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**TUBERCULOSIS - HISTORY**
- Described in ancient civilizations
- 1882 – Koch identifies *Mycobacterium tuberculosis*
- Significant mortality until 20th century
- 1946 – Streptomycin
- 1952 – Isoniazid

**TUBERCULOSIS - WORLDWIDE SIGNIFICANCE**
- 1/3-1/2 population infected
- Leading cause of death due to single microorganism - ? Surpassed by HIV
- 8-10 million new cases active disease/year
- 2 million deaths/year – 4-5% all deaths

**Reported TB Cases, U.S. 1975-2002**

**TUBERCULOSIS - U.S.**
- 1882-1984 - decrease in incidence
- 1985-1992 - 20% increase
- 1992-2002
  * 43% decrease nationally
  * >70% decrease in New York City

**M. tuberculosis Genome**
- Sequenced 1998
- 4.4 million base pairs, 4000 genes
  * 40% proteins - function known
  * 44% proteins - similar to those previously identified
  * 16% proteins - novel
- Genetically homogeneous relatively young organism in evolutionary terms
### M. Tuberculosis Genome
- Two-component sensor/response regulatory systems - few
- Eucaryotic-like systems
- Drug resistance genes
- Lipogenesis/lipolysis
  - High proportion of genome
- Common repetitive sequences
  - ? antigenic variation

### TB - Host Defense Mechanisms
- Same as those against respiratory tract infections in general
- Cellular Immunity
  - T cells
  - Macrophages

### M. tuberculosis – VIRULENCE FACTORS
- High cell wall lipid content
- Growth Requirements
  - Elevated CO\(_2\)
  - Acidic pH
- Slow growth rate
- Latency/dormancy

### M. Tuberculosis – Intracellular Pathogen
- Uptake by cells
- Survive intracellularly
- Evade recognition by cells of immune system

### TB – Transmission/Risk of Infection
- Inhalation of droplet nuclei
- Risk of infection
  - Proportional to exposure
- Infection vs. Active Disease
  - Time
  - Age
  - General health status

### TB - Pathogenesis
- Primary Infection
- Development of immune response
- Progressive primary disease
- Persistence of viable organisms
- Reactivation disease
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- Primary Infection
- Development of immune response
- Progressive primary disease
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### TB – Pulmonary Disease
- Systemic symptoms
- Cough
- (+) Sputum smear for acid fast bacilli
- (+) Sputum culture for *M. tuberculosis*
- Chest X-Ray

### TB – Extrapulmonary Disease
- Dissemination of *M. tuberculosis* during initial infection
- Systemic symptoms
- Diagnosis – biopsy and culture
- Common locations
  - Lymph nodes
  - Central nervous system
  - Miliary disease

### TB in Patients Infected with HIV
- Increased risk of active disease
- Increased risk of progressive primary disease
- Increased incidence of extrapulmonary disease
- Lack of inflammatory response

### Tuberculin Skin Testing
- **PPD** – purified protein derivative
- **Interpretation**
  - ≤ 5 mm = non-reactive or negative
  - ≥ 5 mm = positive in patients at highest risk
  - ≥ 10 mm = positive in patients at some risk
  - ≥ 15 mm = positive in patients without risk
- **Causes of false reactivity**
- **Causes of false negatives**
- **Booster effect**

### QuantiFERON-TB Test
- New blood test FDA approved in 2001
- Measures gamma interferon production by lymphocytes following incubation with PPD or *MTb* antigens
- Limited experience/data to date
- Advantages – requires single visit, more objective
- Disadvantages – requires processing by lab with appropriate capability within 12 hrs,
TB - Diagnosis

- History/Physical Exam
- Tuberculin skin testing
- Direct exam for AFB and/or histopathology
- Culture
- Nucleic acid based testing

Classification of infection with *M. tuberculosis*

Implications for treatment

- (+) Exposure, no infection, PPD (-)
- (+) Infection (PPD(+)), No active disease
  - 2000 Guidelines
  - (+) Infection, active disease
  - 2003 Guidelines

TB – Indications For Treatment

(+) PPD, No Active Disease (Latent TB)

Recently infected individuals

- Recent (≤ 2 years) conversion to (+) PPD
- Close contacts of patients with infectious TB
- Persons living and working in settings with increased likelihood of TB exposure
- Children < 5y/o

Increased risk of progression from LTBI to active TB

- History or chest x-ray evidence of prior TB, previously untreated patients
- Immunosuppressed patients (HIV, drug-related)
- Underlying disease

TB – Indications For Treatment

(+) PPD, No Active Disease (Latent TB)

Increased risk of progression from LTBI to active TB

- Immigration within 5 years from areas with high rates of TB
- Children, adolescents, and young adults
- Underweight persons (> 10% ideal body weight)
- Injection drug users (independent of HIV (+))

TB – Indications For Treatment

(+) PPD, No Active Disease – Regimens

(Treatment of latent TB)

2000 Guidelines

- Isoniazid x 9 mos – preferred regimen
- Other regimens appear effective
  - Rifampin x 4 months
  - Rifampin/PZA x 2 months –no longer recommended - increased hepatotoxicity
- Use of single agent effective
- Not 100% effective
TB – Active Disease Treatment Principles

• Multiple drugs
• Prolonged course of treatment
  • High incidence of spontaneous drug resistance
  • Large burden of organisms
  • Slow replication

TB Drug Resistance Rates

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<td>1992</td>
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<td>≥ 1 drug resistance</td>
<td>14%</td>
<td>33%</td>
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<td>2002</td>
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<tr>
<td>≥ 1 drug resistance</td>
<td>13%</td>
<td>14-15%</td>
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<tr>
<td>MDR</td>
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<td>3%</td>
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TB – Treatment Principles

• Antimicrobial susceptibility testing for all *M. tb* isolates
• Supervised treatment

TB – Treatment Regimens

• Initial treatment – 4 drugs
  • Isoniazid
  • Rifampin
  • Pyrazinamide
  • Ethambutol
• 6 month regimen – minimum
• Extrapulmonary disease
• Multi-drug resistant *M. tb*

BCG Vaccine

• *Bacillus Calmette Guerin*
• Controversies
  • No consistent efficacy
  • Short-lived protection
• Probable benefit in infants and young children
• Effect on skin testing

Non-Tuberculous Mycobacteria

• *Mycobacterium leprae* – cause of leprosy

Other Non-tuberculous mycobacteria

Distinguishing characteristics:

• Differentiated from *M. tb* microbiologically
• Ubiquitous – in soil, H₂O, food
• NO person-person transmission
## Non-Tuberculous Mycobacteria

### Classification by Major Clinical Syndromes

**Pulmonary**
- *M. avium complex, M. kansasii*

**Lymphadenitis**
- *M. avium complex, M. scrofulaceum*

**Skin/Soft Tissue**
- *M. fortuitum, M. chelonae, M. abscessus, M. marinum*

**Disseminated Disease**
- *M. avium complex, M. haemophilum*