Pulmonary Tuberculosis

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Tuberculosis (TB) is one of the most prevalent infections of human beings and contributes considerably to illness and death around the world.
Tuberculosis (TB) is one of the top 10 causes of death worldwide.
It is spread by inhaling tiny droplets from the coughs or sneezes of an infected person.it is a slowly spreading, chronic, granulomatous bacterial infection, characterized by cough , fever ,night sweating and gradual weight loss.
TB is a leading killer of HIV-positive people: approximately 40% of HIV deaths were due to TB.
Tuberculosis is the infectious disease primarily affecting lung parenchyma is most often caused by mycobacterium tuberculosis.it may spread to any part of the body including meninges, kidney, bones and lymph nodes.

With the increased incidence of AIDS, TB has become more a problem in the U.S., and the world. It is currently estimated that **one-quarter** of the world's population is infected with Mycobacterium tuberculosis.

T.B. is Infection with M. tuberculosis, an aerobic, nonmotile, acid-fast rod .
M. bovis infection arises from drinking non-sterilized milk from infected cows.

T.B. Pathogenesis :

Once inhaled, the organisms lodge in the alveoli and initiate the recruitment of macrophages and lymphocytes.
Macrophages undergo transformation into epithelioid and Langhans cells, which aggregate with the lymphocytes to form the classical tuberculous granuloma.
Numerous granulomas aggregate to form a primary lesion or ‘Ghon focus’(a pale yellow, caseous nodule, usually a few millimetres to 1–2 cm in diameter), which is characteristically situated in the periphery of the lung
Spread of organisms to the hilar lymph nodes is followed by a similar pathological reaction, and the combination of the primary lesion and regional lymph nodes is referred to as the‘primary complex of Ranke’.
This lesion eventually calcifies and is clearly seen on a chest X-ray. Without development of TB disease . If these processes fail, primary progressive disease ensues . The estimated lifetime risk of developing disease after primary infection is 10%, with roughly half of this risk occurring in the first 2 years after infection.
The only clue that infection has occurred may be the appearance of a cell-mediated, delayed-type hypersensitivity reaction to tuberculin, demonstrated by tuberculin skin testing. or an interferon gamma release assay (IGRA): so-called latent TB.

Factors increasing the risk of TB:

-Age (children > young adults < elderly)
-Close contacts of patients with smear-positive pulmonary TB
-Overcrowding (prisons, collective dormitories); homelessness (doss houses and hostels)
-Diabetes mellitus
-Immunosuppression: HIV, anti-tumour necrosis factor (TNF) therapy, high-dose corticosteroids, cytotoxic agents.

-Malignancy (especially lymphoma and leukaemia) .
- Smoking: cigarettes and bidis (Indian cigarettes made of tobacco wrapped in temburini leaves)
-Chronic kidney disease .
-Silicosis
-Gastrointestinal disease associated with malnutrition (gastrectomy, jejuno-ileal bypass, cancer of the pancreas, malabsorption)
-First-generation immigrants from high-prevalence countries

Clinical features: pulmonary disease:

-Primary TB
-Post primary T.B. (Pulmonary T.B.)
-Miliary TB

Primary pulmonary TB:

Primary TB refers to the infection of a previously uninfected(tuberculin-negative) individual. A few patients develop a self limiting febrile illness but clinical disease occurs only if there is a hypersensitivity reaction or progressive infection .Progressive primary disease may appear during the course of the initial illness or after a latent period of weeks or months.

Hypersensitivity

•Erythema nodosum
•Phlyctenular conjunctivitis
•Dactylitis

Infection period (4–8 wks):

• Influenza-like illness • Primary complex • Skin test conversion

Primary progressive Disease:

•Lymphadenopathy: hilar (often unilateral), paratracheal or mediastinal
•Collapse (especially right middle lobe)
•Consolidation (especially right middle lobe)
•Obstructive emphysema
•Cavitation (rare)
•Pleural effusion
•Endobronchial
•Miliary
•Meningitis

Post primary T.B. (Pulmonary T.B.):

Post-primary disease refers to exogenous ('new' infection) or endogenous (reactivation of a dormant primary lesion) infection in a person who has been sensitised by earlier exposure.

