Tuberculosis

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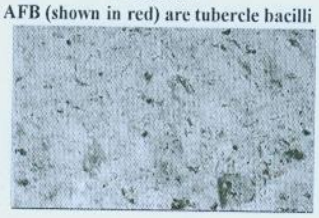
WHAT IS IT?

AFB Smear
AFB (shown in red) are tubercle bacilli



Bacterial infection

Caused by *Mycobacterium tuberculosis* (also called *tubercle bacillus*)

Damages a person's lungs or other parts of the body

Fatal if not treated properly

Clinically Relevant Major Species of Mycobacterium

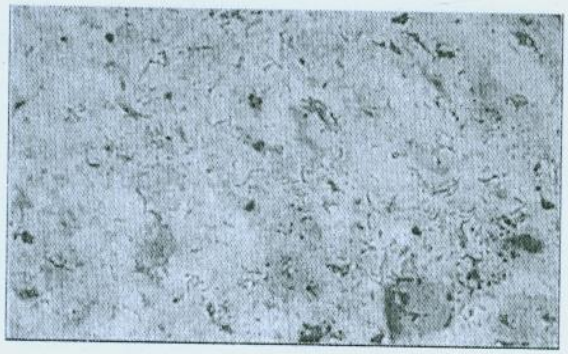
Group	Strict Human Pathogens	Occassional/Potential Human Pathogens	Usually Environmental Rarely Human Pathogens
M. tuberculosis complex	M. Tuberculosis M. Leprae M. Africanum M. Ulcerans	M. Bovis	
Photochromogens		M. Kansasi M. Marinum M. Simiae M. Asiasticum	
Scotochormogens		M. Scrofulaceum M. Szulgai M. Xenopi	M. Gordonae M. Flavescens
Nonchromogens	M. Genavense	M. Avium M. Intracellulare M. Hemophilum M. malmoense	
Rapid growers		M. Fortuitum M. Chelonei	M. Smegmatis

Tuberculosis

Microbiology

- MTB: fastidious, slowly growing, acid alcohol fast, aerobic bacterium (AAFB)
- Cell wall composed of complex peptidoglycans and long chain lipids
  These lipids make MTB hydrophobic thus resistant to many stains routinely used in Laboratory, e.g. Gram & Giemsa stains as well as AA fastness
  (Once stained, cannot be decolorised by alcohol, acid solutions)

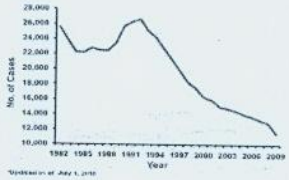
AFB Smear
AFB (shown in red) are tubercle bacilli



Tuberculosis

Epidemiology

- MTB: Common deadly disease worldwide
- 33% world population has been infected with MTB
- 30 million active cases of tuberculosis at any time
- Mid 1980s, rising case rate at 3% while it was declining by 5% ----?

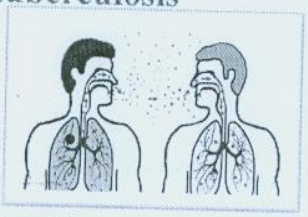


Tuberculosis

Transmission

Resp route – inhalation of airborne droplets following coughing, sneezing and speaking where organism remain airborne and infectious for period of time.

Transmission of M. tuberculosis

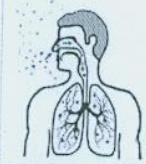


M. tb spread via airborne particles called droplet nuclei

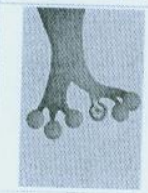
Expelled when person with infectious TB coughs, sneezes, shouts, or sings

Transmission occurs when droplet nuclei inhaled and reach the alveoli of the lungs, via nasal passages, respiratory tract, and bronchi

Pathogenesis

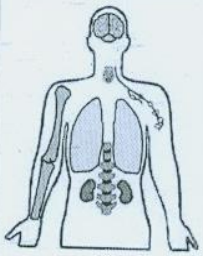


Droplet nuclei containing tubercle bacilli are inhaled, enter the lungs, and travel to the alveoli.



