



# Optimising non-pharmacological interventions in people with non-tuberculous mycobacterial pulmonary disease: a systematic review

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**Non-pharmacological interventions show potential in managing NTM-PD, but gaps in evidence remain. High-quality studies are needed to establish the efficacy of airway clearance, PR, nutritional support and psychological care in people with NTM-PD.** <https://bit.ly/440UVP4>

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## Abstract

**Introduction** Treatment of non-tuberculous mycobacterial pulmonary disease (NTM-PD) is often complex, relying on long treatment courses with multiple antibiotics, which are associated with treatment intolerance and failure. Current guidelines provide limited insight into non-pharmacological treatment, which is believed to be an important component of symptom control and is related to treatment outcomes with an established evidence base in other chronic respiratory diseases.

**Methods** The authors conducted a systematic review following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to identify studies on non-pharmacological interventions for NTM-PD, focusing on airway clearance techniques, pulmonary rehabilitation, nutritional support and psychological care.

**Results** There was little evidence regarding the impact of non-pharmacological interventions in NTM-PD. We identified three studies that described a positive impact of airway clearance techniques, including oscillating positive expiratory pressure, chest physical therapy with devices such as Acapella and Flutter, as well as chest oscillatory techniques (*e.g.* Vest) and hypertonic saline nebulisation. We found no relevant studies in NTM-PD reporting the use of nutrition, pulmonary rehabilitation or psychological care as interventions in this group of patients.

**Conclusions** Non-pharmacological interventions show potential in managing NTM-PD, although significant evidence gaps remain. This review highlights the importance of expanding high-quality studies on the use of these interventions to people with NTM-PD.

## Introduction

Non-tuberculous mycobacterial pulmonary disease (NTM-PD) is increasingly recognised as a significant cause of morbidity, particularly among older adults with underlying structural lung conditions, such as bronchiectasis and COPD [1–4]. The rising incidence of NTM-PD and its associated complex care needs make it an increasing issue for respiratory services [5, 6]. Current treatment regimens for NTM-PD rely heavily on prolonged courses of multiple antibiotics, which are associated with significant adverse effects, treatment intolerance, and high rates of relapse and failure [7–9].

In addition to these pharmacological challenges, NTM-PD is often characterised by persistent respiratory symptoms, such as chronic cough and sputum production, which severely impair patients' quality of life



[10]. These symptoms suggest that sputum clearance could play a crucial role in improving both clinical and psychological outcomes in NTM-PD patients [11, 12]. This argument is further supported by data indicating that pharmacological treatments alone are often insufficient to address the multifaceted nature of the disease [13].

Given these limitations, there is growing interest in non-pharmacological interventions, including pulmonary rehabilitation, airway clearance techniques, nutritional support and psychological care [14]. These approaches have demonstrated benefits in related respiratory conditions such as bronchiectasis and COPD and may offer similar advantages for NTM-PD patients [15–19]. However, the evidence directly supporting their use in NTM-PD remains limited, with much of the current data being extrapolated from studies on related conditions [14, 20].

This review aims to critically assess the current literature on non-pharmacological interventions in NTM-PD, focusing on pulmonary rehabilitation, airway clearance techniques, including mucolytics, as well as nutritional support, and psychological care. By identifying the available evidence and highlighting key gaps, we hope to inform both clinical practice and the direction of future research in the management of NTM-PD.

## Methodology

### Search strategy

The systematic search was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, utilising Scopus, Ovid MEDLINE, and EBSCOhost CINAHL Plus databases, as well as grey literature through Google Scholar and citation search performed up to March 2025 (figure 1) [21, 22]. The search strategy was not restricted by language. The search terms included “non-tuberculous mycobacteria”, “non-pharmacological intervention”, “pulmonary disease”, “rehabilitation”, “nutrition”, “sputum clearance”, “airway clearance”, “physical therapy”, “mucolytics” and “psychological and mental care”. Results were screened for relevant titles and abstracts, with the inclusion of all primary studies. This review protocol has been registered at [www.crd.york.ac.uk/PROSPERO](http://www.crd.york.ac.uk/PROSPERO) (identifier CRD42023480705).

