Chapter 16

Pharmacological airway clearance strategies in bronchiectasis

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Summary

Impaired mucociliary clearance and mucus retention contribute to the chronic cycle of airway inflammation, infection and damage in bronchiectasis. There is a strong rationale for the use of pharmacological strategies to aid airway clearance, often in combination with chest physiotherapy. Despite the availability of many candidate mucoactive agents, the evidence base for recommending these agents is currently limited. Recent research and trials have focused particularly on osmotic agents (hypertonic saline and mannitol), which increase airway hydration, and early studies appear promising for both of these agents. Dornase alfa is not effective in non-cystic fibrosis (CF) bronchiectasis, which underscores the importance of conducting high quality and adequately powered trials that specifically address the therapeutic options for non-CF bronchiectasis.

Keywords: Bronchiectasis, mucoactive, mucociliary clearance, mucus

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Non-cystic fibrosis (CF) bronchiectasis is a heterogeneous disorder defined by irreversible dilatation of the airways [1]. Although a wide variety of underlying pathological processes can initiate the development of bronchiectasis, the final common pathophysiological pathway is one characterised by the vicious cycle of chronic infection and inflammation leading to progressive airway damage [2]. Impaired mucociliary clearance is a feature of the abnormal bronchiectactic airway [3, 4], and may represent the primary abnormality in conditions such as primary ciliary dyskinesia. Mucus retention, the result of defective mucociliary clearance, not only produces the classic symptom of chronic productive cough but also causes airflow obstruction and ventilation/perfusion mismatch and forms a nidus for ongoing infection. Therefore, interventions aimed at promoting clearance of excess mucus may be beneficial in patients with non-CF bronchiectasis.

The normal mucociliary escalator forms an essential element of the innate host defence mechanism against inhaled pathogens. The complex physiology of mucociliary clearance in health and disease has been reviewed in detail elsewhere [5–7]. Briefly, this process is dependent upon normal ciliary function, optimal rheological properties of the airway mucus and an adequate volume of airway surface liquid (ASL). The lung has the additional mechanism of cough for airway mucus clearance, although the effectiveness of cough clearance itself is also dependent upon the viscoelastic properties of mucus [8].

Agents that are intended to facilitate airway mucus clearance are termed mucoactive drugs. A classification of mucoactive agents, based on their mechanism of action, is summarised in table 1. Despite these agents having been available for many years, limited high-quality clinical trials have been undertaken exploring the efficacy of mucoactive agents in non-CF bronchiectasis. Indeed, since the mid-2000s, multiple authors have called for a coordinated approach in order to establish multicentre clinical trials and for funding bodies to consider support for this disease, highlighting the huge unmet needs in non-CF bronchiectatic therapy [9–11]. The present chapter reviews the current pharmacological strategies available for enhancing airway clearance in non-CF bronchiectasis.

Hypertonic saline

Hypertonic saline is a sterile salt solution with a higher concentration of salt (typically 3–7%) than plasma (0.9%), and is delivered by inhalation *via* a nebuliser. Hypertonic saline accelerates mucociliary clearance in both healthy subjects and patients with cystic fibrosis (CF), as demonstrated in radioaerosal studies [12–15]. It is thought to enhance airway clearance by altering the viscoelastic properties of mucus, increasing hydration of the ASL and also directly stimulating cough [15–18].

The hydrating effect of hypertonic saline on mucociliary function has been best characterised in the CF airway. In health, ASL is present as a bilayer, with a superficial mucus layer and a layer of periciliary liquid (PCL) interposed between the mucus and the epithelium. The PCL layer approximates the height of the cilia and provides a low-viscosity fluid in which the cilia beat [5]. A critical depth of PCL is crucial for ciliary function and mucociliary transport [6]. CF transmembrane conductance regulator dysfunction leads to airway dehydration and depletion of the PCL layer of the ASL [19]. The addition of hypertonic saline to the CF epithelium rapidly restores the depth of the ASL by creating an osmotic gradient and drawing water across the

