ClinicalEvidence

Bronchiectasis

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Cecile Magis-Escurra and Monique H.E. Reijers

ABSTRACT

INTRODUCTION: Bronchiectasis is usually a complication of previous lower respiratory infection and/or inflammation. It causes chronic cough, copious production of sputum (often purulent), and recurrent infections, and may cause airway obstruction bearing some similarities with that seen in COPD. It may complicate respiratory conditions such as asthma or COPD. It can be associated with primary ciliary dyskinesia, primary immunodeficiencies, certain systemic diseases such as inflammatory bowel disease and rheumatoid arthritis, and foreign body inhalation. Bronchiectasis can be due to cystic fibrosis but this is excluded from this review. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of treatments in people with non-cystic fibrosis (non-CF) bronchiectasis? We searched: Medline, Embase, The Cochrane Library, and other important databases up to January 2014 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). We performed a GRADE evaluation of the quality of evidence for interventions. RESULTS: We found 23 studies that met our inclusion criteria. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: airway clearance techniques, corticosteroids (inhaled), exercise or physical training, hyperosmolar agents (inhaled), mucolytics, prolonged-use antibiotics, and surgery.

QUESTIONS

INTERVENTIONS

TREATING NON-CYSTIC FIBROSIS BRONCHIECTASIS

Key points

- Bronchiectasis is characterised by irreversible widening of medium to small-sized airways, with inflammation, chronic bacterial infection, and destruction of bronchial walls.

  Bronchiectasis is usually a complication of previous lower respiratory infection and/or inflammation, and causes chronic cough, production of copious sputum (often purulent), and recurrent infections. It may cause airway obstruction bearing some similarities with that seen in COPD.

  Bronchiectasis may complicate respiratory conditions such as asthma or COPD. It can be associated with primary ciliary dyskinesia, primary immunodeficiencies, certain systemic diseases such as inflammatory bowel disease and rheumatoid arthritis, and foreign body inhalation. Bronchiectasis can be due to cystic fibrosis but this is excluded from this review.

- Exercise or inspiratory muscle training may improve quality of life and exercise endurance in people with non-CF bronchiectasis.

- Prolonged-use antibiotics may reduce exacerbation rates and severity of symptoms (physician assessment of diary cards or of overall medical condition, sputum weight or volume).

  Prolonged-use antibiotics may also reduce some measures for infection (such as sputum bacterial density) compared with placebo, although this seems to vary depending on the antibiotic regimen used.

  We don't know whether prolonged-use antibiotics decrease mortality, hospital admission for exacerbations, and number of days off work compared with placebo. Inconsistent results have led to uncertainty on the effect of prolonged-use antibiotics on quality of life scores.

  Interpretation of studies concerning prolonged-use antibiotics and translation of results to individual patient care needs to be considered carefully. There may be a different pathogenesis for the condition and unknown co-existent use of other treatments, such as airway clearance techniques.

- We don't know whether airway clearance techniques, mucolytics, or inhaled hyperosmolar agents are beneficial, as we found few studies.

- We don't know whether inhaled corticosteroids are more effective than placebo at improving symptom scores at 6 months or at reducing exacerbations.

- Surgery is often considered for people with extreme damage to one or two lobes of the lung who are at risk of recurrent infection or bleeding, but we found no good-quality trials.

Clinical context

DEFINITION

Bronchiectasis is defined as irreversible widening of medium to small-sized airways (bronchi) in the lung. It is characterised by inflammation, destruction of bronchial walls, and frequent colonisation with bacteria. The condition may be limited to a single lobe or lung segment, or it may affect one or both lungs more diffusely. Clinically, the condition manifests as chronic cough and chronic overproduction of sputum, which is often purulent. [1] People with severe bronchiectasis may have life-threatening haemoptysis, and may develop features of chronic obstructive airway disease, such as wheezing, chronic respiratory failure, pulmonary hypertension, and right-sided heart failure.

INCIDENCE/ PREVALENCE

We found few reliable data. Overall, over the past 50 years, incidence has declined. However, one study, using data from 640 GP practices in the UK, found that the incidence of people given a diagnosis of bronchiectasis increased over time (18 per 100,000 person-years at risk in 2004; 32 per 100,000 person-years at risk in 2011). [2] Over an 8-year period, 0.7% of patients (27,258 people) had been given a diagnostic code for bronchiectasis, and prevalence increased over time. [2] Prevalence is generally low in higher-income countries, but much higher in lower-income countries, where bronchiectasis is a major cause of morbidity and mortality.

AETIOLOGY/ RISK FACTORS

Bronchiectasis is most commonly a long-term complication of previous lower respiratory infections, such as pneumonia (especially with measles, *Bordetella pertussis*, and *Mycobacterium tuberculosis* complex). Foreign-body inhalation and allergic, autoimmune (for instance, associated with rheumatoid arthritis or ulcerative colitis), and chemical lung damage also predispose to the condition. [3] Underlying congenital disorders such as cystic fibrosis, cilial dysmotility syndromes, alpha$_1$ antitrypsin deficiency, and congenital immunodeficiencies may also predispose to bronchiectasis, and may be of greater aetiological importance in higher-income countries than respiratory infection. Cystic fibrosis is the most common congenital cause (excluded from this review).

PROGNOSIS

Bronchiectasis is a chronic condition, with frequent relapses of varying severity. Long-term prognosis is variable. Data on morbidity and mortality are still sparse. [4] One study reported retrospective data exploring the factors influencing survival. [5] It found lung function characteristics and chronic *Pseudomonas* infection may be associated with mortality. The more recently published FACED score and BSI index (published later than our search for this update) confirm these findings and provide a more detailed scoring system for morbidity and mortality. [6] [7] Bronchiectasis frequently co-exists with other respiratory disease, making it difficult to distinguish prognosis for bronchiectasis alone.

AIMS OF INTERVENTION

To alleviate symptoms; to reduce morbidity and mortality, with minimal adverse effects of treatment.

OUTCOMES

Mortality, **infection rates**, **exacerbation rates**, **symptom severity** (including sputum volume, cough, expectoration rates, haemoptysis), **functional improvement** (including lung function and exercise tolerance), **hospital admission**, **days off work**, **quality of life**, **adverse effects**.

METHODS

Clinical Evidence search and appraisal January 2014. The following databases were used to identify studies for this systematic review: Medline 1966 to January 2014, Embase 1980 to January 2014, and The Cochrane Database of Systematic Reviews 2013, issue 12 (1966 to date of issue). Additional searches were carried out in the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. Titles and abstracts identified by the initial search, run by an information specialist, were first assessed against predefined criteria by an evidence scanner. Full texts for potentially relevant studies were then assessed against predefined criteria by an evidence analyst. Studies selected for inclusion were discussed with an expert contributor. All data relevant to the review were then extracted by an evidence analyst. Study design criteria for inclusion in this review were: published RCTs and systematic reviews of RCTs in the English language, containing 20 or more individuals (10 in each arm), of whom more than 80% were followed up. There was no minimum length of follow-up. Open studies were included. We included RCTs and systematic reviews of RCTs where harms of an included intervention were assessed, applying the same study design criteria for inclusion as we did for benefits. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a

GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 38). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of treatments in people with non-cystic fibrosis (non-CF) bronchiectasis?**

OPTION **AIRWAY CLEARANCE TECHNIQUES**

- For GRADE evaluation of interventions for Bronchiectasis, see table, p 38 .
- We have included the following as airway clearance techniques: tappotage (chest tapping), chest drainage, postural drainage, bronchopulmonary hygiene vibration, and mucociliary clearance.
- We don't know whether airway clearance techniques are beneficial, as we found insufficient evidence to draw firm conclusions.

Benefits and harms

Airway clearance techniques versus no airway clearance techniques:

We found two systematic reviews (search dates 2011; [8] and 2012 [9]). The first review identified no RCTs that met the inclusion criteria for this review. [8] The second review [9] included one small crossover RCT. [10] We have reported the RCT direct from its original report. [10]

Symptom severity

Airway clearance technique compared with no airway clearance technique Airway clearance using an oscillatory positive expiratory pressure device may be more effective at improving measures of symptom severity (Leicester Cough Questionnaire, 24-hour sputum production) at 3 months, but evidence is weak (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[10] RCT **Crossover design**	20 people In review [9]	**Median change in Leicester Cough Questionnaire (LCQ) score , 3 months** +1.3 units with twice-daily airway clearance using an oscillatory positive expiratory pressure device 0 units with no airway clearance The RCT reported that, since the end of the study, a 1.3-unit difference in LCQ score has been established as a clinically significant change	P = 0.002	○○○	airway clearance
[10] RCT **Crossover design**	20 people In review [9]	**Change in 24-hour sputum volume , 3 months** +2 mL with twice-daily airway clearance using an oscillatory positive expiratory pressure device –1 mL with no airway clearance	P = 0.02	○○○	airway clearance

Functional improvement

Airway clearance technique compared with no airway clearance technique Airway clearance using an oscillatory positive expiratory pressure device may be more effective at increasing shuttle walk test scores at 3 months, but evidence is weak (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Lung function					
[10] RCT **Crossover design**	20 people In review [9]	**Change in incremental shuttle walk test , 3 months** +40 m with twice daily airway clearance using an oscillatory positive expiratory pressure device 0 m with no airway clearance The RCT reported no significant differences in other measures of functional improvement (FEV_1, FEF 25%–75%, maximum inspiratory pressure [MIP], or maximum expiratory pressure [MEP])	P = 0.001	○○○	airway clearance

Quality of life

Airway clearance technique compared with no airway clearance technique Airway clearance using an oscillatory positive expiratory pressure device may be more effective at increasing quality of life as measured by St George's Respiratory Questionnaire, but evidence is weak (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[10] RCT **Crossover design**	20 people In review [9]	**Change in St George's Respiratory Questionnaire (SGRQ) , 3 months** +7.8 with twice daily airway clearance using an oscillatory positive expiratory pressure device –0.7 with no airway clearance	P = 0.005	○○○	airway clearance

Mortality

No data from the following reference on this outcome. [10]

Infection rates

No data from the following reference on this outcome. [10]

Exacerbation rates

No data from the following reference on this outcome. [10]

Hospital admission

No data from the following reference on this outcome. [10]

Days off work

No data from the following reference on this outcome. [10]

Adverse effects

No data from the following reference on this outcome. [10]

Further information on studies

[9] The review included five RCTs on airway clearance techniques, one of which [10] we have reported (20 people). The other four RCTs were below the minimum RCT size for this *Clinical Evidence* review. The review noted that the RCT had no information on blinding or allocation concealment, and was at high risk of selective reporting (reporting bias).

