Literature Review

Clinical, Immunological, and Microbiological Aspects of Nontuberculous Mycobacterium (NTM)

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Abstract

Nontuberculous mycobacteria (NTM) refer to all mycobacterial species except *Mycobacterium tuberculosis (M. tuberculosis) complex and M. leprae complex*. These bacteria are acid-fast. The bacteria are environmental bacteria that act opportunistically in humans. The infection can lead to disease, primarily affecting the lungs in susceptible hosts. Risk factors for NTM infection include defects in the body's defence mechanisms, changes in lung structure, and immune system abnormalities, which can be congenital or acquired. The bacteria possess pathogen-associated molecular patterns (PAMPs) and cell wall components that differ from those of *M. tuberculosis,* one of which is the glycopeptidolipid (GPL) component. Different species have distinct cell wall components, enabling them to modulate the immune system in various ways by interacting with multiple pathogen recognition receptors, including toll-like receptors and fibronectin. The cell-mediated immune response plays a role in the response to NTM infection. Alveolar macrophages, as the first line of defence, release interleukin (IL)-12, activating the T-helper-1 (Th1) axis and natural killer (NK) cells, followed by the release of tumour necrosis factor- α (TNF-α), interferon (IFN)-γ, and IL-17. The clinical symptoms of NTM lung disease (NTM-LD) are similar to those of *M. tuberculosis*. Two radiological findings are commonly observed: fibro-cavitary lesions and nodular bronchiectasis. Diagnosis must meet clinical, radiological, and microbiological criteria. The decision to start therapy should consider host factors, clinical conditions, and species type. The treatment approach involves multi-drug therapy and long-term administration, depending on species, disease extent, drug susceptibility testing results, and comorbidities.

Keywords: cell-mediated immunity, diagnosis, NTM-LD, susceptibility host, treatment

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INTRODUCTION

Nontuberculous mycobacteria (NTM) are all species of mycobacteria other than *M. tuberculosis complex* and *M. leprae complex*.[1–3] There are different terms, including *Mycobacterium other than tuberculosis* (MOTT), environmental mycobacteria (found in various parts of the environment), and atypical mycobacteria (in addition to typical bacteria that cause tuberculosis and leprosy). In humans, NTM is an opportunistic bacterium that can cause diseases in various organs, especially the lungs, and can spread disseminately.[3–5]

In sputum culture isolates or bronchial toilet, NTM can be found, which is called NTM infection or simply colonization. It can also manifest into lung disease due to NTM-lung disease (NTM-LD) or NTM pulmonary disease (NTM-PD).[2]

EPIDEMIOLOGY

Incidence and prevalence vary considerably both within a country and between countries. This is influenced by high geographical variation and various environmental factors, including climate, agricultural practices, and socio-economic conditions, which affect transmission. A Study in the United States found that the incidence of NTM ranges from 1.4 to 6.6 per 100,000 individuals. Research in the UK reported an incidence of NTM of 6.1 per 100,000. The prevalence in India ranges from 0.38% to 23.7%. Saptawati et al conducted a study in Indonesia with

9,248 samples of patients suspected of TB. There were 334 (15%) NTM-positive patients. According to various references, the incidence rate of NTM among all NTMs detected from airway isolates was reported to be around 20–66%, with a diagnosis of NTM-LD.[1,6,7]

A study in Indonesia conducted by Saptawati et al too reported that from 2020 to 2021, there were 94 patients with positive NTM isolate, found in group 51% of *M. fortuitum*, 38.3% of *M. abscessus*, 3.1% of *M. intracellular,* 3.1%, 2.1% of *M. neoaurum*, 1.1% of *M. chelonae*, 1.1% of *M. gordonae*, 1.1% of *M. szulgai*, 1.1% of *M. mucogenicum*, and 1.1% of *M. Arupense*.[8] Clinically significant infections are frequently caused by *M. abscessus, M. malmoense, M. xenopi,* and *M. intracellulare,* compared to *M. avium* and *M. kansasii.*[4,5,9,10] Dohal et al reported that, in Slovakia, 358 cases (26.4%) of NTM disease were confirmed among 1,355 NTM-positive cultures from respiratory samples, with the majority of causative bacteria being M. intracellulare and *M. avium*, at 39.9% and 38.5%, respectively.[6]

In recent years, the NTM trend has been on the rise. A systematic review by Dahl et al reported an increasing trend in the prevalence of infection and NTM-LD by 82.1% and 66.7%, respectively. In contrast, the prevalence of annual increase in NTM infections and diseases is 4.0% and 4.1%, respectively. The increase in these trends may be attributed to several factors, including the growing burden of chronic diseases, which is a risk factor for NTM infection, the widespread use and development of immunosuppressant therapies, advancements in diagnostic tools, and heightened clinician vigilance against NTM infection.[1]

MICROBIOLOGICAL ASPECT

General Characteristics

The genus *Mycobacterium* is a member of the *Mycobacteriaceae* family. In this family, there are more than 200 species and 13 subspecies.[1–3,11] Mycobacterial species are divided into three categories: the mycobacteria that cause TB, the mycobacteria that cause leprosy, and NTM.[3,5] Typical species are *M. tuberculosis, M. bovis, M. africanum*, and *M. leprae* (reservoirs are human or animal only and are not water-transmitted). Atypical mycobacterial species are nontuberculous species.[11] Meanwhile, NTM are environmental bacteria that can be found in various places in the environment, including natural water sources, air, dust, drinking water, soil, biofilms, wild animals, plants, food products, and dairy products, as well as in the human respiratory tract.[3,5,10]

The natural environment and sources of NTM include aerosol, water sources, and other sources. Aerosol sources, which consist of showers, hot springs, humidifiers, indoor swimming pools, and hospital heating-cooling units, often harbor *M. avium complex* (MAC)*, M. kansasii, M. gordonae,* and *M. abscessus*. Natural water sources such as streams, rivers, ponds, lakes, and seawater host a variety of NTM species. Bacteria from these environments include MAC*, M. gordonae, M. xenopi, M. marinum, M. fortuitum, M. chelonae,* and *M. kansasii*.[3]