Table 1. Common mucoactive drugs and their mechanisms of action

Agent	Predominant mechanism
Expectorants	
Hypertonic saline	Increases airway hydration; stimulates cough
Mannitol	
Mucolytics	
N-Acetylcysteine	Interrupts disulfide bonds linking mucin polymers; anti-inflammatory and antioxidant effects
Nacystelyn	Interrupts disulfide bonds; increases chloride secretion
Dornase alfa	Cleaves DNA polymers
Mucoregulators	
Carbocisteine	Modulates mucus content; anti-inflammatory and antioxidant effects
Glucocorticoids	Reduces airway inflammation and mucin secretion
Macrolide antibiotics	Reduces airway inflammation and mucin secretion
Anticholinergics	Decreases volume of secretions
Mucokinetics	
β_2-Agonists	Increases cilia beat frequency; improves cough clearance by increasing expiratory flows
Surfactant	Decreases mucus adherence to epithelium

Modified from [8].

respiratory epithelium [15]. Restoration of the depth of ASL not only optimises ciliary function but also causes excess water entering the airway to be stored in the mucus layer, making its rheological properties more favourable for clearance [18].

The efficacy of long-term inhalation (48 weeks) of hypertonic saline has previously been demonstrated in a randomised placebo-controlled trial for patients with CF [20]. Regular hypertonic saline inhalation significantly improved lung function and reduced pulmonary exacerbations. These changes were accompanied by prescription of fewer courses of antibiotics, reduction in absenteeism from school and work, and improved quality of life. A recent Cochrane review, which included 12 trials (442 participants aged 6–46 years), indicated that hypertonic saline is a safe, low-cost and effective therapy in CF [21].

Preliminary evidence suggests that hypertonic saline may be clinically effective in non-CF bronchiectasis. In a randomised crossover trial, KELLETT *et al.* [22] evaluated the effect of hypertonic saline as an adjunct to physiotherapy in 24 stable bronchiectatic patients. Subjects were allocated to receive four different single-session treatments in random order: 1) active cycle of breathing technique (ACBT) alone, 2) nebulised terbutaline followed by ACBT, 3) nebulised terbutaline followed by isotonic saline (0.9%) and then ACBT, and 4) nebulised terbutaline followed by hypertonic saline (7%) and then ACBT. Each single-treatment session was followed by a 1-week washout period. When hypertonic saline was used, physiotherapy yielded greater sputum weight, increased the ease of sputum expectoration and reduced sputum viscosity. Although encouraging, this study has clear limitations. The study only included patients who were minimal sputum producers (<10 g·day^{-1}), a phenotype which is clearly distinct from high sputum producers. Patient blinding was incomplete (taste masking not performed), and the results only represented the effect of a single treatment dose.

More recently, NICOLSON *et al.* [23] reported, in abstract form, the results of a randomised controlled trial on the effect of long-term hypertonic saline inhalation. A total of 40 patients were randomised to hypertonic saline (6%) or isotonic saline (0.9%) though an Aeroneb® Go nebuliser (Aerogen, Galway, Ireland) twice daily for 12 months while performing the ACBT. The mean forced expiratory volume in 1 second (FEV_1) of the study group was 83% of the predicted value. No differences in lung function, number of exacerbations or quality of life were observed at 3, 6 and 12 months between the hypertonic and isotonic saline groups. Both the hypertonic saline and isotonic saline groups demonstrated clinically significant improvement in health-related quality of life compared to baseline. However, this study was substantially underpowered to examine the effect of hypertonic saline relative to isotonic saline. As clinically worthwhile benefits were not excluded by the confidence intervals (CIs), further investigation of this promising agent is warranted.

Hypertonic saline appears to be well tolerated by patients with bronchiectasis. In 50 administrations of hypertonic saline to patients with acute exacerbations, no major bronchoconstriction (fall in FEV_1 of $>20\%$) or oxygen desaturation occurred [24]. Routine premedication with a bronchodilator is recommended (typically 200–400 μg salbutamol delivered *via* a spacer device). We generally recommend that spirometry is performed and oxyhaemoglobin saturation measured before and after delivery of the first dose.