Comment: **Clinical guide:**
There is insufficient evidence to support or refute administration of airway clearance techniques in patients with stable non-CF bronchiectasis.

Given the heterogeneous pathogenesis of bronchiectasis and the physiology of airway clearance, it is likely that a positive outcome in an RCT is only measured in cases of personalised airway clearance techniques. For the clinician, however, airway clearance techniques are a cornerstone for the treatment of patients with non-CF bronchiectasis.

OPTION CORTICOSTEROIDS (INHALED)

- For GRADE evaluation of interventions for Bronchiectasis, see table, p 38 .
- We don't know whether inhaled corticosteroids are more effective than placebo at improving symptom scores at 6 months or at reducing exacerbations.
- Inhaled corticosteroid use may be associated with a modest improvement in FEV_1 or FVC compared with placebo, but the evidence for this is inconsistent.
- We don’t know whether inhaled corticosteroids are more effective than placebo at reducing hospital admissions, mean length of hospital stay, or improvement in quality of life in people with non-CF bronchiectasis.
- Expert opinion does not recommend inhaled corticosteroids routinely.

Benefits and harms

Inhaled corticosteroids versus placebo:

We found one systematic review (search date 2010), [11] which identified six RCTs in people with non-cystic fibrosis bronchiectasis. We found one subsequent RCT. [12]

Exacerbation rates

Inhaled corticosteroids compared with placebo Inhaled corticosteroids may be no more effective than placebo or no corticosteroid at decreasing exacerbations in people with non-CF bronchiectasis (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Exacerbation rates					
[11] Systematic review	57 people Data from 1 RCT	**Average (mean) number of exacerbations per participant , 6 months or less** 1.4 with inhaled fluticasone 1.3 with no corticosteroid	Mean difference +0.09 95% CI –0.61 to +0.79 P = 0.80 RCT unblinded	⟷	Not significant
[11] Systematic review	86 people Data from 1 RCT	**Average (mean) number of exacerbations , above 6 months** 2.2 with inhaled fluticasone 2.7 with placebo	Mean difference –0.49 95% CI –1.49 to +0.51	⟷	Not significant
[12] RCT	77 adults with bronchiectasis	**Proportion of people with exacerbations , 6 months** 48.7% with inhaled budesonide 57.6% with placebo Results based on 70 people	Reported as not significant P value not reported	⟷	Not significant

Symptom severity

Inhaled corticosteroids compared with placebo We don't know whether inhaled corticosteroids are more effective than placebo at improving symptom scores at 6 months in people with non-CF bronchiectasis; we found weak evidence with inconsistent results (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[11] Systematic review	People with bronchiectasis Data from 1 RCT RCT was a 3-armed trial	**Proportion of people with no improvement in dyspnoea (>1, minimum important difference) , 6 months or less** 12/31 (39%) with inhaled fluticasone 21/31 (68%) with no corticosteroid 62 people in this analysis	OR 0.30 95% CI 0.11 to 0.85 RCT unblinded	●●○	fluticasone
[11] Systematic review	People with bronchiectasis Data from 1 RCT RCT was a 3-armed trial	**Daily sputum production (mean) , 6 months or less** 12.4 mL with inhaled fluticasone 20.7 mL with no corticosteroid Absolute results not reported 57 people in this analysis	Difference –8.3 mL 95% CI –16.55 mL to –0.05 mL RCT unblinded	○○○	fluticasone
[11] Systematic review	People with bronchiectasis Data from 1 RCT RCT was a 3-armed trial	**Proportion of people without sputum reduction of above 50% , 6 months or less** 17/31 (55%) with inhaled fluticasone 28/31 (90%) with no corticosteroid	OR 0.13 95% CI 0.03 to 0.52 RCT unblinded	●●●	fluticasone
[11] Systematic review	86 people Data from 1 RCT	**Sputum purulence score , 1 year** 5.7 with inhaled fluticasone 5.5 with placebo	Mean difference +0.2 95% CI –0.94 to +1.34	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[12] RCT	77 adults with bronchiectasis	**Change in total symptom score (scale 0–3) , 6 months** –0.70 with inhaled budesonide –0.18 with placebo Results based on 70 people	Reported as not significant P value not reported	⟷	Not significant

Functional improvement

Inhaled corticosteroids compared with placebo Inhaled corticosteroids may be modestly more effective than placebo or no corticosteroid at improving lung function (measured by FEV_1 or FVC) in people with non-cystic fibrosis bronchiectasis, but evidence was inconsistent, and we don't know whether they are more effective at increasing PFR (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Functional improvement					
[11] Systematic review	101 people 3 RCTs in this analysis	**FEV_1 , 6 months or less** with inhaled corticosteroid with placebo or no treatment Absolute numbers not reported	Mean difference 0.09 L 95% CI 0.03 L to 0.15 L P = 0.0024 See Further information on studies	○○○	inhaled corticosteroid
[11] Systematic review	101 people 3 RCTs in this analysis	**FVC , 6 months or less** with inhaled corticosteroid with placebo or no treatment Absolute numbers not reported	Mean difference 0.09 L 95% CI 0.02 L to 0.16 L P = 0.0078 See Further information on studies	○○○	inhaled corticosteroid
[11] Systematic review	44 people 2 RCTs in this analysis	**PFR , 6 months or less** with inhaled corticosteroid with placebo	Mean difference +26.23 L 95% CI –5.84 L to +58.31 L P = 0.11	⟷	Not significant
[12] RCT	77 adults with bronchiectasis	**FVC difference (initial to final) , 6 months** –1.9% with inhaled budesonide –2.8% with placebo Results based on 70 people	Reported as not significant P value not reported	⟷	Not significant
[12] RCT	77 adults with bronchiectasis	**FEV1 difference (initial to final) , 6 months** –1.90 with inhaled budesonide –3.96 with placebo Results based on 70 people	Reported as not significant P value not reported	⟷	Not significant

Mortality

No data from the following reference on this outcome. [11] [12]

Infection rates

No data from the following reference on this outcome. [11] [12]

Hospital admission

Inhaled corticosteroids compared with placebo We don't know whether inhaled corticosteroids are more effective than placebo at reducing hospital admissions or mean length of hospital stay in people with non-cystic fibrosis bronchiectasis (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Hospital admission					
[12] RCT	77 adults with bronchiectasis	**Hospital admission , 6 months** 2.7% with inhaled budesonide 12% with placebo Absolute numbers not reported Results based on 70 people	Reported as not significant P value not reported	⟷	Not significant
[12] RCT	77 adults with bronchiectasis	**Mean hospital stay , 6 months** 0.27 days with inhaled budesonide 2.18 days with placebo Results based on 70 people	Reported as not significant P value not reported	⟷	Not significant

No data from the following reference on this outcome. [11]

Days off work

No data from the following reference on this outcome. [11] [12]

Quality of life

Inhaled corticosteroids compared with placebo We don't know whether inhaled corticosteroids are more effective than placebo at improving quality of life scores in people with non-cystic fibrosis bronchiectasis (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[12] RCT	77 adults with bronchiectasis	**Change in St George's Respiratory Questionnaire (initial – final) , 6 months** –0.56 with inhaled budesonide –3.78 with placebo Results based on 70 people	Reported as not significant P value not reported	⟷	Not significant

No data from the following reference on this outcome. [11]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[11] Systematic review	People with bronchiectasis	**Adverse events** with inhaled corticosteroids Absolute numbers not reported The review stated that use of high-dose inhaled corticosteroids is associated with adverse events in children and adults that range from mild (candidiasis) to serious (e.g., adrenal insufficiency, osteoporosis, cataracts); it reported that 1 RCT noted that dry mouth, local irritation, and transient dysphonia were the most common adverse effects (further details not reported)	Significance not assessed		

Inhaled corticosteroids versus other treatments:

We found no RCTs comparing inhaled corticosteroids versus other treatments.

Further information on studies

[11] Methods: the review noted that allocation concealment was unclear in all six RCTs; there were significant baseline differences in one RCT (24 people), and another RCT did not report on withdrawals or dropouts (20 people). The same RCT only included people who had a significant post-bronchodilator response, which biased the study in favour of corticosteroids. It also included one three-armed RCT (93 people) using two different doses of inhaled steroids versus no treatment, and only used data from the arm using the higher dosage. All the other RCTs were double-blinded, but this RCT was unblinded for the comparison of inhaled corticosteroid versus no inhaled corticosteroid.

[11] Sensitivity analysis: the review performed a sensitivity analysis excluding the study with a poor-quality score (no placebo), which altered the results for FEV_1 and FVC from being significant to non-significant between inhaled corticosteroids and control groups.

Comment:

Clinical guide:

There is no evidence of a clear positive clinical effect. In clinical practice, an individual therapeutic trial may be warranted in those patients with difficult-to-control symptoms. Expert opinion does not recommend inhaled corticosteroids routinely. [13] Any beneficial effect needs to be balanced against the potential for adverse effects, particularly if high doses are used.

In addition, the occurrence of non-tuberculous mycobacterial (NTM) infections in non-CF patients is increasing with the use of corticosteroids. [14]

OPTION EXERCISE OR PHYSICAL TRAINING

- For GRADE evaluation of interventions for Bronchiectasis, see table, p 38 .
- Exercise or inspiratory muscle training may improve quality of life and exercise endurance in people with non-CF bronchiectasis.
- Adding pulmonary rehabilitation to usual chest physiotherapy may improve quality of life, symptom severity scores (measured by Leicester Cough Questionnaire), and exercise endurance. However, evidence is weak and lung function is not improved.

Benefits and harms

Exercise versus no intervention/sham intervention:

We found one systematic review on inspiratory muscle training (search date 2005, 2 RCTs). [15] We found one subsequent RCT, which compared pulmonary rehabilitation plus chest physiotherapy with no pulmonary rehabilitation plus chest physiotherapy alone. [16] Pulmonary rehabilitation included training with three different cardiovascular equipments, education about chest clearance, self-management plans, and inhaler technique checks over 8 weeks, and chest physiotherapy was given to both groups twice-daily for 8 weeks.

