Nonpharmacological Treatment for Nontuberculous Mycobacterial Pulmonary Disease

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Hyung-Jun Kim, M.D.[1,2]
[1]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, [2]Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea

Address for correspondence
Hyung-Jun Kim, M.D.
Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul National University Bundang Hospital, 82 Gumi-ro 173beon-gil, Bundang-gu, Seongnam 13620, Republic of Korea
Phone 82-31-787-7844
Fax 82-31-787-4052
E-mail dr.hjkim@snu.ac.kr

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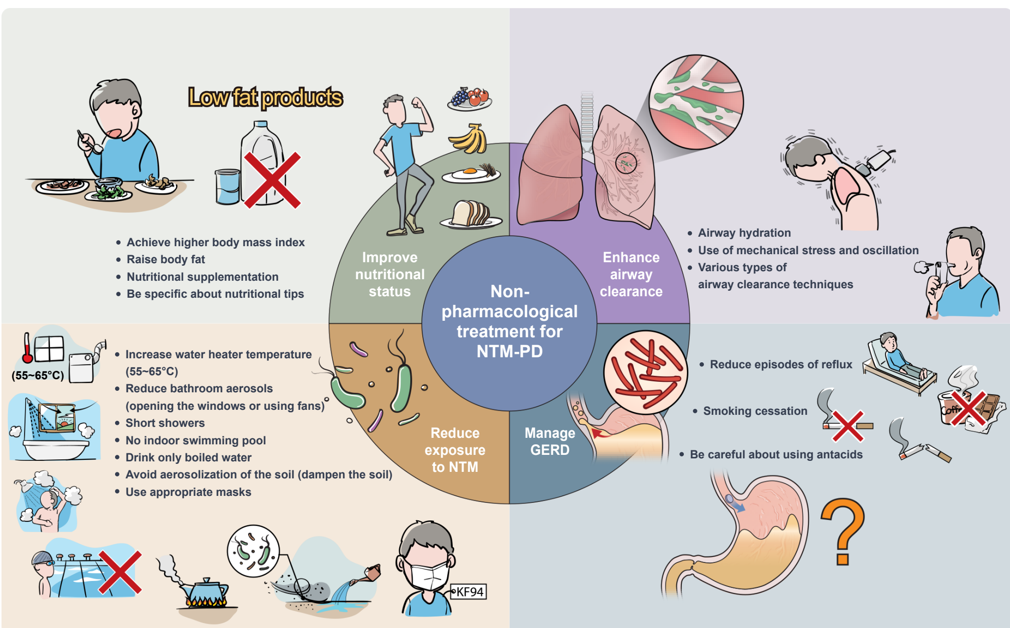


Abstract

Nontuberculous mycobacterial pulmonary disease (NTM-PD) results from the exposure of susceptible hosts to a diverse group of environmental mycobacteria. The emphasis on nonpharmacological strategies is motivated by the widespread presence of NTM in various environments, and the inconsistent success rates of pharmacological treatments. Modifiable factors contributing to NTM-PD development include impaired airway clearance, low body mass index, gastroesophageal reflux disease, and exposure to NTM habitats. This suggests that lifestyle and environmental modifications could affect disease development and progression. The review highlights several modalities that can modify the risk factors. Airway clearance techniques, informed by the "gel-on-brush" model of the bronchial epithelium, aim to enhance mucociliary clearance, and have the potential to alleviate symptoms and improve lung function. The impact of nutritional status is also examined, with a lower body mass index linked to an increased risk and progression of NTM-PD, indicating the importance of targeted nutritional support. Additionally, the theoretical and epidemiological links between gastroesophageal reflux disease and NTM-PD advocate careful management of reflux episodes. Understanding the risk of NTM transmission through environmental exposure to contaminated water and soil is also crucial. Strategies to mitigate this risk, including effective water management and minimizing soil contact, are presented as vital preventive measures. The review supports the inclusion of nonpharmacological treatments within a comprehensive NTM-PD management strategy, alongside conventional pharmacological therapies. This integrated approach seeks to improve the overall understanding and handling of NTM-PD.