It is most frequently pulmonary and characteristically occurs in the apex of an upper lobe where the oxygen tension favours survival of the strictly aerobic organism.The onset is usually insidious, developing slowly over several weeks. Systemic symptoms include fever, night sweats, malaise, and loss of appetite and weight, and are accompanied by progressive pulmonary symptoms .Chronic cough, often with hemoptysis ,pyrexia of unknown origin ,unresolved pneumonia ,exudative pleural effusion ,asymptomatic (diagnosis on chest X-ray) , and spontaneous pneumothorax .

Radiological changes include ill-defined opacification in one or both of the upper lobes, and as progression occurs, consolidation, collapse and cavitation develop to varying degrees .

In extensive disease, collapse may be marked and results in significant displacement of the trachea and mediastinum.

Miliary TB:

Hematogenous dissemination of TB gives rise to miliary TB, which may present acutely but more frequently is characterized by 2–3 weeks of fever, night sweats, anorexia, weight loss and a dry cough. Commonly affects the lungs, liver, spleen, bone marrow, kidneys, and adrenals. Hepatosplenomegaly, and the presence of a headache may indicate coexistent tuberculous meningitis.

Auscultation of the chest is frequently normal, but in more advanced disease, widespread crackles are evident.

The classical appearances on chest X-ray are of fine 1–2 mm lesions (‘millet seed’) distributed throughout the lung fields, although occasionally the appearances are coarser.

Anemia and leucopenia reflect bone marrow involvement. ‘Cryptic’ miliary TB is an unusual presentation sometimes seen in old age,

where the typical radiology and clinical features are absent.

Extrapulmonary TB disease:

Extrapulmonary tuberculosis accounts for about 20% of cases in those who are HIV-negative but is more prevalent in HIV-positive individuals.

Lymphadenitis:

Lymph nodes are the most common extrapulmonary site of disease .Disease may represent primary infection, spread from contiguous sites, or reactivation. The nodes are usually painless and initially mobile but become matted together with time. When caseation and liquefaction occur, the swelling becomes fluctuant and may discharge through the skin with the formation of a ‘collar-stud’ abscess and sinus formation.

Approximately half of cases fail to show any constitutional features, such as fevers or night sweats. The tuberculin test is usually strongly positive. During or after treatment, paradoxical enlargement

Gastrointestinal tuberculosis:

TB can affect any part of the bowel and patients may present with a wide range of symptoms and signs. Upper gastrointestinal tract involvement is rare.

Fever, night sweats, anorexia and weight loss are usually prominent and a right iliac fossa mass may be palpable. Up to 30% of cases present with an acute abdomen.

Ultrasound or CT may reveal thickened bowel wall, abdominal lymphadenopathy, mesenteric thickening or ascites.

Barium enema and small bowel enema reveal narrowing, shortening and distortion of the bowel, with caecal involvement predominating.

Pericardial disease:

TB can cause pericardial effusion and then Constrictive pericarditis

Fever and night sweats are rarely prominent and the presentationis usually insidious, with breathlessness and abdominal swelling. Pulsus paradoxus, a raised JVP, hepatomegaly, prominent ascites and peripheral oedema are common to both types.

Diagnosis is based on the clinical, radiological and echocardiographic findings .The effusion is frequently blood-stained. Open pericardial biopsy can be performed where there is diagnostic uncertainty. The addition of corticosteroids to antituberculosis treatment has been shown to help both forms of pericardial disease.

Central nervous system disease: Meningeal disease represents the most important form of central nervous system TB. Unrecognized and untreated, it is rapidly fatal.

Bone and joint disease:

The spine is the most common site for bony TB (Pott's disease), which usually presents with chronic back pain and typically involves the lower thoracic and lumbar spine. CT or MRI is valuable in gauging the extent of disease, the amount of cord compression, and the site for needle biopsy or open exploration, if required. Presentation is usually insidious, with pain and swelling; fever and night sweats are uncommon.

