Interventions for bronchiectasis: an overview of Cochrane systematic reviews (Review)

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[Overview of Reviews]

Interventions for bronchiectasis: an overview of Cochrane systematic reviews

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ABSTRACT

Background

Bronchiectasis is a chronic respiratory disease characterised by abnormal dilatation of the bronchi, and presents typically with a chronic productive cough (or chronic wet cough in children) and recurrent infective exacerbations. It significantly impacts daily activities and quality of life, and can lead to recurrent hospitalisations, severe lung function impairment, respiratory failure and even death.

Objectives

To provide an overview of the efficacy and safety of interventions for adults and children with bronchiectasis from Cochrane reviews.

To identify gaps in the evidence base that will inform recommendations for new research and reviews, and to summarise information on reported outcomes and make recommendations for the reporting of standard outcomes in future trials and reviews.

Methods

We included Cochrane reviews of non-cystic fibrosis (CF) bronchiectasis. We searched the Cochrane Database of Systematic Reviews. The search is current to 11 February 2015. We also identified trials that were potentially eligible for, but not currently included in, published reviews to make recommendations for new Cochrane reviews. We assessed the quality of included reviews using the AMSTAR criteria. We presented an evidence synthesis of data from reviews alongside an evidence map of clinical trials and guideline data. The primary outcomes were exacerbations, lung function and quality of life.

Main results

We included 21 reviews but extracted data from, and rated the quality of, only nine reviews that reported results for people with bronchiectasis alone. Of the reviews with no usable data, two reviews included studies with mixed clinical populations where data were not reported separately for people with bronchiectasis and 10 reviews did not contain any trials. Of the 40 studies included across the nine reviews, three (number of participants nine to 34) included children. The studies ranged from single session to year-long studies. Each review included from one to 11 trials and 28 (70%) trials in the overview included 40 or fewer participants. The total number of participants included in reviews ranged from 40 to 1040. The age range of adult participants was from 36 to 73 years and children

ranged from six to 16 years. The proportion of male participants ranged from 21% to 72%. Where reported, mean baseline forced expiratory volume in one second (FEV_1) ranged from 1.17 L to 1.66 L and from 47% to 88% predicted. Most of the reviews had search dates older than two years.

We have summarised the published evidence as outlined in Cochrane reviews, but it was not possible to draw definitive conclusions. There was inconclusive evidence on the use of long-term antibiotics and nebulised hypertonic saline for reducing exacerbation frequency and evidence that human deoxyribonuclease (RhDNase) increases exacerbation frequency. Improvements in lung function were reported for inhaled corticosteroids (ICS) though this was small and not clinically relevant. Evidence of benefit for hyperosmolar agents and mucolytics was inconclusive. There was limited evidence of improvements in quality of life with airway clearance techniques and physical therapy but evidence of benefit for hyperosmolar agents was inconclusive. Secondary outcomes were not clearly reported in all trials in the included reviews. Improvements in dyspnoea, wheeze and cough-free days were reported for small trials of ICS and LABA (long-acting $beta_2$-agonsts)/ICS and cough reduction was also reported for a small bromhexine trial. Reduction in sputum production was reported for long-term antibiotics and airway clearance techniques but evidence of benefit for hyperosmolar agents was inconclusive.

Adverse events were included as outcomes in seven reviews. The review of long-term (four weeks to one year) prophylactic courses of antibiotics reported significantly more cases of wheeze (Peto odd ratio (OR) 8.56, 95% confidence intervals (CI) 1.63 to 44.93), dyspnoea (12 versus three, P value = 0.01) and chest pain (seven versus zero, P value = 0.01) from the same trial (74 participants) but no differences in occurrence of diarrhoea, rash or number of withdrawals. In the review of mucolytics versus placebo, relevant outcomes were not reported for erdosteine comparisons and no significant adverse effects were reported for bromhexine, though adverse events were associated with RhDNase (OR 28.19, 95% CI 3.77 to 210.85, 1 study). Of the remaining five reviews, adverse events were not reported in the single trials included in the ICS review or the physical therapy review and the impact of adverse events in the single trial included in the inhaled LABA/ICS combination versus ICS review were unclear. The reviews of short-term courses of antibiotics and inhaled hyperosmolar agents reported no significant differences in occurrence of adverse events. Fewer admissions to hospital were reported for long-term antibiotics, but this outcome was not reported in all reviews. No reviews reported differences in mortality, but again this outcome was not included in all reviews.

We did not explicitly include antibiotic resistance as an outcome in the review, but this was unclear in the Cochrane reviews and evidence from other trials should be considered.

We rated all reviews as high quality (AMSTAR), though opportunities for improved reporting (e.g. summary of findings and GRADE evaluation of the evidence) were identified for inclusion in future updates of the reviews. However, the majority of trials were not high quality and confidence in the effects of treatments, therefore, requires additional evidence from larger and more methodologically robust trials. We evaluated the overall coverage of important topics in bronchiectasis by mapping the quality of the current evidence base against published guidelines and identifying high priority areas for new research on; use of short-course and long-term antibiotics, ICS and oral corticosteroids, inhaled hyperosmolars, mucolytics, and use of airway clearance techniques.

Authors' conclusions

This overview clearly points to significant opportunities for further research aimed at improving outcomes for people with bronchiectasis. We have highlighted important endpoints for studies (particularly exacerbations, quality of life and lung function), and areas of clinical practice that are in most urgent need of evidence-based support (including long-term antibiotics, ICSs and mucolytics).

As the evidence is confined to small trials of short duration, it is not currently possible to assess the balance between the benefits and potential harms of treatments for bronchiectasis.

PLAIN LANGUAGE SUMMARY

Interventions for bronchiectasis: an overview of Cochrane systematic reviews

What is bronchiectasis?

Bronchiectasis is a long-term respiratory disease that is commonly associated with a troublesome cough productive of mucous (or chronic wet cough in children) and recurrent flare-ups (exacerbations) due to lung infections. It significantly impacts upon normal daily activities and quality of life, and can lead to recurrent hospitalisations, loss of lung function and even death.

We looked at the available Cochrane reviews on bronchiectasis and found overall that there are relatively few trials and Cochrane reviews available so it is difficult to draw helpful conclusions about how to treat bronchiectasis.

Overviews are designed to present the contents from a selection of reviews in a concise and helpful manner. To do this, we made an evidence map of the available information from guidelines, clinical trials and Cochrane reviews, and highlighted the need for new research. We have listed the most important outcomes for measuring benefit and harm in bronchiectasis (particularly exacerbations, quality of life and lung function), and areas of clinical practice that are in most urgent need of evidence-based support (including long term antibiotics, inhaled corticosteroids and mucolytics) in future studies.

The key findings for difference medicines and treatments were:

- Long-term antibiotics may reduce sputum (a mixture of saliva and mucous that is coughed up from the airways) production, frequency of exacerbations and hospitalisation, but may also be associated with more frequent side effects (wheeze, dyspnoea (difficulty in breathing) and chest pain).

- Inhaled corticosteroid treatment may improve lung function but the effect is small.

- Bromhexine may reduce cough, but evidence of benefit for hyperosmolar agents and mucolytics is generally unclear.

- Airway clearance techniques may reduce sputum production and improve quality of life.

- RhDNase (a medicine used to treat bronchiectasis) is associated with more frequent exacerbations.

- long-acting beta$_2$-agonists/ICS combination therapy may reduce dyspnoea, wheeze and cough.

About 70% of trials in the reviews included in the overview were small (40 participants or fewer), which limits interpretation.

Side effects were reported in seven reviews:

- Long-term courses of antibiotics were associated with more cases of wheeze, breathlessness and chest pain, but we could not assess the risks of developing antibiotic resistance.

- In the review comparing mucolytics (medicines that make the mucous less thick and sticky and easier to cough up) with placebo (a pretend medicine), side effects were not reported for erdosteine comparisons. No significant side effects were reported for bromhexine, though side effects were associated with RhDNase.

- Side effects were not reported in the single trials included in the inhaled corticosteroid review or the physical therapy review and the impact of adverse events in the single trial included in the inhaled corticosteroid/long-acting beta$_2$-agonists combination versus inhaled corticosteroids review were unclear.

- The reviews of short-term courses of antibiotics and inhaled hyperosmolar agents reported no significant differences in occurrence of side effects. Fewer admissions to hospital were reported for long-term antibiotics.

- No reviews reported significant differences in deaths between treatment and control groups, but only a small number of reviews recorded deaths.

The included evidence came from:

- 21 Cochrane reviews, but there was only useable data in nine reviews.

- Forty trials were included in the nine reviews and 28 (70%) of the trials included 40 or fewer participants. Only three trials (nine to 34 participants) included children.

- Each review included from one to 11 trials.

- The studies ranged from single session to year-long studies.

- The total number of participants included in reviews ranged from 40 to 1040.

- The age range of adult participants was from 36 to 73 years and children ranged from six to 16 years.

- The included reviews were judged to be of high quality.

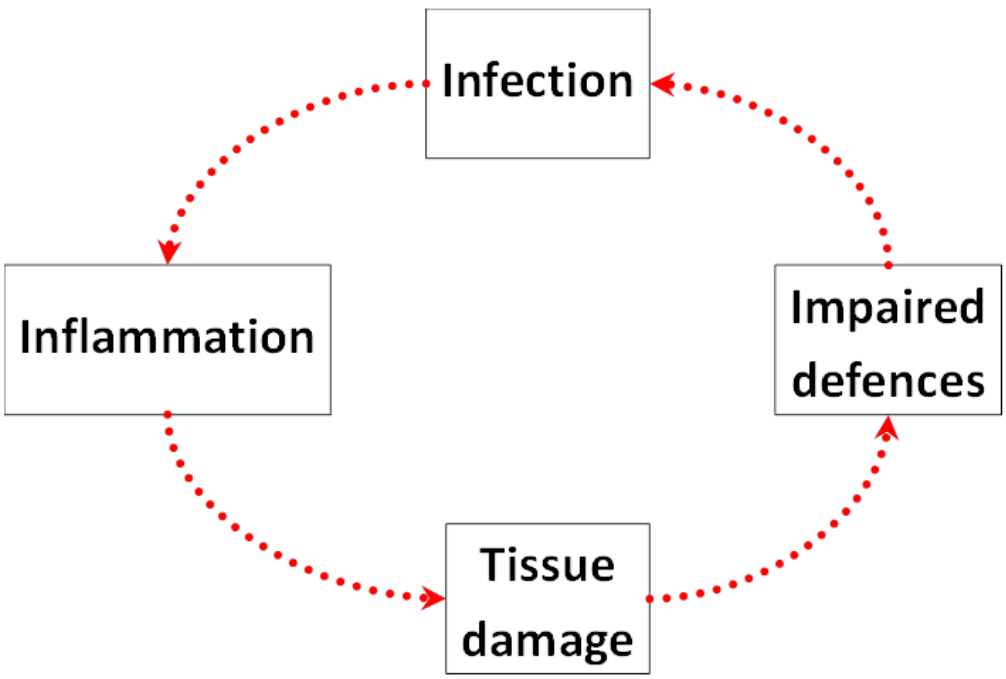
- However, the majority of trials in the bronchiectasis reviews were small and at risk of bias, so confidence in the effects of treatments therefore requires additional evidence from larger and more methodologically robust trials

BACKGROUND

Description of the condition

Bronchiectasis is a condition defined by abnormal dilation of the airways. This is typically associated with progressive airway destruction, due to the 'vicious cycle' of recurrent bacterial infection, inflammatory mediator release, airway damage and consequent further infection (Cole 1997; Figure 1). In severe cases, this may lead to repeated hospitalisation, chronic respiratory failure and death.

Figure 1. The vicious cycle of bronchiectasis (Cole 1986).Treatment of both chronic disease and exacerbations aims to intervene in this cycle. For example, long-term treatment with mucolytics and chest clearance may be considered in an attempt to improve lung clearance, and thus remove the reservoir for infection; vaccination or immunoglobulin replacement (in people who are deficient) targets impaired lung defences; and prompt treatment with antibiotics, bronchodilators and chest clearance in exacerbations aims to accelerate resolution and limit further airway damage.



The diagnosis of bronchiectasis is made on clinico-radiographic grounds, requiring identification of one or more abnormally dilated bronchi using high-resolution computerised tomography (HRCT) scanning, together with appropriate symptoms (Chang 2010; Pasteur 2010). These symptoms may incorporate a chronic and usually productive or wet cough together with recurrent lower respiratory tract infections. People with bronchiectasis may also experience breathlessness, wheeze, or both, and non-specific symptoms related to inflammatory burden, such as chest pains and lethargy. Risk factors for accelerated decline in lung function may include colonisation with *Pseudomonas aeruginosa*, and frequent exacerbations (Evans 1996; Martinez-Garcia 2007). Colonisation with *P aeruginosa*, impaired exercise capacity, wheeze, breathlessness and frequent exacerbations are all associated with a reduction in quality of life (QoL) (Wilson 1997a; Wilson 1997b).

There is no consensus-based definition of bronchiectasis severity but a number of factors are associated with an increased risk of hospitalisation and mortality including: low Forced expiratory volume in one second) FEV_1) % predicted, *P aeruginosa* colonisation, higher proportion of affected lobes, higher Medical Research Council (MRC) dyspnoea score and more frequent annual exacerbation rate (Chalmers 2014; Martinez-Garcia 2014). Co-morbidities were not found to predict either mortality or hospitalisation (Chalmers 2014). The Bronchiectasis Severity Index (Chalmers 2014) or FACED (Martinez-Garcia 2014) may identify high-risk groups, but are unlikely to be used as outcome measures, as a number of component factors (e.g. lung function) are irreversible and, therefore, not modifiable. The main aim of therapeutic management is preservation of lung function, reduction of symptoms and exacerbations, and improvement in QoL (Saleh 2014).

A cause for bronchiectasis should always be sought in the diagnostic work-up. Although the majority of cases are either idiopathic or due to a previous severe lung infection, treatable causes are found in a significant minority of cases, such as immune-deficiency, allergic bronchopulmonary aspergillosis, mycobacterial infection and recurrent aspiration (Goeminne 2012; Pasteur 2000).

Prevalence of bronchiectasis

The true prevalence of bronchiectasis is unknown, with reported figures confounded by variable aetiology and diagnostic strategies (Weycker 2005), higher prevalence in developing countries (Habesoglu 2011), and variability in reported prevalence metrics. In one French series, 2.6% of respiratory outpatients had a confirmed diagnosis (Goeminne 2012). Evidence suggests an increase in the global burden of bronchiectasis, with mortality rate increasing at 3% per year between 2001 to 2007 in England and Wales (Roberts 2010), and hospitalisations increasing by the same percentage over a nine-year period in the US (Seitz 2010). Both studies reported the steepest increase in prevalence rates in people aged 60 years and over, and one further study by Seitz and colleagues reported an increase of 8.7% per year in people over 65 year old in the US, with steeper increases in women compared with men (Seitz 2012). Bronchiectasis prevalence rates may also vary by ethnicity (Chang 2003; Seitz 2012). Prevalence rates are potentially conservative due to under-diagnosis of bronchiectasis (Roberts 2010), and the recent upwards trends may be attributable in part to increasing awareness of the disease and more frequent use of HRCT scanning (Seitz 2012).

Description of the interventions

Bronchiectasis is driven by a vicious cycle of breached defences, infection, inflammation and tissue damage (Figure 1). Interventions are indicated both for long-term management and treatment of exacerbations. In each case these can be divided into pharmacological and non-pharmacological interventions.