Tubercle bacilli multiply in the alveoli.

Pathogenesis



A small number of tubercle bacilli enter the bloodstream and spread throughout the body. The tubercle bacilli may reach any part of the body, including areas where TB disease is more likely to develop (such as the brain, larynx, lymph node, lung, spine, bone, or kidney).

Pathogenesis

Within 2 to 8 weeks, special immune cells called macrophages ingest and surround the tubercle bacilli. The cells form a barrier shell, called a granuloma, that keeps the bacilli contained and under control (LTBI).

If the immune system cannot keep the tubercle bacilli under control, the bacilli begin to multiply rapidly (TB disease). This process can occur in different areas in the body, such as the lungs, kidneys, brain, or bone.

Tuberculosis

Medical conditions predisposing to active tuberculosis, once person infected with organism:

- HIV infection
- Prior MTB (fibrotic changes on Chest X-ray)
- Diabetes
- Steroid or other immuno suppressive meds
- Silicosis (remember job Hx)
- Hematologic diseases, e.g. lymphoma
- ESRD (CKD) / Dialysis patients
- Post gastrectomy and malabsorption states
- Others, malignant wt. Loss …. Etc.

Tuberculosis

Group of People at High Risk for MTB

- HIV infected persons
- Close contact (eg, family members) of patients infected with MTB
- Underlying medical condition that increase risk of acquiring MTB
- Alcoholic IVDU
- H.C.W.
- Long term care facilities, nursing homes, etc.

Several months of exposure needed to get infection with MTB, however, close contacts of infected persons puts others at risks of acquiring infections.

Tuberculosis

Degree of Contagiousness of a Patient Depends on

- Number of organism in sputum (open TB)
- Cavitary lung disease
- Amount of coughing
- Length of time on anti TB Rx
- Others

Tuberculosis

Clinical Syndromes

- Primary infection
- Latent infection
- Reactivation TB
- P. TB and E.P. TB

Medical Evaluation for TB

- Medical history
- Physical examination
- Test for TB infection
- Chest radiograph
- Bacteriologic examination

Medical Evaluation for TB
Medical History

Symptoms of pulmonary TB:

- Prolonged cough (3 weeks or longer), hemoptysis
- Chest pain
- Loss of appetite, unexplained weight loss
- Night sweats, fever
- Fatigue

Medical Evaluation for TB (cont.)
Medical History (cont.)

Symptoms of possible extrapulmonary TB:

- Blood in the urine (TB of the kidney)
- Headache/confusion (TB meningitis)
- Back pain (TB of the spine)
- Hoarseness (TB of the larynx)
- Loss of appetite, unexplained weight loss
- Night sweats, fever
- Fatigue

Tuberculosis

Primary Tubercolosis

- First exposure to MTB often asymptomatic
- Typically pul. Infiltrates: mid or lower lung fields with or without hilar adenopathy, these infiltrates non-specific in appearance and not cavitory
- In most cases pneumonitis clears without specific therapy and latent infections established
- In some cases, primary infection may progress, resembling reactivation disease

Tuberculosis

Latent Infection

- Following primary infection many persons remain asymp.
- Organisms remain latent within macrophages indefinitely
- Tuberculosis skin test (T-PPD) - very important to discover these persons
- If no preventive therapy given, 1:10 persons with MTB infection will develop clinical disease at some time in their lives

