TUBERCULOSIS

Introduction-Causes-Symptoms & Treatments

List of contents for Tuberculosis

Introduction to Tuberculosis

Tuberculosis, also known as TB, is a contagious bacterial infection that can be found nearly anywhere in the body, but is found most commonly in the lungs. Bacteria of tuberculosis may communicate to one person from another by direct contact like coughing, sneezing, or transmission of air. Tuberculosis is a chronic granulomatous disease infected by ***Mycobacterium tuberculosis***. Tuberculosis is a treatable, communicable disease that has two general states: latent infection and active infection. Mostly developing countries are affected by this disease because of improper hygienic and health conditions. If we compare TB with other disease then we will find that bout 1/3 of worlds populations are suffering from Tuberculosis. In India TB kills more adult than any other disease, from this we can understand its severity. New dimension has been added in 1980 due to spread of HIV with high prevalence of tuberculosis infection among these patients, because along with HIV infection TB become 08 times more dangerous. The common most symptoms of tuberculosis includes- cough, fever, night sweats, weight loss, etc. This symptoms may be mild for many months, and people ill with TB can infect up to 10-15 other people through close contact over the course of a year. The most common diagnostic test for TB is a skin test where a small injection of PPD tuberculin, an extract of the TB bacterium, is made just below the inside forearm.

TB infection in breast feeding women is matter of concern. First line antitubercular drugs are compatible with breastfeeding. Full course should be given to the mother, and breastfeeding should be continued. The infant should receive isoniazid preventive treatment after ruling out active TB followed by BCG vaccination. Breast fed infants whose mother is taking isoniazid, and those on isoniazid preventive therapy should be supplemented with pyridoxine 5mg/day.

Tuberculosis

Reference- http://www.healthcommunities.com/tuberculosis/types.shtml

1. Active Tuberculosis- Active TB is an infection in which the TB bacteria are rapidly multiplying and invading different organs of the body as they are in active condition. A person who is suffering from active pulmonary TB disease has strong possibility to spread this infection to others by airborne transmission of infectious particles coughed into the air. The person who is having tis type of TB infection must show a gentle man behavior by informing every possible person with whom he or she is meeting. Because active TB condition is contagious, so that these people should get diagnosed and treated as soon a possible. Multi-drug treatment is employed to treat active TB disease.

2. Latent Tuberculosis- Many people how received the infection of TB may not get infected with it immediately. They have no symptoms and their chest x-ray may be normal. The only manifestation of this encounter may be reaction to the tuberculin skin test (TST) or interferon-gamma release assay (IGRA). However, there is an ongoing risk that the latent infection may escalate to active disease. The risk is increased by other illnesses such as HIV or medications which compromise the immune system.

4. **Tuberculosis Pleurisy-** This is the condition which takes place just after initial infection. A granuloma located at the edge of the lung ruptures into the pleural space, the space between the lungs and the chest wall. In this case few ml of fluid can be found in the pleural space. Once the bacteria invade the space, the amount of fluid increases automatically and compresses the lung, causing shortness of breath (dyspnea) and sharp chest pain that worsens with a deep breath (pleurisy)
5. **Cavitary TB-** This type of TB is generally associated with the upper part of lungs. The bacteria cause severe destruction of lungs by forming cavities, or by making large air spaces. This type of TB is generally seen in reactivation case. The upper lobes of the lung are get into trouble just because there is a high amount of oxygen and TB bacteria love this condition, for their growth. Cavitary TB may occur after primary infection. Symptoms are common like cough, night sweats, fever, weight loss, and weakness.
6. **Miliary Tuberculosis-** This is a rare form of active tuberculoidal disease that occurs when TB bacteria find their way into the bloodstream, means this disease take place only after the entry of TB bacteria into the blood circulations . In this form, the bacteria quickly spread all over the body in tiny nodules and affect multiple organs at once. This form of TB can be rapidly fatal.
7. Laryngeal TB- TB can infect the **larynx, or the vocal chord area**. It is extremely infectious
8. Osteal Tuberculosis
9. Renal Tuberculosis
10. Adrenal Tuberculosis
11. TB Meningitis
12. Tuberculosis Pericarditis.
13. Tuberculosis Peritonitis
14. Lymph Node Disease

Risk factors & cause

Tuberculosis

Medications that suppress the immune system

Medications that suppress the immune system can also put people at risk for developing active TB disease, For example- Immunosuppressant that suppress immune system. Other medications that increase your risk of getting TB include those taken to treat-

Disease/Disorder	Details
Rheumatoid arthritis	**Rheumatoid arthritis** (**RA**) is an autoimmune disease that can cause joint pain and damage throughout your bod
Crohn's disease	**inflammatory bowel disease** (IBD). It causes inflammation of your digestive tract, which can lead to abdominal pain, severe diarrhea, fatigue, weight loss and malnutrition.
Psoriasis	**Psoriasis** is a chronic skin condition caused by an overactive immune system. Symptoms include flaking, inflammation, and thick, white, silvery, or red patches of skin
Lupus	**Lupus** is a systemic autoimmune disease that occurs when your body's immune system attacks your own tissues and organs.
Cancer	**Cancer** is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body

Other risk factors

People who use tobacco or misuse drugs or alcohol long term are more likely to get active TB. Following factors may contribute for the propagation of TB.