Artificial water sources are widespread, encompassing a variety of systems and facilities, including drinking water pipes, hot and cold-water tanks, indoor and outdoor pools, hot springs, household water pipes, shower heads, faucets, hospital water supplies, ice machines, commercial ice, and bottled drinking water. Common NTM species from these artificial sources include *M. avium complex, M. kansasii, M. gordonae, M. xenopi, M. abscessus, M. fortuitum, M. chelonae, M. scrofulaceum, and M. szulgai*. Lastly, other sources, such as potting soil, natural soil dust, household dust, and peat, are environments where the MAC*, M. fortuitum, M. chelonae*, and *M. kansasii* are frequently found.[3]

Physical Characteristics and Types

Mycobacterium is a gram-positive, acid-fast bacterium that is aerobic to microaerophilic, nonmotile, and does not form spores.[2,3,11] These bacteria have an irregular shape and are straight or slightly curved rods measuring 0.2–0.8 µm in width and 1.0–10.0 µm in length.[2,3,11] They are oligotrophic and feature a thick cell wall composed of lipids with

long-chain fatty acids on their outer membranes (mycolates), along with a peptidoglycan layer. This structure supports the adhesion of NTM to rough surfaces, enhances resistance to disinfectants and antibiotics, helps NTM survive in complex environments (in low oxygen and carbon levels), and withstands other adverse conditions.[2,3,11]

Classification and Pathogenicity

Based on its growth characteristics, NTM is divided into rapidly growing mycobacteria (RGM), which grow within 7 days, and slowly growing mycobacteria (SGM), which grow within ≥7 days.[2,3]

Table 1. Classification of NTM by growth rate[10]

Slowly Growing Mycobacteria (≥7 days)	Rapidly Growing Mycobacteria (<7 days)
Group 1. Photochromogenic	Group 4
M. kansasii (true human pathogen)	*M. abscessus complex* (true human pathogen)
M. simiae (true human pathogen)	*M. chelonae* (true human pathogen)
M. marinum (opportunistic human pathogen)	*M. fortuitum* complex (true human pathogen)
	M. peregrinum (true human pathogen)
Group 2. Skotokromogenic	
M. scrofulaceum (true human pathogen)	*M. smegmatis* (saprophyte)
	M. vaccae (saprophyte)
M. szulgai (true human pathogen)	
M. gordonae (saprophyte)	
Group 3. Nonchromogenic	
M. avium complex (true human pathogen)	
M. xenopi (true human pathogen)	
M. malmoense (true human pathogen)	
M. haemophilum (true human pathogen)	
M. genavense (true human pathogen)	
M. terrae complex (saprofit)	
M. ulcerans (opportunistic human pathogen)	

There is a Runyon classification system that creates NTM categories based on colony description, growth rate in media, and dye production.[10,12] Group one is photochromogenic (colorless when in a dark place and yellow when exposed to light due to the production of carotenoid pigments). Group two is scotochromogen (forms a yellow-orange pigment even in darkness or when exposed to light). Group three is nonchromogenic (produces no pigment, either dark or light). Group four is a group of mycobacteria that are fast-growing and usually nonpigmented.[2,3,10]

In virulence, NTM species are less virulent than *M. tuberculosis*. The pathogenicity of NTM varies from rarely causing disease to being considered pathogenic. There are three types of pathogenicity among NTM species: true human pathogens, opportunistic pathogens, and saprophytes. An example of a pathogen with low pathogenicity is *M. gordonae*, whereas a species with high pathogenicity is *M. kansasii*. When *M. gordonae* is found in clinical cultures, it needs to be adequately evaluated to determine whether it is a pathogen. The pathogenicity of NTMs can also vary between different geographic areas.[3,13]

Transmission

The main principles of transmission of NTM are condensed water, aerosolized (inhaled) germs, and direct contact with germ-containing materials. NTM germs are not transmitted from humans to humans or from animals to humans. Instead, they are exposed to the environment. Germs can be transmitted through water-based vectors. However, in a small number of cases, the *M. abscessus* complex can be transmitted indirectly between humans in individuals with cystic fibrosis.[11]

Similar to *M. tuberculosis*, inhalation of NTM-containing aerosols can occur because the fat content on the NTM cell wall allows germs to be aerosolized. Transmission can also occur during medical procedures, such as injections, surgery, and hemodialysis.[4,5,13] In addition, transmission can also occur through ingestion, such as consuming water containing NTM colonization.[11,13]

IMMUNOLOGICAL ASPECTS

Components that Induce the Immune Response

The most well-known component of mycobacterial immunomodulators is the waxy outer layer capsule. The capsule has a complex structure consisting of a cell wall and a plasma membrane,

which contain lipid, fatty acid, and lipoprotein components. Most of its composition consists of lipids, accounting for approximately 60%.[4,5] One of the different components of *M. tuberculosis* and NTM is the presence of Mycobacterial glycopeptidolipids (GPL), which are only produced by NTM. Glycopeptidolipids are essential components in sliding motility and biofilm formation.[4]

There are two classifications of GPLs: nonspecific GPL (nsGPL), which is apolar, and serovar-specific (ssGPL), which is polar, found in *M. avium*. The concentration and composition of GPL vary between species and can affect the morphology of the colony as well as its pathogenesis. There are two morphotypes of *M. abscessus*, namely the fine morphotype and the coarse morphotype. In the fine morphotype, nsGPL is found in the outer layer of the cell wall, covering the phosphatidyl-myo-inositol mannoside residue.[4]

The presence of nsGPL inhibits *M. abscessus* recognition strains by immune cells expressing Toll-like Receptor (TLR)-2. Meanwhile, these subtle variants can infect susceptible hosts. The coarse variant lacks nsGPL, is suggested to be more virulent, and has a more severe and persistent disease clinically. Essentially, human monocytes are capable of eradicating fine-morphotype *M. abscessus*, whereas coarse variants survive and develop within intracellular phagosomes.[4]

On ssGPL, *M. avium* facilitates intracellular resistance processes and influences cytokine responses. The immunomodulatory activity of ssGPL *M. avium* varies and depends on the serovar; e.g., serovars one, two, and eight induce the production of prostaglandin E2 and/or TNF-α by human peripheral blood mononuclear cells (PBMCs). The GPL-specific serovar also promotes the phagocytosis process and inhibits fusion between phagosomes and lysosomes. Other cell envelope components in mycobacteria include lipoarabinomannan (LAM), lipomannan (LM), mycolic acid-arabinogalactan-peptidoglycan (mAGP), and phosphatidylinositol (PI), which function as a barrier and modulate the host's immune response.[4,5]

