

Tuberculosis

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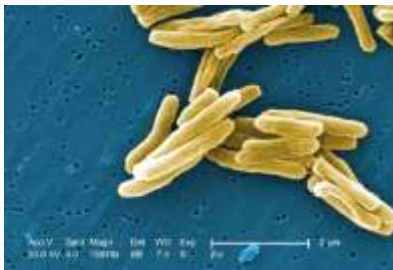
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Introduction



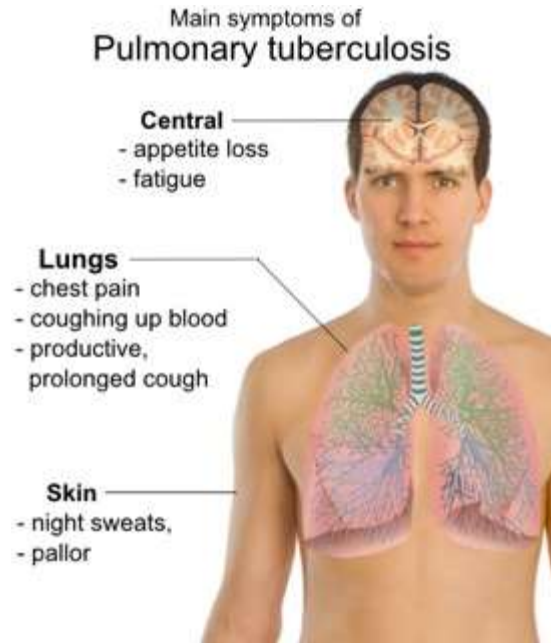
Mycobacterium tuberculosis, which causes tuberculosis (TB), is a non-motile obligate aerobic bacillus (rod) that forms chains. *M. tuberculosis* is neither Gram-negative nor Gram-positive. As an extracellular agent, *M. tuberculosis* needs oxygen to live and multiply, so it is attracted to the upper respiratory tract. It is also a facultative intracellular invader, allowing it to evade the immune system.

Humans serve as the only reservoir for *M. tuberculosis*. *M. tuberculosis*'s virulence is increased because of components of its cell wall:

- Peptidoglycan: Prevents osmotic pressure from destroying the cell.
- Complex lipids: Provide antibiotic resistance.
- Acids: Protect the cell.
- Cord factor: Protects the cell from macrophages and causes toxic reaction in host's lipids (such as in the alveoli).
- Wax-D: Protects the cell envelope.

M. tuberculosis is spread through airborne transmission. When an infected person talks, coughs, or sneezes, small infected particles (1 to 5 micrometers per diameter) enter the air. Larger droplets fall, but the small particles remain suspended in the air and can be inhaled by anyone who comes in contact with them.

Primary pulmonary disease



Wikimedia Commons, M. Haggstro

Once inhaled, the bacilli travel through the airways to the lungs and the alveoli, where they begin to multiply. The bacilli invade the lymph system and can travel to other parts of the body, including the upper lobes of the lungs. The host's immune system attempts to control the spread of *M. tuberculosis* by an inflammatory reaction in which some bacilli are engulfed by phagocytes (neutrophils and macrophages) and TB-specific lymphocytes destroy the bacilli, along with normal tissue. As cells are destroyed, exudate begins to accumulate in the alveoli and causes bronchopneumonia, usually within 2 to 10 weeks after initial exposure.