### Data extraction

We aimed to identify studies addressing non-pharmacological NTM-PD interventions, focusing on airway clearance techniques, pulmonary rehabilitation, nutritional support and psychological healthcare. The main outcomes investigated were patient-reported outcome measures (PROMs), including health-related quality of life, sputum production, cough, frequency of exacerbation, changes in lung function, and microbiological outcomes such as changes in sputum culture positivity.

The information retrieved was presented in a tabular form and discussed in a narrative synthesis, summarising the different interventions under evaluation (table 1).

### Quality assessment

For the quality assessment, a modified Newcastle–Ottawa Quality Assessment Form for cohort studies and the validated Mixed Methods Appraisal Tool (version 2018) for case report studies were used [26, 27]. Two reviewers independently assessed the quality, and a third author resolved potential disagreements.

## Results

Our initial search retrieved 473 articles, with 31 qualifying for full-text evaluation (figure 1). Few studies provided insights into the potential role of non-pharmacological interventions in NTM-PD patients. We found no relevant studies in NTM-PD reporting the use of nutrition, pulmonary rehabilitation or psychological care as interventions or mucolytics. Only two studies qualified for inclusion in this review from the databases [23, 28], and two additional studies were retrieved through grey literature and citation searches [24, 25] (figure 1 and table 1). All four studies focused mainly on airway clearance techniques (ACT); however, in one of these, NTM-PD was present in 32% of a bronchiectasis study population, and we were unable to obtain disaggregated NTM-PD specific data from the authors. Therefore, this study was not assessed further [28]. Overall, the quality of the included studies was rated as poor (supplementary material).

### Characteristics of the included studies

BASAVARAJ *et al.* [23] reported that chest physiotherapy had a significant impact in reducing symptoms and improving static lung function values in a cohort of 77 patients with NTM-PD (92% with *Mycobacterium avium* complex (MAC) infection) not taking antimicrobial therapy. They compared patients using ACT (n=39), with those who were not (n=38). ACT involved mucus mobilisation with chest physical therapy,

