Tuberculosis

What is it?
Tuberculosis (TB), a multisystemic disease with myriad presentations and manifestations, is the most common cause of infectious disease–related mortality worldwide. The disease is becoming more common in many parts of the world. Also, the prevalence of drug-resistant TB is increasing worldwide.

The following organisms are part of the MTB complex - *M. tuberculosis, M. bovis, M. caprae, M. africanum, M. microti, M. pinnipedii, M. canetti.*

Mycobacterium tuberculosis is the human tubercle bacillus.

What's the likely history?

The following factors increase the likelihood that a patient will have tuberculosis (TB):

1. HIV infection
2. History of a positive purified protein derivative (PPD) test result
3. History of prior TB treatment
4. TB exposure
5. Travel to or emigration from an area where TB is endemic
6. Homelessness, shelter-dwelling, incarceration

How does it happen?

Pathogenesis of Tuberculosis

Mycobacterium tuberculosis primarily affects the lung but can also cause disease in almost any other tissue. The way it spreads and damages the body depends on the host's immune response.

The organism and the immune system interact as follows:
1) **Facultative intracellular growth**: With the first exposure (usually by inhalation into the lungs), the host has no specific immunity. The inhaled bacteria cause a local infiltration of neutrophils and macrophages. Due to the various virulence factors such as **Mycobacterial Cord Factor**(MCF), the phagocytosed bacteria are not destroyed. They multiply and survive in the macrophages. The bacteria cruise through the lymphatics and blood to set up camp in distant sites. This period of facultative intracellular existence is usually short-lived because the host rapidly acquires its **prime defense** against the **acid-fast buggers**: cell-mediated immunity.

2) **Cell-mediated immunity**: Some of them macrophages succeed in phagocytosing and breaking up the invading bacteria. These macrophages then run toward a local lymph node and present parts of the bacteria to T-helper cells. The sensitized T-cells then multiply and enter the circulation in search of M. tuberculosis. When the T-cells encounter their antigenic target, they release lymphokines that serve to attract macrophages and activate them when they arrive.
These activated macrophages can now destroy the bacteria. It is during this stage that the macrophage attack actually re-sults in local destruction and necrosis of the lung tissue.
The necrosed tissue looks like a granular creamy cheese and is called caseous necrosis. This soft caseous center is surrounded by macrophages, multinucleated giant cells, fibroblasts, and collagen deposits, and it frequently calcifies. Within this granuloma the bacteria are kept at bay but remain

viable. At some point in the future, perhaps due to a depression in the host's resistance, the bacteria may grow again.

How to identify it?

Classic clinical features associated with active pulmonary TB are as follows:

- Cough
- Weight loss/anorexia
- Fever
- Night sweats
- Hemoptysis
- Chest pain
- Fatigue

Chest pain in patients with TB can also result from tuberculous acute pericarditis. Pericardial TB can lead to cardiac tamponade or constriction.

Elderly individuals with TB may not display typical signs and symptoms of TB infection, because they may not mount a good immune response. Active TB infection in this age group may manifest as non-resolving pneumonitis.

Signs and symptoms of extrapulmonary TB may be nonspecific. They can include leukocytosis, anemia, and hyponatremia due to the release of ADH (antidiuretic hormone)-like hormone from affected lung tissue.

The myriad presentations and manifestations of this disease

Tuberculous meningitis

Patients with tuberculous meningitis may present with a headache that has been either intermittent or persistent for 2-3 weeks. Subtle mental status changes may progress to coma over a period of days to weeks. Fever may be low grade or absent.

Skeletal TB

The most common site of skeletal TB involvement is the spine (Pott disease); symptoms include back pain or stiffness. Lower-extremity paralysis occurs in up to half of patients with undiagnosed Pott disease.
Tuberculous arthritis usually involves only 1 joint. Although any joint may be involved, the hips and knees are affected most commonly, followed by the ankle, elbow, wrist, and shoulder. Pain may precede radiographic changes by weeks to months.

Genitourinary TB

Symptoms of genitourinary TB may include flank pain, dysuria, and frequent urination. In men, genital TB may manifest as a painful scrotal mass, prostatitis, orchitis, or epididymitis. In women, genital TB may mimic pelvic inflammatory disease. TB is the cause of approximately 10% of sterility cases in women worldwide and of approximately 1% in industrialized countries.

