Pulmonary Tuberculosis

Jing ZHANG (张静), MD, PhD
zhang.jing@zs-hospital.sh.cn

Department of Pulmonary Medicine
Zhongshan Hospital
Fudan University
OUTLINE

• Etiologic agents
• Epidemiology
• Pathogenesis and immunity
• Clinical manifestation
• Lab investigations and diagnosis
• Treatment (drugs, regimen, drug-resistant TB)
• Prevention (vaccine, preventive treatment, disease control)
Robert Koch Discovers Mycobacterium (1882)
Etiology

- **Mycobacteria**
  - M. tuberculosis & M. bovis
  - M. tuberculosis - 90% of human disease
  - M. avium, M. intracellulare in AIDS - Atypical TB
- **Bacilli**, aerobic, non motile, no toxins, no spore.
- **Mycolic acid wax** in cell wall
- **Carbol dye** - Acid & alcohol fast (AFB)
Epidemiology

- Infects one third of world population..!
- 8-10 million new cases every year
- 3 million deaths due to TB every year
- 2/3 patients are young adults
- Drug resistance is increasing
A Global Emergency

The Tuberculosis in the beginning of the 21\textsuperscript{st} Century declared as Global Emergency (WHO)

• Under privileged population -
  — Crowding, Poverty, malnutrition, single male..! – economic burden.

• Since 1985 incidence is increasing in west
  — AIDS, Diabetes, Immunosuppressed patients, Diabetes, Drug resistance.
Tuberculosis in the era of HIV / AIDS

- HIV / AIDS epidemic led to large increase of Smear negative pulmonary tuberculosis which in turn has led to poor treatment outcomes, and early mortality
- Frequently involves Lower lobes of Lungs
Tuberculosis - Important communicable disease spread by respiratory route

- Infection sources: patients with infectious pulmonary TB, esp. sputum positive ones
- A disease of respiratory transmission: droplets
  - Patients with the active disease (bacilli) expel them into the air by coughing, sneezing, shouting, or any other way that will expel bacilli into the air
- Determinants of transmission
  - The probability of contact with a case of tuberculosis
  - the intimacy and duration of that contact
  - the degree of infectiousness of the case
  - the shared environment of the contact: crowding, poor ventilated
- Susceptible population
  - elderly people, children, ICH (HIV, DM...
Pathogenesis of TB

Infection - Immunity

MBBS project, Zhongshan Hospital
Two host responses to TB

• Tissue-damaging response
  – Delayed-type hypersensitivity (DTH) reaction to various bacillary antigens
  – It destroys nonactivated macrophages that contain multiplying bacilli
  – Basis of the PPD skin test

• Macrophage-activating response
  – A cell-mediated phenomenon resulting in the activation of macrophages that are capable of killing and digesting tubercle bacilli
Two types of cells are essential in the formation of TB

- Macrophages: directly phagocytize TB and processing and presenting antigens to T lymphocyte

- **T lymphocytes (CD4+)**: induce protection through the production of lymphokines
Tuberculosis Granuloma

- Rounded tight collection of chronic inflammatory cells.
- Central Caseous necrosis.
- Active macrophages - epithelioid cells.
- Outer layer of lymphocytes, plasma cells & fibroblasts.
- Langhans giant cells – joined epithelioid cells.
Tuberculosis Granuloma

Bacterial entry; T Lymphocytes, macrophages, epitheloid cells; Proliferation; Central Necrosis; Giant cell formation; Fibrosis.
Disease outcomes

• Timely and proper chemotherapy, immuno-competent
  – Lesion resolved
  – Fibrosis and calcification: bacilli may remain dormant within macrophages or in the necrotic materials
  – Cured

• Improper use of drug, immuno-compromised
  – Caseous necrosis
  – Liquifaction
  – Cavity
  – Disease dissemination: through bronchi or blood
  – Bacilli multiply
Primary tuberculosis

- In a non immunized individual – children, adult
- Brief acute inflammation – neutrophils
- Develop immunity
Primary Tuberculosis

- **Primary Tuberculosis:**
  - Self Limited disease
  - 5-6 days invoke granuloma formation
  - 2 to 8 weeks – healing – Ghon focus (+ lymph node) Ghon complex or Primary complex

- **Primary Progressive TB**
  - Miliary TB and TB Meningitis.
  - Common in malnourished children
  - 10% of adults, immuno-suppressed individuals
Primary or Ghon’s Complex
Secondary Tuberculosis

- Post Primary in immunized individuals
- Reactivation or reinfection
- Most commonly males 30-50 y
- Slowly Progressive (several months)

- Cavitary granulomatous response
Cavitary Tuberculosis

- When necrotic tissue is coughed up → cavity.
- Cavitation is typical for large granulomas.
- Cavitation is more common in the secondary reactivation tuberculosis - upper lobes.
Secondary Tuberculosis

- Apical lobes or upper part of lower lobes
- Satellite lesion
- Tuberculous pneumonia
- Pulmonary or extra-pulmonary
- Local or systemic spread / Miliary
  - Vein – via left ventricle to whole body
  - Artery – miliary spread within the lung
Clinical manifestation--symptoms