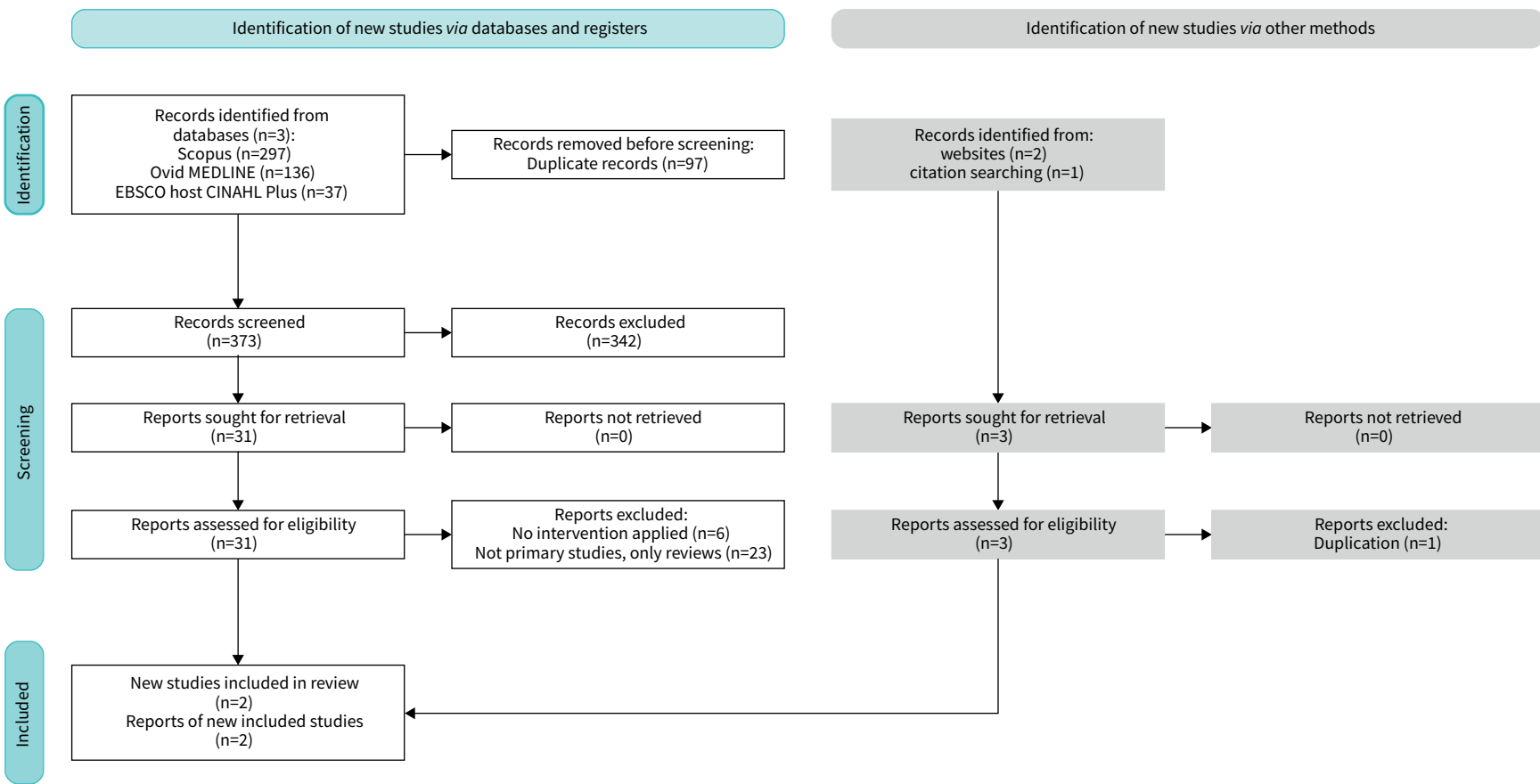


FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

TABLE 1 Characteristics of relevant studies identified by literature search

First author, year [reference], country	Study period	Study design	Population	Radiological disease present	Sample size	Sex	Age years	Intervention	Frequency	Follow-up frequency	Outcomes
BASAVARAJ, 2017 [23], United States of America	2006–2014	Retrospective cohort	Patients with at least one positive NTM culture Not on specific antimicrobial therapy Age: ≥21 years Not pregnant	Bronchiectasis Bronchiolitis Bronchial wall thickening Ground-glass opacities Muroid impaction	77 adults 39 ACT 38 no ACT	Female: 54 (70)	67±14	ACT with high-frequency chest wall oscillation devices (OPEP, Vest)	NA	3, 6, 9, 12, 18 and 24 months	Compared to baseline: ACT group: Cough: significant decrease at 6, 9, 12 and 24 months Sputum production: improved, but not significant at 24 months CT scan findings: decreased overall at 6 and 9 months, with no changes in muroid impaction PFT changes: FVC % pred increased by 4.1% at 6 months, and 11% at 24 months; significant changes in (FEV <sub>1</sub> /FVC %, TLC % and RV % pred) No-ACT group: Cough: significant decrease at 12 months only Sputum production: no change CT scan findings: decrease overall at 3, 6 and 9 months PFT changes: minimal change (no values given)
HUIBERTS, 2019 [24], the Netherlands	2015–2017	Retrospective cohort	NTM-PD using HS for ≥3 months without specific antimicrobial therapy	Nodular-bronchiectatic Fibro-cavitary	25 in total 8 excluded (lost to follow-up) 17 continued after the initial 3 months 5 started antibiotics (excluded) 12 did not receive antibiotics	Female: 19 (76)	69±9.8	HS inhalation followed by an active cycle of breathing techniques	Twice daily	Initially 3 months Overall range 3–36 months	After 3 months (n=21; 4 missing): Symptoms: improvement 9 (36%); stable 7 (28%); deterioration 5 (20%) Radiographic: improvement 3 (12%) (decrease in the size/amount of nodular infiltrates); stable 10 (40%); deterioration 8 (32%) PFT: no significant changes In the final 12 patients: 6 culture conversion to negative (all nodular-bronchiectatic), culture conversion time (23.5±9.9 weeks) 6 no culture conversion, but continued HS due to symptom improvement