Functional improvement

Exercise compared with no intervention/sham intervention Inspiratory muscle training or inspiratory muscle training plus pulmonary rehabilitation may be more effective than no intervention or sham inspiratory muscle training plus pulmonary rehabilitation at improving exercise endurance at 8 weeks in people with non-CF bronchiectasis. Pulmonary rehabilitation plus usual chest physiotherapy may be more effective than usual chest physiotherapy alone at improving exercise endurance (measured by incremental shuttle and endurance walk tests) at 20 weeks, but not lung function (measured by FEV_1 and FVC). However, evidence was weak, and we found no RCTs directly comparing inspiratory muscle training or pulmonary rehabilitation with placebo or no treatment alone (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Exercise endurance					
[15] Systematic review	43 people 2 RCTs in this analysis	**Exercise endurance (method of assessment not described) , 8 weeks** with inspiratory muscle training (IMT) or IMT plus pulmonary rehabilitation with no treatment or sham IMT plus pulmonary rehabilitation Absolute results not reported	WMD 264 m 95% CI 16.4 m to 512 m	○○○	IMT or IMT plus pulmonary rehabilitation
[16] RCT	30 people with bronchiectasis and limited exercise tolerance	**Incremental shuttle walk test , from baseline to 20 weeks** 287.5 to 367.5 m with pulmonary rehabilitation plus usual chest physiotherapy 343.3 to 343.3 m with usual chest physiotherapy only Results based on 27 people	P = 0.04 The RCT also found a significant difference between groups at 8 weeks (P = 0.03) See Further information on studies	○○○	pulmonary rehabilitation plus chest physiotherapy
[16] RCT	30 people with bronchiectasis and limited exercise tolerance	**Endurance walk test , from baseline to 20 weeks** 1102.5 to 1350.0 m with pulmonary rehabilitation plus usual chest physiotherapy 1021.4 to 964.3 m with usual chest physiotherapy only Results based on 27 people	P = 0.003 The RCT also found a significant difference between groups at 8 weeks (P = 0.01) See Further information on studies	○○○	pulmonary rehabilitation plus chest physiotherapy
[16] RCT	30 people with bronchiectasis and limited exercise tolerance	**FEV_1 (L) , from baseline to 20 weeks** 1.9 to 2.1 with pulmonary rehabilitation plus usual chest physiotherapy 1.9 to 1.9 with usual chest physiotherapy only Results based on 27 people	Reported as no significant difference between groups P value not reported See Further information on studies	⟷	Not significant
[16] RCT	30 people with bronchiectasis and limited exercise tolerance	**FVC (L) , from baseline to 20 weeks** 2.9 to 2.9 with pulmonary rehabilitation for 8 weeks plus usual chest physiotherapy	Reported as no significant difference between groups P value not reported See Further information on studies	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		2.7 to 2.8 with usual chest physiotherapy only Results based on 27 people			

Quality of life

Exercise compared with no intervention/sham intervention Inspiratory muscle training or inspiratory muscle training plus pulmonary rehabilitation may be more effective than no intervention or sham inspiratory muscle training plus pulmonary rehabilitation at improving quality of life at 8 weeks in people with non-CF bronchiectasis. Pulmonary rehabilitation plus usual chest physiotherapy may be more effective than usual chest physiotherapy alone at improving quality of life scores (measured by St George's Respiratory Questionnaire) at 20 weeks. However, evidence was weak, and we found no RCTs directly comparing inspiratory muscle training or pulmonary rehabilitation with placebo or no treatment alone (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[15] Systematic review	43 people 2 RCTs in this analysis	**Quality of life (measured on Chronic Respiratory Disease Questionnaire scale) , 8 weeks** with inspiratory muscle training (IMT) or IMT plus pulmonary rehabilitation with no treatment or sham IMT plus pulmonary rehabilitation Absolute results not reported	WMD 12.4 95% CI 2.38 to 22.48	○○○	IMT or IMT plus pulmonary rehabilitation
[16] RCT	30 people with bronchiectasis and limited exercise tolerance	**Quality of life (St George's Respiratory Questionnaire) , from baseline to 8 weeks** 38.6 to 30.6 with pulmonary rehabilitation plus usual chest physiotherapy 40.6 to 39.2 with usual chest physiotherapy only Results based on 27 people	P <0.001 See Further information on studies	○○○	pulmonary rehabilitation plus chest physiotherapy
[16] RCT	30 people with bronchiectasis and limited exercise tolerance	**Quality of life (St George's Respiratory Questionnaire) , from baseline to 20 weeks** 38.6 to 34.6 with pulmonary rehabilitation plus usual chest physiotherapy 40.6 to 45.2 with usual chest physiotherapy only Results based on 27 people	P <0.001 See Further information on studies	○○○	pulmonary rehabilitation plus chest physiotherapy

Mortality

No data from the following reference on this outcome. [15] [16]

Infection rates

No data from the following reference on this outcome. [15] [16]

Exacerbation rates

No data from the following reference on this outcome. [15] [16]

Symptom severity

Exercise compared with no intervention/sham intervention Pulmonary rehabilitation plus usual chest physiotherapy may be more effective than usual chest physiotherapy alone at improving symptom severity scores (measured by Leicester Cough Questionnaire) at 20 weeks. However, evidence was weak, and we found no RCTs directly comparing pulmonary rehabilitation with placebo or no treatment alone (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[16] RCT	30 people with bronchiectasis and limited exercise tolerance	**Leicester Cough Questionnaire, from baseline to 8 weeks** 12.3 to 14.9 with pulmonary rehabilitation plus usual chest physiotherapy 14.4 to 14.6 with usual chest physiotherapy only Results based on 27 people	P <0.001 See Further information on studies	○○○	pulmonary rehabilitation plus chest physiotherapy
[16] RCT	30 people with bronchiectasis and limited exercise tolerance	**Leicester Cough Questionnaire, from baseline to 20 weeks** 12.3 to 16.7 with pulmonary rehabilitation plus usual chest physiotherapy 14.4 to 13.6 with usual chest physiotherapy only Results based on 27 people	P <0.001 See Further information on studies	○○○	pulmonary rehabilitation plus chest physiotherapy

No data from the following reference on this outcome. [15]

Hospital admission

No data from the following reference on this outcome. [15] [16]

Days off work

No data from the following reference on this outcome. [15] [16]

Adverse effects

No data from the following reference on this outcome. [15] [16]

Further information on studies

[16] Three people were excluded from the analysis in the pulmonary rehabilitation group (2 with bereavements, 1 diagnosed with a terminal disease). The RCT did not report an intention to treat analysis. Although there were no statistical differences between groups at baseline, absolute baseline shuttle walk test values differed between groups (baseline: 287 m with pulmonary rehabilitation *v* 343 m with physiotherapy alone). It was unclear what level of blinding of outcome assessment was employed. The RCT reported that people in the intervention group also received free gymnasium membership for 6 months, although the uptake of this was not recorded.

Comment: None.

OPTION HYPEROSMOLAR AGENTS (INHALED)

- For GRADE evaluation of interventions for Bronchiectasis, see table, p 38 .
- We don't know whether inhaled mannitol is more effective than placebo at reducing pulmonary exacerbations or mortality, or at improving severity of symptoms, functional status, or quality of life at 12 weeks in people with non-CF bronchiectasis, as we found insufficient evidence.
- We don't know whether other inhaled hyperosmolar agents (normal saline, hypertonic saline, saline with hyaluronic acid) are beneficial, as we found no direct information from RCTs.

Benefits and harms

Hyperosmolar agents (inhaled) versus placebo:

We found one systematic review (search date 2010), which identified no high-quality RCTs. [17] We found one subsequent RCT, which compared inhaled mannitol versus placebo administered by a dry powder device over a 12-week period (see Further information on studies). [18]

Mortality

Hyperosmolar agents compared with placebo We don't know whether inhaled mannitol is more effective than placebo at reducing mortality in people with non-CF bronchiectasis, as we found insufficient evidence (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[18] RCT	362 adults (age range 18–79 years) with bronchiectasis, clinically stable for 2 or more weeks prior to study entry, and persistent cough present for the majority of days during 3 months prior to enrolment, chronic sputum production, and chronic chest congestion	**Mortality , 12 weeks** 2/231 (1%) with mannitol administered via dry powder device twice a day 0/112 (0%) with placebo	P value not reported The RCT reported that 2 deaths occurred in the mannitol group but that neither was thought to be related to study treatment (further details not reported)		

Exacerbation rates

Hyperosmolar agents compared with placebo We don't know whether inhaled mannitol is more effective than placebo at reducing pulmonary exacerbations at 12 weeks, as we found insufficient evidence (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Exacerbation rates					
[18] RCT	362 adults (age range 18–79 years) with bronchiectasis, clinically stable for 2 or more weeks prior to study entry, and persistent cough present for the majority of days during 3 months prior to enrolment, chronic sputum production, and chronic chest congestion	**Protocol-defined pulmonary exacerbations , 12 weeks** 27/231 (12%) with mannitol administered via dry powder device twice a day 11/112 (10%) with placebo	Reported as 'similar' P value not reported		

Symptom severity

Hyperosmolar agents compared with placebo We don't know whether inhaled mannitol is more effective than placebo at improving symptom severity (as measured by Bronchiectasis Symptoms Questionnaire and Leicester Cough Questionnaire) at 12 weeks, as we found insufficient evidence, but it may be less effective than placebo at reducing mean sputum weight over 24 hours (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[18] RCT	362 adults (age range 18–79 years) with bronchiectasis, clinically stable for 2 weeks or more prior to study entry, and persistent cough present for the majority of days during 3 months prior to enrolment, chronic sputum production, and chronic chest congestion	**Bronchiectasis Symptoms Questionnaire (BSQ) (a study-specific questionnaire) , 12 weeks** with mannitol administered via dry powder device twice a day with placebo Absolute results not reported	Reported as no significant difference between groups P value not reported		
[18] RCT	362 adults (age range 18–79 years) with bronchiectasis, clinically stable for 2 or more weeks prior to study entry, and persistent cough present for the majority of days during 3 months prior to enrolment, chronic sputum production, and chronic chest congestion	**Leicester Cough Questionnaire** with mannitol administered via dry powder device twice a day with placebo Absolute results not reported	Reported as no significant difference between groups P value not reported		
[18] RCT	362 adults (age range 18–79 years) with bronchiectasis, clinically stable for 2 or more weeks prior to study entry, and persistent	**Change in sputum weight (24 hour), mean , 12 weeks** –0.93 g with mannitol administered via dry powder device twice a day –5.25 g with placebo	Difference 4.3 g 95% CI 1.64 g to 7.00 g P = 0.02	○○○	placebo