• Pulmonary
  – Cough and sputum
  – Chest pain
  – Dyspnea
  – Hemoptysis

• Systematic
  – Low grade fever and night sweats, weight loss, anorexia, fatigue, and weakness

• Nonspecific and insidious
Clinical manifestation--signs

- No positive findings if lesions are limited
- Caseous pneumonia: sings of consolidation
- Large cavity: amphoric breath sound
- Pleural effusion
- Systemic features include fever (often low-grade and intermittent) and wasting
- Non-specific and of limited use in diagnosis
Diagnosis of pulmonary tuberculosis

- Symptoms and signs non-specific
- Microbiological test
  - Acid-fast smear and culture
- X-ray and CT scan
- PPD test
- Immunological test
- PCR
- Bronchoscopy and bronchoalveolar lavage
- Tentative anti-tuberculosis chemotherapy
When to suspect Tuberculosis

- Cough longer than 3 weeks
- Fever for 1 month
- Blood stained sputum
- Night sweats, weight loss
- High risk population: migrant worker, immunocompromised patients, ...
Microscopy in Tuberculosis TODAY

In spite of several scientific, and molecular advances Microscopy in Tuberculosis continues to be back bone in Diagnosis.
AFB - Ziehl-Nielson stain
Sputum - TB Auromine/Rhodamine
Acid Fast Bacilli as seen under Fluorescent Microscope

100x mag.
Cultures

- Gold standard for TB diagnosis
- Use to confirm diagnosis of TB
- Drug sensitivity test
- Culture all specimens, even if smear negative

Colonies of *M. tuberculosis* growing on media
Cultures

- **Sensitivity:** 80-85%
- **Specificity:** 98%
- **Times needed**
  - Solid medium - 4-8 wks
  - Liquid medium - 2 wks
Most easily available Investigation
Untreated Tuberculosis CXR
PPD Tuberculin Testing

- Sub cutaneous
- Wheal formation
- Itching – no scratch.
- Read after 72 hours.
- Induration size.
- 5-10-20mm-blister, necrosis
- < 72 hour is not diag
- +ve after 2-4 weeks.
- BCG gives + result.
PPD result after – 72 hours
Granuloma or giant cell is not pathognomonic of TB...!

- Foreign body granuloma.
- Fat necrosis.
- Fungal infections.
- Sarcoidosis.
- Crohn's disease.
PCR How useful to our Patients?

- PCR (Polymerase chain reaction) used by several investigators.
- However most cases can be diagnosed with simple methods if effectively used.
- The definite role of PCR continues to be controversial.
- Above all not cost effective to developing countries.
Real Time PCR replacing older Methods
Emerging Rapid Methods

1. Fast Plaque TB uses phage amplification technology.

2. ELISA (QuantiFERON – TB)

3. Enzyme-Linked immunospot (ELISPOT)
   ELISPOT proved highly useful to detect active tuberculosis in Adults and children.
Atypical Mycobacterium

- A growing concern on infections with less known, uncommon Mycobacterium in immunosuppressed, an emerging infectious disease problem
- Needs the help of reference laboratories.
- Needs different drug regimes, unlike typical Mycobacterium isolates.
- Now a growing concern in the era of AIDS.
Diagnosis of TB

- Clinical features are not confirmatory.
- Zeil Nielson Stain - $1 \times 10^4$/ml, 60% sensitivity
- Release of acid-fast bacilli from cavities intermittent.
- 3 negative smears to assure low infectivity
- Culture most sensitive and specific test.
  - Conventional Lowenstein Jensen media 3-6 wks.
  - Automated techniques within 9-16 days
- PCR is available, but should only be performed by experienced laboratories
- PPD for clinical activity / exposure sometime in life.
Differential diagnosis

- Pneumonia
- COPD
- Lung cancer
- Lung abscess
- Lymph node enlargement diseases
- Others: sepsis etc
Treatment

Aim

• to interrupt tuberculosis transmission by rendering patients noninfectious
• to prevent morbidity and mortality by curing patients with tuberculosis disease
Classification of Drugs

- 3 Groups depending upon the degree of effectiveness and potential side effects
  - First Line (Primary agents)
    - A necessary component of any short-course therapeutic regimen
    - Isoniazid, Rifampin, pyrazinamide
  - First-line supplemental agents
    - Streptomycin, Ethambutol
    - Rifabutin, FQs (cipro, Levo)
  - Second Line
    - p-amino salicylic acid (PAS), Cycloserine, Amikacin, Capreomycin, Ethionamide
Rifampin (REF)

**Mechanism of Action**
- Inhibits DNA-dependent RNA polymerase of the bacilli.

**Bactericidal activity**
- Both intracellular and extracellular

**Distribution**
- Present in effective concentrations in many organs and body fluids including CSF
- With Rifampin you must warn patients: The drug has an orange red color in body excretions, This color will be imparted to all body fluids.
Rifampin

Adverse Effects

- Most common: GI upset
- Hepatic Reactions in children, pregnant women and alcoholics, can result in minor elevations in serum transaminase as some jaundice
- Oths: Allergic Reactions, Fever, Skin Eruptions, Rash, Pruritis
- Rifampin does induce microsomal drug metabolizing enzymes. This will decrease the half-life of some other drugs. (ie. phenytoin, digitoxin)

Dosage: 450mg for adults
Isoniazid (INH)

Mechanism of action
Inhibition of mycolic acid cell-wall synthesis via oxygen-dependent pathways such as the catalase-peroxidase reaction.