Continued

TABLE 1 Continued

First author, year [reference], country	Study period	Study design	Population	Radiological disease present	Sample size	Sex	Age years	Intervention	Frequency	Follow-up frequency	Outcomes
KURAHARA, 2024 [25], Japan	NA	Case report	Patients with NTM-PD under antibiotic therapy including ALIS, who presented daily sputum production	Nodular-bronchiectatic	1 with MAC-PD 1 with <i>Mycobacterium avium</i> plus <i>Mycobacterium intracellulare</i>	Female: 2 (100)	69, 82	High-frequency chest wall oscillation devices (OPEP)	Five times daily for $\geq 5$ min	1 month	Case 1: Symptoms: sputum symptoms improved Radiology: nodules improved HRQoL (LCQ and BCSS scores): improved (+2.36 and -5, respectively) Bodyweight: stable Lung functional gain: FVC +290 mL; FEV <sub>1</sub> +300 mL Case 2: Symptoms: sputum expectoration improved Radiology: consolidation improved HRQoL (LCQ and BCSS scores): improved (+3.24 and -6, respectively) Bodyweight: stable Lung functional gain: FVC +210 mL; FEV <sub>1</sub> +310 mL

Data are presented as n, n (%) or mean $\pm$ sd, unless otherwise stated. NTM: non-tuberculous mycobacteria; ACT: airway clearance techniques; OPEP: oscillating positive expiratory pressure; NA: not available; CT: computed tomography; PFT: pulmonary function test; FVC: forced vital capacity; % pred: % predicted; FEV<sub>1</sub>: forced expiratory volume in 1 s; TLC: total lung capacity; RV: residual volume; PD: pulmonary disease; HS: hypertonic saline; ALIS: amikacin liposome inhalation suspension; MAC: *Mycobacterium avium* complex; HRQoL: health-related quality of life; LCQ: Leicester Cough Questionnaire; BCSS: Breathlessness, Cough and Sputum Scale.

devices such as Acapella and Flutter, and chest oscillatory techniques (e.g. Vest). They found a significant and sustained improvement in cough in the ACT group during 24 months of follow-up, and a tendency toward reduced sputum production compared to baseline. In addition, they reported a forced vital capacity (FVC) increase of 11% predicted over 24 months in the ACT group ( $p=0.028$ ). However, the data on lung function were from 26 patients, and there was no mention of how many in each group dropped out during the study. In addition, the study had a small sample size, was retrospective and used inclusion criteria of one positive NTM culture (not aligning with the more stringent NTM-PD diagnostic criteria of at least two positive cultures separated in time, which would be more often used). Few data were provided on how symptoms were measured, further limiting the generalisability of these findings. Although the groups appeared to be matched, there was potential for selection bias, as the decision to initiate ACT was nonrandomised and based on the physician's choice [23].