Factor	Reason
Poor Economy	Unable to take medicines
Illiteracy	Can not identified symptoms
Disease	Other disease increase risk
Malnutrition	Poor nutrition decrease immunity
Hesitation	Fear that diagnosis will create bad impression in society, and they will made isolated from surroundings.
Other	Transmission via air, droplets. Etc.

Reference- https://www.medicalnewstoday.com/articles/8856.php

Sign and Symptoms

Tuberculosis

Sign/Symptoms	Description with justification
Weight loss	It is considered to be immunosuppressive and leptin is involved in weight regulation and cellular immunity,
Night sweats	It seems likely that the night sweats associated with active tuberculosis are a response in part to signaling molecules released by cells of the immune system as they react to the infectious organism.
High temperature (fever)	The bacteria themselves may also be releasing fever-causing signals. In response to these circulating chemical signals the hypothalamus resets body temperature to a higher level for a while
Tiredness and fatigue	This is because of excessive coughing and tightness in chest along with problem in breathing.
Swellings in the neck	If tuberculosis affects the lymph nodes (about 25% of cases), it can cause swollen glands, usually at the sides and base of the neck
A persistent cough	TB bacteria most commonly grow in the lungs, and can cause symptoms such as: A bad cough that lasts 3 weeks or longer. Pain in the chest. Coughing up blood or sputum
In bone and joints	Bone pain, stiffness, restricted movement of hip and knee joints. Back pain, stiffness of back, several symptoms due to compression of the adjacent nerves like inability to control bowel and bladder activities, weakness to frank paralysis of lower limbs, loss of sensation etc.
Meninges	High fever, excruciating headache, confusion, drowsiness, stiffness of neck etc.
Impairment of liver and kidney	Hepatobiliary tuberculosis is a rare manifestation of *Mycobacterium tuberculosis* infection and is usually secondary to tuberculosis of the lungs or gastrointestinal tract

Diagnosis

Tuberculosis

Diagnostic Methods	Description
Blood test	A blood sample tested on TB bacteria to see how the immune system reacts. Quanti FERON-TB Gold in-Tube test and T-Spot. TB test are two examples of TB blood tests.
Skin test	The most common diagnostic test for TB is a skin test where a small injection of PPD tuberculin, an extract of the TB bacterium, is made just below the inside forearm. The injection site should be checked after 2-3 days, and, if a hard, red bump has swollen up to a specific size, then it is likely that TB is present.
Imaging test	chest X-ray or a CT scan. This may show white spots in your lungs where your immune system has walled off TB bacteria, or it may reveal changes in your lungs caused by active tuberculosis. CT scans provide more-detailed images than do X-rays.
Bronchoscopy	A scope is inserted inside the nostrils or mouth to see inside the lungs and airways.
Sputum examination	A lab examine a sample of the mucus.
Lung biopsy	A small sample of lung tissue is taken to analyze.

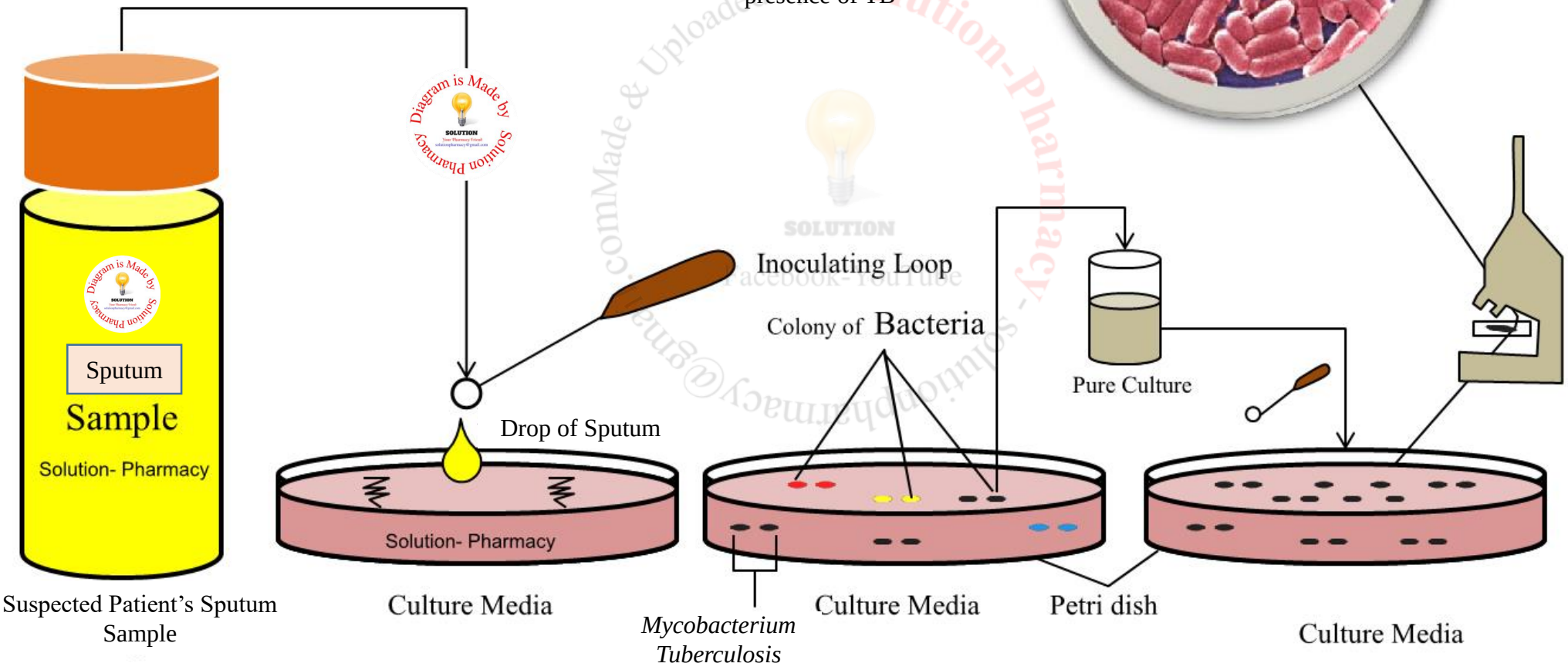
Reference- https://genematics.com/tuberculosis-review/