Latent TB

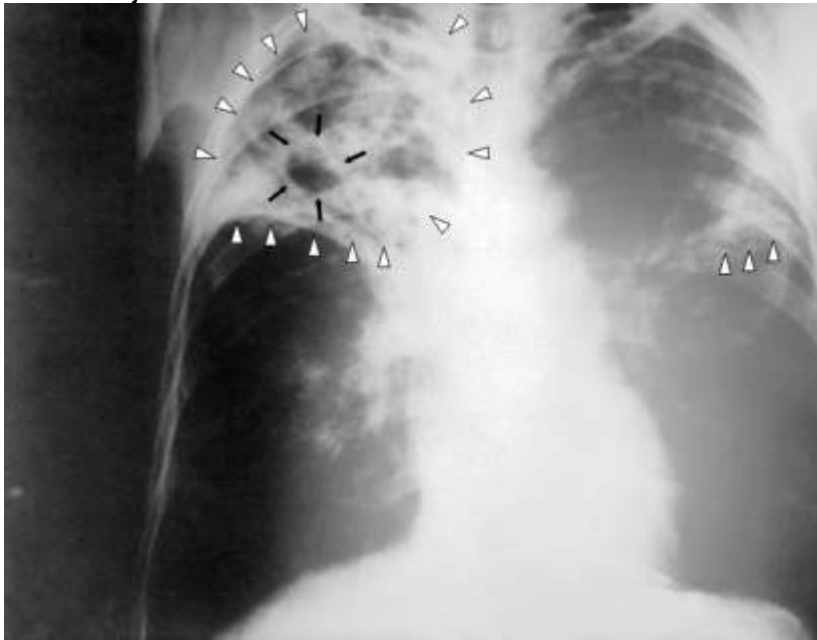
If the host's immune system is adequate, the macrophages wall off the mass of live and dead bacilli, forming a granuloma and causing a positive skin reaction (cell-mediated immune response) but no active infection. This is latent TB. The walled-off granuloma is eventually transformed into fibrous tissue and the center becomes necrotic and cheesy. This center portion is called a Ghon tubercle. The cheesy mass may become calcified, and most of the bacilli die, but some become dormant. People with latent TB have no symptoms and cannot spread the disease to others while the disease remains dormant. Chest x-rays and sputum tests are generally negative, but patients are at risk of active TB and need treatment to prevent TB disease.

Active TB

If the immune system is overwhelmed because of a large number of bacilli or a weak immune system, then the bacilli begin to multiply and to destroy tissue, resulting in active TB and sometimes causing a cavity to form in the lungs. Only about 10% of those with an initial infection develop active disease. Additionally, dormant bacilli may also become reactivated, sometimes years after the initial

infection. The reactivated bacilli activate immune cells to render host cells sensitive to killing and other immune cells to liquefy the cheesy material at the center of the Ghon tubercule, which erodes and releases the infected material into the airway, forming a cavity and allowing the bacilli to become airborne again and spread to others.

Oxygen and carbon dioxide enter the cavity and bacilli begin to rapidly multiply and spread from the cavities through the air passages to other parts of the lungs and to the larynx. As the ruptured tubercle heals, it forms scar tissue and more inflammation, which in turn causes bronchopneumonia and the development of more tubercles. The process of damage to lung tissue spreads to the lung hilum and to adjacent lobes.



PHIL, CDC

In some cases, periods of remission varying in length may be followed by periods of reactivated disease. Reactivation TB often relates to an impaired immune system. Immunity may be impaired in those with HIV, diabetes, transplants, cancer of the head or neck, Hodgkin's disease, leukemia, substance abuse, kidney disease and low body weight. Drugs that impair immunity include immunosuppressants, such as corticosteroids and chemotherapeutic agents. Elderly patients may have less obvious symptoms than children or younger adults.

Symptoms of primary pulmonary TB	
Cough	Persisting 3 weeks or longer. Non-productive or mucopurulent. Hemoptysis (may occur, especially as TB progresses).
Fever	Low grade. Chills.

Night sweats	Frequent. Pronounced (drenched with perspiration).
General malaise	Fatigue. Weight loss. Loss of appetite.
Pain	Chest pain. Pain when breathing or coughing.

While TB has been in a decline in the United States, there has been an increase in the immigrant population with rates of infection among foreign-born residents almost 10 times higher than of native-born residents. Nosocomial outbreaks have occurred, often related to failure to identify an infected source.

Resistant TB

Resistant strains of TB are an increasing cause of concern. In rare cases, people with resistant TB strains have required forced hospitalization and isolation to protect the public:

- **Multi-drug resistant tuberculosis (MDR-TB)** is resistant to at least 2 commonly used first-line drugs, isoniazid (INH) and rifampin.
- **Extensively drug resistant tuberculosis (XDR-TB)** is also resistant to all fluoroquinolones and at least one of the three second-line drugs: amikacin, kanamycin, or capreomycin.