Pathogenesis

The NTM have a lower virulence than TB, so in general, the body's immunity is sufficient to protect against NTM infection. Host immune function factors play a crucial role in the development of diseases caused by NTM. In principle, immune disorders, damage to barriers, or an environment conducive to the accumulation and growth of NTM in the airways increase the risk of infection and NTM diseases. Some of the conditions that contribute to the development of NTM disease include cilia dysfunction, abnormalities in lung structure, defects in mucociliary clearance, and immune suppression.[10]

The innate and adaptive immune responses to NTM infection differ from *M. tuberculosis* infection. The germ pattern is recognized by pattern recognition receptors (PRRs) on the plasma membrane in macrophages. The distinct chemical structures of NTM species, along with various immune mechanisms, can exert different influences on dendritic cells and NK cells, which release receptors for IL-17, TNF-α, IFN-γ, and IL-1β. Currently, there is no evidence related to latent NTM.[3,9,10]

In the case of NTM infection, the primary response is likely to be carried out by innate immunity and Th1, as well as Th1-mediated immunity, as the primary defense mechanism against intracellular NTM. The immune response is initiated by the inhalation of NTM germs, which are inhaled into the alveoli. Alveolar macrophages, as the first line of innate immunity, detect and interact through fibronectin receptors and complement pathways, specifically binding to mannose and fucose moieties. Furthermore, macrophages increase their phagocytic activity by performing phagocytosis through primary phagosomes (destruction of bacilli with acidification, toxic oxygen metabolites, and neutrophil defense). Additionally, it can bind to dendritic-specific intracellular adhesion molecule-3-grabbing nonintegrin, complement, and mannose receptors, surfactant molecules, and TLR (Figure 1-A).[3,9,10]

There are various types of TLRs, including TLR2, which recognizes TLR2/1 and TLR 2/6 recognize triacylated, 19-kDa mycobacterial lipoproteins and glycolipids, and diacylated

lipoproteins, as well as TLR4 and TLR9, which recognize protein 60/65 of heat shock and deoxyribonucleic acid (DNA) mycobacterial unmethylated CpG. The TLR2 receptor is the most researched receptor associated with NTM. A TLR2 gene polymorphism and decreased transcription rate of TLR2 are strongly associated with NTM-LD. In addition, these TLR and TLR2 signals induce the type C leptin pathway and cause an inflammatory response after recognizing dimycolate trehalose, which is a component of the mycobacterium.[9,10]

The interaction between TLR and NTM triggers signaling pathways of mitogen-activated protein kinase (MAPK) and nuclear factor-kB (NF-kB) that activate macrophages and the production of proinflammatory cytokines (such as IL-17 and TNF-α). Activated macrophages secrete IL-12. Interleukin-12 activates T cells and NK cells via IL-12 receptors (heterodimers of IL12RB1 and IL12RB2). Interleukin-12 will activate the secretion of IFN-γ and IL-17 by Th1 cells and NK cells. NK cells secrete TNF-α and IFN-γ. This triggers the activation of other macrophages and neutrophils, produces nitric oxide and superoxide, and increases the levels of specific molecules.[3,9,10]

Activated macrophages also lower the pH of lysosomes, increasing the concentration of intracellular antimicrobial agents and enhancing the mycobactericidal effect. Macrophages also present to T lymphocytes, as well as recruit and multiply specific T lymphocyte cells that can stimulate memory T cell expansion. The axes of IL-12 and IFN-γ lead to coordination between innate and adaptive immunity. In addition, the role of Th17 that produces IL-17 in the increase in neutrophil inflammation. The neutrophils released trigger the activation of elastase and metalloproteinase, which can cause damage to epithelial tissue.[3,9,10] Damages, such as mucosal barrier damage, cilia dysfunction, and hyperplasia and hypersecretion of mucous glands, are shown in Figure 1-A. This can form microabscesses containing NTM and NTM biofilm formations.[10]

Similar to *M. tuberculosis*, MAC can also survive and replicate within macrophages, thereby preventing the fusion of phagosomes and lysosomes. 8-mediated caspase induction in NTM infection is associated with mycobacterial diffusion. This creates an anaerobic environment that supports the growth of NTM. The condition also induces MAC genes to duplicate. MAC germs can inhibit lymphocyte proliferation, macrophage function, and induce macrophage apoptosis by downregulating the expression of Bcl-2 gene products (apoptosis-inhibiting genes)—cytotoxic proteins and cytolytic enzymes that can cause fibrosis and necrosis in the infected area.[5,10]

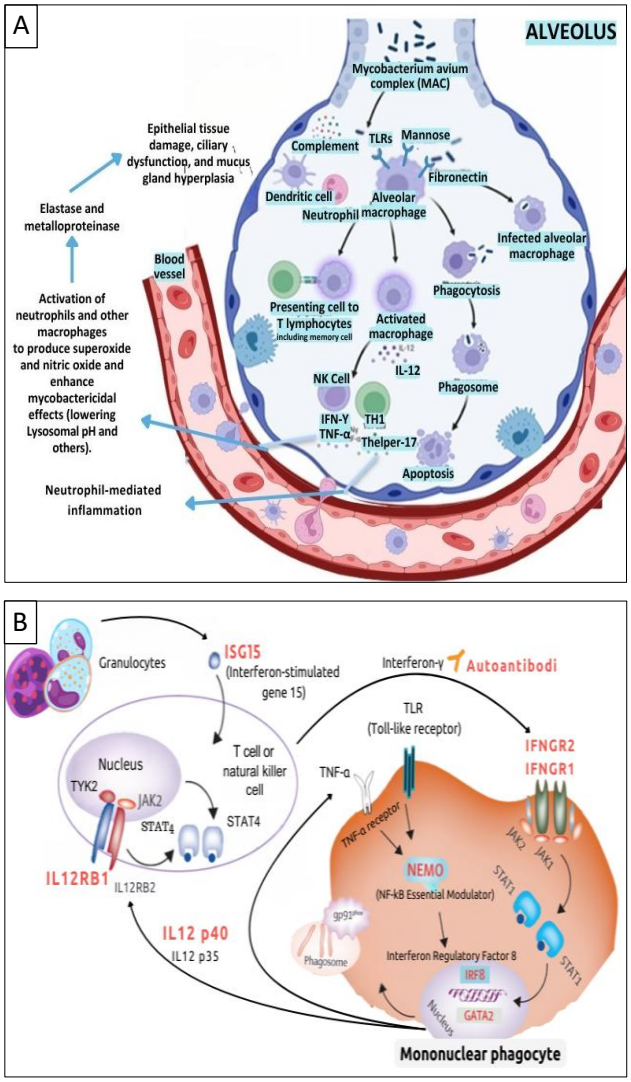

Figure 1. (A) Immunopathogenesis of NTM[10]
(B) Defects in the immune system (marked in red) are a significant factor in the failure of NTM elimination and spread[14]