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	cough present for the majority of days during 3 months prior to enrolment, chronic sputum production, and chronic chest congestion				

Functional improvement

Hyperosmolar agents compared with placebo We don't know whether inhaled mannitol is more effective than placebo at improving exercise endurance (as measured by shuttle walk test) at 12 weeks, as we found insufficient evidence (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Exercise endurance					
[18] RCT	362 adults (age range 18–79 years) with bronchiectasis, clinically stable for 2 or more weeks prior to study entry, and persistent cough present for the majority of days during 3 months prior to enrolment, chronic sputum production, and chronic chest congestion	**Shuttle walk test , 12 weeks** with mannitol administered via dry powder device twice a day with placebo Absolute results not reported	Reported as no significant difference between groups P value not reported		

Quality of life

Hyperosmolar agents compared with placebo We don't know whether inhaled mannitol is more effective than placebo at improving quality of life scores (as measured by St George's Respiratory Questionnaire) as we found insufficient evidence (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[18] RCT	362 adults (age range 18–79 years) with bronchiectasis, clinically stable for 2 or more weeks prior to study entry, and persistent cough present for the majority of days during 3 months prior to enrolment, chronic sputum production, and chronic chest congestion	**Change in St George's Respiratory Questionnaire , at week 12** –3.37 with mannitol administered via dry powder device twice a day –2.11 with placebo	Difference –1.27 95% CI –3.69 to +1.15 P = 0.304	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[18] RCT	362 adults (age range 18–79 years) with bronchiectasis, clinically stable for 2 or more weeks prior to study entry, and persistent cough present for the majority of days during 3 months prior to enrolment, chronic sputum production, and chronic chest congestion	**Proportion of people experiencing adverse events (any)** 82.0% with mannitol administered via dry powder device twice a day 80.4% with placebo	Reported as 'similar' P value not reported		
[18] RCT	362 adults (age range 18–79 years) with bronchiectasis, clinically stable for 2 or more weeks prior to study entry, and persistent cough present for the majority of days during 3 months prior to enrolment, chronic sputum production, and chronic chest congestion	**Proportion of people experiencing at least one serious adverse event** 4.3% with mannitol administered via dry powder device twice a day 5.4% with placebo	Reported as 'similar' P value not reported The RCT reported that no events were related to treatment (further details not reported)		
[18] RCT	362 adults (age range 18–79 years) with bronchiectasis, clinically stable for 2 or more weeks prior to study entry, and persistent cough present for the majority of days during 3 months prior to enrolment, chronic sputum production, and chronic chest congestion	**Proportion of people discontinuing treatment because of adverse events** 11% with mannitol administered via dry powder device twice a day 6% with placebo	P value not reported		

Further information on studies

[18] The double-blinded RCT did not state the method of randomisation or allocation concealment. It had a 12-week intervention phase, which we have reported, and a further open-labelled extension phase, which we have not reported here. At baseline, participants underwent mannitol provocation and lung function testing. Of 80 withdrawals before randomisation, 71 people had a positive airway challenge, as did 2 further people in the placebo group after randomisation, who also withdrew. Results were based on 343/362 (95%) people initially randomised. The RCT found significantly increased antibiotic usage in the placebo group compared with the mannitol group during the first 6 weeks (P = 0.046), but no significant difference between groups at 12 weeks (P = 0.195). The RCT noted that the study sponsor participated in the study design, data collection, analysis, interpretation, and writing of the report.

Comment: We found one further RCT (40 people with non-CF-bronchiectasis) comparing daily inhaled hypertonic saline (6%) with isotonic saline (0.9%). [19] This study was outside our inclusion criteria because the comparison was not one of the other listed interventions in this review, placebo or no treatment. We have, therefore, not extracted data, but include a comment here for interest. The RCT found that inhalation of hypertonic saline (6%) or isotonic saline (0.9%) had similar effects on exacerbations, quality of life, sputum colonisation, and respiratory function over 12 months in people with non-CF-bronchiectasis.

Clinical guide:
The objective of hyperosmolar inhalation treatment is to accelerate tracheobronchial mucociliary clearance, potentially by inducing a liquid flux into the airway surface. This approach differs conceptually from the use of mucolytics, which break down the mucus, making it less viscous and easier to cough up.

OPTION MUCOLYTICS

- For GRADE evaluation of interventions for Bronchiectasis, see table, p 38 .
- We don't know whether mucolytics are beneficial, as we found few studies.

Benefits and harms

Bromhexine versus placebo:

We found one systematic review in people with non-cystic fibrosis bronchiectasis (search date 2010, 1 double-blind RCT). [20]

Symptom severity

Bromhexine compared with placebo Bromhexine may be more effective at reducing sputum volume at about 2 weeks and may also improve symptom scores (difficulty with expectoration, cough, and quality of sputum) at about 2 weeks, although the clinical importance of these score changes is uncertain (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[20] Systematic review	45 people with acute exacerbation of bronchiectasis (defined as morning cough and >20 mL sputum) Data from 1 RCT	**Sputum volume , after about 2 weeks** with bromhexine with placebo Absolute results not reported	WMD –21.5% 95% CI –38.9% to –4.1%	○○○	bromhexine
[20] Systematic review	45 people with acute exacerbation of bronchiectasis (defined as morning cough and >20 mL sputum) Data from 1 RCT	**Symptom score 'quality of sputum' , at day 13** with bromhexine with placebo Absolute results not reported The clinical importance of these score changes is uncertain	WMD –0.45 95% CI –0.87 to –0.034	○○○	bromhexine
[20] Systematic review	45 people with acute exacerbation of bronchiectasis (defined as morning cough and >20 mL sputum) Data from 1 RCT	**Symptom score 'difficulty with expectoration' , at day 10** with bromhexine with placebo Absolute results not reported	WMD –0.45 95% CI –0.89 to –0.03	○○○	bromhexine
[20] Systematic review	45 people with acute exacerbation of bronchiectasis (defined as morning cough and >20 mL sputum) Data from 1 RCT	**Symptom score 'cough score' , at day 13** with bromhexine with placebo Absolute results not reported	WMD –0.48 95% CI –0.89 to –0.06	○○○	bromhexine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		The clinical importance of these score changes is uncertain			

Mortality

No data from the following reference on this outcome. [20]

Infection rates

No data from the following reference on this outcome. [20]

Exacerbation rates

No data from the following reference on this outcome. [20]

Functional improvement

No data from the following reference on this outcome. [20]

Hospital admission

No data from the following reference on this outcome. [20]

Days off work

No data from the following reference on this outcome. [20]

Quality of life

No data from the following reference on this outcome. [20]

Adverse effects

No data from the following reference on this outcome. [20]

Recombinant human deoxyribonuclease (rhDNase) versus placebo:

We found one systematic review in people with non-cystic fibrosis bronchiectasis (search date 2006), which found two double-blind RCTs comparing rhDNase aerosol versus placebo. [20]

Infection rates

Recombinant human deoxyribonuclease (rhDNase) compared with placebo We don't know whether recombinant human deoxyribonuclease is more effective at decreasing infection rates in people with non-cystic fibrosis bronchiectasis (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Infection rates					
[20] Systematic review	42 people Data from 1 RCT	**Infection rates** 0/21 (0%) with rhDNase 4/21 (19%) with placebo	P >0.1	⟷	Not significant

No data from the following reference on this outcome. [21]

Exacerbation rates

Recombinant human deoxyribonuclease (rhDNase) compared with placebo Recombinant human deoxyribonuclease seems no more effective than placebo at decreasing rates of exacerbation in people with non-cystic fibrosis bronchiectasis (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Exacerbation rates					
[21] RCT	349 people In review [20]	**AR for exacerbation , 168 days** 0.66 with rhDNase 0.56 with placebo Absolute results not reported	RR 1.17 95% CI 0.85 to 1.65	⟷	Not significant

Functional improvement

Recombinant human deoxyribonuclease (rhDNase) compared with placebo We don't know whether recombinant human deoxyribonuclease is more effective than placebo at improving lung function in people with non-cystic fibrosis bronchiectasis (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Lung function					
[20] Systematic review	42 people Data from 1 RCT	**Lung function** with rhDNase with placebo Absolute results not reported	Reported as not significant	⟷	Not significant

No data from the following reference on this outcome. [21]

Mortality

No data from the following reference on this outcome. [20] [21]

Symptom severity

No data from the following reference on this outcome. [20] [21]

Hospital admission

No data from the following reference on this outcome. [20] [21]

Days off work

No data from the following reference on this outcome. [20] [21]

Quality of life

No data from the following reference on this outcome. [20] [21]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[20] Systematic review	People with bronchiectasis Data from 1 RCT	**Influenza-type symptoms** 4 people with rhDNase 0 people with placebo	Significance not assessed		

Mucolytics versus other treatments:
We found no RCTs.

Comment: **Clinical guide:**
There is little evidence to recommend mucolytics in stable bronchiectasis. During an exacerbation, some beneficial effects have been demonstrated after 2 weeks' treatment with bromhexine.

OPTION PROLONGED-USE ANTIBIOTICS

- For GRADE evaluation of interventions for Bronchiectasis, see table, p 38 .
- Prolonged-use antibiotics in this instance refers to antibiotics taken for 4 weeks or more. We have included various different antibiotics, including different classes and routes of administration, and where available have reported on any meta-analyses of trials using individual antibiotic regimens grouped together as 'prolonged antibiotics'. However, it should be noted that combining data on macrolides with inhaled antibiotics may be problematic, due

to the other specific anti-inflammatory properties attributed to macrolides in particular, as well as their antibacterial effects (see Comments).

- We don't know whether prolonged-use antibiotics decrease mortality, hospital admission for exacerbations, and number of days off work compared with placebo.
- Prolonged-use antibiotics may reduce exacerbation rates and severity of symptoms (measured by physician assessment of diary cards or of overall medical condition, or sputum weight or volume) compared with placebo. They may also reduce some outcome measures for infection (such as sputum bacterial density) compared with placebo, although this seems to vary depending on the antibiotic regimen used.
- Prolonged-use antibiotics seem to be equally effective as placebo at improving functional status at 4 to 52 weeks. Inconsistent results from trials measuring quality of life scores have led to uncertainty over the effect of prolonged-use antibiotics compared with placebo on quality of life.

