Journal of the Formosan Medical Association (2020) 119, S42—S50

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Review Article

Nonpharmacological treatment for patients with nontuberculous mycobacterial lung disease

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Received 11 March 2020; received in revised form 30 April 2020; accepted 11 May 2020

KEYWORDS
Airway clearance technique;
Bronchiectasis;
Nontuberculous mycobacterial lung disease;
Pulmonary rehabilitation;
Nutrition

Patients with nontuberculous mycobacterial lung disease (NTM-LD) often have significant exercise intolerance and poorer health-related quality of life (HRQL). The goals of treatment for NTM-LD should include reducing the severity of symptoms, improving HRQL, and reducing acute exacerbations. Nonpharmacological treatment, including pulmonary rehabilitation program and optimal nutritional strategy, should be one part of treatment for NTM-LD. A pulmonary rehabilitation (PR) program can comprise education, airway clearance techniques instruction, exercise training program, and inspiratory muscle training (IMT). Airway clearance techniques can improve the volume of sputum expectorated, cough symptom, breathlessness, and HRQL. Exercise training can improve exercise capacity and HRQL, and reduce acute exacerbations and dyspnea. Clinical benefits of IMT remain controversial but high-intensity IMT has been shown to be effective in increasing respiratory muscle strength with concurrent improvement of HRQL and exercise capacity. Body weight and muscle mass loss are common in patients with NTM-LD. An adequate protein and caloric diet combined with antioxidant nutrients might be the most appropriate dietary strategy. Comprehensive treatment for NTM-LD should include the combination of both pharmacological and nonpharmacological treatments. The management programs should be tailored to the individual's condition.

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https://doi.org/10.1016/j.jfma.2020.05.013

Introduction

Nontuberculous mycobacterial lung diseases (NTM-LDs) occur more commonly in patients with structural LDs such as chronic obstructive pulmonary disease (COPD), bronchiectasis, pneumoconiosis, and those from previous tuberculosis[1,2]. In the general population without structural LDs, only 0.055% had NTM isolated from respiratory specimens, but among those with structural LD, about 1.7% had NTM isolates during follow-up[3]. A broad range of radiological patterns are observed in NTM-LD, including bronchiectasis, nodular lesion, cavitary lesion, and parenchymal consolidation patterns[4]. The two main manifestations of NTM-LD are fibrocavitary and nodular bronchiectasis. The fibrocavitary form of NTM-LD presents as increased opacity often in the upper lungs, and it frequently affects elderly men with underlying LD. Nodular bronchiectasis manifests as bilateral, multilobar bronchiectasis with small nodules often located in the middle and lower lobes and often presents along with pleural thickening and volume reduction[4]. In one study, patients with NTM-LD had a significantly poorer health-related quality of life (HRQL) and more comorbidities such as aspergillosis, tuberculosis, bronchiectasis, and chronic respiratory failure than those without NTM-LD[5].

Growing evidence has indicated that NTM pulmonary infection may cause bronchiectasis.[4] However, bronchiectasis can also precede NTM pulmonary infection. Treatment for patients with NTM-LD and bronchiectasis remains highly challenging[6]. The goals of treatment for NTM-LD should include the reduction of symptom severity, improvement of HRQL, reduction of acute exacerbation, and prevention of respiratory failure[7]. Antimicrobial treatment is the main course of treatment for NTM-LD[1]. However, it is sometimes inadequate for patients with poor sputum clearance, immunocompromised condition, and structural LDs[7]. In these patients, despite the use of multiple antibiotics, culture conversion is sometimes difficult to achieve[8]. It has been reported that multidrug treatment regimens yield sputum culture conversion rates of only 13%—86%[9]. Thus, a comprehensive treatment for NTM-LD needs to include the management of concomitant LDs and a combination of both pharmacological and nonpharmacological treatments (Fig. 1 and Table 1). However, studies on nonpharmacological treatments for NTM-LD are relatively scarce; thus, the nonpharmacological treatment strategies mentioned in this review were sourced largely from the literature on bronchiectasis. The focus areas of this review are the following: (1) Pulmonary rehabilitation and (2) nutrition support for patients with NTM-LD.

Pulmonary rehabilitation

The pulmonary rehabilitation (PR) programs comprise education, airway clearance technique, exercise training, inspiratory muscle training (IMT), and postoperative PR[7,10]. PR programs are recommended to be an essential part of the nonpharmacological management and are integral to multidisciplinary programs of care in patients with COPD or bronchiectasis[7,11]. However, the randomized control trials (RCTs) on PR in NTM-LD are quite limited. Although, the role of PR in NTM-LD is undefined, the PR programs used to treat bronchiectasis might be able to serve as references because patients with NTM often have bronchiectasis. Recommendations for PR in patients with bronchiectasis were previously only supported by results from small trials[7]; however, in recent years, there is growing evidence supporting the benefits of PR in patients with bronchiectasis, especially those with dyspnea, exercise intolerance, and poor HRQL[12].

