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Early View

Review

Non-tuberculous mycobacteria pulmonary disease: an integrated approach beyond antibiotics

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Non-tuberculous mycobacteria pulmonary disease: an integrated approach beyond antibiotics

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Summary of the "take home" message: An integrated approach, including risk factors' prevention, management of comorbidities, nutritional evaluation and intervention, and pulmonary rehabilitation should be considered in the optimal management of non-tuberculous mycobacteria pulmonary disease.

Keywords: Non-tuberculous mycobacteria, Non-tuberculous mycobacteria pulmonary disease, nutritional evaluation, comorbidities, pulmonary rehabilitation

Abstract

Non-tuberculous mycobacteria pulmonary disease (NTM-PD) is an emerging condition with heterogeneous manifestations from both the microbiological and the clinical point of view. Diagnostic and therapeutic guidelines are available but unmet patients' and physicians' needs, including therapy-related adverse events, symptom control, management of comorbidities, risk of re-exposure to the pathogen and unfavourable outcomes are still relevant issues.

In the present review, we provide currently available evidence for an integrated approach to NTM-PD beyond antibiotic therapy. This includes: 1) Avoidance of exposure to environments where mycobacteria are present and careful evaluation of lifestyle and habits; 2) Implementation of a personalised pulmonary rehabilitation plan and airway clearance techniques to improve symptoms, exercise capacity, health related quality of life (HRQoL) and functional capacity in daily living activities; 3) A nutritional evaluation and intervention to improve HRQoL and to control gastrointestinal side effects during antimicrobial therapy, particularly in those with low body mass index and history of weight loss; and 4) Management of comorbidities that impact disease outcomes, including structural lung diseases, immune status evaluation and psychological support when appropriate.

Introduction

Non-tuberculous mycobacteria pulmonary disease (NTM-PD) is an emerging condition that affects not only immunocompromised patients but also immunocompetent subjects usually with underlying structural lung diseases [1]. The radiological spectrum varies from cavitations similar to tuberculosis (TB) infection to a bronchiectasis / bronchiolitic pattern (typically expressed as tree-in-bud, bronchial wall thickening and centrilobular nodules with undefined margins). These alterations can be caused by mycobacterial infection in the first instance or be the consequence of a pre-existing anatomical remodelling that favours mycobacterial colonization and later infection. Radiological extent can also vary from diffuse forms to others located in the upper lobes or apical segments of lower lobes and those that preferentially affect the middle lobe and *lingula* (typically the "lady Windermere" phenotype). The clinical manifestations of the disease can also be very heterogeneous and largely dependent on the pathogenicity of the mycobacterium and on the patient's immune status, ranging from paucisymptomatic forms to chronic symptoms such as cough and sputum production, particularly associated with bronchiectasis, and chronic fatigue with weight loss and haemoptysis in the most advanced forms.

Because of the interaction between pathogen-related factors (NTM-specific virulence, bacterial load and exposure) and host-related factors (patient's immune status, pre-existing anatomical changes and comorbidities), Table 1, the spectrum of mycobacterial infections may vary from silent colonization to incipient and overt pulmonary disease when bacterial load increases and dissemination occurs. In this scenario, an integrated approach that includes avoidance of exposure to environments where mycobacteria are present, implementation of respiratory physiotherapy and airway clearance techniques, a nutritional evaluation, particularly in case of low body mass index (BMI) and weight loss, and management of comorbidities, including psychological support when appropriate, should be considered.

In this review, we focus on NTM-PD management considering those aspects that go beyond antibiotic therapy and concentrating on an integrated approach since the early stages of the disease, Figure 1.

Literature search strategy

We conducted a literature search in the English language using the PubMed/MEDLINE and

EMBASE databases including all type of studies up until the end of July 2020. Keywords used to perform the research are reported in Table 2. Conference abstracts were excluded.

1. Behavioural change and education in NTM-PD

NTM are ubiquitous environmental organisms, commonly found in soil and water biofilms. The significant geographic differences in the distribution of NTM species in human isolates depends on several factors, such as the geochemical characteristics of the environment, the climate, the population density, and the presence of specific environmental niches. Soils serve as a large natural source of mycobacteria, and certain soil properties are major determinants of NTM growth and persistence in the environment. Counties at high-risk of NTM-PD have a higher content of copper, sodium, and silt, but low manganese and clay content in the soil [2–4]. High atmospheric water content may also promote NTM growth in soil. In fact, high humidity levels, greater levels of precipitation, warmer temperatures, high daily evapotranspiration (i.e. movement of water from land to the atmosphere by evaporation from the soil and other surfaces and by transpiration from plants) rates, and high percentages covered by surface water are associated with an increased risk of NTM infection [2, 5]. NTM growth and persistence in surface waters is favoured by low pH, water temperature up to 55°C, low dissolved oxygen content, and a high content of salt, soluble zinc, humic acid, and fulvic acid [6–8].

Epidemiologic studies demonstrated that counties at high-risk of NTM-PD were significantly larger, had greater population densities, and higher education and income levels [2]. Living in an urban or in a rural setting has been associated with altered rates and patterns of NTM infection; for example, living in an area of higher population density was associated with *M. kansasii* infection, whereas *M. avium complex* has been associated with living in rural areas [9]. A recent epidemiologic study found a correlation between the incidence of NTM-PD and higher air concentration of particulate matter and benzo[a]pyrene, a polycyclic aromatic hydrocarbon, suggesting that airborne pollution in urban and industrial areas represents a potential risk factor for NTM-PD, probably through the production of reactive oxygen species causing airways chronic inflammation and pulmonary tissue damage [10].

Well-known NTM environmental niches include pine forest (boreal rich) and peat rich soils, water bodies (including lakes, rivers, and streams), brackish marshes, and potable waters [6, 7, 11]. Furthermore, NTM can survive and persist in household and industrial plumbing systems, despite ozonation and filtration, due to the ability of the bacteria to grow at a low

nutrient concentration, associate in biofilms, and chlorine resistance [12, 13]. Studies of the homes of NTM-PD patients have found NTM isolates in showerheads, bathtub water, drain outlets, humidifiers, heating/ventilation systems, bathroom inlets, bathroom and kitchen faucets, refrigerator tap [3, 14, 15].

NTM infection can be acquired through inhalation of aerosolized droplets containing NTM, from natural surface water or hot water systems, or ingestion with subsequent aspiration. Therefore, activities potentially increasing domestic, occupational, or recreational NTM exposure in water (e.g. swimming), soils (e.g. gardening, mining, coal working, agriculture, landscaping, construction, tunnel work) and aerosols (e.g. showering, hot tubs) are associated with increased NTM-PD prevalence [5, 14, 16–20]. In particular, in a recent case-control study, NTM isolation from shower aerosols was associated with a higher risk of NTM-PD [21]. *Maekawa et al*. found that engaging in soil-related activities greater than two times per week was strongly associated with NTM lung disease in a bronchiectasis patient population [22].

Interestingly, based on the observation of a global increase in the incidence and prevalence of NTM-PD, especially in geographic areas hit by natural disasters, it has been suggested that natural disaster survivors might be at increased risk for NTM-PD because of inhalation or aspiration of contaminated water-soil mixtures [23]. In facts, during and after natural disasters, such as tsunamis, hurricanes, earthquakes, and tornados, the ecosystem, normally inhabited by NTM, is disrupted with large-scale mixing of ocean water with fresh water and of water with soil, causing widespread water-soil NTM aerosolization [23]. Nevertheless, long-term prospective epidemiologic and microbiologic studies in disaster-prone areas are needed to validate this hypothesis of natural disaster-associated NTM-PD, a new potential public health issue.

Given the wide diffusion and the high variety of environments where NTM can proliferate and the high number of situations in which NTM can be inhaled, it's difficult to devise practical and effective strategies for avoidance of NTM disease and, to date, no guideline specifically address NTM disease prevention.[24]

Since soils are a large natural source of mycobacteria, and considering that it's impossible to change the soil composition, the possible strategies to decrease NTM infections from soils are to drain the marshlands and to combat global warming in order to decrease the evapotranspiration rate.