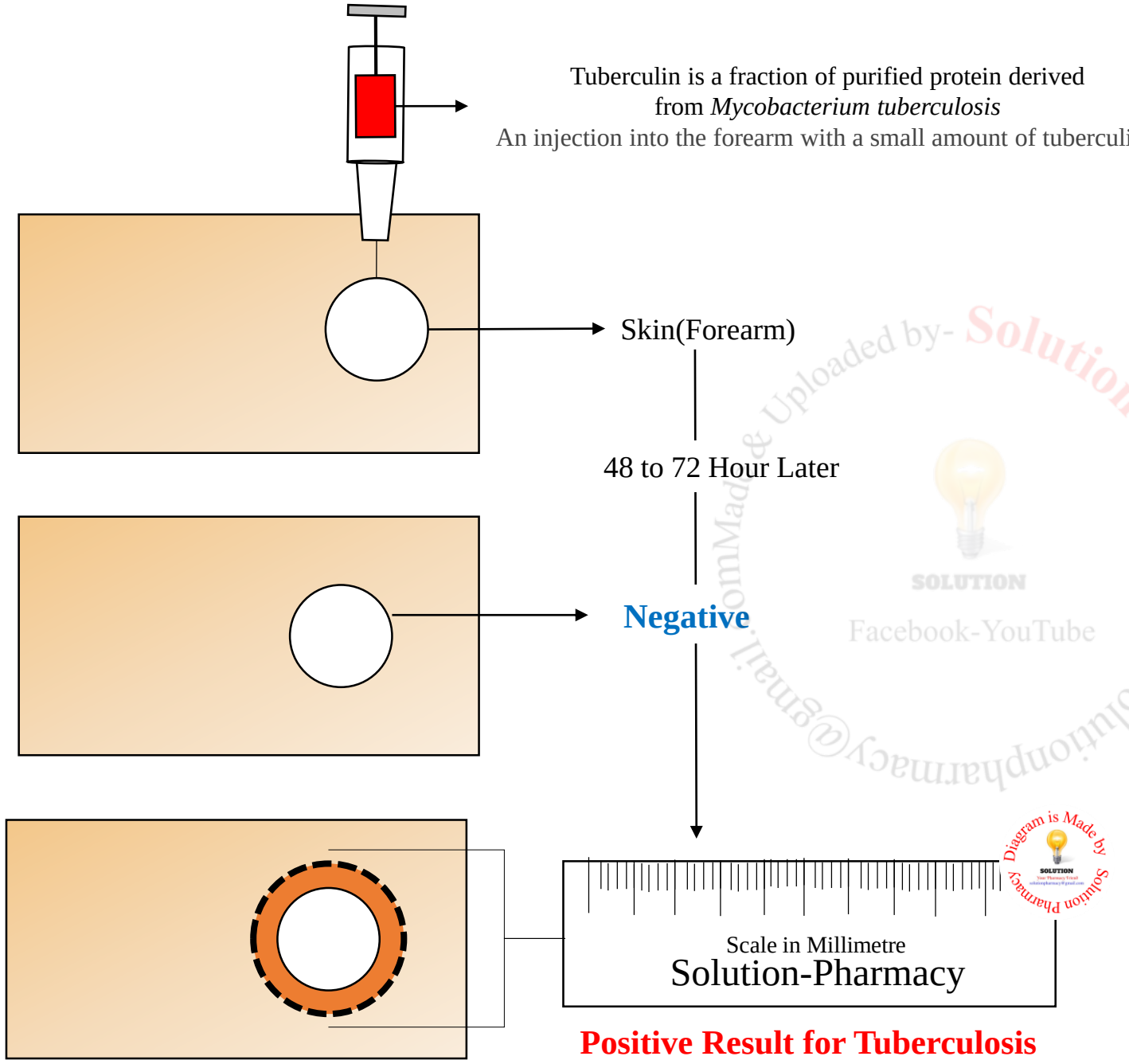
Tuberculosis- Sputum Diagnosis *

*Representation Only

E Mail- solutionpharmacy@gmail.com &
Reach solution at- www.facebook.com/pharmavideo/

Presence of *Mycobacterium Tuberculosis* In Patient's sputum confirms the presence of TB





Skin Test for Tuberculosis

The most common diagnostic test for TB is a skin test, The skin test for TB, otherwise known as a **Mantoux tuberculin test**. where a small injection of PPD tuberculin, an extract of the TB bacterium, is made just below the inside forearm. **Tuberculin is a fraction of purified protein derived from *Mycobacterium tuberculosis***. If an individual is infected with TB, their immune system will react to the tuberculin given in the TB skin test. The injection site should be checked after 2-3 days, and, if a hard, red bump has swollen up to a specific size, then it is likely that TB is present.

