Official Journal of the Asian Pacific Society of Respirology
Respirology

SYSTEMATIC REVIEW

Mucoactive agents for chronic, non-cystic fibrosis lung disease: A systematic review and meta-analysis

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ABSTRACT

Inhaled mucoactive agents are used in respiratory disease to improve mucus properties and enhance secretion clearance. The effect of mannitol, recombinant human deoxyribonuclease/dornase alfa (rhDNase) and hypertonic saline (HS) or normal saline (NS) are not well described in chronic lung conditions other than cystic fibrosis (CF). The aim of this review was to determine the benefit and safety of inhaled mucoactive agents outside of CF. We searched Medline, Embase, CINAHL and CENTRAL for randomized controlled trials investigating the effects of mucoactive agents on lung function, adverse events (AEs), health-related quality of life (HRQOL), hospitalization, length of stay, exacerbations, sputum clearance and inflammation. There were detrimental effects of rhDNase in bronchiectasis, with average declines of 1.9–4.3% in forced expiratory volume in 1 s (FEV_1) and 3.7–5.4% in forced vital capacity (FVC) (n = 410, two studies), and increased exacerbation risk (relative risk = 1.35, 95% CI = 1.01–1.79 n = 349, one study). Some participants exhibited a reduction in FEV_1 (≥10–15%) with mucoactive agents on screening (mannitol = 158 of 1051 participants, rhDNase = 2 of 30, HS = 3 of 80). Most AEs were mild and transient, including bronchospasm, cough and breathlessness. NS eased symptomatic burden in COPD, while NS and HS improved spirometry, HRQOL and sputum burden in non-CF bronchiectasis. Mannitol improved mucociliary clearance in asthma and bronchiectasis, while the effects of N-acetylcysteine were unclear. In chronic lung diseases outside CF, there are small benefits of mannitol, NS and HS. Adverse effects of rhDNase suggest this should not be administered in non-CF bronchiectasis.

Systematic review registration: CRD42014015496 at crd.york.ac.uk/PROSPERO

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Received 6 September 2016; invited to revise 7 November 2016 and 26 January 2017; revised 19 December 2016 and 6 February 2017; accepted 26 February 2017 (Associate Editor: Chi Chiu Leung).

Key words: expectorants, humans, lung diseases, respiratory function tests, sputum.

Abbreviations: , 6MWD, 6-min walk distance; ACBT, active cycle of breathing technique; AE, adverse event; bd, twice daily; BSQ, Bronchiectasis Symptoms Questionnaire; CENTRAL, The Cochrane Central Register of Controlled Trials; CF, cystic fibrosis; CINAHL, Cumulative Index to Nursing and Allied Health Literature; COPD, chronic obstructive pulmonary disease; FER, forced expiratory ratio; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HRCT, high-resolution computed tomography; HRQOL, health-related quality of life; HS, hypertonic saline; IPPB, intermittent positive-pressure breathing; ISW, incremental shuttle walk; ITT, intention to treat; IV, inverse variance; LCQ, Leicester Cough Questionnaire; LOS, length of stay; M–H, mantel-haenszel; MCC, mucociliary clearance; MID, minimum important difference; MMFR, maximum mid-expiratory flow rate; NAC, N-acetylcysteine; NS, normal saline; PDE, protocol-defined exacerbation; PEFR, peak expiratory flow rate; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial; rhDNase, recombinant human deoxyribonuclease/dornase alfa; RR, relative risk; SF-36, The Short Form (36) Health Survey; SGRQ, St George's Respiratory Questionnaire; SOB, shortness of breath; VC, vital capacity; WOB, work of breathing.

INTRODUCTION

The term 'mucoactive agent' refers to drugs that promote secretion clearance.[1] Inhaled mucoactive agents are used in the management of lung diseases including asthma, cystic fibrosis (CF), non-CF bronchiectasis and COPD.

Mucoactive agents promote cough, improve mucociliary clearance (MCC), reduce sputum adhesion and thin purulent secretions.[1] Expectorants, such as normal saline (NS), increase the airway surface liquid layer and decrease mucus adhesiveness, while mucolytics, such as both N-acetylcysteine (NAC) and recombinant human deoxyribonuclease/dornase alfa (rhDNase), reduce sputum viscosity.[1] Medications such as inhaled mannitol, rhDNase and hypertonic saline (HS) have proven efficacy in CF,[2–4] but there is limited evidence to guide practice in other conditions. The aims of this review were to determine the impact of inhaled

mucoactive agents on (i) respiratory function; (ii) clinical and health service outcomes including health-related quality of life (HRQOL), exercise capacity, exacerbation rate and hospital length of stay (LOS); (iii) physiological outcomes including oxygenation, inflammation and MCC; and (iv) adverse events (AEs) in non-CF lung disease.

METHODS

Studies

Only parallel and crossover randomized controlled trials (RCTs) were included. Studies published in a language other than English were excluded unless an English abstract was available.