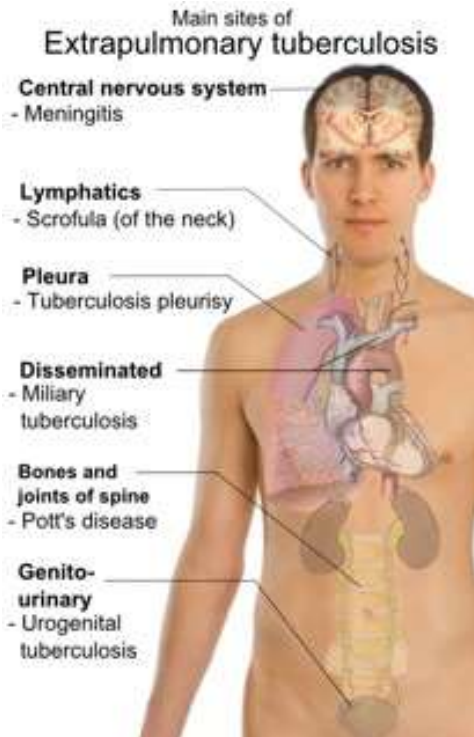
XDR-TB emerged as a worldwide concern in 2005. In the United States, most XDR-TB is found in patients who are foreign born or immunocompromised (such as with HIV/AIDS). Active TB requires treatment for extended periods of time, usually 18-24 months, with multiple drugs, and some people cannot or will not comply with this regimen. Since the 1980s, resistance has caused an increased need for second-line drugs to combat infection.

The primary causes for increased resistance include:

- Failure to complete a course of treatment
- Mismanaged treatment, including incorrect medication, dosage, or duration of therapy.

People who have had previous TB are at especially increased risk of developing resistant strains and should be monitored carefully. Drug resistant TB increasingly poses a risk for patients and staff in healthcare facility.

Extrapulmonary Tuberculosis



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Extrapulmonary or disseminated tuberculosis has spread from the lungs to other parts of the body through the circulatory system. It is also sometimes referred to as miliary TB. With this type of tuberculosis, the lesions tend to be small (1 to 5 mm) and widely disseminated throughout the lungs. When a lesion erodes into the pulmonary vein, the bacilli are carried throughout the body. In the United States, primary pulmonary tuberculosis is the most common, but about 1 to 3 percent goes on to develop disseminated tuberculosis. Patients at increased risk are those who are immunocompromised, such as HIV/AIDS patients. In fact, about half of AIDS patients with CD4 counts <200 and co-infected with tuberculosis develop the disseminated disease. Infants and the elderly are also at increased risk because their immune systems are less effective. The onset of disseminated infection varies from weeks to years after initial infection. Since the initial infection begins in the lungs, symptoms at onset are the same as those of primary pulmonary tuberculosis, but as the infection spreads, more symptoms become evident.

Symptoms of extrapulmonary (disseminated) TB	
Organ	Splenomegaly. Hepatomegaly. Anorexia and weight loss. Abdominal distention. Jaundice.
Bone (spine most)	Back pain (most common). Compression fractures.

common).	Back deformity. Joint pain.
Genitourinary	Flank pain. Dysuria (frequency, nocturia). Pyuria. Hematuria. Urgency, incontinence. Pain in suprapubic area and/or costovertebral angle. Thickened epididymis. Urethral stricture. Scrotal/vesicovaginal fistula.
Meningeal	Fever. Nausea and vomiting. Nuchal rigidity. Loss of consciousness. Seizures. Severe headache. Photophobia.
Neck (scrofula)	Cervical lymph nodes (often bilateral) swollen and firm, hardening as disease progresses. Fistula with drainage sometimes evident.
Pleurisy (granuloma ruptures into pleural space)	Marked increase of fluid in pleural space. Dyspnea. Mild to low-grade fever. Pleuritic pain on inspiration.
Peritoneal	Abdominal distention (ascites). Abdominal pain.
Pericardial	Fever. Dysrhythmia General malaise with poor appetite. Sharp piercing chest pain.
Adrenal involvement	Fever Nausea and vomiting. Abdominal pain. Weakness and general fatigue. Disorientation, confusion. Hypotensive shock. Dehydration. Electrolyte imbalance with hyperkalemia, hypercalcemia,

hypoglycemia and hyponatremia.

