REVIEW

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Infection Source and Epidemiology of Nontuberculous Mycobacterial Lung Disease

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Nontuberculous mycobacteria (NTM) are ubiquitous organisms that are generally found not only in the natural environment but also in the human engineered environment, including water, soil, and dust. These organisms can form biofilms and can be readily aerosolized because they are hydrophobic owing to the presence of the lipid-rich outer membrane. Aerosolization and subsequent inhalation were the major route of NTM lung disease. Water distribution systems and household plumbing are ideal habit for NTM and the main transmission route from natural water to household. NTM have been isolated from drinking water, faucets, pipelines, and water tanks. Studies that used genotyping have shown that NTM isolates from patients are identical to those in the environment, that is, from shower water, showerheads, tap water, and gardening soil. Humans are likely to be exposed to NTM in their homes through simple and daily activities, such as drinking, showering, or gardening. In addition to environmental factors, host factors play an important role in the development of NTM lung disease. The incidence and prevalence of NTM lung disease are increasing worldwide, and this disease is rapidly becoming a major public health problem. NTM lung disease is associated with substantially impaired quality of life, increased morbidity and mortality, and high medical costs. A more comprehensive understanding of the infection source and epidemiology of NTM is essential for the development of new strategies that can prevent and control NTM infection.

Keywords: Nontuberculous Mycobacteria; Biofilms; Epidemiology; Lung Diseases

Introduction

The term nontuberculous mycobacteria (NTM) generally refers to mycobacteria species other than the *Mycobacterium tuberculosis* complex and *M. leprae*[1,2]. Although, NTM were first identified in the late 19th century, NTM were not widely recognized as a cause of human disease until the late 1950s[3]. They have been called by various names including "atypical mycobacteria," "environmental mycobacteria," and "mycobacteria other than tuberculosis." As these names imply, NTM disease have received less attention than tuberculosis (TB) and were considered as a minor disease.

Currently, NTM, which are evidently different from *M. tuberculosis*, have emerged as important pathogens worldwide[4,5]. The incidence and prevalence of NTM diseases are increasing, and their impact on human health has been a topic of interest. The diagnosis and treatment of NTM lung disease remains challenging for clinicians[6]. Microbiological eradication using the currently available dugs is difficult[7]. Furthermore, microbiological recurrence is common even after a successful treatment, with a substantially high reinfection rate[8-10]. Therefore, to appropriately prevent and treat NTM diseases, the infection sources and epidemiology of NTM infection should be understood.

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Infection Source

1. Environmental source of infection

1) Natural environment

NTM are naturally occurring environmental pathogens. These organisms have been isolated from natural water, including rivers, lakes, swamps, and streams, as well as soil (Table 1)[11,12]. NTM have a lipid-rich outer membrane[13], which is a key factor in its survival and proliferation in the natural environment[11]. As an effect of the lipid-rich outer membrane, these organisms are resistant to acid[14], antibiotics[15], disinfectants[16], and high temperature[17]. NTM can survive within amoebae[18]. These pathogens are quite hydrophobic due to their lipid-rich outer membrane and prefer to attach to surfaces and subsequently form biofilms[19]. NTM are readily aerosolized from natural water and soils due to its surface hydrophobicity[20]. Naturally occurring aerosolization and subsequent inhalation were the major route of NTM lung disease.

Epidemiology studies have supported the claims that environmental factors could affect the risk for NTM lung disease. In the United States, eight of 55 states were identified as hot spots, with a high incidence of NTM lung disease[21]. The eight states had a higher mean daily potential evapotranspiration levels and percentages covered by surface water and were more likely to have greater copper and sodium levels in the soil[21]. Another study on a registry of patients with cystic fibrosis has reported that high saturated vapor pressure is associated with the increased prevalence of NTM lung disease[22].

Table 1. Source of nontuberculous mycobacteria

Natural environment
Natural water in lakes, rivers, streams, and swamps
Soils and dust from soils
Household environment
Household plumbing systems
Drinking water and distribution systems
Shower heads and faucets
Hot tubs, spas, hydrotherapy pools, and footbaths
Humidifiers
Refrigerator water and ice
Garden and potting soils
Hospital environment
Hospital plumbing systems
Hospital water and distribution system
Contaminated medical device: heater-cooler devices
Filter and ice machines

2) Household environment

NTM are widely distributed in human engineered and household environment. Water distribution systems are thought to be a main transmission route from natural surface water reservoirs to the household. NTM have been isolated from drinking water pipelines[23,24] and water tanks[25]. The number of NTM increases by 2-fold in a drinking water distribution system, that is, from the treatment plant to the end user[26]. Cell surface hydrophobicity is a major determinant of the survival and proliferation of NTM in the water distribution systems. These organisms can attach to pipe surfaces and form biofilms, which prevents them from being flushed from the water distribution system. Furthermore, NTM are more resistant to common water disinfectants, such as chlorine, than other microorganisms. Therefore, the use of disinfects kills off competitors and selects NTM.

