LUMEN ET VIRTUS
ISSN: 2177-2789

# THE IMMUNE SYSTEM OF THE RESPIRATORY TRACT AND ITS RELATIONSHIP WITH PULMONARY TUBERCULOSIS

https://doi.org/10.56238/levv15n43-069

**Date of submission:** 19/11/2024 **Date of publication:** 19/12/2024

**Renata Oliveira Marques Bomfim, Kim Fonseca Gomes de Sá, Aline Cristina Rocha and Paulo Sérgio Soares Júnior**

## ABSTRACT

Tuberculosis is one of the oldest diseases of humanity, caused by bacteria belonging to the Mycobacterium tuberculosis complex. According to the World Health Organization, around 100 million people are infected each year with M. tuberculosis and, in underdeveloped countries, between 30% and 60% of them, adults are infected. A bibliographic review of specific literature was carried out to identify scientific articles in the MEDLINE, PubMed, and Scielo databases, published between 2018 and 2022, using the terms "Mycobacterium tuberculosis (M. tuberculosis), anatopathology, histopathology, and pathophysiological processes". The tuberculosis bacillus is transmitted by inhalation of infectious droplets dispersed in the air by an infected patient by coughing, sneezing, and talking. The importance of histological, anatomical, and immunological knowledge is crucial to guide the health professional towards the best care.

**Keywords:** Mycobacterium tuberculosis. Anatopathology. Histopathology and pathophysiological processes.

## INTRODUCTION

Tuberculosis is a disease that has been present since the beginning of human life. Mycobacterium is thought to have originated about 150 million years ago and likely killed more people than any other pathogenic microbe when exposed to humans. Records of disease in Egyptian mummies, passages in the Hebrew books of the Bible, ancient Chinese writings, and the studies of Hippocrates in ancient Greece describe disease killing the pathogen in great nations.1

Tuberculosis, in its early stages, must have mainly infected animals by a species prior to Mycobacterium bovis. The disease can be transmitted when people eat contaminated meat or milk. At the very least, it can be shown that the new mutant strains, contained in tubes with better airborne transport and less harmful, which facilitate the spread of the pathogen, are large parasites of the human race2.

The disease spread throughout America through contact with European sailors during the Great Voyage. The oldest bacterial evidence of the presence of this pathogen in America dates back to 1100 B.C. In an Indian Inca woman, the environmental conditions in which she was buried preserved clinical symptoms and bacilli in her mummified body. Although M. tuberculosis and M. bovis were already present among pre-Columbian tribes, the long stay with European explorers contributed to the spread of the disease. But later, in the twentieth century, when urbanization affected the Americas, there was an explosion of tuberculosis throughout the country, including Brazil3.

Transmission of tuberculosis occurs mainly through the air and inhalation of respiratory droplets containing the infectious agent. The important thing is that this disease can manifest itself in different ways, from asymptomatic latent diseases to severe cases of active tuberculosis, which demonstrates the diversity and complexity of this pathology. Tuberculosis is a disease that requires a multifaceted approach and a great understanding of the interaction between Mycobacterium tuberculosis and the host immune system4.

Understanding the respiratory system is important in the context of pulmonary tuberculosis. This system consists of several layers of defense, each of which plays an important role in protecting against infectious diseases. In addition to the physical and mechanical barriers that prevent pathogenic microorganisms from entering the lungs, the immune system contains the defense mechanisms necessary to fight and prevent diseases, including pulmonary tuberculosis5.

Common cold pathogens are organisms that cause respiratory illnesses, including viruses and bacteria. They can produce a wide range of symptoms such as chronic cough,

high fever, respiratory problems, sore throat and other respiratory diseases. In addition, these pathogens can cause more serious problems such as pneumonia and bronchitis6.

To prevent these diseases, it is essential to understand the nature of pathogens and the immune system's reaction to influenza. When detecting the signs of an attack by a pathogen, the immune system activates an inflammatory response, mobilizing protective cells and releasing chemicals to fight off the invading agent. However, on some occasions, the immune response can be overwhelmed, leading to tissue damage and the appearance of more severe symptoms7.