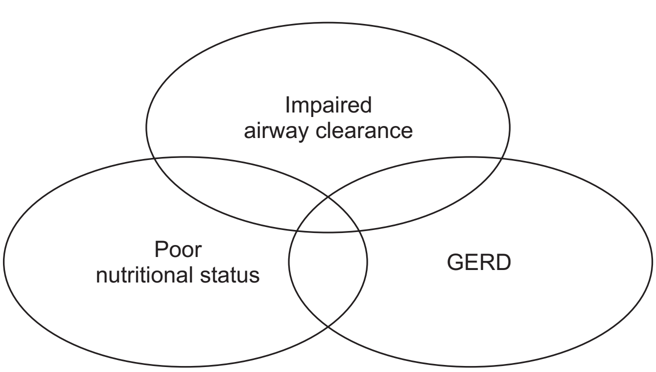
Keywords: Nontuberculous Mycobacteria; Nonpharmacological Management; Lifestyle

Introduction

Nontuberculous mycobacteria (NTM) represent a diverse group of acid-fast bacilli, distinct from tuberculosis and leprosy bacteria, comprising over 200 species[1,2]. Despite this diversity, these organisms are categorized together due to specific phenotypic characteristics. Found in a variety of environmental settings, NTM can cause nontuberculous mycobacterial pulmonary disease (NTM-PD) through interactions between the host, environment, and microbe itself[3,4].

The necessity for nonpharmacological treatment against NTM-PD stems from several reasons. Firstly, the ubiquity of NTM in the environment does not always result in disease. Its presence around and within us was demonstrated in a study that found NTM in the nostrils, buccal samples, oropharynx, and dental plaque of healthy individuals[5]. The factors determining why these individuals do not develop NTM-PD point to the critical role of susceptible phenotypes, including impaired airway clearance, weakened immune responses, and other risk factors, like gastroesophageal reflux disease (GERD)[6]. This suggests that modifiable factors could alter the disease course (Figure 1).

Figure 1. Modifiable host risk factors for development of nontuberculous mycobacterial pulmonary disease. GERD: gastroesophageal reflux disease.



Secondly, the results from pharmacological treatments are less than satisfactory. The treatment success rates for *Mycobacterium abscessus* pulmonary disease and *Mycobacterium avium* complex pulmonary disease (MAC-PD) are relatively low, ranging 33% to 60%, depending on the species[7,8]. Compounded by the adverse effects of anti-NTM drugs, patient adherence to guideline-based therapies is challenging. A study of 1,038 MAC-PD patients in the United States noted adverse effects in 21% of therapy recipients, with 33% discontinuing therapy[9]. Given that microbiological cure correlates with better prognosis in MAC-PD[10], employing every possible strategy is essential.

Third, the process for species identification and drug susceptibility testing is time-consuming. Different NTM species exhibit varying levels of virulence and pathogenicity, making species identification crucial for selecting appropriate treatment regimens[11-13]. This period of uncertainty underscores the need for patient education on appropriate behavior during the diagnostic interval.

Fourth, NTM-PD exhibits a variable clinical course. Studies have shown that a significant portion of patients with MAC-PD remain stationary without treatment, and some patients with *M. abscessus* pulmonary disease experience spontaneous culture conversion[14,15]. Although major guidelines recommend initiating treatment rather than observation[1,2,16], watchful waiting supplemented by nonpharmacological strategies can be a viable strategy, considering the high rates of adverse reactions to antibiotics.

