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Review Article

Tuberculosis Management: A Review

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ABSTRACT
Tuberculosis (TB) is a disease caused by germs that are spread from person to person through the air. TB usually affects the lungs, but it can also affect other parts of the body, such as the brain, the kidneys, or the spine. A person with TB can die if they do not get treatment. The general symptoms of TB disease include feelings of sickness or weakness, weight loss, fever, and night sweats. The symptoms of TB disease of the lungs also include coughing, chest pain, and the coughing up of blood. Symptoms of TB disease in other parts of the body depend on the area affected. TB germs are put into the air when a person with TB disease of the lungs or throat coughs, sneezes, speaks, or sings. These germs can stay in the air for several hours, depending on the environment. Persons who breathe in the air containing these TB germs can become infected; this is called latent TB infection.

Keywords: Tuberculosis, Medicine, Mycobacterium

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INTRODUCTION

Tuberculosis (TB) is the most common cause of infection related death worldwide. Mycobacterium tuberculosis is the most common cause of TB. Very rare causes are mycobacterium bovis and mycobacterium africanum. Tubercle bacilli belong to the family mycobacteriaceae and the order actinomycetales. The acid-fast characteristic of the mycobacteria is their unique feature. Mycobacterium tuberculosis is an aerobic, non-spore-forming, non motile, and slow-growing bacillus with a curved and beaded rod-shaped morphology. It is a very hardy bacillus that can survive under adverse environmental conditions. Humuns are the only known reservoirs for tuberculosis[1]. Tuberculosis (TB) is a disease caused by bacteria called mycobacterium tuberculosis. The bacteria usually attack the lungs. But, TB bacteria can attack any part of the body such as the kidney, spine, and brain. If not treated properly, TB disease can be fatal. TB is spread through the air from one person to another. The bacteria are put into the air when a person with active TB disease of the lungs or throat coughs or sneezes. People nearby may breathe in these bacteria and become infected.

However, not everyone infected with TB bacteria becomes sick. People who are not sick have what is called latent TB infection. People who have latent TB infection do not feel sick, do not have any symptoms, and cannot spread to others. But, some people with latent TB infection go on to get TB disease[2].

People with active TB disease can be treated and cured they seek medical help. Even better, people with latent TB infection can take medicine so that they will not develop active TB disease[3].

CLASSIFICATION

A. Pulmonary TB

a) Endobranchial TB with Enlargement of Lymph Nodes.
b) Tubercular Pleural Effusion

c) Progressive Primary TB
d) Reactivation TB

B. Extrapulmonary TB

1. Lymphadenopathy
2. Tubercular Meningitis
3. Military TB
4. Bone Or Joint TB
5. Additional Sites[1]

A) Pulmonary TB:-

Symptoms of primary pulmonary disease in the pediatric population often are meager. Symptoms are more likely to occur in infants. Fever, night sweats, anorexia, non productive cough, failure to thrive, and difficult gaining may occur.

It include

a) Endobranchial TB With Enlargement of Lymph Nodes:

This is the most common variety of pulmonary TB. Symptoms are the result of impingement on various structures by the enlarged lymph nodes. Persistent cough may be indicative of bronchial obstruction, while difficulty in swallowing may result from esophageal compression. Vocal cord paralysis may be suggested by hoarseness or difficulty breathing.

b) Tubercular Pleural Effusion:

Pleural effusions due to TB usually occur in older children rather than in infants and rarely are associated with military disease. Typically history reveals an acute onset of fever, chest pain that increases in intensity on deep inspiration, and shortness of breath. Fever usually persists for 14-21 days.

c) Progressive Primay TB:

Progression of the pulmonary parenchymal component leads to enlargement of the caseous area and may lead to pneumonia, atelectasis, and air trapping. This is more likely to occur in young children than adolescents. The child usually appears ill with symptoms of fever, cough, malaise and weight loss.

d) Reactivation TB:

This condition usually has a sub acute presentation with weight loss, fever, cough and rarely, hemoptysis. TB typically occurs in older children and adolescents. The condition is more common in patients who acquire TB when older than1years.[1]

B) Extrapulmonary TB:-

a) Lymphadenopathy:

Patients with lymphadenopathy (ie., scrofula) may have a history of enlarged nodes. Fever, weight loss, fatigue, and malaise are either absent or minimal. Lymp node involvement typically occurs 6-9 months following infection by the tubercle bacilli. More superficial nodes commonly are involved. Frequent sites of involvement are the anterior cervical, submandibular, and supraclavicular nodes. TB of the skeletal system may lead to involvement of the inguinal, epitrochlear or auxiliary lymph nodes.

b) Tubercular Meningitis:

One of the most severe complications of TB is tubercular meningitis. Tubercular meningitis develops in 5-10% of children who become infected when younger than 2 years thereafter, the frequency drops to less than 1%. A very high index of suspicion is required to make a timely diagnosis because of the insidious onset of the disease. A sub acute presentation usually occurs within 3-6 months after the initial infection. Nonspecific symptoms such as anorexia, weight loss and fever may be present. After 1-2 weeks patients may experience vomiting and seizures or alteration in the sensorium. Deterioration of mental status, coma and death may occur despite prompt diagnosis and early intervention.

c) Miliary TB:

This is a complication of primary TB in young children. It may manifest sub acutely with low-grade fever, malaise, weight loss, and fatigue. A rapid onset of fever and associated symptoms also may be observed. History of cough and respiratory distress may be obtained

d) Bone Or Joint TB:

This may present acutely or sub acutely. Vertebral TB may go unrecognized for months to years because of its indolent nature[8].

e) Additional Sites:

Other unusual sites for TB include the middle ear, gastrointestinal tract. Skin, kidneys, and ocular structures

ETIOLOGY:

Tuberculosis infection is caused by tubercle bacilli. Pulmonary tuberculosis is more common than extra pulmonary tuberculosis. Sites of extra pulmonary tuberculosis can include the pleura, lymph nodes, pericardium, kidney, meninges, bones, joints, larynx, skin, intestine, peritoneum and eye. Lymph nodes are the commonest site for extra pulmonary disease[9]

TB is spread through the air from one person to another. The bacteria are put into the air when a person with active TB disease of the lungs or throat coughs or sneezes. The people nearby may breath in these bacteria are become infected. When a person breathes in TB bacteria, it can settle in the lungs and begin to grow. From there, they can move through the blood to other parts of the body, such as the kidney, spine and brain.

People with active TB disease are most likely to

spread it to others. TB bacteria become active if the immune system cannot stop them from growing. The active bacteria begin to multiply in the body and cause active TB disease. The bacteria attack the body and destroy tissue. If this occurs in the lungs, the bacteria can actually create a hole in the lungs.some people develop active TB disease soon after becoming infected, before their immune system can fight the TB bacteria. Other people may get sick later, when their immune system become weak for another reason.

- ❖ People have weak immune system especially with
  - ➢ Diabetes mellitus
  - ➢ Cancer of head
  - ➢ Leukemia
  - ➢ Severe kidney disease
  - ➢ Low body weight
  - ➢ Substance abuse
  - ➢ Silicosis
- ❖ Certain medical treatment

A person with active TB disease has symptoms.

- ➢ May spread TB to others
- ➢ Usually has a positive skin test
- ➢ May have an abnormal chest x-ray

In some people who breathe in TB bacteria and become infected, the body is able to fight the bacteria to stop them from growing. The bacteria become inactive, but they remain alive in the body and can become active later. This is called latent TB infection.

- ❖ People with latent TB infection.
- ➢ Have no symptom
- ➢ Do not feel sick
- ➢ Cannot spread TB to others
- ➢ Usually have a positive skin test
- ➢ Can develop active TB disease if they do not receive
- ➢ Treatment.
- ➢ Has a normal chest x-ray.

The tuberculosis infection depends upon the following factors

- Agent factors

Agent: tuberculosis is caused by m. Tuberculosis
Source of infection: there are two source of infection
Human source: the most common source of infection is human whose sputum is positive with tubercle bacilli
Bovine source: the bovine source of infection is usually infected milk.
Communicability: patients are infective as long as they remain untreated.

- Host factors:

Age: tuberculosis affects all ages
Sex: more prevalent in males than in females
Heredity: tuberculosis is not a hereditary disease
Nutrition: malnutrition is widely predispose to TB
Immunity: man have no inherited immunity against TB. It is acquired as a result of natural infection or BCG vaccination.

- Social factors

It include poor quality of life, poor housing, and over crowding, population explosion, under nutrition, lack of education, large families, lack of awareness of causes of illness.[4]

PATHOPHYSIOLOGY:

TB occurs when individuals inhale bacteria aerosolized by infected persons. The organism is slow growing and tolerates the intracellular environment, where it may remain metabolically inert for years before reactivation and disease. The main determinant of the pathogenicity of TB is its ability to escape host defense mechanisms, including macrophages and delayed hypersensitivity responses.