**bacteriostatic against resting bacilli and bactericidal against rapidly multiplying organisms** both extracellularly and intracellularly.

Adverse effects

Hepatotoxicity

Peripheral neuropathy: uncommon, higher risk for patients with preexisting disorders, vitamin B6 deficiency

**Daily dose for adults:** 300 mg
Pyrazinamide (PZA)

Bactericidal drug to slowly metabolizing organisms located within the acidic environment of the phagocyte or caseous granuloma.

Side effect: hepatotoxicity

Adult daily dose: 500mg tid
Ethambutol (EMB)

Mechanism of action
- inhibition of an arabinosyltransferase that mediates the polymerization of arabinose into arabinogalactan within the cell wall.

Adverse effect
- Retrobulbar optic neuritis, axial or central neuritis

Standard adult daily dose: 750mg
Streptomycin (S)

Mechanism of action
  inhibits protein synthesis by disruption of ribosomal function
Adverse reactions
  Ototoxicity and renal toxicity
The usual adult dose of streptomycin for a 70-kg patient is 0.5 to 1.0 g (10 to 15 mg/kg) given intramuscularly daily or five times per week; the pediatric dose is 20 to 40 mg/kg daily, with a maximum of 1 g/d.
Short-course Regimens

• An initial, or bactericidal, phase and a continuation, or sterilizing, phase
  – Daily regimen: 2HRZE/4HR
  – Intermittent regimen: 2H3R3Z3E3/4H3R3

• Patients with cavitary pulmonary tuberculosis and delayed sputum-culture conversion (i.e., those who remain culture-positive at 2 months)
  – a total course of 9 months.

• For patients with sputum culture-negative pulmonary tuberculosis
  – the duration of treatment may be reduced to a total of 4 months.
Strategies to increase compliance

- Direct observation of treatments (DOTS) - all patients should have their therapy directly supervised, especially during the initial phase
- Provision of fixed-drug-combination (FDC) products
Follow-up during the treatment

- AFB smear examination and cultures
  - Monthly
  - If sputum cultures remain positive at ≥3 months, treatment failure and drug resistance should be suspected
  - Smears positive after 5 months are indicative of treatment failure
- Serial chest radiographs not recommended
- Liver function monitoring
Treatment failure

• Drug susceptibility test
• Rule for empirical therapy
  — add more than one drug at a time to a failing regimen
  — at least two and preferably three drugs
    • that have never been used
And
• to which the bacilli are likely to be susceptible should be added
Drug-resistant tuberculosis

- Spontaneous point mutations in the mycobacterial genome
- Primary drug resistance is that in a strain infecting a patient who has not previously been treated. (18.6%)
- Acquired resistance develops during treatment with an inappropriate regimen. (46.5%)
- MDR (multi-drug resistant): 0.5 million cases (WHO, 2006) (resistant to H & R: 10.5%)
Prevention

• Best way
  – the prompt detection of cases and the provision of short-course chemotherapy to all tuberculosis patients under proper case-management conditions, including directly observed therapy, with emphasis on the cure of sputum smear-positive cases

• BCG vaccination

• Treatment of persons with latent tuberculosis infection who are at high risk of developing active disease
BCG Vaccine

- Calmette & Guérin (1906-1921)
- Attenuated M. bovis
- First used in 1921
- 1928 recommended for wide spread use by League of nations
- Widespread use after 1945
- Most widely used vaccine
Chemoprophylaxis of TB
Used only in high risk groups

- Household members and other close contacts of a patient with active TB.
- A positive skin test in persons less than 35 years.
- A positive skin test reactive in the immunosuppressed, persons with leukemia, and Hodgkin's Disease,
- HIV + patients with a positive TB test
- The drug of choice for chemoprophylaxis is isoniazid. Prophylaxis uses only one drug.
Summary

• Commonest fatal infection in the world.
• Chronic, Mycobacterial, infection - Weight loss, fever, night sweats, lung damage.
• AIDS, Diabetes, malnutrition & crowding.
• Two forms Primary, Secondary
• Pulmonary, extrapulmonary, miliary.
• AFB positivity - infectiousness - isolation
• Multi drug to prevent selection of resistance
• Patient management--DOTS
• Prevention depends on PPD & INH prophylaxis
Questions

• Please describe the key points of the diagnosis of active pulmonary tuberculosis.

• Please describe the DOTS strategy in the management of patients with pulmonary tuberculosis. What are the drugs commonly used in the treatment? How to monitor response to the treatment and side effects?
Further readings

Thank you!

Questions are welcome 😊

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