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Non-antimicrobial airway management of non-cystic fibrosis bronchiectasis

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ABSTRACT

Bronchiectasis are often encountered in clinical practice, and are characterized by abnormal airway dilatation and distortion associated with impaired mucociliary clearance and mucous plugging, which are frequently associated with recurrent infections. Numerous etiologies can underlie the development of bronchiectasis, but the most important distinction in research and clinical practice is between bronchiectasis due to cystic fibrosis (CF) and bronchiectasis due to all other reasons (non-CF bronchiectasis). The causes of non-CF bronchiectasis are varied and often unclear. Patients disease severity and phenotypes of non-CF bronchiectasis also varied, which can influence disease trajectory, frequency of exacerbations and mortality. This article reviews the published evidence and suggests interventions to enhance airways clearance in patients with non-CF bronchiectasis, which are key components of an individualized therapeutic program in order to achieve symptomatic relief and prevention of exacerbations and functional decline.

1. Introduction

Bronchiectasis is a chronic lung disease that is frequently encountered in both pulmonary and infectious disease clinics. As imaging techniques improve, more patients with bronchiectasis are being identified. Bronchiectasis is characterized by abnormal bronchial dilatation and distortion associated with impaired mucociliary clearance and/or mucous plugging and airway obstruction frequently leading to recurrent infections. Numerous etiologies can underlie the development of bronchiectasis, but the most important distinction in research and clinical practice is between bronchiectasis due to cystic fibrosis (CF) and bronchiectasis due to all other reasons (non-CF bronchiectasis). The causes of non-CF bronchiectasis are varied and often unclear. They include pulmonary infections and their sequelae; defective host immunity including hypogammaglobulinemic states; mucociliary dysfunction; alpha-1 antitrypsin deficiency; autoimmune disorders; aspiration; allergic bronchopulmonary aspergillosis or fungosis; airway obstruction; and cigarette smoking, among others. [1–3] The proposed pathogenesis of recurrent pulmonary infections in both patients with CF and those with non-CF bronchiectasis is impaired mucociliary clearance leading to retained secretions resulting in airway obstruction, inflammation, and retention of infectious organisms. Disease severity in non-CF bronchiectasis is highly variable, as are the clinical and microbiological characteristics (i.e. the disease “phenotypes”). As such, there is considerable heterogeneity among patients with non-CF bronchiectasis and substantial variability with respect to disease progression, frequency of exacerbations, and mortality. [1,2] Although predictive multivariate scores (i.e. Bronchiectasis severity index or BSI- and E-FACED score, based on number of **e**xacerbations, **F**EV1, **a**ge, **c**hronic colonization by *Pseudomonas aeruginosa*, radiological **e**xtension, and **d**yspnea) have been proposed to characterize disease severity and prognosis, those scores do not help to identify which aspects of patient management should be individualized in daily clinical practice. [1,4,5] Therefore, in addition to appropriate evaluation and effective treatment of infections and comorbidities, individualized interventions to enhance bronchial clearance are the mainstay of therapy in patients with symptomatic non-CF bronchiectasis in order to achieve symptomatic relief and prevention of exacerbations and functional decline. [3]

1.1. Mechanical bronchial clearance in cystic fibrosis

Chest physiotherapy (CPT) techniques with mechanical and/or postural interventions have long been a key component in the management of patients with CF leading to improvements in symptoms, pulmonary function, quality of life, and potentially survival. [6,7] These techniques are also commonly used in non-CF patients with symptomatic bronchiectasis to improve mucous airway clearance in order to prevent mucous plugging and potentially prevent airway inflammation and recurrent infections. [3] As described in Table 1, there are a variety of different CPT techniques that have been utilized in these

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Table 1
Chest physiotherapy techniques to enhance airways clearance for patients with bronchiectasis.

CPT Technique	Method
Autogenic drainage	Tidal breathing at low, mid, and high lung volumes
Active cycle of breathing	Thoracic expansion exercises followed by controlled breathing ending with forced expiratory technique (huff cough)
Postural drainage and percussion	Chest clapping with gravity-assisted positioning
High frequency chest compression	External oscillation via inflatable vest or jacket to vibrate airways
Oscillatory positive expiratory pressure	Oscillatory positive expiratory pressure applied via flutter valve or acapella device during expiration

patients, some of which can be implemented independently without a physiotherapist. [3,8] However, most patients would benefit from teaching of these CPT techniques by a respiratory therapist or other trained health professional for appropriate and effective treatment. [3]

As early as the 1950 s, CPT has been a pillar in the care of patients with CF. Studies have shown that CPT in addition to cough improves both central and peripheral airway clearance compared to cough alone, the latter seemingly only effective for central airway clearance. [9] Furthermore, sputum production is increased in patients treated with CPT and cough versus cough alone, supporting the therapeutic role of CPT to increase mucous clearance. [9] In patients with non-CF bronchiectasis, the use of oscillatory positive expiratory pressures devices (i.e. flutter valves such as Acapella and Aerobika) and active cycle of breathing techniques are associated with improvement in sputum volume, breathlessness, and quality of life, but studies were small in size. [10–13] High-frequency airway clearance (i.e. inflatable vest) in comparison with other CPT techniques also improves dyspnea, airway obstruction, and inflammatory markers, but one prospective study included only a small number of patients. [11]