Among the several virulence factors in the mycobactyerial cell wall are the cord factor lipoarabinomannan (lam) and a highly immunogenetic 65-kd m. Tuberculosis heat shock protein. Cord factor is a surface glycolipid present only in virulent strains that causes m. Tuberculosis to grow in serpent cords in vitro. Lam is a hetero polysaccharide that inhibits macrophage activation by interferon - □ and induces macrophages to secrete tumor necrosis factor - (tnf), which causes fever, weight loss, and tissue damage. Heat shock protein have a role in autoimmune reaction induced by m. Tuberculosis.

The infective droplet nucleus is very small, measuring 5 micrometers or less, and may contain approximately 1 - 10 bacilli. Although a single organism may cause disease, 5-200 inhales bacilli are usually necessary for infection. The small size of the droplets allows them to remain suspended in the air for a prolong period of time. Primary infection of the respiratory tract occurs as a result of inhalation of these aerosols upon inhalation, the bacilli are deposited into the distal respiratory bronchiole or alveoli, which are sub pleural in location. Subsequently, the alveoli macrophages phagocytose the inhaled bacilli. However, these macrophages are unable to kill the mycobacteria and bacilli continue to multiply.[1]

Pathophysiology For Primary Infection:-

Primary phase of m. Tuberculosis infection begins with inhalation of the mycobacteria and

ends with a t cell - mediated immune response that induces hypersensitivity to the organisms and controls 95% of infections. Inhaled m. Tuberculosis is first phagocytosed by alveolar macrophages and transported by these cells to hilar lymph nodes.

Naive macrophages are unable to kill the mycobacteria, which multiply, lyses the host cell, infect other macrophages and sometimes disseminate through blood to other parts of the lung and elsewhere in the body. After a few weeks t-cell mediated immunity demonstrable by a positive purified protein derivative (ppd) test reaction develops.

Mycobacteria activated t-cells interact with macrophages in three ways. First, cd4+ helper t-cells secrete interferon-, which activates macrophages to kill intracellular mycobacteria through reactive nitrogen intermediates, including no, no2, and hno3. This is associated with the formation of epithelioid cell granulomas and clearance of mycobacteria.

Second cd8+ suppressor t-cells lyse macrophages infected with mycobacteria through a fas-independent, granule dependent reaction and kill mycobacteria. Third, cd4 – cd8 t-cell lyse macrophages in a fas-dependent manner, without killing mycobacteria.

Lyses of macrophages results in the formation of caseating granulomas (delayed type hypersensitivity reaction). Direct toxicity of the mycobacteria to the macrophages may contribute to the necrotic caseous centers. Mycobacteria cannot grow in this acidic, extra cellular environment lacking in oxygen, and so the mycobacterial infection is controlled. The ultimate residuum of the primary infection is a calcified scar in the lung parenchyma and in the hilar lymph node, together referred to as ghon complex.

Secondary and Disseminated Tuberculosis:-

Some individuals become reinfected with mycobacteria, reactivate dormant disease or progress directly from the primary mycobacterial lesions in to disseminated disease. This may be because the strain of mycobacterium is particularly virulent or the host is particulary susceptible.

Granulomas of secondary tuberculosis most often occur in the apex of the lungs but may be widely disseminated in the lungs, kidney, meninges, marrow and other organs. These granulomas, which fail to contain the spread or the mycobacterial infection, are the major cause of tissue damage in tuberculosis and are a reflection of delayed type hypersensitivity.

Two special features of secondary tuberculosis are caseous necrosis and cavities; necrosis may cause rupture into blood vessels, spreading mycobacteria through out the body, and break into air ways, releasing infections mycobacteria in aerosols[7]

SIGNS AND SYMPTOMS:

Symptoms of TB depend on where in the body the TB bacteria are growing. TB bacteria usually grow in the lungs. TB in the lungs may cause symptoms such as

- A bad cough that lasts 3 weeks or longer
- Pain in the chest
- Coughing up blood or sputum

Other symptoms of active TB disease are

- Weakness or fatigue
- Weight loss
- No appetite
- Chills
- Fever
- Night sweats
- Constant tiredness[2]

INVESTIGATION:

- Tuberculin Test:-

Tuberculin test is used to confirm infection. Two tests are commonly used. They are (a) heaf (multiple puncture) test and (b) mantoux tests. Both use solution of tuberculin purified protein derivative (ppd). Several strengths of ppd are available, and it is important that correct solution is used.

- Heaf Test:-

Heaf test is quick and simple. It is particularly useful where large numbers of tests are performed, such as in bcg vaccination programmes in schools. A solution of 100000 units per ml of ppd is applied in sufficient amount to spread over the gun head and the heaf gun, with six needles arranged in a circle, is used to puncture the skin. The result is ideally read in 7 days but can be react from 3-10 days. There are 5 grades response.[8]

Grade 1: no induration at puncture sites. Erythema only present.

