Host immune response against environmental nontuberculous mycobacteria and the risk populations of nontuberculous mycobacterial lung disease

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Received 10 March 2020; received in revised form 21 April 2020; accepted 4 May 2020

KEYWORDS
Host factors; Immune response; Risk; Lung disease; Nontuberculous mycobacteria

Nontuberculous mycobacterial lung disease (NTM-LD) prevalence has been increasing over the recent decades. Numerous host factors are associated with NTM-LD development, including susceptible phenotypes such as ciliary defect and lung structural change, pulmonary clearance defect with poor clearance of secretions, and immune suppression. Specifically, regarding the susceptible host phenotypes without clear pathogenesis, a slender body, pectus excavatum, and postmenopausal female status are common. Also, decreased host immunity to NTM, especially T helper 1 cell responses is frequently observed. Even so, the underlying mechanisms remain unclear and relevant large-scale studies are lacking. Infections due to host genetics associated defects are mostly untreatable but rare in Asia, particularly Taiwan. Nevertheless,
some risks for NTM-LD are controllable over disease progression. We suggest that clinicians first manage host factors and deal with the controllable characteristics of NTM-LD, followed by optimizing anti-NTM treatment. Further research focusing on NTM-LD pathogenesis, especially the host—NTM interaction may advance understanding the nature of the disease and develop efficient therapeutic regimens.

Nontuberculous mycobacteria belong to the environmental microbiota

Nontuberculous mycobacteria (NTM) are a group of small, and rod-shaped aerobic mycobacteria known as environmental mycobacteria. NTM comprise diverse bacterial members of more than 150 species widely distributed in different water and soil environments as reservoirs. The living environments of NTM closely overlap with those of humans and domesticated animals; therefore, NTM frequently coexist with humans. Unlike the notorious pathogens Mycobacterium tuberculosis (MTB) and Mycobacterium leprae, NTM are generally not considered obligate human pathogens.

Environmental NTM frequently exist in respiratory tracts

Exposure within the home of humans to NTM, both pathogenic and nonpathogenic, might be associated with point-of-use water sources and soil reservoirs used for gardening. For instance, a major pathogen, Mycobacterium avium complex (MAC), can be discovered in the endpoints of drinking water systems and aerosol samples from showerheads. In addition, M. avium, Mycobacterium kansasii, Mycobacterium lentiflavum, and Mycobacterium abscessus can be enriched to a high level in showerhead biofilms. In addition to existing in the environment, NTM is present as airway microbiota and colonizes the respiratory tracts of humans. The result of 16S rRNA gene and nested mycobacteriome sequencing approaches to characterize microbiota composition have demonstrated that the percentage of NTM in lower airway samples varies, and taxa identified as nonpathogens of oral commensals are frequently associated with the inflammatory status of the host. The correlation between microbiota data and lower airway inflammation suggests a critical role of mycobacteria in airway inflammatory processes.

NTM cross over to humans

NTM from natural water environments can cross over to humans under certain circumstances and cause infections. Unlike the transmission of tuberculosis and leprosy, animal-to-human or human-to-human transmission of NTM rarely occurs. NTM causes not only lung disease (LD) but also extrapulmonary manifestations, including skin lesions, lymphadenitis, osteomyelitis, and wound infection. However, more than 90% of clinical cultures of NTM are isolated from pulmonary specimens. Nevertheless, the clinical significance of a positive sputum culture is far lower than 100% and depends on the species. For instance, only 35%—42% of patients who are sputum positive for MAC have clinical MAC-LD. Therefore, NTM-LD is diagnosed not by only sputum positive for NTM but based on the American Thoracic Society (ATS) diagnostic guidelines. In brief, they need to fulfill (1) microbiological criteria: at least two sputum samples or one bronchial sample, or one lung tissue culture-positive for the same NTM species; (2) clinical criteria: presence of respiratory symptoms and compatible radiographic lesion; and (4) exclusion of other pulmonary causes.

NTM-LD prevalence has increased over the last 20 years, and it has become the major clinical manifestation of NTM infection. This trend has been reported worldwide. Scholars have proposed that this increase is positively correlated with the increasing number of immunocompromised subjects and advances in mycobacterial laboratory techniques as well as a decrease in tuberculosis prevalence. Although the common NTM species vary geographically in their prevalence, MAC and M. abscessus complex are two of the most common pathogenic species isolated from patients with NTM-LD, particularly in the United States and Southeast Asia.