Result-Test bump smaller than 5 millimeters (mm), test result negative. test bump larger than 5 mm, test result in the positive range

Prevention

Tuberculosis

Infected people's coughs, sneezes, talking, singing or anything similar will emit droplets of moisture which can contain the bacteria. When other people breathe in this moisture they have a chance of getting infected as well. All stages afterwards are contagious and infected people are often isolated to stop the spreading of TB. Despite this, *Mycobacterium Tuberculosis* is a slow growing bacterium, and does not transfer easily from one person to another. In fact, people that stay close to an infected person for 6 months have a roughly 50% chance of acquiring the disease as well. Following preventive approaches should be followed by both patient and healthy individuals

Go for a check-up if you suspect that you could be suffering from TB.
Stay away from work, school or college until your TB treatment team advises you it's safe to return
Always cover your mouth when coughing, sneezing or laughing
Carefully dispose of any used tissues in a sealed plastic bag
Open windows when possible to ensure a good supply of fresh air in the areas where you spend time
Avoid sleeping in the same room as other people
People who are infected with active TB should also wear a surgical mask, known as a respirator, to keep TB particles from spreading through the air.
Keep your immune system functioning properly by adopting healthy eating habits, exercising regularly and getting sufficient sleep

Treatment of Tuberculosis

Classification Ref- KD Tripathi- 8th Ed.

First Line Drugs

Isoniazid, Rifampin, Pyrazinamide, Ethambutol, Streptomycin

Second Line Drugs

Fluoroquinolones

Ofloxacin, Levofloxacin

Moxifloxacin, Ciprofloxacin

Other oral drugs

Rifabutin

Terizidone

Cycloserine

Rifapentine

Ethionamide

Prothionamide

Paraamino-saliculic acid (PAS)

Injectable drugs

Amikacin

Kanamycin

Capreomycin

Alternative Classification

For more details about Grouping criteria- KD Tripathi- (8th Ed- 816)

Group-I (First line oral drugs)	Isoniazid, Rifampin, Pyrazinamide, Ethambutol
Group-II (Injectable drugs)	Streptomycin, Kanamycin, Amikacin, Capreomycin
Group-III (Fluoroquinolones)	Ofloxacin, Levofloxacin, Moxifloxacin, Ciprofloxacin
Group-IV (2nd line oral drugs)	Ethionamide, Prothionamide, Cycloserine, Terizidone, PAS, Rifabutin, Rifapentine
Group-V (Unclear efficacy)	Dedaquiline, Clarithromycin, Clofazimine, Linezolid, Impipenem, Cilastatin

Isoniazid

Mechanism of Action

Mycolic acids are long fatty acids found in the cell walls of the *Mycobacterium tuberculosis* the causative agent of the disease tuberculosis. They form the major component of the cell wall of mycolata species. Mycolic acids are composed of a longer beta-hydroxyl chain with a shorter alpha-alkyl side chain Each molecule contains between 60 and 90 carbon atoms. *M. tuberculosis* produces three main types of mycolic acids: alpha-, methoxy-, and keto-. Alpha-mycolic acids make up at least 70% of the mycolic acids of the organism and contain several cyclopropane rings. Mycolic acids have been involved in maintaining a rigid cell shape but also they contribute to the resistance to chemical injury and to the protection of cells against hydrophobic antibiotics