On the contrary, several strategies may be adopted to decrease the NTM contamination of household and industrial plumbing systems. The water network should be renovated, replacing old and corroded pipelines, and reducing the water stagnation time in pipelines and

household plumbing systems. Furthermore, the disinfectant choice seems to be crucial because it not only influences the frequency of NTM detection at the tap, but also increases NTM persistence in the system and may select for specific pathogenic NTM species [15]. Chloramine, indeed, is less efficient than chlorine at controlling NTM colonization [15]. Last but not least, given that NTM growth and persistence in warm water with temperature up to 55°C [4], the most appropriate set-point for the household water heater should be defined in order to prevent scalding injuries and, at the same time, decrease NTM survival.

The drinking water supply networks should be reconsidered, because drinking water systems using surface water were more likely to have NTM than systems using a groundwater source [25].

Finally, considering the high rates of NTM relapses or re-infections, up to 50% of patients who completed treatment [26–29], it's suggested for patients with a known NTM-PD or at higher risk of NTM-PD, to avoid the exposure to potentially contaminated environments. Specifically, possible sources of exposure to NTM in water, soils, and aerosols, including domestic, occupational, and recreational activities, are summarised in Table 1.

2. Nutritional evaluation and intervention

Typical characteristics of patients with NTM-PD are low body mass index (BMI) and history of weight loss [30–32]. Such features are among those that make the clinician suspect a NTM infection and are so typical of middle-aged women that a specific phenotype called "Lady Windermere syndrome" has been identified [33]. Most of the authors who studied alterations of the nutritional status in respiratory diseases focused their attention on chronic obstructive pulmonary diseases (COPD) in which systemic inflammation represents one of the most relevant factors in the development of the nutritional abnormalities (5). Much less is known about the nutritional implications of other chronic respiratory diseases, such as bronchiectasis, that are characterized by chronic lung infections that cause persistent inflammation. In specific types of respiratory infections, such as NTM-PD, weight loss and low BMI are not only characteristic elements of the clinical picture but are also associated with disease spread and severity of radiological scores [34] and with negative outcomes [35–37].

Prospective studies on NTM-PD patients found that female patients were significantly thinner than control subjects, with a lower self-reported BMI before NTM disease [37–41]. A plausible mechanism by which individuals with slender body habitus and low body fat content may be predisposed to NTM infections is the altered expression of adipokines, such as leptin and

adiponectin, with known immunomodulatory functions [42]. Leptin is not only a satiety hormone but also promotes both the adaptive immune response, by activating T-helper 1 cells and stimulating the release of gamma interferon (IFN-γ), and the innate immunity, by increasing phagocytic function, chemotaxis, and proliferation and activation of natural killer cells [43]. Leptin is produced mainly by white adipose tissue, thus thin individuals have lower leptin levels and a relative deficiency in leptin levels has been observed in NTM-PD patients [42]. Conversely, adiponectin, whose levels are inversely related to the amount of body fat, decrease the production of the host protective cytokine tumour necrosis factor-α (TNF-α) [43].

In chronic inflammatory lung diseases, such as COPD, there has been increased evidence of vitamin D deficiency and alterations in calcium metabolism often associated with negative outcomes [44]. Vitamin D seems to have an immunomodulatory effect stimulating cell-mediated immunity by favouring the proliferation and activity of T helper 2 over T helper 1 and enhancing phagocytosis and granuloma formation. In *in vitro* studies on tuberculosis, vitamin D also showed to support innate immune response and to promote an anti-inflammatory effect with reduction of tissue damage [45]. Furthermore, 25(OH)D was demonstrated to restrict *M. tuberculosis* grown through cytokines production, particularly LL-37, in macrophages and epithelial cells [45].

Severe vitamin D deficiency was initially found to have a high prevalence in NTM-PD representing an independent risk factor for the disease,[46] but this observation has been disproved by subsequent studies [32, 47]. Furthermore, several studies have suggested an association between vitamin D receptor gene polymorphism and the risk of pulmonary TB, but they were not conclusive in regard to NTM-PD. In a study by *Fujita et al.* bone mineral density was found to be decreased in patients with MAC pulmonary disease without relation to serum vitamin D level [32].

Altered vitamin status was also evaluated in patients with NTM-PD. *Oh et al.* measured concentrations of vitamins A, D, and E along with homocysteine and methylmalonic acid as indicators of vitamin B12 deficiency in a case-control study including 150 patients with NTM-PD and 150 healthy controls [47]. The serum concentrations of vitamins A and E were significantly lower in patients with NTM-PD than in healthy controls, in particular vitamin A deficiency was associated with an 11-fold increase in risk of NTM-PD [47].

Oh et al. also measured the serum concentrations of 7 trace elements (cobalt, copper, chromium, manganese, molybdenum, selenium, and zinc) and observed higher serum concentrations of copper and molybdenum and lower serum concentrations of selenium and

zinc in patients with NTM lung disease compared to healthy controls [48]. None of the 7 trace elements were associated with treatment outcomes [48]. Therefore, the exact impact of these alterations in vitamins and micronutrients on disease pathogenicity and progression is still unknown and requires further studies.

Physical deconditioning is frequent in patients with COPD as well as bronchiectasis [49], however the presence of sarcopenia and the evaluation of muscle mass in patients with NTM-PD were only marginally evaluated. *Morimoto et al* described a decreased in muscle mass in patients with MAC pulmonary disease and found that percentage of triceps skinfold and mid-upper arm muscle circumference were negatively correlated with the severity of radiological scores [30].

To date, there are no studies that fully evaluated the nutritional status nor the impact of the initiation of antibiotic therapy on the nutritional parameters of NTM-PD patients. From the limited evidence available, it is not yet clear what the prevalence of nutritional and metabolic disorders is. Therefore, it is not possible to give any precise nutritional indication with the exception of supplementation in case of vitamin deficiencies and specific nutritional assessment in case of cachexia. Sarcopenia may require joint nutritional and rehabilitative intervention. Probiotics and dietary supplements do not currently have a clear indication either. Prospective studies that fully evaluate the nutritional status of these patients are necessary.

3. Pulmonary rehabilitation, exercise training and respiratory physiotherapy

Pulmonary rehabilitation (PR) is defined by the ATS and ERS as a "comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, educational and behavioural changes, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence of health-enhancing behaviours" [50, 51]. PR is the ideal setting where an interdisciplinary team including pulmonary physicians, physiotherapists, respiratory therapists, nurses, psychologists, nutritionists, occupational therapists, can cooperate to improve symptoms and exercise performance, to promote autonomy, to enhance quality of life and to effect long term health enhancing behavioural changes. PR role and benefits have been well defined in patients with COPD [50, 52] and emerging evidence suggests that these benefits could be extended to other chronic respiratory conditions, such as interstitial lung disease, alpha-1-antitrypsin (AAT) deficiency,

asthma, bronchiectasis, and lung transplantation. NTM-PD typically occurs in the setting of these pre-existing structural lung disease, Table 1. [53–56] The benefits of PR can be summarize as follows: reduce hospitalization and symptoms of dyspnoea, improve exercise capacity, health related quality of life and functional capacity in the activities of daily living, enhance self-efficacy, knowledge and collaborative self-management [53–59].

However, not all these benefits are reached together and maintained for the same time. In patients with progressive ILDs, such as idiopathic pulmonary fibrosis, the benefits in exercise capacity and dyspnoea reduction are rarely sustained 6 months following intervention [53]. In diseases with a more favourable prognosis, results can be maintained for longer periods. To the best of our knowledge, there are no studies specifically assessing the role of PR and respiratory physiotherapy in patients with NTM-PD. However, part of the evidence can be derived from other diseases that show similarities with NTM-PD, such as bronchiectasis and TB [60]. The main objective of PR in patients with bronchiectasis is to encourage airway-clearing techniques (ACT), while improving ventilatory capacity and exercise tolerance. In this scenario, two different interventions play a fundamental role: 1) exercise training which is associated with short term improvement in exercise capacity, dyspnoea, fatigue and fewer exacerbations over 12 months [55, 61]; 2) ACT used regularly to reduce the respiratory symptoms related to cough and, thus, improve health-related quality of life [62].

Since no technique has currently shown superiority over another, a personalised approach is recommended for all interventions and strategies to promote behavioural change and adherence are needed to ensure successful implementation in clinical practice.