Assessments, including those of exercise capacity and HRQL, are crucial and should be a part of PR programs[13]. Exercise capacity is recommended to be evaluated before and after PR, and even small changes in exercise capacity may reflect important changes in health[14]. The 6-min walk test (6MWT), incremental shuttle walking test (ISWT), endurance shuttle walk test, or cardiopulmonary exercise test (CPET)[14] are often used tools to assess the exercise capacity. The advantages of the CPET are its ability to measure maximum exercise capacity and maximum oxygen uptake, identify physiological limitation factors, and evaluate prognoses. However, the CPET is difficult to perform in patients with severe dyspnea or arrhythmia[15]. In such patients, the 6MWT is simple and feasible to provide acceptable estimations of prognosis. One study by Yagi et al. showed that the 6-min walk distance is a useful parameter for evaluating exercise capacity in patients with *Mycobacterium avium* complex—LD[16]. However, the 6MWT cannot measure a person's maximum exercise capacity or identify physiological limitation factors[14]. The ISWT is similar to the CPET in that the exercise power can be gradually increased to measure maximum exercise capacity, and it is much simpler than the CPET[14]. Lee et al. suggested that the 6MWT and ISWT are reliable and responsive measures of exercise capacity in individuals with bronchiectasis[17], and found that the minimal important differences for patients with bronchiectasis were 25 m in the 6MWT and 35 m in the ISWT[17]. HRQL assessment before and after PR is also essential, and commonly used questionnaires such as the Short Form-36 Health Survey, St. George's Respiratory Questionnaire, COPD assessment test, and Leicester Cough Questionnaire have been employed in studies investigating NTM-LD[14,16,18].

Education should be offered by health care practitioners with the objective of improving patients' understanding and management of NTM-LD and associated diseases such as bronchiectasis[14]. Courses could be tailored to individual needs, covering, for example, self-care techniques, exercise training, medication use, inhaler techniques (if used by the patient), airway clearance techniques, infection management, oxygen therapy, nutrition, and hospice care, if necessary[14].

Airway clearance techniques

The vicious cycle hypothesis is widely accepted to explain the development and progression of bronchiectasis. The hypothesis suggests that failure of host defense leading to a host-mediated chronic inflammatory response[19] causes further impairment of mucociliary clearance and host defenses. Impaired mucociliary clearance results in microbial colonization of the bronchial trees. The microbial infection further causes chronic inflammation resulting in tissue damage and impaired mucociliary motility. This leads to more infection with a cycle of progressive inflammation

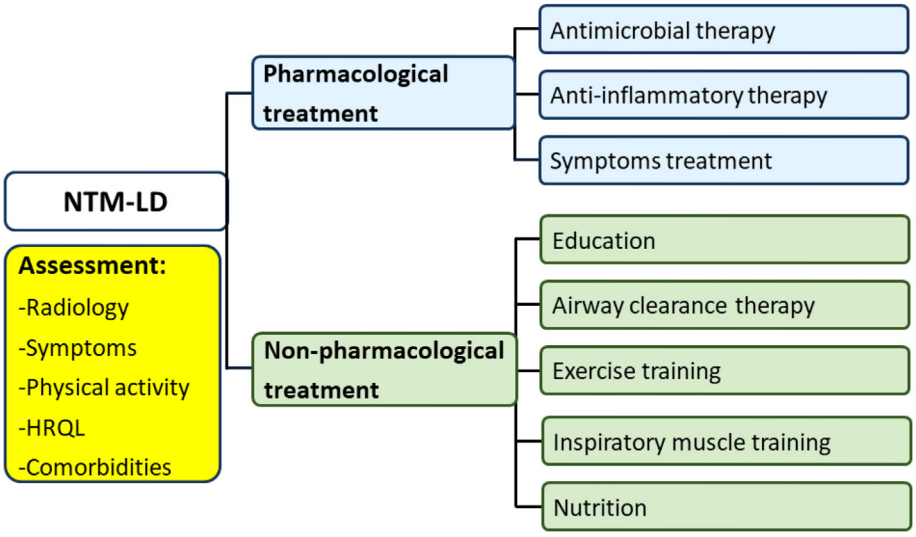

Figure 1 Comprehensive treatment of NTM-LD.

causing lung damage. Therefore, it is suggested that bronchial anatomic changes and airway clearance impairment appear to be the risk factors of chronic NTM infection[20]. Clearance of the mucus may help to break this vicious cycle[6]. Therefore, we suggest airway clearance techniques as part of the treatment plan for patients with NTM-LD.

Several airway clearance techniques can be used to treat individuals with NTM-LD, including the active cycle of breathing techniques (ACBT), autogenic drainage, forced expiration technique (FET), manual techniques, postural drainage (PD), oscillating positive expiratory pressure (OPEP) therapy, and high-frequency chest wall oscillation (HFCWO)[21–23]. ACBT is composed of breathing control, thoracic expansion exercises, and huffing, and helps patients to clear airway secretions[21]. The FET is a maneuver that uses thoracic expansion exercises to move secretions towards the mouth. PD uses gravity and percussion to loosen the thick, sticky secretions and lets the secretions to be removed by coughing[21]. OPEP therapy uses a device with positive end-expiratory pressure and air-flow oscillations to increase mobilization and elimination of airway secretions[21]. HFCWO is an airway clearance technique using a machine that produces external chest wall oscillations and loosening of the secretions[23].