Neonatal tuberculosis does not have specific characteristics, but is usually accompanied by multiple organ involvement. The newborn may demonstrate a weakened state of health, either in an acute or chronic phase, in addition to presenting fever, lethargy, breathing difficulties or pneumonia that does not respond to treatment, as well as hepatomegaly and splenomegaly, or even an unsatisfactory weight development8.

All newborns with suspected congenital tuberculosis, as well as infants born to mothers with active tuberculosis, need to undergo tests that include chest X-rays and cultures for acid-fast bacilli, using material from tracheal aspirate, gastric lavage, and urine. Lumbar puncture should be performed to analyze cell, glucose, and protein counts, and to allow cerebrospinal fluid culture. It is also critical to examine and obtain culture of the placenta. Although skin tests have low sensitivity, especially early in infection, they should be performed. Tuberculosis-specific interferon-gamma release assays, which are useful in adults, are not approved for use in neonates due to their low sensitivity. To confirm the diagnosis, a biopsy of the liver, lymph nodes, lungs, or pleura may be necessary. In addition, neonates should be tested for HIV9,10.

In a detailed analysis of lung tissue, the importance of a deeper understanding of the host immune response to pulmonary tuberculosis becomes apparent. The tissues that make up the airways include the upper airways, such as the nose, pharynx, and larynx, as well as the lower airways, such as the trachea, bronchi, and usually the lungs11. Each of these tissues exhibits unique histological features, such as the presence of cilia and mucus-secreting cells, which are responsible for filtering and humidifying trapped air. It is worth noting that the presence of mucus-associated lymphoid tissue (MALT) in the lower respiratory tract plays an important role in the local immune response and is important in the prevention of respiratory infections, including Mycobacterium tuberculosis, the etiologic agent of tuberculosis11,12.

## METHODOLOGY

A bibliographic review of the specific literature was carried out to identify scientific articles in the MEDLINE, PubMed, and Scielo databases, published between 2018 and 2022, using the terms "Mycobacterium tuberculosis (M. tuberculosis), anatopathology, histopathology and pathophysiological processes".

Only articles written in Portuguese or English were included, as well as review articles on epidemiological, diagnostic, and therapeutic aspects. Studies in experimental animals were excluded.

## DEVELOPMENT

Tuberculosis is an infectious disease caused by Mycobacterium tuberculosis that mainly affects the lungs, but can manifest clinically in many ways and in different organs. The agent has a transitional form between eubacteria and actinomycetes, including non-motil, non-encapsulated, non-sporulated, and non-colonial bacilli, differing between 0.2 and 0.6 x 1 to 10 microns. They form clusters of long, curved branches called filaments, which are important for the visualization and differentiation of bacilli in microscopic analyses13.

Its generation time varies from three hours for fast-growing species to 18 hours for slow-growing species, a characteristic due to the high lipid content present in its capsules14. The pathogen grows slowly, with its metabolism focused especially on building the capsule that protects it from chemical agents, and can survive for weeks or months on inanimate objects. However, it is easily destroyed by physical agents such as heat, ultraviolet rays from sunlight and ionizing radiation. Its resistance to desiccation, to the action of alcohol, acids and antimicrobials, is established due to the constitution of its wall, organized by mycolic acids and lipids, forming a resistant hydrophobic barrier. On the other hand, the presence of a high lipid content in the membrane provides important biological effects, such as the pathogen's property of inducing the formation of granulomas in infected tissues14,15.

With aerobic metabolism, the half-life is between 18 and 48 hours, as a facultative intracellular parasite, and favors the destruction of macrophages. If left alone and undifferentiated, the disease becomes difficult to eradicate and treatment leads to the recurrence of chronic diseases16.

M. tuberculosis, known as the M. tuberculosis complex model, is part of the family M. bovis, M. microti, M. africanum and M. canetti, which are similar in appearance and sex, and share 99% of their genes, as indicated by the presence of the IS6110 fragment in the genome17.

## EPIDEMIOLOGY

According to the World Health Organization (WHO), one-third of the world's population is infected with M tuberculosis. In this context, between 8 and 10 million people will contract this disease in their lifetime, and approximately half of them are contagious18. The number of new cases is estimated at 8.7 million, of which 80% are in 22 underdeveloped countries, including Brazil. In addition to this scenario, there are three million known and undiagnosed diseases each year, which the World Health Organization proposed in 1993 to establish the global situation of tuberculosis as a global emergency, called a "public health emergency"[18,19].