Bacille Calmette-Guérin (BCG) Vaccine

While a vaccine is available for TB, it is not routinely recommended for use in the United States. BCG (Bacille Calmette-Guérin) is a tuberculosis vaccine that is commonly administered to children in countries with high incidences of childhood tuberculous meningitis and disseminated TB. BCG has been used for about 80 years, but it has limitations. BCG has proven to be about 80% effective in preventing TB infection, but the results last only about 15 years, and effectiveness appears to vary according to the environment, so it is more effective in some parts of the world than in others. BCG does not prevent primary infection or reactivation of latent pulmonary infection.

BCG is not recommended in the United States because infection with *Mycobacterium tuberculosis* has a low incidence, BCG is not always effective to prevent adult pulmonary TB, and adult immunization is variable. Further, BCG often results in false positives on skin testing, making subsequent diagnosis of TB more difficult.

Immigrants or visitors from other countries may have been vaccinated as infants or children, so those showing positive skin testing should be questioned carefully about previous vaccination before treatment is prescribed since skin testing is not reliable for this population. Blood tests are more accurate and are less likely to render a false positive.

Recommendations

In the United States, BCG vaccine is recommended only for the following:

- Health care workers may receive BCG vaccinations if they work with a large number of TB patients with resistant strains of TB, there is ongoing transmission of this disease to healthcare workers, and TB control precautions are unsuccessful.
- Children who have a negative skin test and live in circumstances in which they are continually exposed to adults who have resistant strains of TB or who are untreated or ineffectively treated for TB.

Contraindications:

- Positive skin test for TB.
- Immunocompromised condition.
- Pregnancy

BCG Administration

- Those receiving BCG should first be receive skin testing to ensure that they are not infected as those with positive skin tests should not receive the vaccine.

- The vaccine should be administered intradermally with a 26-gauge needle at the insertion point of the deltoid muscle in the upper arm, bevelled side of needle facing upward: usually 0.05 mL for infants and 0.1 mL for children and adults.
- Subcutaneous administration may result in a skin abscess or ulceration.
- About one to three weeks after administration, an indurated papule develops, usually reaching maximal diameter (10 to 20 mm) at about 6 weeks. The papule crusts over, leaving a small ulcerated area that may have purulent exudate. The lesion usually heals by about the tenth week, leaving a small scar.
- Regional lymph nodes may enlarge painlessly, but this enlargement usually recedes within a few months.

Tuberculosis skin test (TST)

Two types of testing are available for diagnosing tuberculosis: skin testing and blood testing. In both cases, the tests can only indicate whether or not the person has become infected with TB but not whether the infection is active or latent.

Tuberculosis skin test (TST) is a relatively safe testing method that can be used for most people, including infants and young children. It is only contraindicated for those who had a previous severe skin (ulceration) or allergic (anaphylaxis) reaction.

Mantoux skin test (PPD)

Injection

0.1 ml tuberculin purified protein derivative (PPD) containing 5 tuberculin units is injected intradermally into the inner surface of the forearm. The needle should be advanced approximately 3 mm with the bevel facing upward. The tuberculin is injected slowly, producing an elevated wheal 6 to 10 mm in diameter over the needle bevel.



PHIL, CDC

Reading

48 to 72 hours after injection, the individual must return so that the injection site can be examined. The elevated, indurated area must be measured (horizontal measurement across the forearm) but not the erythematous area, which may be much larger. The most accurate method is to use the nail to



mark the edge of the induration and then to mark that side with a pen. Both sides are marked and then the distance between the two markings is measured.	PHIL, CDC
Positive results	
≥5 mm	Positive for immunocompromised individuals (post transplant, HIV positive) or those taking immunosuppressant drugs (equivalent of >15 mg prednisone/day for 30 days). Positive for those with evidence of TB on x-ray or who have had recent contact with active case of TB.
≥10 mm	Positive for recent (<5 years) immigrants from countries with high prevalence of TB, injection drug users, those with high risk clinical conditions, resident/employees in high risk environments, and mycobacteriology lab staff. Positive for children <4 years and infants, children, and adolescents exposed to adults who are at high risk of becoming infected with TB..
>15 mm	Always considered a positive reading for all individuals.

