CHAPTER-X
TUBERCULOSIS

R. KAVITHA, M.PHARM,
LECTURER, DEPARTMENT OF PHARMACEUTICS,
SRM COLLEGE OF PHARMACY,
SRM UNIVERSITY, KATTANKULATHUR.
INTRODUCTION

- Tuberculosis is a chronic infectious disease
  - caused by *M. tuberculosis/M. bovis*
  - mainly affecting the lung causing Pulmonary TB
  - also affect other parts causing Extra Pulmonary TB

- Characterized by
  - Cough lasting > 3 wks and not respond. to usual antibiotic
  - Production of purulent, sometimes blood- stained sputum
    - Evening rise of temp.
    - Night sweats
    - Weight loss
CHARACTERISTICS OF M. TUBERCULOSIS

- gram +ve bacilli
- Non motile, non sporing, & noncapsulated
- Strict aerobes
- Branching filamentous forms $\approx$ fungal mycelium
  $\Rightarrow$ MYCOBACTERIUM
- A.F.B $\Rightarrow$ when stained by Carbol Fuschin by
  Z-N Stain they resist decolorisation by 25% $H_2SO_4$ & Abs. alcohol
- Cell wall is lipid rich with mycolic acid which is essential & unique component
CAUSES:

- The primary cause of TB, *Mycobacterium tuberculosis*, is a small aerobic non-motile bacillus.

- The *M. tuberculosis* complex includes four other TB-causing mycobacteria: *M. bovis, M. africanum, M. canetti* and *M. microti*. *M. africanum* is not widespread, but in parts of Africa it is a significant cause of tuberculosis.

- The high lipid content of this pathogen accounts for many of its unique clinical characteristics.

- *M. microti* is mostly seen in immunodeficient people, although it is possible that the prevalence of this pathogen has been underestimated.
RISK FACTORS OF TUBERCULOSIS

- Low socioeconomic status
- Crowded living conditions
- Diseases that weakens immune system like HIV
- Person on immunosuppressants like steroid
- Health care workers
  - Migration from a country with a high number of cases
- Alcoholism
- Recent Tubercular infection(within last 2 year)
- HIV infection
- Children exposed to high risk adults
- Close contacts of persons known or suspected to have active disease
- Silicosis
- Prolonged corticosteroid therapy
- Other immunosuppressive therapy
- Low body weight (10% or more below the ideal)
- Diabetes mellitus
- Residents and employees of high-risk congregate settings
- Patients with CRF
SIGNS AND SYMPTOMS:

- When the disease becomes active, 75% of the cases are pulmonary TB, that is, TB in the lungs.

- Symptoms include chest pain, coughing up blood, and a productive, prolonged cough for more than three weeks.

- Systemic symptoms include fever, chills, night sweats, appetite loss, weight loss, pallor, and often a tendency to fatigue very easily.
TRANSMISSION OF THE DISEASE

- Pulmonary tuberculosis is a disease of respiratory transmission. 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.

- Transmission is dependent on closeness and time of contact.

- Once inhaled by a tuberculin free person, the bacilli multiply 4-6 weeks and spreads throughout the body. The bacilli implant in areas of high partial pressure of oxygen:
  - lung
  - renal cortex
  - reticuloendothelial system
It is currently estimated that 1/2 of the world's population (3.1 billion) is infected with *Mycobacterium tuberculosis*. *Mycobacterium avium* complex is associated with AIDS related TB.

The proportion of people who become sick with tuberculosis each year is stable or falling worldwide but, because of population growth, the absolute number of new cases is still increasing.

In 2007 there were an estimated 13.7 million chronic active cases, 9.3 million new cases, and 1.8 million deaths, mostly in developing countries.