Benefits and harms

Prolonged-use antibiotics versus placebo:

We found one systematic review (search date 2011, 9 RCTs, 378 people) [22] and one additional RCT comparing prolonged-use antibiotics with placebo or as-required treatment, [23] as well as seven subsequent RCTs. [24] [25] [26] [27] [28] [29] [30] The review included prolonged antibiotic therapy of 4 or more weeks, comparing any dose with placebo or as-required treatment. Only limited meta-analysis was possible in the review, [22] owing to the diversity of the trial end points and the differing ways in which the data were presented. The review reported that the duration of included RCTs varied from 4 weeks to 1 year, routes of administration included nebulised (2 RCTs), oral (7 RCTs), and inhaled (1 RCT), and all the studies were placebo-controlled, except for three RCTs where the control groups were usual medical care (see Further information on studies). The subsequent RCTs included a wide variety of different drug regimens, outcome measurements, and time periods (see Further information on studies).

Mortality

Prolonged-use antibiotics compared with standard management with or without placebo We don't know whether prolonged-use antibiotics are more effective than standard management with or without placebo at decreasing mortality in people with non-CF bronchiectasis (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[22] Systematic review	128 people 2 RCTs in this analysis	**Mortality** 2/83 (2%) with prolonged-use antibiotics 2/45 (4%) with or without added placebo 1 RCT used oral oxytetracycline or oral penicillin compared with placebo The other RCT used inhaled antibiotics (ceftazidime plus tobramycin) compared with usual medical care	OR 0.59 95% CI 0.07 to 4.70 P = 0.62	⟷	Not significant
[24] RCT	65 people	**Mortality , 12 months** 2/27 (7%) with nebulised gentamicin 0/30 (0%) with placebo (nebulised 0.9% saline) The RCT reported the causes of the deaths as: 1 previously undiagnosed metastatic colorectal cancer and 1 MI	Significance not assessed		

No data from the following reference on this outcome. [23] [25] [26] [27] [28] [29] [30]

Infection rates

Prolonged-use antibiotics compared with placebo Prolonged-use antibiotics may be more effective than placebo at improving some outcomes, such as sputum bacterial density, in people with non-CF bronchiectasis. However, results varied by the outcome measure reported and the individual drug regimen used (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Bacterial density					
[24] RCT	65 people	**Sputum bacterial density , after 12 months' treatment** 2.96 $\log_{10}$ colony-forming units (cfu)/mL with nebulised gentamicin 7.67 $\log_{10}$ cfu/mL with placebo (nebulised 0.9% saline)	P <0.0001	○○○	nebulised gentamicin
[24] RCT	65 people	**Sputum bacterial density , 3 months after the end of treatment** 7.29 $\log_{10}$ cfu/mL with nebulised gentamicin 7.49 $\log_{10}$ cfu/mL with placebo (nebulised 0.9% saline)	P <0.12	⟷	Not significant
[25] RCT	117 adults with a history of frequent pulmonary exacerbations (2 or more exacerbations in the preceding year)	**Eradication of sputum pathogens (negative sputum culture in week 48 sputum sample, from participants with pathogenic bacteria in baseline samples)** 17 people (30%) with oral erythromycin 6 people (11%) with placebo	OR 3.6 95% CI 1.3 to 10.6 P = 0.01	●●○	oral erythromycin
[26] RCT	42 adults with bronchiectasis with at least 2 exacerbations in the prior 12 months and ciprofloxacin-sensitive *Pseudomonas aeruginosa* at screening	**Bacterial density: mean change in sputum *P aeruginosa* density (reported as $\log_{10}$ CFU/g of sputum) , from baseline to the end of the first treatment cycle (day 28)** –4.2 with inhaled ciprofloxacin –0.08 with placebo Trial medication was discontinued once participants reached a pulmonary exacerbation endpoint	P = 0.002 See Further information on studies	○○○	inhaled ciprofloxacin
[26] RCT	42 adults with bronchiectasis with at least 2 exacerbations in the prior 12 months and ciprofloxacin-sensitive *P aeruginosa* at screening	**Failure to culture *P aeruginosa* (sputum) , at day 28** 12/20 (60%) with inhaled ciprofloxacin 3/22 (14%) with placebo Trial medication was discontinued once participants reached a pulmonary exacerbation endpoint	OR 9.5 95% CI 1.8 to 63.0 P = 0.003 See Further information on studies	●●●	inhaled ciprofloxacin
[27] RCT	141 adults with at least 1 exacerbation requiring antibiotics in the last year	**Change in total sputum cell counts , 12 months** –22% with oral azithromycin +23% with placebo Absolute numbers not reported	Difference –36.6% 95% CI –68.7% to +28.5% P = 0.203	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[28] RCT	89 Indigenous children in Australia or urban Maori or Pacific Islander children in New Zealand; age 1–8 years; with bronichiectasis and at least 1 exacerbation in the last 12 months	**Bacterial carriage (deep nasal swab) , at end of study** 22/41 (54%) with oral azithromycin 22/37 (60%) with placebo	OR 0.60 95% CI 0.21 to 1.65 P = 0.32	⟷	Not significant

No data from the following reference on this outcome. [22] [23] [29] [30]

Exacerbation rates

Prolonged-use antibiotics compared with placebo Prolonged-use antibiotics seem to be more effective than placebo at resulting in modest but clinically relevant reductions in exacerbation rates over 3 to 12 months in people with non-CF bronchiectasis (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Exacerbation rates					
[22] Systematic review	120 people 3 RCTs in this analysis	**Exacerbation rates** 5/61 (8%) with prolonged antibiotic treatment 5/59 (8%) with or without added placebo	OR 0.96 95% CI 0.27 to 3.46 P = 0.95 There was significant heterogeneity among groups (I^2 73%; P for heterogeneity = 0.02) for this analysis The review noted different delivery method, dosage, and type of antibiotic between RCTs	⟷	Not significant
[24] RCT	65 people	**Number of exacerbations , 12 months** 0 with nebulised gentamicin 1.5 with placebo (nebulised 0.9% saline)	P <0.0001	○○○	nebulised gentamicin
[24] RCT	65 people	**Median time to first exacerbation , 12 months** 120.0 days with nebulised gentamicin 61.5 days with placebo (nebulised 0.9% saline)	P = 0.02	○○○	nebulised gentamicin
[25] RCT	117 adults with a history of frequent pulmonary exacerbations (2 or more exacerbations in the preceding year)	**Mean rate of protocol-defined pulmonary exacerbations (PDPEs) per person per year** 1.29 with oral erythromycin 1.97 with placebo These data included 76 PDPEs in the erythromycin group and 114 PDPEs with placebo	Incidence rate ratio 0.57 95% CI 0.42 to 0.77 P = 0.003	●○○	oral erythromycin
[26] RCT	42 adults with bronchiectasis with 2 or more pulmonary exacerbations in the prior 12 months and ciprofloxacin-sensi-	**Pulmonary exacerbations , by day 168** 11/20 (55%) with inhaled ciprofloxacin 17/22 (77%) with placebo	P value not reported See Further information on studies		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	tive *Pseudomonas aeruginosa* at screening	Trial medication was discontinued once participants reached a pulmonary exacerbation endpoint			
[27] RCT	141 adults with at least 1 exacerbation requiring antibiotics in the last year	**Exacerbations , over 6 months on treatment** 0.59 per person with oral azithromycin 1.57 per person with placebo	RR 0.38 95% CI 0.26 to 0.54 P <0.0001	●●○	oral azithromycin
[27] RCT	141 adults with at least 1 exacerbation requiring antibiotics in the last year	**People with at least 1 exacerbation , over 6 months on treatment** 22/71 (31%) with oral azithromycin 46/70 (66%) with placebo	RR 0.48 95% CI 0.32 to 0.71 P <0.0001	●●○	oral azithromycin
[27] RCT	141 adults with at least 1 exacerbation requiring antibiotics in the last year	**Exacerbations , over 12-month period (6 months on treatment and 6 months on follow-up)** 1.58 per person with oral azithromycin 2.73 per person with placebo	RR 0.58 95% CI 0.46 to 0.74 P <0.0001	●○○	oral azithromycin
[27] RCT	141 adults with at least 1 exacerbation requiring antibiotics in the last year	**People with at least 1 exacerbation , over 12-month period (6 months on treatment and 6 months on follow-up)** 44/71 (62%) with oral azithromycin 58/70 (83%) with placebo	RR 0.75 95% CI 0.61 to 0.93 P = 0.005	●○○	oral azithromycin
[28] RCT	89 Indigenous children in Australia or urban Maori or Pacific Islander children in New Zealand; age 1 8 years; with bronchiectasis and at least one exacerbation in the last 12 months	**Pulmonary exacerbations, median** 2 with oral azithromycin 4 with placebo	Incidence rate ratio 0.50 95% CI 0.35 to 0.71 P <0.0001 In total, there were 104 exacerbations with azithromycin and 195 with placebo	●○○	oral azithromycin
[29] RCT	36 adults with stable disease (no change in medication or symptoms, emergency room visits, or hospitalisations in last 4 weeks); mean 3.3 exacerbations in last year	**Exacerbations , at 3 months** 0.1 with oral azithromycin 1.2 with placebo Results based on 30 people	P <0.05	○○○	oral azithromycin
[30] RCT	83 adults with a minimum of 3 or more lower respiratory tract infections in the preceding year and at least 1 sputum culture yielding 1 or more bacterial pathogens in last year	**Number of exacerbations, median , during 12 months of treatment** 0 with oral azithromycin 2 with placebo	P <0.001	○○○	oral azithromycin

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[30] RCT	83 adults with a minimum of 3 or more lower respiratory tract infections in the preceding year and at least 1 sputum culture yielding 1 or more bacterial pathogens in last year	**Number of patients with at least 1 exacerbation , in 12 months** 20/43 (47%) with oral azithromycin 32/40 (80%) with placebo	ARR 33.5% 95% CI 14.1% to 52.9%	○○○	oral azithromycin

No data from the following reference on this outcome. [23]

