised host
- not transmitted man - man
  – healthy people
Atypical mycobacterial diseases

- tuberculosis-like
- leprosy-like
Mycobacteria and AIDS

• *M. avium* is much less virulent than *M. tuberculosis*
  – does not infect healthy people
  – infects AIDS patients

• *M. avium* infects
  – when CD4 count greatly decreased

• *M. tuberculosis* infection
  – infects healthy people
  – infects AIDS patients
  • earlier stage of disease
  • more systemic
Clinical features with AIDS

- **systemic disease (versus pulmonary)**
  - greater in AIDS

- lesions often lepromatous
Other atypicals

- pigmented or not
- pigmentation
  - light
  - dark
- growth
  - fast
  - slow
Mycobacterium Kansasii
Mycobacterium leprae
Mycobacterium leprae

• **Epidemiology**
  - more than 620,000 new cases were reported in 2002, with most cases in India, Nepal, and Brazil
  - Few cases under treatment in Saudi Arabia (Haddah Hospital)
  - Lepromatous form, but not tuberculoid form, is highly infectious
  - Person to person spread by direct contact or inhalation of aerosols
Mycobacterium leprae

- **Physiology and Structure:**
  - acid fast rods
  - lipid rich cell wall
  - unable to be cultured on artificial media
  - diagnosis made with specific skin test (tuberculoid form of disease) or acid-fast stain (lepromatous form)
Mycobacterium leprae

- **Virulence:**
  - Capable of intracellular growth
  - Disease primarily from host response
Mycobacterium leprae

- **Disease:**
  - tuberculoid form of leprosy
  - lepromatous form of leprosy
Leprosy

- tuberculoid
- few organisms
- active cell-mediated immunity

- lepromatous
- immunosuppression
- few organisms
Mycobacterium leprae

• **Clinical Manifestations:**
  
  **Tuberculoid form:**
  - hypopigmented skin lesions
  - nerve damage with complete sensory loss
  - visible enlargement of nerves

  **Lepromatous Form:**
  - Extensive tissue destruction (e.g. nasal cartilage, bones, ears)
ulcers, resorption of bone
worsened from careless use of hands (nerve damage)
Lepromatous Leprosy
Mycobacterium leprae
Production of *M. leprae* antigens and pathogenesis studies

- *in vitro*
  - unculturable

- *in vivo* growth
  - low temperature
  - armadillo
  - mouse footpad
Mycobacterium leprae

- **Diagnosis:**
  - skin testing (to confirm tuberculoid form)
  - microscopy (with lepromatous form) - acid-fast staining of skin biopsies
  - clinical picture
Mycobacterium leprae

Treatment and Prevention

- Tuberculoid form treated with rifampicin and dapsone for 6 months
- Lepromatous form treated for 12 months with rifampicin + dapsone + clofazimine
- Control through prompt diagnosis and treatment of infected people