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Oral versus inhaled antibiotics for non-cystic fibrosis bronchiectasis (Protocol)

Spencer S, Felix LM, Milan SJ, Normansell R, Goeminne PC, Chalmers JD

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[Intervention Protocol]

Oral versus inhaled antibiotics for non-cystic fibrosis bronchiectasis

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To determine the comparative efficacy and safety of oral versus inhaled antibiotics in the treatment of adults and children with non-cystic fibrosis bronchiectasis.

BACKGROUND

Description of the condition

Bronchiectasis is a chronic inflammatory lung disease that presents with cough, sputum production and recurrent respiratory tract infections (Pasteur 2010). It is defined radiologically by the presence of permanently dilated airways usually visualised on computed tomography (CT). Bronchiectasis represents a final common pathway of multiple disorders with the most common associations being with severe infections (pneumonia, childhood infection and *Mycobacterial* infection), allergic bronchopulmonary aspergillosis, rheumatological diseases, inflammatory bowel disease and disorders of mucociliary clearance such as primary ciliary dyskinesia (Lonni 2015). Treatments for bronchiectasis have historically been extrapolated from cystic fibrosis with a focus on antibiotic treatments and physiotherapy (Chalmers 2016).

Although it has previously been considered a relatively rare disease (Kolbe 1996), bronchiectasis is increasing, with higher rates in developing countries, women and those aged over 60 years (Chang 2003; Weycker 2005; Habesoglu 2011; Seitz 2012). Global prevalence rates vary, with estimates of 0.5 in Finland and 3.7 in New Zealand per 100,000 though some of these data are more than 10 years old (European Lung White Book 2013). Recent data suggest that incidence and prevalence in the UK may be higher than previously estimated (Quint 2016). Over a 9-year period to 2013, point prevalence rates increased by over 60% to 566 in women and 485 in men per 100,000, with approximately 263,000 adults living with bronchiectasis in 2013. Similarly, the rate of new cases rose by 63% to 35 per 100,000 in women and 27 per 100,000 in men, with over 15,000 new cases in 2013. However, higher

prevalence rates may be due to the increasing use of CT scanning and a greater awareness of the disease (Goeminne 2016).
Mortality rates in England and Wales rose by 3% per year between 2001 to 2007 (Roberts 2010), and hospitalisations also increased by 3% per year over a 9-year period in the US (Seitz 2010). Average mortality rates in Europe are estimated at 0.3 per 100,000 general population in 27 of the 28 EU countries (ranging from 0.01 in Germany to 1.18 in the UK) and 0.2 per 100,000 in 9 non-EU countries (ranging from 0.01 in Azerbaijan to 0.67 in Kyrgyzstan), based on 2005 to 2009 data (European Lung White Book 2013). Quint reported higher age-adjusted mortality rates for the UK, with estimates 2.26 times higher in women and 2.14 times higher in men compared to the general population (Quint 2016).

Description of the intervention

Bronchiectasis is characterised by a common pathophysiological pathway that consists of a vicious cycle. Three elements play a pivotal role in this cycle: inflammation, infection and airway damage by enzymatic components. In this cycle, infection or colonisation by various micro-organisms cause an inflammatory response. When this inflammation is not able to clear the micro-organism, the inflammation can become chronic and even excessive compared to the bacterial burden. This can then finally result in airway damage and remodelling (Goeminne 2010).
Interventions aiming to reduce or break this vicious cycle often focus on the treatment of the chronic bacterial infection. Data show that these chronic infections are most often caused by Gram-negatives, with a special focus on *Pseudomonas aeruginosa* as this has been linked with more severe disease and increased morbidity and mortality (Wilson 2016). To treat or eradicate these chronic infections, long courses and high dosage of systemic antibiotic treatment are often required. This is frequently accompanied by side effects and can also result in resistance. Therefore, inhaled antibiotics are increasingly being considered, as they can deliver high concentrations of the antibiotic at the site of infection with less systemic absorption and toxicity, but can result in increased airway irritation or bronchospasm (Geller 2009).