Participants

Participants had a diagnosis of any chronic lung disease, excluding CF. Stable lung disease was analysed separately from acute exacerbations. Only human trials were included. Data were also obtained for acute lung conditions with no prior respiratory morbidity, and will be reported separately.

Interventions

Inhaled, mucoactive medications at any dose, frequency or duration using any device were compared with usual care, comparison, control or placebo. Each medication was analysed separately. Studies combining mucoactive agents with other treatments were included and reported. Long-term studies (≥3 months of treatment) were analysed separately to short-term studies (<3 months). Inhaled surfactants were considered outside the scope of this review.

Outcome measures

The primary outcome was any measure of lung function (e.g. forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC)).

Secondary outcomes included safety or AEs; HRQOL; symptoms; physical capacity; hospital LOS; readmission or exacerbation rates; radiological findings; oxygenation; microbiology; antimicrobial use; inflammation; MCC; and any sputum measure such as colour, weight or rheology.

Data extraction

B.J.T. and R.S. or C.L. examined title and abstract. Studies that met criteria or were unclear were examined in full text. Excluded full texts were recorded (Fig. 1).

Data were extracted using standardized forms. The Cochrane Collaboration's Risk of Bias Assessment Tool[5] was applied by B.J.T. and C.L. (Fig. 2). If disagreement arose, a third investigator (A.E.H.) was included.

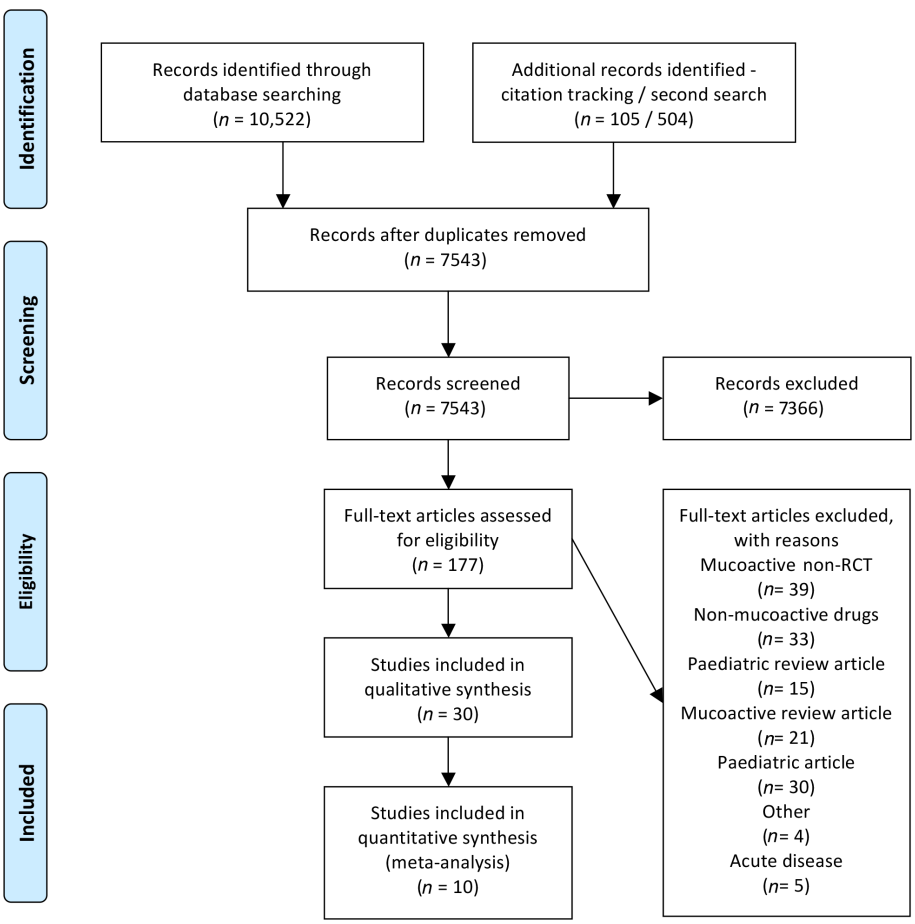

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram of study selection.