Host factors affecting susceptibility to NTM-LD

NTM-LD development is indicative of host susceptibility. The well-known predisposing factors are pulmonary structural changes and immune deficiency, such as history of pulmonary tuberculosis or previous use of tumor necrosis factor (TNF) $\alpha$ antagonist, corticosteroids, immunosuppressants, chemotherapeutic agents, or neutralizing anti-interferon (IFN) $\gamma$ autoantibodies. However, one group of patients was noted to have no known risk factors: those who are physically thin in appearance and postmenopausal women, presenting as Lady Windermere syndrome. The underlying pathogenesis and factors increasing vulnerability to NTM infection remain unclear. A possible
underlying mechanism is that slender individuals may be predisposed to NTM infections because of their low body fat and relative deficiency of leptin, which has several immunomodulatory functions that potentially enhance host immunity against NTM. 18 Notably, NTM-LD can cause lung dysfunction and have a lethal prognosis. 19 Therefore, after a patient is diagnosed as having NTM-LD, their immune response to NTM and susceptibility factors must be reviewed to aid patient evaluation in clinical practice.

Host immune responses to NTM

Pulmonary immune defense against NTM

In NTM-LD, T helper 1 cell (Th1) immunity was predicted to be a major protection mechanism against NTM intracellular infection. 20 Immune response is initiated after a host inhales aerosolized NTM and their alveolar macrophages recognize specific molecular patterns on NTM through pattern recognition receptors. The most well characterized pattern recognition receptors for NTM are toll-like receptors (TLRs). Interaction between NTM and TLRs triggers downstream Mitogen-activated protein kinase and nuclear factor-κB signaling for macrophage activation and downstream proinflammatory cytokine production. TLR2 is responsible for the recognition of 19-kDa mycobacterial lipoproteins and glycolipids, whereas TLR2/1 and TLR2/6 heterodimers interact with triacylated and diacylated lipoproteins, respectively. TLR4 senses heat shock protein 60/65, and TLR9 detects mycobacterial unmethylated CpG DNA. 31 Among all TLRs, TLR2 is the most well investigated with regard to NTM infections. A decrease in the TLR2 transcriptional level in patients with NTM-LD 22 and TLR2 gene polymorphism are strongly associated with MAC-LD. 23 In addition to TLRs and TLR2 signaling, the macrophage-inducible C-type lectin pathway 33 can induce an inflammatory response after the mycobacterial component of trehalose dimycolate is encountered.

The defense system against NTM is regulated by macrophages through direct killing of mycobacteria and the production of interleukin (IL) 12, which activate natural killer (NK) 25 or T cells to secrete IFN-γ. IL-12 and the IFN-γ axis create cross talk between innate and adaptive immunity against NTM-LD. Defects in genes related to the IL-12–IFN-γ pathway may enhance host susceptibility to disseminated NTM infection. 26 The underlying immune mechanisms are entirely different between localized and disseminated NTM diseases. TNF-α, produced by macrophages and NK cells, is also considered to be the major mediator of NTM growth inhibition and granuloma construction in the lungs. 27 Therefore, efficient Th1 immunity—mediated by IL-12, IFN-γ, and TNF-α—is essential to clearing or restricting NTM intracellular infection. The role of Th17 (IL-17-producing CD4+ T cells) has been studied in lung bacillus Calmette–Guérin and MTB-infected mouse models, showing that IL-17 functions as an antimycobacterial cytokine by enhancing the IFN-γ-mediated Th1 response. 28 Th17 in MAC-LD has previously been investigated in T-bet-deficient mice, which were discovered to have increased neutrophil inflammation and lower resistance to MAC compared with wild-type mice.

Immune defense mechanism against NTM outside the lungs

In addition to infecting the lungs, NTM can cause systemic responses. For NTM-LD patients without AIDS, weak systemic immune responses to NTM infection has been reported but there are some conflict data (Table 1). Here, we summarize the relevant studies regarding NTM and report the key roles and changes in IFN-γ, TNF-α, and CD4+ T cells in the defense immune system.

Decreased Th1 cytokine response (IFN-γ and IL-12) 22,29 but increased Th2 (TGF-β) 30 has been observed in the cell response to NTM or other antigens (Table 1). Furthermore, some Th2-associated biomarkers, such as serum levels of immunoglobulin E and number of eosinophils in circulation, were reported to be increased in patients with MAC-LD. 31 Levels of immunosuppressive molecules, including IL-10, 29 and PD-1/PD-L1, 32 are higher in patients with NTM-LD than in healthy controls.