Symptom severity

Prolonged-use antibiotics compared with placebo Prolonged-use antibiotics may be more effective at improving response rates (physician assessment of diary cards or of overall medical condition) and sputum weight or volume, but we don't know about general health or Leicester Cough Questionnaire scores (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[22] Systematic review	110 people 2 RCTs in this analysis	**Response rate (physician assessment of diary cards, or of overall medical condition)** 34/54 (63%) with prolonged antibiotic treatment 18/56 (32%) with or without added placebo	OR 3.37 95% CI 1.60 to 7.09 P = 0.0014	●●○	prolonged antibiotic treatment
[23] RCT	74 people with bronchiectasis colonised with *Pseudomonas*	**Improved general health by physician assessment , after 4 weeks** 62% with aerosolised tobramycin solution 38% with placebo Absolute numbers not reported Worse: 22% with tobramycin *v* 13% with placebo Unchanged: 16% with tobramycin *v* 49% with placebo	Significance not assessed		
[24] RCT	65 people	**Proportion of people with clinically important improvement in Leicester Cough Questionnaire (LCQ) , 12 months** 81% with nebulised gentamicin 20% with placebo (nebulised 0.9% saline) Clinically important improvement defined as improvement of >1.3 units in LCQ	P <0.01	○○○	nebulised gentamicin
[25] RCT	117 adults with a history of frequent pulmonary exacerbations (2 or more exacerbations in the preceding year)	**24-hour sputum weight , at 48 weeks (median)** –5.4 g with oral erythromycin –1.7 g with placebo	Mean difference –4.3 g 95% CI –1.0 g to –7.8 g P = 0.01	○○○	oral erythromycin

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[25] RCT	117 adults with a history of frequent pulmonary exacerbations (2 or more exacerbations in the preceding year)	**Change in Leicester Cough Questionnaire , at 48 weeks** 1.16 with oral erythromycin 0.52 with placebo	Mean difference +0.79 95% CI –0.2 to +1.8	⟷	Not significant
[29] RCT	36 adults with stable disease (no change in medication or symptoms, emergency room visits, or hospitalisations in last 4 weeks); mean 3.3 exacerbations in last year	**Change in dyspnoea score (units not reported) , at 3 months** –0.4 with oral azithromycin +0.1 with placebo Results based on 30 people	P <0.05	○○○	oral azithromycin
[29] RCT	36 adults with stable disease (no change in medication or symptoms, emergency room visits, or hospitalisations in last 4 weeks); mean 3.3 exacerbations in last year	**Volume of sputum (daily average recorded over 3 days) , at 3 months** –8.9 mL with oral azithromycin +2.1 mL with placebo Results based on 30 people	P <0.05	○○○	oral azithromycin

No data from the following reference on this outcome. [26] [27] [28] [30]

Functional improvement

Prolonged-use antibiotics compared with placebo Prolonged-use antibiotics may be equally effective as placebo at increasing functional improvement (measured by FEV_1, 6-minute walk test) at 4–52 weeks in people with non-CF bronchiectasis (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Lung function					
[22] Systematic review	40 people 2 RCTs in this analysis	**Lung function (FEV_1 % predicted)** prolonged antibiotic treatment with with or without added placebo with Absolute results not reported	WMD –1.05 95% CI –6.93 to +4.83 P = 0.73	⟷	Not significant
[23] RCT	74 people with bronchiectasis colonised with *Pseudomonas*	**Decline in pulmonary function , after 4 weeks** 2.3% with aerosolised tobramycin solution 1.5% with placebo Absolute results reported graphically	Significance not assessed		
[24] RCT	65 people	**Change from baseline in 10 m incremental field walking test , 12 months** From 350 m to 510 m with nebulised gentamicin From 345 m to 415 m with placebo (nebulised 0.9% saline)	P = 0.03	○○○	nebulised gentamicin

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		The RCT reported no significant improvements in other functional improvement outcomes (FEV_1, FVC, or mid-expiratory flow rates)			
[25] RCT	117 adults with a history of frequent pulmonary exacerbations (2 or more exacerbations in the preceding year)	**Median change in 6-minute walk test , at 48 weeks** 2 m with oral erythromycin 0 m with placebo	Mean difference +3.55 m 95% CI –17.6 m to +24.7 m	⟷	Not significant
[26] RCT	42 adults with bronchiectasis with 2 or more pulmonary exacerbations in the prior 12 months and ciprofloxacin-sensitive *Pseudomonas aeruginosa* at screening	**6-minute walk test , at day 28** +0.6 with inhaled ciprofloxacin –7.6 with placebo Units not reported Trial medication was discontinued once participants reached a pulmonary exacerbation endpoint	P = 0.54 See Further information on studies	⟷	Not significant
[26] RCT	42 adults with bronchiectasis with 2 or more pulmonary exacerbations in the prior 12 months and ciprofloxacin-sensitive *P aeruginosa* at screening	**Changes in FEV_1 , at day 28** 0.05 with inhaled ciprofloxacin 0.00 with placebo Trial medication was discontinued once participants reached a pulmonary exacerbation endpoint	P = 0.18 See Further information on studies	⟷	Not significant
[27] RCT	141 adults with at least 1 exacerbation requiring antibiotics in the last year	**Change in 6-minute walk test distance , at 6 months on treatment** +0.88 m with oral azithromycin –9.63 m with placebo	Difference +10.52 m 95% CI –5.12 m to +26.15 m P = 0.185	⟷	Not significant
[27] RCT	141 adults with at least 1 exacerbation requiring antibiotics in the last year	**Change in 6-minute walk test distance (m) , at 12 months (6 months on treatment + 6 months follow-up)** +1.19 m with oral azithromycin –5.28 m with placebo	Difference+ 6.48 m 95% CI –11.28 m to +24.22 m P = 0.471	⟷	Not significant
[29] RCT	36 adults with stable disease (no change in medication or symptoms, emergency room visits, or hospitalisations in last 4 weeks); mean 3.3 exacerbations in last year	**Change in FEV_1 (L) , at 3 months** 0.06 with oral azithromycin 0.04 with placebo Results based on 30 people	Reported as not significant P value not reported	⟷	Not significant
[29] RCT	36 adults with stable disease (no change in medication or symptoms, emergency room visits, or hospitalisations in last 4 weeks); mean 3.3 exacerbations in last year	**Change in FVC (L) , at 3 months** –0.07 with oral azithromycin –0.08 with placebo Results based on 30 people	Reported as not significant P value not reported	⟷	Not significant
[30] RCT	83 adults with a minimum of 3 or more lower respira-	**Change in percent of predicted FEV_1**	P = 0.047	◌◌◌	oral azithromycin

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	tory tract infections in the preceding year and at least 1 sputum culture yielding 1 or more bacterial pathogens in last year	with oral azithromycin with placebo			

No data from the following reference on this outcome. [28]

Quality of life

Prolonged-use antibiotics compared with placebo We don't know whether prolonged-use antibiotics are more effective than placebo at improving quality of life scores, as we found inconsistent results between studies (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
St George's Respiratory Questionnaire (SGRQ)					
[24] RCT	65 people	**Proportion of people with clinically important improvement in SGRQ , 12 months** 87% with nebulised gentamicin 19% with placebo (nebulised 0.9% saline) Absolute numbers not reported Clinically important improvement defined as improvement of >4 units in SGRQ	P <0.004	○○○	nebulised gentamicin
[25] RCT	117 adults with a history of frequent pulmonary exacerbations (2 or more exacerbations in the preceding year)	**Mean change in St George's Respiratory Questionnaire total score , at week 48** –3.9 with oral erythromycin –1.3 with placebo	Mean difference –2.9 95% CI –7.3 to +1.6	⟷	Not significant
[25] RCT	117 adults with a history of frequent pulmonary exacerbations (2 or more exacerbations in the preceding year)	**Mean change in St George's Respiratory Questionnaire symptom score , at week 48** –6 with oral erythromycin –3 with placebo	Mean difference –5.3 95% CI –12.6 to +2.1	⟷	Not significant
[26] RCT	42 adults with bronchiectasis with 2 or more pulmonary exacerbations in the prior 12 months and ciprofloxacin-sensitive *Pseudomonas aeruginosa* at screening	**St George's Respiratory Questionnaire total score , at day 28** –1.3 with inhaled ciprofloxacin –6.4 with placebo Units not reported Trial medication was discontinued once participants reached a pulmonary exacerbation endpoint	P = 0.08 See Further information on studies	⟷	Not significant
[27] RCT	141 adults with at least 1 exacerbation requiring antibiotics in the last year	**Change in St George's Respiratory Questionnaire total score , at 6 months** –5.17 with oral azithromycin –1.92 with placebo	Difference –3.25 95% CI –7.21 to +0.72 P = 0.108	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[27] RCT	141 adults with at least 1 exacerbation requiring antibiotics in the last year	**Change in St George's Respiratory Questionnaire total score , at 12 months (6 months on treatment and 6 months on follow-up)** –2.89 with oral azithromycin –4.71 with placebo	Difference +1.82 95% CI –0.27 to +6.32 P = 0.425	⟷	Not significant
[29] RCT	30 adults with stable disease (no change in medication or symptoms, emergency room visits, or hospitalisations in last 4 weeks); mean 3.3 exacerbations in last year	**Change in St George's Respiratory Questionnaire , at 3 months** –7.9 with oral azithromycin +4.1 with placebo	P <0.05	○○○	oral azithromycin
[30] RCT	83 adults with a minimum of 3 or more lower respiratory tract infections in the preceding year and at least 1 sputum culture yielding 1 or more bacterial pathogens in last year	**St George's Respiratory Questionnaire , at end of treatment** with oral azithromycin with placebo Absolute results not reported	P = 0.046	○○○	oral azithromycin
[30] RCT	83 adults with a minimum of 3 or more lower respiratory tract infections in the preceding year and at least 1 sputum culture yielding 1 or more bacterial pathogens in last year	**Lower respiratory tract infection visual analogue scale (LRTI-VAS) , at the end of treatment** with oral azithromycin with placebo Absolute results not reported	P = 0.047	○○○	oral azithromycin

No data from the following reference on this outcome. [22] [23] [28]

Hospital admission

Prolonged-use antibiotics compared with placebo We don't know whether prolonged-use antibiotics are more effective than placebo at reducing hospital admission for pulmonary exacerbations or the median length of hospital stay in people with non-CF bronchiectasis (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Hospital admission					
[28] RCT	89 Indigenous children in Australia or urban Maori or Pacific Islander children in New Zealand; age 1–8 years; with bronchiectasis and at least 1 exacerbation in the last 12 months	**Number of hospital-managed pulmonary exacerbations, median** 8 with oral azithromycin 14 with placebo	Incidence rate ratio 1.08 95% CI 0.19 to 6.26 P = 0.93	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[28] RCT	89 Indigenous children in Australia or urban Maori or Pacific Islander children in New Zealand; age 1–8 years; with bronchiectasis and at least 1 exacerbation in the last 12 months	**Median length of hospital stay** 7.2 days with oral azithromycin 12.0 days with placebo	P = 0.58	⟷	Not significant