Both *M. tuberculosis* and MAC can form granulomas that exhibit similar features. However, their molecular and cellular profiles differ significantly. In granulomas, *M. tuberculosis* exhibits an organized and robust granuloma structure characterized by

active bacterial replication, a good Th1 immune response, and caseous necrosis. In MAC granuloma caused by chronic inflammation, a weakened immune response and the formation of fibrosis occur. Granulomas of MAC are characterized by disorganization, fibrotic lesions, fewer giant cells, and more diffuse inflammation, less necrosis, and higher levels of foamy macrophages.[10]

In addition, mycobacterial infections can also increase IL-10, which can decrease the regulation of the inflammatory response, making individuals more susceptible to NTM infections. The IL-10 pathway is an anti-inflammatory pathway. The anti-inflammatory process in NTM, in addition to passing through the IL-10 pathway, also involves the HMOX1 pathway. Both pathways intersect through the STAT3 pathway, triggering the expression of SOCS1, which subsequently inhibits the NF-κB pathway.[5,10]

HOST VULNERABILITY FACTOR

The NTM bacteria are classified as bacteria with low to moderate pathogenicity, so that host risk factors play a significant role in the occurrence of NTM disease. Patients with defects in the molecular receptors or cytokine genes involved in NTM eradication are more susceptible to NTM (Figure 1-B). For example, Mendelian Susceptibility to Mycobacterial Diseases (MSMD) is associated with the production of neutralizing autoantibodies and the use of TNF-α inhibitors. Abnormalities in the immune system that typically respond to NTM infection are significant factors in the development of NTM disease, resulting from the failure of the protective cascade in combating mycobacterial infections. This finding is consistent with various studies, including the observation of a decrease in IFN-γ response to mitogenic stimulation and T cell function in patients with NTM infection.[3,10,14]

The NTM lung disease often affects lungs with anatomical abnormalities (such as bronchiectasis) or immune abnormalities caused by acquired or genetic factors. There are cases where risk factors are unknown and may be related to multiple genes and/or multiple causes. In contrast to extrapulmonary cases or disseminated NTM, they almost always have underlying diseases of immunodeficiency, which can be acquired or genetic in nature. Primary immunodeficiency can occur in childhood and adulthood, so that NTM disease can be found in different ages.[3,4]

Defects in the Pulmonary Defense Mechanism as Risk Populations of NTM-LD

Defects in the cilia are one of the risk factors for NTM-LD. The ability of the cilia to clean is essential in determining the risk of NTM-LD. This is evidenced by the increased NTM-LD prevalence in cystic fibrosis patients and primary ciliary dyskinesia (PCD) despite having normal immune function. In addition, in NTM-LD patients, the expression of the cilia gene was found to be reduced, consistent with the decrease in the number of ciliated cells, suggesting that NTM infection also affects cilia function. Examples of ciliary defect disorders include PCD and bronchiectasis.[4,5,9,15,16]

Table 2. Host Factors Associated with NTM-LD[9]

Mechanism	Type of dysfunction	Disease
Defect of pulmonary clearance and physiology	1. Ciliary defect	a. Primary ciliary dyskinesia
		b. Bronchiectasis
	2. Inspissated secretion	Cystic fibrosis
	3. Structural lung change	a. Cartilage and elastin deficiency in the airway (Tracheobronchomegaly; Mounier-Kuhn syndrome)
		b. Bronchiectasis
		c. COPD
		d. Alpha-1 antitrypsin deficiency
	4. Macrophage dysfunction	Pulmonary alveolar proteinosis
Immune suppression	1. Immune deficiency in the lungs	Using ICS
	2. Systemic immune deficiency	Anti-TNF-a therapy

Note: COPD=chronic obstructive pulmonary disease; ICS=inhaled corticosteroid; TNF-α=tumor necrosis factor-alpha

Bronchiectasis can lead to damage and dysfunction of the mucociliary system. Bronchiectasis can also occur due to NTM infection. However, the relationship between bronchiectasis and NTM, such as the chicken-and-egg scenario, is unclear (it cannot be determined which came first). The underlying factor for NTM in bronchiectasis is not only poor airway clearance but also decreased local immunity, which triggers NTM growth.[4,9]

Cystic fibrosis (CF) itself is a hereditary genetic disorder mainly occurring in Caucasian races with an autosomal recessive pattern. Cystic fibrosis is rare in Asians. In Caucasian cystic fibrosis patients, the prevalence of NTM-LD was found to be 3–13%.[9]

Changes in the Structure of the Lungs

Changes in the structure of the lungs can result from congenital/genetic diseases or from acquired conditions, such as Williams-Campbell syndrome, Alpha-1-antitrypsin deficiency (AATD) and Tracheobronchomegaly. Williams-Campbell syndrome is a disorder characterized by cartilage deficiency in the airways, specifically in the subsegmental bronchi. The affected bronchi will collapse, and bronchiectasis (cystic bronchiectasis) may develop.[4,9,16] Alpha-1-antitrypsin deficiency is a codominant autosomal disorder that causes emphysema and bronchiectasis. In this condition, macrophage dysfunction occurs, reducing the ability to control NTM infection. The onset of this disorder typically occurs between the ages of 20 and 50.[4,5,9,17] Tracheobronchomegaly (Mounier–Kuhn syndrome) is a disorder characterized by airway elastin deficiency. In the large airways, a lack of elastic fibres and smooth muscle leads to atrophy or loss of tissue, resulting in significant dilation of the trachea and main bronchi, as well as diverticula of the airway wall that can serve as a reservoir for recurrent infections, including NTM.[4,5,9,15]