Although few studies have evaluated airway clearance techniques in patients with NTM-LD, such techniques have long been used to treat bronchiectasis. The first RCT to compare OPEP and ACBT with and without PD in random treatment order was performed in 36 subjects with bronchiectasis[21]. The total sputum weight of the ACBT plus PD group was twice that of the ACBT group and OPEP group. All techniques were well accepted and tolerated by patients. The patients' preferences were 44% for OPEP, 22% for ACBT, and 33% for ACBT plus PD. In a systematic review on airway clearance techniques in patients with bronchiectasis[22], Snijders et al. reviewed 35 articles in the 1989—2014 international medical literature and discovered that ACBT could increase the amount of sputum expectorated and improve breathlessness, lung residual volume (RV), functional respiratory capacity (FRC), and total lung capacity (TLC) but had no effects on forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC). The FET can also increase the amount of sputum expectorated and improve RV, FRC, and TLC. PD with ACBT significantly increased sputum expectoration and improved cough symptoms and HRQL[22]. OPEP devices such as Acapella® and Flutter® can increase the quantity of sputum expectorated and improve RV, FRC, and TLC. These OPEP devices, however, have no effects on FEV1 and FVC.[22] HFCWO can improve sputum clearance, HRQL, FEV1, and FVC and it was more comfortable for patients relative to other techniques[22]. A recent systematic review covering six studies with a total of 120 participants noted that all airway clearance techniques were safe and reported no severe adverse reactions[23]. The ACBT may be more effective at improving gas exchange, sputum volume, and HRQL than PD. Participants in two studies preferred OPEP devices over the ACBT or PD techniques[23]. These studies have revealed that airway clearance techniques improve sputum clearance, symptoms, and HRQL in a bronchiectasis population. A retrospective single-center study[8] analyzed the effects of chest physical therapy (including manual chest percussion, HFCWO, and OPEP) in patients with NTM over a period of 8 years and observed an increase in TLC but not FEV1. Large RCTs on airway clearance techniques in NTM-LD are scarce. The effects of airway clearance techniques are summarized in Table 2.

Exercise training

Although studies on exercise training in patients with NTM-LD are relatively few, increasing evidence has indicated that exercise training increases exercise capacity and HRQL in patients with bronchiectasis. The exercise training program reported by Lee at al. included treadmill or land-based walking conducted twice weekly for 8 weeks[24]. The exercise intensities were 75% of the maximal speed achieved on the ISWT, 60% of the maximal work rate on a bike[24]. Mandal et al. conducted an exercise training program over two supervised sessions and one unsupervised

Table 1 Non-pharmacological treatment of NTM-LD.

Therapies	Items	Indications	Benefits
Education	- Knowledge about disease - Self-care technique - Pharmacological treatment - Non-pharmacological treatment - Smoking cessation - Hospice care	- All patients	- Improve self-management[14]
Airway Clearance Therapy	- Active cycle of breathing techniques - Autogenic drainage - Forced expiration technique - Manual techniques - Postural drainage - Positive expiratory pressure - Oscillating positive expiratory pressure - High frequency chest wall oscillation	- Copious secretions - Respiratory infection with retained secretions - Acute atelectasis	- Increase amount of sputum expectorated[8,21–23] - Improve symptoms (cough, dyspnea)[8,22] - Improve HRQL[8,22] - Decrease RV, FRC, and TLC[8,22]
Exercise training	- Bike - Treadmill - Walking - Swimming - Resistance training (with hand weights or bands)	- Poor exercise capacity - Poor HRQL - Persistent dyspnea	- Improve exercise capacity[12,24–26] - Improve HRQL[12,25,26] - Improve symptoms (dyspnea, fatigue)[24,26] - Decrease acute exacerbation[24]
Inspiratory muscle training	- IMT device	- Low MIP and MEP	- Increase respiratory muscle strength[28–30] - Improve exercise capacity[29,30] - Improve HRQL[29,30] - Decrease dyspnea[30]
Nutrition	- High-calorie intake/High protein content - Fruits and vegetables - Vitamin and mineral supplements - Oral nutritional supplements	- Malnutrition (BMI< <20 kg/m^2, serum albumin <3.5 g/dL)	- Increased muscle strength and HRQL (with PR)[44]

Abbreviation: BMI = body mass index, FEV1 = forced expiratory volume in 1 s, FRC = functional respiratory capacity, FVC = forced vital capacity, HRQL = health-related quality of life, MEP = maximal expiratory pressure, MIP = maximal inspiratory pressure, PR = pulmonary rehabilitation, TLC = total lung capacity.

session per week for 8 weeks[25]. After a warm up, patients completed 10-min sessions on the treadmill, bike, and ski machine. The intensity was 85% of maximum oxygen uptake[25]. Zanini et al. implemented a 3-week inpatient exercise training program including 12–15 supervised sessions[26]. All patients participated in sessions of 30–40 min, exercising on a treadmill or cycle ergometer. Exercise intensity was 60%–70% of the maximum heart rate achieved on the 6MWT and adjusted according to patients' tolerance, with the aim being a Borg dyspnea score of 3–5. Patients were also instructed on pursed lip breathing, airway clearance techniques, IMT, and nutritional support. The total daily duration of the training program was 2–3 h[26]. Patel et al. offered an outpatient exercise training program involving two supervised sessions and one home session per week for 8 weeks[12]. Exercise training was individualized and included cycling, aerobic walking, and four-limb resistance training.