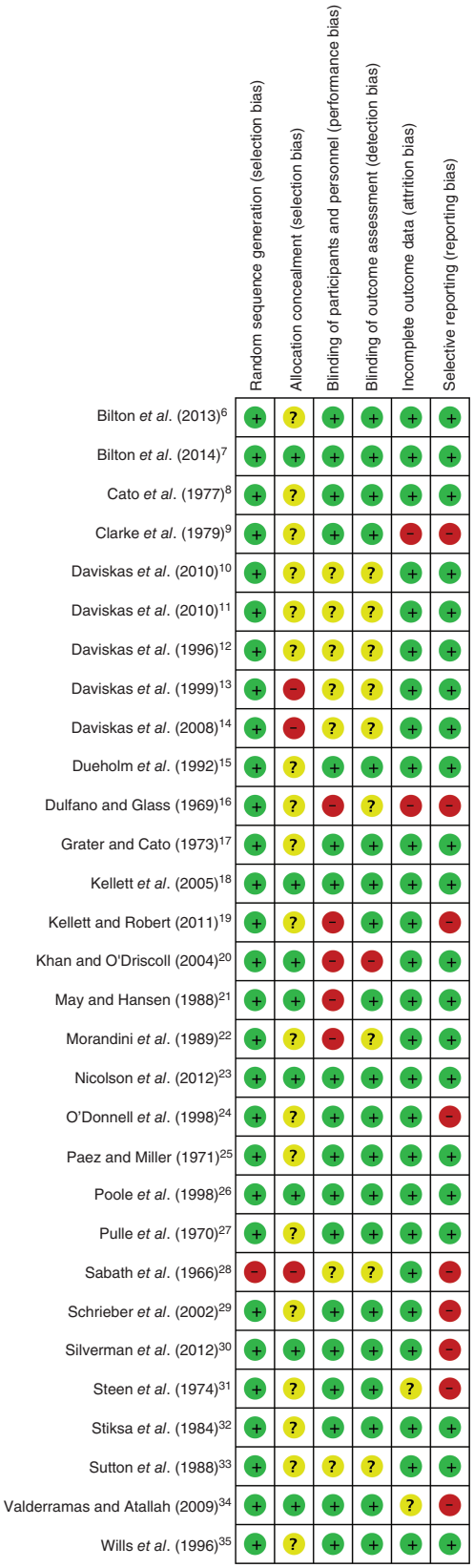

Figure 2 Assessment of risk of bias: low risk, +; high risk, –; unclear risk, ?

Databases

Medline, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and The Cochrane Central Register of Controlled Trials (CENTRAL) were systematically searched (Appendix S1, Supplementary Information). The initial search was dated 4 March 2015 and updated on 31 March 2016.

Statistical analysis

Intention to treat (ITT) data were used when possible. Dichotomous variables were expressed as relative risk (RR) or risk difference with 95% CI. For continuous data, we recorded mean change from baseline or mean post-intervention values and SDs. We reported outcomes as mean differences or standardized mean differences with 95% CI. Meta-analysis was performed where possible using Review Manager 5.3 using a fixed effects model.[36] Generic inverse variance (IV) methods were used for crossover trials.[5]

Where a quantitative synthesis was not possible, a qualitative appraisal was presented. Where an outcome was evaluated in a single study with a sample size ≤20 and was not suitable for quantitative analysis, these data were presented in Supplementary Appendix S2. Sensitivity analyses were carried out when appropriate to investigate the effect of participant, investigator and assessor blinding and ITT on effect size.

RESULTS

The initial search identified 6934 citations, 28 suitable for inclusion. Citation tracking revealed 105 citations, with five further articles included. The updated search identified two additional RCTs (Fig. 1). Thirty studies satisfied eligibility criteria (Table S1, Supplementary Information). Diagnoses included non-CF bronchiectasis,[6,7,11,13,14,18,19,23,24,33,35] COPD[9,15,16,20–22,25–29,31,32,34] and asthma.[8,10,12,17,30]

Mannitol was investigated in six studies,[6,7,10,11,13,14] rhDNase in three,[24,30,35] NAC in five,[8,15,17,27,32] NS in seven[12,18,20,21,25,26,33] and HS in five.[12,18,19,23,34] Mesna, Sobrerol and Ascoxal (AstraZeneca, Cambridge, United Kingdom) were investigated across six trials.[9,16,22,28,29,31] There were 11 parallel RCTs and 19 crossover trials. Numbers ranged from 7 to 485. Most trials were short term (n = 24). One trial was pseudo-randomized by hospital identification number.[28] Twenty-two trials were at risk of selection bias, blinding was described in 18 studies, 12 studies were at risk of performance bias and 10 were at risk of detection bias (Fig. 2). Within-study assessment[5] revealed four trials were at an overall low risk.[7,18,23,26] The remainder were at an unclear or high risk of overall bias, judged when any one of the six determinants of bias exceeded low risk.[5] Meta-analysis was deemed appropriate on 11 occasions, concerning four medications in all diseases (Figs 3–5 and S1–S8 (Supplementary Information)). A qualitative analysis can be found below. When an outcome was investigated in a single trial with $n \leq 20$, this analysis can be found in Appendix S2 (Supplementary Information). Raw data are reported in Table S2 (Supplementary Information).