Genitourinary disease:

Fever and night sweats are rare with renal tract TB and patients are often only mildly symptomatic for many years. Hematuria, frequency and dysuria are often present, with sterile pyuria found on urine microscopy and culture. In women, infertility from endometritis, or pelvic pain and swelling from salpingitis or a tuboovarian abscess occurs occasionally. In men, genitogenitourinary TB may present as epididymitis or prostatitis.

T.B. Diagnosis :

Unexplained cough for more than 2-3 weeks, particularly in an area where TB is highly prevalent,

-Typical chest X-ray changes should prompt further investigation

-Sputum exam for TB bacilli

A positive smear is sufficient for the presumptive diagnosis of TB but definitive diagnosis requires culture.

Staining:The sputum is stained with Ziehl-Neelsen (ZN) stain for acid and alcohol-fast bacilli (AAFB) oran auramine-phenol fluorescent test performed.

• Stain →→ Ziehl–Neelsen Auramine fluorescence

-Fibreoptic bronchoscopy with washings from the affected lobes is useful if no sputum is available. This has replaced former techniques such as gastric washings. Transbronchial biopsies can also be obtained for histology and microbiological assessment.

-Culture. The sputum is cultured on special media for 4-8 weeks. Cultures to determine the sensitivity of the bacillus to anti TB drugs take a further 1 to 3-weeks.

Smear-negative sputum should also be cultured, as only 10-100 viable organisms are required for sputum to be culture-positive.

-Biopsies of the pleura ,lymph nodes and solid lesions within the lung (tuberculomas) may be required to confirm the diagnosis.

-Pleural fluid analysis : High protein contain, high WBC count predominately lymphocytic, low sugar contain ,high LDH , adenosine deaminase +ve, and only 15% positive acid fast bacilli(AFB) in pleural fluid.

Response to empirical anti -tuberculous drugs (usually seen after 5–10 days)

Baseline blood tests • FBC, CRP, ESR, U&E and LFTs.

A diagnosis of smear-negative TB may be made in advance of culture if the chest X-ray appearances are typical of TB and there is no response to a broad-spectrum antibiotic.

-Interferon Gamma Release Assays: to be used interchangeably with the tuberculin skin testing in the diagnosis of latent tuberculosis infection. Specificity is high greater than 95%.better than Tuberculin skin test.

-Nucleic Acid Amplification Test (NAAT). detects DNA sequences specific for Mycobacterium tuberculosis and rifampicin resistance by polymerase chain reaction It is based on the **GeneXpert** system.

T.B. Management: The goals of TB .Treatment are : eradication M. tuberculosis infection. prevention of the development of drug resistance, preventing relapse of disease and prevention of M. tuberculosis transmission
Standard treatment involves 6 months course
The intensive phase consists of treatment with 3 or 4 drugs Isoniazid 300mg, Rifampicin 600 mg, Pyrazinamide 2 grams ± Ethambutol 2,5 grams daily for 2 months .
The continuation phase consists of Isoniazid and Rifampicin in fixed dose combination taken for 4 months.
The treatment of TB is based on the principle of an initial intensive phase to reduce the bacterial population rapidly, followed by a continuation phase to destroy any remaining bacteria.
9-12 months of therapy is recommended for meningeal TB, including involvement of the spinal cord in cases of spinal TB or HIV positive.
Pyridoxine should be prescribed in pregnant women and malnourished patients to reduce the risk of peripheral neuropathy with isoniazid. Where drug resistance is not anticipate patients can be assumed to be non-infectious after 2 weeks of appropriate therapy.

Streptomycin is rarely used in the UK, but is an important component of short-course treatment regimens in developing nations.
Underlying comorbidity (renal and hepatic dysfunction, eye disease, peripheral neuropathy and HIV status), as well as the potential for drug interactions, must be considered.
Baseline liver function and regular monitoring are important for patients treated with standard therapy including rifampicin, isoniazid and pyrazinamide,
Mild asymptomatic increases in transaminases are common but serious liver damage is rare.
Adverse drug reactions occur in about 10% of patients, but are significantly more common in the presence of HIV co-infection.
Corticosteroids are recommended when treating pericardial or meningeal disease, and in TB of the ureter, pleural effusions. Can suppress hypersensitivity drug reactions.
Surgery is still occasionally required (e.g. for massive haemoptysis, loculated empyema, constrictive pericarditis, lymph node suppuration, spinal disease with cord compression), but usually only after a full course of antituberculosis treatment.