In addition to reduction in the number of circulating Th1 in patients with MAC-LD, an attenuated Th17 response was observed after MAC stimulation through the upregulation of PD-1 expression in patients compared with healthy controls. 32 Moreover, Lim et al. proposed a trend of sensitine-induced IL-10 production from non-CD4+ T cells and attenuated Th17 in patients with NTM and nodular bronchiectasis. 33 Regulation among T-cell populations may play a key role in host susceptibility to the systemic NTM infection mechanism. The differences in immune cell response between patients with NTM-LD and controls are summarized in Table 1.

Although Th1 and innate immunity attenuation has been speculated on, the causal relationship between host vulnerability and NTM evasion mechanisms cannot be easily determined because most studies on NTM and systemic immunity have been cross-sectional. Future studies validating the disease cause and pathogenesis of immune attenuation and NTM-LD are required.

Known host factors of NTM-LD

In contrast to its occurrence in patients without clear underlying diseases, 34 NTM-LD occurs predominantly in patients with anatomic lung abnormalities with or without an identifiable genetic basis and in those with immunologic disorders. 12,14,16,35 The associated pathogenic mechanisms—such as anatomic, immunologic, and genetic disorders—that lead to isolated NTM-LD are listed in Table 2.

Defects in pulmonary defenses

Many diseases lead to defects in pulmonary defenses that predispose an individual to NTM-LD. These diseases are grouped according to the dysfunction mechanism, and some of these diseases may have several pathogenic factors.

Ciliary defect
Capability of bronchial ciliary clearance is a critical determinant of NTM-LD risk, a finding supported by the increasing prevalence of the disease in patients with cystic fibrosis (CF) and primary ciliary dyskinesia (PCD), 36 whose
related immune functions appear normal. A recent study indicated that bronchial ciliary functions, including beat frequency, are impaired in patients with NTM-LD.

**PCD.** PCD is defective ciliary structure and function and chronic otosinopulmonary disease due to genetic defects. The clinical phenotype of PCD is broad and overlaps with those of other chronic airway diseases and that of situs inversus. The prevalence was estimated to be 12,000–17,000 in studies conducted in Norway and Japan. A recent US study revealed that approximately 3% of individuals in the bronchiectasis registry have PCD. By contrast, precise data have not yet been collected in Taiwan and many other countries. Only some cases of suspected PCD have been reported in Taiwan. Regarding NTM isolated in the airways of patients with PCD, Roden et al. reported a 1.9% isolation rate and Aksamit et al. reported that 1.1% of patients with PCD-induced bronchiectasis had coexistent NTM.

**Bronchiectasis.** Bronchiectasis leads to mucociliary damage and dysfunction. In Germany, the annual overall prevalence of bronchiectasis has increased significantly from 52.5 to 94.8 per 100,000 population. Based on data from Taiwan National Health Insurance Research Database, bronchiectasis incidence is approximately 130 per 100,000

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**Table 1** Literature on immune cell response in patients with nontuberculous mycobacterial lung disease (NTM-LD) compared with healthy controls. Papers in which the number of cases was <3 and that used serum data as well as nonstimulated reports are not included.