As an additional approach to enhancing airway clearance, HUIBERTS *et al.* [24] evaluated the use of hypertonic saline inhalation twice daily without antimicrobial therapy in a single arm study of 25 NTM-PD patients for  $\geq 3$  months as part of their NTM specialist centre treatment protocol. The study was initiated based on earlier *in vitro* findings suggesting that 5.8% hypertonic saline could kill MAC and inhibit *Mycobacterium abscessus* growth, in addition to its beneficial effects in bronchiectasis. The aim was to measure whether hypertonic saline had similar *in vivo* effects in NTM-PD patients. Participants were initially assessed by a physiotherapist, who instructed them on active breathing techniques to improve sputum clearance. Sputum samples were analysed throughout the study, with an average follow-up time of  $16.2 \pm 19.0$  months. After 3 months, from data available on 21 patients, 36% reported symptomatic improvement, and 12% showed radiographic improvement. Data on sputum culture results at this time were not available, limiting the assessment of microbiological outcomes at a pre-determined time point. However, they found no significant changes in lung function parameters over the first 3 months of hypertonic saline therapy.

After the initial 3-month follow-up, 17 patients continued hypertonic saline. Five of these started antibiotic therapy in addition at some point later in the study (the specific time being unclear from the data provided). 12 patients completed treatment; six of whom became mycobacterial culture negative at a mean follow-up of  $10.8 \pm 9.9$  months, and six continued on hypertonic saline as they had a symptomatic improvement, despite the absence of sputum culture conversion. The study's main conclusion was that hypertonic saline, together with ACT, was well tolerated and may be beneficial for NTM-PD patients by facilitating both clinical improvement and microbiological response. Although these results are encouraging, the small sample size, lack of a control group, minimal data on patient selection and *a priori* outcomes limit the generalisability of these findings [23].

KURAHARA *et al.* [25] also supported the potential role of airway clearance by demonstrating improvements in respiratory symptom scores and spirometry values in a case report of two NTM-PD patients using oscillating positive expiratory pressure (OPEP) devices, at least five times per day for a minimum of 5 min. The first patient was a 69-year-old woman with noncavitary nodular bronchiectatic macrolide-resistant MAC-PD with persistent symptoms despite antibiotic treatment, which included 6 months of amikacin liposome inhalation suspension (ALIS). The second was an 82-year-old woman with nodular bronchiectatic *M. avium* and *M. intracellulare* co-infection pulmonary disease, who despite achieving culture conversion with antibiotic treatment (ALIS plus azithromycin and ethambutol), had no symptomatic response. After initiating OPEP therapy, both patients had improvements in symptoms and radiology, and, after the first month, increased their FVC and forced expiratory volume in 1 s ( $FEV_1$ ) by  $>200$  mL and nearly 300 mL, respectively. Both patients also had improvements in Leicester Cough Questionnaire total scores and the Breathlessness, Cough and Sputum Scale. There was no change in either sputum cultures or bodyweight during the study. Inevitably, this work is limited by its small sample size, lack of comparator population and failure to report the total number of patients using OPEP who may not have had similar success [25].

## Discussion

Our systematic review found few studies reporting the impact of non-pharmacological interventions in patients specifically with NTM-PD. Furthermore, the identified literature had major methodological limitations and was missing important data that would have helped outcomes to be compared between studies, including the lack of standardised PROMs such as the Quality of Life Questionnaire – Bronchiectasis NTM module (QoL-B-NTM) and St George's Respiratory Questionnaire (SGRQ). Given the significant challenges associated with the pharmacological treatment of NTM-PD, including adverse effects, treatment intolerance, and high rates of relapse and failure in a population often with complex symptoms or comorbid conditions [7, 8, 13], there is an urgent need to explore these complementary

treatment approaches specifically in people with NTM-PD, who may be different to the populations from which the current evidence is derived, such as people with bronchiectasis without NTM [2, 29, 30].