Despite the lack of specific recommendations in major guidelines for nonpharmacological treatment strategies against NTM-PD, evidence from observational studies and trials of similar diseases, like tuberculosis and bronchiectasis, provides valuable insights. Conducting randomized controlled trials for NTM-PD is challenging, due to ethical concerns regarding the omission of nonpharmacological advice to patients, and the inherently low-risk nature of these treatments, which are intuitively beneficial. This review aims to recommend several nonpharmacological treatment strategies that are potentially beneficial for managing patients with NTM-PD (Tables 1, 2).

Airway Clearance Techniques

Several known host factors increase the risk of developing NTM-PD. These include underlying lung disease, impaired airway clearance, weakened immune response, low body mass index (BMI), female sex, and GERD[17-20]. Among them, only a few are modifiable, with impaired mucus clearance from the airways being a major modifiable risk factor.

The bronchial epithelia comprise a “gel-on-brush model,” which consists of a mucus layer (gel) and a periciliary layer (brush)[21]. When the concentration of the gel exceeds that of the brush, the cilia are compressed by osmotic pressure, leading to impaired airway clearance. Compared to normal controls, sputum from patients with bronchiectasis has a higher solid percentage, mucin, and osmotic pressure; however, the expression of mucin genes does not increase[22]. This suggests that hydrating the mucus could lower the concentration of “gel,” which can facilitate better airway clearance. Introducing mechanical stress on the airway epithelia is crucial to promote hydration. In particular, oscillatory stress has been shown to stimulate airway surface hydration and enhance mucociliary transport rates[23,24].

The application of mechanical stress to the airway epithelia has resulted in various airway clearance techniques[25]. Although these techniques may vary, the core mechanism involves creating oscillations to induce shear forces on the mucus layer, and generating back-pressure that opens the airways and improves the delivery of air behind the mucus[26]. A randomized crossover study involving 20 patients with noncystic fibrosis bronchiectasis concluded that the use of an oscillating positive expiratory pressure device led to decreased cough and increased exercise capacity, as well as greater sputum production, indicating enhanced airway clearance[27]. An observational retrospective review of 77 patients with NTM-PD found that airway clearance techniques were associated with improvements in cough, sputum production, and total lung capacity[28]. In practical terms, implementing pursed-lip breathing, huffing, active cough training, manual chest percussion, and the use of an oscillating positive expiratory pressure device can be effective.

Nutritional Support

Lower BMI is associated with higher incidence of NTM-PD[20]. Patients with NTM-PD often experience lifelong thinness, which is attributed to increased metabolic demand and anorexia resulting from the symptoms of the disease and side effects of the medication. While lower BMI is linked to higher disease incidence, it is also one of the major factors leading to poorer prognosis[29]. Studies have shown that patients with NTM-PD have lower body fat, with a notable case-control study in the USA including 204 patients finding this trend in an osteoporosis-dominant group[30]. Another study in South Korea identified that decrease in cholesterol

Table 1. Nonpharmacological strategies to alter the vulnerable host phenotype against NTM-PD

Strategy	Detail
Airway clearance	Airway hydration Use of mechanical stress and oscillation Various types of airway clearance techniques
Nutritional support	Achieve higher body mass index Raise body fat Nutritional supplementation Be specific about nutritional tips
Management of GERD	Reduce episodes of reflux Smoking cessation Be careful about using antacids

NTM-PD: nontuberculous mycobacterial pulmonary disease; GERD: gastroesophageal reflux disease.

Table 2. Methods to reduce exposure to nontuberculous mycobacteria from the environment

Exposure	Methods to reduce exposure
Water	(Abruptly) Increase water heater temperature >55°C to 65°C Reduce bathroom aerosols (opening the windows or using fans) Short showers No indoor swimming pool Drink only boiled water
Soil	Avoid aerosolization of the soil (dampen the soil) Use appropriate masks

level is associated with NTM-PD progression[31]. The relationship between body fat and NTM-PD may be explained by changes in adipokine expression[32]. Leptin, primarily produced by white adipose tissue, enhances the adaptive immune response, activates T-helper 1 cells, and promotes interferon γ release[33]. Conversely, adiponectin, which inversely relates to body fat, reduces tumor necrosis factor α production, a cytokine protective against the host[34].