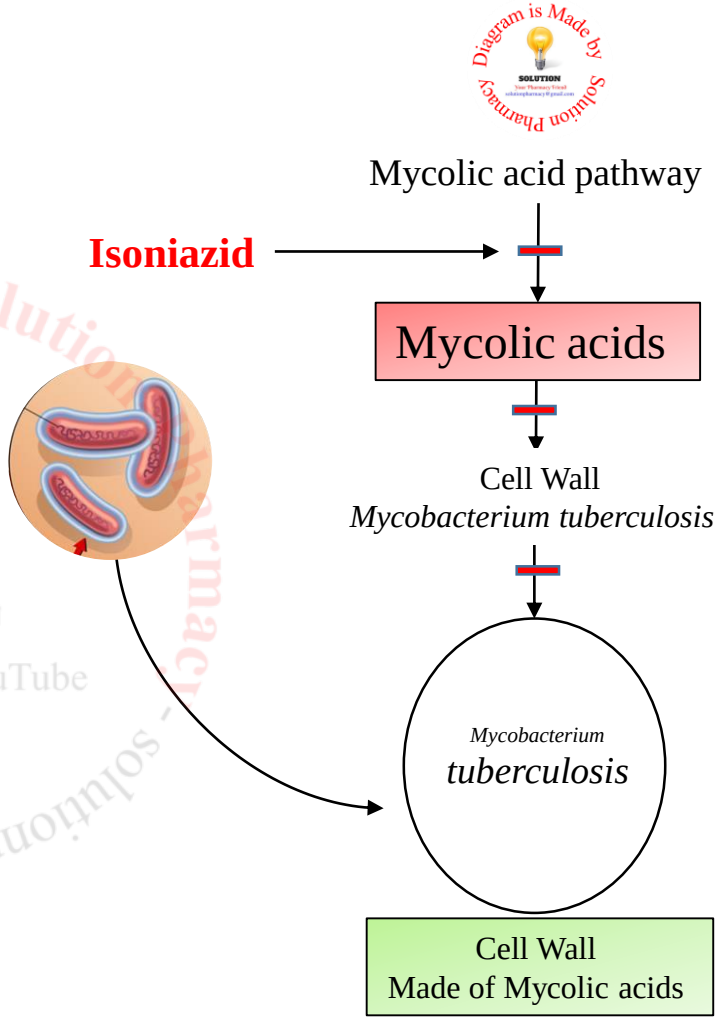


Image- Possible mechanism of action for Isoniazid
Diagram made by- Solution-Pharmacy

Reference- http://www.cyberlipid.org/fa/acid0006.htm

Rifampin (Rifampicin)

Mechanism of Action

A semisynthetic antibiotic produced from *Streptomyces Mediterranean*. It has a broad antibacterial spectrum, including activity against several forms of Mycobacterium. **In susceptible organisms it inhibits DNA-dependent RNA polymerase activity by forming a stable complex with the enzyme**. It thus suppresses the initiation of RNA synthesis. Rifampin is bactericidal, and acts on both intracellular and extracellular organisms. Rifampicin (Rif) is one of the most potent and broad spectrum antibiotics against bacterial pathogens and is a key component of anti-tuberculosis therapy.

Rifampin is an antibiotic that inhibits DNA-dependent RNA polymerase activity in susceptible cells. Specifically, it interacts with bacterial RNA polymerase **but does not inhibit the mammalian enzyme**. It is bactericidal and has a very broad spectrum of activity against most gram-positive and gram-negative and specifically ***Mycobacterium tuberculosis***. Because of rapid emergence of resistant bacteria, use is restricted to treatment of mycobacterial infections and a few other indications. Rifampin is well absorbed when taken orally and is distributed widely in body tissues and fluids, including the CSF. It is metabolized in the liver and eliminated in bile and, to a much lesser extent, in urine, but dose adjustments are unnecessary with renal insufficiency.