How the intervention might work

The principals of treatment for bronchiectasis are to improve QoL as well as day-to-day symptoms (especially cough and breathlessness), to minimise the frequency and severity of exacerbations or to reduce microbial load. Further aims of therapy, although more difficult to demonstrate in short- or medium-term randomised controlled trials (RCT), are to slow the decline in lung function and reduce mortality.

Long-term management of bronchiectasis

Pharmacological interventions

Mucolytics are available in oral (e.g. carbocysteine, erdosteine) and inhaled (e.g. mannitol, hypertonic saline) formulations and work by reducing sputum viscosity, which eases expectoration, potentially leading to reduced symptoms and exacerbation frequency (Wilkinson 2014). Recombinant human DNase I (RhDNase) has been used for the treatment of cystic fibrosis (CF) bronchiectasis, with the aim of reducing the incidence of respiratory tract infection and improving lung function. However one trial of RhDNase in adults with bronchiectasis was reported to show the treatment to be 'ineffective and potentially harmful' (O'Donnell 1998).

Inhaled bronchodilators act by relaxing smooth muscle, either by activating the $beta_2$-adrenoreceptor (salbutamol, terbutaline) or blocking cholinergic transmission (ipratropium, tiotropium) (Franco 2003; Sheikh 2001). Therefore, they are most effective in people with bronchial smooth muscle hypertrophy, hyper-reactivity, or both. Theoretically bronchodilators may also improve mucous clearance (Restrepo 2007). Conversely in people with severe bronchial wall damage, bronchodilators may worsen symptoms if the reduction in smooth muscle tone leads to further loss of structural integrity.

Anti-inflammatory medications in bronchiectasis include several drug classes(e.g. corticosteroids, leukotriene receptor antagonists, theophyllines and macrolides (given for their anti-inflammatory rather than antibiotic effect)) (Corless 2000; Crosbie 2009; Kapur 2007; Steele 2000). The mechanism of action differs by drug class

and there may be different effects in people with specific subgroups of disease.

Long-term antibiotics may be used where bacteria colonise the airways, on the assumption that these bacteria cause persistent symptoms and exacerbations (Evans 2003; Evans 2007). Antibiotics may be given either in nebulised or oral form.

Vaccination with both influenza and pneumococcal (pneumonia) vaccines is recommended in British Thoracic Society (BTS) guidelines (Pasteur 2010).

Non-pharmacological interventions

Respiratory physiotherapy techniques "include mobilising and aiding expectoration of bronchopulmonary secretions, improving efficiency of ventilation, maintaining or improving exercise tolerance, improving knowledge and understanding, and reducing breathlessness and (thoracic) pain" (Pasteur 2010). Chest clearance methods, which can be assisted with positive expiratory pressure devices, aim to improve chest clearance to reduce sputum (and bacterial) load, improve day-to-day symptoms and reduce exacerbation frequency (Clarke 1989).

Where disease is isolated to a single anatomical area of the lung and there is not an underlying and ongoing driver for bronchiectasis that may predict recurrence, surgical removal of a section of the lung may be indicated (Warburton 2000).

Pulmonary rehabilitation and exercise may help by improving respiratory fitness.

Long-term oxygen therapy and the treatment of secondary pulmonary hypertension are other treatment options. However, detailed discussion of these is beyond the scope of this review and readers are directed to consensus statements, guidelines and government resources (Chang 2010; Hill 2011; NHLBI; Pasteur 2010).

Interventions for exacerbations of bronchiectasis

Pharmacological interventions

Mucolytics may be used in exacerbations, with the aim of improving sputum clearance and shortening recovery time. Bronchodilators (often nebulised) are used with the aim of easing breathlessness, decreasing wheeze and promoting sputum clearance.

Anti-inflammatory treatments used in exacerbations may include oral corticosteroids, typically where there is an asthmatic element to the disease such as in allergic bronchopulmonary aspergillosis.

Theophyllines have both anti-inflammatory and bronchodilator effects, and likewise are sometimes used early in exacerbations to accelerate recovery, reduce breathlessness and improve sputum clearance.

Exacerbations in bronchiectasis are often mediated by bacteria, hence antibiotics (oral, nebulised or intravenous) are almost always prescribed. The spectrum of bacteria responsible for exacerbations in bronchiectasis is not the same as for other respiratory diseases such as chronic obstructive pulmonary disease (COPD); therefore, antibiotic choice should preferably be guided by knowledge of a person's previous sputum cultures (Pasteur 2010).

Non-pharmacological interventions

Chest clearance techniques are used during exacerbations, both self-administered and given by physiotherapists, especially where inpatient treatment is required (Pasteur 2010).

Why it is important to do this overview

The purpose of a Cochrane overview is to compile evidence systematically from a range of reviews of interventions for the same disease or condition into a single comprehensive and user-friendly document (Becker 2011).

A number of therapeutic interventions are currently available for the management of bronchiectasis including pharmacological, surgical and physical therapy-based treatments. Clinical guidelines for management of the condition have highlighted a paucity of good-quality evidence with which to inform treatment choices and clinical decision-making (Pasteur 2010). There are currently 20 bronchiectasis reviews on *The Cochrane Library* and there is a need to present a clear and accessible synthesis of this evidence for users, clinicians and policy-makers. This overview will document the evidence for the efficacy, safety and tolerability of the range of interventions covered by the reviews. Analysis of the evidence will provide a basis for recommendations for future clinical trials and Cochrane reviews. The overview will also enable an assessment of reported outcomes that may be used to inform a set of standard outcomes for future research studies.

OBJECTIVES

To provide an overview of the efficacy and safety of interventions for adults and children with bronchiectasis from Cochrane reviews.

To identify gaps in the evidence base that will inform recommendations for new research and reviews, and

To summarise information on reported outcomes and make recommendations for the reporting of standard outcomes in future trials and reviews.

METHODS

Criteria for considering reviews for inclusion

Types of reviews

We included non-CF bronchiectasis reviews published in the Cochrane Database of Systematic Reviews (CDSR) regardless of whether they included a clinical trial. We included Cochrane reviews of RCTs and controlled clinical trials (CCTs, such as quasi-controlled trials). In order to ensure comprehensive and up-to-date coverage of the evidence base, we also searched for and considered primary clinical trials.

Types of participants

We included reviews of adults and children with physician or radiographically diagnosed non-CF bronchiectasis. Ideally, we planned to include only studies with diagnoses based on HRCT, but, since this overview is based on Cochrane reviews, we were led by their inclusion criteria and discussed the limitations of the inclusion criteria where this arose. Although we recognised that treatments for adults and children may vary, we included evidence for both because the majority of reviews have done so, but presented data for adults and children separately where possible. We scanned inclusion criteria of included studies to confirm that reviews did not contain a substantial proportion of people with CF. We planned to include trials of people with stable bronchiectasis and people experiencing an exacerbation; however, we only found reviews in stable bronchiectasis.

Types of interventions/comparisons

We included all interventions for bronchiectasis and divided them into the following subgroups to provide structure for the evidence synthesis.

Pharmacological interventions

- Antibiotics.
- Vaccines.
- Bronchodilators.
- Anti-inflammatory medication.
- Bronchodilator and anti-inflammatory combination medication.
- Mucous clearance agents.

Non-pharmacological interventions

- Physiotherapy - airway clearance techniques (ACT); pulmonary rehabilitation; physical training techniques.
- Disease management and education - education; nurse specialist management.
- Surgery - lobectomy, pneumonectomy, lung transplantation.
- Other - interventions for massive haemoptysis; oxygen therapy; ventilation (e.g. continuous positive airway pressure (CPAP), bilevel positive airway pressure (BPAP)); pulmonary hypertension management; nutrition.

We described diagnostic criteria and trial duration for each included review. We reported trials that included concomitant medications or complex interventions according to the original review.

Types of outcome measures

Primary outcomes

- Exacerbations measured as frequency, proportion of people with one or more exacerbations, or duration of exacerbations.
- Lung function measured as forced expiratory volume in one second (FEV_1) in litres or as per cent of predicted.
- QoL using measures validated in a clinical setting.

Secondary outcomes

- Symptoms (e.g. dyspnoea, cough, wheeze).
- Sputum characteristics (volume and validated sputum colour tool).
- Adverse events (e.g. haemoptysis).
- Hospitalisation.
- Mortality.

We tabulated the range of outcomes used in the reviews.

Search methods for identification of reviews

We searched the CDSR on *The Cochrane Library* (Issue 2, 2015). We applied no date or language restrictions applied (see Appendix 1 for the search strategy).

We searched the Cochrane Airways Group trials register on 11 February 2015 using the search term 'bronchiectasis' to identify trials that were not included in reviews. The register contains trial reports identified through systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and handsearching of respiratory journals and meeting abstracts.

Data collection and analysis

Selection of reviews and trials

Two overview authors (EJW, SS) reviewed the results of the search and obtained full-text Cochrane reviews for further scrutiny.

One overview author (EJW) reviewed the search for new primary studies, excluding duplicates and those already included in reviews. We tabulated relevant trials and the author team evaluated them for inclusion in the overview. We added relevant RCTs on bronchiectasis to the evidence map (Table 1), and graded each intervention as either 'high' or 'low' priority based on appraisal of the evidence by the clinical author team (SF and DE).

Data extraction and management

Two overview authors (EJW, SS) extracted and tabulated data from included reviews. We resolved disagreements by consensus. We extracted the following data:

- assessment of methodological quality;
- diagnostic criteria;
- study duration;
- details of study participants;
- interventions;
- comparisons;
- outcomes and time points.

We presented data in a series of summary tables. We planned to extract information on the definition of exacerbations used in the reviews but there was not scope to include it in the overview. We planned to contact review authors for additional information not reported in the original reviews.

Assessment of methodological quality of included reviews

Methodological quality of included reviews

Two overview authors (EJW, SS) independently assessed the methodological quality of included reviews using the 'assessment of multiple systematic reviews' (AMSTAR) instrument (Shea 2007; Appendix 1). We planned to conduct sensitivity analyses to explore the consequences of synthesising reviews of differing quality, but reviews were generally of high quality and therefore there was no basis for a sensitivity analysis.

Quality of evidence in included reviews

We planned to summarise the quality of the evidence in included reviews that themselves included studies in the 'Summary of Findings' and 'Risk of Bias' tables according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and recommendations in the *Cochrane Handbook of Systematic Reviews of Interventions*, respectively (Balshem 2011; Higgins 2011).

Data synthesis

We presented data as a narrative synthesis supported by tables of statistical outcomes reported in the original reviews. The comparisons presented were determined by data in the included reviews. Although we had planned to update Cochrane reviews with new studies identified for inclusion, we did not do this because the scope of a number of the reviews requires modification before they are updated.

In order to reflect and prioritise clinical decision-making in the overview, we summarised the evidence using an evidence map, incorporating Cochrane reviews and RCTs not yet included in the reviews (Table 1). These were set in the context of practice recommendations using the BTS guidelines for bronchiectasis (Pasteur 2010).

We grouped data by intervention and outcome against the following framework: pharmacological interventions (antibiotics, vaccines, bronchodilators, anti-inflammatories, bronchodilators and anti-inflammatories combinations, mucous clearance agents); and non-pharmacological interventions (physiotherapy, disease management and education, surgery, other interventions).

We tabulated the evidence separately (post-hoc) for each of our planned outcomes and classified them by consensus taking into account the BTS/Scottish Intercollegiate Guidelines Network (SIGN) bronchiectasis guidelines (Pasteur 2010). The following classifications are listed in the tables under 'Evaluation':

- no evidence of benefit - no statistically significant or clinically relevant effect;
- evidence of statistical benefit - statistically significantly effect in favour of intervention;
- evidence of statistical benefit but not clinically relevant change - as above but magnitude of effect below published threshold of minimum clinically important difference (MCID) for the outcome, where available (MCID listed in table footnote);
- evidence of clinically relevant benefit - as point 2. above and mean effect of MCID or greater;
- evidence of harm - statistically significant effect in favour of control;
- unclear - conflicting evidence of effects.

Summary of the evidence base

We analysed and discussed limitations in the evidence base, including the number of participants and overall methodological quality of the reviews, and this informed recommendations for future research and Cochrane reviews.

Reliability of the outcomes

We planned to examine heterogeneity of the evidence for each primary outcome in the overview by summarising the range of the I^2 statistic variation. We planned to evaluate the role and relevance of each outcome measure critically by comparing the sensitivity

and stability of measures across the tranche of reviews to inform recommendations for a core set of outcomes for future studies.

Subgroup analysis

We categorised the review by pharmacological and non-pharmacological interventions in order to aid interpretation, imposed clinically relevant structure on the review and compared outcomes by diagnostic technique. We planned to analyse studies of adults (aged 19 years and older) and children (aged 18 years and younger) separately.

Sensitivity analysis

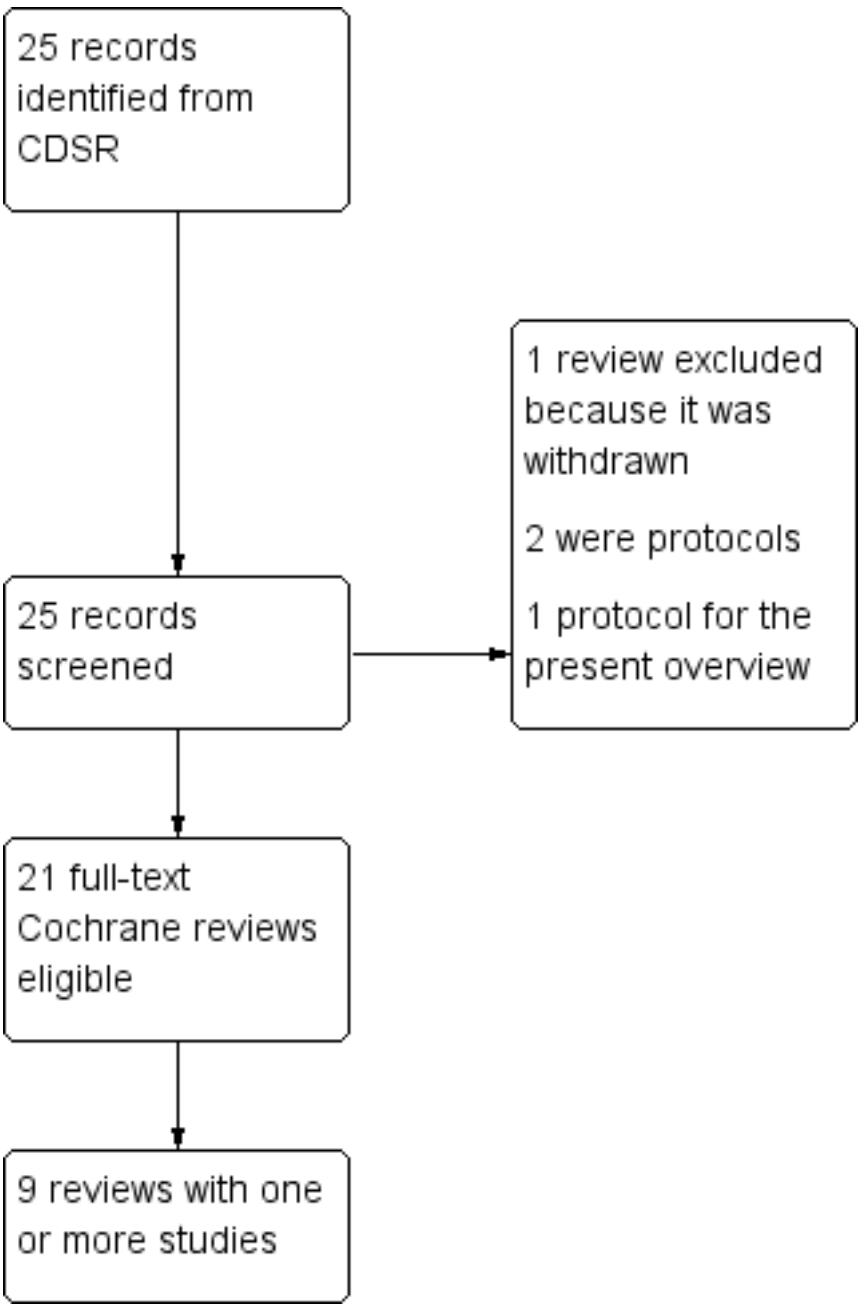
We planned to conduct sensitivity analyses for methodological quality based on GRADE criteria, by comparing results from all studies with the results following exclusion of low-quality studies.