In these studies, exercise training programs lasted approximately 8 weeks or 12–16 sessions. The frequency of exercise training was two supervised sessions a week with or without one session at home. The intensity of exercise training was approximately 60%–75% of maximal exercise capacity or heart rate.

Mandal et al. conducted a pilot RCT comparing an 8-week exercise training program plus respiratory physiotherapy with respiratory physiotherapy alone[25]. In the group that engaged in exercise training with respiratory physiotherapy, significantly greater improvement was achieved in the ISWT, Leicester Cough Questionnaire, and St. George's Respiratory Questionnaire, relative to the group that engaged in respiratory physiotherapy only. Lee et al. conducted another RCT comparing an 8-week exercise training group with a control group[24]. Significant improvements were obtained by the intervention group with respect to the exercise capacity, acute

Table 2 Effects of airway clearance techniques.

Interventions	Study design	Patient numbers	Results	Reference
- **PD** - **HFCWO** - **OPEP**	Retrospective	77 patients with NTM-LD	- Improved cough and sputum production - increase in TLC	8
- **OPEP (Flutter®) vs. ACBT vs. ACBT-PD**	Randomized controlled trial	36 patients with bronchiectasis	- All techniques were well accepted and tolerated. - The total sputum weight of the ACBT-PD group was twice than that of the ACBT group and OPEP group - The patients' preferences were 44% for OPEP, 22% for ACBT, and 33% for ACBT-PD	21
- **ACBT** - **ACBT-PD** - **FET** - **OPEP** - **HFCWO**	Systematic review	655 patients with bronchiectasis	- ACBT improved sputum expectorated, RV, FRC, and RLC - ACBT-PD improved sputum expectorated, cough symptoms and HRQL. - FET improved sputum expectorated, RV, FRC, and TLC - OPEP (Acapella® and Flutter®) improved sputum expectorated, RV, FRC, and TLC - HFCWO improved sputum clearance, HRQL, FEV1, and FVC - HFCWO was more comfortable relative to other techniques	22
- **ACBT** - **PD** - **FET** - **OPEP** - **HFCWO**	Systematic review	120 patients with bronchiectasis	- All airway clearance techniques were safe and reported no severe adverse reactions. - ACBT was more effective at improving gas exchange, sputum volume, and HRQL than PD - Participants preferred OPEP devices over the ACBT or PD	23

Abbreviation: ACBT = active cycle of breathing techniques, FET = forced expiration technique, FEV1 = forced expiratory volume in 1 s, FRC = functional respiratory capacity, FVC = forced vital capacity, HFCWO = high-frequency chest wall oscillation, HRQL = health-related quality of life, OPEP = oscillating positive expiratory pressure, PD = postural drainage, TLC = total lung capacity.

exacerbations, dyspnea, and fatigue domains of the Chronic Respiratory Disease Questionnaire. However, in their study, exercise training did not improve cough-related quality of life. A retrospective study evaluated the effect of a 3-week inpatient PR program on individuals with bronchiectasis[26]. This PR program had a significant effect on 6-min walk distance, HRQL, and dyspnea score. Their regression analysis suggested that male sex and severe disease were factors predicting improvement in HRQL and exercise capacity. Recently, Patel et al. performed a real-life, propensity-matched control study to compare the effects of supervised outpatient PR in patients with bronchiectasis versus patients with COPD[12]. They revealed that the bronchiectasis group had a similar completion rate (74%) as did the COPD group[12]. The changes in ISWT distance and Chronic Respiratory Disease Questionnaire score after PR were also similar between the two groups.[12] However, the bronchiectasis group had less improvement in the fatigue domain of the Chronic Respiratory Disease Questionnaire than did the COPD group[12]. These studies support the clinical provision of PR to patients with bronchiectasis. The effects of exercise training are summarized in Table 3.

IMT and postoperative PR

IMT is a method to train the respiratory muscle strength using a device[27]. The training is mostly conducted using a threshold or incentive spirometry, but the intensity and frequency of IMT programs have varied in studies. In most studies, IMT has been performed two to five days a week[27], with the intensity ranging from 30% to 80% of maximum inspiratory pressure[27] and the training duration ranging from 1 week to 1 year[27]. Although many studies have performed IMT for patients with pulmonary diseases, the clinical benefits of IMT remain controversial. In a previous study of patients with bronchiectasis, an 8-week IMT intervention group was compared with a control group[28]. IMT intervention resulted in significant improvements to inspiratory and expiratory muscle strength. However, the two groups did not significantly differ with respect to lung function, HRQL, and walking capacity. A recent RCT compared a control group with an intervention group that u-

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Table 3 Effects of Exercise training.