False negatives

Results may not always be accurate. False negative readings can occur even though people are infected. Common causes for false negative readings include:

- Weakened immune system prevents skin response.
- Recent (≤ 8 to 10 weeks) or old (multiple years) TB infection.
- <6 months of age.
- Recent vaccination with live virus (measles, smallpox).
- Incorrect administration or reading of reaction.

False positives

False positives can also occur for a variety of reasons:

- Previous vaccination with BCG.
- Infection with other mycobacteria (such as *M. avium*).
- Incorrect administration or reading of reaction.

Two step procedure and the booster phenomenon

A two-step procedure is now recommended for those who require periodic retesting (such as healthcare workers or residents in nursing homes) to compensate for false negatives and to prevent misdiagnosis because of the **booster phenomenon**. A negative TST can occur if a person has an old TB infection because sensitivity wanes over time; however, subsequent tests months later might react positively because of the “boost” in response caused by the first test, suggesting an acute or recent infection (rather than an old non-active infection) and leading to unnecessary treatment.

Therefore, with the **two-step procedure**, a second test is done 1 to 3 weeks after the first to determine the effect of the first test:

- If the second test converts to positive in this short period of time, then it is considered evidence of a boosted reaction to a previous infection.
- If the second test is negative, it is considered a true negative and subsequent changes to positive would be considered new infections.

Positive tests are followed by chest x-rays, sputum cultures, and clinical evaluation to confirm diagnosis and establish whether an infection is latent or active.

Tuberculosis blood tests

Interferon-gamma release assays (IGRAs) are blood tests that measure the immune response to *Mycobacterium tuberculosis*. Infection causes white blood cells to release interferon-gamma (IFN-g) in response to antigens from *M. tuberculosis*. The fresh blood is mixed with antigen and controls and examined for production of antibodies. Processing must begin within 8 to 16 hours (depending on the test) after collection of blood in order to obtain accurate results.

While results are received faster than with TST, these tests are more expensive and are not generally recommended for testing of the general public except for those who have received the BCG vaccine. IGRAs are not recommended for children <5 because of limited data. However, IGRAs are sometimes used for workplace testing because of efficiency. As with other TST, IGRAs cannot differentiate between latent and active infection.

The FDA has approved 3 different IGRAs:

Test	Process within	Measures	Results
QuantiFERON®-TB Gold Test (QFT-G)	12 hours	IFN-g concentration	Positive Negative Indeterminate
QuantiFERON®-TB Gold In-Tube Test (QFT-GIT)	16 hours	IFN-g concentration	Positive Negative Indeterminate
T-SPOT®.TB	8 hours	IFN-g producing cells (spots)	Positive Negative Indeterminate Borderline

As with TST, positive tests are followed by chest x-rays, sputum cultures, and clinical evaluation to confirm diagnosis and determine if an infection is latent or active.

Other diagnostic tests

If TST or blood testing is positive, further diagnostic procedures are required to determine if TB is latent or active.

History	Demographic information (national origin, age, ethnic group, occupation) TB exposure. Medical conditions that may impact treatment or progress of the disease.
Physical exam	Complete assessment.
Chest x-ray	Posterior-anterior.
Sputum acid-fast microscopy and culture	Acid-fast microscopy indicates acid-fast bacilli, which is often but not always <i>M. tuberculosis</i> . Culture confirms diagnosis.

Treatment for TB

Latent TB protocols

Four different protocols are suggested for the treatment of latent TB, with the first protocol (9 months of Isoniazid) generally the preferred treatment. Twice weekly dosing requires directly observed therapy (DOT).