Household and building plumbing systems provide a stable, nutrient-limited, disinfectant-containing habitat that is ideal for NTM growth and persistence. As NTM are relatively resistant to high temperature, these organisms can survive in water heaters and hot water pipes. Households with water heater temperatures <50°C were more likely to yield NTM (17/20, 85%) than those with water temperature >55°C (6/15, 40%)[27]. Numerous studies have shown that showerheads and tap water as well as the end points of drinking water distribution systems are the reservoirs of NTM in the household[28]. Studies that used genotyping have shown that NTM isolates from patients are identical to those in the environment, that is, from shower water[29,30], showerheads[31], and household tap water[32].

NTM species have been isolated from house dust[33] and soils[34]. Dry potting soil is a problem because the soil particles can be aerosolized during gardening, and thus, an individual can inhale these particles. DNA fingerprinting methods have shown that NTM isolates from a patient and those from the patient's dried potting and garden soil were identical[34].

3) Hospital environment

NTM are also found in hospital environment. Hospital water distribution system may serve as a reservoir of NTM. These organisms contaminate hospital materials and can cause nosocomial outbreaks and pseudo-outbreaks[35]. Recently, several outbreaks due to *M. chimaera* have occurred from heater-cooler devices used during open-heart surgery[36,37].

2. Transmission

NTM are generally acquired from the environment via ingestion, inhalation, and dermal contact[1,2]. These organisms are everywhere in the human environment and can be readily aerosolized. NTM in household plumbing systems are readily aerosolized from taps, showerheads, and hot tubs. Home humidifiers filled with household water could be a potential generator of a high number of NTM in aerosols[12]. Use of indoor swimming pools has been associated with NTM lung disease among individuals with cystic fibrosis[38]. Dusts generated during potting of plants or gardening are also likely sources of NTM infection. Humans are likely to be exposed to NTM in their homes through simple daily activities, such as drinking, showering, or gardening[39]. The most common routes for pulmonary NTM infection involve the inhalation of aerosols generated by hot tubs and showerheads. Indeed, the global increase in NTM infections may reflect the use of showers rather than bathing[40].

1) Human to human transmission

Traditionally, it was believed that human-to-human NTM transmission is not possible. Whole genome sequencing, a new molecular technique, has provided the first genetic evidence of human-to-human transmission of *M. abscessus* complex among patients with cystic fibrosis[41,42]. Bryant et al.[42] have performed a whole genome sequencing analysis of 1,080 clinical isolates of *M. abscessus* complex obtained from 517 patients from cystic fibrosis centers in seven countries. Results have shown that most *M. abscessus* complex infections were acquired via human-to-human transmission, potentially via fomites and aerosols.

3. Preventive measure

Strategies that are effective in preventing NTM lung disease are still limited. Vaccines and prophylaxis medications are not available. Unlike TB, preventive therapy is only recommended in patients with advanced human immunodeficiency virus (HIV) disease. A more comprehensive understanding of NTM transmission can help in establishing targeted prophylactic measures. Some preventive measures are recommended to avoid NTM exposure and reduce the number of NTM in the household[12]. Although the efficacy of these recommendations has not yet been validated via clinical trials, these are still helpful for vulnerable individuals with a high risk for infection.

Preventive measures recommended by experts are the following[12]: (1) raise hot water temperature to 55°C; (2) use bacteriologic filters (pore size <0.45 mm) on taps and showerheads; (3) utilize well water rather than piped utility supply; (4) clean and disinfect showerheads regularly to remove the biofilm; (5) use showerheads with large holes to reduce mist formation; (6) avoid spas and hot tubs or any water with an aerator; (7) increase bathroom exhaust rate; (8) boil drinking water for 10 minutes to kill NTM; (9) wear mask when gardening; and (10) moisten garden and potting soils.

Epidemiology

1. Incidence and prevalence of NTM

The identification of the epidemiology of NTM lung disease has been challenging because reporting of cases is not mandatory in most countries. Furthermore, diagnosis is difficult because simple isolation of the organism does not necessarily indicate the actual lung disease. Various epidemiological methodologies have been used, including surveillance, population-based studies, analysis of large linked datasets, studies that used laboratory-based convenience samples, and combinations of these approaches[43].