LTBI vs. TB Disease

Person with LTBI (Infected)	Person with TB Disease (Infectious)
Has a small amount of TB bacteria in his/her body that are alive, but inactive	Has a large amount of active TB bacteria in his/her body
Cannot spread TB bacteria to others	May spread TB bacteria to others
Does **not** feel sick, but may become sick if the bacteria become active in his/her body	May feel sick and may have symptoms such as a cough, fever, and/or weight loss
Usually has a TB skin test or TB blood test reaction indicating TB infection	Usually has a TB skin test or TB blood test reaction indicating TB infection
Radiograph is typically normal	Radiograph may be abnormal
Sputum smears and cultures are negative	Sputum smears and cultures may be positive
Should consider treatment for LTBI to prevent TB disease	Needs treatment for TB disease
Does **not** require respiratory isolation	May require respiratory isolation
Not a TB case	A TB case

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Reactivation Tuberculosis

- Consitutional sx and generalised wasting
- Weight loss
- Fever at night, sweating
- Diagnosis maybe difficult as pul sx mild or lacking.

Tuberculosis

Pulmonary Tuberculosis

- Majority of cases of active pul TB result from reactivating of latent organism
- Reactivation occurs more likely in upper lobes and superior segment of lower lobes (why?)
- However any area of the lungs may be involved, especially elderly diabetics, AIDS patients, etc.
- Absence of apical infiltrates would not exclude TB
- Practically: TB should be included in DDX any undiagnosed pneumonia

P. TB extent quite variable : Ranging from subtle CXR infiltrate with minimal cough to classic cavitary TB with Hemoptysis

If Untreated: pul. lesions develop caseation or central necrosis with partial liquefaction

Tuberculosis

Extra Pulmonary Tuberculosis

- TB outside lungs may be even more difficult to diagnose
- E. P. TB may manifest clinically during phase of primary infection especially in children
- More commonly, E.P TB represents Reactivation of Latent Infection
- Pulmonary lesions may be absent in more than 50% cases of E.P. TB
- It is more uncommon to see CXR with active pulmonary infiltrate or cavities in cases of E.P. TB

Tuberculosis

E.P. TB Includes

- Pleural disease with effusion: common form of E.P TB
- TB meningitis
  - Usu. Ch. Meningitis but may be as:
  - Fulminant as pyogenic together with cranial nn. Deficits: TB meningitis must be considered (because there is often basilar meningitis)
  - CSF: High protein, Low glucose, lymphocytic pleocytosis
  - This CSF pattern seen in other disease, thus if TB meningitis highly suspected (+ve TST, CSF lymphocytic pleocytosis) Anti – TB Rx should be initiated

Tuberculosis

EPTB (cont.)

- Pericarditis and peritonitis
- TB adenitis or scrofula (ch – TB infection of cervical L. nodes)
- Osteomyelitis including Pott's disease (TB of spine)
- G.U. TB + GI TB
- Ocular infection including chorioretinitis
- Cutaneous TB (Lupus vulgaris)
- Miliary Tuberculoss: disseminated form of TB into lymphohematogenous system during primary TB infection or more commonly during reactivation

This type can also be difficult to diagnose, CXR can be normal in the early stages of the disease.

Tuberculosis

Diagnosis

- High index of suspicion is essential
- MTB manifestations are protean, thus lab. Confirmation is also essential
- Close communication between the clinician and microbiology lab. Is mandatory to identify microorganism causing disease and determine their susceptibility to antimicrobial agent that assist in their eradication.
- Tuberculosis Skin Test (TST),(PPD, Mantoux) important first step in identifying infected patients
- Lab Techniques for MTB identification:
  - A.F.B. smear and cultures of resp. secretion (e.g. sputum)
  - A.F.B. smear and cultures of potentially infected body fluids or tissues: CSF, gastric fluid, urine, LN BX bone marrow BX, joint fluids, etc.
  - Rapid methods: PCR (polymerase chain reactions) and nucleic acid probes

Tuberculosis

Diagnostic Tests / Procedures

- Acid Fast Stain
  - AFB Smear
  - A typical mycobacterium smear
  - Kinyoun stain
  - Mycobacterial smear
  - TB smear
  - Ziehl – Neelson stain (ZN stain)
  - Auramine – Rhodamine stain

Tuberculosis

Diagnostic Tests / Procedures (cont.)