Gastrointestinal TB

Any site along the gastrointestinal tract may become infected. Symptoms of gastrointestinal TB are referable to the infected site and include the following:

1. Nonhealing ulcers of the mouth or anus
2. Difficulty swallowing - With esophageal disease
3. Abdominal pain mimicking peptic ulcer disease - With stomach or duodenal infection

4. Malabsorption - With infection of the small intestine
5. Pain, diarrhea, or hematochezia - With infection of the colon

Physical Examination

Physical examination findings associated with TB depend on the organs involved.

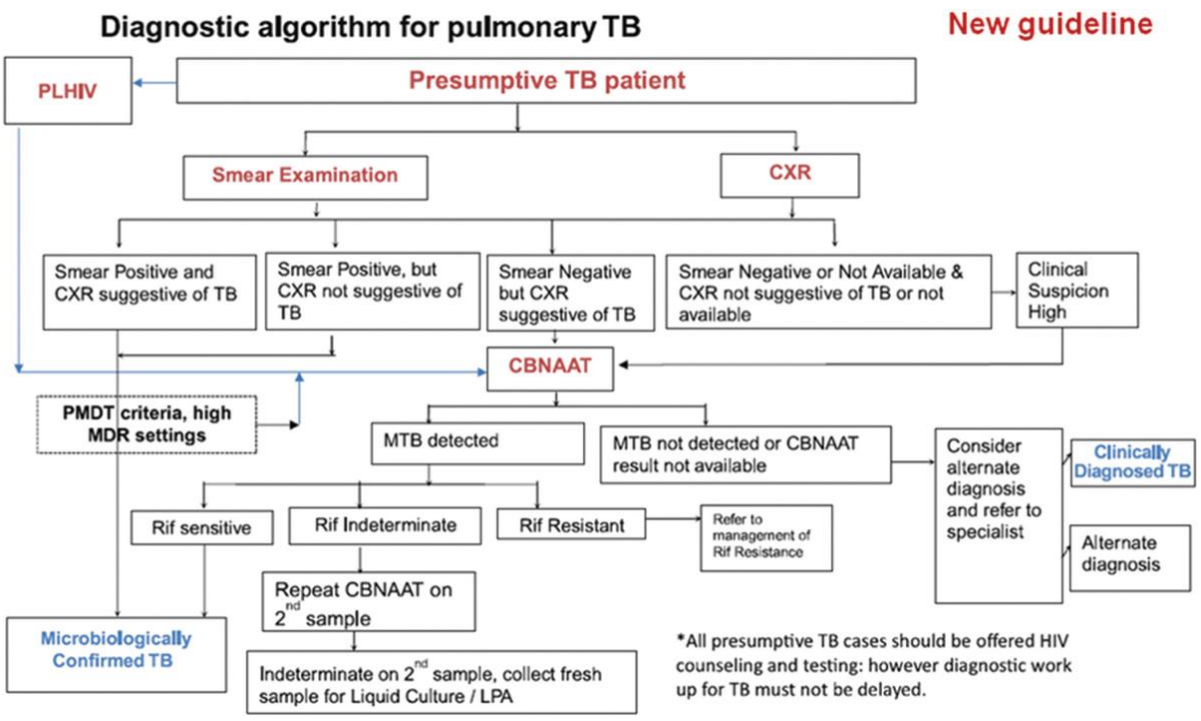
1. Patients with pulmonary TB have abnormal breath sounds, especially over the upper lobes or involved areas. Rales or bronchial breath signs may be noted, indicating lung consolidation.

2. Signs of extrapulmonary TB differ according to the tissues involved. They may include the following:
    1. Confusion
    2. Coma
    3. Neurologic deficits
    4. Chorioretinitis
    5. Lymphadenopathy
    6. Cutaneous lesions

3. Lymphadenopathy in TB occurs as painless swelling of 1 or more lymph nodes. Lymphadenopathy is usually bilateral and typically involves the anterior and posterior cervical chain or supraclavicular nodes.

The absence of any significant physical findings does not exclude active TB.
Classic symptoms are often absent in high-risk patients, particularly those who are immunocompromised or elderly.
Up to 20% of patients with active TB may deny symptoms.
Therefore, sputum sampling is essential when chest radiographic findings are consistent with TB.

DIAGNOSIS



Approach Considerations

The primary screening method for tuberculosis (TB) infection (active or latent) is the Mantoux tuberculin skin test with purified protein derivative (PPD).