Interventions	Study design	Patient numbers	Results	Reference
- Session: two supervised sessions and one home session per week - Duration: 8 weeks - Exercise program: cycling, aerobic walking, and four-limb resistance training	Propensity-matched control study	213 patients with bronchiectasis vs. 213 patients with COPD	- Significant improvements in exercise capacity and HRQL. - The changes in exercise capacity and HRQL were similar between the two groups	12
- Session: two sessions per week - Duration: 8 weeks - Exercise program: treadmill or land-based walking - Intensity: 75% of the maximal speed on the ISWT, or 60% of the maximal work rate on a bike	Randomized controlled trial	85 patients with bronchiectasis	- Significant improvements in exercise capacity, acute exacerbations, dyspnea, and HRQL.	24
- Session: two supervised and one unsupervised session per week - Duration: 8 weeks - Exercise program: treadmill, bike, and ski machine - Intensity: 85% of maximum oxygen uptake	Randomized controlled trial	30 patients with bronchiectasis (15 patients in chest physiotherapy group, 15 patients in chest physiotherapy with exercise training)	- Exercise training plus chest physiotherapy with more improvement in exercise capacity and HRQL	25
- Session: total 12—15 sessions - Duration: 3 weeks - Exercise program: treadmill or cycle ergometer. - Intensity: 60%—70% of the maximum heart rate	Retrospective study	135 patients with bronchiectasis	- Significant improvement in exercise capacity, HRQL, and dyspnea score. - Regression analysis: male gender and severe disease predicting improvement in HRQL and exercise capacity.	26

Abbreviation: COPD = chronic obstructive pulmonary disease, ISW = incremental shuttle walk, HRQL = health-related quality of life.

derwent an 8-week high-intensity IMT (70% maximal inspiratory pressure)[29]; high-intensity IMT resulted in increased respiratory muscle strength, HRQL, and exercise capacity. Another study demonstrated that an 8-week home-based high-intensity IMT improved inspiratory muscle strength and HRQL (measured using the St. George's Respiratory Questionnaire) and reduced dyspnea during daily activity; however, such IMT did not reduce the 6-min walk distance in patients with advanced LD[30]. The benefits were sustained for 3 months[30].

Some types of NTM-LD are difficult to control with antimicrobial therapy alone[4], and surgical resection may be beneficial in some patients. However, lung surgery often decreases physical fitness and HRQL[4]. Intervention of PR programs either before or after surgery, might be considered for patients with NTM-LD. Morino et al. investigated preoperative PR in 19 patients with NTM-LD who received video-assisted thoracic surgery with lung resection[31] and discovered that PR reduced postoperative atelectasis and pneumonia. Thus, preoperative PR may be effective in preventing postoperative complications.

Nutrition

Weight and muscle mass loss tend to be high in patients with chronic inflammatory LDs, such as NTM-LD, emphysema[32], and COPD[33]. The unintentional weight loss in NTM-LD can be attributed to increased calorie needs, decreased appetite, early satiety, nausea, taste bud changes, medication side effects, and inflammatory response to NTM-LD[34]. Chronic inflammatory status could also account for increased body weight loss and the catabolization of lean body protein[35]. Among patients with NTM-LD, failure to stabilize body weight is closely associated with poorer outcomes during treatment[36]. Besides, lower serum albumin level and higher C reactive protein level were associated with a higher risk of disease progression[37] and a lower probability of responding to therapy[38].

Common indicators of malnutrition in patients with pulmonary disease are (1) body mass index, (2) fat free mass, (3) the fat free mass index (calculated as the fat free mass divided by the squared of height), and (4) multifrequency bioelectrical impedance spectroscopy results. Although body mass index is a useful indicator of overall health status, it does not measure composition of fat and muscle mass. Fat free mass and multifrequency bioelectrical impedance spectroscopy provide more details on muscle and fat composition, thus fat free mass is more capable than body mass index in evaluating malnutrition or muscle wasting and could be a better malnutrition screening tool and predictor of nutritional status[39,40].

Sufficient caloric and protein intake plays a crucial role to help patients fight infection[41], but studies addressing the benefits of nutritional supplementation in patients with NTM-LD remain scarce. However, chronic inflammatory status, such as bronchiectasis, is frequently noted in patients with NTM-LD and it could lead to hypermetabolism with increased protein catabolism, loss of lean body mass, and exercise intolerance, and contribute to a poor quality of life[35]. Thus, an adequate protein and caloric diet combined with antioxidant nutrients might be the most appropriate dietary strategy[42,43]. In bronchiectasis patients, an RCT showed that the addition of a hyperproteic oral nutritional supplement enriched with beta-hydroxy-beta-methylbutyrate to PR could improve body composition, muscle strength, and HRQL[44]. A practical strategy to increase appetite could include appetite-stimulating medication, frequent meals, and nutritional supplement drinks. Frequent small meals with high-calorie foods might benefit patients with poor appetite[45], since the respiratory load during a small meal (250—500 kcal) is relatively low. Animal proteins, such as meat, fish, eggs, poultry, legumes, and dairy products, can provide essential amino acids. Meanwhile, vegetarians can obtain complete protein through foods such as tofu or other soy products.

Nutrients with antioxidant ability and other supplements

Although the studies on nutrients with antioxidant ability in NTM-LD are lacking, previous studies in COPD[46] and cystic fibrosis[47] revealed that nutrients with antioxidant ability might help in alleviating lung function loss and airway inflammation. Micronutrients such as vitamins and minerals can affect several components of innate immunity[48,49]. The deficiencies in these micronutrients affect a person's immunity to fight infections. Significantly lower serum concentrations of vitamins A, D, and E have been reported in patients with tuberculosis relative to healthy control groups[48,49]. A few studies also demonstrated that patients with NTM-LD have multiple significant vitamin deficiencies and the intake of multivitamin and mineral supplements may be beneficial[50].