Protocol	Duration	Interval	Dosage/kg
Isoniazid (INH)	9 months	Daily	Adults 5mg/kg Children 10-20 mg/kg (Maximum dose of 300 mg)
		2 X weekly	Adults 15 mg/kg Children 20-40 mg/kg (Maximum dose of 900 mg)
Isoniazid	6 months		Varies
Rifampin	4 months	Daily	Adults 10 mg/kg. Children 10-20 mg/kg (Maximum dose 600 mg)
		2 X weekly	Adults 10 mg/kg Children (not recommended) (Maximum dose 600 mg).
Rifampin/ Pyrazinamide	Usually not recommended for LTb because of the danger of liver damage.		

Directly-observed therapy (DOT)

Directly-observed therapy (DOT) requires that a healthcare worker, such as a nurse, monitor every dose of prescribed anti-tuberculosis medication to ensure that all medications are taken as prescribed for the entire duration of treatment. State regulations regarding DOT vary from state to state, so the nurse should

check state requirements. Drug protocol is sometimes changed from daily administration to two to three times weekly to facilitate DOT. DOT is most commonly used for these situations:

- Sputum cultures are positive for acid-fast bacilli.
- Co-morbid conditions that require concurrent treatment with antiretroviral (HIV) drugs or methadone (addiction).
- Infection is MDR-TB or XDR-TB.
- Co-morbidity with psychiatric disease that renders patient unreliable.
- Cognitive impairment interferes with patient's ability to manage care.
- Patient is homeless and lacks adequate facilities.
- Patient has demonstrated a lack of reliability in taking treatments.
- Treatment is administered twice weekly instead of daily.

When a patient requiring DOT is discharged from the hospital, discharge plans must include DOT management as an outpatient. In some cases, home health agencies administer medications, but in other cases, the patient returns to an outpatient clinic for treatment.

Active TB protocols

There are a number of different regimens for treating active TB. For drug-susceptible TB, the four core drugs include isoniazid, rifampin, ethambutol, and pyrazinamide although 10 drugs are FDA-approved. Regimens vary:

- Initial phase: 2 months.
- Continuation phase: 4 to 7 months (longer duration if cavitation on initial chest x-ray and positive sputum after 2 months of treatment).

Preferred Regimen	Alternative Regimen	Alternative Regimen
Initial Phase Daily INH, RIF, PZA, and EMB* for 56 doses (8 weeks)	Initial Phase Daily INH, RIF, PZA, and EMB* for 14 doses (2 weeks), then twice weekly for 12 doses (6 weeks)	Initial Phase Thrice-weekly INH, RIF, PZA, and EMB* for 24 doses (8 weeks)
Continuation Phase Daily INH and RIF for 126 doses (18 weeks) or Twice-weekly INH and RIF for 36 doses (18 weeks)	Continuation Phase Twice-weekly INH and RIF for 36 doses (18 weeks)	Continuation Phase Thrice-weekly INH and RIF for 54 doses (18 weeks)

CDC

Regimens may require adjustment for patients who are immunocompromised (such as HIV positive) or when tests show that the tuberculosis is drug resistant. Rifampin may interact with antiretroviral drugs, so rifabutin may be used as an alternative for patients with HIV. In all cases of drug-resistant TB, DOT should be used to ensure that treatment is taken properly.

MDR is treated with second-line TB drugs, which are less effective and more toxic than INH and rifampin. XDR is often resistant to both first line and second-line drugs, so treatment can be very challenging. Treatment for XDR may not be effective, and these patients may require prolonged isolation to prevent transmission to others. For both MDR and XDR, treatment may require multiple drugs and extended period of treatment. A study of XDR treatment (2008) (not including HIV-infected patients), showed that >60 percent of XDR patients can eventually be cured, but average duration of treatment was over 26 months, and they received an average of over 5 different drugs.

Hospital airborne precautions

Airborne infection isolation should be initiated with suspicion or confirmation of a diagnosis of disease that has airborne transmission, such as TB. Isolation should be continued until confirmation that patient is not infective. Isolation procedures include:

- Placing patient in a private room with ≥ 12 air exchanges per hour (ACH) under negative pressure with air from the outside in and exhaust, preferably, to the outdoors, or recirculation provided through high-efficiency particulate air (HEPA) filters.
- Keeping door to the room closed and using a sign or color/coding to alert medical staff to isolation.
- Using an N95 respirator when entering the patient's room.
- Transporting patient in clean linens and wearing a facemask.
- Doing procedures in the room whenever possible.