Therefore, according to current evidence, ACT and PR, should be offered to all patients with bronchiectasis, including those with NTM-PD and a bronchiectasis / bronchiolitic pattern [56, 63].

PR also plays a key role in the treatment of pulmonary TB sequelae and is recommended in all patients with pulmonary impairment after TB treatment and as preparation in candidates for surgery, including those with localised bronchiectasis and aspergillomas [64]. TB patients, as well as NTM-PD, may have different types of lung impairment: the most prevalent pattern is airflow limitation due to sequelae affecting the airways, including bronchiectasis and tracheobronchial stenosis, while a restrictive pattern due to lung parenchyma destruction (cavitations and pulmonary fibrosis) and pleural alterations (fibrothorax) is less frequent [64]. Obstructive and restrictive patterns may coexist. In this scenario, PR comprehending pulmonary physiotherapy and aerobic exercise, even in short-term programs, produced a significant improvement of both aerobic capacity, symptoms control and quality of life [65,

66].

Despite the absence of trials specifically assessing the role of PR and ACT in patients with NTM-PD, the experience obtained from bronchiectasis and TB patients and the guidelines recommendation [67] suggest the importance of offering these personalized non-pharmacological treatment options to all patients to improve quality of life and treatment outcomes and to prevent disease recurrence.

4. Management of comorbidities

Comorbidities may play a fundamental role in increasing subject susceptibility to NTM-PD, therefore structural lung diseases and immunological defects should be suspected and investigated every time a NTM isolate is found in respiratory samples. Systemic diseases may also act both as a cause (e.g. minor immune deficiencies such as diabetes mellitus or nutrient malabsorption causing nutritional deficiencies), and a consequence (e.g. anxiety and depression) of NTM-PD.

Structural lung disease. NTM-PD typically occurs in the setting of pre-existing structural lung disease, because of impaired mucociliary clearance, abnormal composition of sputum, and airway damage caused by persistent inflammation [5].

Bronchiectasis and NTM-PD frequently coexist, raising the question about whether NTM infection is a cause or a consequence (or both) of bronchiectasis. In some diseases, such as cystic fibrosis (CF) or post-TB bronchiectasis, it seems reasonable that anatomic bronchial alterations precede NTM infection and that stagnant secretions provide an important medium for NTM to proliferate. On the other hand, few reports have described cases in which pulmonary NTM lesions preceded the development of bronchiectasis by cartilage and smooth muscle destruction [68].

The prevalence of COPD in NTM-PD patients is also high [69]. Interestingly, AAT deficiency association with NTM-PD is likely due not only to underlying emphysema or bronchiectasis, but also to AAT deficiency itself as shown in a recent study [70]. In fact, AAT itself may enhance host immunity against microbial pathogens and Bai et al. observed that macrophages obtained after a session of AAT infusion were significantly better able to control *M. intracellulare* infection compared to those pre-AAT infusion (38).

In regard to interstitial lung disease, a higher incidence of NTM-PD has been described in idiopathic pulmonary fibrosis patients by *Park et al*. Although many IPF patients were still

treated with immunosuppressive drugs at the time the study was conducted, a higher incidence of NTM-PD compared with general population was also found in immunosuppressants naïve patients, probably due to the anatomical honeycombing alterations caused by the disease [71].

Rare associations between NTM-PD and other respiratory diseases such as silicosis [72], Kartagener syndrome [73] and Pneumocystis pneumonia [74] have also been described. Silicosis, in particular, seems to be associated with a higher incidence of environmental mycobacterial exposure and lower cure rates after treatment [72].

It is increasingly recognized that NTM-PD occurs also in patients without underlying lung disease. This condition was first described in a cohort of white, postmenopausal, thin, tall women with pectus excavatum and mitral valve prolapse who develop predominantly middle lobe and lingula bronchiectasis; a cluster of features described as "Lady Windermere Syndrome" [75]. At first, voluntary cough suppression was considered a potential explanation for this condition. A recent whole-exome sequencing study defined genetic predisposition for this disease phenotype, identifying minor mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, unassociated with a diagnosis of cystic fibrosis, and mutations in genes involved in immune regulation, ciliary function, and connective tissue [37, 76, 77].

Furthermore, NTM-PD patients without underlying structural lung disease present some typical demographic and constitutional features. To begin with, epidemiologic data indicate that older age and female gender are risk factors for NTM-PD [1]. Since oestrogen binds macrophages and augments their phagocytic function, it's postulated that the observed low post-menopausal oestrogen levels in NTM-PD patients may increase disease susceptibility [78].

Interestingly, smoking seems to be a protective factor for NTM infection [79, 80], as similarly reported in other granulomatous lung diseases such as sarcoidosis and hypersensitivity pneumonitis, suggesting that smoking might inhibit granuloma formation [81].

In addition, a substantial proportion of patients with NTM-PD also have thoracic cage abnormalities such as scoliosis, flattened thoracic cage ("platythorax"), pectus excavatum and a nearly vertical vertebral column in lateral chest X-ray ("straight back syndrome"), a condition that can be associated with mitral valve prolapse [37, 43, 82].

Immune defects. Inherited or acquired immunodeficiencies should be considered particularly in case of recurrent, persistent or severe pulmonary infections and with NTM

species that are normally non-pathogenic, as well as in young patients or in subjects presenting with NTM disease in the absence of structural lung disease [5].

Primary immunodeficiencies include very rare disorders characterized by defective macrophage and dendritic cell function (e.g. chronic granulomatous disease), defective T-cells (e.g. common variable immunodeficiency (CVID), and severe combined immune deficiency (SCID), and the so-called "Mendelian susceptibility to mycobacterial disease",[83] due to mutations in 11 genes encoding cytokines, receptors and downstream signal-transducing proteins of the IFN-γ-interleukin-12 pathway [84].

On the contrary, acquired immunodeficiencies are far more frequent and include untreated acquired immune deficiency syndrome (AIDS)/human immunodeficiency virus (HIV) infection, presence of anti-IFN-γ autoantibodies, active solid or hematologic malignancy, diabetes mellitus, chronic renal failure, and alcohol abuse [5]. Interestingly, although disseminated NTM infection is a well-known complication of AIDS, isolated NTM-PD is uncommon among HIV-positive patients and may occur when the CD4+ T cell count is very low (< 50 cells/mm^3) [85].

An increased risk of NTM disease has also been reported with the use of immunosuppressant medications, including biological agents, especially TNF-α antagonists, inhaled and oral corticosteroids, and other immunosuppressive treatments for hematopoietic stem cell and solid organ transplantation. In particular, lung transplantation is the strongest risk factor for NTM disease after organ transplantation, because of a combination of factors, including immune suppression, local defects in the transplanted allograft resulting in abnormal ciliary function, bronchial devascularisation, denervation, and lymphatic insufficiency post-transplant. Most of NTM infection occurs in the first 8 months post-transplant and are associated with high mortality [86, 87].

The increasingly widespread use of TNF-α antagonists, as an effective treatment of many inflammatory and autoimmune disorders, such as rheumatoid arthritis, vasculitis, inflammatory bowel disease, and psoriasis, has led to an increased incidence of NTM-PD, suggesting that anti-TNF-α intrinsically predispose to new NTM infections and exacerbate indolent infections [88, 89].

Similarly, the increasing incidence rate of NTM-PD in the last years has been attributed to the rise in inhaled corticosteroids (ICS) use for the treatment of several chronic pulmonary diseases, such as asthma and COPD. In fact, several case-control studies showed that ICS current use or ICS use within the past year was associated with an increased risk of NTM-PD compared with non-use [90–93]. Furthermore, the same studies showed a strong dose-

response relationship between higher CSI doses and the risk of NTM-PD [90–93], and a greater risk for fluticasone compared with budesonide,[91, 93] likely due to differences in pharmacokinetic and pharmacodynamic properties.