RESULTS

Results of the search

The search of *The Cochrane Library* Issue 2, 2015 identified 25 records for Cochrane reviews. We excluded four reviews for the following reasons (Figure 2): one review was withdrawn (Jones 2011); one was in people with cough rather than bronchiectasis (Marchant 2005), one was a protocol (McCullough 2014), and one was the protocol for the present overview (Welsh 2013).

Figure 2. Study flow diagram.



We included 21 reviews but extracted data from, and rated the quality of, only nine reviews that reported results for people with bronchiectasis alone (Bradley 2002; Evans 2007; French 2003; Goyal 2014; Hart 2014; Kapur 2009; Lee 2013; Wilkinson 2014; Wurzel 2011). Of the reviews with no usable data, two reviews included studies with mixed clinical populations where data were not reported separately for people with bronchiectasis (32% of participants in Pizzutto 2010 and 12% of participants in Chang 2009 had bronchiectasis only) and the remaining 10 reviews contained no any trials (Chang 2007; Corless 2000; Franco 2003; Irons 2010; Kapur 2007; Lasserson 2001a; Lasserson 2001b; Sheikh 2001; Steele 2000; Warburton 2000).

In total, the search identified 645 references. We identified 46 studies that could be included in Cochrane review updates or in new Cochrane reviews.

Description of included reviews

We presented a table of the main characteristics of the included reviews (see Table 2).

Study design

Nine reviews included RCTs. Approximately two-thirds of trials were parallel group designs while the remaining one-third were cross-over studies. The studies ranged from single session to year-long studies. Each review included from one to 11 trials and 40 individual studies were included in the overview. Seventy per cent (28) of the trials in the overview included 40 or fewer participants. The total number of participants included in reviews ranged from 40 (Goyal 2014) to 1040 (Hart 2014).

Included participants

Of the 40 studies included across the reviews, three (nine to 34 participants) included children. Where reported in the included reviews, in studies reporting an age range, the age of adults ranged from 36 to 73 years and children ranged from six to 16 years, and in studies reporting mean ages, the mean age ranged from 50 to 70 years and in one study of children and adolescents the mean age was 13 years. The proportion of male participants ranged from 21% to 72%. Where reported, mean baseline FEV_1 ranged from 1.17 L to 1.66 L and from 47% to 88% predicted.

Diagnosis of bronchiectasis in included trials

Three reviews defined inclusion criteria as a clinical diagnosis of non-CF bronchiectasis, two reviews specified radiographic diagnosis and four reviews specified radiographic or clinical diagnosis, or both.

Interventions

We mapped the Cochrane reviews onto the framework of interventions specified in our protocol (Welsh 2013) in Table 1 covering the two broad classes of pharmacological and non-pharmacological interventions.

Pharmacological interventions

There were 17 reviews on pharmacological interventions.

- Two separate reviews for inhaled hyperosmolar agents and mucolytics, treatments that aim to ease expectoration (Hart 2014; Wilkinson 2014), both contained trials.
- One review compared long-acting $beta_2$-agonists (LABA) and inhaled corticosteroids (ICS) combination with ICS alone (Goyal 2014), and contained trials.
- Two reviews on antibiotics, one on short-term courses (Wurzel 2011), and one on long-term therapy (Evans 2007), both contained trials.
- Five reviews on anti-inflammatory treatments: ICS (Kapur 2009); oral corticosteroids (Lasserson 2001b), leukotriene receptor antagonists (Corless 2000), and non-steroidal anti-inflammatory drugs (Kapur 2007; Pizzutto 2010). Only the ICS review included any trials.
- Four reviews on bronchodilators compared with placebo, covering short-acting $beta_2$-agonists (SABA) (Franco 2003), LABA (Sheikh 2001), anticholinergics (Lasserson 2001a), and xanthines (Steele 2000). These reviews did not include any trials.
- One review on influenza vaccines (Chang 2007), one on pneumococcal vaccines (Chang 2009), and one on surgery for bronchiectasis (Warburton 2000) did not include any trials.

Non-pharmacological interventions

There were four reviews on non-pharmacological interventions:

- One review on ACT (Lee 2013), one on physical training (Bradley 2002), and one on management strategies for bronchiectasis comparing nurse- versus doctor-led care (French 2003), all contained trials.
- One review on singing for bronchiectasis did not include any trials (Irons 2010).

Methodological quality of included reviews

Quality of included reviews

An overview of methodological quality using the AMSTAR tool is in Appendix 3. All nine reviews that included trials provided: an a priori design as a published Cochrane protocol; duplicate

study selection and data extraction; comprehensive search of the Cochrane Airways Group specialised register and searches of grey literature. All reviews contained tables of included and excluded studies and rated study quality, though they did not all use the latest Cochrane 'Risk of bias' tool (Higgins 2011). Eight of the nine reviews incorporated study quality in their conclusions. One review did not identify whether randomisation sequence generation was adequate (French 2003). Six reviews that included study synthesis used appropriate methods to combine studies. There were too few trials in any reviews to enable assessment of publication bias by a funnel plot. All reviews included conflict of interest statements. One review included a trial conducted by one or more authors of the review (French 2003).

Quality of evidence in included reviews

The reviews used various tools to assess the quality of the evidence or risk of bias (Table 3). Three reviews assessed the risk of bias using the Jadad scale (a composite scale of five points in which five is the best protected against bias); one review awarded a score of 1/5 (Bradley 2002), one awarded 3/5 (French 2003), and one gave 4/5 or 5/5 (Evans 2007). Seven reviews incorporated a Cochrane risk of bias assessment and review authors judged most of the studies to contain a mixture of high, low and unclear risk of bias. The review comparing inhaled LABA/ICS combination with ICS alone included a study described as blinded, but judged inadequate following correspondence with the trial authors. Blinding was not possible for trials in the ACT and nurse- versus doctor-led care reviews.

Four reviews contained a 'Summary of findings' table. Three reviews judged the outcomes reported in the 'Summary of findings' table to be low quality (Goyal 2014; Lee 2013; Wilkinson 2014), while one review on hyperosmolar agents judged the evidence to be of moderate quality (Hart 2014).

There were a number of incidences of poor reporting in the reviews. For example, one review did not report the number of participants in studies and another had more extensive reporting issues including inadequate 'Characteristics of included studies' tables and reporting of outcome data. These issues were reported back to the author teams responsible for updating the reviews.

Overall, the quality of the evidence was limited by lack of high-quality studies in the included reviews. Furthermore, where there was more than one study, it was often not possible to pool results due to heterogeneity in either the treatment or the outcomes. For example, FEV_1 was reported as a difference in absolute end-of-trial point estimates, as per cent of predicted point estimates, as differences in change from baseline (litres or % predicted) and as annual decline rates, with some change analyses not controlling for baseline variation. The quality of reporting was also variable with some comparisons described as 'significant' and others reported as mean difference (MD) but without measures of spread (e.g. standard deviation (SD)) or precision (confidence interval (CI)), and some comparisons reported only in terms of statistical significance (P value). The variation may be attributable to poor reporting in the original trials, the review, or both.

Effect of interventions

We present a series of tables including data for each outcome from the included reviews (see Table 4; Table 5; Table 6; Table 7; Table 8; Table 9; Table 10). We summarise the information from reviews that contribute data to each outcome below. Comparisons are versus placebo unless otherwise stated.

Primary outcome: exacerbation

Nine reviews included exacerbations as an outcome measure (Table 4). Evaluation in column 6 of Table 4 is based on reference values for MCID shown in the table footnote. Trials included in the reviews on short-term antibiotics (Wurzel 2011) and physical therapy (Bradley 2002) did not report exacerbation data. Of the 12 comparisons covered by the seven reviews with exacerbation outcomes, 10 were each based on a single trial and seven of those trials included 40 or fewer participants.

Pharmacological interventions

Impact of long-term antibiotics on exacerbations was unclear (Evans 2007). One small study reported a significant reduction of 31% in exacerbations requiring antibiotics (12 participants, five events versus 16 events, P value = 0.019) but three larger studies reported no significant reduction in exacerbation frequency (odds ratio (OR) 0.96, 95% CI 0.27 to 3.46, 120 participants, 2 trials; MD -0.4, P value = 0.33, 30 participants, 1 trial, Evans 2007).

The impact of hyperosmolar agents was also unclear. The review reported a statistically significant and clinically relevant reduction in annual exacerbation rate with hypertonic saline (HTS) compared with isotonic saline, based on one small study (2.14 with hypertonic saline versus 4.85 with isotonic saline, P value < 0.05, 30 participants, Hart 2014), but a similar study reported no significant benefit for the same comparison (values not reported, 40 participants, Hart 2014). One large study in the same review reported no significant benefit with mannitol (risk ratio (RR) 0.92, 95% CI 0.78 to 1.08, 461 participants, Hart 2014).

The mucolytics review reported a significantly higher exacerbation risk of 35% with RhDNase (2.5 mg) compared with placebo from one moderately sized trial (RR 1.35, 95% CI 1.01 to 1.79, 176 participants, Wilkinson 2014). The trials comparing RhDNase 5 mg with placebo, bromhexine with placebo or erdosteine with no intervention did not report exacerbations.

The ICS review showed no conclusive evidence of benefit. One small study reported fewer exacerbations with ICS compared with placebo (1 with fluticasone versus 3 with placebo, 24 participants,

Kapur 2009), but there were too few events to draw firm conclusions. Two larger studies in the same ICS review reported no significant reduction in exacerbation frequency over six or 12 months (MD 0.09, 95% CI -0.61 to 0.79, 57 participants; MD -0.49, 95% CI -1.49 to 0.51, 86 participants, Kapur 2009).

The review of LABA/ICS combination versus ICS included one small study showing no significant reduction in the proportion of people experiencing an exacerbation (four with LABA/ICS versus seven with ICS, 40 participants) but this was based on a small number of events and significance values were not reported (Goyal 2014).

Non-pharmacological interventions

There was no significant reduction in participant-reported exacerbations for nurse specialist management compared with doctor-led care based on one moderately-sized trial (MD 0.05, 95% CI -1.07 to 1.17, 80 participants, French 2003). The review of ACTs reported no significant reduction in risk of exacerbation based on one small study of adults (RR 0.71, 95% CI 0.23 to 2.25, 20 adults, Lee 2013).

Primary outcome: lung function

Eight reviews reported FEV_1. Table 5 summarises outcome data and evaluation of benefit, based on reference values for MCID. Of the 18 comparisons covered by the eight reviews with relevant outcomes, 13 were each based on a single trial and 10 comparisons included 40 or fewer participants. Trials included in the physical therapy review did not report FEV_1 data (Bradley 2002).

Pharmacological interventions

One review reported evidence of benefit. The ICS review reported a significant, but not clinically relevant, difference in FEV_1 (MD 0.09 L, 95% CI 0.03 to 0.15, P value = 0.002, 101 participants, 3 studies, Kapur 2009), but the effect was dependent on only one trial without a placebo comparison. The MD of 90 mL was less than the MCID reference value (100 mL in COPD), indicating a clinically unimportant change for the majority of people.

Two reviews reported unclear evidence of benefit. The inhaled hyperosmolar review reported a statistically significant and clinically relevant benefit for FEV_1 % predicted with hypertonic saline compared with isotonic saline (MD 13.3%, P value < 0.01, 30 participants, 1 study) but not for FEV_1 L (MD 0.19 L, 95% CI -0.37 to 0.75, P value = 0.5, 40 participants, 1 trial, Hart 2014). There was no evidence of benefit for mannitol versus placebo based on three trials (372 participants, Hart 2014). The mucolytics review also reported inconclusive evidence of benefit. The review reported a statistically significant and clinically relevant increase with erdosteine for FEV_1 L (MD 200 mL, 95% CI 40 to 360, 30 participants, 1 trial), but not for FEV_1 % predicted in the same trial (MD 4.5%, 95% CI -3.11 to 12.11) (Wilkinson 2014). There was conflicting evidence of benefit for RhDNase 2.5 mg, with one trial showing no difference and one showing a more rapid decline in FEV_1 (MD 2.10%, 95% CI -4.05 to -8.25; MD -1.9%; 237 participants, 2 trials), and there was no evidence of benefit from trial of the RhDNase 5 mg dose (40 participants). There was no evidence of benefit for bromhexine compared with placebo (MD 184.00 mL, 95% CI -149.75 to 517.75, 88 participants, 1 trial) (Wilkinson 2014).

The two antibiotics reviews showed no evidence of benefit in FEV_1 based on four small trials of long-term antibiotics (study power unclear) (86 participants, Evans 2007) and one trial of short-course antibiotics (74 participants, Wurzel 2011).

The inhaled LABA/ICS combination review reported no evidence of benefit for FEV_1, based on one small trial (study power unclear) (MD -14.00 mL, 95% CI -84.14 to 56.14, 40 participants, 1 trial, Goyal 2014).

Non-pharmacological interventions

The ACTs review reported a statistically significant benefit in FEV_1 for children (difference 8.86%, 9 children, 1 trial) but not for adults (MD 0.0 L, P value = 0.7, 38 adults, 3 trials), though values were not clearly reported (Lee 2013).

The review of nurse-led care reported no evidence of benefit, based on one trial (MD 2.37, 95% CI -7.37 to 12.11, 80 participants, 1 trial, French 2003).

Primary outcome: quality of life

Nine reviews included QoL as an outcome measure but none of the trials included in the short-term antibiotics review (Wurzel 2011), the ICS review (Kapur 2009), or the mucolytics review (Wilkinson 2014) reported QoL data. Of the nine comparisons covered by the six reviews with QoL data, five were each based on a single trial and five comparisons included 43 or fewer participants. Table 6 summarises outcome data and evaluation of benefit, based on reference values for MCID.

Pharmacological interventions

The inhaled hyperosmolar review reported significantly lower St. George's Respiratory Questionnaire (SGRQ) scores (i.e. better QoL) with mannitol (MD -2.05, 95% CI -3.69 to -0.40, 840 participants, 3 studies, Hart 2014). However, the effects of hypertonic saline were unclear, showing evidence of clinically relevant improvement in Bronchiectasis Quality of Life (QoL-B) scores (MD -11.6, SD 17.7; P value = 0.03) but conflicting evidence for SGRQ (2 trials) and Leicester Cough Questionnaire (LCQ) scores (2 trials).

The effects of LABA/ICS combination on QoL were unclear. There was no statistically significant improvement in SGRQ total scores (MD -4.57, 95% CI -12.38 to 3.24, 40 participants, 1 trial) but there was insufficient information to judge whether the study

was underpowered (risk of type II error), and the MD exceeded the four unit threshold for clinically important change (Goyal 2014). The long-term antibiotics review reported no evidence of benefit in SGRQ total scores, but the power of this study to detect an effect was also unclear (MD -0.07, 95% CI -3.69 to 3.55, 30 participants, 1 trial, Evans 2007).