Currently, the leading causes of death in the world among men aged 15 to 44 are road traffic accidents, followed by tuberculosis, violence and suicide. Among women, tuberculosis is the first and causes more deaths than suicide, war and blood loss18,19,20.

According to the WHO, tuberculosis and acquired immunodeficiency syndrome is a chronic disease (AIDS) and is currently unprecedented disasters in history. The state of immunosuppression caused by AIDS creates favorable conditions for transmission and death. Therefore, the progression from the infectious form to the clinical manifestations of tuberculosis differs between uninfected and HIV-infected individuals21,22.

In the United States, there are between 40,000 and 50,000 deaths each year, with Brazil being the country with the highest number of deaths. However, statistics analyzed by the Pan American Health Organization show that Peru and Ecuador are the countries with the highest mortality rates on the planet, while the lowest mortality rates are found in the United States, Canada, and Cuba23.

## HISTORY OF DISEASE EVOLUTION AND PATHOPHYSIOLOGY

The source of the disease comes from people with pulmonary tuberculosis. The ability of the bacillus to transmit to another person is a result of the nature of the bacillus in question and the intensity of the contact in terms of proximity, time, duration of exposure and the favourable environmental context that seems to be required for a successful infection, for example, it is said to take between 100 and 200 hours, depending on the intensity and proximity of the contact24.

It is estimated that, in a community, a source of disease can infect up to 15 people on average in a year. Talking, sneezing, and coughing send particles called Flügge droplets into the air. Heavier substances tend to become volatile in the environment, while lighter substances become radioactive in the air25. Only water-fine droplets, up to 5 microns in diameter, containing 1-2 suspended bacilli, reach the bronchioles and alveoli of the lungs,

thus initiating the infection process. The infectious particles are called primary Weels. Most environmental particles are retained by mucus from the upper respiratory tract and removed from the bronchi through the mucus system. Bacilli eliminated in this way are eaten, not digested in gastric juice, and excreted in the feces. The smallest particles reach the alveoli, where the microbe grows. Environmental pathogens are often dispersed in airborne particles and do not play an important role in disease transmission25,26.

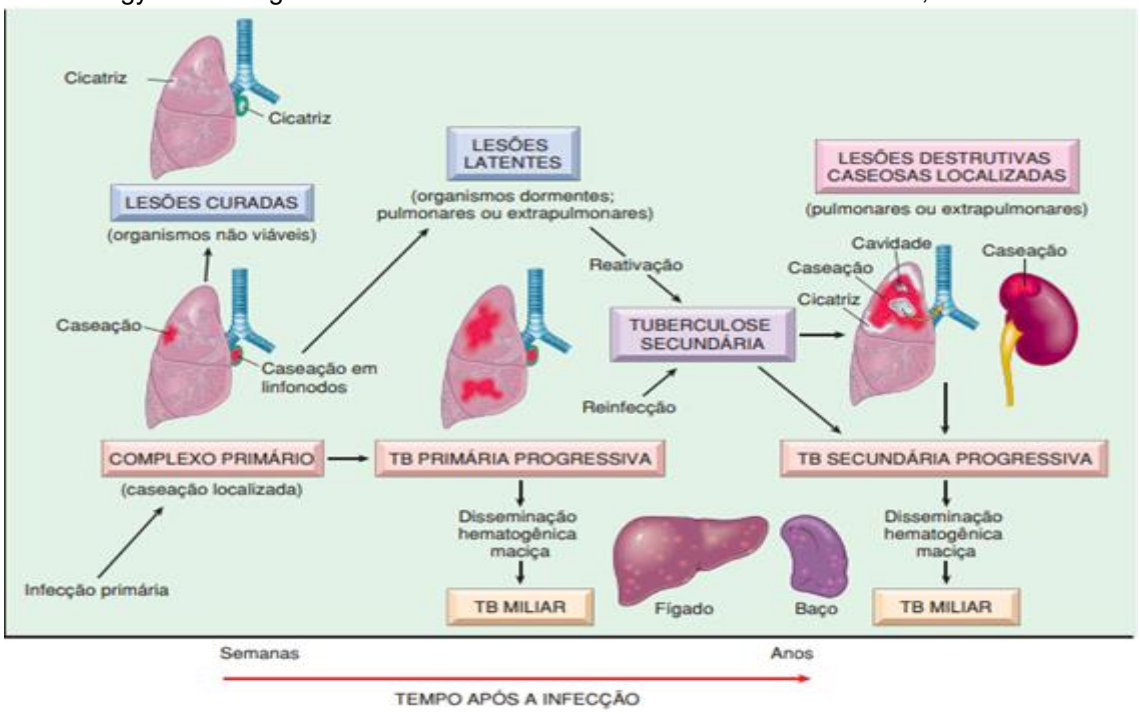
The characteristics of a cough and a person coughing interfere with the transmission of the bacillus between the source of infection and the contact. Patients with better general condition and diet are more likely to cough up and disperse bacilli-producing particles with greater transmission27. The discharge is also influenced by the physicochemical properties of the sputum, such as thickness and viscosity. In this context, it can be observed that the duration of treatment can lead to complications. If there is no previous treatment of the patient or any other risk of resistance, it is considered that after 15 days of treatment, if the clinical condition improves, the patient is considered non-infectious. However, due to the nature of the bacilli resistant to the first drugs, it is recommended to show the patient's disease under treatment by means of a negative smear and Paucybacillus control27,28.