Various lung diseases typically cause changes in the structure of the lungs. Various lung diseases can be risk factors for NTM-LD. Chronic obstructive pulmonary disease (COPD) is the most common disease found with NTM infection, with a prevalence of about 14–39% of cases. This is related to the phenotype of COPD, namely emphysema, and is related to cigarettes.[9] Bronchiectasis is the most common risk factor for NTM-LD. Acquired bronchiectasis can result from the sequelae of infection, silicosis, or chronic aspiration. Another disease, namely tuberculosis, although of the same genus, has a prevalence of approximately 2%. Other conditions include lung cancer and lung transplantation (prevalence is around 1.5–22.4%). [4,9]

Macrophage Dysfunction

Pulmonary alveolar proteinosis (PAP) is a condition that occurs in the absence of surfactant clearance by alveolar macrophages. This causes the accumulation of lipoproteinase material in the distal air cavity. Congenital disorders of PAP are caused by mutations in genes encoding a-subunits or b-subunits of the granulocyte-macrophage colony-stimulating factor (GM-CSF) receptors, or surfactant B-proteins.[4,9]

Abnormalities are observed when autoantibodies to GM-CSF are present. The subsequent process causes macrophages to lose their function, leading to the activation of adaptive immunity and triggering opportunistic infections. In about 90% of PAP cases, it is an autoimmune disorder. A study reported that 42% of patients with PAP were found to have NTM isolates.[4,9]

Immune Deficiency

There are two conditions associated with immune deficiency: immune suppression in the lungs and systemic immune deficiency. The use of inhaled corticosteroids in patients with COPD and asthma increases the risk of pneumonia, including TB and NTM. A study reported that the use of inhaled corticosteroids had an OR value of 1.86–2.74 against the incidence of NTM. Acquired factors, such as the use of anti-TNF-α therapy, are often associated with an increased incidence of NTM, typically due to systemic immune system deficiency. A study in the UK reported that the incidence of NTM was 40% in patients receiving anti-TNF-α therapy.[9]

Based on the previous explanation, abnormalities or disruptions in the IL-12, IFN-γ, and

TNF-α pathways are associated with susceptibility to NTM infection. In addition, diseases and therapies that can lower cell-mediated immunity occur in conditions, such as organ transplantation, HIV with low CD4, and the use of corticosteroids.[9]

Other Conditions

Other contributing conditions include GERD and autoimmune diseases. Reflux of stomach acid that irritates the airways is associated with various lung diseases, including bronchial asthma, bronchiectasis, chronic bronchitis, and NTM. As a result of the irritation caused by gastric asthma, the bronchial epithelium is damaged, leading to chronic bronchial inflammation. Studies report that 26–44% of those with NTM-LD have GERD.[9] Rheumatoid arthritis (RA) and Sjögren syndrome are also reported to be associated with NTM. Various factors, such as autoimmune lung abnormalities, the use of immunosuppressant drugs, and immune dysfunction, may increase the risk of NTM in these autoimmune conditions.[9]

The NTM disease is often found in individuals with unknown risk factors, typically in those with an asthenic habitus (characterized by pectus excavatum and scoliosis), abnormalities of the thoracic cavity, and in postmenopausal women. The X chromosome can inhibit the immunoregulatory response. Additionally, increased levels of TLR7, IFN-α, and IFN-β in women may contribute to immune fatigue. However, the underlying mechanisms and factors cannot be clearly explained.[4,5]

In addition, reduced body fat is a risk factor for NTM. This is due to a relative deficiency of the hormone leptin (a hormone produced from fat that regulates satiety). The hormone also plays a role in promoting the differentiation of T0 cells into the TH1 cell phenotype (cells that produce IFN-γ). In the study, rats with leptin deficiency were found to be more susceptible to M. abscessus lung infections.[4,5]

The evidence suggests that NTM infection is a complex disease, resulting from a combination of various factors, including genetic, physical, and environmental factors. There is an accumulation of risk factors, including behavioral and environmental factors that increase exposure to NTM, host genetic susceptibility, acquired risk factors, and age-related factors, all of which combine to increase the risk of developing NTM-LD.[4,10]