Non-pharmacological interventions

Two reviews reported evidence of clinically relevant benefit. The physical therapy review reported significantly better QoL, using the Chronic Respiratory Questionnaire (CRQ) (MD 12.4, 95% CI 2.38 to 22.43, P value = 0.015, 43 participants, 2 trials), that exceeded the MCID threshold (0.5 units) (Bradley 2002). The ACTs review reported better QoL of both statistical and clinical significance, based on the SGRQ and LCQ outcome measures in one small study (SGRQ median difference 8.5, P value = 0.005; LCQ median difference 1.3, P value = 0.002; 20 participants, Lee 2013).

The nurse specialist management review reported no evidence of benefit in SGRQ scores (MD -1.70, 95% CI -10.00 to 6.60, 80 participants, 1 trial, French 2003).

Secondary outcome: symptoms

Eight reviews included symptoms as an outcome measure (Table 7), but trials in four of those reviews did not report relevant data (Bradley 2002; Evans 2007; Lee 2013; Wurzel 2011), and one review did not include symptoms as an outcome measure (French 2003). The eight comparisons reported in the four reviews with symptom data were each based on a single trial.

Pharmacological interventions

The ICS review reported evidence of clinically relevant reduction in dyspnoea using the Transition Dyspnea Index (TDI) (OR 3.33, 95% CI 1.17 to 9.43, 62 participants, 1 trial, Kapur 2009), but no evidence of benefit for wheeze in the same trial (OR 0.87, 95% CI 0.31 to 2.44, 62 participants, 1 trial). The LABA/ICS combination review also reported evidence of clinically relevant reduction in dyspnoea using the TDI, for people on the combination inhaler (MD 1.29, 95% CI 0.40 to 2.18, 40 participants, 1 trial), and significantly more cough-free days (MD 12.3%, 95% CI 2.38 to 22.2), based on the same small trial (Goyal 2014).

The inhaled hyperosmolar review reported no evidence of benefit in symptoms or cough in the same single mannitol trial (Bronchiectasis Symptoms Questionnaire, MD -1.20, 95% CI -3.91 to 1.51; Leicester Cough Questionnaire, MD 0.00, 95% CI -0.81 to 0.81, 343 participants) and no evidence of benefit for hypertonic saline (no values, P value > 0.16, 40 participants, 1 trial) (Hart 2014).

The mucolytics review reported a significantly lower cough score at the end of the bromhexine trial (MD -0.48, 95% CI -0.89 to -0.06, 88 participants, 1 trial, Wilkinson 2014).

Non-pharmacological interventions

Symptoms were not reported in trials included in the physical therapy or ACTs reviews (Bradley 2002; Lee 2013), and not included as an outcome in the nurse specialist management review (French 2003).

Secondary outcome: sputum characteristics

Eight reviews included one or more sputum characteristics as an outcome measure (Table 8), but trials included in three reviews did not report data (Bradley 2002; Goyal 2014; Wurzel 2011), and one review did not include sputum as an outcome measure (French 2003). Fifteen trials reported sputum outcomes and 11 of those trials included 40 or fewer participants. A total of 13 sputum outcome comparisons were reported, with nine comparisons each based on a single trial.

Pharmacological interventions

The long-term antibiotics review reported significantly lower sputum leukocyte and purulence scores in one small paediatric trial (values not reported, P value < 0.01, 27 children, Evans 2007), and significantly reduced sputum volume in another small paediatric trial (values not reported, P value = 0.0001, 34 children). Impact of antibiotics on sputum reduction in adults was less clear, with one small trial reporting no significant difference in sputum volume (median difference 1 mL, P value not reported, 12 adults). Sputum outcomes were not reported in the trial included in the short-term antibiotics review (Wurzel 2011).

In the ICS review, two trials of less than six months' duration reported significantly lower daily sputum volume (MD -8.30 mL, 95% CI -16.55 to -0.05, 93 participants, 1 trial; and no values, P value = 0.003; 20 participants, 1 trial). One longer trial (12 months) reported no difference in sputum volume or purulence (volume, values not reported; purulence, MD 0.2, 95% CI -0.94 to 1.34, 89 participants). Sputum outcomes were not reported in the trial included in the LABA/ICS combination review (Goyal 2014).

The impact of inhaled hyperosmolar agents was largely unclear (Hart 2014). Two small studies reported a significant reduction in sputum volume for people receiving mannitol (MD 21.9%, CI not reported, P value < 0.001, 14 participants; MD 22.3%, CI not reported, P value < 0.0001, 11 participants) but a larger study reported a significant difference in sputum weight in favour of placebo (MD 4.32 g, 95% CI 1.60 to 7.04, 362 participants), but benefits from the larger study were attributed to higher antibiotic frequency in the placebo group. Hypertonic saline was associated with higher sputum weight than isotonic saline (median difference

2.13 g, P value not reported, 24 participants) but significance of the effect was unclear.

The mucolytics review reported no significant difference in sputum purulence for people receiving RhDNase (MD 0.28, 95% CI -0.04 to 0.60, 40 participants, 1 trial, Wilkinson 2014). There was no significant difference in volume production (scored on 0 to 2 scale) for people receiving erdosteine (MD 0.40, 95% CI -0.03 to 0.83, N = 30, 1 trial) and the significance of the difference in sputum volume in one bromhexine trial was unclear (MD -21.5% change at end of trial, 95% CI -38.9 to -4.1, 88 participants, 1 trial).

Non-pharmacological interventions

The review of ACTs reported a significant increase in sputum volume for people receiving the intervention, based on two small studies (MD 8.4 mL, 95% CI 3.4 to 13.4, 8 participants, 1 trial; MD 3 mL, P = 0.02, 20 participants, 1 trial) and sputum weight, based on two small studies (MD 17 g, P value < 0.01, 8 participants, 1 trial; MD 24 g, P value < 0.05, 10 participants, 1 trial) (Lee 2013).

Trials in the review of physical therapy did not report sputum outcomes (Bradley 2002), and the review of nurse-led care did not include sputum production as an outcome (French 2003).

Secondary outcome: adverse events

Adverse events were reported in six reviews (see Table 9).

Pharmacological interventions

The review of long-term courses of antibiotics reported no significant difference in withdrawals (Peto OR 1.06, 95% CI 0.42 to 2.65, 260 participants, 5 trials), cases of diarrhoea (Peto OR 2.47, 95% CI 0.91 to 6.71, 148 participants, 2 trials) or rash (Peto OR 1.94, 95% CI 0.19 to 19.47, 54 participants, 2 trials). However there were more cases of wheeze (Peto OR 8.56, 95% CI 1.63 to 44.93), dyspnoea (Peto OR 4.41, 95% CI 1.43 to 13.61) and chest pain (Peto OR 8.84, 95% CI 1.88 to 41.50) in one trial (74 participants) of nebulised antibiotics (Evans 2007). One adult study in the short-term antibiotics review reported no difference in adverse events (OR 2.24, 95% CI 0.86 to 5.82, 74 adults) (Wurzel 2011).

There were more adverse events with LABA/ICS combination compared with ICS alone (37 events with ICS, 12 events with LABA/ICS) but it was unclear whether the unit of analysis was the number of events or the number of people experiencing one or more event (Goyal 2014). The review of ICS monotherapy did not report adverse events (Goyal 2014).

In the review of hyperosmolar agents, there was no significant difference in adverse or serious adverse events for mannitol (873 participants, 3 trials) or hypertonic saline (59 participants, 2 trials) (Hart 2014).

The review of mucolytics reported no significant difference in adverse events with bromhexine (88 participants, 1 trial, Wilkinson 2014). There was no significant difference in adverse events with RhDNase 5 mg (40 participants, 1 study) except for more cases of influenza, but data were unclear as values were not reported (Wilkinson 2014). Significantly more cases of elevated antibodies were reported with RhDNase 2.5 mg (OR 28.19, 95% CI 3.77 to 210.85, 176 participants, 1 trial). Data on adverse events were not reported for erdosteine.

Non-pharmacological interventions

The review of ACTs reported no adverse events or withdrawals (Lee 2013).

The physical therapy review did not report adverse events (Bradley 2002), and the review of nurse-led care did not include adverse events (French 2003).

Secondary outcome: hospitalisations

Five reviews reported data on hospitalisation (Table 10).

Pharmacological interventions

The review of long-term antibiotics reported evidence of benefit in a reduced rate of admissions in one small trial (MD -1.9, P value = 0.023, 17 adults, 1 trial) and reduced number of admissions in another small trial (MD -0.6, P value = 0.038, 30 adults, 1 trial, Evans 2007). The review of short-term antibiotics did not include hospitalisations as an outcome (Wurzel 2011).

The review of LABA/ICS combination therapy reported no significant difference in number of admissions (OR 0.26, 95% CI 0.02 to 2.79, 40 participants, 1 trial, Goyal 2014).

The trial in the review of ICS monotherapy did not report hospitalisations (Kapur 2009).

The review of hyperosmolar agents reported no evidence of benefit with mannitol versus placebo (461 participants, Hart 2014), and the evidence for hypertonic saline was unclear (40 participants, Hart 2014).

The review of mucolytics reported no evidence of benefit with RhDNase 5 mg (40 participants, Wilkinson 2014), Trials on bromhexine or erdosteine did not report hospitalisations.

Non-pharmacological interventions

The review of nurse-led care reported no evidence of benefit in number of hospitalisations (RR 1.59, 95% CI 0.75 to 3.39, 80 participants, 1 trial, French 2003).

The reviews of physical therapy or ACTs did not report hospital admissions.

Secondary outcome: mortality

Three reviews reported data on mortality (Evans 2007; Goyal 2014; Hart 2014), and the remaining reviews either did not include mortality outcomes (Bradley 2002; Wurzel 2011), or the outcome was not reported in the included trials (French 2003; Kapur 2007; Lee 2013; Wilkinson 2014) (Table 11).

Pharmacological interventions

The review of long-term antibiotics reported no evidence of harm (Peto OR 0.57, 95% CI 0.07 to 4.54, 128 adults, 2 studies, Evans 2007), though this was based on only four events.

The review of LABA/ICS combination included one small trial (40 participants) in which there were no deaths (Goyal 2014).

The review of inhaled hyperosmolar agents reported two deaths in one large mannitol trial that were unrelated to the intervention and no deaths in two smaller trials (25 participants). The four small hypertonic saline trials reported no deaths (113 participants) (Hart 2014).

Non-pharmacological interventions

Trials included in the nurse-led care (French 2003) and ACTs (Lee 2013) reviews did not report mortality outcomes and the review of physical therapy did not include mortality as an outcome measure (Bradley 2002).

Evidence map

We present an overview of the evidence for non-CF bronchiectasis in Cochrane reviews, trials and BTS guideline recommendations, together with recommendations for Cochrane reviews and research priorities (Table 1).

The level of evidence for treatments for bronchiectasis in the BTS guideline was variable (Pasteur 2010). There were relatively few trials in bronchiectasis, reviews without data or with inadequate data, and guidelines based on low-quality evidence. The evidence base for bronchiectasis is broadly lacking in large, high-quality RCTs that provide robust evidence to inform clinical practice.

We make the following recommendations for Cochrane reviews:

New reviews needed

- Long-term courses of antibiotics for bronchiectasis (Evans 2007) should be separated into two new reviews: one on macrolides and one on antibiotics that should also include rotating antibiotics as a separate comparison.
- Replace the two reviews on mucolytics (Wilkinson 2014) and inhaled hyperosmolar agents (Hart 2014) with a single review on mucolytics for bronchiectasis and include a subgroup analysis on inhaled versus oral mucolytics.

Changes to existing reviews

- Short-term course of antibiotics (Wurzel 2011): expand scope to include head-to-head trials (i.e. one antibiotic compared with another antibiotic) and dual antibiotic trials (more than one antibiotic administered at once). Include inpatients versus outpatients as a subgroup analysis.
- Expand the review on SABA to include head-to-head trials (Franco 2003).
- Expand the review on LABA to include head-to-head trials (Sheikh 2001).
- Refocus the review on physical training as pulmonary rehabilitation (Bradley 2002).
- Add head-to-head trials of chest clearance techniques to the ACT review (Lee 2013).

DISCUSSION

Summary of main results

We examined the evidence from published reviews for the treatment of non-CF bronchiectasis (in adults and children) in this overview. While we have been able to document the published evidence, it was not possible to draw definitive conclusions from published results with respect to a range of clinically relevant issues. The primary outcomes of our overview were exacerbations, lung function and QoL.

A small number of trials on long-term antibiotics and hyperosmolar agents reported a reduction in exacerbation rate but the overall evidence was conflicting and inconclusive. RhDNase was associated with an increased risk of exacerbation. There was no evidence of benefit from ICS, nurse-led care or ACTs. The impact of LABA/ICS combination on exacerbations was unclear.

Improvements in lung function were reported for ICS but evidence for impact of hyperosmolar agents and mucolytics was conflicting and inconclusive. There was no evidence of benefit for short-term antibiotics and nurse-led care and unclear evidence for long-term antibiotics, ACTs and LABA/ICS combination.

Improvements in QoL were reported for ACTs and physical therapy but benefit for hyperosmolar agents was conflicting and inconclusive. There was no evidence of benefit for nurse-led care and the evidence for long-term antibiotics and LABA/ICS was unclear.

Secondary outcomes were poorly reported in trials included in the reviews. Small studies on ICS therapy and LABA/ICS combination therapy reported improvements in dyspnoea, wheeze and cough-free days. One small bromhexine study also reported improvements in cough. ACTs reduced in sputum volume, but evidence for long-term antibiotics, ICS and hyperosmolar agents was conflicting and inconclusive. Long-term antibiotics and RhDNase increased adverse events and long-term antibiotics were also as-

sociated with fewer admissions to hospital. No reviews reported differences in mortality.

Many comparisons reporting no significant evidence of benefit were based on single small trials, or unpooled combinations of small trials, where power of the trials to detect an effect was unclear. The clinical impact of statistically significant differences between comparison groups was also unclear for many outcomes as reference points (MCID) for clinical interpretation were not available.

Overall completeness and applicability of evidence

We highlighted a number of evidence gaps, as outlined in Table 1. There were relatively few reports of high-quality trials in bronchiectasis and many trials were small, with fewer than 40 participants, and potentially unable to detect an effect. Trial populations were relatively narrow and extrapolation of findings to the wider bronchiectasis population may be limited. Furthermore, all trials were conducted in stable bronchiectasis rather than during exacerbations.

We also identified opportunities for new Cochrane reviews and updates of existing reviews, to summarise the evidence base better. Therefore, this overview summarised the available evidence and highlighted the need for new evidence reviews and new research.

Pharmacological interventions

Antibiotics

The evidence base for long-term antibiotics suggests that there may be some benefits but further research is required to clarify remaining uncertainty (Evans 2007).

Areas of uncertainty yet to be explored in Cochrane reviews include longer-term macrolide use, *P aeruginosa* colonisation (versus other sputum microbiology - such as *Haemophilus influenzae*) and emerging antibiotic resistance. In particular, while previous studies may have suggested that antibiotic resistance is not an issue for sputum microbiology among those individuals not colonised with *P aeruginosa* on long-term treatment, some caution is advised. Furthermore the emergence of other non-*P aeruginosa* colonising species in people on longer-term antibiotics (including bacteria not previously thought to be clinically relevant - often with resistance patterns), is also a concern. Patterns of resistance for *P aeruginosa* remain an issue and the benefits of oral/inhaled prophylaxis for these people continues to be unresolved. Therefore, a balanced clinical approach considering the possible benefits arising from transition of sputum purulence to mucoid with lessened symptoms needs to be weighed against the limited available evidence.