How the intervention might work

A recent Cochrane review of 18 trials in patients with bronchiectasis receiving prolonged antibiotics, showed that there was a significant reduction of exacerbation risk (Hnin 2015). Furthermore, recent data clearly suggest an important relationship between inflammation and bacterial load/presence in bronchiectasis. Chronic *Pseudomonas aeruginosa* infection was associated with increased matrix metalloprotease activity and a higher bacterial load was associated with an increase in hospitalisations, exacerbations and symptom severity (Chalmers 2012; Goeminne 2014). Chalmers et al. also showed that both short- and long-term antibiotic treatment significantly reduced airway and systemic inflammation. This is in line with a series of long-term systemic antibiotic therapy trials with macrolides, proving that long-term oral macrolides are useful for patients with bronchiectasis in reducing exacerbations and improving clinical symptoms (Wong 2012; Altenburg 2013; Serisier 2013). It is speculated that macrolides not only act through their antibacterial activity but also have anti-inflammatory and immunomodulatory effect (Altenburg 2011a). These long-term oral macrolide treatments, however, raise some concerns as to safety and bacterial resistance (Altenburg 2011b). Inhaled antibiotics may provide an effective suppressive antibiotic therapy with an acceptable safety profile in adult patients with stable non-cystic fibrosis (CF) bronchiectasis and chronic bronchial infection. Their use has been widespread in CF since the early 1990s, as inhaled antibiotics improve lung function and reduce exacerbation rates (Ryan 2011). For inhaled antibiotics, different antibiotic regimens have been investigated in non-CF bronchiectasis, including inhaled amikacin, aztreonam, ciprofloxacin, gentamicin, colistin and tobramycin. The antibiotics chosen often have a concentration-dependent effect, where an increased greater area under the curve/minimum inhibitory concentration ratio improves bacterial killing (Restrepo 2015). As resistance is one of the concerns in chronic antibiotic treatment, these inhaled antibiotics may achieve very high concentrations of the drug in the airways, overcoming bacterial resistance (Dudley 2008; Rubin 2008; Quon 2014). On the other hand, inhalation antibiotic treatment is hampered by a delivery that is not uniform, creating a concentration gradient with lower concentrations in deeper parts of the lung (Rubin 2008). In non-CF bronchiectasis, a recent review found that long-term inhaled antibiotics can effectively reduce the sputum bacterial density, increase *Pseudomonas aeruginosa* eradication and attenuate the risk of exacerbation, but with higher risk of wheeze and bronchospasm (Yang 2015).

Why it is important to do this review

In meta-analyses of trials involving participants with non-CF bronchiectasis, authors have concluded that inhaled antibiotics reduced sputum bacterial load and the risk of acute exacerbation, with an acceptable safety profile, when compared to symptomatic treatment or placebo (Brodt 2014; Yang 2015). However, in reality, clinicians will often be faced with the choice between various routes of delivering antibiotics, not only the choice whether or not to give them. A comparison between the oral and inhaled route was highlighted as a priority in a recently published overview of interventions for bronchiectasis (Welsh 2015).The potential benefits of improved bacterial killing and reduced risk of bacterial resistance described above need to be weighed against the cost of drug delivery via inhalation and specific side effects associated with this route, such as bronchospasm and wheeze (BNF (online); Brodt 2014; Yang 2015).

Therefore in this review we will include studies that directly compare the effectiveness and safety of delivering antibiotics by inhalation or orally, both in an acute setting and for longer-term prophylaxis. We intend to summarise the evidence to provide the most up-to-date information for guideline developers, clinicians and patients, and highlight future research needs. This review is being conducted alongside four other closely related Cochrane reviews: Macrolide antibiotics for non-cystic fibrosis bronchiectasis (Kelly 2016); Dual antibiotics for non-cystic fibrosis bronchiectasis (Felix 2017a); Head to head trials of antibiotics for non-cystic fibrosis bronchiectasis (Kaehne 2017); and Continuous versus intermittent antibiotics for bronchiectasis (Felix 2017b).

OBJECTIVES

To determine the comparative efficacy and safety of oral versus inhaled antibiotics in the treatment of adults and children with non-cystic fibrosis bronchiectasis.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs). We will include studies reported as full-text, those published as abstract only, and unpublished data.

Types of participants

We will include adult and child participants diagnosed with bronchiectasis by bronchography, plain film chest radiograph, or high-resolution computed tomography. Studies will be excluded if patients have been receiving continuous or high-dose antibiotics immediately before the study, or if they have received a diagnosis of cystic fibrosis (CF), sarcoidosis, active allergic bronchopulmonary aspergillosis or active non-tuberculous *Mycobacterial* infection.