Main adverse reactions of first-line:

Isoniazid INH: Peripheral neuropathy, Hepatitis,skin rash,lupoid reactions ,Seizures and Psychosis.

Rifampicin: induces liver enzymes, which may be transiently elevated in the serum of many patients. The drug should be stopped only if the serum bilirubin becomes elevated or if liver enzyme are >3time elevated from base line level, Major adverse reaction : Febrile reactions, Hepatitis ,Rash,Gastrointestinal disturbance, Interstitial nephritis ,Thrombocytopenia, Hemolytic anemia. With using Rifampicin urine, tears and other secretions will develop a bright orange/red coloration. Women taking the oral contraceptive pill must be warned that its efficacy will be reduced and alternative contraception may be necessary.

Pyrazinamide: adverse reactions : Hepatitis, Gastrointestinal disturbance ,hyperuricemia ,skin rash, photosensitivity and gout.

Streptomycin : 8th nerve damage, rash, nephrotoxicity, and agranulocytosis

Ethambutol: optic neuritis, arthralgia ,peripheral neuropathy and rash.

The effectiveness of therapy for pulmonary TB is assessed by further sputum smear at 2 months and at 5 months. Treatment failure is defined as a positive sputum smear or culture at 5 months or any patient with a multidrug resistant strain, regardless of whether they are smear-positive or negative.

Directly observed therapy (DOT):

Poor adherence to therapy is a major factor in prolonged infectious illness, risk of relapse and the emergence of drug resistance. In order to improve compliance, special clinics are used to supervise treatment regimens directly.to those : uncooperative patients, homeless ,serious mental illness and those with a history of non-compliance and abuse alcohol.

Thrice weekly and improves adherence. It has become an important control strategy

Drug-resistant TB: the presence of resistance to any first-line agent.

Multidrug-resistant (MDR) TB is defined by resistance to at least **rifampicin** and **isoniazid**, with or without other drug resistance.

Multidrug resistance (MDR) is a major therapeutic problem with a high mortality and occurs mainly in HIV infected patients. transmission of multi drug resistant tuberculosis to healthcare workers and to other patients is a major public health problem.

it requires prolonged treatment with less effective, more toxic and more expensive therapies(second line anti TB drugs). Mortality rate from MDR-TB is high .

Factors contributing to the emergence of drug-resistant tuberculosis:

- Drug shortages
- Poor-quality drugs
- Lack of appropriate supervision
- Transmission of drug-resistant strains
- Prior antituberculosis treatment
- Treatment failure (smear-positive at 5 months)

Second Line Anti T.B drugs :

Second-line drugs available for treatment of resistant M. tuberculosis are aminosalicylic acid capreomycin, cycloserine, clarithromycin, azithromycin, ciprofloxacin, Levofloxacin ,ofloxacin، ethionamide, kanamycin, amikacin, moxifloxacin and rifabutin.

Extensively drug-resistant (XDR) TB is defined by resistance to at least rifampicin and isoniazid, in addition to any **quinolone** and at least one injectable **second-line agent.**

Latent Tuberculosis Infection(LTBI):

About one-quarter of the world's population has latent TB. Don’t have active disease and cannot transmit the organism but +ve Tuberculin skin test. However, reactivation of disease may occur if host immunity are impair .

Approximately 20% of close contacts of patients with smear-positive pulmonary TB and 5% of those with smear-negative, culture-positive disease have evidence of TB infection(latent TB). Cases are commonly identified using the tuberculin skin test or IGRA.

Latent T.B. Diagnosis :

The diagnosis of latent TB infection is dependent on a positive tuberculin test, which does not necessarily indicate active disease, but only previous infection.