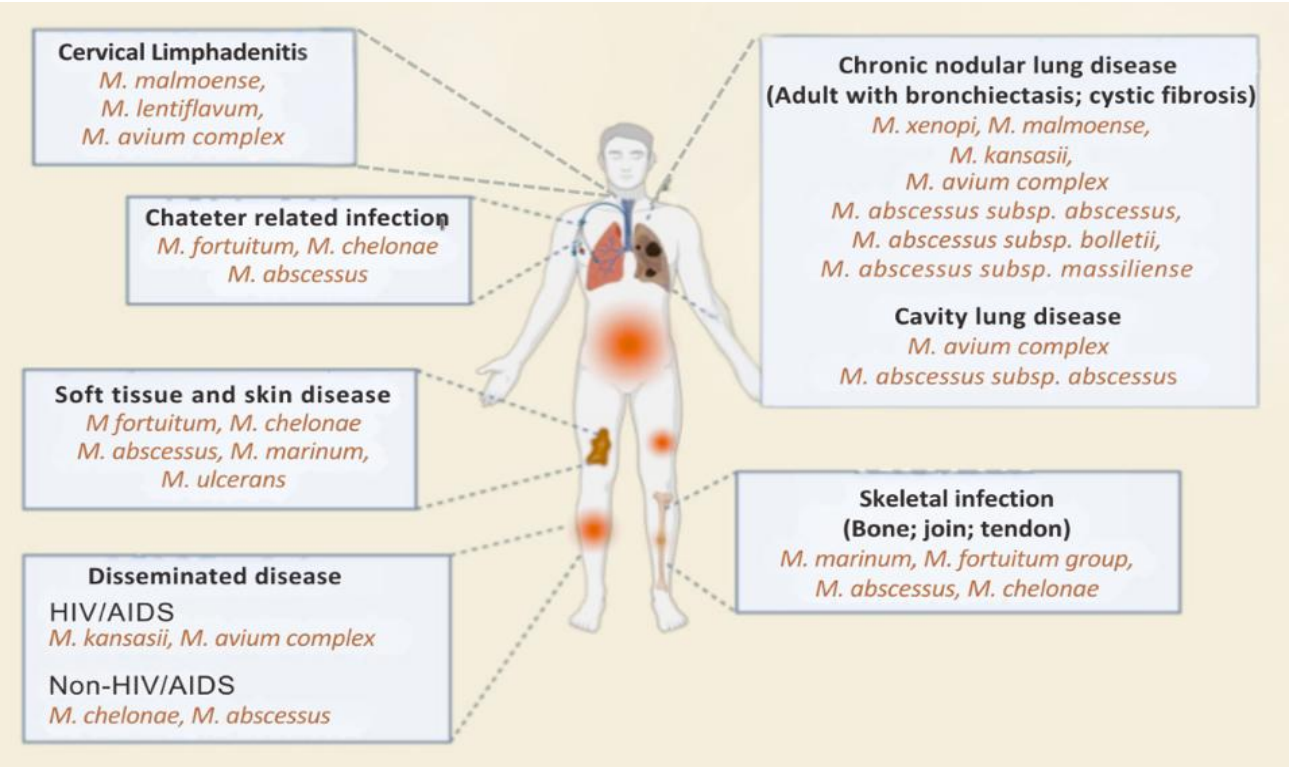

Figure 2. Clinical manifestation of NTM in various organs[10]

CLINICAL ASPECTS

The clinical manifestations of NTM are very diverse, depending on the transmission pathway. A person can become infected with NTM, but it often goes undetected for many years until the individual is examined for NTM. In immunocompetent individuals, NTM infection is rare and usually manifests clinically as a localized lung disease.[10,18]

The NTM germs can manifest severe and disseminate in patients with immunosuppression. NTM-LD exhibits symptoms similar to those of other respiratory diseases, such as TB and lung cancer, including persistent cough, sputum production, coughing up blood, shortness of breath, fever, night sweats, drastic weight loss, and significant weakness or lethargy. Another condition that warrants inquiry is recurrent lower respiratory tract infections, even with adequate antibiotics. In COPD and bronchiectasis, distinguishing between them is often difficult, so anamnesis regarding symptom duration or persistence is a crucial factor.[10,18]

DIAGNOSIS NTM-LD

Diagnosis Criteria

According to the guidelines of the Infectious Diseases Society of America (IDSA), there are three criteria for diagnosing NTM lung disease: clinical, radiological, and microbiological. Culture results showing the presence of NTM isolates in sputum, which meet clinical and radiological criteria, must consider the specific species types and the number of positive cultures.[13]

The NTM can be found as an environmental contaminant in the isolates of respiratory specimens, and in many cases, it does not lead to progressive disease. Therefore, to diagnose NTM lung disease, more than one sample showing NTM-positive cultures and identifying the same species is required to establish the NTM diagnosis.[13]

For diagnosis, sputum culture results must meet the following criteria: ≥2 samples and identification of the same NTM species, with a minimum interval of at least one week between samples. This is in accordance with significant clinical findings from 2 or more samples. For pathogens with low levels, such as *M. gordonae*, which have been associated with months of positive cultures and strong radiological and clinical evidence, it remains to be ascertained whether they are causal. This is different if the findings from the sputum culture are *M. kansasii*, which can be strong evidence to start therapy.[13]

Radiological Overview

In all patients suspected of having NTM-LD, a thoracic imaging examination is necessary, and a high-resolution computed tomography (HRCT) examination is recommended. Evaluate the imaging of lung lesions as a sign of NTM-LD and to determine whether patients meet the diagnostic criteria for NTM-LD as outlined in the guidelines.[18]

Table 3. NTM-LD Diagnosis Criteria[13]

Criterion	Findings	Information
Clinical	Pulmonary or systemic symptoms	Must meet both criteria
Radiology	1. Nodular or cavity opacities on thoracic photographs or HRCT indicate bronchiectasis with multiple small nodules.	
	2. Accuracy in the exclusion of other diagnoses	
Microbiology	1. Sputum Positive culture results are obtained from at least two separate samples (a minimum of one week or more apart). If the results are not diagnostic, consider repeating the acid-fast bacilli (AFB) staining and sputum culture. OR	
	2. Bronchoscopy Positive culture results from at least one bronchial lavage or wash. OR	
	3. Biopsy results a. Transbronchial biopsy or other lung biopsy with features of mycobacterial histological (inflammatory granulomatous or AFB) and culture positive for NTM, OR b. A biopsy showing features of mycobacterial histological (granuloma inflammation or AFB) and one or more sputum or bronchial wash samples showing a positive culture for NTM.	

There are two main descriptions of NTM-LD: 1) (1) fibrocavity disease, characterized by multiple features, a thin-walled cavity, and typically located in the upper lobe; and (2) nodular bronchiectasis disease, characterized by nodules, bronchiectasis, and thickening of the bronchial wall. Another reference mentions that a mixed picture can also be found, namely fibrocavity with nodular bronchiectasis.[18]

Sampling and Sample Culture Conditions

For NTM-LD with a cavity, a sputum sample is usually sufficient to establish a diagnosis. In some studies, bronchoalveolar lavage and cultures were reported to be more sensitive than sputum cultures for diagnosing nodular NTM disease or bronchiectasis. Sampling of at least three respiratory samples with a gap of at least one week was examined. Bronchoscopy is only performed on patients with suspected NTM lung disease whose sputum samples cannot be obtained, even though induction has been performed.[13]

Respiration sample cultures are recommended to be carried out on both media, namely, liquid and solid, to increase sensitivity. In some studies, comparing various solid media, Lowenstein-Jensen was found to be more sensitive in detecting NTM. The Clinical and Laboratory Standards Institute (CLSI) recommends solid media that use 7H10 and 7H11.[13]

Species Identification

Identification of NTM species is of great importance for NTM infection regarding the clinical relevance of isolates and the selection of combination therapies. Spectrometry-based molecular and mass methods can be used to identify species. Molecular identification is more accurate and can be done using probes or gene sequencing. *Probe-based* assays are easier to use and implement, but less effective at distinguishing and too simple in classifying the phylogeny and epidemiology of NTMs. Gene sequencing has higher discriminating power, even at the subspecies level, but the tools are limited.[13]