Types of interventions

We will include studies comparing oral antibiotics with inhaled antibiotics. Short-term use (< 4 weeks) for treating acute exacerbations and longer-term use as a prophylactic (≥ 4 weeks) will be considered separately. We will consider intraclass as well as interclass comparisons. We will include the following comparison groups.

1. Inhaled aminoglycosides versus oral antibiotics
2. Inhaled polymyxin versus oral antibiotics
3. Inhaled beta-lactam versus oral antibiotics

Types of outcome measures

Primary outcomes

We will include the following primary outcomes for short-term therapy, longer-term therapy or both, as indicated.

1. Duration of exacerbation (short-term)
2. Exacerbation (both), e.g. frequency during follow-up or time to first exacerbation
3. Hospitalisations due to exacerbations (both)
4. Serious adverse events (both)

Secondary outcomes

1. Response rates as defined by study authors (e.g. diary cards of physician global assessment)
2. Sputum volume and purulence
3. Measures of lung function (e.g. forced expiratory volume in one second (FEV_1))
4. Adverse events (e.g. cardiac arrhythmias, gastrointestinal symptoms, hearing impairment, bronchospasm)
5. Mortality
6. Emergence of resistance to antibiotics or treatment emergent pathogens
7. Exercise capacity (e.g. Six-Minute Walk Test (6MWT))
8. Quality of life (QOL) (e.g. St George Respiratory Questionnaire (SGRQ) or alternative QOL tools)
9. Eradication of pathogens

Reporting one or more of the outcomes listed here in the study is not an inclusion criterion for the review.

We will include the above secondary outcomes for both short-term and long-term therapy.

Search methods for identification of studies

Electronic searches

We will identify studies from the Cochrane Airways Group's Specialised Register (CAGR), which is maintained by the Information Specialist for the Group. The Register contains trial reports identified through systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, CINAHL, AMED, and PsycINFO, and handsearching of respiratory journals and meeting abstracts (please see Appendix 1 for further details). We will search all records in the CAGR using the search strategy in Appendix 2.

We will also conduct a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the WHO trials portal (www.who.int/ictrp/en/). We will search all databases from their inception to the present, and we will impose no restriction on language of publication.

Searching other resources

We will check the reference lists of all primary studies and review articles for additional references. We will search relevant manufacturers' websites for study information.
We will search for errata or retractions from included studies published in full text on PubMed and report the date this was done within the review.

Data collection and analysis

Selection of studies

Two review authors (PG and LF) will screen the titles and abstracts of the search results independently and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full-text study reports of all potentially eligible studies and two review authors (PG and LF) will independently screen them for inclusion, recording the reasons for exclusion of ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third person/review author (SS/SJM). We will identify and exclude duplicates and collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Moher 2009).

Data extraction and management

We will use a data collection form for study characteristics and outcome data, which has been piloted on at least one study in the review. One review author (LF) will extract the following study characteristics from included studies.

1. Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, withdrawals and date of study.
2. Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications and excluded medications.
4. Outcomes: baseline exacerbation data (e.g. frequency, duration), primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for studies and notable conflicts of interest of trial authors.

Two review authors (RN and LF) will independently extract outcome data from included studies. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We will resolve disagreements by consensus or by involving a third person/review author (SS/SJM). One review author (LF) will transfer data into the Review Manager file (RevMan 2014). We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (SS) will spot-check study characteristics for accuracy against the study report.

Assessment of risk of bias in included studies

Two review authors (RN and LF) will assess risk of bias independently for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreements by discussion or by involving another author (SS/SJM). We will assess the risk of bias according to the following domains:

1. random sequence generation;
2. allocation concealment;
3. blinding of participants and personnel;
4. blinding of outcome assessment;
5. incomplete outcome data;
6. selective outcome reporting; and
7. other bias.

We will judge each potential source of bias as high, low or unclear risk, and provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We will summarise the 'Risk of bias' judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient-reported pain scale). Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table.
When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and justify any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data as odds ratios (ORs) and continuous data as mean differences (MDs) or standardised mean differences (SMDs). We will enter data presented as a scale (e.g.

quality of life measures) with a consistent direction of effect. We will describe skewed data narratively (for example, as medians and interquartile ranges for each group).