According to the history of tuberculosis, most people know how to generate immune responses against M. tuberculosis, but these responses are not enough to kill the invading pathogen28. In this context, only 10 to 30 percent of people exposed to the bacillus become infected, and only 5 to 10 percent of them develop active tuberculosis. However, many people have a form of immunodeficiency against bacillus-specific antigens, which favors the rapid multiplication of the agent and the development of the disease. Using the model proposed by Rich, the development of the disease is proportional to the number of bacilli, the severity of the strain involved, and the development of hypersensitivity in the host29.

After inhalation of the bacillus, a series of non-specific mechanical barriers will act against infection. Nasal hairs, angulation of the airways, air turbulence, tracheobronchial secretion, and mainly mucociliary clearance, are the main elements that prevent the bacillus from entering the pulmonary alveoli of the exposed contact30. Mycobacterium, by overcoming the physical barriers of the upper respiratory tract and entering the pulmonary alveolar environment, faces macrophages, cells that are part of local innate immunity. The macrophages resident in the tissue, after phagocytosing the bacillus, producing the phagosome, fuse the vesicle formed with the lysosomes, and at this stage the processing of the antigens can occur, and the subsequent presentation of the latter to the helper T lymphocytes, through the major histocompatibility complex of class II. During the phagocytosis process, cytokines and chemokines are produced, which signal the presence

of the pathogen to the immune system, causing the recruitment and migration of neutrophils, monocytes and lymphocytes to the site of infection. However, due to the specific resistance mechanisms of tuberculosis bacilli, the pathogen is not successfully exterminated. Through the inhibition of lysosome-to-phagosome fusion caused by macrophagocytic activity that allows mycobacteria to survive during this period of host immune activation, the phagocytic cell dies and continues to propagate extracellularly30,31.

Natural History and Spectrum of Tuberculosis – Taken from KUMAR, V.; ABBAS, A.; FAUSTO, N. Robbins and Cotran – Pathology – Pathological Bases of Diseases. 8. ed. Rio de Janeiro: Elsevier, 2010.




Pathological manifestations: Granuloma caseosum and cavitation are the result of sensitization and immune response. Granuloma is primarily a necrosis factor surrounded by epithelioid cells and large multinucleated Langhans-type cells and a ring of lymphocytes. Macrophages are the primary cells infected by the agent. The bacillus enters macrophages by endocytosis through receptors such as mannose. Inside the cell, they multiply into phagosomes and prevent the formation of phagolysosomes by inhibiting calcium signals. In the first stage, the agent increases in alveolar macrophages and in the respiratory tract. 3 weeks after infection, there is a T-Help 1 response (IL-12-dependent for differentiation), due to the introduction of mycobacterial antigens to drain lymph nodes and activate macrophages for their bactericidal activity. Importantly, mature Th1 cells produce IFN-γ, which stimulates the formation of phagolysosomes in macrophages and provides an acidic environment for bacteria. The Th1 response also induces granuloma and caseous necrosis32.