The use of macrolides has attracted attention following the discovery that these drugs may exert effects through both antibacterial and immunosuppressive (anti-inflammatory) effects (King 2007). Therefore, macrolide use remains a matter of clinical judgement on a case-by-case basis without definitive evidence in favour and a Cochrane review is needed.

The role of antibiotics in the management of bronchiectasis is unclear, with Cochrane reviews unable to support their prescription conclusively (Evans 2007; Wurzel 2011). There have been no trials on treating exacerbations with antibiotics, though this is a commonly used intervention. Future research into the use of long-term antibiotics might separately address people colonised and not colonised with pseudomonas, in particular with respect to the use of macrolides.

Bronchodilators, anti-inflammatory medication and combination therapy

Despite the lack of evidence of benefit in the overview for ICS and bronchodilators, their use is widespread in bronchiectasis. The BTS national audits surveyed secondary and tertiary care practice in the UK and reported findings based on 1460 and 2404 people seen in outpatient departments over a two-month period in 2010 and 2011 respectively (Hill 2012). Of these, approximately 80% were using regular ICS, 67% using SABA and 64% using LABA, and 10% short-acting and 30% long-acting anti-muscarinics. The BTS guidelines suggest ICS/bronchodilator therapy should be used only where there is co-existent asthma, although this is unlikely to account solely for such high use seen in the audit (Hill 2011). Other potential reasons may include a previous misdiagnosis of bronchiectasis as asthma or COPD, with people remaining on medications even after the correct diagnosis has been made. The risk-benefit of these medications is unknown in bronchiectasis, but ICS may raise particular concerns as their use has been associated with an increased risk of pneumonia in COPD and it is possible that this risk is even greater in bronchiectasis, especially in people with severe disease (Singh 2009).

ICS monotherapy may improve lung function and reduce dyspnoea; however, there was no conclusive evidence of benefit for exacerbations. LABA/ICS combination may reduce dyspnoea, wheeze and cough, but there was no significant reduction in exacerbations and impact on QoL was unclear. These outcomes were based on a small number of studies in review of ICS and LABA/ICS combination. ICS are widely prescribed, but this practice is not currently supported by robust evidence in bronchiectasis. A large, high-quality clinical trial is needed to investigate their role, ideally with stratification to allow for assessment of the subgroup with physiological or inflammatory (or both) evidence of asthma.

Mucolytic agents

We considered two reviews studying a range of mucolytic agents (carbocysteine, erdosteine, mannitol, hypertonic saline, bromhexine and RhDNase) (Hart 2014; Wilkinson 2014). The reviews

reported inconclusive results, with sporadic and minimal beneficial effects for agents such as hypertonic saline (exacerbations), erdosteine (FEV_1) and mannitol (QoL), but no overall persuasive evidence of efficacy for any of the mucolytic drugs in key areas of bronchiectasis management. Findings suggest some concern for the use of RhDNase in non-CF bronchiectasis given isolated study data suggesting an increase in exacerbations and influenza. No concerns over adverse effects were raised for other treatments, though there were minimal data. While these results have not been substantiated in further trials, at this stage caution is advised.

Non-pharmacological interventions

Physiotherapy - airway clearance techniques, pulmonary rehabilitation, physical training techniques

Respiratory physiotherapy has several potential roles in bronchiectasis: airway mucous clearance, pulmonary rehabilitation and physical training.

Airway clearance is a cornerstone of current therapy in bronchiectasis (Pasteur 2010), and there are several theoretical mechanisms of benefit. For example, effective clearance of sputum might be expected to: improve breathlessness and QoL by clearing blocked airways; decrease the microbial and inflammatory burden and, thus, reduce airways damage and exacerbation frequency; and improve airway deposition of inhaled drugs. The review summarised here did indeed show that airway clearance improved disease-specific QoL (SGRQ), cough symptoms (LCQ) and sputum production, based on five small studies (55 participants) (Lee 2013). It is perhaps unsurprising that there were few data available to inform guidelines; it may arguably now be unethical to perform a sham-controlled trial of chest clearance in people with clinically significant disease. However, there are trial results available comparing methods of chest clearance (e.g. Eaton 2007; Naraparaju 2010; Paneroni 2011; Patterson 2005; Su 2012; Syed 2009; Thompson 2002; Venturelli 2012), and this would be a worthwhile focus for a future Cochrane review. Novel methods should undergo equivalence trials *versus* current practice before being recommended for use.

At the time of writing the Cochrane overview, there were no specific trials of pulmonary rehabilitation in bronchiectasis (Bradley 2002). Since then, pulmonary rehabilitation (with or without inspiratory muscle training) has been shown to improve exercise capacity and QoL (Newall 2005), and is recommended in the BTS guidance for people with bronchiectasis and breathlessness affecting daily activities (Pasteur 2010). Data have since emerged to support further the impact of pulmonary rehabilitation on QoL and exercise tolerance in bronchiectasis (Mandal 2012), and also suggest a reduction in exacerbation rate over the subsequent 12 months (Lee 2014).

Disease management and education

Only one study to date has addressed the impact of specialist-nurse versus doctor-led care, and it found no difference in exacerbation rate, FEV_1 or QoL (French 2003). The sample size calculation in the sole included study was "on the basis of establishing equivalence of nurse practitioner led care and doctor led care", so it would not have been powered to identify a difference. There are a few trials in patient education and self management (e.g. Lavery 2011), and we would suggest that this is prioritised as a future review topic, especially as bronchiectasis is a condition that is not widely recognised in the general population, yet has significant impacts on daily QoL and is often associated with exacerbations and hospitalisations, all of which could potentially be improved by better patient understanding and self management (Lavery 2007)

Surgery, other

Limited data were available to guide when surgery should be considered in bronchiectasis and there were no trials in the Cochrane review (Warburton 2000). Sham-controlled studies are unlikely to be performed, and cases where surgery may be considered by the treating clinicians are rare such that an RCT would be unlikely to recruit sufficient numbers of people. The current recommendations by the BTS are that surgery may be considered in people with poorly controlled localised disease or where there is massive haemoptysis (as an alternative to bronchial artery embolisation) (Pasteur 2010).

Coverage and quality of bronchiectasis trials

The survey of the literature and the BTS guidelines in Table 1 revealed that the evidence base for interventions for bronchiectasis is poor. There are some bronchiectasis trials in progress, we looked for ongoing trials on bronchiectasis at www.clinicaltrials.gov on the 12 February 2015 and there were two trials on the inhaled antibiotic tobramycin (NCT01677403; NCT02102152); four trials on the inhaled antibiotic ciprofloxacin (NCT01515007; NCT01764841; NCT02104245; NCT02106832); one trial on POL7080, an antibiotic active against *P aeruginosa* (NCT02096315); and one trial of long-term ACTs (NCT02324855). One protocol for a study on 10-valent pneumococcal-*Haemophilus influenzae* protein D conjugate vaccine for preventing exacerbations was returned in the search for trials (O'Grady 2013). However, there are only 500 references for controlled trials on bronchiectasis on CARG and over half of the Cochrane reviews on bronchiectasis contain no trials. Many of the recommendations in the BTS/SIGN guidelines are necessarily based on evidence from non-RCTs and expert opinion (Pasteur 2010). Guidelines and current clinical practice are, in places, based on extrapolating treatments from asthma, COPD and CF bronchiectasis to bronchiectasis. For example, bronchodilators are used to treat people with bronchiectasis on the basis that they have

shown to be beneficial for people with asthma, but there have been no trials to show that they are safe and effective. Currently, in bronchiectasis, based on this overview, there lacks a solid foundation to inform good clinical practice and informed patient decision-making. There are limited data available in children, with only three paediatric trials (number of children = nine to 34).

Quality of Cochrane reviews on bronchiectasis

Authors of some overviews of Cochrane reviews in other disease areas have revisited the original study reports to supplement data reported in the Cochrane reviews (e.g. Cahill 2013 used study-level data to perform network meta-analyses, Cates 2012 updated the literature search of all included reviews). However, we decided to focus on summarising the evidence and issuing recommendations for new and revised Cochrane reviews.

Clinical guidelines and Cochrane reviews are closely intertwined. Guidelines frequently rely on Cochrane reviews to underpin specific recommendations. We have drawn heavily on the BTS guideline (Pasteur 2010) to help us map the evidence available for bronchiectasis and to highlight gaps where more trials or Cochrane reviews are needed or to highlight gaps in the reviews themselves. To best inform guidelines, our Cochrane reviews should aim to cover the relevant clinical questions and this overview shows notable gaps in review topics for bronchiectasis. We suggest that overviews can be used by CRGs to assess individual disease areas.

Quality of the reviews

The quality of the reviews was considered on two levels; the quality of the selection of the Cochrane reviews (i.e. the coverage of the possible trials) and the quality of the reviews themselves. To assess the coverage of the available evidence, we used the framework developed for the protocol to this overview to map the currently available evidence from Cochrane reviews, trials and the BTS guideline (Table 1). We added our judgements on the implications for Cochrane (e.g. whether a Cochrane review should be expanded or where a new review is needed).

Eight out of 21 reviews had search dates of over 5 years old and 19 out of 21 reviews had search dates of over two years old.

The reviews scored highly on the AMSTAR scale (reviews scored 9/10 to 10/10), but on several occasions we found several issues in reviews that would require us to revisit the trial reports and that may necessitate updating of the Cochrane review, which is beyond the scope of this overview. For instance, the hospital admission data were unclear in French 2003; the total number of admissions was reported together with the number of re-admissions and it would be helpful to have some explanation of this information. Development of a tool to appraise the quality of Cochrane reviews based on the Methodological Expectations of Cochrane Intervention Reviews (MECIR) standards may be beneficial to future overviews.

While the reviews scored from 9/10 to 10/10 using the AMSTAR tool, we had problems in finding enough data from the Cochrane reviews to complete our overview in a few cases. We urge the incorporation of the MECIR standards as a minimum for all new and updated reviews on *The Cochrane Library*.

Only four reviews contained a 'Summary of findings' table and a GRADE evaluation of the evidence. We felt that a GRADE evaluation of the evidence would require a significant amount of work, which would be necessary at the review level and is, therefore, beyond the scope of this overview. However, due to the paucity of consistent evidence from high-quality trials in the reviews, we believe that further evidence is likely to change our confidence in the effect of all the treatments. We recommend that 'Summary of findings' tables are completed in future updates of the Cochrane reviews in line with Cochrane Airways Group editorial policy.

Potential biases in the overview process

We identified potentially eligible studies by screening all trials coded as bronchiectasis and added these to Table 1. It is possible that this list is incomplete and further more specific searches would be done for each systematic review or update.

We included only Cochrane reviews and there may be other systematic reviews on interventions for bronchiectasis published outside of *The Cochrane Library*, but we are unable to comment on that.

Agreements and disagreements with other studies or reviews

One systematic review and meta-analysis on inhaled antibiotics for bronchiectasis, published in 2014, included 12 trials with 1264 adults (Brodt 2014). The trials were on the following antibiotics and included some of the inhaled antibiotics that would be included in an update of the Cochrane antibiotics reviews:**a**mikacin, aztreonam, ciprofloxacin, gentamicin, colistin and tobramycin. The review included trials of between four weeks' and 12 months' duration. The review showed that antibiotics reduced bacterial load and the risk of acute exacerbations, and both antibiotic and placebo groups had the same withdrawal rate due to adverse effects. The authors concluded that "Inhaled antibiotics may provide an effective suppressive antibiotic therapy with an acceptable safety profile in adult patients with stable non-CF bronchiectasis and chronic bronchial infection" (Brodt 2014). We did not update the antibiotics reviews, so some of this evidence in missing from this overview. Funders looking at this overview to make decisions about trials to fund, should consider the more recent antibiotics trials before making a decision.

One economic analysis of long-term humidification therapy in people with COPD or bronchiectasis concluded that therapy was

"moderately cost-effective for patients with moderate to severe chronic obstructive pulmonary disease or bronchiectasis" and that it met thresholds for funding in New Zealand (Milne 2014).

We found three systematic reviews published on macrolide therapy. One review included nine RCTs on 530 participants and showed that long-term macrolides compared with placebo/usual care reduced the risk of exacerbations, dyspnoea and 24-hour sputum volume; improved QoL and slowed the decline in lung function (FEV_1) (Wu 2014). Another review of nine trials on 559 participants concluded, "Macrolide maintenance therapy, both in adults and children, was effective and safe in reducing bronchiectasis exacerbations, but not the admissions for exacerbations. In addition, macrolide administration in adults was associated with improvement in QoL and spirometry, but not 6MWT [six-minute walking test]" (Gao 2014a). Another review on four studies concluded, "Macrolide maintenance therapy was effective in reducing pulmonary exacerbations, and improving lung function in adults with NCFB [non-CF bronchiectasis]. However, it did not improve QoL, and could have led to macrolide resistance" (Zhuo 2014). The conclusions were stronger than in the Cochrane review, but the non-Cochrane reviews were more up-to-date including newer trials.

A review on mucolytics for children with bronchiectasis found no studies on children, which agrees with the findings of the Cochrane review (Snijders 2013).

AUTHORS' CONCLUSIONS

Implications for practice

The key findings of this overview, in terms of the major outcomes that we felt were most important in people with bronchiectasis, were as follows:

- long-term antibiotics may reduce sputum production, frequency of exacerbations and hospitalisation, but may also be associated with more frequent adverse events (wheeze, dyspnoea and chest pain);
- inhaled corticosteroid monotherapy may improve lung function but the effect is small;
- bromhexine may reduce cough, but evidence of benefit for hyperosmolar agents and mucolytics is generally unclear;
- airway clearance techniques may reduce sputum production and improve quality of life;
- RhDNase is associated with more frequent exacerbations;
- long-acting $beta_2$-agonsts/inhaled corticosteroid combination therapy may reduce dyspnoea, wheeze and cough;
- 70% of trials in the reviews included in the overview were small (40 or fewer participants), which limits interpretation.

Implications for research

We believe that research should focus on measuring exacerbations, quality of life and, in longer-term trials, lung function. Future studies must be powered to detect differences and adverse events should be rigorously reported. More research should be undertaken with children either separately or reported separately in studies with combined populations.