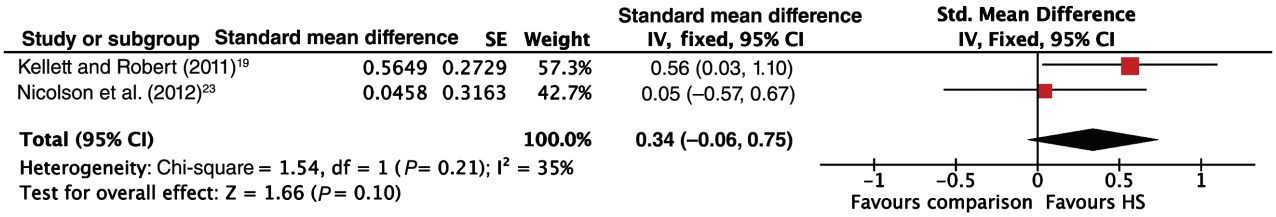

Figure 3 HS in bronchiectasis. Meta-analysis of FEV_1 at 3 months. CI, confidence interval; FEV_1, forced expiratory volume in 1 s; HS, hypertonic saline; IV, inverse variance; SE, standard error.

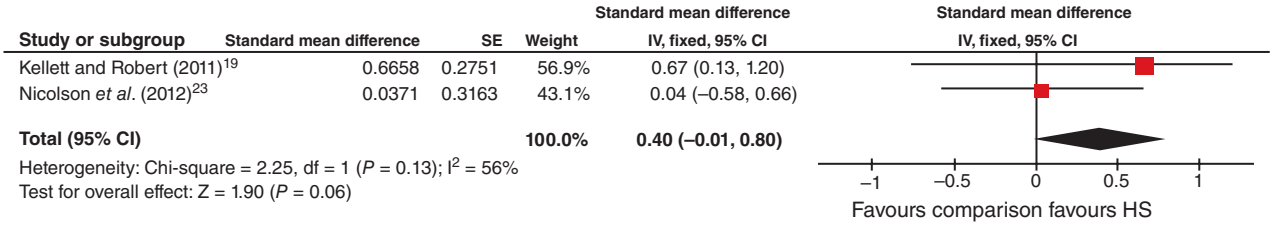

Figure 4 HS in bronchiectasis. Meta-analysis of FVC at 3 months. CI, confidence interval; FVC, forced vital capacity; HS, hypertonic saline; IV, inverse variance; SE, standard error.

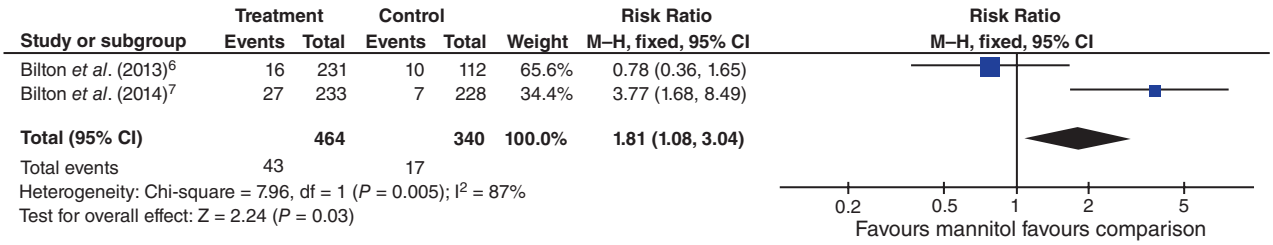

Figure 5 Mannitol in bronchiectasis. Meta-analysis of adverse events leading to study withdrawal. CI, confidence interval; M–H, mantel-haenszel.

Lung function

Hypertonic saline

Three trials with 23–40 participants tested HS in bronchiectasis.[18,19,23] Results favoured HS over active cycle of breathing technique (ACBT) after one dose[18] and HS over NS after 3 months (Figs 3,4)[19,23]; however, effects were not significant at 12 months.[23]

Sensitivity analysis that excluded one trial due to lack of participant blinding[19] reduced the difference for FEV_1 from 0.34 to 0.05 L, and FVC from 0.4 to 0.04 L at 3 months.

Mannitol

Two trials measured spirometry in bronchiectasis. After 12 weeks (n = 343), there were no significant differences in FEV_1, FVC, forced expiratory ratio (FER), carbon monoxide diffusing capacity or peripheral airway function compared with placebo.[6] No change was found after 52 weeks in FEV_1 or FVC (n = 461).[7]

N-acetylcysteine

Five trials (n = 20–62) were identified.[8,15,17,27,32] In one trial, 1 week of NAC in asthma (n = 30) failed to improve FEV_1, FVC and maximum mid-expiratory flow rate (MMFR) over placebo,[17] whereas in another, there were significant improvements in FEV_1 and FVC over NS by 280 and 350 mL, respectively (n = 62).[8] Three trials investigated NAC in COPD[15,27,32] with differing results. At 1 week, one of two trials reported improvements in FEV_1 and FVC.[27,32] After 16 weeks, there was no effect on FEV_1, FVC or peak expiratory flow rate (PEFR).[15]

Recombinant human deoxyribonuclease

In 50 acute asthmatic patients, rhDNase did not improve FEV_1. Sub-group analysis revealed a small significant FEV_1 improvement in patients with a baseline FEV_1 ≤39% after 60 min (6.5%, P = 0.045) and 120 min (9.6%, P = 0.039).[30]

Two trials analysed bronchiectasis.[24,35] After 2–24 weeks of bd rhDNase (n = 410), FVC reduced significantly (–5.4%[35] and –3.7%[24]), as did FEV_1 by –4.3% (P = 0.18)[35] and –1.9% (P ≤ 0.05)[24] over placebo.