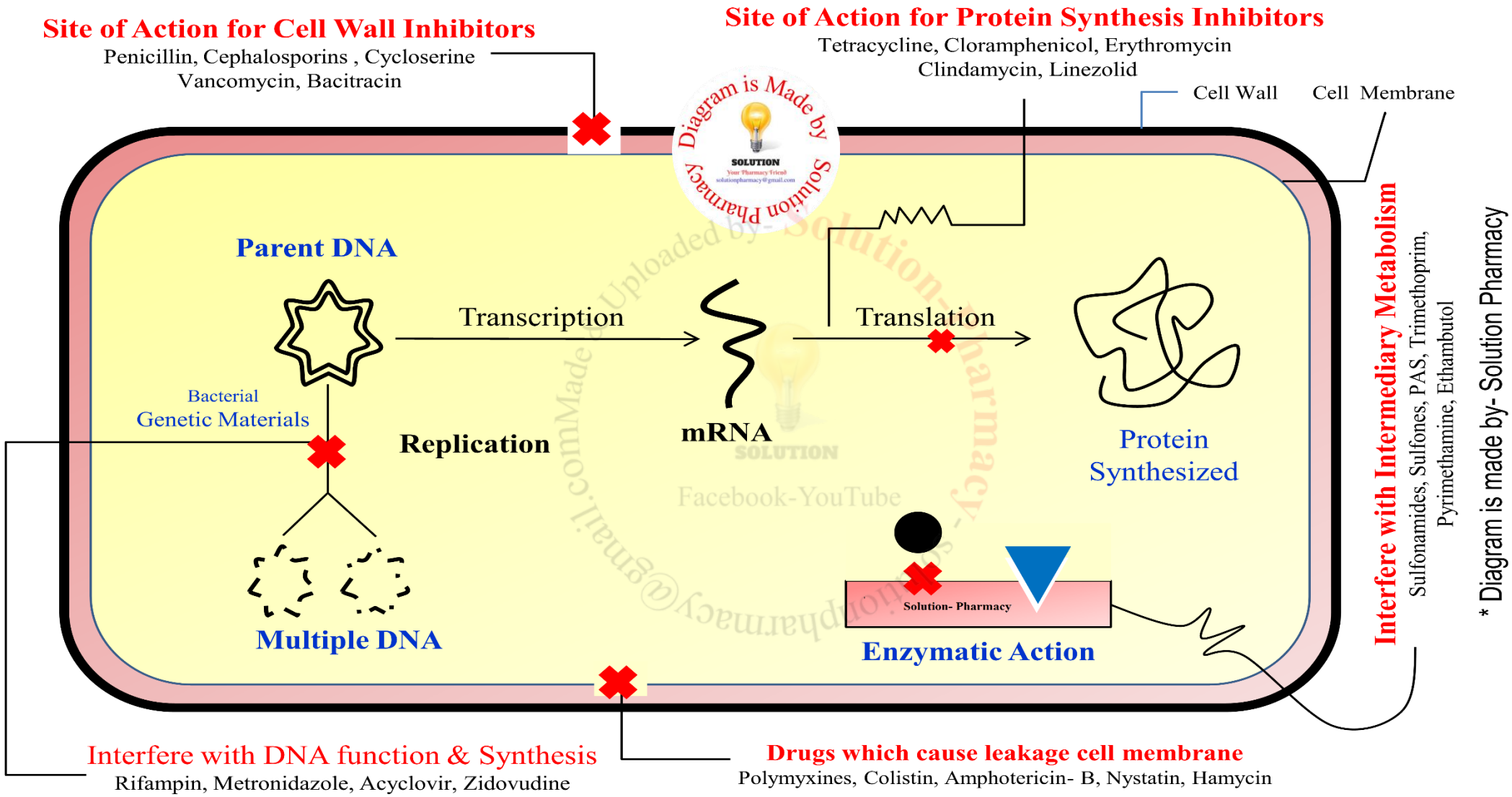


Diagram- General Mechanism of Action for Alternative Drugs

Anti Microbial Drugs
Classification According to Mechanism of Action

Classification Reference- KD Tripathi (Pharmacology)

Inhibit Cell wall synthesis
- **Penicillin**
- **Cephalosporins**
- Cycloserine
- Bacitracin
- Vancomycin

Cause Leakage From cell membrane
- Polymyxines
- Colistin
- Nystatin
- Bacitracin polymers
- **Amphotericin- B**
- Hamycin

Inhibit Protein Synthesis
- **Tetracycline**
- Cloramphenicol
- Erythromycin
- Clindamycin
- Linezolid

Cause misreading or RNA and affect permeability
- Aminoglycosides
- Streptomycin
- Gentamycin

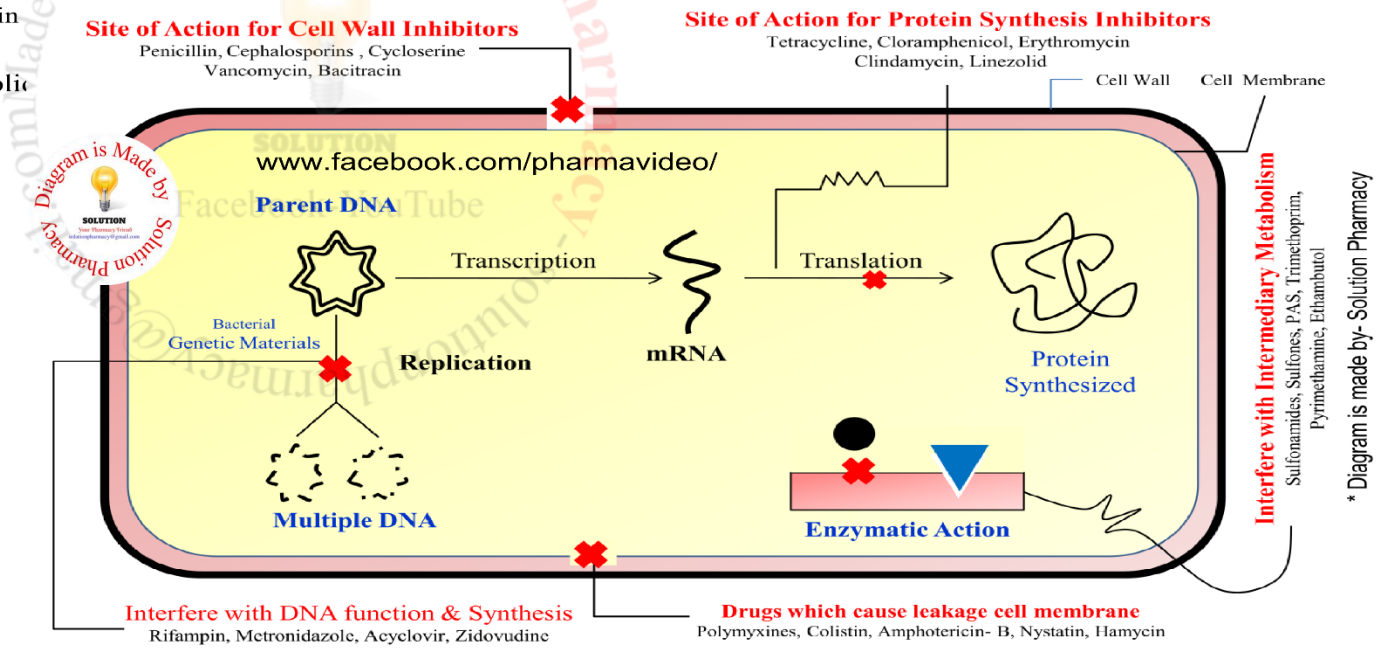
Inhibit DNA gyrase
- Fluoroquinolones
- Ciprofloxacin etc