- Acid Fast Bacilli

Because surrounded by waxy lipid containing envelope that Resistant to destaining by acid alcohol.

- Stain can penetrate cell wall by:
  - Heat (classic ZN) method, or
  - Detergent (Tergitol Kinyoun) method
- Once stained: acid fast bacteria resist de colorization (AAFB)
- Whereas other bacteria (destained) with acid alcohol

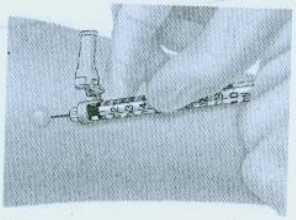
Medical Evaluation for TB
Bacteriologic Examination of Specimens

Smear examination

- Detecting AFB in smears may be first evidence of mycobacteria
  - Quickest (results within 24 hours) and easiest procedure
  - Provides a preliminary presumptive diagnosis of TB
  - AFB in a smear are counted and classified as 4+, 3+, 2+, or 1+

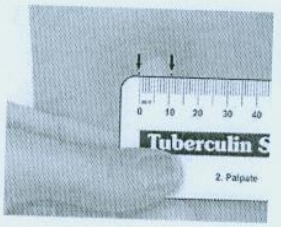
Administering the TST

- Inject 0.1 ml of PPD (5 tuberculin units) into forearm between skin layers
- Produce wheal (raised area) 6–10 mm in diameter
- Follow universal precautions for infection control



Reading the TST

- Trained health care worker assesses reaction 48–72 hours after injection
- Palpate (feel) injection site to find raised area
- Measure diameter of induration across forearm; only measure induration, not redness
- Record size of induration in millimeters; record "0" if no induration found



Interpreting the TST Reaction

≥5 mm induration is classified as positive in

- HIV-infected persons
- Recent contacts of infectious TB
- Persons with fibrotic changes on chest radiograph consistent with prior TB
- Patients with organ transplants and other immunosuppressed patients

Interpreting the TST Reaction (cont.)

≥10 mm induration is classified as positive in

- Recent arrivals from high-prevalence countries
- Injection drug users
- Residents and employees of high-risk congregate settings

Interpreting the TST Reaction (cont.)

≥10 mm induration is classified as positive in

- Mycobacteriology laboratory personnel
- Persons with conditions that increase risk for progressing to TB
- Children <4 years of age, or children and youth exposed to adults at high risk

Interpreting the TST Reaction (cont.)

≥15 mm is classified as positive in

- Persons with no known risk factors for TB

Targeted skin testing should only be conducted among high-risk groups

Interferon Gamma Release Assays (IGRAs)

- IGRAs detect *M. tb* infection by measuring immune response in blood
- Cannot differentiate between TB and LTBI; other tests needed
- May be used for surveillance/screening, or to find those who will benefit from treatment
- FDA-approved IGRAs are QFT Gold In-Tube and T-Spot.*TB* test

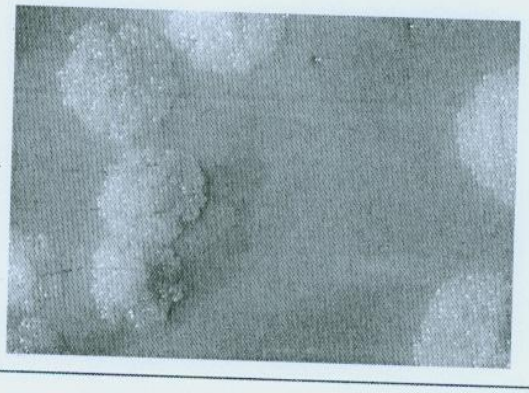
Direct Detection Using Nucleic Acid Amplification (NAA)

- NAA tests rapidly identify a specimen via DNA and RNA amplification
- Benefits may include
  - Earlier lab confirmation of TB disease
  - Earlier respiratory isolation and treatment initiation
  - Improved patient outcomes; interruption of transmission
- Perform at least 1 NAA test on each pulmonary TB suspect
- A single negative NAA test does not exclude TB