The National Institute for Occupational Safety and Health (NIOSH) establishes requirements for respirators. An N95 respirator must filter 95% of 0.3 μm -sized particles in order to protect against *Mycobacterium tuberculosis*. The disposable N95 can be reused if not visibly damaged or dirty.

Positive and negative pressure rooms

A positive pressure room creates a protective environment for patients who are immunocompromised. In these rooms, the pressure is positive within the room so that clean air usually flows out of the room to the "dirty" area of the hallways, protecting the patient from pathogens. Air exchanges are >12 per hour, and filtration is by 99.97% HEPA filters. Windows are sealed for protection and the room has self-closing doors. Patients who have TB and are immunocompromised, such as those co-infected with HIV pose particular problems because they need both positive AND negative pressure rooms. In some cases a positive pressure room is inside a negative pressure room. Another solution is a freestanding positive pressure facility with the air exiting through filters into the fresh air.

Negative pressure rooms protect those outside the room from airborne pathogens because air flows from the outside (clean) into the room (dirty) and then to the exterior of the building so that it doesn't recirculate. If recirculation is necessary, it must be through a HEPA filter. Air exchanges are ≥ 6 in renovated rooms or ≥ 12 in new construction. Windows must remain sealed and doors closed as much as possible to maintain negative pressure. Negative pressure rooms are used primarily for active infections with *Mycobacterium tuberculosis* (TB) causing a cough with aerosolized infectious particles.

Healthcare provider exposure

Exposure to tuberculosis (TB) in a healthcare facility is almost always the result of inadequate or delayed diagnosis of active TB in a patient. Once a diagnosis is made, immediate contact investigation must be done to determine all those who might be at risk of infection, including physician nursing, laboratory, and housekeeping staff. In order to identify those who may be infected, a two-step PPD skin testing or the QuantiFERON®-TB Gold test should be done. Those who test positive must be further evaluated by chest x-ray and sputum culture to ensure that they do not have active TB. Treatment protocols for latent or active TB must be initiated as soon as possible. Healthcare workers with active pulmonary or laryngeal TB or who stopped treatment must be excluded from work until symptoms subside and 3 sputum tests are negative or treatment is completed.

Summary

Mycobacterium tuberculosis is a bacillus that causes TB, which is spread through airborne transmission. Tiny particles enter the airway and travel to the lungs. If the body's immune response is adequate, the bacteria are destroyed or walled off in granulomas within the lung. This latent infection is not infective but can reactivate into active TB. . In some cases, latent TB reactivates, usually because of a compromised immune system. Active pulmonary TB occurs when the bacilli begin to multiply in the lung. Multi-drug resistant TB (MDR-TB) is resistant to at least 2 commonly-used first-line drugs. Extensively drug resistant TB (XDR-TB) is also resistant to fluoroquinolones and at least one of the second-line drugs. . In disseminated TB, the bacilli migrate through the circulatory system to other parts of the body, causing a wide range of symptoms depending on the areas of infection. The Bacille Calmette-Guérin (BCG) vaccine is available but is used primarily for children in countries with high incidence of childhood tuberculosis meningitis, as it is not effective for primary pulmonary TB.

The two testing methods are the tuberculosis skin test (TST) and blood tests. Tests cannot differentiate between latent and active TB. The two-step procedure is used to account for the booster phenomenon, which gives a false positive. Confirming diagnostic procedures include history, physical examination, chest x-ray, and sputum acid-fast microscopy and culture. Treatment protocols vary for

latent and active TB, but isoniazid (INH) and rifampin are commonly-used drugs. Directly-observed therapy (DOT) is sometimes used to ensure compliance with drug treatment. Hospitalized patients with active TB should be isolated in negative pressure rooms and healthcare workers should wear N95 respirators.

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