Mesna

Three trials studying COPD (n = 52) reported that Mesna did not improve lung function over 1–16 days.[9,29,31] The comparison was 7.1% HS in one trial, with no differences reported after 4 days.[9]

Ascoxal

Two trials studying COPD showed positive results (n = 19). After 1 day, there was a lasting improvement in 1-s vital capacity (VC) over control (57–166 mL) (n = 9).[28] After 1 week (n = 20), there were significant improvements over control in FEV_1, FVC and maximum voluntary ventilation (0.13 L, 0.24 L and 4.6 L/min, respectively).[16]

Adverse events

Ten trials did not include AE data. Five reported no intervention-related AEs. No deaths were attributed to study medication. No AEs were reported with Sobrerol. Fifteen trials reported on AEs (Table S3, Supplementary Information).

Mesna

Nine participants reported AEs using Mesna on 13 occasions in two COPD trials (n = 41).[29,31] Meta-analysis (Figs S1,S2, Supplementary Information) suggests more AEs with Mesna with marked heterogeneity (I^2 = 85% and 93%). AEs were reported as mild and transient, including wheeze, gastric discomfort, shortness of breath (SOB) and increased work of breathing (WOB).

Normal saline

One trial reported no AEs post NS in COPD (n = 40).[20]

Hypertonic saline

Three trials reported AEs (n = 139) studying HS.[19,23,34] Seven participants with COPD reported AEs including bronchospasm, cough, chest tightness and cardiovascular dysfunction, causing withdrawal in four participants.[34] Screening resulted in 3 of 80 participants being excluded before randomization in two bronchiectasis trials (reduction in $FEV_1 \geq 15\%$).[19,23]

N-acetylcysteine

Four of five studies reported events including SOB, cough and upper respiratory tract discomfort (n = 199).[8,15,17,27,32] There was little difference between treatment (n = 13 participants) and comparison AEs (n = 12 participants). Meta-analysis revealed no increased risk of AE in COPD (Fig. S3, Supplementary Information) and asthma (Fig. S4, Supplementary Information, RR = 0.53) patients.

Mannitol

Screening in 158 of 1051 patients in four trials showed a >15–20% reduction in FEV_1.[6,7,13,14] Meta-analysis revealed an increased risk of withdrawal due to AEs (RR = 1.81) with marked heterogeneity (I^2 = 87%) in bronchiectasis patients (Fig. 5), despite no significant increase in events over comparison (Fig. S5, Supplementary Information).[6,7]

Recombinant human deoxyribonuclease

Three trials (n = 460) reported AEs in 27 participants post rhDNase (comparison = 18).[24,30,35] 'Flu syndrome' was most common.[35]

In acute asthma, FEV_1 decreased (≥10%) in 2 of 30 participants following rhDNase.[30] Two trials examined sputum drug levels in bronchiectasis patients (n = 410).[24,35] After 14 days, these were no different to placebo.[35] Antibodies to rhDNase after 24 weeks were 7.2% (placebo = 0.6%), and there was no difference in serum or haematological markers.[24]

Symptoms and HRQOL

Normal saline

Three trials reported on effects of NS in COPD patients (n = 18–40). In two of the three trials, SOB improved, while symptom relief and expectoration improved in one of the trials. Subjective disease severity was not altered.[20,25,26]

Hypertonic saline

Eight weeks of 3% HS plus pulmonary rehabilitation in COPD failed to improve SOB over NS (n = 64). HRQOL (SF-36) was significantly better post NS only.[34]

Three trials investigated HS in bronchiectasis patients (n = 71).[18,19,23] Cough frequency was unchanged,[23] but ease of expectoration was significantly better with HS.[18,19] Two trials assessed HRQOL via the St George's Respiratory Questionnaire (SGRQ) and Leicester Cough Questionnaire (LCQ).[19,23]

One trial reported a significant benefit in SGRQ,[19] the other reported no impact of HS over NS on LCQ after 3 months.[23] There was no benefit over NS at 12 months, although both groups improved from baseline.[23] In one trial at 3 months, the improvement in SGRQ (total, symptoms and impact) with HS reached the minimum important difference (MID).[19,37] At 12 months, there were no between-group differences in LCQ.[23,38]

Mesna

In two trials over 3–8 days in COPD patients (n = 42), there was no change to SOB, sputum, cough, chest tightness, sleep or expectoration.[9,31]