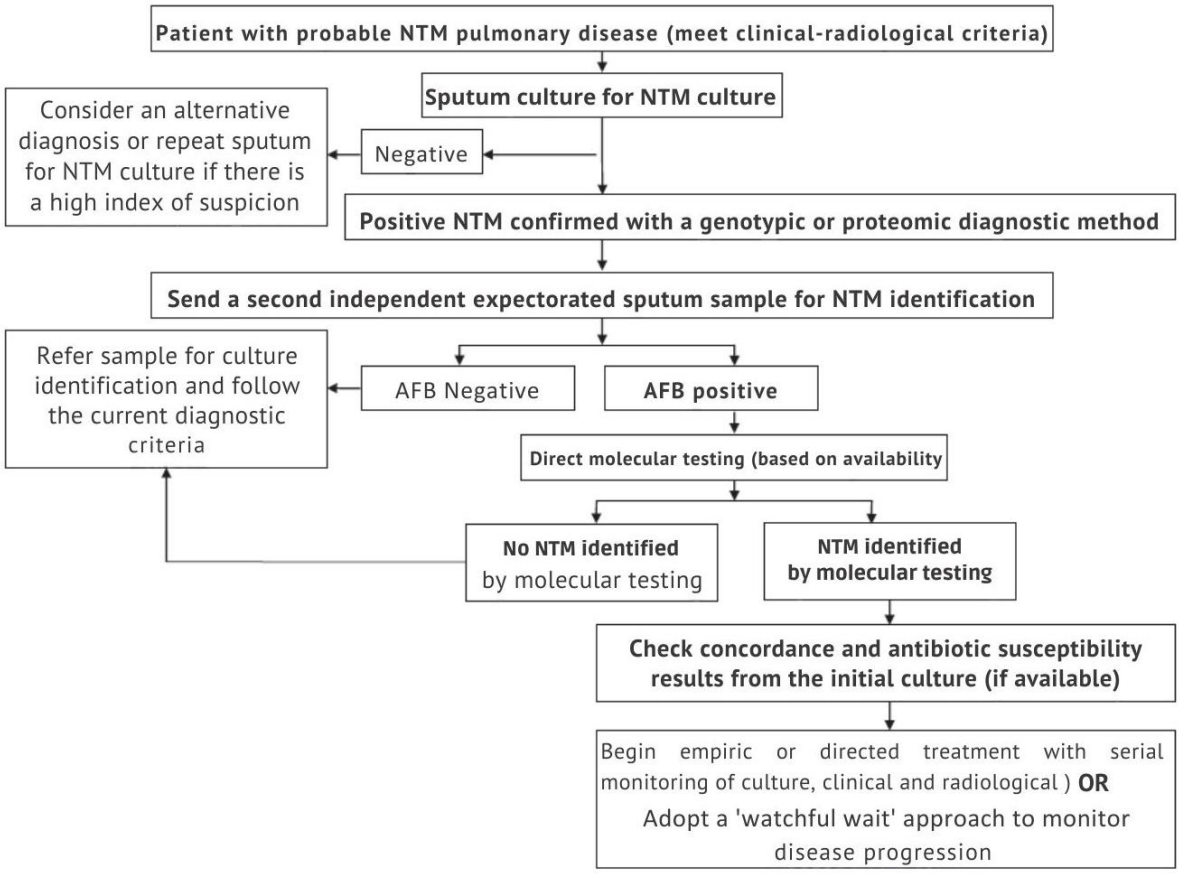

Figure 3. The proposed flow of NTM diagnosis by Opperman et al includes a molecular test[19]

Molecular identification should be conducted on all clinically relevant NTM isolates and on follow-up isolates from patients undergoing treatment for NTM lung disease. If feasible, isolates from treated patients should be frozen and stored to differentiate between reinfection and relapse. Examples of identified gene targets include 16S rRNA (*M. abscessus-M. chelonae group*), hsp65, rpoB, and the 16S–23S internal transcribed spacer (ITS). The discriminating ability of the mass spectrometry method in matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) has improved with advances in protein extraction protocols and related data. However, not all species and subspecies are distinguishable by this technique.[13]

The chart of the diagnostic flow recommended by Opperman et al, which includes molecular examination in the diagnostic process (in contrast to the current diagnostic guide, which requires at least two NTM-positive cultures of the same species), is shown in Figure 3. The proposed algorithm has some limitations. This algorithm is effective only for specimens of positive preparations, thus limiting its usefulness in cases with a low disease load. The proposed diagnostic pipeline is expensive, and not all facilities can afford it, as it includes molecular testing. In addition, there is a risk of overdiagnosis that can lead to unnecessary treatment.[19]

The algorithm also cannot predict the conversion of sputum cultures to negative, so it does not allow for quantitative evaluations that can help assess the severity of the disease and monitor the course of treatment. Finally, the response to treatment of NTM lung disease varies greatly, so reaching an earlier diagnosis does not always guarantee a favorable treatment response. Therefore, further research is needed to validate this strategy.[19]

DRUG SENSITIVITY TEST

Based on IDSA's recommendations, drug sensitivity tests were conducted on the drugs used in the treatment regimen, demonstrating a clear link between in vitro activity and in vivo treatment outcomes. Drug sensitivity tests are not routinely performed except in cases where diseases do not respond to treatment, such as slow-growing NTM infections (MAC or *M. kansasii*) or rapid NTM growth (*M. Abscessus*). For patients whose NTM isolates are considered clinically significant, drug sensitivity tests are performed on both primary isolates and those that have relapsed or failed. According to CSLI, the drug sensitivity test is conducted using a microdilution method with broth.[13]

MANAGEMENT OF NTM-LD

The management of NTM depends on the species or subspecies, the extent of the disease (such as fibrocavitary disease or nodular bronchiectasis), results of drug susceptibility tests, and underlying comorbidities (including those related to drug interaction considerations). Treatment typically involves multiple drugs over an extended period, so side effects must be carefully considered. However, treatment outcomes are sometimes still less than ideal, and reinfection can happen with different strains or the same bacterial species.[20]