Numerous studies have shown that the incidence and prevalence of NTM lung disease are increasing worldwide[44]. Population-based data from the United States[45], Canada[46], the United Kingdom[47], and Australia[48] have shown that the prevalence of NTM lung disease has been increasing. Large tertiary care facility-based studies in East Asian countries, including Japan[49], Taiwan[50], and South Korea[51,52], have also suggested an increasing prevalence of NTM lung disease. In South Korea, no population-based study on the epidemiology of NTM lung disease was conducted. Most studies were conducted in a single institution using laboratory-based convenience samples. Those studies have consistently shown that the proportion

Table 2. Changes in the proportions of nontuberculous mycobacteria among mycobacterial isolates from clinical respiratory specimens in South Korea

Study	Hospital	Study period	Proportion of nontuberculous mycobacteria	
			Start of study period	End of study period
Park et al. (2010)[53]	Seoul National University Hospital	2002–2008	427/1,921 (22%)	781/1,701 (46%)
Lee et al. (2012)[54]	Severance Hospital	2006–2010	268/1,041 (26%)	970/2,064 (47%)
Yoo et al. (2012)[55]	Asan Medical Center	2002–2010	403/1,921 (21%)	1,530/2,648 (59%)
Koh et al. (2013)[56]	Samsung Medical Center	2001–2011	548/1,283 (43%)	3,341/4,800 (70%)
Kim and Rheem (2013)[57]	Dankook University Hospital	2005–2011	26%	44%
Lee et al. (2014)[58]	Ulsan University Hospital	2010–2013	25%	38%
Kim et al. (2017)[59,*]	Pusan National University Hospital	2009–2015	24.8%	44.8%

*This study included both respiratory and non-respiratory specimens.

of NTM among positive mycobacterial cultures is increasing (Table 2)[53-59]. In a 10-year observational study[56], the proportion of NTM among all positive mycobacterial cultures increased from 43% in 2001 to 70% in 2011. Furthermore, the recovery rate of NTM isolates from acid-fast bacilli smear-positive specimens increased from 9% in 2001 to 64% in 2011. This finding has suggested that early differentiation between pulmonary TB and NTM lung disease has become a clinically important issue in South Korea due to the increasing incidence and prevalence of NTM lung disease. Recently, Yoon et al.[60] have reported a nationwide increasing trend in the prevalence of NTM disease from 2009 to 2016 in South Korea based on the claims data of the Health Insurance Review and Assessment Service (Figure 1). Interestingly, the increase in the proportion of NTM lung disease may be associated with a simultaneous decrease in the incidence of TB in most countries[61], including South Korea[60].

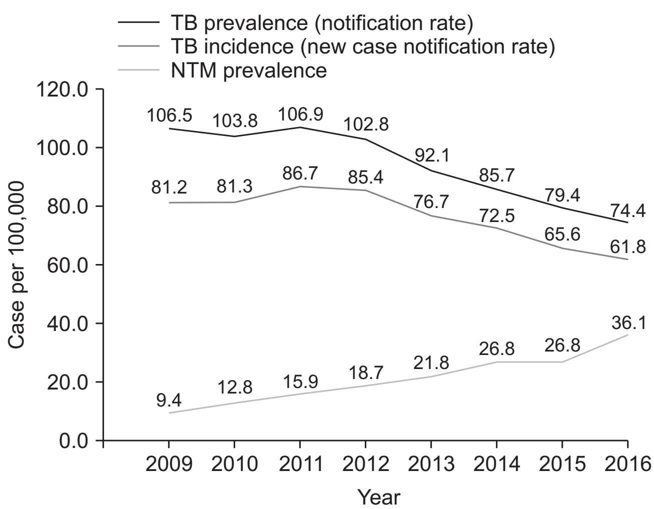

Figure 1. Trend in the prevalence of tuberculosis (TB) and nontuberculous disease from 2009 to 2016 in South Korea. NTM: nontuberculous mycobacteria. Adopted from Yoon et al. BMC infect Dis 2017;17:432, according to Creative Commons license[60].

2. Species distribution

The distribution of NTM species varies by region and country. This geographical diversity can provide important clues to identify factors associated with the acquisition of NTM infection, such as geographic factors, population density, or host factors. In 2008, the NTM-Network European Trials Group provided species identification data for 20,182 patients from 62 laboratories in 30 countries[62]. This study has shown that the *Mycobacterium avium* complex (MAC) predominated in most countries. However, there were important differences in the geographical distribution of *M. xenopi*, *M. kansasii*, and other rapid-growing mycobacteria. *M. xenopi* and *M. malmoense* were extremely rare in East Asia. However, they are predominantly found in Europe.