Other systemic diseases. There are conflicting data regarding an increased prevalence of gastroesophageal reflux disease (GERD) and proton pump inhibitors (PPI) prescription in patients with NTM lung infection [5, 41]. It has been speculated that PPI promotes gastrointestinal survival of NTM, and, subsequently, reflux delivers NTM into airways through chronic gastric micro-aspiration [94]. Data from the US Bronchiectasis Research Registry observed a higher prevalence of GERD in patients with NTM compared to those without [41]. No data are available in regards to psychological eating disorders and malabsorption that might influence the high prevalence of low BMI and weight loss in these patients.

Conclusions

Initial suggestions for the holistic management of patients with NTM-PD beyond antibiotic therapy should comprehend four main domains: 1) a careful evaluation of lifestyle and habits that can favour mycobacterial exposure in order to promote disease prevention; 2) PR and ACT that may be effective, low-budget, therapeutic interventions, to improve symptoms such as dyspnoea and exercise capacity, health related quality of life and functional capacity in the activities of daily living and enhance self-efficacy; 3) nutritional evaluation that may be required for a prevention purpose, but also to improve quality of life and to control gastrointestinal side effects during antimicrobial therapy; and 4) comorbidities must be investigated because they are fundamental in the pathogenesis of the disease and, therefore, acting on these factors may improve disease outcome and prevent relapses or re-infections.
In consideration of the complexity of NTM-PD that requires multiple expertises, the involvement of a multidisciplinary team may favor the optimization of patient management, Figure 2. Multidisciplinary discussion (MDD) has been effectively introduced in the diagnostic work-out and management of other respiratory diseases including lung tumors and interstitial lung diseases (95,96). In particular, respiratory medicine and infectious disease specialists should prescribe antibiotic therapy and monitor possible adverse events, but also evaluate and treat comorbidities and predisposing factors that may impact of disease prognosis. Nutritionists should be involved to evaluate nutritional status and to implement a nutritional intervention as needed. Physiotherapists and respiratory therapists are a

fundamental part of the therapeutic and prevention process with ACT and PR programs. Finally, pharmacists might also be included to discuss the best treatment option.

MDD should be organised periodically with the aim of discussing new cases to promptly introduce an integrated approach. However, the clinical cases may also be re-discussed as needed to optimize the management and follow-up.

Bibliography

1. Daley CL, Iaccarino JM, Lange C, et al. Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline. Eur Respir J 2020; 56:2000535.

2. Adjemian J, Olivier KN, Seitz AE, Falkinham JO, Holland SM, Prevots DR. Spatial clusters of nontuberculous mycobacterial lung disease in the United States. *Am. J. Respir. Crit. Care Med.* 2012; 186: 553–558.

3. Lipner EM, Knox D, French J, Rudman J, Strong M, Crooks JL. A Geospatial Epidemiologic Analysis of Nontuberculous Mycobacterial Infection: An Ecological Study in Colorado. *Ann. Am. Thorac. Soc.* 2017; 14: 1523–1532.

4. Parikh A, Vinnard C, Fahrenfeld N, Davidow AL, Patrawalla A, Lardizabal A, Gow A, Panettieri R, Gennaro M. Revisiting John Snow to Meet the Challenge of Nontuberculous Mycobacterial Lung Disease. *Int. J. Environ. Res. Public. Health* 2019; 16.

5. Haworth CS, Banks J, Capstick T, Fisher AJ, Gorsuch T, Laurenson IF, Leitch A, Loebinger MR, Milburn HJ, Nightingale M, Ormerod P, Shingadia D, Smith D, Whitehead N, Wilson R, Floto RA. British Thoracic Society guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD). *Thorax* 2017; 72: ii1–ii64.

6. Kirschner RA, Parker BC, Falkinham JO. Epidemiology of infection by nontuberculous mycobacteria. Mycobacterium avium, Mycobacterium intracellulare, and Mycobacterium scrofulaceum in acid, brown-water swamps of the southeastern United States and their association with environmental variables. *Am. Rev. Respir. Dis.* 1992; 145: 271–275.

7. Falkinham JO. Surrounded by mycobacteria: nontuberculous mycobacteria in the human environment. *J. Appl. Microbiol.* 2009; 107: 356–367.

8. Falkinham JO. Ecology of nontuberculous mycobacteria--where do human infections come from? *Semin. Respir. Crit. Care Med.* 2013; 34: 95–102.

9. Marras TK, Daley CL. Epidemiology of human pulmonary infection with nontuberculous mycobacteria. *Clin. Chest Med.* 2002; 23: 553–567.

10. Modrá H, Ulmann V, Caha J, Hübelová D, Konečný O, Svobodová J, Weston RT, Pavlík I. Socio-Economic and Environmental Factors Related to Spatial Differences in Human Non-Tuberculous Mycobacterial Diseases in the Czech Republic. *Int. J. Environ. Res. Public. Health* 2019; 16.

11. Ulmann V, Kracalikova A, Dziedzinska R. Mycobacteria in water used for personal hygiene in heavy industry and collieries: a potential risk for employees. *Int. J. Environ. Res. Public. Health* 2015; 12: 2870–2877.

12. Revetta RP, Gomez-Alvarez V, Gerke TL, Santo Domingo JW, Ashbolt NJ. Changes in bacterial composition of biofilm in a metropolitan drinking water distribution system. *J. Appl. Microbiol.* 2016; 121: 294–305.

13. Vaerewijck MJM, Huys G, Palomino JC, Swings J, Portaels F. Mycobacteria in drinking water distribution systems: ecology and significance for human health. *FEMS Microbiol. Rev.* 2005; 29: 911–934.

14. Honda JR, Virdi R, Chan ED. Global Environmental Nontuberculous Mycobacteria and Their Contemporaneous Man-Made and Natural Niches. *Front. Microbiol.* 2018; 9: 2029.

15. Donohue MJ, Mistry JH, Donohue JM, O'Connell K, King D, Byran J, Covert T, Pfaller S. Increased Frequency of Nontuberculous Mycobacteria Detection at Potable Water Taps within the United States. *Environ. Sci. Technol.* 2015; 49: 6127–6133.

16. Falkinham JO. Current Epidemiologic Trends of the Nontuberculous Mycobacteria (NTM). *Curr. Environ. Health Rep.* 2016; 3: 161–167.

17. Lee J-W, Myong J-P. Association between Occupational and Radiological Factors and Nontuberculous Mycobacteria Lung Infection in Workers with Prior Dust Exposure. *Int. J. Environ. Res. Public. Health* 2019; 16.

18. Sonnenberg P, Murray J, Glynn JR, Thomas RG, Godfrey-Faussett P, Shearer S. Risk factors for pulmonary disease due to culture-positive M. tuberculosis or nontuberculous mycobacteria in South African gold miners. *Eur. Respir. J.* 2000; 15: 291–296.

19. Corbett EL, Churchyard GJ, Clayton T, Herselman P, Williams B, Hayes R, Mulder D, De Cock KM. Risk factors for pulmonary mycobacterial disease in South African gold miners. A case-control study. *Am. J. Respir. Crit. Care Med.* 1999; 159: 94–99.

20. De Groote MA, Pace NR, Fulton K, Falkinham JO. Relationships between Mycobacterium isolates from patients with pulmonary mycobacterial infection and potting soils. *Appl. Environ. Microbiol.* 2006; 72: 7602–7606.

21. Tzou CL, Dirac MA, Becker AL, Beck NK, Weigel KM, Meschke JS, Cangelosi GA. Association between Mycobacterium avium Complex Pulmonary Disease and Mycobacteria in Home Water and Soil. *Ann. Am. Thorac. Soc.* 2020; 17: 57–62.

22. Maekawa K, Ito Y, Hirai T, Kubo T, Imai S, Tatsumi S, Fujita K, Takakura S, Niimi A, Iinuma Y, Ichiyama S, Togashi K, Mishima M. Environmental risk factors for pulmonary Mycobacterium avium-intracellulare complex disease. *Chest* 2011; 140: 723–729.

23. Honda JR, Bernhard JN, Chan ED. Natural disasters and nontuberculous mycobacteria: a recipe for increased disease? *Chest* 2015; 147: 304–308.

24. Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, Holland SM, Horsburgh R, Huitt G, Iademarco MF, Iseman M, Olivier K, Ruoss S, von Reyn CF, Wallace RJ, Winthrop K. An Official ATS/IDSA Statement: Diagnosis, Treatment, and Prevention of Nontuberculous Mycobacterial Diseases. *Am. J. Respir. Crit. Care Med.* 2007; 175: 367–416.