Culture

- Remains gold standard for confirming diagnosis of TB
- Culture all specimens, even if smear or NAA negative
- Results in 4–14 days when liquid medium systems used
- Culture monthly until conversion, i.e., 2 consecutive negative cultures

Colonies of M. tuberculosis Growing on Media



Major Goals of TB Treatment

- Cure patient, minimize risk of death/disability, prevent transmission to others
- Provide safest, most effective therapy in shortest time
- Prescribe multiple drugs to which the organisms are susceptible
- Never treat with a single drug or add single drug to failing regimen
- Ensure adherence and completion of therapy

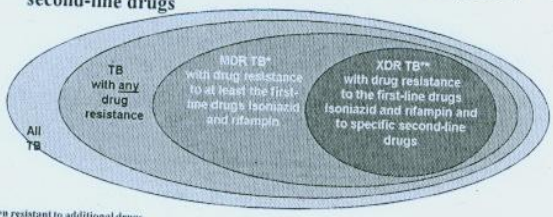
Drug-Susceptibility Testing

- Conduct drug-susceptibility testing on initial *M. tb* isolate
- Promptly forward results to the health department
- Repeat for patients who
  - Do not respond to therapy or
  - Have positive cultures despite 3 months of therapy

Multidrug-Resistant (MDR) and Extensively Drug-Resistant (XDR) TB

MDR TB caused by bacteria resistant to best TB drugs, isoniazid and rifampin

- **XDR TB caused by organisms resistant to isoniazid and rifampin, plus fluoroquinolones and ≥1 of the 3 injectable second-line drugs**



*Often resistant to additional drugs
**Resistant to any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin

Tuberculosis

Treatment

TB treatment based on certain principles:

- MTB resistance to drugs occurs at random, spontenceous, genetic mutation. Eg. INH natural resist. Occurs at 1: 10^6 and Rif at 1 bacterium in 10^8
- Regimen containing multiple drugs to which organism susceptible should be used and sensitivity testing should be done on all isolates.
- Both Isoniazid – resistant MTB and MDR – MTB are increasing problems
- In case of poor compliance, D.O.T. given 3x weekly in outpatient setting should be considered strongly
- Failure of therapy often due to noncompliance
- Non-compliance may lead to emergence of MDR organisms
- Patient immune status must be taken into account

Tuberculosis

Drug Theraphy

- First Line drugs:
  - Isoniazid (INH)
  - Rifampicin
  - Pyrazinamide
  - Streptomycin
  - Ethambutol

Tuberculosis

Drug Theraphy (cont.)

- Second Line Drugs
  - Capreomycin
  - Ciprofloxacin
  - Cycloserine
  - Ethionamide
  - Kanamycin
  - Ofloxacin
  - Para-amino salicylic acid (PAS)

These drugs:

- *Less effective*
- *More expensive*
- *More toxic*

Tuberculosis

Commonly Used Regimends to treat TB

- Initial phase (first two months) 3-4 drugs
  INH, RIF, PZA, Streptomycin or Ethambutol
- Continuation phase (4-10 months)
  INH, RIF

Duration of Drugs Therapy for TB

Depends on the site of disease:

- Pulmonary TB - 6 months
- Cervical lymphacloropathy – 6-9 months
- Hilar adenopathy - 9 months
- E.P. TB
  - TB Meningitis
  - Bone / Joint
  - Disseminated Disease

} 2 months with 4 drugs + 10 months with INH + RIF

BCG Contraindications

- Contraindicated in persons with impaired immune response from
  - HIV infection, congenital immunodeficiency
  - Leukemia, lymphoma, generalized malignancy
  - High-dose steroid therapy
  - Alkylating agents
  - Antimetabolites
  - Radiation therapy
- BCG vaccination should not be given to pregnant women