The distribution of tuberculosis is not uniform across the globe; about 80% of the population in many Asian and African countries test positive in tuberculin tests, while only 5-10% of the US population test positive.
Most TB cases were in India and China.
PATHOGENESIS OF TUBERCULOSIS

- Pathogenesis in a previously unexposed, immunocompetent person depends on the development of anti-mycobacterial cell-mediated immunity, which confers resistance to bacteria and development of hypersensitivity to mycobacterial antigens.
- Pathologic manifestation of tuberculosis like caseating granuloma and cavitation are result of hypersensitivity that develops in concert with the protective host immune response.
- Macrophages are the primary cells infected by M. tuberculosis.
DIAGNOSIS OF PULMONARY TB

- **Routine investigations-** Hb, TLC, DLC (lymphocytosis), ESR.
- **Chest x-ray-**
  - 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.

Arrow points to cavity in patient's right upper lobe.
The Mantoux skin test consists of an intradermal injection of 5 IU PPD on the extensor aspect of forearm tuberculin.

The size of induration is measured 48–72 hours later. Erythema (redness) should not be measured.

Mantoux test injection site in a subject without chronic conditions or in a high risk group clinically diagnosed as negative at 50 hours.
• **SPUTUM EXAMINATION** – Sputum examination are essential to confirm TB
  • Best collected in morning before any meal.
  • Sputum examination on 3 days increase chances of detection.
  • Sputum can be collected from laryngeal swab or bronchial washing.
  • In small children, gastric lavage can be examined.
  • Smear should be prepared from thick dirty part of sputum & stained with Ziehl-Neelson technique.

➤ **Culture** - Use to confirm diagnosis of Tuberculosis.

Conventional cultures take up to 10 weeks.

Culture all specimens, even if smear report is negative.

Culture is done in Lowenstein Jansen media.

Susceptibility testing *is essential*.

Result in 4-14 days when liquid medium system is used.

*For example* - BACTEC can confirm TB growth within one week by indirectly measuring TB bacilli growth in special bottles and medium.
DIFFICULT TO TREAT:

1. Most antibiotics are effective against rapidly growing organism in contrast to *M.tb* ⇒ slow growing

2. Mycobacterium Cell can be dormant, thus completely resistant to many antibiotics or killed very slowly by few drugs

3. The lipid rich mycobacterium Cell wall is impermeable to many drugs.

4. A substantial proportion are intracellular & chemotherapeutic agents penetrate poorly

5. Mycobacterium ⇒ develop resistance to any single drug

6. Caseation & fibrosis block the b.v. supplying necrotic area thus penetration of antitubercular drug difficult
TREATING TB DISEASE
(GENERAL PRINCIPLES)

- Always treat with multiple drugs.
- Never add a single drug to a failing regimen.
- DOTS (Directly Observed Treatment Shortcourse) is given.
- Treatment course depends on the categories of the patient.
- Usually 6 months, sometimes 9 months.
- Four drugs for two months.
  Isoniazid – Rifampicin – Ethambutol - Pyrazinamide
- Two drugs for four or seven months.
  Isoniazid - Rifampicin
CLASSIFICATION OF ANTITUBERCULAR DRUGS

First line Drug (Essential AntiTB)

- High Anti TB effect
- Acceptable degree of toxicity
- Used routinely

- ISONIAZID (H)
- RIFAMPICIN (R)
- PYRAZINAMIDE (Z)
- ETHAMBUTOL (E)
- STREPTOMYCNIN (S)
SECOND LINE DRUG  (RESERVE ANTI TB DRUG)
- low anti tb effect
- high toxicity
- or both
- used in special circumstances only

- PAS
- AMIKACIN
- CAPREOMYCIN
- ETHIONAMIDE
- KANAMYCIN
- CYCLOSERINE

NEWER DRUGS
- CIPROFLOXACILLIN
- OFLOXACILLIN
- CLARITHROMYCIN
- AZITHROMYCIN
- KANAMYCIN
- RIFABUTIN
SECOND LINE DRUGS:

- **Aminoglycosides**: least effective and more toxic
  
  *Capreomycin - Viomycin – Kanamycin*

Adverse effects:

- *These drugs are: Nephrotoxic will cause* Proteinuria, Hematuria, Nitrogen metabolism, and Electrolyte disturbances
  
  However effect is reversible when drug is stopped

- Capreomycin has replaced viomycin because of less toxic effects, but all three drugs have the same effects.
Cycloserine:

- Can cause CNS disturbances
- Therapeutic States:
  - Cycloserine should be used when re-treatment is necessary or when the micro-organism is resistant to the other drugs.
- It must be given in combination with other anti-tuberculosis drugs.