25. Falkinham JO, Norton CD, LeChevallier MW. Factors influencing numbers of Mycobacterium avium, Mycobacterium intracellulare, and other Mycobacteria in drinking water distribution systems. *Appl. Environ. Microbiol.* 2001; 67: 1225–1231.

26. Wallace RJ, Brown-Elliott BA, McNulty S, Philley JV, Killingley J, Wilson RW, York DS, Shepherd S, Griffith DE. Macrolide/Azalide therapy for nodular/bronchiectatic mycobacterium avium complex lung disease. *Chest* 2014; 146: 276–282.

27. Wallace RJ, Zhang Y, Brown-Elliott BA, Yakrus MA, Wilson RW, Mann L, Couch L, Girard WM, Griffith DE. Repeat positive cultures in Mycobacterium intracellulare lung disease after macrolide therapy represent new infections in patients with nodular bronchiectasis. *J. Infect. Dis.* 2002; 186: 266–273.

28. Field SK, Fisher D, Cowie RL. Mycobacterium avium complex pulmonary disease in patients without HIV infection. *Chest* 2004; 126: 566–581.

29. Xu H-B, Jiang R-H, Li L. Treatment outcomes for Mycobacterium avium complex: a systematic review and meta-analysis. *Eur. J. Clin. Microbiol. Infect. Dis. Off. Publ. Eur. Soc. Clin. Microbiol.* 2014; 33: 347–358.

30. Morimoto K, Yoshiyama T, Kurashima A, Sasaki Y, Hoshino Y, Yoshimori K, Ogata H, Gemma A, Kudoh S, Shiraishi Y. Nutritional indicators are correlated with the radiological severity score in patients with Mycobacterium avium complex pulmonary disease: a cross-sectional study. *Intern. Med. Tokyo Jpn.* 2014; 53: 397–401.

31. Faverio P, Stainer A, Bonaiti G, Zucchetti SC, Simonetta E, Lapadula G, Marruchella A, Gori A, Blasi F, Codecasa L, Pesci A, Chalmers JD, Loebinger MR, Aliberti S. Characterizing Non-Tuberculous Mycobacteria Infection in Bronchiectasis. *Int. J. Mol. Sci.* 2016; 17.

32. Fujita K, Ito Y, Oguma T, Mio T, Niimi A, Hirai T. Association between Mycobacterium avium complex lung disease and serum vitamin D status, antimicrobial peptide levels, and bone mineral density. *Medicine (Baltimore)* 2018; 97: e12463.

33. Chan ED, Iseman MD. Slender, older women appear to be more susceptible to nontuberculous mycobacterial lung disease. *Gend. Med.* 2010; 7: 5–18.

34. Ikegame S, Maki S, Wakamatsu K, Nagata N, Kumazoe H, Fujita M, Nakanishi Y, Kawasaki M, Kajiki A. Nutritional assessment in patients with pulmonary nontuberculous mycobacteriosis. *Intern. Med. Tokyo Jpn.* 2011; 50: 2541–2546.

35. Gochi M, Takayanagi N, Kanauchi T, Ishiguro T, Yanagisawa T, Sugita Y. Retrospective study of the predictors of mortality and radiographic deterioration in 782 patients with nodular/bronchiectatic Mycobacterium avium complex lung disease. *BMJ Open* 2015; 5: e008058.

36. Hayashi M, Takayanagi N, Kanauchi T, Miyahara Y, Yanagisawa T, Sugita Y. Prognostic factors of 634 HIV-negative patients with Mycobacterium avium complex lung disease. *Am. J. Respir. Crit. Care Med.* 2012; 185: 575–583.

37. Kim RD, Greenberg DE, Ehrmantraut ME, Guide SV, Ding L, Shea Y, Brown MR, Chernick M, Steagall WK, Glasgow CG, Lin J, Jolley C, Sorbara L, Raffeld M, Hill S, Avila N, Sachdev V, Barnhart LA, Anderson VL, Claypool R, Hilligoss DM, Garofalo M, Fitzgerald A, Anaya-O'Brien S, Darnell D, DeCastro R, Menning HM, Ricklefs SM, Porcella SF, Olivier KN, et al. Pulmonary nontuberculous mycobacterial disease: prospective study of a distinct preexisting syndrome. *Am. J. Respir. Crit. Care Med.* 2008; 178: 1066–1074.

38. Kartalija M, Ovrutsky AR, Bryan CL, Pott GB, Fantuzzi G, Thomas J, Strand MJ, Bai X, Ramamoorthy P, Rothman MS, Nagabhushanam V, McDermott M, Levin AR, Frazer-Abel A, Giclas PC, Korner J, Iseman MD, Shapiro L, Chan ED. Patients with nontuberculous mycobacterial lung disease exhibit unique body and immune phenotypes. *Am. J. Respir. Crit. Care Med.* 2013; 187: 197–205.

39. Lee SJ, Ryu YJ, Lee JH, Chang JH, Shim SS. The impact of low subcutaneous fat in patients with nontuberculous mycobacterial lung disease. *Lung* 2014; 192: 395–401.

40. Wakamatsu K, Nagata N, Maki S, Omori H, Kumazoe H, Ueno K, Matsunaga Y, Hara M, Takakura K, Fukumoto N, Ando N, Morishige M, Akasaki T, Inoshima I, Ise S, Izumi M, Kawasaki M. Patients with MAC Lung Disease Have a Low Visceral Fat Area and Low Nutrient Intake. *Pulm. Med.* 2015; 2015: 218253.

41. Aksamit TR, O'Donnell AE, Barker A, Olivier KN, Winthrop KL, Daniels MLA, Johnson M, Eden E, Griffith D, Knowles M, Metersky M, Salathe M, Thomashow B, Tino G, Turino G, Carretta B, Daley CL, Bronchiectasis Research Registry Consortium. Adult Patients With Bronchiectasis: A First Look at the US Bronchiectasis Research Registry. *Chest* 2017; 151: 982–992.

42. Tasaka S, Hasegawa N, Nishimura T, Yamasawa W, Kamata H, Shinoda H, Kimizuka Y, Fujiwara H, Hirose H, Ishizaka A. Elevated serum adiponectin level in patients with Mycobacterium avium-intracellulare complex pulmonary disease. *Respir. Int. Rev. Thorac. Dis.* 2010; 79: 383–387.

43. Chan ED, Iseman MD. Underlying host risk factors for nontuberculous mycobacterial lung disease. *Semin. Respir. Crit. Care Med.* 2013; 34: 110–123.

44. Graumam RQ, Pinheiro MM, Nery LE, Castro CHM. Increased rate of osteoporosis, low lean mass, and fragility fractures in COPD patients: association with disease severity. *Osteoporos. Int. J. Establ. Result Coop. Eur. Found. Osteoporos. Natl. Osteoporos. Found. USA* 2018; 29: 1457–1468.

45. Brighenti S, Bergman P, Martineau AR. Vitamin D and tuberculosis: where next? *J Intern Med.* 2018 May 27. doi: 10.1111/joim.12777.

46. Jeon K, Kim S-Y, Jeong B-H, Chang B, Shin SJ, Koh W-J. Severe vitamin D deficiency is associated with non-tuberculous mycobacterial lung disease: a case-control study. *Respirol. Carlton Vic* 2013; 18: 983–988.

47. Oh J, Park H-D, Kim S-Y, Koh W-J, Lee S-Y. Assessment of Vitamin Status in Patients with Nontuberculous Mycobacterial Pulmonary Disease: Potential Role of Vitamin A as a Risk Factor. *Nutrients* 2019; 11.

48. Oh J, Shin SH, Choi R, Kim S, Park H-D, Kim S-Y, Han SA, Koh W-J, Lee S-Y. Assessment of 7 trace elements in serum of patients with nontuberculous mycobacterial lung disease. *J. Trace Elem. Med. Biol. Organ Soc. Miner. Trace Elem. GMS* 2019; 53: 84–90.