We will undertake meta-analyses only where this is meaningful; that is, if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense.

Where multiple trial arms are reported in a single study, we will include only the relevant arms. If two comparisons (e.g. drug A versus placebo and drug B versus placebo) are combined in the same meta-analysis, we will either combine the active arms or halve the control group to avoid double-counting.

If adjusted analyses are available (ANOVA or ANCOVA) we will use these as a preference in our meta-analyses. If both change from baseline and endpoint scores are available for continuous data, we will use change from baseline scores unless there is low correlation between measurements in individuals. If a study reports outcomes at multiple time points (repeated observations), we will perform separate analyse for different periods of follow-up.

We will use intention-to-treat (ITT) analyses where they are reported (i.e. all those who were randomised are analysed) instead of completer or per protocol analyses.

Unit of analysis issues

For dichotomous outcomes, we will use participants, rather than events, as the unit of analysis (i.e. number of children admitted to hospital, rather than number of admissions per child). However, if rate ratios are reported in a study, we will analyse them on this basis. We will only meta-analyse data from cluster-RCTs if the available data have been adjusted (or can be adjusted), to account for the clustering.

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as an abstract only). Where this is not possible, and the missing data are thought to introduce serious bias, we will take this into consideration in the GRADE rating for affected outcomes.

Assessment of heterogeneity

We will use the I^2 statistic to measure heterogeneity among the studies in each analysis. If we identify substantial heterogeneity we will report it and explore the possible causes by prespecified subgroup analysis.

Assessment of reporting biases

If we are able to pool more than 10 studies, we will create and examine a funnel plot to explore possible small study and publication biases.

Data synthesis

We will use a random-effects model and perform a sensitivity analysis with a fixed-effect model.

'Summary of findings' table

We will create a 'Summary of findings' table using the following outcomes: duration of exacerbations, exacerbations (frequency and time to first exacerbation), frequency of hospitalisations due to exacerbations, serious adverse events, response rates, mortality and quality of life. We will use the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data for the prespecified outcomes. We will use the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using GRADEpro software (GRADEpro GDT). We will justify all decisions to downgrade the quality of studies using footnotes and we will make comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses.

1. Adults versus children (18 years or younger)
2. Patients chronically infected with *Pseudomonas aeruginosa* versus those not infected with *Pseudomonas aeruginosa*
3. Macrolide versus non-macrolide oral antibiotic

We will use the following outcomes in subgroup analyses.

1. Exacerbation duration (short-term therapy)
2. Exacerbation, e.g. frequency during follow-up or time to first exacerbation
3. Hospitalisation due to exacerbations
4. Adverse events

We will use the formal test for subgroup interactions in Review Manager (RevMan 2014).

Sensitivity analysis

We plan to carry out the following sensitivity analyses, removing the studies judged as high risk of bias from the primary outcome analyses.

1. Exacerbation duration (short-term therapy)
2. Exacerbation, e.g. frequency during follow-up or time to first exacerbation (both)
3. Hospitalisation due to exacerbations
4. Adverse events

We will compare the results from a fixed-effect model with the random-effects model.

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REFERENCES

Additional references

Altenburg 2011a
Altenburg J, de Graaff CS, van der Werf TS, Boersma WG. Immunomodulatory effects of macrolide antibiotics - part 1: biological mechanisms. *Respiration* 2011;**81**(1):67–74.

Altenburg 2011b
Altenburg J, de Graaff CS, van der Werf TS, Boersma WG. Immunomodulatory effects of macrolide antibiotics - part 2: advantages and disadvantages of long-term, low-dose macrolide therapy. *Respiration* 2011b;**81**(1):75–87.

Altenburg 2013
Altenburg J, de Graaff CS, Stienstra Y, Sloos JH, van Haren EH, Koppers RJ, et al. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial. *Journal of the American Medical Association* 2013;**309**(12):1251–9.

BNF (online)
Joint Formulary Committee. British National Formulary. www.medicinescomplete.com/mc/?utm_source=bnforg&utm_medium=homepage&utm_campaign=medicinescomplete (accessed 13 October 2016).