While direct interventional evidence of nutritional support for NTM-PD is scarce, insights from similar diseases are informative. A study in Spain involving 30 patients with noncystic fibrosis bronchiectasis found that hyper-protein nutrition supplementation (330 kcal with 18 g of protein) improved muscle strength and quality of life[35]. Additionally, a large-scale cluster-randomized controlled trial in India, including household contacts of pulmonary tuberculosis patients, showed that providing food rations (750 kcal with 23 g of protein) reduced tuberculosis incidence by 39%[36].

Given the chronic underweight condition observed in NTM-PD patients, mere advice to “gain weight” may not suffice. Physicians should provide specific guidance, such as limiting non-caloric beverages, increasing caloric intake per meal, and consuming regular high-calorie snacks. Scheduling four to six small, frequent meals or snacks daily is recommended over consuming a single large meal[37]. Regarding protein intake, the advisable 18 to 23 g of protein can typically be met by consuming about four eggs, half a chicken breast, or three cups of milk[38].

Managing GERD

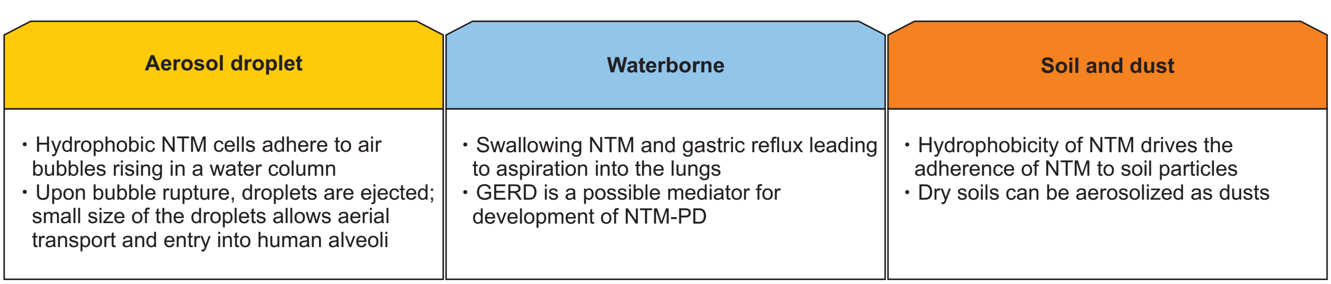
GERD has been linked to an increased incidence of NTM-PD[17]. The transmission of NTM from the environment to humans, particularly through waterborne pathways leading to NTM aspiration into the lungs following gastric reflux, supports this association[39,40]. The inherent resistance of *M. avium* to acidity underlines the potential role of GERD in NTM-PD development[41]. Consequently, the use of antacids, which could theoretically enhance NTM survival by reducing stomach acidity, warrants cautious consideration. A small case-control study found antacid use more common among MAC-PD patients, although causality remains uncertain[42].

Based on the current evidence, several recommendations can be formulated to minimize episodes of gastroesophageal reflux without diminishing stomach acidity. Dietary modifications are essential, specifically avoiding foods known to decrease lower esophageal sphincter pressure. Such foods include alcohol, caffeine, carbonated beverages, chocolate, citrus fruits, coffee, as well as fatty and spicy foods, garlic, onion, peppermint, and tomatoes[37]. Additionally, patients are advised to elevate the head of their bed or to sleep on their left side, which measures can help prevent nocturnal reflux. It is also recommended that after eating, patients remain in an upright position for a period, to allow gravity to assist in the digestion process. Finally, cessation of smoking is strongly recommended, as it can significantly contribute to the reduction of GERD symptoms by improving the function of the lower esophageal sphincter and reducing reflux episodes[37,43].