An in-vitro blood test based on interferon-gamma release assay (IGRA) with antigens specific for *Mycobacterium tuberculosis* can also be used to screen for latent TB infection. IGRA assays offer certain advantages over tuberculin skin testing.

Sputum Smear

Patients suspected of having TB should submit sputum for Acid-fast bacilli (AFB) smear and culture. Sputum should be collected in the early morning on 3 consecutive days. In hospitalized patients, sputum may be collected every 8 hours. Early-morning gastric aspirate may also produce a good specimen, especially in children.

Ziehl-Neelsen staining of sputum is a simple process that takes approximately 10 minutes to accomplish. **While highly specific for mycobacteria, however, this stain is relatively insensitive, and detection requires at least 10,000 bacilli per mL**;
most clinical laboratories currently use a more sensitive auramine-rhodamine fluorescent stain (auramine O).

What if there's a negative smear?

TB detection following negative smear

The absence of a positive smear result does not exclude active TB infection.

Approximately 35% of culture-positive specimens are associated with a negative smear result.

An *M. tuberculosis* –specific enzyme-linked immunospot (ELISpot) assay can be used to differentiate TB cases with negative sputum smears from latent TB infection.

Nucleic Acid Amplification Tests

Deoxyribonucleic acid (DNA) probes specific for mycobacterial ribosomal RNA identify species of clinically significant isolates after recovery. In tissue, polymerase chain reaction (PCR) amplification techniques can be used to detect *M tuberculosis* -specific DNA sequences and thus, small numbers of mycobacteria in clinical specimens.

Ribosomal RNA probes and DNA PCR assays allow identification within 24 hours.

The DNA probes are approved for direct testing on smear-positive or smear-negative sputa. However, smear-positive specimens yield higher sensitivity.

The CDC recommends performing one of these nucleic acid amplification tests when the diagnosis of pulmonary TB is being considered but has not yet been established.

Culture

1. Culture for AFB is the most specific test for TB and allows direct identification and determination of susceptibility of the causative organism. Access to the organisms may require lymph node/sputum analysis, bronchoalveolar lavage, or aspirate of cavity fluid or bone marrow.
   In addition, obtaining the test results is slow (3-8 wk), and they have a very low positivity in some forms of disease.

   Routine culture uses a nonselective egg medium (Lowenstein-Jensen or Middlebrook 7H10) and often requires more than 3-4 weeks because of the 22-hour doubling time of *M tuberculosis*.

2. Radiometric broth culture (BACTEC radiometric system) of clinical specimens is found to significantly reduce the time (10-14 days) for mycobacterial recovery.

3. Newer broth culture media and systems for isolation, based on a fluorescent rather than a radioactive indicator, are available for use in clinical laboratories. The indicator is inhibited by oxygen; as mycobacteria metabolize substrates in the tubes and use the oxygen, the tube begins to fluoresce.

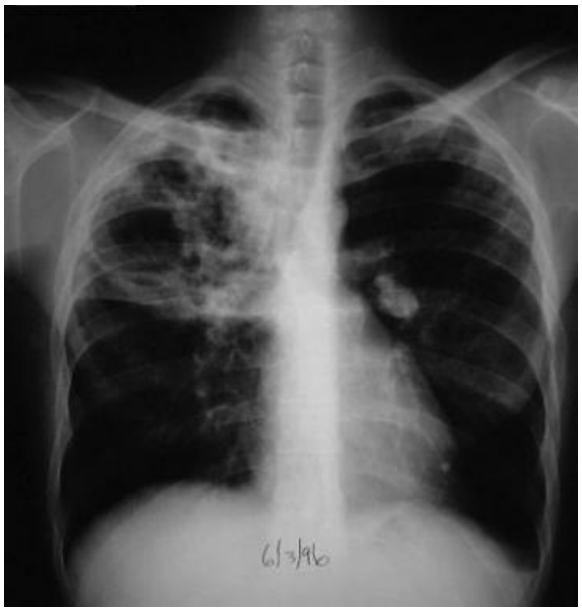
Drug Susceptibility Testing

Positive cultures should be followed by drug susceptibility testing. Symptoms and radiographic findings do not differentiate MDR-TB from fully susceptible TB. One should suspect MDR-TB if the patient has a history of previous treatment for TB, was born in or lived in a country with a high prevalence of MDR-TB, has a known exposure to an MDR-TB case, or is clinically progressing despite standard TB therapy.