Interfere with DNA function
- Rifampin
- Metronidazole

Interfere with DNA synthesis
- Acyclovir
- Zidovudine

Sulfonamides, PAS, Sulfones, Trimethoprim, Ethambutol,

Interfere with Intermediary Metabolism



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Pyrazinamide

Mechanism of Action

Pyrazinamide kills or stops the growth of certain bacteria that cause tuberculosis (TB). It is used with other drugs to treat tuberculosis. It is a highly specific agent and is active only against *Mycobacterium tuberculosis*. The drug is active only at a slightly acid pH. Pyrazinamide gets activated to Pyrazinoic acid in the bacilli where it interferes with fatty acid synthase FAS I. This interferes with the bacteriums ability to synthesize new fatty acids, required for growth and replication. Pyrazinamide diffuses into M. tuberculosis, where the enzyme pyrazinamidase converts pyrazinamide to the active form pyrazinoic acid. Under acidic conditions, the pyrazinoic acid that slowly leaks out converts to the protonated conjugate acid, which is thought to diffuse easily back into the bacilli and accumulate.

Ethambutol

Mechanism of Action

An antitubercular agent that inhibits the transfer of mycolic acids into the cell wall of the tubercle bacillus. The action is usually bactericidal, and the drug can penetrate human cell membranes to exert its lethal effect. Ethambutol is an oral chemotherapeutic agent which is specifically effective against actively growing microorganisms of the genus Mycobacterium, including *M. tuberculosis*. **Ethambutol inhibits RNA synthesis and decreases tubercle bacilli replication.** Nearly all strains of *M. tuberculosis* and *M. kansasii* as well as a number of strains of MAC are sensitive to ethambutol. Ethambutol inhibits arabinose transferases which is involved in cell wall biosynthesis. By inhibiting this enzyme, the bacterial cell wall complex production is inhibited. This leads to an increase in cell wall permeability

Reference Taken from- https://www.drugbank.ca/

Streptomycin

Mechanism of Action

Streptomycin is an aminoglycoside antibiotic produced by the soil actinomycete Streptomyces griseous. It acts by binding to the 30S ribosomal subunit of susceptible organisms and disrupting the initiation and elongation steps in protein synthesis. Aminoglycosides like Streptomycin "irreversibly" bind to specific 30S-subunit proteins and 16S rRNA. Specifically Streptomycin binds to four nucleotides of 16S rRNA and a single amino acid of protein S12. This interferes with decoding site in the vicinity of nucleotide 1400 in 16S rRNA of 30S subunit. This region interacts with the wobble base in the anticodon of tRNA. This leads to interference with the initiation complex, misreading of mRNA so incorrect amino acids are inserted into the polypeptide leading to nonfunctional or toxic peptides and the breakup of polysomes into nonfunctional monosomes.

Fluoroquinolones

Mechanism of Action

Quinolones and fluoroquinolones inhibit bacterial replication by **blocking their DNA replication pathway**. DNA is the core genetic material of the cells, and is responsible for proper functioning of the cell. During protein synthesis and DNA replication, the double-stranded DNA needs to unwind into a single stranded structure, which allows for complementary base pairing to occur and synthesis of mRNA to proceed. This unwinding of DNA in the bacteria is done by enzymes in the bacteria called DNA gyrase or DNA topoisomerase. DNA gyrase is a topoisomerase II type enzyme that unwinds the DNA by introducing negative supercoils and can also help relax positive supercoils. Quinolones and fluoroquinolones inhibit this enzyme by binding to the A-subunit of the enzyme due to which the bacteria is unable to replicate.

Treatment of Tuberculosis

Reference- KD Tripathi- 8th Ed. 826

Mycobacterium tuberculosis is an aerobic organism. In unfavourable condition its constant or it may be in dormant condition for long time till it gets favourable condition. It could be present in patient in various forms-

1. Rapidly growing with high bacillary load- As in the wall of capillary lesion where oxygen tension is high and pH is neutral.
2. Slow growing- Located intracellularly and at the inflamed site where pH is low.
3. Sputers- Found mostly within caseous materials where oxygen tension is low but pH is neutral.
4. Dormant- Some bacilli remain totally inactive for prolonged periods of time, no antitubercular drug is effective in this case.

Note- Goal of treatments- Kill dividing bacilli, Kill persisting bacilli, Prevent emergence of resistance

Standard RNTCP regimen for MDR-TB	
Invasive phase (6-9 months)	Continuation phase (18 months)
Kanamycin	Levofloxacin
Levofloxacin	Ethionamide
Ethionamide	Cycloserine
Cycloserine	Ethambutol
Pyrazinamide	
Ethambutol	
+ Pyridoxine 100 mg/day	

As per revised National Tuberculosis Control Programme Guidelines- 2016

Multidrug resistance (MDR) in treatment of TB

Adopted as such from WHO website

he bacteria that cause tuberculosis (TB) can develop resistance to the antimicrobial drugs used to cure the disease. Multidrug-resistant TB (MDR-TB) is TB that does not respond to at least isoniazid and rifampicin, the 2 most powerful anti-TB drugs.