Reducing Exposure to NTM

Unlike tuberculosis bacteria, which infects only living hosts, NTM is widespread in soil and natural water sources, due to its unique biological characteristics[44]. The lipid-rich, hydrophobic surface of NTM aids in attachment to various surfaces and the formation of biofilms, thereby conferring resistance to disinfectants, antibiotics, and amoebae. Their ability to thrive in environments with low oxygen and carbon concentrations, as well as to withstand high temperatures, enables their survival in hot water systems and recirculating aqua systems.

Figure 2. Mechanisms of transmission of nontuberculous mycobacteria (NTM) from environment to host. GERD: gastroesophageal reflux disease; NTM-PD: nontuberculous mycobacterial pulmonary disease.



NTM may be inhaled in aerosolized form from both water and soil (Figure 2). Studies among Medicare beneficiaries in the United States have identified a higher prevalence of NTM-PD in regions characterized by significant daily evapotranspiration and extensive surface water areas[45]. Additionally, frequent soil exposure (≥2 episodes/week) has been linked to the presence of MAC-PD, compared to controls[46]. Furthermore, NTM is not limited to outdoor environments; indoor exposure also poses a risk. A whole genome sequencing study conducted in South Korea provided concrete evidence of environmental transmission from indoor water sources to patients[47], while another study from the United States revealed a higher presence of NTM in the shower aerosols of MAC-PD patients, compared to controls[48]. Exposure to water sources, such as indoor swimming pools, and rusty or unclear tap water, has also been associated with NTM-PD[49,50].

Several strategies can be employed to minimize exposure to NTM from environmental water sources. One effective method is to heat the water prior to use, as NTM populations are significantly reduced at temperatures exceeding 55°C to 65°C. Given the capacity of NTM to adapt to temperature changes, it may be advantageous to implement sudden alterations in water temperature to ensure its efficacy[51,52]. In regions like South Korea, where home boilers are prevalent, adjusting the hot water temperature to at least 65°C can provide additional safety. While point-of-use filters offer a potential solution, it is important to note that *M. avium* can proliferate in filters if exposed to water for more than 3 weeks[53]. Furthermore, purified bottled water is not immune to NTM contamination[54], suggesting that boiling water remains the most reliable method to ensure its safety from NTM (Table 2).

Mitigating exposure to NTM from environmental soil and dust involves relatively direct measures. Patients are advised to avoid activities that bring them into contact with soil, including gardening, farming, and tending to flowers. When avoidance is impractical, measures should be taken to prevent the aerosolization of soil into dust. Strategies such as moistening the soil with water to reduce dust generation or covering the soil can significantly reduce the risk of NTM exposure. To further reduce the risk of inhalation of dust and aerosols containing NTM, wearing appropriate masks during activities that generate dust can be an effective preventive measure (Table 2).

Conclusion

In this review, a variety of nonpharmacological treatment strategies for NTM-PD were examined. The "gel-on-brush" model highlights the role of hydration in facilitating effective airway clearance, with mechanical stress and oscillation playing key roles in enhancing mucociliary transport. These foundational techniques in airway clearance serve to alleviate symptoms, while also offering the potential to enhance lung function. Furthermore, an observed trend of lower BMI among NTM-PD patients, associated with disease progression, points to a possible link with the altered expression of adipokines. Consequently, nutritional supplementation is presented as a viable strategy, leveraging its established benefits in the management of related conditions, such as bronchiectasis and tuberculosis. The theoretical and epidemiological associations between GERD and NTM-PD underscore the necessity for patients to carefully manage reflux episodes, including the judicious use of antacids. Considering the ubiquitous presence of NTM in diverse environmental settings, implementing strategies to minimize exposure to contaminated water and soil is deemed essential for infection risk reduction. This holistic management approach for NTM-PD advocates the combination of lifestyle adjustments, dietary modifications, and environmental measures alongside conventional pharmacological therapies, aiming to provide a comprehensive strategy for the management of the disease.

Conflicts of Interest

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

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