Of interest is the recent report of 5-year longitudinal United States Bronchiectasis and NTM Research Registry data, which assessed the impact of NTM on mortality and clinical outcomes in bronchiectasis. This suggested that exacerbation frequency, hospitalisation rates, FEV<sub>1</sub> reduction and mortality rates were similar in bronchiectasis patients with NTM (n=1549, 58.8%; MAC 63%) and without NTM (n=1085, 41.2%). This was despite the NTM group having risk factors for mortality such as overall lower body mass index (BMI), higher prevalence of gastro-oesophageal reflux disease (GORD) and significantly greater macrolide use (41% versus 13%, p<0.0001), with long-term macrolide use identified in the study as a key risk factor for mortality, along with increased age, hospitalisation rates, lower BMI, low FEV<sub>1</sub> % pred, increased modified Medical Research Council dyspnoea score, use of oral steroid and antibiotics, GORD medications, male sex, and COPD. However, this study did not use standard diagnostic criteria to define NTM disease for all cases, and there were several other differences between the groups' baseline characteristics and treatments, which might have affected outcomes. Therefore, it is difficult to assess the independent effect of NTM disease in this study [31].

Understanding whether differences do exist between people with underlying lung disease and the presence or absence of persistent pulmonary NTM is important, as in other studies, those with NTM-PD experience more pulmonary infections with difficult-to-eradicate micro-organisms, specific airway pathology and mucus viscosity abnormalities compared to populations with either bronchiectasis and no NTM, or COPD [16, 32–34].

#### Airway clearance techniques

Our systematic review found that most of the evidence was for airway clearance techniques in people with NTM-PD. They appeared to improve symptoms such as cough and sputum production, even without antimicrobial therapy [23–25]. However, these studies were limited either by small sample sizes (n=77, n=25 and n=2) or by a larger cohort of people with bronchiectasis (n=905, including 255 (32%) with NTM) that did not provide sufficient data to distinguish between NTM-PD and non-NTM populations [28]. In addition, they lacked randomisation and had unclear methodologies when measuring and reporting changes in symptom scores for variables such as sputum production and cough severity [23–25, 28]. This underscores the need for more rigorous, well-designed research that include PROMs such as QoL-B-NTM and SGRQ to validate their findings.

The use of hypertonic saline nebulisation (with limited evidence) or mucolytic agents (with no evidence) alongside airway clearance techniques in both NTM-PD and bronchiectasis populations warrants further exploration, along with pulmonary rehabilitation programmes, including exercise training and respiratory muscle training (for which we found no evidence in the current literature). The CLEAR trial is investigating the effectiveness of carbocysteine (a mucolytic used to reduce mucus viscosity and promote expectoration) alone and in combination with hypertonic saline, alongside standard care in patients with bronchiectasis, with or without NTM [35]. While the trial does not specifically analyse NTM-PD separately, its findings may provide valuable insights into optimal airway clearance strategies for both groups. This highlights the need to develop evidence-based pulmonary rehabilitation programmes tailored to NTM-PD populations [14, 20].

#### Nutritional support

Although there were no data identified on the impact of nutritional interventions on NTM-PD, several studies have linked BMI to clinical outcomes in NTM-PD patients [36]. MOON *et al.* [37] found that patients with a lower BMI had worse outcomes, including higher mortality and treatment intolerance. In another study, IKEGAME *et al.* [38] demonstrated that patients with MAC-PD had decreased BMI despite normal serum albumin and that falling BMI was strongly correlated with the intrapulmonary spread of MAC infection, measured as the number of affected lung segments on chest computed tomography (CT) scans. A recent study by CHUNG *et al.* [39] used the Mini Nutritional Assessment Short Form (MNA-SF) to assess nutritional status in elderly patients with NTM-PD. They found an association between lower scores and risk of malnutrition and disease severity, evaluated using CT scanning. However, there was no correlation between the MNA-SF and changes in lung function parameters. They found no significant differences in calorie and protein intake between patients with low and normal scores, suggesting that an individualised nutritional evaluation and management is warranted for optimal treatment. Although there is increasing evidence on how to screen NTM-PD patients for malnutrition, no randomised controlled trials have been conducted on nutritional interventions and their prognostic impact on the disease, highlighting the need for targeted research [36].