A national or international organisation for bronchiectasis should be established, with patient values at its core, to support the design and development of high quality pragmatic trials that will serve to improve the evidence base. Useful work could include evaluation of the need for a bronchiectasis-specific quality of life measure, and development of a core set of outcome measures for future research.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Evidence map

Intervention	Cochrane review	Number of included studies (number of participants)	Potential new studies[1]	BTS guideline recommendation (evidence grade: A-D)	Overview team recommendations for new Cochrane reviews, or changes to existing reviews	Overview team suggested research priorities based on evidence presented in this evidence map
Pharmacological interventions						
Antibiotics	**Long term** (Evans 2007)	9 (378)	Altenburg 2013; Anthony 2014; Chen 2013; Haworth 2014; Liu 2012; Lourdesamy 2014; Murray 2011; Rogers 2014 (aka Serisier 2013a); Serisier 2013b; Valery 2013; Wilson 2013a; Wong 2012	- Recommended for people with ≥ 3 exacerbations per year requiring antibiotics or exacerbations causing significant morbidity (C). Start on low dose (C), determine regimen by sputum microbiology (nebulised C and oral D) - Insufficient evidence for: long-term quinolones	Separate review for macrolides	High 1. Targeted antibiotic treatment for colonisation or recurrent infection with the same organism (e.g. Pseudomonas, Haemophilus) 2. Non-targeted macrolide treatment

Table 1. Evidence map (*Continued*)

				(C), macrolides (C) - No evidence: children, rotational antibiotics		
	Short term (Wurzel 2011)	1 (74)	Antoniu 2013; Barker 2014; Chang 2013; De Diego 2013	- Recommended: high-dose specific antibiotics (B to C). If no previous bacteriology, first-line treatment amoxicillin 500 mg 3 x daily (B) or clarithromycin 2 x daily (C) for 14 days, while waiting for sputum microbiology (D) - IV antibiotics considered for people resistant to therapy (C) - Antiviral drugs not recommended for exacerbations (D) No evidence: children, RCTs for exacerbations	Expand to include head-to-head trials and dual antibiotic therapy. Subgroup: inpatients vs. outpatients	High 1. Treatment duration 2. Dual therapy vs. monotherapy for pseudomonas 3. Outpatient vs. inpatient therapy 4. Routes of administration e.g. prolonged infusion vs. 3 x daily or oral vs. IV
Vaccines	**Pneumococcal** (Chang 2009)	1 ongoing study (O'Grady 2013)	None identified	No recommendation	Update if new trials	Low
	Influenza (Chang 2007)	0	None identified	No recommendation	Update if new trials	Low
Bronchodilators	**LABA** (Sheikh 2001)	0	None identified	Assess bronchodilator reversibility and prescribe accordingly (D)	Expand to include head-to-head trials	Low

Table 1. Evidence map (*Continued*)

	SABA (Franco 2003)	0	Ding 2006		Update review. Expand to include head-to-head trials	Low
	Anticholinergics (Lasserson 2001a)	0	None identified		Update when new trials	Low
Anti-inflammatory medication	**ICS** (Kapur 2009)	6 (276)	Ding 2006; Hernando 2012	Not recommended routinely for adults (B) or children (D) except for concomitant asthma	Update review	High 1. Validate routine prescription of ICS 2. Stratify by reversibility
	OCS for acute exacerbations (Lasserson 2001b)	0	None identified	No evidence	Update if new trials	High
	LTRA (Corless 2000)	0	None identified	Not recommended (D)	Update if new trials	Low
	Inhaled NSAIDs (Pizzutto 2010)	0	None identified	Not recommended (D)	Update if new trials	Low
	Oral NSAIDs (Kapur 2007)	0	None identified	Not recommended (D)	Update if new trials	Low
	Oral methylxanthines (Steele 2000)	0	None identified	Not recommended routinely (D)	Update if new trials	Low
Combination bronchodilator and anti-inflammatory medication	**LABA/ICS combination** (Goyal 2014)	1 (40)	None identified	None for combination	None	Low (pending ICS trials)
Mucous clearance agents	**Inhaled hyperosmolar** (Hart 2014)	11 (927)	None identified	May be considered (B)	Combine the 2 reviews and subgroup: inhaled vs. oral	High

Table 1. Evidence map (*Continued*)

	Mucolytics (Wilkinson 2014)	4 (528)	Bilton 2014	Trials of mucolytics required (U). RhD-Nase not recommended (A and D)		High
Intervention	**Cochrane review**	**Number of included studies (number of participants)**	**New studies**	**BTS guideline recommendation (evidence grade; A-D)**	**Recommendations for Cochrane reviews**	**Priority for research**
Non-pharmacological interventions						
Physiotherapy	**PR/exercise therapy** (Bradley 2002)	2 (52)	Bernabeu 2014; Gurses 2013; Lee 2014; Mandal 2012, Newall 2005; Ong 2001	- Recommended: PR for ADL-related breathlessness (B) - IMT with rehabilitation for maintenance of effect (B)	Low priority for updating	Low
	ACTs (Lee 2013)	5 (38)	Bernabeu 2014; Eaton 2007; Liaw 2011; Mandal 2012; Murray 2009; Naraparaju 2010; Nicolini 2013; Paneroni 2011; Patterson 2004; Patterson 2005; Su 2012; Syed 2009; Tambascio 2011; Thompson 2002; Tsang 2003; Venturelli 2012	- Should be considered: active cycle of breathing (B), oscillating PEP devices (A). Autogenic drainage, PEP or gravity-assisted methods if other techniques not effective, appropriate or acceptable (D) . Manual techniques can be added during acute exacerbation (D) - No evidence on who benefits most	Update and expand to include head-to-head trials	High

Table 1. Evidence map (*Continued*)

Disease management and education	**Nurse-led care** (French 2003)	1 (80)	Lavery 2011 Liaw 2011	Successful management of people with asthma and COPD in primary care by well-trained nurses and GPs provides model for development of better care for people with bronchiectasis. People with bronchiectasis should as a minimum be referred to a chest physician, physiotherapist and respiratory nurse with expertise in the condition	Low priority for updating	Low for nurse-led care, since care now delivered by multidisciplinary teams Self management of exacerbations is medium priority
	Communication strategy	-	Yang 2012	-	-	-
Surgery	**Surgery** (Warburton 2000)	0	None identified	Consider for people with poorly controlled localised disease (D). Potential first-line therapy for massive haemoptysis (D)	Update if new trials	Low (RCTs unlikely)
Other	**Singing** (Irons 2010)	0	Maa 2007 (acupuncture)	- NIV can improve QoL in some people with concomitant chronic respiratory failure (D) - No evidence: lung transplantation	Update of review on singing deemed unnecessary'. Extrapolate evidence on complementary therapies from asthma and COPD reviews	Low
	Statins	n/a	Mandal 2014	Not included in guideline	-	-

Table 1. Evidence map (*Continued*)

	Neutrophil elastase inhibitors	n/a	Stockley 2013	-	-	-
	Immunostimulating agents	n/a	Gao 2014b; Pavord 2013	-	-	-
	Humidification of air	-	Milne 2014	-	-	-

1. These studies may be included in future Cochrane reviews.

Abbreviations: ACT: airways clearance technique; ADL: activities of daily living; aka: also known as; COPD: chronic obstructive pulmonary disease; GP: general practitioners; ICS: inhaled corticosteroids; IMT: inspiratory muscle training; IV: intravenous; LABA: long-acting beta$_2$-agonist; LTRA: leukotriene receptor antagonist; N: number of studies; n/a: not applicable; NIV: non-invasive ventilation; NSAID: non-steroidal anti-inflammatory drug; OCS: oral corticosteroids; PEP: positive expiratory pressure; PR: pulmonary rehabilitation; QoL: quality of life; RCT: randomised controlled trial; RhDNase: recombinant human deoxyribonuclease I; SABA: short-acting beta$_2$-agonists; U: ungraded.

Table 2. Characteristics of included reviews

Review (search date*)	Intervention dose (number of studies)	Comparison	Number studies, design, duration	Study participants - treatment, n, baseline FEV_1, age, gender
Pharmacological interventions				
Antibiotics (long term) (Evans 2007) (Jan 2011)	*Children*: oral clarithromycin 15 mg/kg/day (1); oral roxithromycin 4 mg/kg twice/day (1) *Adults*: nebulised tobramycin 300 mg twice/day (2); inhaled tobramycin 100 mg twice/day (1); oral amoxicillin 3 g twice/day (1); oral azithromycin 500 mg twice/day (1); oral erythromycin 500 mg twice/day (1); oral oxytetracycline 500 mg 4 times/day (1)	6 placebo 3 usual care	9 RCTs: 7 double-blind (including 1 cross-over); 2 open-label (including 1 cross-over) Duration: 4 weeks to 1 year	*Children*: n = 61, FEV_1 not stated, mean age 13 years, 52-56% male *Adults*: n = 317, mean FEV_1 50-83% predicted, mean age 50-70 years, 50-64% male
Antibiotics (short-term) (Wurzel 2011) (Feb 2011)	Nebulised tobramycin 600 mg/day	Placebo	1 RCT: double-blind Duration: 4 weeks	n = 74, FEV_1 not stated, mean age 65 years, 39% male

Table 2. Characteristics of included reviews (*Continued*)

ICS (Kapur 2009) (Oct 2010)	Beclomethasone: 800 mcg/day (1), 1500 mcg/day (1) Fluticasone propionate: 500 vs. 1000 mcg/day (1), 1000 mcg/day (3)	5 placebo 1 nothing	6 RCTs: double-blind Duration 4 weeks to 1 year	Beclomethasone: n = 40, mean age 50 years, 40-55% male Fluticasone propionate: n = 263, mean age 51-70 years, 34-72% male Baseline FEV_1 not stated
LABA/ICS combination (Goyal 2014) (Mar 2014)	Budesonide 640 mcg/day + formoterol 18 mcg/day	Budesonide 1600 mcg/day	Open-label Duration: 3 months	n = 40, mean FEV_1 61% predicted, mean age 70 years, 45% male
Inhaled hyperosmolar (Hart 2014) (Apr 2014)	Mannitol: dose unknown (1), 480 or 320 mg (1), 400 mg (3), 320 mg (1), 300 mg (1) per day HTS 6% vs. ITS 7% (2) per day	5 placebo 2 nothing 4 dose comparison	11 RCTs: 7 double-blind (includes 3 cross-overs); 2 single blind (includes 1 cross-over); 2 open-label cross-overs Duration: 4 days to 1 year	Mannitol; n = 927, mean FEV_1 62-88% predicted, age 52-63 years; 21-36% male HTS: n = 113, mean FEV_1 57-82% predicted, mean age 57-61 years, 29-50% male
Mucolytics (Wilkinson 2014) (Jan 2010)	Oral bromhexine 30 mg twice/day (1); nebulised RhDNase 2.5 mg twice/day (2); oral erdosteine 225 mg twice/day (1) Single or repeat doses alone or combined with: glucocorticosteroids, $beta_2$-agonists or xanthines	Placebo	4 RCTs: 3 double-blind; 1 open-label Duration: 15 days to 24 weeks	Bromhexine: (30 mg in 1st week): n = 88, mean FEV_1 1.66 L, mean age 52 years, 64% male RhDNase: n = 410, mean FEV_1 51-58% predicted, age 53-60 years, 38-46% male Erdosteine: n = 30, mean FEV_1 47% predicted, mean age 70 years, 70% male
Review (search date)	**Intervention, dose (number of studies)**	**Control**	**Number of studies, design, duration**	**Study participants - treatment, n, baseline FEV_1, age, gender**
Non-pharmacological interventions				
PR/exercise therapy (Bradley 2002) (Feb 2005)	IMT: (1) + PR (1)	1 no treatment 1 sham IMT/PR or no treatment	Unblinded RCT Duration: 8 weeks	n = 52, FEV_1 not stated, mean age 60-62 years, gender not stated
ACTs (Lee 2013) (Oct 2012)	*Children*: oscillating PEP with flutter (1) *Adults*: oscillat-	2 PEP vs. sham PEP 1 PEP vs. no intervention	5 cross-over RCTs Duration: single session - 6 months	PEP: *Adults*: n = 38, mean FEV_1 53-76% predicted, age 47-

Table 2. Characteristics of included reviews (*Continued*)

	ing PEP with flutter (2) or acapella (1) Postural drainage + FET (1)	1 PEP vs. PD vs control 1 PD + FET vs. resting		73 years *Children*: n = 9, FEV_1 not stated, age 6-16 years PD: n = 8, mean FEV_1 1.17 L, age 36-71 years Gender not stated
Nurse-led care (French 2003) (Jul 2008)	Nurse-led	Doctor-led care	1 cross-over RCT Duration: 1 year each arm	n = 80, mean FEV_1 70% predicted, mean age 58 years, 31% male

Abbreviations: ACT: airway clearance technique; FET: forced expiratory technique; FEV_1: forced expiratory volume in 1 second; HTS: hypertonic saline; ICS: inhaled corticosteroids; IMT: inspiratory muscle training; ITS: isotonic saline; LABA: ; n: number of participants; PD: postural drainage; PEP: positive expiratory pressure therapy; PR: pulmonary rehabilitation; RCT: randomised controlled trial; RhDNase: recombinant human deoxyribonuclease I; vs: versus.

* Date the most recent literature search was fully incorporated into the review (month and year).

Table 3. Quality of the evidence in included reviews

Review	Summary of findings	Quality assessment tool	Risk of bias	Comments
Pharmacological interventions				
Antibiotics (long term) (Evans 2007)	No	Yes Jadad = 4/5 or 5/5	Allocation concealment only, mixture of unclear and low RoB	-
Antibiotics (short term) (Wurzel 2011)	No	No	Allocation concealment unclear, but study blinded. 6 participants withdrew from placebo group due to need for another antibiotic	-
ICS (Kapur 2009)	No	No	Allocation concealment unclear. Most studies blinded. Follow-up over 90% in half of studies. 1 study included only people with reversible airflow obstruction, which biased results towards people with an asthma component	-

Table 3. Quality of the evidence in included reviews (*Continued*)

LABA/ICS combination (Goyal 2014)	Yes, low-quality evidence (QoL, TDI, cough-free days, HA/exacerbations)	No	High RoB due to inadequate blinding and unclear randomisation procedures	-
Inhaled hyperosmolar (Hart 2014)	Yes. Moderate-quality evidence	No	Mostly unclear. 5 trials had issues with randomisation procedure	-
Mucolytics (Wilkinson 2014)	Yes. Bromhexine: low-quality evidence (AEs symptoms, FEV_1); RhDNase: low-quality evidence (HA, symptoms, FEV_1); erdosteine: low-quality evidence (mucous production, FEV_1)	No	Mixed judgements	-
Non-pharmacological interventions				
PR/exercise therapy (Bradley 2002)	No	Yes. Jadad = 1/5	Pre-dates RoB tool. Not possible to blind the participants or personal	Reported as abstracts and randomisation procedures not reported. Baseline imbalance affected internal validity of trials
ACTs (Lee 2013)	Yes. Low-quality evidence (exacerbations, QoL)	No	RoB judgements mixed, blinding of participants and personnel not possible	Judgements mixed and limited by small sample size and inadequate reporting
Nurse-led care (French 2003)	No	Yes. Jadad = 3/5	Blinding of participants and personal not possible. Randomisation method unclear	Possible carry over effect since no wash-out period between cross-over study periods

Abbreviations: ACT: airway clearance technique; AE: adverse events; FEV_1: forced expiratory volume in 1 second; HA: hospital admission; PR: pulmonary rehabilitation; QoL: quality of life; RhDNase: recombinant human deoxyribonuclease I; RoB: risk of bias; TDI: Transitional Dyspnoea Index.