Mannitol

Mannitol is a six-carbon monosaccharide (sugar alcohol), and is commercially available in an encapsulated stable dry powder formulation for inhalation. Similar to hypertonic saline, creation of an osmotic gradient causing influx of water into the airway and increasing the ASL layer is considered to be its primary mechanism of action [25]. In addition, mannitol may cause the release of mediators that may stimulate ciliary beat frequency [26, 27], although direct evidence that mannitol stimulates the cilia has not been established. Mannitol may also alter the viscoelastic properties of mucus by breaking the hydrogen bonds between mucins [28]. Mannitol (160–480 mg) increases mucociliary clearance in a dose-dependent manner in radioaerosal studies [29–31].

In a phase-3 randomised double-blind placebo-controlled trial in CF, inhalation of mannitol (400 mg *b.i.d.*) for 6 months resulted in an early and sustained improvement in FEV1 compared to placebo (118 mL change from baseline to week 26; $p<0.001$) [32]. The benefit in FEV1 was seen irrespective of the concurrent use of dornase alfa. The study was not sufficiently powered to show a reduction in the secondary end-point of exacerbations. Results from the 12-month open-label phase of the study have also been reported. The improvement in lung function with mannitol appeared to be maintained for up to 18 months of treatment [33]. The full results of this study are yet to be published.

There is emerging evidence that mannitol is an effective treatment in non-CF bronchiectasis. In an open-label pilot study, DAVISKAS *et al.* [34] treated nine patients with bronchiectasis with 400 mg mannitol daily for 12 days. Lung function was unchanged by treatment apart from an improvement in forced expiratory flow (FEF). However, health-related quality of life had improved at the end of the treatment period and was maintained for 1 week thereafter. Mannitol reduced the surface tension, increased the wettability and reduced the cohesiveness and solids content of sputum. Cough transportability, measured by an *in vitro* simulated cough machine, also increased. All subjects tolerated treatment well, without report of any adverse events.

A phase-3 multicentre randomised controlled trial has recently been completed and its data presented in abstract form [35]. Subjects with bronchiectasis and mild-to-moderate lung function impairment (FEV1 of >50% pred and $\geqslant$1 L) were randomised to 320 mg inhaled mannitol (n=185) or placebo (n=95), given twice daily for 3 months. Subjects treated with mannitol exhibited a significant reduction in the St George's Respiratory Questionnaire total score of 3.9 units compared to 2.0 units in the placebo group. In the mannitol group, the time to first antibiotic use was longer and total antibiotic use was less than for placebo. The full report of this study is awaited with interest.

Dornase alfa

Dornase alfa is a proteolytic enzyme that cleaves DNA polymers [8]. DNA is released into the airway mucus in large amounts by degenerating neutrophils, and neutrophilic inflammation is a feature of both CF and non-CF bronchiectasis. Purulent airway secretions, particularly in CF, show an abundance of highly polymerised DNA, which contributes to mucus hyperviscosity and adhesiveness [36].

Daily inhalation of dornase alfa is a well-established therapy in CF bronchiectasis, resulting in improvement in lung function and reduction in exacerbations, in both mild and severe disease [37–40]. In contrast, clinical studies in non-CF bronchiectasis have shown that dornase alfa is of no benefit, and may even be harmful. In a short-term study of WILLS *et al.* [41], dornase alfa was not associated with any improvement in lung function and quality-of-life measures in patients with non-CF bronchiectasis. Indeed *in vitro* sputum transportability fell following the addition of dornase alfa to non-CF bronchiectatic sputum. A subsequent international multicentre study randomised 349 patients with stable non-CF bronchiectasis to either dornase alfa or placebo over a 24-week period (and remains the largest therapeutic trial in non-CF bronchiectasis to date) [42]. Pulmonary exacerbations were more frequent, and FEV1 decline was greater in patients who received dornase alfa.

The reasons for this difference in response between patients with CF and non-CF bronchiectasis remain unclear. The biological rationale for the use of dornase alfa in non-CF bronchiectasis was strong, but the unexpected detrimental finding highlights the importance of performing well-designed studies that address the therapeutic options for non-CF bronchiectasis, rather than merely extrapolating the results of trials involving patients with CF.