### Psychological care

Psychological distress is prevalent among patients with chronic diseases, and NTM-PD is no exception [12, 40, 41]. JUNG *et al.* [12] reported that 22% of patients with NTM-PD experienced anxiety or depression symptoms at diagnosis, using the Hospital Anxiety and Depression Scale at least twice annually, with those affected more likely to report severe respiratory symptoms and receive antibiotic treatment more frequently. Throughout treatment, anxiety and depression improved significantly over the follow-up, suggesting that effective symptom management may positively impact psychological wellbeing. Despite this, no studies have specifically evaluated the effectiveness of psychological interventions such as cognitive behavioural therapy in NTM-PD patients, leaving a critical gap in the literature regarding how best to address psychological need. This also raises the question of how to identify this, as studies have highlighted just how infrequently psychological need is discussed during a medical consultation, even though PROMs can provide valuable insight into these concerns [42, 43].

### Other approaches

An additional key component of holistic NTM-PD patient management is the assessment of associated comorbidities. Structural lung diseases and states of immunosuppression (whether hereditary or acquired) are associated with an increased risk of both the development and progression of NTM-PD, emphasising the importance of managing these comorbid conditions carefully in people with NTM-PD [1, 44, 45]. Furthermore, GORD has been linked to an increased susceptibility to NTM infection and higher all-cause and respiratory disease-related emergency department visits or hospitalisations [28, 46, 47]. Therefore, an effective approach to GORD management may help to mitigate disease progression and improve outcomes in patients with pre-existing lung conditions [20, 23]. BASAVARAJ *et al.* [23] described the relationship between heartburn and cough, as well as the former's association with a mild reduction in total lung capacity in NTM-PD patients. However, cough appeared to improve irrespective of acid-suppressive therapy.

Clinical practice appears to be caught in a bind where a lack of robust evidence means that the logic of addressing comorbidities as part of a comprehensive treatment approach in NTM-PD to improve patient outcomes is not translated into specific guidance integrating their management with non-pharmacological interventions [8].

Currently, most studies on NTM are focused on the clinical perspective of physicians [3]. Apart from the importance of the other members of the multidisciplinary team's perspective on research and care, we need to ensure that we hear and respond to the patient's voice when prioritising future NTM research [3, 48]. In line with recent bronchiectasis guidelines, integrating patient advocacy into NTM guideline development could help ensure the perspectives and priorities of individuals living with NTM-PD are adequately represented, leading to more patient-centred approaches in both research and clinical care [16]. Indeed, both the NTM Research Consortium from the United States and the European Multicenter Bronchiectasis Audit and Research Collaboration (EMBARC) of the European Respiratory Society have explored NTM-PD patients' experiences and difficulties in dealing with the disease, and identified what patients felt to be their top research priorities [49, 50]. One of these was the importance of developing and testing the efficacy of non-pharmacological treatments, such as airway cleaning devices and exercise training, as well as holistic medicine approaches. Given that for many NTM patients, the most challenging issues to manage are fatigue, cough and pulmonary exacerbations, it is of considerable importance to investigate the impact of specific adjunctive therapies on such symptoms and concerns [14].

### Conclusion

While non-pharmacological interventions show potential in the management of NTM-PD, significant gaps in the evidence remain. And where there is evidence, it is derived from associated diseases, which may not capture all of the issues that pertain to people with NTM-PD. High-quality randomised controlled trials and longitudinal studies are urgently needed to establish the efficacy of interventions such as airway clearance, pulmonary rehabilitation, nutritional support and psychological care in this population. Until such evidence becomes available, clinicians should consider incorporating these interventions into patient care through carefully monitored protocols. By complementing antibiotic therapy with a comprehensive, patient-centred approach that addresses the multifaceted nature of NTM-PD, healthcare providers can offer more holistic and practical treatment options for this challenging disease.

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