<table>
<thead>
<tr>
<th>Immune response</th>
<th>Cell type</th>
<th>Stimulus</th>
<th>Target</th>
<th>Methods</th>
<th>Results: NTM-LD compared with healthy controls unless other description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLR2</td>
<td>PB monocytes</td>
<td><em>M. avium</em> and LTA</td>
<td>mRNA</td>
<td>qPCR</td>
<td>Reduced&lt;sup&gt;22&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>MDM</td>
<td>MAC</td>
<td>mRNA</td>
<td>qPCR</td>
<td>Reduced&lt;sup&gt;32,93&lt;/sup&gt;</td>
</tr>
<tr>
<td>IL-12</td>
<td>PB monocytes</td>
<td><em>M. avium</em> and LTA</td>
<td>Secreted protein</td>
<td>ELISA</td>
<td>Reduced&lt;sup&gt;22&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>MDM</td>
<td>MAC</td>
<td>Secreted protein</td>
<td>ELISA</td>
<td>Reduced&lt;sup&gt;32&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>PBMC</td>
<td>MAC</td>
<td>Secreted protein</td>
<td>ELISA</td>
<td>Reduced&lt;sup&gt;29&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>PB monocytes</td>
<td><em>M. avium</em> and LTA</td>
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<td>Reduced&lt;sup&gt;22&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>MDM</td>
<td>MAC</td>
<td>Secreted protein</td>
<td>ELISA</td>
<td>Reduced&lt;sup&gt;32&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>PBMC</td>
<td>MAC</td>
<td>Secreted protein</td>
<td>ELISA</td>
<td>Reduced&lt;sup&gt;94,29&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>PBMC</td>
<td>LPS + IFN-γ</td>
<td>Secreted protein</td>
<td>ELISA</td>
<td>Reduced&lt;sup&gt;95&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>PBMC</td>
<td>PMA</td>
<td>TNF-α&lt;sup&gt;+&lt;/sup&gt; CD8&lt;sup&gt;+&lt;/sup&gt; cells</td>
<td>FCW</td>
<td>Reduced&lt;sup&gt;96&lt;/sup&gt;</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>PBMC</td>
<td>Anti-CD3</td>
<td>Secreted/surface protein</td>
<td>ELISA</td>
<td>Reduced&lt;sup&gt;97&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>PBMC</td>
<td>PHA + IL-12</td>
<td>Secreted protein</td>
<td>ELISA</td>
<td>Reduced&lt;sup&gt;17,95&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>PBMC</td>
<td>MAC</td>
<td>Secreted protein</td>
<td>ELISA</td>
<td>Reduced&lt;sup&gt;34,29&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>PBMC</td>
<td>Staphylococcal enterotoxin</td>
<td>Secreted/surface protein</td>
<td>ELISA/FCW</td>
<td>Increased&lt;sup&gt;98&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>PBMC</td>
<td>Sensitin</td>
<td>CD4&lt;sup&gt;+&lt;/sup&gt; IFN-γ T cells</td>
<td>FCW</td>
<td>Increased&lt;sup&gt;98&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Whole blood</td>
<td>MAC</td>
<td>Secreted protein</td>
<td>ELISA</td>
<td>Reduced&lt;sup&gt;30&lt;/sup&gt;</td>
</tr>
<tr>
<td>IL-17</td>
<td>Lymphocytes</td>
<td>MAC-activated MDM</td>
<td>Secreted protein</td>
<td>ELISA</td>
<td>Reduced&lt;sup&gt;32&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>PBMC</td>
<td>Staphylococcal enterotoxin</td>
<td>Secreted protein</td>
<td>ELISA</td>
<td>Reduced&lt;sup&gt;98&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>PBMC</td>
<td>Staphylococcal enterotoxin</td>
<td>Surface protein</td>
<td>FCW</td>
<td>Reduced&lt;sup&gt;98&lt;/sup&gt;</td>
</tr>
<tr>
<td>IL1-β</td>
<td>PBMC</td>
<td>LPS</td>
<td>Secreted protein</td>
<td>ELISA</td>
<td>Reduced&lt;sup&gt;17&lt;/sup&gt;</td>
</tr>
<tr>
<td>IL-10</td>
<td>PBMC</td>
<td>PPD</td>
<td>Secreted protein</td>
<td>ELISA</td>
<td>Increased&lt;sup&gt;92,98&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>PBMC</td>
<td>Tuberculin and sensitin</td>
<td>Secreted protein</td>
<td>ELISA</td>
<td>Increased&lt;sup&gt;98&lt;/sup&gt;</td>
</tr>
<tr>
<td>TGF-β</td>
<td>Whole blood</td>
<td>Live MAC</td>
<td>Secreted protein</td>
<td>ELISA</td>
<td>Increased&lt;sup&gt;92&lt;/sup&gt;</td>
</tr>
<tr>
<td>Eosinophil count</td>
<td>PB</td>
<td>Nil</td>
<td>Eosinophil count</td>
<td>Cell counting</td>
<td>Compared with MTB, higher in NTM-LD&lt;sup&gt;31&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Abbreviations: ELISA, enzyme-linked immunosorbent assay; FCW, flow cytometry; IFN-γ, interferon-gamma; IL, interleukin; LTA, lipoteichoic acid; MAC, *Mycobacterium avium* complex; MDM, monocyte-derived macrophage; MTB, *M. tuberculosis*; PB, peripheral blood; PBMC, peripheral blood mononuclear cell; PPD, purified protein derivatives; qPCR, quantitative polymerase chain reaction; SEB, Staphylococcal enterotoxin B; TLR, toll-like receptor; TGF-β, transforming growth factor-beta; TNF-α, tumor necrosis factor-alpha.
Bronchiectasis might be secondary to NTM but their relationship are like chicken and egg. Regardless of the cause of bronchiectasis, its sequelae are poor airway clearance and decreased local immunity that promotes NTM growth. In preliminary data obtained from the US Bronchiectasis Research Registry, history of NTM disease or NTM isolated at baseline evaluation existed in as many as 63% of patients with bronchiectasis. A registry may result in selection bias, but using a prospective cohort of 6274 patients with bronchiectasis in Europe, NTM species from respiratory tracts were detected in only 1.7% of the patients with bronchiectasis over 7 years of follow-up. Because a mycobacterial culture was checked only for 30% patients, a prevalence of 1.7% may be an underestimation. A Spanish study revealed the prevalence of NTM isolation in a screening of patients with bronchiectasis but without CF to be 8.3%; in these patients, NTM-LD prevalence was 2.3%.