49. Gale NS, Bolton CE, Duckers JM, Enright S, Cockcroft JR, Shale DJ. Systemic comorbidities in bronchiectasis. *Chron. Respir. Dis.* 2012; 9: 231–238.

50. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, Hill K, Holland AE, Lareau SC, Man WD-C, Pitta F, Sewell L, Raskin J, Bourbeau J, Crouch R, Franssen FME, Casaburi R, Vercoulen JH, Vogiatzis I, Gosselink R, Clini EM, Effing TW, Maltais F, van der Palen J, Troosters T, Janssen DJA, Collins E, Garcia-Aymerich J, Brooks D, Fahy BF, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am. J. Respir. Crit. Care Med.* 2013; 188: e13-64.

51. Rochester CL, Vogiatzis I, Holland AE, Lareau SC, Marciniuk DD, Puhan MA, Spruit MA, Masefield S, Casaburi R, Clini EM, Crouch R, Garcia-Aymerich J, Garvey C, Goldstein RS, Hill K, Morgan M, Nici L, Pitta F, Ries AL, Singh SJ, Troosters T, Wijkstra PJ, Yawn BP, ZuWallack RL, ATS/ERS Task Force on Policy in Pulmonary Rehabilitation. An Official American Thoracic Society/European Respiratory Society Policy Statement: Enhancing Implementation, Use, and Delivery of Pulmonary Rehabilitation. *Am. J. Respir. Crit. Care Med.* 2015; 192: 1373–1386.

52. Gloeckl R, Halle M, Kenn K. Interval versus continuous training in lung transplant candidates: a randomized trial. *J. Heart Lung Transplant. Off. Publ. Int. Soc. Heart Transplant.* 2012; 31: 934–941.

53. Holland AE, Hill CJ, Conron M, Munro P, McDonald CF. Short term improvement in exercise capacity and symptoms following exercise training in interstitial lung disease. *Thorax* 2008; 63: 549–554.

54. Mendes FAR, Gonçalves RC, Nunes MPT, Saraiva-Romanholo BM, Cukier A, Stelmach R, Jacob-Filho W, Martins MA, Carvalho CRF. Effects of aerobic training on psychosocial morbidity and symptoms in patients with asthma: a randomized clinical trial. *Chest* 2010; 138: 331–337.

55. Newall C, Stockley RA, Hill SL. Exercise training and inspiratory muscle training in patients with bronchiectasis. *Thorax* 2005; 60: 943–948.

56. Nishiyama O, Kondoh Y, Kimura T, Kato K, Kataoka K, Ogawa T, Watanabe F, Arizono S, Nishimura K, Taniguchi H. Effects of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. *Respirol. Carlton Vic* 2008; 13: 394–399.

57. Langer D, Burtin C, Schepers L, Ivanova A, Verleden G, Decramer M, Troosters T, Gosselink R. Exercise training after lung transplantation improves participation in daily activity: a randomized controlled trial. *Am. J. Transplant. Off. J. Am. Soc. Transplant. Am. Soc. Transpl. Surg.* 2012; 12: 1584–1592.

58. Lee AL, Hill CJ, Cecins N, Jenkins S, McDonald CF, Burge AT, Rautela L, Stirling RG, Thompson PJ, Holland AE. The short and long term effects of exercise training in non-cystic fibrosis bronchiectasis--a randomised controlled trial. *Respir. Res.* 2014; 15: 44.

59. Ochmann U, Kotschy-Lang N, Raab W, Kellberger J, Nowak D, Jörres RA. Long-term efficacy of pulmonary rehabilitation in patients with occupational respiratory diseases. *Respir. Int. Rev. Thorac. Dis.* 2012; 84: 396–405.

60. O'Neill K, O'Donnell AE, Bradley JM. Airway clearance, mucoactive therapies and pulmonary rehabilitation in bronchiectasis. *Respirol. Carlton Vic* 2019; 24: 227–237.

61. Liaw M-Y, Wang Y-H, Tsai Y-C, Huang K-T, Chang P-W, Chen Y-C, Lin M-C. Inspiratory muscle training in bronchiectasis patients: a prospective randomized controlled study. *Clin. Rehabil.* 2011; 25: 524–536.

62. Moran F, Piper A, Elborn JS, Bradley JM. Respiratory muscle pressures in non-CF bronchiectasis: repeatability and reliability. *Chron. Respir. Dis.* 2010; 7: 165–171.

63. Severiche-Bueno D, Gamboa E, Reyes LF, Chotirmall SH. Hot topics and current controversies in non-cystic fibrosis bronchiectasis. *Breathe Sheff. Engl.* 2019; 15: 286–295.

64. Muñoz-Torrico M, Cid-Juárez S, Galicia-Amor S, Troosters T, Spanevello A. Tuberculosis sequelae assessment and rehabilitation. In: Migliori GB, Bothamley G, Duarte R, Rendon A, editors. *Tuberculosis* [Internet] Sheffield, United Kingdom: European Respiratory Society; 2018 [cited 2020 Feb 20]. p. 326–342Available from: http://erspublications.com/lookup/doi/10.1183/2312508X.10022317.

65. Rivera JA, Wilches-Luna EC, Mosquera R, Hernandez NL, Orobio OMH. Pulmonary rehabilitation on aerobic capacity and health-related quality of life in patients with sequelae of pulmonary TB. *Physiotherapy* 2015; 101: e1288.

66. Ando M, Mori A, Esaki H, Shiraki T, Uemura H, Okazawa M, Sakakibara H. The effect of pulmonary rehabilitation in patients with post-tuberculosis lung disorder. *Chest* 2003; 123: 1988–1995.

67. Polverino E, Goeminne PC, McDonnell MJ, Aliberti S, Marshall SE, Loebinger MR, Murris M, Cantón R, Torres A, Dimakou K, De Soyza A, Hill AT, Haworth CS, Vendrell M, Ringshausen FC, Subotic D, Wilson R, Vilaró J, Stallberg B, Welte T, Rohde G, Blasi F, Elborn S, Almagro M, Timothy A, Ruddy T, Tonia T, Rigau D, Chalmers JD. European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur. Respir. J.* 2017; 50.

68. Bonaiti G, Pesci A, Marruchella A, Lapadula G, Gori A, Aliberti S. Nontuberculous Mycobacteria in Noncystic Fibrosis Bronchiectasis. *BioMed Res. Int.* 2015; 2015: 197950.

69. Adjemian J, Olivier KN, Seitz AE, Holland SM, Prevots DR. Prevalence of nontuberculous mycobacterial lung disease in U.S. Medicare beneficiaries. *Am. J. Respir. Crit. Care Med.* 2012; 185: 881–886.

70. Bai X, Bai A, Honda JR, Eichstaedt C, Musheyev A, Feng Z, Huitt G, Harbeck R, Kosmider B, Sandhaus RA, Chan ED. Alpha-1-Antitrypsin Enhances Primary Human Macrophage Immunity Against Non-tuberculous Mycobacteria. *Front. Immunol.* 2019; 10: 1417.

71. Park IK, Olivier KN. Nontuberculous mycobacteria in cystic fibrosis and non-cystic fibrosis bronchiectasis. *Semin. Respir. Crit. Care Med.* 2015; 36: 217–224.

72. Blanco Pérez JJ, Pérez González A, Morano Amado LE, Guerra Vales JL, Vázquez Gallardo R, Salgado Barreira Á, Cruz Carmona MJ, González Barcala FJ. Clinical Significance of Environmental Mycobacteria Isolated From Respiratory Specimens of Patients With and Without Silicosis. *Arch. Bronconeumol.* 2016; 52: 145–150.

73. Kim JH, Song WJ, Jun JE, Ryu DH, Lee JE, Jeong HJ, Jeong SH, Kang HK, Kim JS, Lee H, Chon HR, Jeon K, Kim D, Kim J, Koh W-J. Mycobacterium abscessus Lung Disease in a Patient with Kartagener Syndrome. *Tuberc. Respir. Dis.* 2014; 77: 136–140.

74. Chen F, Sethi G, Goldin R, Wright AR, Lacey CJ. Concurrent granulomatous Pneumocystis carinii and Mycobacterium xenopi pneumonia: an unusual manifestation of HIV immune reconstitution disease. *Thorax* 2004; 59: 997–999.