N-Acetylcysteine, carbocisteine and other thiol derivatives

N-Acetylcysteine (NAC) is the classic mucolytic agent, and disrupts the disulfide bonds in mucus when delivered *via* the aerosolised route [8]. In addition to reducing sputum viscosity, NAC

demonstrates antioxidant, anti-inflammatory and potentially antibacterial properties [43–45]. NAC exhibits extremely low bioavailability, and is not readily detectable in bronchoalveolar lavage fluid following oral administration [46]. Thus the mechanism of action of oral NAC is unlikely to be mediated *via* its mucolytic properties. Carbocisteine, although commonly regarded as a mucolytic, has a mechanism of action that differs from that of the classical mucolytics. Mucus produced under the action of carbocisteine shows an increase in sialomucin content. Sialomucins, which are structural components of mucus, influence the viscoelastic properties of mucus [47]. Similar to NAC, carbocisteine also exerts anti-inflammatory actions, and, in pre-clinical studies, it has been shown to decrease levels of the cytokines interleukin (IL)-6 and IL-8 and reduce neutrophil influx into the airway lumen [48, 49].

The majority of clinical studies of NAC and thiol derivatives have been performed in chronic obstructive pulmonary disease (COPD), with conflicting results. The Bronchitis Randomized on NAC Cost–Utility Study (BRONCUS), which randomised 523 patients (Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 2 and 3) to 600 mg oral NAC daily or placebo, showed that NAC was ineffective at reducing pulmonary exacerbations and decline in lung function over a 3-year period [50]. This is in contrast to the large Chinese Preventive Effects on Acute Exacerbations of COPD with Carbocisteine (PEACE) study, which randomised 709 patients (GOLD stage 2, 3 and 4) to receive carbocisteine or placebo for 1 year [51]. The primary end-point of exacerbation rate over the 1-year period was met, with carbocisteine demonstrating a significant reduction in exacerbations (risk ratio 0.74; 95% CI 0.61–0.89). The discrepant findings between these two large randomised controlled trials may have been explained by the different rates of inhaled corticosteroid usage (less in the PEACE study) and phenotypic differences in COPD across ethnicities.

The evidence supporting the use of NAC and thiol derivative in bronchiectasis is even more limited. There are several studies of oral and inhaled NAC in CF, but most studies have only evaluated changes in the rheologicaal properties of CF sputum [52]. The few controlled clinical studies in CF performed to date have consistently shown no clinical benefit [53–55].

There are currently no well-designed studies of NAC and thiol derivatives in non-CF bronchiectasis. This is supported by a Cochrane review, which concluded that there is insufficient evidence to evaluate the routine use of these agents in non-CF bronchiectasis [56].

Bronchodilators

β_2-Agonists are commonly prescribed to treat airflow obstruction and bronchial hyperreactivity, and as an adjunct to physiotherapy in patients with bronchiectasis. Between 20 and 46% of patients with bronchiectasis display bronchodilator reversibility [57, 58]. β_2-Agonists may facilitate airway clearance by increasing ciliary beat frequency *via* stimulation of β_2-receptors and downstream increase in cyclic adenosine monophosphate (cAMP) signalling [59]. cAMP is a regulator of ciliary beat frequency in human airway epithelia [60, 61]. The bronchodilatory effect of β_2-agonists may serve to increase expiratory flow rates and thus enhance cough clearance.

Two small studies have demonstrated that nebulised terbutaline, given immediately prior to physiotherapy, yields greater sputum production [22, 62], and also improved mucociliary clearance in a radioaerosal study [62]. Although it seems reasonable and logical that β_2-agonists be used to treat airflow limitation (particularly if objective bronchodilator reversibility is demonstrated), and as an adjunct to chest physiotherapy in non-CF bronchiectasis, this is currently not supported by the evidence. The relevant Cochrane reviews found no randomised controlled trials of the use of short-acting or long-acting β_2-agonists in non-CF bronchiectasis [63, 64].

Surfactant

A thin layer of airway surfactant phospholipid separates the PCL layer and the mucus gel layer, and effectively functions as a lubricant to facilitate mucus transport [8]. Furthermore, depletion of

the PCL layer leads to entanglement and adhesion of mucus to the underlying epithelial surface. Surfactant is a potential therapeutic candidate for enhancing mucociliary clearance by reducing the molecular interactions that bind mucus to the airway. Patients with CF display alterations in the composition of the pulmonary surfactant system, with a reduction in the surface-active fractions, such as phosphatidylcholine and phosphatidylglycerol [65, 66]. This suggests that surfactant dysfunction may contribute to impaired mucociliary function in CF.