Patients with significantly reduced body weight or food intake might benefit from nutritional supplements between meals[51]. These can improve patient's nutritional status and stabilize their weight and muscle mass[51]. A balanced formula containing the basic daily nutrients requirement is the first recommended choice. In addition, palatability, volume, and energy density of liquid diet are also important factors when selecting a commercial formula[52]. A special formula with high proportion of fat might help to reduce demand of carbon dioxide, but it might cause slow gastric emptying, and increase satiety and decrease appetite[53].

Future work

Studies concerning PR programs and nutrition support in patients with NTM-LD remain limited. Only small-sample and retrospective studies have been performed. PR and nutrition support were recommended for patients with NTM-LD based on the results of a few small clinical studies and extrapolations from guidelines for bronchiectasis or COPD. Further studies, especially large RCTs on PR programs and nutrition support are necessary. The cost of treatment of NTM-LD is substantial, especially the cost of drugs and hospitalization[54]. Studies investigating the cost-effectiveness of PR programs in patients with NTM are lacking, and further investigation is necessary.

Conclusions

Patients with NTM-LD have been reported to have a significantly poorer HRQL and exercise intolerance than healthy controls do. The goals of treatment for NTM-LD should include reducing symptom severity, improving HRQL, improving exercise capacity, and reducing acute exacerbation. Medical treatment is the main course of treatment for NTM-LD, but it is sometimes inadequate in managing patients with NTM-LD. Nonpharmacological treatment strategies, including PR programs involving airway clearance techniques, exercise training, IMT, education, and nutrition support are well known to improve HRQL, exercise capacity, and acute exacerbation in patients with lung diseases such as bronchiectasis and COPD. The combination of medical treatment and nonpharmacological management is integral in the management of these diseases. It is rational to apply these treatments to NTM-LD. However, further studies, especially large RCTs are needed.

Declaration of Competing Interest

The authors have no conflicts of interest relevant to this article.

Acknowledgements

This work is supported by Taiwan Society of Pulmonary and Critical Care Medicine.

References

1. Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Gordin F, Holland SM, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med* 2007;**175**(15):367416.
2. Chien JY, Lai CC, Sheng WH, Yu CJ, Hsueh PR. Pulmonary infection and colonization with nontuberculous mycobacteria, Taiwan, 2000-2012. *Emerg Infect Dis* 2014;**20**(8):1382—5.
3. Shteinberg M, Stein N, Adir Y, Ken-Dror S, Shitrit D, Bendayan D, et al. Prevalence, risk factors and prognosis of