Table 4. Outcomes in Cochrane reviews - exacerbations

Intervention/ comparison	Outcome	Number of participants (number of studies)	Results: treatment effect (95% CI) unless otherwise stated	Interpretation of result[1]	Evaluation[1]
Pharmacological interventions					
Antibiotics (long term) vs. placebo (Evans 2007)	≥ 1 exacerbations	90 (2, adults) 30 (1, children)	Peto OR 0.96 (0.27 to 3.46), P value = 0.95 (I^2 = 71%)	NSD	No evidence of benefit
	Mean exacerbations per person	30 (1, adult)	MD -0.4, SD not reported, P value = 0.33	NSD	No evidence of benefit
	Frequency of exacerbations requiring antibiotics	12 (1, adult)	5 events vs. 16, P value = 0.019, unclear whether absolute frequency or per person	Statistically significant difference	Evidence of statistical benefit
Antibiotics (short term) vs. placebo (Wurzel 2011)	Outcome not reported in trial				
ICS vs. placebo/no treatment (Kapur 2009)	Mean exacerbations per person	57 (1) 86 (1)	MD 0.09 (-0.61 to 0.79), P value = 0.8 MD -0.49 (-1.49 to 0.51), P value not reported	NSD	No evidence of benefit
	≥ 1 exacerbations	24 (1)	FP = 1, placebo = 3, too few events to establish benefit	Not reported	Unclear
LABA/ICS combination vs. ICS (Goyal 2014)	Frequency of exacerbations	40 (1)	LABA/ICS = 4, ICS = 7, P value not reported Unclear whether absolute frequency or per person	NSD	No evidence of benefit
Inhaled hyperosmolar vs. placebo or ITS (Hart 2014)	Mannitol vs. placebo Frequency: rate/ year	461 (1)	RR 0.92 (0.78 to 1.08), P value not reported	NSD	No evidence of benefit

Table 4. Outcomes in Cochrane reviews - exacerbations (*Continued*)

	HTS vs. ITS frequency: rate/year	30 (1)	HTS 2.14 vs. ITS 4.85, MD 2.71, CI not reported, P value < 0.05	Statistically significantly difference	Evidence of clinically relevant benefit
	HTS vs. ITS frequency: rate/year	40 (1)	Values not reported	NSD	No evidence of benefit
Mucolytics vs. placebo (Wilkinson 2014)	Bromhexine vs. placebo: outcome not reported in trial				
	RhDNase 5 mg vs. placebo: outcome not reported in trial				
	RhDNase 2.5 mg vs. placebo Frequency: rate/year	176 (1)	RR 1.35 (1.01 to 1.79) favoured placebo	Risk of exacerbation significantly higher (35%) with RhDNase	Evidence of harm
	Erdosteine vs. nothing: outcome not reported in trial				
Non-pharmacological interventions					
Physical therapy: IMT vs. no intervention or sham treatment (Bradley 2002)	Outcome not reported in trial				
Nurse-led vs. doctor-led care (French 2003)	Infective exacerbations (participant reported): rate/year	80 (1)	MD 0.05 (-1.07 to 1.17), P value not reported	NSD	No evidence of benefit
ACTs vs. no treatment (Lee 2013)	Frequency: > 12 weeks	20 (1, adult) (PEP-based ACT)	RR 0.71 (0.23 to 2.25)	NSD	No evidence of benefit

1. Minimum clinically important difference: ≥ 11% reduction in exacerbation frequency (Chapman 2013) or difference of ≥ 1 exacerbations per year (Pellegrino 2005).

Abbreviations: ACT: airway clearance technique; CI: confidence interval; FP: fluticasone propionate; HTS: hypertonic saline; ICS: inhaled corticosteroids; IMT: inspiratory muscle training; ITS: isotonic saline; LABA: long-acting beta$_2$-agonist; MD: mean difference; NSD: no statistically significant difference; OR: odds ratio, PEP: positive expiratory pressure therapy; RhDNase: recombinant human deoxyribonuclease I; RR: risk ratio; SD: standard deviation; vs: versus.

Table 5. Outcomes in Cochrane reviews - lung function

Intervention/ comparison	Outcome	Number of participants (number of studies)	Results: treatment effect (95% CI) unless otherwise stated	Interpretation of result[1]	Evaluation[1]
Pharmacological interventions					
Antibiotics (long term) vs. placebo (Evans 2007)	FEV_1 % predicted at end of trial	27 (1, children) 17 (1, adults)	MD -1.05% (-6.93 to 4.83), P value = 0.7	NSD	No evidence of benefit
	FEV_1 (unit not reported)	59 (3)	Not pooled but all reported no difference (values not reported)	NSD	No evidence of benefit
Antibiotics (short term) vs. placebo (Wurzel 2011)	*Tobramycin vs. placebo*: FEV_1 % predicted change from baseline	74 (1, adults)	MD and CI not reported, tobramycin -2.2%; placebo 1.5%, P value = 0.41	NSD	No evidence of benefit
ICS vs. placebo/no treatment (Kapur 2009)	Short-term follow-up < 6 months: FEV_1 L change from baseline	101 (3, adults)	MD 0.09 L (0.03 to 0.15), P value = 0.002 Effect based on 1 study without placebo comparison	Statistically significant difference	Evidence of statistical benefit
LABA/ICS combination vs. ICS (Goyal 2014)	FEV_1 mL change from baseline	40 (1)	MD -14.00 mL (-84.14 to 56.14), P value not reported	NSD	No evidence of benefit
Inhaled hyperosmolar vs. placebo or ITS (Hart 2014)	*Mannitol vs. placebo*: FEV_1 % predicted change from baseline	17 (1)	MD 2.70% (-8.53 to 13.93), P value not reported	NSD	No evidence of benefit
	Mannitol vs. placebo FEV_1 L: at end of trial	343 (1)	MD 0.03 L (-0.10 to 0.16), P value not reported	NSD	No evidence of benefit
	Mannitol vs. placebo FEV_1: change (unit not reported)	12 (1)	Not reported	NSD	No evidence of benefit
	HTS vs. ITS: FEV_1 % predicted change from baseline	30 (1)	MD 13.30% (CI not reported), P value < 0.01	Statistically significant difference	Evidence of clinically relevant benefit

Table 5. Outcomes in Cochrane reviews - lung function (*Continued*)

			Favoured HTS		
	HTS vs. ITS: FEV_1 L at end of trial	40 (1)	MD 0.19 L (-0.37 to 0.75), P value = 0.5	NSD	No evidence of benefit
Mucolytics vs. placebo (Wilkinson 2014)	*Bromhexine vs. placebo:* FEV_1 mL at end of trial	88 (1)	MD 184.00 mL (-149.75 to 517.75), P value not reported	NSD	No evidence of benefit
	RhDNase 5 mg vs. placebo: FEV_1 L % change from baseline	40 (1)	MD 2.10% (-2.90 to 7.10), P value not reported	NSD	No evidence of benefit
	RhDNase 2.5 mg vs. placebo: FEV_1 L % change from baseline	237 (2)	n = 197, MD -1.9% decline, P value < 0.05, *favoured placebo*; n = 40, MD 2.10% (-4.05 to -8.25), P value not reported	Statistically significant difference (1 trial) NSD (1 trial)	Unclear
	Erdosteine vs. nothing: FEV_1 mL change from baseline	30 (1)	MD 200 mL (40 to 360), P value not reported	Statistically significant difference	Evidence of clinically relevant benefit
	Erdosteine vs. nothing: FEV_1 % predicted change from baseline	30 (1)	MD 4.50% (-3.11 to 12.11), P value not reported	NSD	No evidence of benefit
Non-pharmacological interventions					
Physical therapy: IMT vs. no intervention or sham treatment (Bradley 2002)	Outcome not reported in trial				
Nurse-led vs. doctor-led care (French 2003)	FEV_1 % predicted at end of trial	80 (1)	MD 2.37 (-7.37 to 12.11), P value not reported	NSD	No evidence of benefit
ACTs vs no treatment (Lee 2013)	FEV_1 L at end of trial	38 (3, adults)	Median difference 0.0 L, P value = 0.7 (1 study, no values for other 2 studies)	NSD	No evidence of benefit

Table 5. Outcomes in Cochrane reviews - lung function (*Continued*)

	FEV_1 (unit not reported) at end of trial	9 (1, children)	Difference 8.86% (values not reported), P value not reported, favoured ACT	Statistically significant difference	Unclear

1. No minimum clinically important difference for FEV_1 in bronchiectasis. Reference values from American Thoracic Society/European Respiratory Society recommendations as follows: change of at least 100 mL or change of ≥ 20% in short-term trials (of weeks of duration) and ≥ 15% in long-term trials (≥ 1 year) (Pellegrino 2005).

Abbreviations: ACT: airway clearance technique; CI: confidence interval; FEV_1 : forced expiratory volume in 1 second; HTS: hypertonic saline; ICS: inhaled corticosteroids; IMT: inspiratory muscle training; ITS: isotonic saline; LABA: long-acting $beta_2$-agonist; n: number of participants; MD: mean difference; NSD: no statistically significant difference; RhDNase: recombinant human deoxyribonuclease I; vs: versus.

Table 6. Outcomes in Cochrane reviews - quality of life

Intervention/ comparison	Outcome	Number of participants (number of studies)	Results: treatment effect (95% CI) unless otherwise stated	Interpretation of result[1]	Evaluation[1]
Pharmacological interventions					
Antibiotics (long term) vs. placebo (Evans 2007)	SGRQ Total: change from baseline	30 (1, adults)	MD -0.07 (-3.69 to 3.55), P value = 0.9 Did not control for baseline values	NSD	Unclear
Antibiotics (short term) vs. placebo (Wurzel 2011)	Outcome not reported in trial				
ICS vs. placebo/no treatment (Kapur 2009)	Outcome not reported in trial				
LABA/ICS combination vs. ICS (Goyal 2014)	SGRQ Total: change from baseline	40 (1)	MD -4.57 (-12.38 to 3.24), P value not reported Exceeds MCID but wide CI	NSD	Unclear
Inhaled hyperosmolar vs. placebo or ITS (Hart 2014)	*Mannitol vs. placebo* SGRQ Total: change from baseline	840 (3)	MD -2.05 (-3.69 to -0.40), P value = 0.015 Favoured mannitol	Statistically significant difference	Evidence of statistical benefit

Table 6. Outcomes in Cochrane reviews - quality of life (*Continued*)

	HTS vs. ITS SGRQ: Symptoms, Activity, impacts at end of trial	70 (2)	n = 40 (1 trial), SGRQ: Symptom, MD 1.60 (-12.53 to 15.73), P value = 0.8; SGRQ: Activity MD 2.70 (-13.11 to 18.51), P value = 0.7; SGRQ: Impacts 4.40 (-7.50 to 16.30), P value = 0.4 n = 30 (1 trial), significant changes reported but values not reported	NSD (1 trial) Statistically significant difference (1 trial)	Unclear
	HTS vs. ITS QoL-B: Respiratory Symptoms (endpoint not reported)	19 (1)	MD -11.6 (SD 17.7); P value = 0.03 Exceeds MCID threshold of 8 units	Statistically significant difference	Evidence of clinically relevant benefit
	HTS vs. ITS LCQ: Physical, Psycho- logical, Social (endpoint not reported)	59 (2)	n = 19 (1 trial), Physical, MD -0.8 (SD 0.9), P value = 0.01, benefits HTS n = 40 (1 trial), Physical, MD -0.20 (-0.95 to 0.55), P value = 0.6; Psychological, MD 0.20 (-0.63 to 1.03), P value = 0.6; Social, MD -0.10 (-0.85 to 0.65), P value = 0.8	Statistically significant difference (1 trial) NSD (1 trial)	Unclear
Mucolytics vs. placebo (Wilkinson 2014)	Outcome not reported in trials				
Non-pharmacological interventions					
Physical therapy: IMT vs. no intervention or sham treatment (Bradley 2002)	CRQ Total: change from baseline	43 (2)	MD 12.4 (2.38 to 22.43), P value = 0.015 Exceeds MCID threshold of 0.5 units	Statistically significant difference	Evidence of clinically relevant benefit

Table 6. Outcomes in Cochrane reviews - quality of life (*Continued*)

Nurse-led vs. doctor-led care (French 2003)	SGRQ Total: (endpoint not reported)	80 (1)	MD -1.70 (-10.00 to 6.60), P value not reported	NSD	No evidence of benefit
ACTs vs. no treatment (Lee 2013)	LCQ Total: (endpoint not reported)	20 (1, adults)	Median difference 1.3 (CI not reported), P value = 0.002, favoured ACT Meets MCID threshold of 1.3 units	Statistically significant difference	Evidence of clinically relevant benefit
	SGRQ Total: (endpoint not reported)	20 (1, adults) *(same as above)*	Median difference 8.5, (CI not reported), P value = 0.005, favoured ACT Exceeds MCID threshold of 4 units	Statistically significant difference	Evidence of clinically relevant benefit

1. MCID values: CRQ > 0.5 units (Chauvin 2008); SGRQ > 4 units (Jones 2005); QoL-B ≥ 8 units (Quittner 2014); LCQ ≥ 1.3 units (Raj 2009).

Abbreviations: ACT: airway clearance technique; CI: confidence interval; CRQ: Chronic Respiratory Questionnaire; HTS: hypertonic saline; ICS: inhaled corticosteroid; IMT: inspiratory muscle training; ITS: isotonic saline; LABA: long-acting beta2-agonist; LCQ: Leicester Cough Questionnaire; MCID: minimally clinically important difference; MD: mean difference; n; number of participants; NSD: no statistically significant difference; QoL-B: Quality of Life - Bronchiectasis; SD: standard deviation; SGRQ: St George's Respiratory Questionnaire; vs: versus.

Table 7. Outcomes in Cochrane reviews - symptoms

Intervention/ comparison	Outcome	Number of participants (number of studies)	Results: treatment effect (95% CI) unless otherwise stated	Interpretation of result[1]	Evaluation[1]
Pharmacological interventions					
Antibiotics (long term) vs. placebo (Evans 2007)	Outcome not reported in trial				
Antibiotics (short term) vs. placebo (Wurzel 2011)	Outcome not reported in trial				
ICS vs. placebo/no treatment (Kapur 2009)	Dyspnoea: number with no improvement in TDI by end of trial	62 (1)	OR 3.33 (1.17 to 9.43) Favoured ICS	Statistically significant difference	Evidence of clinically relevant benefit

Table 7. Outcomes in Cochrane reviews - symptoms (*Continued*)

			Exceeds MCID threshold of 1 unit		
	Wheeze: number with regular (no definition) wheeze by end of trial	62 (1)	OR 0.87 (0.31 to 2.44)	NSD	No evidence of benefit
LABA/ICS combination vs. ICS (Goyal 2014)	Cough-free days: percentage by end of trial	40 (1)	MD 12.3% (2.38 to 22.2) P value not reported Favoured combination	Statistically significant difference	Evidence of statistical benefit
	Dyspnoea: TDI, change from baseline	40 (1)	MD 1.29 (0.40 to 2.18) Favoured combination Exceeds MCID threshold of 1 unit	Statistically significant difference	Evidence of clinically relevant benefit
Inhaled hyperosmolar vs. placebo or ITS (Hart 2014)	*Mannitol vs. placebo*: Bronchiectasis Symptoms Questionnaire: score at end of trial	343 (1)	MD -1.20 (-3.91 to 1.51) P value not reported	NSD	No evidence of benefit
	Mannitol vs. placebo: LCQ: score at end of trial	343 (1)	MD 0.00 (-0.81 to 0.81) P value not reported	NSD	No evidence of benefit
	HTS vs. ITS: Cough: VAS frequency at trial endpoints	40 (1)	No difference at 3, 6 or 12 months (values not reported), P value > 0.16	NSD	No evidence of benefit
Mucolytics vs. placebo (Wilkinson 2014)	*Bromhexine vs. placebo*: Cough score (no detail) (endpoint not reported)	88 (1)	MD -0.48 (-0.89 to -0.06), P value not reported Favoured bromhexine	Statistically significant difference	Evidence of statistical benefit
Non-pharmacological interventions					
Physical therapy: IMT vs. no intervention or sham treatment (Bradley 2002)	Outcome not reported in trial				

Table 7. Outcomes in Cochrane reviews - symptoms (*Continued*)

Nurse-led vs. doctor-led care (French 2003)	Not an outcome in the review
ACTs vs. no treatment (Lee 2013)	Outcome not reported in trial

1. Minimum clinically important difference for Transition Dyspnoea Index > 1 unit in COPD (Pellegrino 2005); LCQ ≥ 1.3 units (Raj 2009).

Abbreviations: ACT: airway clearance technique; CI: confidence interval; HTS: hypertonic saline; ICS: inhaled corticosteroid; IMT: inspiratory muscle training; ITS: isotonic saline; LABA: long-acting beta2-agonist; MCID: minimal clinically important difference; MD: mean difference; NSD: no significant difference; OR: odds ratio; TDI: Transitional Dyspnoea Index; VAS: visual analogue scale; vs: versus.