Table 2 Host factors associated with nontuberculous mycobacteria—lung disease (NTM-LD).

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Dysfunction type</th>
<th>Disease representative</th>
<th>Population size, general</th>
<th>Population size, Taiwan</th>
<th>Association with NTM-LD</th>
<th>Treatable/controllable?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defense defect of pulmonary physiology and clearance</td>
<td>Ciliary defect</td>
<td>Primary ciliary dyskinesia</td>
<td>12,000 to 17,000 in Norway and Japan; 3% in bronchiectasis in the United States</td>
<td>Rare</td>
<td>NTM isolation has been reported as 1.1–1.9%</td>
<td>No</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td></td>
<td>Prevalence 94.8 per 100,000 population</td>
<td>Prevalence 130 per 100,000 population</td>
<td>1.7%–8.3% with NTM isolation and 0.48%–2.3% met microbiologically defined NTM-LD; OR of 2.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inspissated secretion</td>
<td>Cystic fibrosis</td>
<td>30,000 people in the United States</td>
<td>Very rare</td>
<td>3%–13% NTM-LD has been reported in patients with CF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structural lung change</td>
<td>Cartilage and elastin deficiency in airway</td>
<td>Bronchiectasis COPD</td>
<td>Rare</td>
<td>No adequate data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrophage dysfunction</td>
<td>Pulmonary alveolar proteinosis</td>
<td>40 cases per million</td>
<td>Rare</td>
<td>No large study. Might be compatible with COPD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune suppression</td>
<td>Immune deficiency in lung</td>
<td>ICS</td>
<td>Common drug</td>
<td>Common drug OR of 1.86–2.74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune suppression</td>
<td>Systemic immune deficiency</td>
<td>Anti-TNF-α therapy</td>
<td>Not uncommon; approximately 0.4%</td>
<td>Not uncommon OR of 2.19</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; NTM, nontuberculous mycobacteria; LD, lung disease; OR, odds ratio; TNF-α, tumor necrosis factor-alpha.

patients. Bronchiectasis might be secondary to NTM but their relationship is like chicken and egg. Regardless of the cause of bronchiectasis, its sequelae are poor airway clearance and decreased local immunity that promotes NTM growth. In preliminary data obtained from the US Bronchiectasis Research Registry, history of NTM disease or NTM isolated at baseline evaluation existed in as many as 63% of patients with bronchiectasis. A registry may result in selection bias, but using a prospective cohort of 6274 patients with bronchiectasis in Europe, NTM species from respiratory tracts were detected in only 1.7% of the patients with bronchiectasis over 7 years of follow-up. Because a mycobacterial culture was checked only for 30% patients, a prevalence of 1.7% may be an underestimation. A Spanish study revealed the prevalence of NTM isolation in a screening of patients with bronchiectasis but without CF to be 8.3%; in these patients, NTM-LD prevalence was 2.3%.

**Inspissated secretion**

CF is common inherited disorder among Caucasians with the autosomal recessive pattern and affects approximately 30,000 people in the United States, with approximately 900–1000 cases reported to be newly diagnosed each year. By contrast, CF is considered rare among Asians. There is considerable variation in the incidence reported
for native Asians, mainly from small retrospective studies: 1 in 2000 individuals to 1 in 350,000 individuals. To date, few cases of CF have been reported in Taiwanese individuals. Among the Caucasian patients with CF, 3%—13% have been reported to have NTM-LD.