Grade 2 : discrete induration at 4 or more needle sites.

Grade 3 : confluent areas of induration forming a ring with a clear centre.

Grade 4 : a disc of induration 5-10 mm wide.

Grade 5 : solid induration greater than 10 mm. Vesiculation. Or ulceration may also occur.

Grade 3 and 4 reactions are considered to indicate infection along with grade 2 response in a tuberculosis contact who has not previously had the bcg (bacille calmette guerin) vaccine.

Grade 3 and grade 4 are said to be strongly positive. Anyone heaf tested as a TB contact, or in a vaccination programme, and found to have these reactions needs to be referred to a chest clinic for further investigation, including chest radiography.

- The Mantoux Test:-

It is more time consuming and requires greater skill to administer. The ppd for routine use in this test contains 100 units per ml. (for individuals in whom tuberculosis is suspected, or who are known to be hyper sensitive to tuberculin, the preparation containing 10 units/ml should be used). In this test 0.1 ml of the appropriate solution is injected intradermally so that a bleb is produced. The results should be read 48-72 hours later, but a valid reading can be obtained upto 96 hours. A positive result consists of induration with a transverse diameter of at least 5mm following injection of 0.1 ml of ppd 100 units/ml[15].

- Sputum Examination:-

Sputum smear examination by direct microscopy is considered the method of choice. The reliability, cheapness and ease of direct microscopic examination has made it number one case-finding method all over the world. It enables us to discover the epidermologically most important case of pulmonary tuberculosis. Direct microscopy sputum using zichl-neelsen or fluorescent rhodamine-auramine stains is the simplest and quickest method of detecting the infectious patient, although this test is used to be positive in only 60% of culture confirmed cases.[9]

- Sputum Culture:-

These are much less useful in non-pulmonary and childhood disease, the diagnosis of which depends more on culture. With conventional culture methods, such as the lowenstein-jensen medium, growth may take up to 6 weeks.[4] culture examinations of sputum is only second in importance in a case finding programme. It is not only difficult, lengthy (take at least 6 weeks) and expensive but also need special training and expertise. This method of examination is offered only to patients presenting themselves with chest symptoms, whose sputum smear is negative by direct microscopic examination. Culture of sputum is necessary for carrying out sensitivity tests and monitoring drug treatment.

Goals Of Anti Tubercular Chemotherapy:-

- **Kill Dividing Bacilli:**

Drugs with early bactericidal action rapidly reduce bacillary load in the patient and achieve quick sputum negatively so that the patient is non-contagious to the community: transmission of TB is interrupted. This also affords quick symptom relief

- **Kill Persisting Bacilli:**

To effect cure and prevent relapse. This depends on sterilizing capacity of the drug. Prevent emergence of resistance so that the bacilli remain susceptible to the drugs.

ANTI TUBERCULAR DRUGS[15]:

They are classified in to

A) First line drugs

Have high antitubercular efficacy and less toxicity. They are bactericidal drugs[5]

B) Second line drugs

Have low antitubercular efficacy and high toxicity. They are bacteriostatic drugs.

A.First Line Drugs:

1) Isoniazide (Inh):

Most powerful drug in the treatment of TB. It can easily penetrate to cell membrane, and is active against intracellular and extra cellular bacilli. Its action is most marked on rapidly multiplying bacilli. It is less active against slow multipliers and atypical mycobacteria.

MOA: it inhibit mycolic acid synthesis which is unique for mycobacterial cell wall.

Pharmacokinetics: absorbed orally and penetrate all body tissues. Metabolized in liver, excreted through urine.

Dose: single daily dose 4-5 mg/kg of body weight or 300mg oral i.m, i.v qd adverse effect: peripheral neuritis and a varity of neurological manifestations. These are due to interference with utilization of pyridoxine and its increased excretion in urine. Inh neurotoxicity is treated by pyridoxine 100mg/day given prophylactically. Other side effects rashes, fever, etc.

2) Rifampicin (R):

It is a better sterilizing agent than inh. It is equally effective against intracellular and extra cellular bacilli. It is the only bactericidal drug active against dormant bacilli. In combination with inh, it can cure extensive tuberculosis in about 9 months. Bactericidal action covers all subpopulation of TB bacilli, but acts best on slowly or intermittently dividing bacilli as well as on many atypical mycobacteria[10]

MOA: it inhibit dna dependant rna synthesis

Pharmacokinetics: well absorbed orally. Widely distributed in the body. Metabolized in liver to an active deacetylated metabolite. Excreted mainly in bile, some in urine also.

Dose: daily dose 10-12mg/kg body weight or 450-600mg oral, i.v qd.