Tuberculin skin test: The standard Mantoux test is an intradermal injection of 0.1 mL (5 tuberculin units) of purified protein derivative (PPD) tuberculin in the skin of the forearm. The injection site is evaluated 48 to 72 hours later. The reading is based on the diameter of the indurated or swollen area don't depend on redness area .

Skin Test Interpretation: Consider positive tuberculin skin test in the following condition :

+ ve PPD >/= 5 mm: if People with medical conditions that place them at high risk for active TB.

- ❖ HIV patients
- ❖ Recent contacts of someone with TB
- ❖ Fibrotic changes on CXR or patient had old TB
- ❖ Organ transplant recipients
- ❖ Immunosuppressed (includes patients receiving the equivalent of 15 mg/day or more of prednisone for one month or more).

+ ve PPD >/= 10 mm: if People with medical conditions that place them at high risk for active TB

- ❖ Chronic renal failure
- ❖ Diabetes mellitus
- ❖ Silicosis
- ❖ Leukemias/lymphomas
- ❖ Carcinoma of the head/neck or lung
- ❖ Weight loss > 10% of ideal body weight
- ❖ Gastrectomy/jejunoileal bypass

+ ve PPD >/= 15 mm for people without a known risk factor for TB indicates a positive reaction.

- ❖ **False positives:**
  - – Non-tuberculous mycobacterial(**NTM**) infection
  - – BCG vaccination (in children)
- ❖ **False negatives:** Severe TB (25% of cases negative) • Newborn and elderly

• HIV (if CD4 count < 200 cells/mL) • Malnutrition
• Recent infection (e.g. measles) or immunisation
• Immunosuppressive drugs • Malignancy • Sarcoidosis

Latent T.B. Treatment :INH 300 mg daily x 6 months or RIF 600 mg daily x 4 months.

TB and Pregnancy:

Treatment TB in pregnancy should be treated as for non pregnant patients regardless of gestational age. If possible Fetotoxic drugs should be avoided in pregnancy The safety of the first line drugs has been established except streptomycin. Experience with 2nd line drugs in pregnancy is limited**.**

Breast feeding in TB mother:

Breastfeeding is not contraindicated if the mother is being treated for tuberculosis or latent TB with first-line agents. The infant should receive pyridoxine if mother is receiving Isoniazid.
Breast feeding is contraindicated if the mother is receiving rifabutin or fluoroquinolone.in active lesions breast feeding is avoided and the baby is isolated from mother .
Baby should be given prophylactic INH 10 -20 mg/kg/day for 3 months when mother is suffering from active TB.
Breast feeding should be avoid if the infant also taking the drug to avoid excess drug level.
BCG vaccine should be given to the baby as early as possible.

LTBI vs. TB Disease

Latent TB Infection (LTBI)	TB Disease (in the lungs)
Inactive, contained tubercle bacilli in the body	**Active**, multiplying tubercle bacilli in the body
TST or blood test results usually positive	TST or blood test results usually positive
Chest x-ray usually **normal**	Chest x-ray usually **abnormal**
Sputum smears and cultures **negative**	Sputum smears and cultures may be **positive**
No symptoms	**Symptoms** such as cough, fever, weight loss
Not infectious	**Often infectious** before treatment
Not a case of TB	**A case** of TB

TB VACCINE: BCG (the Calmette–Guérin bacillus), It was first used medically in 1921 a live attenuated vaccine derived from M. bovis, is the most established TB vaccine. It is administered by intradermal injection and is highly immunogenic. BCG appears to be effective in preventing disseminated disease, including tuberculous meningitis, in children, but its efficacy in adults is less.
BCG vaccination can cause a false positive Mantoux test.
Rates of protection against tuberculosis infection vary widely and protection lasts up to twenty years. Among children it prevents about 20% from getting infected.
Serious side effects are rare. Often there is redness, swelling, and mild pain at the site of injection. A small ulcer may also form with some scarring after healing. Side effects are more common and potentially more severe in those with poor immune function. It is not safe for use during pregnancy.
Additionally BCG is sometimes used as part of the treatment of bladder cancer.