nontuberculous mycobacterial infection among people with bronchiectasis: a population survey. *Eur Respir J* 2018;**51**(5): 1702469.
4. Ryu YJ, Koh WJ, Daley CL. Diagnosis and treatment of nontuberculous mycobacterial lung disease: clinicians' perspectives. *Tuberc Respir Dis* 2016;**79**(2):74—84.
5. Yeung MW, Khoo E, Brode SK, Jamieson FB, Kamiya H, Kwong JC, et al. Health-related quality of life, comorbidities and mortality in pulmonary nontuberculous mycobacterial infections: a systematic review. *Respirology* 2016;**21**(6): 1015—25.
6. Horne D, Skerrett S. *Recent advances in nontuberculous mycobacterial lung infections. F1000Res*, vol. 8. F1000 Faculty Rev; 2019. p. 1710.
7. Polverino E, Goeminne PC, McDonnell MJ, Aliberti S, Marshall SE, Loebinger MR, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Respir J* 2017;**50**(3):1700629.
8. Basavaraj A, Segal L, Samuels J, Feintuch J, Feintuch J, Alter K, et al. Effects of chest physical therapy in patients with non-tuberculous mycobacteria. *Int J Respir Pulm Med* 2017; **4**(1):65.
9. Haworth CS, Banks J, Capstick T, Fisher AJ, Gorsuch T, Laurenson IF, et al. British Thoracic Society guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD) *Thorax* 2017;**72**(Suppl 2):ii1—64.
10. Lee CT, Hsieh PL, Chien MY, Chien JY, Wu HD, Lin JS, et al. Trajectories of functional exercise capacity in patients undergoing pulmonary rehabilitation. *Int J Chronic Obstr Pulm Dis* 2019;**14**:863—70.
11. Dong J, Li Z, Luo L, Xie H. Efficacy of pulmonary rehabilitation in improving the quality of life for patients with chronic obstructive pulmonary disease: evidence based on nineteen randomized controlled trials. *Int J Surg* 2020;**73**:78—86.
12. Patel S, Cole AD, Nolan CM, Barker RE, Jones SE, Kon S, et al. Pulmonary rehabilitation in bronchiectasis: a propensity-matched study. *Eur Respir J* 2019;**53**(1). pii: 1801264.
13. Pulmonary rehabilitation-1999. American thoracic society. *Am J Respir Crit Care Med* 1999;**159**:1666—82.
14. Hill AT, Sullivan AL, Chalmers JD, Soyza AD, Elborn SJ, Floto AR, et al. British thoracic society guideline for bronchiectasis in adults. *Thorax* 2019;**74**(Suppl 1):1—69.
15. Wu CW, Hsieh PC, Yang MC, Tzeng IS, Wu YK, Cc L. Impact of peak oxygen pulse on patients with chronic obstructive pulmonary disease. *Int J Chronic Obstr Pulm Dis* 2019;**14**: 2543—51.
16. Yagi K, Asakura T, Namkoong H, Suzuki S, Asami T, Okamori S, et al. Association between six-minute walk test parameters and the health-related quality of life in patients with pulmonary Mycobacterium avium complex disease. *BMC Pulm Med* 2018;**18**(1):114.
17. Lee AL, Hill CJ, Cecins N, Jenkins S, McDonald CF, Burge AT, et al. Minimal important difference in field walking tests in non-cystic fibrosis bronchiectasis following exercise training. *Respir Med* 2014;**108**(9):1303—9.
18. Hama M, Ushiki A, Kosaka M, Yamazaki Y, Yasuo M, Yamamoto H, et al. Health-related quality of life in patients with pulmonary non-tuberculous mycobacteria infection. *Int J Tubercul Lung Dis* 2016;**20**(6):747—52.
19. Amati F, Simonetta E, Gramegna A, Tarsia P, Contarini M, Blasi F, et al. The biology of pulmonary exacerbations in bronchiectasis. *Eur Respir Rev* 2019;**28**(154):190055.
20. Faverio P, Stainer A, Bonaiti G, Zucchetti SC, Simonetta E, Lapadula G, et al. Characterizing non-tuberculous mycobacteria infection in bronchiectasis. *Int J Mol Sci* 2016;**17**(11): E1913.
21. Eaton T, Young P, Zeng I, Kolbe J. A randomized evaluation of the acute efficacy, acceptability and tolerability of flutter and active cycle of breathing with and without postural drainage in non-cystic fibrosis bronchiectasis. *Chron Respir Dis* 2007;**4**(1): 23—30.
22. Snijders D, Fernandez Dominguez B, Calgaro S, Bertozzi I, Montaner AE, Perilongo G, et al. Mucociliary clearance techniques for treating non-cystic fibrosis bronchiectasis: is there evidence? *Int J Immunopathol Pharmacol* 2015;**28**(2):150—9.
23. Phillips J, Lee A, Pope RWH. Effect of airway clearance techniques in patients experiencing an acute exacerbation of bronchiectasis: a systematic review. *Physiother Theory Pract* 2019;**18**:1—16.
24. Lee AL, Hill CJ, Cecins N, Jenkins S, McDonald CF, Burge AT, et al. The short and long term effects of exercise training in non-cystic fibrosis bronchiectasis-a randomised controlled trial. *Respir Res* 2014;**15**:44.
25. Mandal P, Sidhu MK, Kope L, Pollock W, Stevenson LM, Pentland JL, et al. A pilot study of pulmonary rehabilitation and chest physiotherapy versus chest physiotherapy alone in bronchiectasis. *Respir Med* 2012;**106**(12):1647—54.
26. Zanini A, Aiello M, Adamo D, Cherubino F, Zampogna E, Sotgiu G, et al. Effects of pulmonary rehabilitation in patients with non-cystic fibrosis bronchiectasis: a retrospective analysis of clinical and functional predictors of efficacy. *Respiration* 2015;**89**(6):525—33.
27. Beaumont M, Forget P, Couturaud F, Reychler G. Effects of inspiratory muscle training in COPD patients: a systematic review and meta-analysis. *Clin Res J* 2018;**12**(7): 2178—88.
28. Liaw MY, Wang YH, Tsai YC, Huang KT, Chang PW, Chen YC, et al. Inspiratory muscle training in bronchiectasis patients: a prospective randomized controlled study. *Clin Rehabil* 2011; **25**(6):524—36.
29. Ozalp O, Inal-Ince D, Cakmak A, Calik-Kutukcu E, Saglam M, Savci S, et al. High-intensity inspiratory muscle training in bronchiectasis: a randomized controlled trial. *Respirology* 2019;**24**(3):246—53.
30. Hoffman M, Augusto VM, Eduardo DS, Silveira BMF, Lemos MD, Parreira VF. Inspiratory muscle training reduces dyspnea during activities of daily living and improves inspiratory muscle function and quality of life in patients with advanced lung disease. *Physiother Theory Pract* 2019:1—11.
31. Morino A, Murase K, Yamada K. Complications after video-assisted thoracic surgery in patients with pulmonary non-tuberculous mycobacterial lung disease who underwent preoperative pulmonary rehabilitation. *J Phys Ther Sci* 2015; **27**(8):2541—4.
32. Ceelen JJM, Schols A, van Hoof SJ, de Theije CC, Verhaegen F, Langen RCJ. Differential regulation of muscle protein turnover in response to emphysema and acute pulmonary inflammation. *Respir Res* 2017;**18**(1):75.
33. Hsieh MJ, Yang TM, Tsai YH. Nutritional supplementation in patients with chronic obstructive pulmonary disease. *J Formos Med Assoc* 2016;**115**(8):595—601.
34. Wassilew N, Hoffmann H, Andrejak C, Lange C. Pulmonary disease caused by non-tuberculous mycobacteria. *Respiration* 2016;**91**(5):386—402.
35. Powers SK, Lynch GS, Murphy KT, Reid MB, Zijdewind I. Disease-induced skeletal muscle atrophy and fatigue. *Med Sci Sports Exerc* 2016;**48**(11):2307—19.
36. Wakamatsu K, Nagata N, Maki S, Omori H, Kumazoe H, Ueno K, et al. Patients with MAC lung disease have a low visceral fat area and low nutrient intake. *Pulm Med* 2015;**2015**:218253.
37. Cowman SA, Jacob J, Obaidee S, Floto RA, Wilson R, Haworth CS, et al. Latent class analysis to define radiological subgroups in pulmonary nontuberculous mycobacterial disease. *BMC Pulm Med* 2018;**18**(1):145.
38. Kim SJ, Park J, Lee H, Lee YJ, Park JS, Cho YJ, et al. Risk factors for deterioration of nodular bronchiectatic