Mannitol

Two trials measured HRQOL in bronchiectasis (n = 804).[6,7] Mannitol did not improve LCQ or Bronchiectasis Symptoms Questionnaire (BSQ), and only improved the impact sub-score of the SGRQ after 12 weeks[6] and the activity sub-score after 52 weeks over placebo,[7] both exceeding the MID.[37]

Recombinant human deoxyribonuclease

One dose in acute asthma (n = 50) failed to significantly lower SOB over NS (post Borg scores = 3.4 and 2.7, respectively).[30] Two trials studying bronchiectasis (n = 410) revealed no impact on QOL.[24,35]

N-acetylcysteine

Two trials studying asthma over 1 week (n = 92) showed no improvement in subjective asthma or cough severity, SOB, sputum volume or inhaler use, but sputum viscosity was significantly lower post NAC over NS.[8,17]

Three trials investigated NAC in COPD patients (n = 20–51).[15,27,32] Cough severity and burden plus sputum viscosity were significantly improved in one of the three trials,[32] SOB was unchanged in two studies[15,27] and NAC was no more effective than placebo in improving ease of expectoration in three trials.[15,27,32]

Physical capacity

Hypertonic saline

Pulmonary rehabilitation plus 3% HS in COPD patients (n = 64) led to a 56-m improvement in 6-min walk distance (6MWD), with a greater improvement (P < 0.001) following NS (204 m).[34]

Mannitol

After 12 weeks in bronchiectasis (n = 343), incremental shuttle walk (ISW) distance improved by 22.3 m, compared with 19.4 m post placebo (P = NS).[6]

Exacerbations

Mannitol

Two trials (n = 804) involving bronchiectasis patients conducted over 12–52 weeks showed no change in protocol-defined exacerbations (PDEs) (mannitol 11.7%, placebo 9.8%)[6] or annual exacerbation rate over placebo (1.69 and 1.84).[7] More participants receiving mannitol remained exacerbation free (31.3% vs 21.9%, P = 0.027) and showed longer times to first exacerbation over 1 year (165 days vs 124 days, P = 0.021).[7]

Recombinant human deoxyribonuclease

In two trials involving bronchiectasis patients (n = 410),[24,35] withdrawal due to exacerbation was reported once post rhDNase, with three exacerbations following bd rhDNase after 14 days.[35] Over 24 weeks, rhDNase did not change PDE rate (0.66, placebo 0.56) but non-PDEs were significantly higher (RR = 2.01). There were more exacerbations overall post rhDNase (0.95 vs 0.71 per patient, per study period, RR = 1.35).[24]

N-acetylcysteine

Twice daily NAC in COPD patients for 16 weeks (n = 51) had no effect on exacerbation number (9 vs 7) or days (88) over placebo.[15]

Hypertonic saline

Two trials involving bronchiectasis patients (n = 68) found a significant reduction in annual exacerbation rate over placebo after 3 months (2.14 and 4.85),[19] but there was no difference at 12 months in exacerbation rate (HS = 3, NS = 1) or days (HS = 12, NS = 2).[23]

Healthcare utilization

Recombinant human deoxyribonuclease

Two trials involving bronchiectasis patients (n = 410) reported three hospitalizations in two participants (15%) over 2 weeks,[35] and an increase in hospitalizations per participant (0.39, 0.21 placebo, RR = 1.85) with bd use over 24 weeks.[24] In acute asthma, rhDNase use did not change hospitalization rate (63% vs 45%) over placebo.[30]

Hypertonic saline

In bronchiectasis (n = 68), HS led to fewer annualized hospitalizations over NS (NS = 4.85 vs HS = 2.14) at 3 months[19] but not at 12 months (NS = 3 vs HS = 1).[23] Hospital days were no different (NS = 69 vs HS = 68).[23]

Mannitol

One trial studying bronchiectasis (n = 461) reported that mannitol failed to significantly lower hospitalizations over placebo after 52 weeks (0.14 vs 0.20 hospitalizations per year, 31% lower post mannitol).[7]

Microbiology

Hypertonic saline

After 12 months of use in bronchiectasis (n = 40), colonized sputum samples decreased from 55% (HS) and 60% (NS) to 15% in both groups.[23]

N-acetylcysteine

There were no changes in sputum Gram stains after 1 week of NAC compared with NS in asthma/chronic restrictive lung disease (n = 92).[8,17]

Mannitol

Two studies in bronchiectasis (n = 804) reported that although mannitol showed no difference over placebo in bacterial sputum colonization after 12 weeks,[6] the percentage of pathogens at 52 weeks decreased significantly by 13.1% (from 52.7%) after mannitol, compared with 8.3% (from 50.5%) after placebo.[7]

Antimicrobial use

Hypertonic saline

Two studies examined antibiotic use over 3–12 months in bronchiectasis patients (n = 68).[19,23] Compared with NS, HS did not reduce annualized antibiotic use after 3 months (NS = 5.43, HS = 2.43),[19] and annual exacerbations requiring antibiotics were unchanged at 12 months (NS = 0.5, HS = 1.0).[23] Exacerbation days requiring antibiotics were no different at 1 year (NS = 1.0, HS = 2.0).[23]