Brodt 2014
Brodt AM, Stovold E, Zhang L. Inhaled antibiotics for stable non-cystic fibrosis bronchiectasis: a systematic review. *European Respiratory Journal* 2014;**44**(2):382–93. [DOI: 10.1183/09031936.00018414]

Chalmers 2012
Chalmers JD, Smith MP, McHugh BJ, Doherty C, Govan JR, Hill AT. Short- and long-term antibiotic treatment reduces airway and systemic inflammation in non-cystic fibrosis bronchiectasis. *American Journal of Respiratory and Critical Care Medicine* 2012;**186**(7):657–65.

Chalmers 2016
Chalmers JD, Aliberti S, Polverino E, Vendrell M, Crichton M, Loebinger M, et al. The EMBARC European Bronchiectasis Registry: protocol for an international observational study. *European Respiratory Journal* 2016;**2**(1):00081–2015. [DOI: 10.1183/23120541.00081-2015]

Chang 2003
Chang AB, Bell SC, Byrnes CA, Grimwood K, HolmesP, King PT, et al. Chronic suppurative lung disease and bronchiectasis in children and adults in Australia and New Zealand: a position statement from the Thoracic Society of Australia and New Zealand and the Australian Lung Foundation. *Medical Journal of Australia* 2010;**193**(6):356–65.

Dudley 2008
Dudley MN, Loutit J, Griffith DC. Aerosol antibiotics: considerations in pharmacological and clinical evaluation. *Current Opinion in Biotechnology* 2008;**19**(6):637–43.

European Lung White Book 2013
Gibson GJ, Loddenkemper R, Lundback Bo, Sibille Y (eds). Bronchiectasis. *European Lung White Book: Respiratory Health and Disease in Europe*. European Respiratory Society, 2013. [http://www.erswhitebook.org/]

Felix 2017a
Felix Lambert M, Grundy S, Milan Stephen J, Armstrong R, Harrison H, Lynes D, et al. Dual antibiotics for non-cystic fibrosis bronchiectasis. *Cochrane Database of Systematic Reviews* 2017, Issue 1. [DOI: 10.1002/14651858.CD012514]

Felix 2017b
Felix LM, Chalmers JD, Spencer S, Donovan T, Milan SJ, Mathioudakis AG. Continuous versus intermittent antibiotics for non-cystic fibrosis bronchiectasis. Cochrane Database of Systematic Reviews.

Geller 2009
Geller DE. Aerosol antibiotics in cystic fibrosis. *Respiratory Care* 2009;**54**(5):658–70.

Goeminne 2010
Goeminne P, Dupont L. Non-cystic fibrosis bronchiectasis: diagnosis and management in 21st century. *Postgraduate Medical Journal* 2010;**86**(1018):493–501.

Goeminne 2014
Goeminne PC, Vandooren J, Moelants EA, Decraene A, Rabaey E, Pauwels A, et al. The Sputum Colour Chart as a predictor of lung inflammation, proteolysis and damage in non-cystic fibrosis bronchiectasis: a case-control analysis. *Respirology* 2014;**19**(2):203–10.

Goeminne 2016
Pieter G, De Soyza A. Bronchiectasis: how to be an orphan with many parents?. *European Respiratory Journal* 2016;**47**(1):10–3.

GRADEpro GDT [Computer program]
GRADE Working Group, McMaster University. GRADEpro GDT. Version accessed 1 March 2017. Hamilton (ON): GRADE Working Group, McMaster University, 2014.

Habesoglu 2011
Habesoglu MA, Ugurlu AO, Eyuboglu FO. Clinical, radiologic, and functional evaluation of 304 patients with bronchiectasis. *Annals of Thoracic Medicine* 2011;**6**(3):131–6.

Higgins 2011
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Hnin 2015
Hnin K, Nguyen C, Carson KV, Evans DJ, Greenstone M, Smith BJ. Prolonged antibiotics for non-cystic fibrosis bronchiectasis in children and adults. *Cochrane Database of Systematic Reviews* 2015, Issue 8. [DOI: 10.1002/14651858.CD001392.pub3]

Kaehne 2017
Kaehne A, Milan SJ, Felix LM, Spencer S, Sheridan E, Marsden PA. Head to head trials of antibiotics for non-cystic fibrosis bronchiectasis. Cochrane Database of Systematic Reviews 2017.