Treatment decisions in NTM-LD patients are made carefully. Several considerations must be taken into account when starting NTM treatment. Not all patients with NTM should receive antibiotic treatment, even if they meet the diagnostic criteria for NTM lung disease. Based on the previous explanation, related to multidrug, long-term, and sometimes suboptimal treatments, a careful assessment of the pathogenesis of the organism, the risks and benefits of therapy, the patient's desires, ability to receive treatment, and consideration of the purpose of therapy needs to be discussed with the patient before starting treatment. In some cases, the handling is carried out by monitoring and waiting.[13]

Some factors support treatment, while others support delaying treatment, based on three key factors: host factors, imaging factors (radiology), and pathogenic factors. Factors that support starting treatment include: (1) host factors, include age, severity, comorbidities, pre-existing lung disease, immunosuppression status, and symptom severity;

(2) imaging factors, namely the expansion of lung disease (the number of cavities, the area of the lung area involved); (3) pathogenic factors, namely pathogens with high virulence. Factors that delay treatment include: (1) host factors, including poor body performance, intolerance to antimicrobial agents, potential reinfection, and patient preference; (2) imaging factors, including characteristics of local lesions and/or nodules; (3) pathogenic factors, namely coinfection with other pathogens such as fungi, bacteria, and others.[10]

Based on the IDSA guidelines related to the findings of NTM-LD cases, several recommendations are available for determining whether to treat immediately or monitor and wait. Patients who met the diagnostic criteria for NTM lung disease were given initiation treatment versus monitoring and waiting. Drug administration is based on clinical factors, the species infecting, and the patient's priorities. Things that need to be discussed with the patient include potential side effects, the uncertainty of the benefits of antimicrobial therapy, and the risk of potential recurrence or reinfection (especially in cases of bronchiectasis).[13]

Regarding treatment based on empirical first principles or drug sensitivity tests, it depends on the type of species infecting. In MAC, it is recommended to examine drug sensitivity tests first for macrolides and amikacin, rather than initiating empirical therapy. Before commencing therapy for *M. kansasii*, it is recommended that the drug sensitivity be tested first to rifampicin rather than empirical treatment. In *M. Xenopi*, there are no recommendations or prohibitions for treatment based on drug sensitivity tests. In *M. Abscessus*, it is recommended that the drug sensitivity test be first examined against macrolides and amikacin. The relationship between in vitro and in vivo has not been fully proven for all antimicrobial drugs. Baseline data on resistance to certain medications is recommended based on Clinical and Laboratory Standards Institute (CLSI) guidelines.[13]

Surgical Resection and Nonpharmacological Therapy

Other therapies for NTM infection are pharmacological therapy and surgical considerations. Nonpharmacological therapies can be given, including pulmonary rehabilitation and nutritional improvement. Surgical considerations can be made with or without medical therapy in NTM.[3,13]

In some cases, surgical resection and adjuvant therapy can be carried out after medical therapy, following a process of discussion and consultation with various multidisciplinary professionals and experts. Conditions considered for surgery are those that are localized and have good lung function. In patients who experience failure of medical therapy treatment, cavities, drug-resistant isolates, or complications, such as hemoptysis or severe bronchiectasis, may be considered for surgical resection.[3,13]

Monitoring of Response to Therapy and Treatment Completion Criteria

Things that must be evaluated in determining the therapeutic response include clinical, radiological, and microbiological data. Thoracic photos and CT scans may be more recommended in determining response to therapy. The duration of treatment, based on the time of culture conversion, makes it essential to obtain the frequency of sputum sample collection for culture (1–2 months) to document when the sputum culture is negative. If the sputum sample cannot be removed, sputum induction with hypertonic saline can be performed.[3,13,17]

Bronchoscopy may be considered to determine if a culture conversion has occurred. NTM treatment was continued for up to 12 months after the conversion culture was declared. The criteria for conversion culture are that if three consecutive negative sputum cultures are obtained, collected at least within 3 months, the conversion time is calculated from the first negative culture among the three cultures or from one negative culture, based on bronchial wash or lavage cultures. Bronchoscopy for NTM culture evaluation examination can be performed every 6–12 months.[3,13,17]

The disease is said to be recurrent if an NTM-positive culture is obtained again after being declared a conversion culture. Genomic testing can help distinguish relapse or reinfection. The disease is

considered refractory if the culture fails to convert after 12 months of treatment.[3,13,17]

Monitoring of Drug Side Effects

Based on the latest research, more than 90% of patients experience side effects. It is essential to educate and monitor patients regularly. This aims to detect and treat side effects early, thereby reducing the risk of treatment complications and increasing the likelihood of completing treatment. There is no standard frequency in monitoring drug side effects. Still, it can be adjusted to the needs of patients by considering many factors, including age, comorbidities, other drugs consumed, overlapping drug toxicity, and resources.[13]

CONCLUSION

The NTM are all mycobacterial species except those that cause tuberculosis and leprosy. They are gram-positive, acid-resistant, rod-shaped, and have a specific cell membrane component different from that of *M. tuberculosis*, namely GPL. NTM have distinct cell membrane constituents that act as a barrier and modulate various immune cells. Approximately 20–66% of NTM findings in respiratory specimens are accompanied by clinical manifestations of the disease, most of which affect the pulmonary organs, but can also occur in extrapulmonary infections and disseminate to other organs. The onset of clinical manifestations in NTM infection is influenced by various factors, such as environmental factors and host factors (host susceptibility).

Three diagnostic criteria must be met to diagnose NTM, namely clinical criteria, radiological, and microbiological. The principles of pharmacological management depend on the type of species, the extent of the disease, the results of drug susceptibility tests, and comorbidities. Initiating therapy for NTM-LD should not be based solely on positive cultures but guided by an individualized assessment of host factors, radiological patterns, and the virulence of the infecting species. Drug susceptibility testing should inform regimen selection to improve outcomes and minimize the risk of toxicity.

Nonpharmacological measures remain essential to optimize care. Lifestyle and environmental modifications—such as reducing exposure to aerosolized water sources, quitting smoking, and improving nutrition—help prevent reinfection and support the host's immunity. Pulmonary rehabilitation and airway clearance techniques can enhance lung function and quality of life, while surgical resection may be appropriate for localized, refractory, or complicated disease after multidisciplinary evaluation. Together, these considerations ensure therapy is both timely and appropriately tailored, avoiding unnecessary toxicity and preserving lung function.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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