Pulmonary structural change

Similar with PCD, diseases related to pulmonary structural changes may lead to poor airway clearance. The diseases associated with changes in airway are caused by congenital and acquired disorders, described subsequently.

Congenital disease. Cartilage deficiency in the airway (e.g., Williams–Campbell syndrome [WCS]), and elastin deficiency in the airway (e.g., Mounier–Kuhn syndrome) are two examples of congenital disease. In WCS, the bronchi are defective; it is a rare form of congenital cystic bronchiectasis, which may lead to collapse of the airway and thus bronchiectasis. Mounier–Kuhn syndrome is characterized by marked tracheobronchial dilation (tracheobronchomegaly) and is a rare clinical condition causing recurrent infections in the lower respiratory tract.

Alpha-1 antitrypsin deficiency (AATD) is an inherited autosomal codominant disorder that leads emphysema and bronchiectasis, and its prevalence varies by population. Recently, macrophage dysfunction during AATD has been reported during NTM-LD. For individuals with European ancestry, this disorder affects approximately 3—5 in 1500 persons. It is uncommon in Asians, and only case reports of AATD in Taiwan have been published. The onset of lung problems occurs typically between the ages of 20 and 50 years. NTM, especially rapidly growing mycobacteria, were reported to be associated with AATD. A synthetic inhibitor of serine proteases and alpha-1 antitrypsin has reportedly suppressed M. abscessus infection in in vitro studies using monocyte-derived macrophages.

Acquired disease. Of the acquired diseases other than the previously described bronchiectasis, chronic obstructive pulmonary disease (COPD) is the most common, with a frequency only second to those of pulmonary tuberculosis infection (odds ratio [OR] = 178.3) and bronchiectasis (OR = 187.5). COPD coexists with NTM-LD in as many as 14%—39% of NTM-LD cases. COPD prevalence is as high as 6.1% in Taiwan, 9.9% in the United Kingdom, and 14.3% in Latin America. The association between COPD and NTM-LD is positive (OR = 10—15.7). In Taiwan, a recent multicenter study on NTM-LD demonstrated COPD to be an independent risk factor for NTM-LD (OR = 1.17).

Tuberculosis might coexist with NTM-LD in around 2%. Previous tuberculosis (OR: 9.6) and premorbid focal radiological scarring (OR: 7.4) are additional significant risk factors for NTM-LD. The OR may vary according to differences in local NTM prevalence and ethnicity. In addition, lung cancer and lung transplantation are reportedly associated with NTM-LD. Lung transplantation is an effective treatment for poor respiratory reserve, but NTM-LD is a concern both before and after transplantation. In one study, NTM were isolated from five patients (22.4%) in a median follow-up of 25 months, and the NTM-LD incidence was 1.1 per 100 persons per year. The NTM-LD prevalence in lung transplantation recipients has been found to be 1.5%—22.4% in other case series.

Macrophage dysfunction

Pulmonary alveolar proteinosis (PAP) is an uncommon disease caused by defective surfactant clearance of alveolar macrophages. Approximately 90% of PAP cases have autoimmune pathogenesis. The incidence varies among countries from 4 to 40 cases per 1 million people. MAC was isolated from 8 of 19 patients with PAP in one study.

Others

Gastrointestinal reflux disease (GERD) is characterized by the reflux of stomach content. It is associated with various lung diseases, including chronic bronchitis, bronchiectasis, and bronchial asthma as well as NTM-LD. The normal mucosa of the bronchial epithelium is broken once gastric juice has been aspirated, and chronic bronchial inflammation ensues. Recent studies have reported that 26%—44% of patients with NTM-LD have GERD, and GERD is more common in patients with NTM than in people without NTM. Of patients with MAC-LD, aspiration was suspected in 15.5%—higher than that in patients without MAC-LD. Autoimmune diseases are associated with NTM-LD and have been reported mostly in rheumatoid arthritis and Sjögren syndrome. NTM-LD risk may be complex and comprise lung involvement due to autoimmune disease, the use of immunosuppressive drugs, and disease-related immune dysfunction. Approximately 10% of patients with rheumatoid arthritis also have rheumatoid lung disease, which causes bronchiolitis and bronchiectasis, both of which are risk factors for NTM infection. The OR for NTM-LD in patients with rheumatoid arthritis was 2.07 in Canada, 6.24-fold higher than that for nondisease controls in a Taiwanese report. Patients with Sjögren syndrome were more likely to develop NTM-LD than controls (hazard ratio = 17.77).