If the above protective measures cannot eliminate the infectious bacilli, an inflammatory process and the development of non-specific pneumonia will occur. In this new inflammatory

environment, the mycobacterium begins to multiply and take advantage of the lack of a specific immune response, which occurs between fifteen and twenty days after death. Thus, after fifteen days, up to 105 bacilli can be found at the primary focus of the infection, and then the infection spreads to other organs lymphatic and/or hematogenously33.

The pulmonary focus formed in the infectious process, called Ghon's complex, measures 1 to 2 mm, has a soft consistency, and develops over a period of 3 to 4 weeks, during which the development of cellular immunity occurs, with the consequent change in the tuberculin test34. Simultaneously with the phagocytic phenomenon, dendritic cells with M. tuberculosis inside migrate to the regional lymph nodes, activating the local CD4 and CD8 lymphocytes, which migrate to the site of infection, guided by the chemokines produced by the infected cells. The accumulation of activated lymphocytes, macrophages, dendritic cells, fibroblasts and endothelial cells, among others, leads to the formation of the granuloma that surrounds the bacillus in a hypoxic and unhealthy environment, limiting its dissemination, and forms a microcontext, where the members of this immune response interact with the aim of eliminating the invading pathogen, providing containment of the infectious focus34, 35.

In protecting against tuberculosis infection, the study of different lymphocyte populations showed the important role of TCD8+ lymphocytes in the primary fight against the bacillus and the prevention of primary infection. Therefore, CD8+ T cells stimulated by endogenous mycobacterial antigens released into the circulation during infection have the ability to destroy mycobacteria-infected cells and can be eliminated, becoming one of the primary care methods. On the other hand, there seems to be very little threat to combat this disease, since antibodies that are not secreted by the animals' plasma can enter infected macrophages36.

In this period of the first disease, in 95% of cases, the infectious process disappears with the formation of calcification or fibrosis of the Ghon complex, which can be observed on X-rays. On the other hand, if the infectious lens does not occur, in only 5% of cases, it is due to the lack of immunity of the host cell, or to the conditions of the disease, resistance, or strain of the host cell. Infectious bacillus blessing disease, liquefaction of caseum and cancer occurs. This pathophysiology results from the development of tuberculosis from the primary lung complex that develops within the first five years after initial infection and is termed primary tuberculosis. These can also occur in different diseases and show lymph node, ganglion-pneumonic, bronchioneumonic, cavitary, atelectasis or miliary symptoms37.

Symptoms of tuberculosis may be seen later, in the first few years after the first infection. In this case, the disease occurs at the end of the period of the first infection, and the person has acquired immunological memory for antigens, and the clinical picture shows that it is longer and the damage is less and the formation of caries and the formation of caries38. A

fibrotic process in itself is accompanied by many hypersensitivity reactions. Infection may arise from a new source of external infection by more virulent or resistant strains, or it may arise from the reactivation of a fixed focus of dormant bacilli. Stimulation of the lens occurs with the formation of granulomas, mostly in the upper part of the lung, which progress to necrosis and death. Leakage of fluid into the bronchus can cause bronchogenic proliferation and create a collecting duct at the drainage site. This new release can lead to new treatments for the disease or problems related to a new invasion, through the destruction of the lung parenchyma itself or the invasion of other nearby structures, such as the development of infectious bronchial cancers. A vein known as Rasmussen's aneurysm38,39.

**CLINICAL AND DIAGNOSTIC**

Tuberculosis usually presents as a mild or chronic disease, characterized by indolent symptoms that increase in intensity, with periods of remission and recovery. Therefore, it takes a long time to seek medical help, and 66% of patients take three months to contact the healthcare system. Among the various symptoms that appear during the disease, the patient is more likely to report and caregivers are more likely to monitor some signs and symptoms. Therefore, symptoms such as cough, hemoptysis, shortness of breath, chest pain, fatigue, fever, sweating, weight loss, are an important and classic part of the wide range of possible symptoms. However, it is important to remember that there are many non-specific symptoms of the disease, depending on the organ affected by the bacillus40.