75. Reich JM, Johnson RE. Mycobacterium avium complex pulmonary disease presenting as an isolated lingular or middle lobe pattern. The Lady Windermere syndrome. *Chest* 1992; 101: 1605–1609.

76. Szymanski EP, Leung JM, Fowler CJ, Haney C, Hsu AP, Chen F, Duggal P, Oler AJ, McCormack R, Podack E, Drummond RA, Lionakis MS, Browne SK, Prevots DR, Knowles M, Cutting G, Liu X, Devine SE, Fraser CM, Tettelin H, Olivier KN, Holland SM. Pulmonary Nontuberculous Mycobacterial Infection. A Multisystem, Multigenic Disease. *Am. J. Respir. Crit. Care Med.* 2015; 192: 618–628.

77. Cowman SA, Jacob J, Hansell DM, Kelleher P, Wilson R, Cookson WOC, Moffatt MF, Loebinger MR. Whole-Blood Gene Expression in Pulmonary Nontuberculous Mycobacterial Infection. *Am. J. Respir. Cell Mol. Biol.* 2018; 58: 510–518.

78. Uwamino Y, Nishimura T, Sato Y, Tamizu E, Asakura T, Uno S, Mori M, Fujiwara H, Ishii M, Kawabe H, Murata M, Hasegawa N. Low serum estradiol levels are related to Mycobacterium avium complex lung disease: a cross-sectional study. *BMC Infect. Dis.* 2019; 19: 1055.

79. Wickremasinghe M, Ozerovitch LJ, Davies G, Wodehouse T, Chadwick MV, Abdallah S, Shah P, Wilson R. Non-tuberculous mycobacteria in patients with bronchiectasis. *Thorax* 2005; 60: 1045–1051.

80. Shteinberg M, Stein N, Adir Y, Ken-Dror S, Shitrit D, Bendayan D, Fuks L, Saliba W. Prevalence, risk factors and prognosis of nontuberculous mycobacterial infection among people with bronchiectasis: a population survey. *Eur. Respir. J.* 2018; 51.

81. Maier LA. Is smoking beneficial for granulomatous lung diseases? *Am. J. Respir. Crit. Care Med.* 2004; 169: 893–895.

82. Iseman MD, Buschman DL, Ackerson LM. Pectus excavatum and scoliosis. Thoracic anomalies associated with pulmonary disease caused by Mycobacterium avium complex. *Am. Rev. Respir. Dis.* 1991; 144: 914–916.

83. Rosain J, Kong X-F, Martinez-Barricarte R, Oleaga-Quintas C, Ramirez-Alejo N, Markle J, Okada S, Boisson-Dupuis S, Casanova J-L, Bustamante J. Mendelian susceptibility to mycobacterial disease: 2014-2018 update. *Immunol. Cell Biol.* 2019; 97: 360–367.

84. Mortaz E, Moloudizargari M, Varahram M, Movassaghi M, Garssen J, Kazempour Dizagie M, Mirsaeidi M, Adcock IM. What Immunological Defects Predispose to Non-tuberculosis Mycobacterial Infections? *Iran. J. Allergy Asthma Immunol.* 2018; 17: 100–109.

85. Horsburgh CR, Gettings J, Alexander LN, Lennox JL. Disseminated Mycobacterium avium complex disease among patients infected with human immunodeficiency virus, 1985-2000. *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* 2001; 33: 1938–1943.

86. Rao M, Silveira FP. Non-tuberculous Mycobacterial Infections in Thoracic Transplant Candidates and Recipients. *Curr. Infect. Dis. Rep.* 2018; 20: 14.

87. Longworth SA, Blumberg EA, Barton TD, Vinnard C. Non-tuberculous mycobacterial infections after solid organ transplantation: a survival analysis. *Clin. Microbiol. Infect. Off. Publ. Eur. Soc. Clin. Microbiol. Infect. Dis.* 2015; 21: 43–47.

88. Wallis RS, Schluger NW. Pulmonary infectious complications of tumor necrosis factor blockade. *Infect. Dis. Clin. North Am.* 2010; 24: 681–692.

89. Winthrop KL, Chang E, Yamashita S, Iademarco MF, LoBue PA. Nontuberculous mycobacteria infections and anti-tumor necrosis factor-alpha therapy. *Emerg. Infect. Dis.* 2009; 15: 1556–1561.

90. Hojo M, Iikura M, Hirano S, Sugiyama H, Kobayashi N, Kudo K. Increased risk of nontuberculous mycobacterial infection in asthmatic patients using long-term inhaled corticosteroid therapy. *Respirol. Carlton Vic* 2012; 17: 185–190.

91. Andréjak C, Nielsen R, Thomsen VØ, Duhaut P, Sørensen HT, Thomsen RW. Chronic respiratory disease, inhaled corticosteroids and risk of non-tuberculous mycobacteriosis. *Thorax* 2013; 68: 256–262.

92. Liu VX, Winthrop KL, Lu Y, Sharifi H, Nasiri HU, Ruoss SJ. Association between Inhaled Corticosteroid Use and Pulmonary Nontuberculous Mycobacterial Infection. *Ann. Am. Thorac. Soc.* 2018; 15: 1169–1176.

93. Brode SK, Campitelli MA, Kwong JC, Lu H, Marchand-Austin A, Gershon AS, Jamieson FB, Marras TK. The risk of mycobacterial infections associated with inhaled corticosteroid use. *Eur. Respir. J.* 2017; 50.

94. Thomson RM, Armstrong JG, Looke DF. Gastroesophageal reflux disease, acid suppression, and Mycobacterium avium complex pulmonary disease. *Chest* 2007; 131: 1166–1172.

95. Luppi F, Faverio P, Wuyts WA. Multidisciplinary approach to systemic diseases: benefits for diagnosis and management of complex disorders. In: Wuyts WA, Cottin V, Spagnolo P, et al., eds. Pulmonary Manifestations of Systemic Diseases (ERS Monograph). Sheffield, European Respiratory Society, 2019; pp. 1–13 [https://doi.org/10.1183/2312508X.10013719].

96. Ung KA, Campbell BA, Duplan D, Ball D, David S. Impact of the lung oncology multidisciplinary team meetings on the management of patients with cancer. Asia Pac J Clin Oncol 12:e298-e304, 2016.

Table 1. Risk factors / Predisposing factors for NTM pulmonary disease

Exposure	
Domestic	Household plumbing fixtures Showerheads Taps Humidifiers Heating/ventilation systems Homelessness, incarceration or institutionalization
Occupational	Mining Healthcare Steel industry Farming and breeding Veterinary Waste collection Fish farming Geology and speleology
Recreational	Gardening Camping Horse-riding Fishing Swimming Hot tubs
Damage substrate	
Pre-existing lung disease	CF Non-CF bronchiectasis Primary ciliary dyskinesia Previous pulmonary tuberculosis Asthma COPD Alpha-1 antitrypsin deficiency Pneumoconiosis (especially silicosis) Interstitial lung diseases (especially, pulmonary alveolar proteinosis) ABPA Williams-Campbell syndrome Congenital tracheobronchomegaly (Mounier-Kuhn syndrome)
Demographic and constitutional factors - "Lady Windermere syndrome"	Older age (>40-70 years) Female sex Non-smoking history Slender body habitus Low BMI – Low body fat Scoliosis Pectus excavatum Flattened thoracic cage ("platythorax") "Straight back syndrome" Low vitamin D

	GERD
Defective immunity	
Primary immunodeficiency	Mutations in the IFNγ-IL12 pathway (e.g., IFNγ-R1, IFNγ-R2, IL-12R, STAT, tyrosine kinase 2) Deficiency in NF-κB essential modulator (NEMO) Defective macrophage and dendritic cell function (e.g., chronic granulomatous disease) Defective T-cells (eg, CVID, SCID) Complement C4 deficiency
Acquired immunodeficiency	HIV-AIDS Acquired neutralizing anti-IFNγ antibodies Diabetes mellitus Chronic kidney disease Malignancy Alcohol abuse
Medications	Oral corticosteroids Inhaled corticosteroids TNF-α antagonists Solid-organ transplantation (particularly, lung transplant) Hematopoietic stem cell transplantation Cancer chemotherapy

Footnotes: ABPA = allergic bronchopulmonary aspergillosis; AIDS = acquired immune deficiency syndrome; CF = cystic fibrosis; COPD = chronic obstructive pulmonary disease; CVID = common variable immunodeficiency; GERD = gastro-esophageal reflux disease; HIV = infection with human immunodeficiency virus; IFNγ = interferon gamma; SCID = severe combined immune deficiency; TNF = anti-tumor necrosis factor.