- Mechanism of Action:
  - An analog of D-alanine synthetase, will block bacterial cell wall synthesis.
PHARMACOKINETICS:

- Cys absorbed orally, diffuses all over.
- About 1/3 of a dose is metabolised the rest is excreted unchanged by kidney.

Toxicity:
- Most common in the CNS: Headache, Tremor, Vertigo, Confusion, Nervousness,
THIOACETAZONE & ETHIONAMIDE:

- These are first anti tubercular drugs.
- It is a tuberculostatic drug.
- Low efficacy drug.
- Side effects:
  - hepatitis,
  - optic neuritis,
  - mental disturbances
  - impotence
**Para- amino salicylic acid:**

- PAS is a tuberculostatic and one of least active drugs.
- It inhibits denovo folate synthesis.
- PAS is completely absorbed by oral route and distributed all over.
- T1/2 is 1hr.
- Patient acceptability of PAS is poor.
- Adverse effects;
  - Rashes, fever, liver dysfunction
Chemotherapy

DOTS (Directly Observed Treatment Shortcourse):

To control tuberculosis requires:
- Effective, inexpensive, simple and standardised technology.

The success of the DOTS strategy depends on:
- Government commitment to a national tuberculosis programme.
- Case detection –finding by smear microscopy examination of TB susceptible in general health services.
- Regular uninterrupted supply of essential anti-TB drugs.
- Monitoring system for programme supervised and evaluation.
Short Course Chemotherapy:

- These are regimens of 6-9 month duration.
- All regimens have an initial intensive phase lasting 2-3 months to kill the TB bacilli and afford symptomatic relief.
- This is followed by continuation phase for 4-6 months so that relapse does not occur.
## REGIMENS:

<table>
<thead>
<tr>
<th>Type of patient</th>
<th>Duration of treatment</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Category-1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. New sputum positive</td>
<td><strong>Intensive phase(2months)</strong></td>
<td>INH+RMP+ETB+PZA</td>
</tr>
<tr>
<td>2. Seriously ill, sputum negative, Pulmonary</td>
<td><strong>Continuation phase(4months)</strong></td>
<td>INH+RMP</td>
</tr>
<tr>
<td>3. Seriously ill</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Category-2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retreatment group</td>
<td><strong>Intensive phase(3months)</strong></td>
<td>INH+RMP+ETB+PZA</td>
</tr>
<tr>
<td>1. Relapse</td>
<td><strong>Continuation phase(5months)</strong></td>
<td>INH+RMP+ETB</td>
</tr>
<tr>
<td>2. Treatment failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Category-3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. New smear negative pulmonary</td>
<td><strong>Intensive phase(2months)</strong></td>
<td>INH+RMP+PZA</td>
</tr>
<tr>
<td>2. Extrapulmonary</td>
<td><strong>Continuation phase(4months)</strong></td>
<td>INH+RMP</td>
</tr>
</tbody>
</table>
Multiple Drug Resistance (MDR):

- Resistance to both Isoniazid and Rifampin and number of other anti-TB drugs. MDR-TB has a more rapid course, (some die in 4-16 weeks).
- Treatment is difficult as second line drugs are less efficacious, less convenient, more expensive and toxic.
- Therapy depends on drugs used in earlier regimen, dosage and regularity with which they have been taken.
- In India >200,000 patients have been treated under DOTS by early 2001 with cure rate of 75-80%.
- In other countries 80-93% cure rates have been obtained.