Mannitol

Antibiotic use in participants with bronchiectasis (n = 804) was studied over 12–52 weeks in two trials.[6,7] Mannitol was no more effective than placebo in reducing commencement of antibiotics after 12 weeks,[6] but over 52 weeks led to a reduction in antibiotic days to treat exacerbations by 24%, from 26.03 (placebo) to 19.88.[7]

Mucociliary clearance

Recombinant human deoxyribonuclease

One trial (n = 61) studying bronchiectasis revealed no effect on in vivo MCC between groups.[35] In vitro MCC revealed that rhDNase lowered transportability index from 26 (control) to 13 (P = 0.003). Eight samples (32%) were completely liquefied.[35]

Mannitol

One trial investigated the effect of one dose on MCC in asthma (n = 7).[10] Doses of 240 and 480 mg improved whole-lung MCC significantly from 5.5% (baseline) and 7.3% (control) to 19.5% and 26.4% respectively, and was improved again with cough.[10]

In two bronchiectasis studies (n = 25),[13,14] MCC significantly improved following mannitol plus cough in all lung regions over control, with doses up to 480 mg. Radioaerosol clearance improved by 30–50% after 45–90 min compared with control (10–17%).[13,14] Meta-analysis (Fig. S6, Supplementary Information) shows marked heterogeneity (I^2 = 85%).

Sputum colour

Recombinant human deoxyribonuclease

After 14 days in bronchiectasis (n = 61), sputum colour was no different between placebo (3.2), once daily (3.4) and bd rhDNase (3.5).[35]

Sputum weight

Mesna

Results of two trials in COPD patients (n = 27) are conflicting. Over 8 days, Mesna improved sputum wet weight more than NS,[31] but failed to change dry weight over control.[9]

Ascoxal

Two trials report conflicting results in COPD patients (n = 25). In one trial, sputum expectorated increased after 1 day, but was not significant (n = 5).[28] In another trial, there was an improvement in 24-h sputum over control after 1 week by 17.8 mL (n = 20).[16]

Normal saline

In bronchiectasis patients (n = 8), NS significantly increased sputum wet weight (25 g) compared with chest physiotherapy (5 g) after one dose.[33] Three weeks of NS in COPD patients (n = 20) proved ineffective in increasing sputum weight.[25]

Hypertonic saline

After a single dose of HS, there was a significant increase in sputum expectorated (5.3 g) over NS in bronchiectasis (n = 23).[18]

N-acetylcysteine

One week of use did not alter sputum production in COPD (n = 20)[27] or asthma (n = 62) patients.[8]

Mannitol

Sputum weight was assessed in two bronchiectasis trials (n = 461) following bd mannitol. Twelve weeks of use increased 24-h sputum wet weight by 4.3 g over placebo. This was greater in patients producing >10 g at baseline (+5.6 g).[6] After 52 weeks, sputum weight decreased post mannitol by 6.6 g compared with placebo (9.42 g).[7]

Sputum rheology

Hypertonic saline

In two trials studying bronchiectasis (n = 51), subjective sputum viscosity post HS improved after 3 months,[19] as did sputum 'pourability' after one dose compared with NS.[18]

Ascoxal

There were conflicting results in two COPD trials (n = 26). No improvement in sputum viscosity (n = 5) or osmolarity (n = 6) over NS was seen after 1 day,[28] but after 1 week, sputum 'apparent' viscosity was significantly reduced over bronchodilator (n = 20).[16]

N-acetylcysteine

After 1 week in general respiratory patients (n = 20), NAC significantly improved objective sputum viscosity over bronchodilator and placebo.[27]

Two trials studying asthma or chronic restrictive lung disease characterized by inspissated sputum (n = 92) showed that NAC significantly lowered objective and subjective (RR = 2.43) viscosity (Figs S7,S8, Supplementary Information).[8,17]

Inflammation

Mannitol

In one trial over 12 weeks in bronchiectasis (n = 343), there were no significant changes to inflammatory markers over placebo.[6]

N-acetylcysteine

White cell count did not change after 1 week in stable asthma or restrictive respiratory disease over NS (n = 92).[8,17]

Radiology

Mannitol

Twelve weeks of mannitol use in bronchiectasis patients (n = 343) significantly reduced small airway mucus plugging on HRCT compared with placebo (difference of –6.59).[6]

DISCUSSION

We analysed 30 RCTs assessing eight agents. Both HS and NS improved FEV_1, FVC and forced expiratory $flow_{25–75\%}$ in bronchiectasis after one dose and 3–12 months,[18,19,23] while NS did not improve spirometry in COPD. Mannitol failed to improve spirometry in bronchiectasis,[6,7] but may prolong exacerbation-free