Preliminary clinical studies of exogenous surfactant therapy have only been performed in COPD and CF populations. A single randomised controlled trial of 66 patients with COPD and symptoms of chronic bronchitis showed that aerosolised surfactant for 2 weeks increased *in vitro* sputum transportability, improved FEV_1 and forced vital capacity (FVC) by >10%, and reduced gas-trapping [67]. The result of a phase-2 study of pulmonary surfactant in CF was recently reported in abstract form. In this placebo-controlled crossover trial, 16 subjects (aged >14 years and with an FEV_1 of >40% pred) were assigned to five doses of nebulised surfactant or five doses of nebulised saline (0.9%) over a 24-hour period, with a washout period of 2 weeks. Aerosolised surfactant was well tolerated and not associated with any serious adverse events. No difference in mucociliary clearance (quantified by radioaerosal labelling) was observed between surfactant and saline (0.9%) treatment.

Humidification

Humidification is commonly used to relieve sputum retention. CONWAY *et al.* [68] performed a small crossover study evaluating the role of humidification as an adjunct to chest physiotherapy in seven subjects with moderate-to-severe bronchiectasis. Humidification with cold water *via* a jet nebuliser for 30 minutes prior to chest physiotherapy was compared to chest physiotherapy alone. Radioaerosal clearance and sputum weight both increased when humidification was performed prior to chest physiotherapy.

In a recent study of REA *et al.* [69], long-term domiciliary humidification was evaluated in a randomised placebo-controlled trial. A total of 108 subjects with COPD (n=63) or bronchiectasis (n=45) were randomly assigned to humidification or usual care for 12 months. Fully saturated humidified air at 37°C was delivered *via* nasal cannulae at a flow rate of 20–25 $L \cdot min^{-1}$ *via* a humidifier and flow source. Patients were encouraged to use humidification for $\geqslant$2 $hours \cdot day^{-1}$. The primary end-point of the study, exacerbation frequency during the study period, was nonsignificant but showed a trend favouring the humidification group (3.36 *versus* 2.97; p=0.067). However, patients on long-term humidification therapy showed significantly fewer exacerbation days and increased time to first exacerbation compared to usual care. Quality-of-life scores and lung function had also improved significantly with humidification therapy at 3 and 12 months. The authors hypothesised that improvement in mucociliary clearance with humidification was one of the main mechanisms accounting for the observed benefit. The limitations of this study include the absence of a placebo, which resulted in subjects and investigators being unblinded to the intervention assignment. The study population included both COPD and bronchiectasis, which are clearly two very distinct disorders. Compliance with therapy was poor (mean 1.6 $hours \cdot day^{-1}$), but, despite this, the secondary outcomes of the study were still significantly in favour of humidification therapy. The high flow rate of the humidification system was equivalent to the delivery of 1–3 cmH_2O of positive end-expiratory pressure (PEEP). PEEP, even at this low pressure, may by physiologically relevant in reducing the work of breathing by offsetting intrinsic PEEP, recruiting alveolar units to improve ventilation/perfusion matching and providing partial stabilisation of the upper airway if used during sleep. Thus the mechanisms *via* which long-term high flow humidification might be beneficial in obstructive airways disease remain uncertain.

Conclusion

Bronchiectasis is increasingly recognised as a major cause of respiratory morbidity. Research projects are required in order to establish therapies for this under-investigated, under-recognised and

undertreated disease. Such trials should focus on the experimental agent's effects on quality of life, use of healthcare resources and participation. Hypertonic saline, NAC and carbocisteine are promising candidates for such trials. There is proof of concept for the use of bronchodilators in combination with physiotherapy, but trials with clinically important outcome measures are needed. Mannitol appears effective, but clinicians must await publication of the full results of the most recent trials and commercial availability of the dry powder formulation. Humidification also appears effective. Dornase alfa has detrimental effects and should not be used in non-CF bronchiectasis.

Statement of interest

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