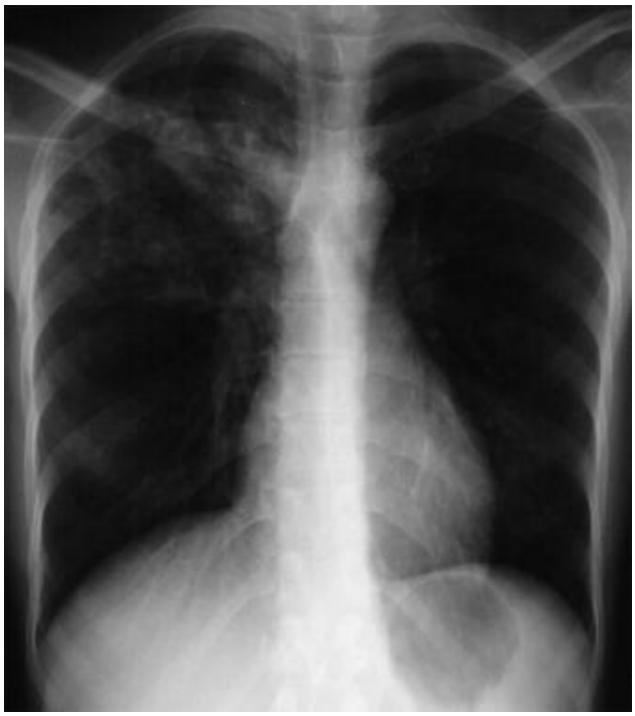
Susceptibilities should be repeated if cultures remain positive after 2 months, even when initial susceptibilities have not revealed any resistance.

Chest Radiography

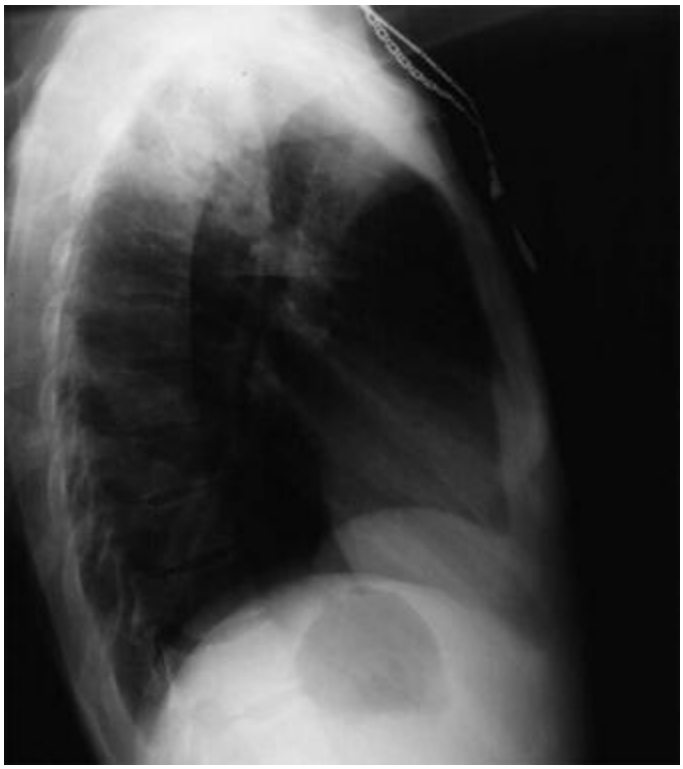
1. One must obtain a chest radiograph to evaluate for possible TB-associated pulmonary findings (demonstrated in the images below).
2. A traditional lateral and posteroanterior (PA) view should be ordered.
3. In addition, an apical lordotic view may permit better visualization of the apices and increase the sensitivity of chest radiography for indolent or dormant disease.



‘This radiograph shows a patient with typical radiographic findings of tuberculosis.



Anteroposterior chest radiograph of a young patient who with cough and malaise. The radiograph shows a classic posterior segment right upper lobe density consistent with active tuberculosis. This woman was admitted to isolation and started empirically on a 4-drug regimen in the ED. Tuberculosis was confirmed on sputum testing.