Table 1 Summary of benefit

Strength of findings[†]	Low	Unclear	High	No benefit
Bronchiectasis		Mannitol[6,7,11–14]	HS[18,19,23,33] NS[23,33]	Dornase alfa[‡24,35]
COPD	NS[20,21,25,26,34] Mesna[§9,29,31]	NAC[15,27,32]		HS[9,34]
Asthma	Dornase alfa[¶30]	HS[12] NAC[8,17] Mannitol[10]		

[†]Strength of findings defined according to Higgins and Green.[5]
[‡]Detrimental.
[§]Single study, single outcome.
[¶]Sub-study significance only.
Benefit, one or more trials show positive results in one or more outcomes; dornase alfa, recombinant human deoxyribonuclease/rhDNase; HS, hypertonic saline; NAC, N-acetylcysteine; No benefit, lack of positive results in any trial; NS, normal saline.

periods. In acute asthma, rhDNase improved spirometry only in those with severe disease.[30] In bronchiectasis, rhDNase caused significant reductions in FEV_1 and FVC.[24,35] The impact of NAC on symptoms and spirometry in COPD[15,27,32] and asthma[8,17] was inconsistent. It should be noted that a lack of improvement in spirometry does not always rule out improvement in other important, patient-related parameters.[39–41] A summary of findings is presented in Table 1.

In bronchiectasis,[24] rhDNase increased exacerbation rate and reduced spirometry. All other agents were safe, albeit with minor, transient AEs including wheeze, SOB, increased WOB, cough and haemoptysis. Only mannitol (n = 43)[6,7] and HS (n = 4)[34] caused AEs resulting in study withdrawal. Patients commencing these medications should undergo challenge testing prior to use.

HRQOL was investigated in 20 trials. These studies showed a lack of consistent improvement in HRQOL and exacerbations, apart from promising results following mannitol,[7] HS or NS in bronchiectasis.[19,23] It is disappointing that mucoactive agents do not seem to impact on these outcomes that are important to patients and to long-term prognosis. Apart from short-term benefit from NS in COPD, we do not recommend using mucoactive agents for symptom or HRQOL improvement.

Limitations of this review include study age, low participant numbers and unclear methods. Nine trials were published in the last 10 years, questioning whether older interventions and outcomes are still relevant. One-third of trials had <20 participants and only seven trials reported power calculations. The utility of mucoactive agents in severe disease also needs to be addressed. The majority of trials were conducted over ≤3 months; therefore, the impact of these results with long-term use is unknown.

It is unclear what effect adjunctive airway clearance or exercise had, such as Acapella (Smiths Medical, Ashford, UK),[6,7] intermittent positive-pressure breathing (IPPB),[16,27,28] ACBT[18] or pulmonary rehabilitation.[34] Bronchodilator medication was co-administered to all groups in 12 trials, which may confound results. Inhaled medication efficacy relies on appropriate equipment, particle size and technique.[42] All but three trials described device used, but only nine described technique and four disclosed particle size. We recommend future trials outline these methods.

In conclusion, we do not recommend rhDNase for use in non-CF bronchiectasis,[24,35] but there may be promise in asthmatic patients with severe disease.[30] HS was not consistently more effective than NS for lung function, HRQOL and hospitalization in bronchiectasis.[18,19,23] NS can be safely used in COPD for symptom relief,[20,26] but does not improve spirometry. HS was not beneficial in COPD.[34] Apart from NS in COPD, we do not recommend using mucoactive agents for symptomatic relief. Mannitol in bronchiectasis[6,7,11,13,14] benefits MCC, sputum load and exacerbation rate, but lacks evidence over long periods. Screening is required before initiating mannitol and HS, particularly in bronchiectasis, due to potential for bronchospasm.[6,7,19,23]

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Supplementary Information

Additional supplementary information can be accessed via the *html* version of this article at the publisher's website.

Appendix S1 Search strategy.
Appendix S2 Qualitative analysis of outcomes from single studies $n \leq 20$.
Figure S1 Mesna in COPD. Meta-analysis of the number of patients experiencing adverse events.
Figure S2 Mesna in COPD. Meta-analysis of the number of occasions of adverse events.
Figure S3 N-acetylcysteine in COPD. Meta-analysis of the number of patients experiencing adverse events.
Figure S4 N-acetylcysteine in asthma. Meta-analysis of the number of patients experiencing adverse events.
Figure S5 Mannitol in bronchiectasis. Meta-analysis of treatment-related adverse events.
Figure S6 Mannitol in bronchiectasis. Meta-analysis of whole right lung clearance.
Figure S7 N-acetylcysteine in asthma. Meta-analysis of objective sputum viscosity at 1 week.
Figure S8 N-acetylcysteine in asthma. Meta-analysis of subjective sputum viscosity at 1 week.
Table S1 Study descriptions.
Table S2 Raw data.
Table S3 Adverse events.