No data from the following reference on this outcome. [22] [23] [24] [25] [26] [27] [29] [30]

Days off work

Prolonged-use antibiotics compared with placebo We don't know whether prolonged-use antibiotics are more effective than placebo at reducing school absence in children aged 6 to 8 years with non-CF bronchiectasis (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Days off work/school					
[28] RCT	89 Indigenous children in Australia or urban Maori or Pacific Islander children in New Zealand; age 1–8 years; with bronchiectasis and at least 1 exacerbation in the last 12 months	**Number of children aged at least 6 years old reporting reduced school attendance as a result of cough** 3/18 (17%) with oral azithromycin 6/22 (27%) with placebo	P = 0.48	⟷	Not significant

No data from the following reference on this outcome. [22] [23] [24] [25] [26] [27] [29] [30]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[22] Systematic review	260 people 5 RCTs in this analysis	**Withdrawals from study (treatment failure or intolerable side effects)** 11/149 (7%) with prolonged-use antibiotics 10/111 (9%) with or without added placebo	OR 1.06 95% CI 0.42 to 2.65 P = 0.9	⟷	Not significant
[22] Systematic review	148 people 2 RCTs in this analysis	**Diarrhoea** 15/93 (16%) with prolonged-use antibiotics 5/55 (9%) with placebo	OR 2.47 95% CI 0.91 to 6.71 P = 0.075	⟷	Not significant
[22] Systematic review	57 people 2 RCTs in this analysis	**Rash** 2/28 (7%) with prolonged-use antibiotics	OR 1.94 95% CI 0.19 to 19.47 P = 0.57	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		1/29 (3%) with placebo			
[23] RCT	74 people with bronchiectasis colonised with *Pseudomonas*	**Adverse effects** with aerosolised tobramycin solution with placebo Absolute results not reported More treatment-emergent adverse events with tobramycin. The most common complaints were dyspnoea, wheezing, and chest pain	Significance not assessed		
[24] RCT	65 people	**Treatment-related withdrawals, 12 months** 2/32 (6%) people with nebulised gentamicin 2/27 (7%) people with placebo (nebulised 0.9% saline) 7 people in the gentamicin group reported bronchospasm and received adjunctive nebulised beta$_2$ agonist treatment; 5 of these people completed the study and 2 withdrew 2 people in the placebo group reported bronchospasm and received adjunctive nebulised beta$_2$ agonist treatment; both people withdrew from the study The RCT reported no nephrotoxicity or ototoxicity	Significance not assessed		
[25] RCT	117 adults with a history of frequent pulmonary exacerbations (2 or more exacerbations in the preceding year)	**Serious adverse event apart from protocol defined pulmonary exacerbation (PDPE)** 0 with oral erythromycin 1 with placebo 1 person was hospitalised for a respiratory viral infection without meeting PDPE criteria	P value not reported		
[25] RCT	117 adults with a history of frequent pulmonary exacerbations (2 or more exacerbations in the preceding year)	**Any adverse event (excluding bronchiectasis-related adverse event)** 17/59 (28.8%) with oral erythromycin 15/58 (25.9%) with placebo	P value not reported		
[25] RCT	117 adults with a history of frequent pulmonary exacerbations (2 or more exacerbations in the preceding year)	**Discontinued study due to adverse event** 1/59 (2%) with oral erythromycin 1/58 (2%) with placebo 1 person with placebo had nausea; 1 person with erythromycin discontinued the study with QT prolongation The participant had been enrolled with QTc of 480 ms and discontinued study at week 24 with QTc 470 ms. No participant developed a new cardiac arrhythmia during the study	P value not reported		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[26] RCT	42 adults with bronchiectasis with 2 or more pulmonary exacerbations in the prior 12 months and ciprofloxacin-sensitive *Pseudomonas aeruginosa* at screening	**Non-respiratory adverse effects leading to discontinuation** 4/20 (20%) with inhaled ciprofloxacin 3/22 (14%) with placebo Adverse effects with inhaled ciprofloxacin were 2 nausea, 1 sinusitis, 1 fatigue Adverse effects with placebo were 1 anal ulcer, 1 sinusitis, 1 skin graft infection	P value not reported		
[26] RCT	42 adults with bronchiectasis with 2 or more pulmonary exacerbations in the prior 12 months and ciprofloxacin-sensitive *P aeruginosa* at screening	**Treatment-emergent adverse effects: lung disorder** 11/20 (55%) with inhaled ciprofloxacin 19/22 (86%) with placebo	P value not reported		
[26] RCT	42 adults with bronchiectasis with 2 or more pulmonary exacerbations in the prior 12 months and ciprofloxacin-sensitive *P aeruginosa* at screening	**Treatment-emergent adverse effects: product taste abnormal** 4/20 (20%) with inhaled ciprofloxacin 0/22 (0%) with placebo	P value not reported		
[26] RCT	42 adults with bronchiectasis with 2 or more pulmonary exacerbations in the prior 12 months and ciprofloxacin-sensitive *P aeruginosa* at screening	**Treatment-emergent adverse effects: nausea** 4/20 (20%) with inhaled ciprofloxacin 0/22 (0%) with placebo	P value not reported		
[26] RCT	42 adults with bronchiectasis with 2 or more pulmonary exacerbations in the prior 12 months and ciprofloxacin-sensitive *P aeruginosa* at screening	**Treatment-emergent adverse effects: headache** 1/20 (5%) with inhaled ciprofloxacin 4/22 (18%) with placebo	P value not reported		
[27] RCT	141 adults with at least 1 exacerbation requiring antibiotics in the last year	**Adverse events (any)** 59/71 (83%) with oral azithromycin 65/70 (93%) with placebo	P value not reported		
[27] RCT	141 adults with at least 1 exacerbation requiring antibiotics in the last year	**Severe adverse events** 4/71 (6%) with oral azithromycin 9/70 (13%) with placebo	P value not reported		
[27] RCT	141 adults with at least 1 exacerbation requiring antibiotics in the last year	**Gastrointestinal adverse events (diarrhoea, nausea, vomiting, epigastric discomfort, or constipation)**	P = 0.005	○○○	placebo

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		19/71 (27%) with oral azithromycin 9/70 (13%) with placebo			
[27] RCT	141 adults with at least 1 exacerbation requiring antibiotics in the last year	**Discontinued because of gastrointestinal adverse events** 2/71 (3%) with oral azithromycin 2/70 (3%) with placebo	P value not reported		
[28] RCT	89 Indigenous children in Australia or urban Maori or Pacific Islander children in New Zealand; age 1 8 years; with bronichiectasis and at least one exacerbation in the last 12 months	**Serious adverse events requiring admission to hospital** 11/45 (24%) with oral azithromycin 19/44 (43%) with placebo	P value not reported		
[30] RCT	83 adults with a minimum of 3 or more lower respiratory tract infections in the preceding year and at least 1 sputum culture yielding 1 or more bacterial pathogens in last year	**Proportion of people with no adverse events , 12 months** 25/43 (58%) with oral azithromycin 23/40 (58%) with placebo	RR 1.01 95% CI 0.70 to 1.46	⟷	Not significant
[30] RCT	83 adults with a minimum of 3 or more lower respiratory tract infections in the preceding year and at least 1 sputum culture yielding 1 or more bacterial pathogens in last year	**Proportion of people experiencing diarrhoea , 12 months** 9/43 (21%) with oral azithromycin 1/40 (3%) with placebo	RR 8.36 95% CI 1.10 to 63.15	●●●	placebo
[30] RCT	83 adults with a minimum of 3 or more lower respiratory tract infections in the preceding year and at least 1 sputum culture yielding 1 or more bacterial pathogens in last year	**Proportion of people experiencing abdominal pain , 12 months** 8/43 (19%) with oral azithromycin 1/40 (3%) with placebo	RR 7.44 95% CI 0.97 to 56.88	⟷	Not significant

No data from the following reference on this outcome. [29]

Further information on studies

[22] The review reported, with regard to study quality, that two RCTs had a Jadad scale score of two, three RCTs had a Jadad score of three, three RCTs had a Jadad score of four, and one RCT had a Jadad score of five. [25] [31]

[22] The double-blind RCT (BLESS trial) compared twice-daily oral erythromycin versus placebo for 48 weeks. A pulmonary exacerbation (PDPE) was considered to have occurred when antibiotics were needed for a sustained (>24 hours) increase in sputum volume or purulence with new deteriorations in at least two additional symptoms. It reported that erythromycin significantly increased the proportion of macrolide-resistant commensal oropharyngeal streptococci (median change: 27.7% with erythromycin *v* 0.04% with placebo, difference 25.5%, P <0.001). The RCT concluded that the 12-month use of erythromycin resulted in a modest decrease in the rate of pulmonary exacerbations and an increased rate of macrolide resistance.

[26] The RCT (ORBIT-2 trial) compared nebulised dual-release ciprofloxacin for inhalation once daily with placebo for up to three treatment cycles of 28 days 'on' inhaled therapy and 28 days 'off' (24 weeks in total). Trial medication was discontinued once participants reached the pulmonary exacerbation endpoint. Of 42 people randomised, only one person completed to cycle three in the active treatment group, and five people completed to cycle three in the placebo group. The RCT reported that the identification of *Pseudomonas aeruginosa* isolates with lowered categorical susceptibility to ciprofloxacin occurred in eight placebo subjects and 10 active treatment subjects (P value not reported). The RCT noted that the participants were a selected group of *P aeruginosa*-infected people; hence, the results were not more broadly generalisable.

[27] The double-blind RCT (EMBRACE trial) compared oral azithromycin three times a week with placebo for 6 months, with a further 6 months' follow-up. Macrolide resistance testing was not routinely undertaken, but two people (4%) in the azithromycin group developed macrolide-resistant *Streptococcus pneumoniae* on sputum microbiological testing at 6 months.

[28] The RCT compared oral azithromycin or placebo once per week for up to 24 months. The trial was stopped early due to slow recruitment and funding issues. The mean duration of intervention was 20.7 months in each group. The RCT found that the odds of carrying azithromycin-resistant bacteria were significantly higher in the antibiotic group (azithromycin-resistant bacteria [any] by deep nasal swab at end of study:19/41 [46%] with azithromycin *v* 4/37 [11%] with placebo; OR 7.39, 95% CI 2.15 to 25.39, P = 0.002).