Mycobacterium avium complex lung disease. *Int J Tubercul Lung Dis* 2014;**18**(6):730—6.
39. de Blasio F, de Blasio F, Miracco Berlingieri G, Bianco A, Greca ML, Franssen FME, et al. Evaluation of body composition in COPD patients using multifrequency bioelectrical impedance analysis. *Int J Chronic Obstr Pulm Dis* 2016;**11**:2419—26.
40. de Blasio F, Santaniello MG, de Blasio F, Mazzarella G, Bianco A, Lionetti L, et al. Raw BIA variables are predictors of muscle strength in patients with chronic obstructive pulmonary disease. *Eur J Clin Nutr* 2017;**71**(11):1336—40.
41. Katona P, Katona-Apte J. The interaction between nutrition and infection. *Clin Infect Dis* 2008;**46**(10):1582—8.
42. Kurutas EB. The importance of antioxidants which play the role in cellular response against oxidative/nitrosative stress: current state. *Nutr J* 2016;**15**(1):71.
43. Yang PH, Lin MC, Liu YY, Lee CL, Chang NJ. Effect of nutritional intervention programs on nutritional status and readmission rate in malnourished older adults with pneumonia: a randomized control trial. *Int J Environ Res Publ Health* 2019;**16**(23).
44. Olveira G, Olveira C, Doña E, Palenque FJ, Porras N, Dorado A, et al. Oral supplement enriched in HMB combined with pulmonary rehabilitation improves body composition and health related quality of life in patients with bronchiectasis. *Clin Nutr* 2016;**35**(5):1015—22.
45. Torricelli P, Antonelli F, Ferorelli P, Borromeo I, Shevchenko A, Lenzi S, et al. Oral nutritional supplement prevents weight loss and reduces side effects in patients in advanced lung cancer chemotherapy. *Amino Acids* 2020;**52**(3):445—51.
46. Zhai T, Li S, Hu W, Li D, Leng S. Potential micronutrients and phytochemicals against the pathogenesis of chronic obstructive pulmonary disease and lung cancer. *Nutrients* 2018;**10**(7).
47. Papas KA, Sontag MK, Pardee C, Sokol RJ, Sagel SD, Accurso FJ, et al. A pilot study on the safety and efficacy of a novel antioxidant rich formulation in patients with cystic fibrosis. *J Cyst Fibros* 2008;**7**(1):60—7.
48. Aibana O, Franke MF, Huang CC, Galea JT, Calderon R, Zhang Z, et al. Vitamin E status is inversely associated with risk of incident tuberculosis disease among household contacts. *J Nutr* 2018;**148**(1):56—62.
49. Qiuzhen Wang1 AM, Gao1 Tianlin, Liu2 Yufeng, Ren3 Lisheng, Lei Han3, Wei1 Boyang, et al. Poor vitamin D status in active pulmonary tuberculosis patients and its correlation with leptin and TNF-a. *J Nutr Sci Vitaminol* 2019;**65**:390—8.
50. Sagel SD, Khan U, Jain R, Graff G, Daines CL, Dunitz JM, et al. Effects of an antioxidant-enriched multivitamin in cystic fibrosis. A randomized, controlled, multicenter clinical trial. *Am J Respir Crit Care Med* 2018;**198**(5):639—47.
51. Aniwidyaningsih W, Varraso R, Cano N, Pison C. Impact of nutritional status on body functioning in chronic obstructive pulmonary disease and how to intervene. *Curr Opin Clin Nutr Metab Care* 2008;**11**(4):435—42.
52. Nieuwenhuizen WF, Weenen H, Rigby P, Hetherington MM. Older adults and patients in need of nutritional support: review of current treatment options and factors influencing nutritional intake. *Clin Nutr* 2010;**29**(2):160—9.
53. Crescl G. *Nutrition support for the critically ill patient : a guild to practice*. 2005.
54. Prevots DR, Loddenkemper R, Sotgiu G, Migliori GB. Nontuberculous mycobacterial pulmonary disease: an increasing burden with substantial costs. *Eur Respir J* 2017;**49**(4):1700374.