Cough is present in almost all patients, as it stimulates alveolar inflammation and granulomatous involvement of the airways. Initially, a dry cough develops into a productive cough with mucous or purulent sputum, usually in small amounts and sometimes accompanied by hemoptysis. The diagnosis of tuberculosis should be suspected in patients who have a persistent cough for more than three weeks.41

Hemoptysis is not a mandatory symptom, but there may be an abnormality of blood mixed with sputum (hemoptosis) or severe hemoptysis, which is rare, associated with a Rasmussen aneurysm. On the other hand, hemoptysis can occur even in small lesions, and can end up as a sign of disease when parenchymal cavities form42.

Shortness of breath is an alarming symptom due to some aspects of the pathophysiology of mycobacterial action on the intestinal parenchyma. Damage to lung tissue due to the inflammatory process, including the alveolar environment and surrounding vessels, does not cause a significant change in the area's air/perfusion ratio. The configuration of this characteristic is different in many other stages of disease development. Atelectasis, large cavities, miliary pattern, lesions with excessive inflammatory involvement, development of

pneumothorax, pleural effusion and chronic lesions of the disease, due to the nature of the fibrotic ligament was created, and shortness of breath appears as an important manifestation of this43.

Chest pain associated with pleural effusion. This occurs early in human disease due to the proximity of the alveoli, the primary site of infection, to the pleural surface44.

Hoarseness, as well as forms of lung disease associated with laryngeal involvement, may not be detected by the patient, are rarely reported and are seen if there are no other signs and symptoms45.

## DISCUSSION

Based on the analysis of the pathophysiology of mycobacterial growth, we found that the growth of intra- and extraphagocytic bacilli is greater during peak periods of adrenal cortisol production, between 11:00 and 12:00 hours. Simultaneously with the slow spread of the pathogen, the death and destruction of infected macrophages also occurs and, in the following hours, the inflammatory content is released into the lung parenchyma, so a local inflammatory process occurs. The host's response appears as a tab. Therefore, fever is characteristic in the afternoon, between 5:00 p.m. and 9:00 p.m., and a lot of sweating at night, after the fever rises, instead of the body increasing body temperature. However, fever can be detected at a not too high temperature, which is explained by the slowness and multiplication of the bacillus and is accompanied by a local inflammatory process of low intensity45,46.

The chronic inflammatory context established by the insidious Mycobacterium infection can cause a wasting syndrome, proportional to the duration and extent of the disease, which manifests as weight loss, anorexia, weakness, arthralgias, and myalgia. In this scenario, patients who already suffer from pathologies that exhaust the immune system, such as AIDS, alcoholism, malnutrition and drug addiction, end up presenting an intense nutritional deterioration, with the consequent exacerbation of the infectious picture and worsening of the prognosis47. The findings of the physical examination are proportional to the extent of the infectious process, the duration of the disease, and the site affected by the bacillus. Specifically, in the context of lung disease, rales may be found in the region of granulomatous lesions, usually apical and posterior. Wheezing and rhonchi may also occur in case of bronchial involvement. In caseous pneumonia, there may be a decrease in gallbladder murmur and bronchophony when there is pleural effusion, in addition to the classic amphoteric murmur in the tuberculous cavities. Focusing on the bacillus or its components,

usually during the first infection, is observed in erythema nodosum, squamous keratoconjunctivitis, polyserositis, and erythema induratum.47,48

## CONCLUSION

In view of the presence of a body of epidemiological and social evidence pointing to tuberculosis, several other tests are used to confirm the initial diagnostic hypothesis. As it is an infectious disease, diagnostic confirmation is made by identifying the agent at the origin of the lesion. According to this hypothesis, confirmatory tests should be chosen based on the understanding, specificity and relevance of the test in the context in which the patient and healthcare workers find themselves. The tests used in the diagnosis of tuberculosis are: bacteriological, biochemical, cytological, radiological, histopathological, immunological and tests based on molecular biology.

Thus, given the need to disseminate knowledge about the disease and its prevention to the population, in order to guide them on risk factors, tuberculosis contamination, this education and prevention is generated through health prevention actions, and especially vaccination with BCG. It is worth mentioning that health professionals are a group that should be paid attention to, due to the exposure and educational approaches that are effective in the control and spread of the pathology.

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