The 2 reasons why multidrug resistance continues to emerge and spread are mismanagement of TB treatment and person-to-person transmission. Most people with TB are cured by a strictly followed, 6-month drug regimen that is provided to patients with support and supervision. Inappropriate or incorrect use of antimicrobial drugs, or use of ineffective formulations of drugs (such as use of single drugs, poor quality medicines or bad storage conditions), and premature treatment interruption can cause drug resistance, which can then be transmitted, especially in crowded settings such as prisons and hospitals. Drug resistance can be detected using special laboratory tests which test the bacteria for sensitivity to the drugs or detect resistance patterns. These tests can be molecular in type (such as Xpert MTB/RIF) or else culture-based. Molecular techniques can provide results within hours and have been successfully implemented even in low resource settings.

Solutions to control drug-resistant TB are to:

1. cure the TB patient the first time around
2. provide access to diagnosis
3. ensure adequate infection control in facilities where patients are treated
4. ensure the appropriate use of recommended second-line drugs.

Treatment of breastfeeding women

Reference- K.D. Tripathi. 8th Edition.

First line antitubercular drugs are compatible with breastfeeding. Full course should be given to the mother, and breastfeeding should be continued. The infant should receive isoniazid preventive treatment after ruling out active TB followed by BCG vaccination. Breast fed infants whose mother is taking isoniazid, and those on isoniazid preventive therapy should be supplemented with pyridoxine 5mg/day.

Tuberculosis in AIDS patients- The association of HIV and TB infection is a serious problem. TB and HIV co-infection is when people have both HIV infection, and also either latent or active TB disease. When someone has both HIV and TB each disease speeds up the progress of the other. In addition to HIV infection speeding up the progression from latent to active TB, TB bacteria also accelerate the progress of HIV infectionThe risk of developing TB in HIV positive subject increase by about 8 times. HIV positive cases have a higher incidence of extrapulmonary , more serious, more lethal and more infectious TB. HIV infection is strongest risk for unmasking latent Tb. Apart from this the adverse drug reaction to anti TB drugs are more common in HIV patients. When people have a damaged immune system, such as people with HIV who are not receiving antiretroviral (ARVs), the natural history of TB is altered. Instead of there being a long latency phase between infection and development of disease, people with HIV can become ill with active TB disease within weeks to months, rather than the normal years to decades

Flow chart
Communication to Treatment

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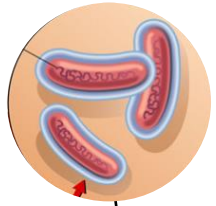
Invasive phase (6-9 months)	Continuation phase (18 months)
Kanamycin	Levofloxacin
Levofloxacin	Ethionamide
Ethionamide	Cycloserine
Cycloserine	Ethambutol
Pyrazinamide	
Ethambutol	
+ Pyridoxine 100 mg/day	

Mycolic acid pathway

Isoniazid → Mycolic acids → Cell Wall *Mycobacterium tuberculosis*



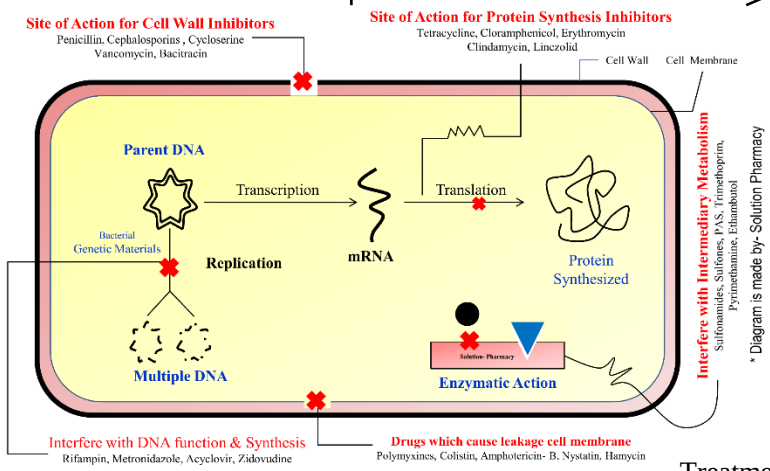
Mycobacterium tuberculosis

Tuberculosis Patients → Normal Individuals → Poor Immunity
AIDS or Immune disorders

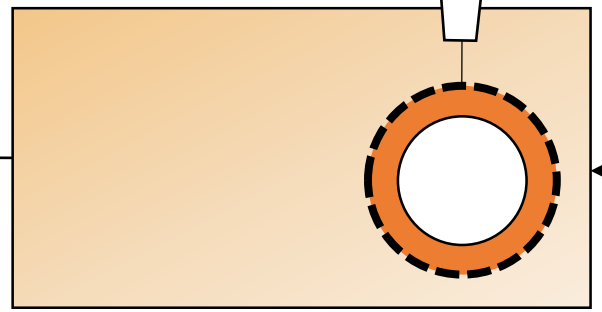
Latent Condition | Active Condition

Sign & Symptoms
Coughing with blood*, Fever, Night Sweating

Diagnosis



Treatment Approaches



Skin Test

Method	Description
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Sputum	A lab examine a sample of the mucus.
Lung biopsy	A small sample of lung tissue is taken to analyze.

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