In South Korea, the MAC is the most common organism causing NTM lung disease (Table 3)[53,54,58,60,63-65], which is similar to other countries. *M. abscessus* complex is the second most common organism, whereas *M. kansasii* does not commonly cause the disease. However, *M. kansasii* was the second most common NTM species in Ulsan[58].

3. Risk factor

Exposure to NTM is quite common. However, NTM disease is relatively rare. This observation suggests that host susceptibility likely plays a key role in the development of NTM lung disease. Patients who develop NTM lung disease usually have

Table 3. Etiologic species of nontuberculous mycobacterial lung disease in South Korea

	Koh et al. (2006)[63]	Park et al. (2010)[53]	Lee et al. (2012)[54]	Jang et al. (2014)[64]	Lee et al. (2014)[58]	Kim et al. (2014)[65]	Yoon et al. (2017)[60]
Study period	2002–2003	2002–2008	2006–2010	2012	2010–2013	2007–2011	2011–2016
No. of patients	195	651	345	111	245	90	64
Mycobacterium avium complex	94 (48)	NA (63)	263 (76)	73 (66)	132 (54)	61 (68)	29 (45)
M. avium	38	NA	141	32	39	42	13
M. intracellulare	56	NA	122	41	93	19	16
M. abscessus complex	64 (33)	NA (27)	63 (18)	32 (29)	22 (9)	15 (17)	27 (42)
M. abscessus	NA	NA	NA	21	NA	11	NA
M. massiliense	NA	NA	NA	11	NA	4	NA
M. kansasii	7 (4)	NA	7 (2)	1 (1)	80 (33)	1 (1)	4 (6)
Others	30 (15)	NA (10)	12 (3)	5 (5)	11 (4)	13 (14)	4 (6)

Values are presented as number (%).
NA: not available.

some degree of host impairment that make them vulnerable to these infections. NTM lung disease is more prevalent in patients with structural lung disease, such as cystic fibrosis, non-cystic fibrosis bronchiectasis, primary ciliary dyskinesia, chronic obstructive pulmonary disease (COPD), previous TB, and pneumoconiosis[66]. An immunosuppressed status, which is related to HIV infection, transplantation, or the use of tumor necrosis factor α inhibitor, is also associated with NTM disease[66].

However, patients can develop NTM lung disease without any obvious underlying cause. These patients are typically postmenopausal women who have a unique body morphotype[67,68]. Recently, a whole-exome sequencing study has begun to identify genetic predispositions for those patients and found an increased prevalence of genetic mutations that control the function of the immune system, ciliary body, and connective tissues[69]. This suggests that NTM lung disease is a multigenic disease, which is characterized by a combination of variants across gene categories and environmental exposures that increase susceptibility to infection.

4. Impact on public health

The impact of NTM infection on public health has been underestimated. Generally, NTM have been considered to have a low pathogenicity, and it was believed that these organisms cannot be transmitted from person to person. However, NTM lung disease is associated with a substantially impaired quality of life[70], increased morbidity and mortality[71], and high medical costs[43]. Huang et al.[72] have shown that patients with COPD who have NTM isolates had a greater decline in lung function and more frequent exacerbation than those with no isolate. Park et al.[73] have shown that treatment failure was associated with a substantial decline in lung function in individuals with NTM lung disease. A recent study in Germany have revealed that a higher mortality, direct costs, and indirect costs were observed among patients with NTM lung disease than in matched controls[74]. Considering the increasing burden of NTM lung disease globally, this disease may soon become a significant health and economic burden.

Conclusion

NTM are generally found not only in the natural but also in the human engineered environment. Remarkable changes in the human environment and lifestyle habits were observed during the past several decades. These changes have made humans more comfortable but also resulted in a more favorable environment for NTM growth. In addition, with the development of medicine, an aging population with multiple comorbidities who are vulnerable to NTM infection is growing rapidly. As a result, the incidence and prevalence of NTM lung disease are increasing worldwide, and this disease is rapidly becoming a major public health problem. NTM lung disease is more difficult to treat and prevent than TB. The elimination of NTM from environmental sources and the destruction of the transmission route are critical issues that must be urgently addressed. Further comprehensive works to investigate the source, transmission route, and epidemiology of NTM are needed to develop new strategies that can prevent and control NTM infection.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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