Lateral chest radiograph of a patient with posterior segment right upper lobe density consistent with active tuberculosis

The following patterns may be seen on chest radiographs:

1. Cavity formation - Indicates advanced infection and is associated with a high bacterial load
2. Noncalcified round infiltrates - May be confused with lung carcinoma
3. Homogeneously calcified nodules (usually 5-20 mm) - Tuberculomas; represent old infection rather than active disease
4. Miliary TB - Characterized by the appearance of numerous small, nodular lesions that resemble millet seeds on chest radiography (go to Miliary Tuberculosis for complete information on this topic)

TREATMENT

Anti-tubercular drugs can be classified into:

First line drugs:

1. Isoniazid (H)
2. Rifampin (R)
3. Pyranzinamide (Z)
4. Ethambutol (E)
5. Streptomycin (S)

Second line drugs:

1. Ethionamide
2. Quinolones – ofloxacin, ciprofloxacin
3. Aminoglycosides - kanamycin, capreomycin and amikacin.

4. Macrolides -clarithromycin

Treatment of Tuberculosis aims to:

• Interrupt transmission by rendering patient s non- infectious.

• Prevent morbidity and death by curing patients.

• Prevent the emergence of drug resistance.

- Prevent relapse

To achieve the aims, the following strategies are followed:

• **Multi-drug therapy**: Combination of more than one drug for rapid and effective killing of tubercle bacilli.

Drug	Recommended dose			
	Daily		**3 times per week**	
	Dose and range (mg/kg body weight)	**Maximum (mg)**	**Dose and range (mg/kg body weight)**	**Daily maximum (mg)**
Isoniazid	**5 (4–6)**	**300**	**10 (8–12)**	**900**
Rifampicin	**10 (8–12)**	**600**	**10 (8–12)**	**600**
Pyrazinamide	**25 (20–30)**	**–**	**35 (30–40)**	**–**
Ethambutol	**15 (15–20)**	**–**	**30 (25–35)**	**–**
Streptomycin	**15 (12–18)**		**15 (12–18)**	**1000**

• **Short course chemotherapy** lasting for 6 months (or 8 months in previously treated cases).

• **2 phase chemotherapy**: The short course is divided into-

1. Intensive phase (initial phase, 2-3 months): Aims at aggressive treatment with 4 first line drugs that rap idly kill the bacilli making the patient smear negative, followed by:3
2. Continuation phase (given for 4-5 months, with 2 or 3 first line drugs): Aims at killing the remaining dormant bacilli) and prevents relapse.

- **DOTS strategy (Directly Observed Treatment, Short course**) is recommend by RNTCP and WHO.

  Here, the strategies used are:
  - The entire treatment course is supervised to improve the patient's compliance.
  - Treatment response is also monitored by periodic sputum smear microscopy.

• **Treatment regimens**: There are two treatment regimens, **category I and II**; each having different indications

Category-wise treatment regimen for tuberculosis (WHO guideline, 2010)

CATEGORY	INDICATIONS	INTENSIVE PHASE	CONTINUATION PHASE	DURATION (MONTHS)
I	New patients • New sputum smear- positive • New sputum smear- negative • New extrapulmonary	2 months H+R+Z+E	4 months H+R	6months
II	Previously treated patients Sputum smear positive cases such as: • Relapse	2 months H+R+Z+E+S + 1-month H+R+Z+E	5 months H+ R +E	8 months (for patients with low risk of MDR · TB)
	• Treatment failure • Return after default Patient waiting for Drug Susceptibility Test (DST) result	Empirical MDR** regimen	Empirical MDR regimen	18- 24 months or till DST results (for patients with high risk of MDR · TB

KEY: • DST: drug susceptibility test. MDR: multidrug resistant. Relapse- A patient who was declared cured after treatment, returns smear positive ; Treatment failure-A smear positive patient remains smear positive after 5 months of treatment; Return after default - A patient who returns smear positive after having left treatment for at least 2 months

Some trivia

Tuberculosis "Rule of Fives"

• Droplet nuclei are 5 micrometers and contain 5 Mycobacterium tuberculosis bacilli.

• Patients infected with Mycobacterium tuberculosis have a 5% risk of reactivation in the first 2 years and then a 5% lifetime risk.

- Patients with "high five" HIV will have a 5 + 5% risk of reactivation per year.

EMBED VIDEO: - https://www.youtube.com/watch?v=yR51KVF4OX0