3) Streptomycin (S)

It is an amino glycoside antibiotics. It acts entirely on rapidly multiplying bacilli. It is less

active against slow multipliers. No action of dormant bacilli. It is act only on extracellular bacilli.

MOA: bind to 30s and 50s sub units of ribosomes as well as their interface, freeze initiation, interfere with polysome formation and cause misreading of mrna code, thus inhibit protein biosynthesis.

Pharmacokinetics: it is neither absorbed nor destroyed in the g.i.t. It is absorbed from injection site in muscles is rapid. It is distributed only extra cellularly. It is not metabolized - excreted unchanged in urine.

Dose: daily dose 0.75 - 1g in a single injection i.m, i.v qd.

Adverse Effects: Ototoxicity, Nephrotoxicity

4) Pyrazinamide (Z):

It is active against the slow multiplying intra cellular bacilli. It has been found to increase the sterilizing ability of rifampicin. Therefore, it has been incorporated in short-course chemotherapy regimen.its use has enabled regimens to be shortened and risk of relapse to be reduced.

MOA: it inhibit mycolic acid synthesis.[12]

Pharmacokinetics: it is absorbed orally, widely distributed, has good penetration in csf, extensively metabolized in liver and excreted in urine.

Dose: daily dose 20-30 mg/kg of body weight oral qd or bid

Adverse effect: hepatotoxicity. It is contra indicated in liver disease. Hyperuricemia is due to inhibition of uric acid secretion in kidney.

5) Ethambutol (E):

It is bacteriostatic and active than streptomycin. Fast multiplying bacilli are more susceptible than many atypical mycobacteria. Added to the triple drug regimen of rhz it has been found to hasten the rate of sputum conversion and to prevent the development of resistance.

MOA: interfere with mycolic acid incorporation in to mycobacterial cell wall.

Pharmacokinetics: absorbed orally. It is distributed widely but penetrate meninges. Less metabolized excreted in urine.

Dose: daily dose 15mg/kg body weight oral, i.v. Qd17

Adverse effect: loss of visual acuity/color vision due to optic neuritis, hyper urecimea.

B.Second Line Drugs:-

1) Thiacetazons (Tzn):

It is tuberculostatic, low efficacy drug, do not add the therapeutic effect of isoniazid, streptomycin or ethambutol, but delay resistance to these drugs.

Pharmacokinetic: orally active, excreted unchanged in urine with t½ of 12 hr.

Dose: 150mg od in adults, 2.5 mg/kg in children

Side effects: hepatitis, gastrointestinal disturbances, blurred vision, haemolytic anoumia, utricasia and bone marrow depression.

2) Para Amino Salicylic Acid (PAS):

It is tuberculostatic, one of the least active drug used as sodium and calcium salts. Resistance to pas is slow to develop.

MOA: inhibit the paba in corporation in to bacterial cell wall.

Pharmacokinetic: absorbed completely by the oral rout and distributed all over except in csf. It is metabolized by acetylation and excreted by glomerular filtration.

Dose: 10-12g per day in divided dose oral bid or tid

Side effects: anorexia, nausea, epigasteric pain, rashes, fever, goiter, liver dysfunction and blood dyscrasias.

3)Ethionamide (Etm):

It acts on both extra and intra cellular organism. It is a tuberculostatic drug. A typical bacteria are sensitive. But it has low efficacy.

MOA: it inhibit peptide synthesis in bacteria by blocking incorporation of sulfur containing amino acids such as methionine and cystine[18]

Pharmacokinetics: absorbed orally distributed all over including csf. Completely metabolized and has a short duration of action.

Dose: 0.5 - 0.75g/per day oral qd or bid

Side effects: anorexia, nausea, vomiting, abdominal upset, rashes, pain, hepatitis, mental disturbances and impotence[19]

4) Cycloserine (Cys):

It is bacteriostatic and inhibit some other gram positive bacteria e coli, chlamydia. Resistance to cyclosexine develop slowly. No cross resistance.

MOA: inhibit bacterial cell wall synthesis by inactivating the enzyme which recemize l-alanine and link two d-alanine residue.[17]

Pharmacokinetics: it is absorbed orally. Diffuses all over csf concentration equal to plasma. About 1/3 of the dose metabolized, rest excreted unchanged by kidney.

Dose: 250-500 mg oral qd or bid

Side effects: cns toxiary- sleepiness, headache, tremor and psychosis.[18]

CONCLUSION

Even though TB is an infections disease it is curable if proper treatment and care are given so as to safeguard our newer generation from the shadow of this disease they should be given BCG vaccines. Prophylactics measurement should be taken in order to prevent spread of the epidemic

infection.

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