[29] The open-label RCT compared oral azithromycin three times a week with placebo over 3 months. Initially, 36 people were randomised. Six people were lost to follow-up (further details not reported), and 30/36 (83%) people were analysed.

[30] The double-blind RCT (BAT trial) compared oral azithromycin daily versus placebo for 12 months. The RCT noted that resistance patterns were compatible between groups at baseline on sputum microbiology (P = 0.75). During treatment, 53 of 60 pathogens (88%) tested for sensitivity in 20 people in the azithromycin group became macrolide resistant, compared with 29 of 112 pathogens (26%) in the placebo group (P <0.001).

Comment:

Clinical guide

The use of prolonged antibiotics has shown some positive results for clinically relevant outcome parameters, such as exacerbation frequency. However, it should be considered that combining results from both macrolides and inhaled antibiotics and grouping them together as 'prolonged antibiotics' may be problematic. The anti-inflammatory, immunomodulatory, and antibacterial effects attributed to macrolides could very well be incomparable with the results of the sole antibacterial effects of other (inhaled) antibiotics. Macrolides may alter the intraluminal physiological state of the bronchus by inhibiting bacterial protein synthesis, reducing bacterial adherence and bacterial toxin production, inhibiting biofilm function, and reducing the generation of oxygen free radicals. Moreover, macrolides interfere with mucin function both at DNA and at protein production level. Finally, several immunomodulatory effects, such as a change in chemotaxis and alveolar macrophage phagocytosis, have not yet been elucidated. [32] [33]

OPTION SURGERY

- For GRADE evaluation of interventions for Bronchiectasis, see table, p 38 .
- Surgery is often used in bronchiectasis, but we found no good-quality studies.
- Surgery is often considered for people with extreme damage to one or two lobes of the lung who are at risk of severe infection or bleeding.

Benefits and harms

Surgery versus no surgery:

We found one systematic review (search date 2011), which found no RCTs comparing surgical resection with standard non-surgical treatments. [34]

Comment: We found five retrospective cohort studies (1347 people in total) assessing the long-term effect of surgery on bronchiectasis-related symptoms. [35] [36] [37] [38] [39] With a follow-up period of approximately 4.3 years, 68% to 84% of people became asymptomatic after surgery, 14% to 24% improved, and 5% to 15% worsened.

Clinical guide:
RCTs are very difficult to perform in this area for a number of reasons, including the small number of people with bronchiectasis eligible for surgery, the long follow-up time required to draw definitive conclusions, variations in surgical techniques currently in use, and ethical considerations. There is some general consensus about the indications for surgery — most physicians consider surgical resection in cases of extremely damaged lung segments or lobes that may be a focus for recurrent infections or bleeding. Surgery may be an option to prevent recurrent exacerbations of pneumonia in cases of localised bronchiectasis (1 or 2 lobes of one lung). It is preferably performed if there are no current active infections, especially not a non-tuberculous mycobacterial (NTM) pulmonary infection. If a patient has an active infection, he or she is treated with appropriate antibiotics for several weeks and will continue on the antibiotic regimen after surgery.

GLOSSARY

Jadad scale This measures factors that have an impact on trial quality. Poor description of the factors, rated by low figures, is associated with greater estimates of effect. The scale includes three items: was the study described as randomised? (0–2); was the study described as double blind? (0–2); was there a description of withdrawals? (0–1). [40]

Inspiratory muscle training (IMT) People are required to breathe through inspiratory devices of progressively decreasing diameter, with the goal of increasing the load on the respiratory muscles. Another technique involves the use of a threshold loading device that lets inspiration commence only after a certain threshold mouth pressure is reached. The threshold pressure can be set by means of a weighted plunger. In most programmes, subjects have to train for 30 minutes a day, 5 days a week.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

Visual Analogue Scale (VAS) A commonly used scale in pain assessment. It is a 10-cm horizontal or vertical line with word anchors at each end, such as 'no pain' and 'pain as bad as it could be'. The person is asked to make a mark on the line to represent pain intensity. This mark is converted to distance in either centimetres or millimetres from the 'no pain' anchor to give a pain score that can range from 0–10 cm or 0–100 mm.

SUBSTANTIVE CHANGES

Airway clearance techniques Previous option title, 'Bronchopulmonary hygiene physical therapy (airway-clearance techniques)', clarified to new title. One systematic review added. [9] Categorisation unchanged (unknown effectiveness).

Corticosteroids (inhaled) One previously included systematic review updated; [11] new evidence added. [12] Categorisation unchanged (unknown effectiveness).

Exercise or physical training One RCT added. [16] Categorisation unchanged (likely to be beneficial).

Hyperosmolar agents (inhaled) Title clarified to list the hyperosmolar agents that are searched for. One RCT added. [18] Categorisation unchanged (unknown effectiveness).

Prolonged-use antibiotics One systematic review updated [22] and six RCTs added. [25] [26] [27] [28] [29] [30] Categorisation unchanged (likely to be beneficial).

Surgery One previously included systematic review updated; [34] no new data added. Categorisation unchanged (unknown effectiveness).

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Cecile Magis-Escurra
Respiratory Disease Specialist
Radboud University Medical Centre
Radboud University
Nijmegen
The Netherlands

Monique HE Reijers
Respiratory Disease Specialist
Radboud University Medical Centre
Radboud University
Nijmegen
The Netherlands

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GRADE **Evaluation of interventions for Bronchiectasis.**

Important outcomes	Days off work, Exacerbation rates, Functional improvement, Hospital admission, Infection rates, Mortality, Quality of life, Symptom severity								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of treatments in people with non-cystic fibrosis (non-CF) bronchiectasis?									
1 (20) [10]	Symptom severity	Airway clearance techniques versus no airway clearance techniques	4	–2	0	0	0	Low	Quality points deducted for sparse data and weak methods
1 (20) [10]	Functional improvement	Airway clearance techniques versus no airway clearance techniques	4	–2	–1	0	0	Very low	Quality points deducted for sparse data and weak methods; consistency point deducted for conflicting results with different measures of lung function
1 (20) [10]	Quality of life	Airway clearance techniques versus no airway clearance techniques	4	–2	0	0	0	Low	Quality points deducted for sparse data and weak methods
3 (220) [11] [12]	Exacerbation rates	Inhaled corticosteroids versus placebo	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and weak methods
3 (224) [11] [12]	Symptom severity	Inhaled corticosteroids versus placebo	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and weak methods
at least 4 (at least 178) [11] [12]	Functional improvement	Inhaled corticosteroids versus placebo	4	–3	0	0	0	Very low	Quality points deducted for incomplete reporting of results, sparse data, and weak methods
1 (70) [12]	Hospital admission	Inhaled corticosteroids versus placebo	4	–3	0	0	0	Very low	Quality points deducted for incomplete reporting of results, sparse data, and weak methods
1 (70) [12]	Quality of life	Inhaled corticosteroids versus placebo	4	–3	0	0	0	Very low	Quality points deducted for incomplete reporting of results, sparse data, and weak methods
3 (70) [15] [16]	Functional improvement	Exercise versus no intervention/sham intervention	4	–3	0	–1	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, weak methods, and not stating method of assessment for endurance in 1 RCT; directness point deducted for co-intervention in active control groups
3 (70) [15] [16]	Quality of life	Exercise versus no intervention/sham intervention	4	–3	0	–1	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and weak methods; directness point deducted for co-intervention in active control groups
1 (27) [16]	Symptom severity	Exercise versus no intervention/sham intervention	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and weak methods; directness point deducted for co-intervention in active control group
1 (243) [18]	Mortality	Hyperosmolar agents (inhaled) versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for weak methods and incomplete reporting of results; directness point deducted for short follow-up

Important outcomes	Days off work, Exacerbation rates, Functional improvement, Hospital admission, Infection rates, Mortality, Quality of life, Symptom severity								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
1 (243) [18]	Exacerbation rates	Hyperosmolar agents (inhaled) versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for weak methods and incomplete reporting of results; directness point deducted for short follow-up
1 (243) [18]	Symptom severity	Hyperosmolar agents (inhaled) versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for weak methods and incomplete reporting of results; directness point deducted for short follow-up
1 (243) [18]	Functional improvement	Hyperosmolar agents (inhaled) versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for weak methods and incomplete reporting of results; directness point deducted for short follow-up
1 (243) [18]	Quality of life	Hyperosmolar agents (inhaled) versus placebo	4	–2	0	–1	0	Very low	Quality point deducted for weak methods and incomplete reporting of results; directness point deducted for short follow-up
1 (45) [20]	Symptom severity	Bromhexine versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results; directness point deducted for uncertainty about clinical importance
1 (42) [20]	Infection rates	Recombinant human deoxyribonuclease (rhDNase) versus placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and uncertainty about length of follow-up
1 (349) [20] [21]	Exacerbation rates	Recombinant human deoxyribonuclease (rhDNase) versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (42) [20]	Functional improvement	Recombinant human deoxyribonuclease (rhDNase) versus placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and uncertainty about length of follow-up
3 (193) [22] [24]	Mortality	Prolonged-use antibiotics versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
5 (454) [24] [25] [26] [27] [28]	Infection rates	Prolonged-use antibiotics versus placebo	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and early discontinuation in 1 RCT
10 (693) [22] [24] [25] [26] [27] [28] [29] [30]	Exacerbation rates	Prolonged-use antibiotics versus placebo	4	–2	0	0	0	Low	Quality points deducted for weak methods and incomplete reporting of results
6 (402) [22] [23] [24] [25] [29]	Symptom severity	Prolonged-use antibiotics versus placebo	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and weak methods
9 (598) [22] [23] [24] [25] [26] [27] [29] [30]	Functional improvement	Prolonged-use antibiotics versus placebo	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and weak methods
6 (478) [24] [25] [26] [27] [29] [30]	Quality of life	Prolonged-use antibiotics versus placebo	4	–2	0	0	0	Low	Quality points deducted for weak methods and incomplete reporting of results
1 (89) [28]	Hospital admission	Prolonged-use antibiotics versus placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data; directness point deducted for small number of comparators

Important outcomes	Days off work, Exacerbation rates, Functional improvement, Hospital admission, Infection rates, Mortality, Quality of life, Symptom severity								
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
1 (89) [28]	Days off work	Prolonged-use antibiotics versus placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data; directness point deducted for small number of comparators

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.