1.1.1. Interventions to augment mechanical bronchial clearance in cystic fibrosis

To improve upon CPT alone, many studies have trialed different aerosolized medications to enhance mucociliary clearance. In a study assessing nebulized hypertonic saline versus isotonic saline in patients with cystic fibrosis, long-term administration of nebulized hypertonic saline demonstrated sustained improvement in pulmonary function and was associated with fewer exacerbations. [14–16] The addition of mucolytic agents such as DNase has also been studied in patients with CF and has been associated with improved outcomes, specifically improvement in pulmonary function and decreased number of exacerbations. [17]

1.2. Interventions to augment bronchial clearance interventions in non−CF bronchiectasis

As with CF, bronchial clearance is a mainstay of therapy in non-CF bronchiectasis and treatment of patients with non-CF bronchiectasis is often inferred from studies of CF. [18] However, this extrapolation has its limits, as it is important to note that non-CF bronchiectasis does not generally encompass the electrolyte and water transport dysfunction seen in CF. While a great deal of research has been conducted to determine the most efficacious interventions to enhance bronchial clearance in CF, there has been less investigation into those interventions for patients with non-CF bronchiectasis. [18] Furthermore, patient factors in those with non-CF bronchiectasis are often quite different than those with CF and may include older age, increased frailty, cognitive decline, etc. Consequently, application and tolerance of treatments to enhance bronchial clearance should be individualized in this population.

Similarly, interventions to augment the bronchial clearance effect of CPT in non-CF bronchiectasis have not been well studied and those studies have yielded somewhat conflicting results, albeit in the setting of important methodological limitations including small sample sizes. [3] Of note, a randomized study (N = 40) that compared the use of 6% nebulized hypertonic saline with nebulized normal saline in non-CF bronchiectasis showed similar degrees of improvement in both groups over one year with respect to pulmonary function, frequency of acute exacerbations, sputum colonization, and quality of life. A randomized single-blinded cross-over study in non-CF patients compared the use of 7% nebulized hypertonic saline vs. nebulized normal saline and showed a greater improvement in lung function, quality of life, antibiotic usage, emergency care utilization, sputum viscosity, and ease of expectoration in the nebulized hypertonic saline group. Another study has also suggested a trend towards improvement. [19] Recent international guidelines suggest the use of "long-term mucoreactive treatment (≥ 3 months) in patients with non-CF bronchiectasis who have difficulty in expectorating sputum or poor quality of life and where standard airway clearance techniques have failed to control symptoms" but the authors of those guidelines report a low quality of evidence. [3] Along these lines, inhaled mannitol and nebulized terbutaline have also been studied as add-ons to CPT in non-CF bronchiectasis with mixed results. [3,19–21] In regard to terbutaline, a small study demonstrated that its use before CPT enhanced secretion clearance suggesting that other more contemporary bronchodilators may be beneficial adjuncts to CPT in addition to their use in alleviating airflow obstruction. [3,21] Despite this evidence, recent guidelines suggest not routinely offering long-acting bronchodilators with the exception of patients with significant dyspnea and/or comorbid asthma or chronic obstructive pulmonary disease. [3] Similar treatment suggestions and caveats were made for the use of inhaled corticosteroids, but the quality of evidence was also low. [3] Mucolytic agents, which in CF have clear benefit and are widely used, have not been shown to provide therapeutic benefit in patients with non-CF bronchiectasis. [22] For example, the use of bromhexine has been associated with decreased sputum production compared to placebo and the use of recombinant human DNase has been associated with decline in forced expiratory volume in one second (FEV_1). [3,22,23] Accordingly, the use of those mucolytic agents in patients with non-CF bronchiectasis is discouraged. [3]

Studies have suggested that in patients with CF and non-CF bronchiectasis there may be bacterial biofilms preventing eradication of infection with systemic antibiotics leading to chronic infection and perpetuation of bronchial destruction. [24] This has led to research examining the role of N-acetylcysteine (NAC) in preventing development of biofilms, though the mechanisms of such interference remain unknown. Most studies have only demonstrated inhibition of biofilms in vitro. Moreover, the majority of research has studied oral or intramuscular formulations, not inhaled NAC with the intention of topical application for specific targeting against respiratory colonizers. [24] More studies are necessary to demonstrate its effectiveness in both CF and non-CF bronchiectasis.

Pulmonary rehabilitation is another important aspect of non-antimicrobial interventions in symptomatic patients with non-CF bronchiectasis. [3] Tailored pulmonary rehabilitation programs have shown improvement in exercise tolerance and probably quality of life and rate of exacerbations. [25-27]

Because of the lack of strong evidence to support CPT and other bronchial clearance interventions, an individualized approach, based on known data as discussed above, is suggested when developing a non-antimicrobial treatment plan for patients with non-CF bronchiectasis. Specifically, a program with CPT, inhaled therapies, and preventive