Table 2. Keywords used to perform the research

(Non-tuberculous Mycobacteria OR Non-tuberculous Mycobacteria Pulmonary Disease) AND (Nutritional status OR Nutritional evaluation OR Nutritional intervention), (Non-tuberculous Mycobacteria OR Non-tuberculous Mycobacteria Pulmonary Disease) AND (Vitamin D OR Vitamin), (Non-tuberculous Mycobacteria OR Non-tuberculous Mycobacteria Pulmonary Disease) AND (Nutraceutical OR Probiotics), (Non-tuberculous Mycobacteria OR Non-tuberculous Mycobacteria Pulmonary Disease) AND (Behavioral change OR Health education OR Environmental exposure OR Risk Factors), (Non-tuberculous Mycobacteria OR Non-tuberculous Mycobacteria Pulmonary Disease) AND (Pulmonary Rehabilitation OR Exercise Training OR Respiratory Physiotherapy OR Airway Clearing Techniques OR Airway Clearance Techniques), (Non-tuberculous Mycobacteria OR Non-tuberculous Mycobacteria Pulmonary Disease) AND (Comorbidities OR Structural Lung Disease OR Asthma OR Alpha-1 Antitrypsin Deficiency OR Idiopathic Pulmonary Fibrosis OR Interstitial Lung Disease OR Bronchiectasis), (Non-tuberculous Mycobacteria OR Non-tuberculous Mycobacteria Pulmonary Disease) AND (Systemic Diseases OR Gastroesophageal Reflux Disease OR Immunodeficiency OR Immune deficits OR Immune defects)

Figure 1. First and second level interventions for patients with NTM pulmonary disease

First level (first ring) and second level (second ring) interventions for patients with NTM pulmonary disease

Figure 2. Clinical figures involved in the multidisciplinary team for the holistic management of patients with NTM pulmonary disease

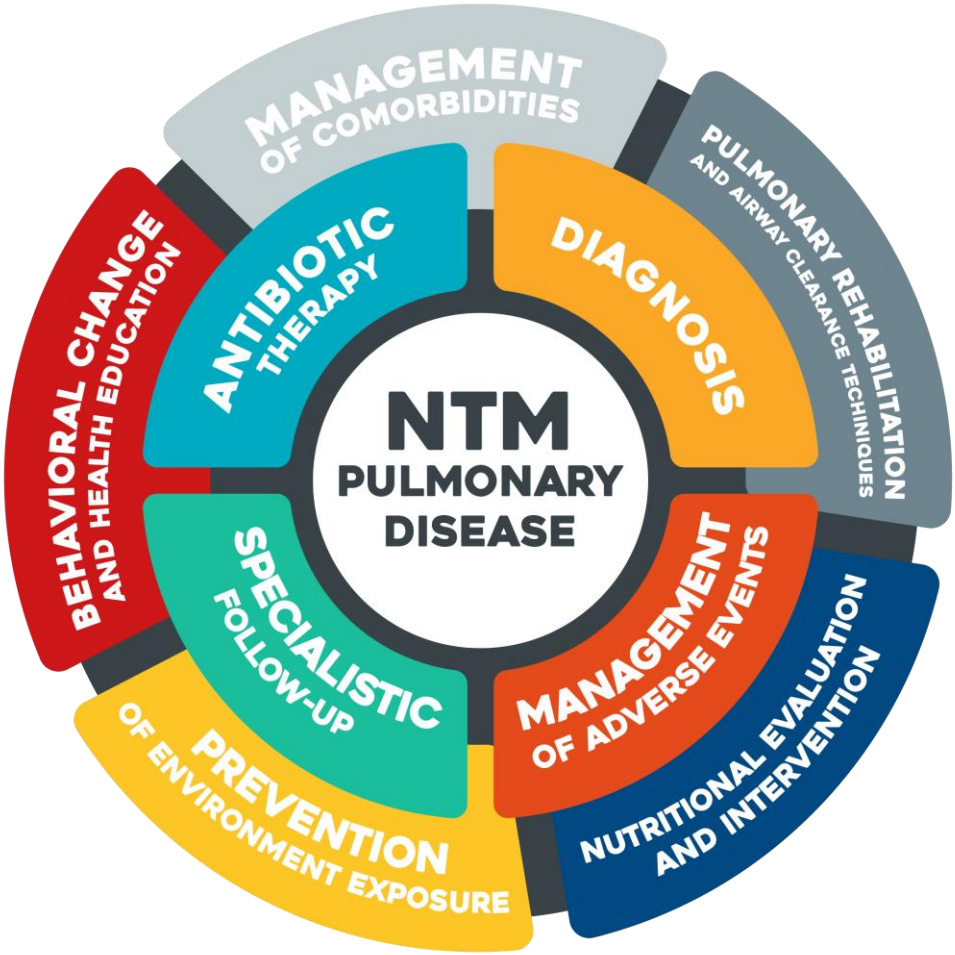
MANAGEMENT
OF COMORBIDITIES
PULMONARY REHABILITATION
AND AIRWAY CLEARANCE TECHINIQUES
DIAGNOSIS
ANTIBIOTIC
THERAPY
BEHAVIORAL CHANGE
AND HEALTH EDUCATION
NTM
PULMONARY
DISEASE
MANAGEMENT
OF ADVERSE EVENTS
NUTRITIONAL EVALUATION
AND INTERVENTION
SPECIALISTIC
FOLLOW-UP
PREVENTION
OF ENVIRONMENT EXPOSURE

Figure 1

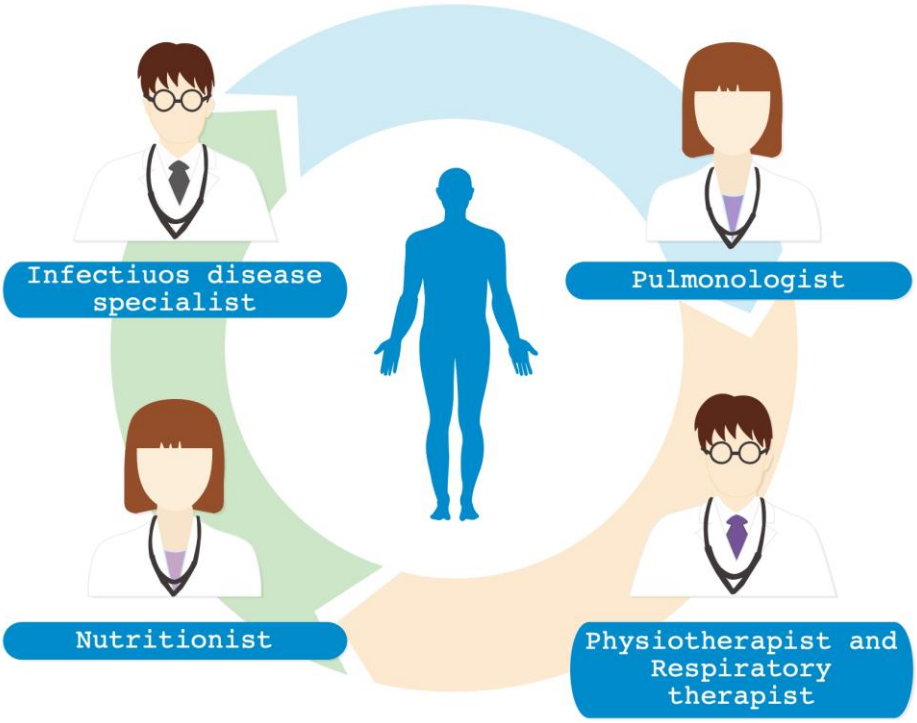
Infectiuos disease specialist
Pulmonologist
Nutritionist
Physiotherapist and Respiratory therapist

Figure 2