Immune deficiency

In addition to pulmonary structural changes, immune suppression is another host factor correlated with NTM-LD.

Immune suppression in lungs

Inhaled corticosteroids (ICSs) are recommended to patients with severe COPD and asthma to decrease exacerbation of their condition. However, ICS therapy increases the likelihood of pneumonia. Under ICS therapy, pulmonary tuberculosis risk is also increased, as is the occurrence of NTM-LD. Brode et al. reported that NTM-LD was associated with current ICS use compared with nonuse (adjusted OR = 1.86—2.74). The OR for NTM-LD increases according to ICS dose. Therefore, patients receiving ICS therapy are considered to have an underlying risk of NTM-LD.

Systemic immune deficiency

Immunocompromised status is usually acquired. NTM-LD is significantly associated with anti-TNF-α therapy.
that approximately 0.5%–1.0% of the US population has rheumatoid arthritis and almost 40% of these individuals receive anti-TNF-α therapy, NTM-LD risk is becoming of concern. In addition, new biological agents are being developed and used each year. Therefore, patients receiving anti-TNF-α therapy have higher NTM-LD incidence than do other patient groups. M. avium is the most common species. In another study, NTM disease was found to be more likely to develop in patients undergoing anti-TNF-α therapy (compared with nonuse; adjusted OR = 2.19).

Diseases and therapies that reduce cell-mediated immunity—such as organ transplantation, AIDS with CD4+ T-cell depletion, and corticosteroid use—increase NTM-LD risk. MAC remains the most frequent cause of NTM-LD, but rapid growing mycobacteria are important in skin- and catheter-related infections.

Survey risk for NTM-LD

When NTM-LD is diagnosed, a further risk factor survey, performed using a history and medication review and general study, is suggested (Fig. 1). For correctable factors such as cigarette smoking, we suggest cessation of smoking or the corresponding action. For environmental mycobacteria, evidence regarding surveys of environmental mycobacteria and the strategy of avoidance is lacking. However, we suggest that shower heads are cleaned, bathrooms are kept dry, and exposure to high-risk water and soil is avoided, because such practices may theoretically protect patients from NTM infection. In addition, use of surgical masks for the population with risk for NTM-LD is suggested when having exposure to environmental NTM although the evidence is lacking. If controllable risk factors exist, such as ICS and anti-TNF-α therapy use, it is crucial to judge the advantages and disadvantages and explore alternative options to modify the risks posed by the medications and disease. The results of immunological and genetic studies have mostly not yet been established. Regarding bronchiectasis or previous tuberculosis, secondary infection can be prevented through vaccination; moreover, elimination of the vicious cycle of bronchiectasis progression should be considered when performing routine care. For patients without known risk factors, nutrition and body weight control are suggested; although the evidence is scarce, such control is theoretically favorable and harmless.

Summary

NTM-LD pathogenesis requires the exposure to a sufficient number of environmental mycobacteria and it depends on host risk factors. NTM has been found to evade lung and immune cell mechanisms; nevertheless, host vulnerability may also play a role in NTM-LD pathogenesis. Moreover, pulmonary structural changes and immunosuppression increase NTM-LD risk. In patients without comorbidities, host immune response, particularly Th1 and innate immune responses, are attenuated, and this may have an effect on NTM-LD pathogenesis. However, the specific immune defects responsible for host vulnerability and the causal relationship between NTM and immune response require elucidation. After NTM-LD is diagnosed, risk factors should be identified and corrected or controlled as much as possible concurrently when anti-NTM treatment is commenced.

Author contributions

Shu CC, Wu MF, and Wu TS conceptualized this review. Shu CC, Wu MF, Pan SW, Lai HC, Wu TS, and Lin MC were involved in manuscript preparation. Professors Wu TS and Lai HC were responsible for coordination.

Declaration of Competing Interest

The authors do not have any conflicts of interest to declare.
Acknowledgements

This work is supported by Taiwan Society of Pulmonary and Critical Care Medicine, Chang Gung Medical Foundation (Grant No. CMRP3G3E1141), and National Taiwan University Hospital (Grant No. 107-5388S and 109-5452).