Table 8. Outcomes in Cochrane reviews - sputum characteristics

Intervention/ comparison	Outcome	Number of participants (number of studies)	Results: treatment effect (95% CI) unless otherwise stated	Interpretation of result[1]	Evaluation[1]
Pharmacological interventions					
Antibiotics (long term) vs. placebo (Evans 2007)	Sputum leukocyte scores (endpoint and units not reported)	27 (1, children)	-0.52 (CI not reported), P value < 0.01 Favoured antibiotics	Statistically significant difference	Evidence of statistical benefit
	Sputum purulence scores (endpoint and units not reported)	27 (1, children)	-1.22 (CI not reported), P value < 0.01 Favoured antibiotics	Statistically significant difference	Evidence of statistical benefit
	Sputum volume (endpoint not reported)	12 (1, adults) 34 (1, children)	Adults: median difference 1 mL (values not reported), P value not reported Children: values not reported, P value = 0.0001	NSD (1 trial) Statistically significant difference (1 trial)	Unclear
Antibiotics (short term) vs. placebo (Wurzel 2011)	Outcome not reported in trial				

Table 8. Outcomes in Cochrane reviews - sputum characteristics (*Continued*)

ICS vs. placebo/no treatment (Kapur 2009)	Sputum volume: < 6 months trial: mean 24 hour mL	113 (2)	1 study, n = 93: MD -8.30 mL (-16.55 to -0.05), P value not reported. Difference described as 'trend' 1 study, n = 20: values not reported, P value = 0.003 Favoured ICS	NSD (1 trial) Statistically significant difference (1 trial)	Unclear
	Sputum volume: > 6 months trial: mean 24 hour mL	89 (1)	Data not reported in review because skewed. Stated as NSD P value not reported	NSD	No evidence of benefit
	Sputum purulence: score (0-8 scale) at end of trial (12 months)	89 (1)	MD 0.2 (-0.94 to 1.34) P value not reported	NSD	No evidence of benefit
LABA/ICS combination vs. ICS (Goyal 2014)	Outcome not reported in trial				
Inhaled hyperosmolar vs placebo or ITS (Hart 2014)	*Mannitol vs. placebo* Sputum weight: 24 hour change from baseline	362 (1)	n = 362, 1 trial, MD 4.32 g (1.60 to 7.04) P value not reported Favoured placebo (attributed to more antibiotics)	Statistically significant difference	Unclear
	Mannitol vs. nothing Sputum volume: mean in 75 minutes	25 (2)	n = 14,1 trial, mannitol 480 mg MD 21.9%, CI not reported, P value < 0.001 n = 11, 1 trial: mannitol 300 mg, MD 22.3%, CI not reported, P value < 0.0001	Statistically significant difference	Evidence of statistical benefit
	HTS vs. ITS sputum weight: (endpoint not reported)	24 (1)	HTS median 5.3 g (IQR 2.97 to 9.33) ; ITS median 3.17 g (IQR 1.45 to 6.25) Difference	Unclear	Unclear

Table 8. Outcomes in Cochrane reviews - sputum characteristics (*Continued*)

			described as significant but P value not reported		
Mucolytics vs. placebo (Wilkinson 2014)	*Bromhexine vs. placebo* Sputum volume: % change at end of trial	88 (1)	MD -21.5% (-38.9 to -4.1), significance not reported P value not reported	Unclear	Unclear
	RhDNase 5 mg vs. placebo Sputum colour (scale not referenced in trial) at end of trial	40 (1)	MD 0.28 (-0.04 to 0.60) P value not reported No evidence of benefit for RhDNase 2.5 mg	NSD	No evidence of benefit
	Erdosteine vs. no treatment Mucous volume: score (0 = low, 1 = moderate, 2 = high) at end of trial	30 (1)	MD 0.40 (-0.03 to 0.83), P value not reported	NSD	No evidence of benefit
Non-pharmacological interventions					
Physical therapy: IMT vs. no intervention or sham treatment (Bradley 2002)	Outcome not reported in trial				
Nurse-led vs. doctor-led care (French 2003)	Not an outcome in the review				
ACTs vs. no treatment (Lee 2013)	Sputum volume: mL (end of session)	28 (2)	n = 8, 1 trial, MD 8.40 mL (3.40 to 13.4), favoured ACT, P value not reported n = 20, 1 trial, MD 24-hour volume, MD 3 mL, P value = 0.02, favoured ACT	Statistically significant difference	Evidence of statistical benefit
	Sputum weight: g (endpoint not re-	18 (2)	n = 8, 1 trial, MD 17 g, P value < 0.01,	Statistically significant difference	Evidence of statistical benefit

Table 8. Outcomes in Cochrane reviews - sputum characteristics (*Continued*)

	ported)		favoured ACT n = 10, 1 trial, MD 24 g, P value < 0.05, favoured gravity-assisted drainage; MD 0.01 g, P value > 0.05, favoured control		

1. People with bronchiectasis may expectorate 4-145 mL sputum in a 24-hour period (Tsang 2000), with mean daily volumes (based on 4 studies) ranging from 65 to 567 mL(Pasteur 2010). We have not identified an MCID for sputum volume for bronchiectasis, cystic fibrosis or chronic obstructive pulmonary disease.

For the purpose of this review, we regard increased expectoration of sputum as a positive outcome.

Abbreviations: ACT: airway clearance technique; CI: confidence interval; HTS: hypertonic saline; ICS: inhaled corticosteroid; IMT: inspiratory muscle training; IQR: interquartile range; ITS: isotonic saline; LABA: long-acting beta$_2$-agonist; MCID: minimal clinically important difference; MD: mean difference; NSD: no significant difference; RhDNase: recombinant human deoxyribonuclease I; TDI: Transitional Dyspnoea Index; vs: versus.

Table 9. Outcomes in Cochrane reviews - adverse events

Intervention/ comparison	Outcome	Number of participants (number of studies)	Results: treatment effect (95% CI) unless otherwise stated	Interpretation of result	Evaluation
Pharmacological interventions					
Antibiotics (long term) vs. placebo (Evans 2007)	Withdrawals due to treatment failure or adverse effects	260 (5)	Peto OR 1.06 (0.42 to 2.65)	NSD	No evidence of harm
	Diarrhoea	148 (2)	Peto OR 2.47 (0.91 to 6.71)	NSD	No evidence of harm
	Rash	54 (2)	Peto OR 1.94 (0.19 to 19.47)	NSD	No evidence of harm
	Wheeze	74 (1)	Peto OR 8.56 (1.63 to 44.93) More cases with antibiotics	Statistically significant difference	Evidence of harm
	Dyspnoea	74 (1)	Peto OR 4.41 (1.43 to 13.61) Nebulised antibiotics: 12/37 vs. placebo: 3/37, P value = 0.01 More cases with antibiotics	Statistically significant difference	Evidence of harm

Table 9. Outcomes in Cochrane reviews - adverse events (*Continued*)

	Chest pain	74 (1)	Peto OR 8.84 (1.88 to 41.50) Nebulised antibiotics: 7/37 vs. placebo: 0/37, P value = 0.01 More cases with antibiotics	Statistically significant difference	Evidence of harm
Antibiotics (short term) vs. placebo (Wurzel 2011)	AEs	74 (1, adults)	OR 2.24 (0.86 to 5.82) 31/37 (84%) people in each group reported at least 1 adverse event	NSD	No evidence of harm
Inhaled corticosteroids vs. placebo/no treatment (Kapur 2009)	Outcome not reported in trial				
LABA/ICS combination vs. ICS (Goyal 2014)	AEs: frequency	40 (1)	More adverse events reported in the ICS group (37) than the LABA/ICS group (12), but unclear whether number of events or number of people experiencing ≥ 1 events reported	Unclear	Unclear
Inhaled hyperosmolar vs. placebo or ITS (Hart 2014)	*Mannitol vs. placebo* AEs	823 (2)	OR 0.96 (0.61 to 1.51). The number of AEs was high in 1 study (placebo: 80% vs. mannitol: 82%), but most AEs unrelated to treatment	NSD	No evidence of harm
	Mannitol vs. placebo SAEs	823 (2)	OR 0.79 (0.52 to 1.19)	NSD	No evidence of harm
	Mannitol vs. placebo: AEs	50 (1)	2 people receiving mannitol had dry mouth; 4 reported headache, fatigue, and chest pain, but unclear if AEs experienced in	NSD	No evidence of harm

Table 9. Outcomes in Cochrane reviews - adverse events (*Continued*)

			the same person. No AEs reported in the placebo group		
	HTS vs. ITS Adverse events	59 (2)	OR 8.20 (0.40 to 169.9)	NSD	No evidence of harm
Mucolytics vs. placebo (Wilkinson 2014)	*Bromhexine vs. placebo* AEs	88 (1)	OR 2.93 (0.12 to 73.97) 1 event (bromhexine)	NSD	No evidence of harm
	RhDNase 5 mg vs. placebo AEs	40 (1)	Total of 19 AEs, not different between groups but more cases of influenza syndrome in RhDNase (values not reported) No difference in AE frequency for RhDNase 2.5 mg	Unclear	Unclear
	RhDNase (2.5 mg) vs. placebo Antibody levels: frequency	176 (1)	OR 28.19 (3.77 to 210.85)	Statistically significant difference	Evidence of harm
	Erdosteine vs. no treatment: outcome not reported in trial				
Non-pharmacological interventions					
Physical therapy: IMT vs. no intervention or sham treatment (Bradley 2002)	Outcome not reported in trial				
Nurse-led vs. doctor-led care (French 2003)	Not an outcome in the review				
ACTs no treatment (Lee 2013)	AEs	28 (2)	None reported	NSD	No evidence of harm
	Withdrawals: intervention-related	38 (3)	No ACT-related withdrawals	NSD	No evidence of harm

Abbreviations: ACT: airway clearance technique; AE: adverse events; CI: confidence interval; HTS: hypertonic saline; ICS: inhaled corticosteroid; IMT: inspiratory muscle training; ITS: isotonic saline; LABA: long-acting beta$_2$-agonist; NSD: no significant difference; OR: odds ratio; RhDNase: recombinant human deoxyribonuclease I; SAE: serious adverse event; vs: versus.

Table 10. Outcomes in Cochrane reviews - hospitalisations

Intervention/ comparison	Outcome	Number of participants (number of studies)	Results: treatment effect (95% CI) unless otherwise stated	Interpretation of result	Evaluation
Pharmacological interventions					
Antibiotics (long-term) vs. placebo (Evans 2007)	Mean number of admissions per participant	17 (1, adults)	MD -1.9, CI not reported, P value = 0.023 Fewer admissions with antibiotics	Statistically significant difference	Evidence of statistical benefit
	Number of admissions	30 (1, adults)	MD -0.6, CI not reported, P value = 0.038 Fewer admissions with antibiotics	Statistically significant difference	Evidence of statistical benefit
Antibiotics (short term) vs. placebo (Wurzel 2011)	Not an outcome in the review				
ICS vs. placebo/no treatment (Kapur 2009)	Outcome not reported in trial				
LABA/ICS combination vs. ICS (Goyal 2014)	Number of admissions	40 (1)	4 events (1 LABA/ICS vs. 3 ICS), OR 0.26 (0.02 to 2.79)	NSD	No evidence benefit
Inhaled hyperosmolar vs. placebo or ITS (Hart 2014)	*Mannitol vs. placebo*: Participants experiencing 1 or more hospitalisations	461 (1)	RR 0.61 (0.34 to 1.09)	NSD	No evidence benefit
	Mannitol vs. nothing: Outcome not reported in trial				
	HTS vs. ITS Number of*a*dmissions	40 (1)	HTS 1 vs. ITS 3, P value = 0.34 Only 4 events overall	NSD	Unclear

Table 10. Outcomes in Cochrane reviews - hospitalisations (*Continued*)

Mucolytics vs placebo (Wilkinson 2014)	*Bromhexine vs. placebo*: Outcome not reported in trial				
	RhDNase 5 mg vs. placebo	40 (1)	OR 5.54 (0.25 to 123.08) 0 events in placebo group	NSD	No evidence of benefit
	Erdosteine vs. no treatment: Outcome not reported in trial				
Non-pharmacological interventions					
Physical therapy: IMT vs. no intervention or sham treatment (Bradley 2002)	Outcome not reported in trial				
Nurse-led vs. doctor-led care (French 2003)	Number of admissions	80 (1)	RR 1.59 (0.75 to 3.39). Doctor-led = 42 admissions, nurse-led = 66 admissions. More than 1 admission per person	NSD	No evidence of benefit
ACTs vs. no treatment (Lee 2013)	Outcome not reported in trial				

Abbreviations: ACT: airway clearance technique; CI: confidence interval; HTS: hypertonic saline; ICS: inhaled corticosteroids; IMT: inspiratory muscle training; ITS: isotonic saline; LABA: long-acting beta$_2$-agonist; MD: mean difference; NSD: no significant difference; OR: odds ratio; RhDNase: recombinant human deoxyribonuclease I; RR: risk ratio; vs: versus.

Table 11. Outcomes in Cochrane reviews - mortality

Intervention/ comparison	Outcome	Number of participants (number of studies)	Results: treatment effect (95% CI) unless otherwise stated	Interpretation of result	Evaluation
Pharmacological interventions					

Table 11. Outcomes in Cochrane reviews - mortality (*Continued*)

Antibiotics (long term) vs. placebo (Evans 2007)	Deaths	128 (2, adults)	Peto OR 0.57 (0.07 to 4.54) 4 deaths	NSD	No evidence of harm
Antibiotics (short term) vs. placebo (Wurzel 2011)	Not an outcome in the review				
ICS vs. placebo/no treatment (Kapur 2009)	Outcome not reported in trial				
LABA/ICS combination vs. ICS (Goyal 2014)	Deaths	40 (1)	0 deaths	-	-
Inhaled hyperosmolar vs. placebo or ITS (Hart 2014)	*Mannitol vs. placebo*: Deaths	363 (1)	2 deaths in the mannitol group that were not treatment related	Unclear	Unclear
	Mannitol vs. nothing: Deaths	25 (2)	0 deaths	-	-
	HTS vs. ITS: Deaths	113 (4)	0 deaths	-	-
Mucolytics vs. placebo (Wilkinson 2014)	Outcome not reported in trials				
Non-pharmacological interventions					
Physical therapy: IMT vs. no intervention or sham treatment (Bradley 2002)	Not an outcome in the review				
Nurse-led vs. doctor-led care (French 2003)	Outcome not reported in trial				
ACTs vs. no treatment (Lee 2013)	Outcome not reported in trial				

Abbreviations: ACT: airway clearance technique; CI: confidence interval; HTS: hypertonic saline; ICS: inhaled corticosteroids; IMT: inspiratory muscle training; ITS: isotonic saline; LABA: long-acting $beta_2$-agonist; NSD: no significant difference; OR: odds ratio; vs: versus.

CONTRIBUTIONS OF AUTHORS

EJW - screening search, extracting data, conducting AMSTAR classification, drafting tables and results, drafting non-clinical sections of the discussion, co-ordinating team and process, editing review sections drafted by others.

SS - screening search, extracting data, conducting AMSTAR classification, drafting tables and results, editing review sections drafted by others.

DJE - contributing clinical expertise to team discussions, critical commenting on review drafts, drafting clinical sections of the discussion.

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DECLARATIONS OF INTEREST

Two of the overview authors are Editors with Cochrane Airways Group (EW, SS) and two overview authors are authors of included reviews (DE, SF).

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