Kelly 2016
Kelly C, Evans David J, Chalmers James D, Crossingham I, Spencer S, Relph N, et al. Macrolide antibiotics for non-cystic fibrosis bronchiectasis. *Cochrane Database of Systematic Reviews* 2016, Issue 10. [DOI: 10.1002/14651858.CD012406]

Kolbe 1996
Kolbe J, Wells AU. Bronchiectasis: a neglected cause of respiratory morbidity and mortality. *Respirology* 1996;**1**(4):221–5.

Lonni 2015
Lonni S, Chalmers JD, Goeminne PC, McDonnell MJ, Dimakou K, De Soyza A, et al. Etiology of non-cystic fibrosis bronchiectasis in adults and its correlation to disease severity. *Annals of the American Thoracic Society* 2015;**12**(12):1764–70.

Moher 2009
Moher D, Liberati A, Tetzlaff J, Altman D. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine* 2009;**6**(7):e1000097. [DOI: 10.1371/journal.pmed.1000097]

Pasteur 2010
Pasteur MC, Bilton D, Hill AT, British Thoracic Society Bronchiectasis non-CF Guideline Group. British Thoracic Society guideline for non-CF bronchiectasis. *Thorax* 2010;**65**(Suppl 1):i1–58.

Quint 2016
Quint JK, Millett ER, Joshi M, Navaratnam V, Thomas SL, Hurst JR, et al. Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004 to 2013: a population-based cohort study. *European Respiratory Journal* 2016;**47**(1):186–93.

Quon 2014
Quon BS, Goss CH, Ramsey BW. Inhaled antibiotics for lower airway infections. *Annals of the American Thoracic Society* 2014;**11**(3):425–34.

Restrepo 2015
Restrepo MI, Keyt H, Reyes LF. Aerolized antibiotics. *Respiratory Care* 2015;**60**(6):762-1; discussion 771-3.

RevMan 2014 [Computer program]
Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Roberts 2010
Roberts HJ, Hubbard R. Trends in bronchiectasis mortality in England and Wales. *Respiratory Medicine* 2010;**104**:981–5.

Rubin 2008
Rubin BK. Aerosolized antibiotics for noncystic fibrosis bronchiectasis. *Journal of Aerosol Medicine and Pulmonary Drug Delivery* 2008;**21**(1):71–6.

Ryan 2011
Ryan G, Singh M, Dwan K. Inhaled antibiotics for long-term therapy in cystic fibrosis. *Cochrane Database of Systematic Reviews* 2011, Issue 3. [DOI: 10.1002/14651858.CD001021.pub2]

Seitz 2010
Seitz AE, Olivier KN, Steiner CA, Montes de Oca R, Holland SM, Prevots DR. Trends and burden of bronchiectasis-associated hospitalizations in the United States, 1993-2006. *Chest* 2010;**138**:944–9.

Seitz 2012
Seitz AE, Olivier KN, Adjemian J, Holland SM, Prevots DR. Trends in bronchiectasis among Medicare beneficiaries in the United States, 2000-2007. *Chest* 2012;**142**(2):432–9.

Serisier 2013
Serisier DJ, Martin ML, McGuckin MA, Lourie R, Chen AC, Brain B, et al. Effect of long-term, low-

dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis: the BLESS randomised controlled trial. *JAMA* 2013;**309**(12):1260–7.

Welsh 2015
Welsh EJ, Evans DJ, Fowler SJ, Spencer S. Interventions for bronchiectasis: an overview of Cochrane systematic reviews. *Cochrane Database of Systematic Reviews* 2015, Issue 7. [DOI: 10.1002/14651858.CD010337.pub2]

Weycker 2005
Weycker D, Edelsberg J, Oster G, Tino G. Prevalence and economic burden of bronchiectasis. *Clinical Pulmonary Medicine* 2005;**12**(4):205–9.

Wilson 2016
Wilson R, Aksamit T, Aliberti S, De Soyza A, Elborn JS, Goeminne P, et al. Challenges in managing pseudomonas aeruginosa in non-cystic fibrosis bronchiectasis. *Respiratory Medicine* 20165;**117**:179–89.

Wong 2012
Wong C, Jayaram L, Karalus N, Eaton T, Tong C, Hockey H, et al. Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. *Lancet* 2012;**380**(9842):660–7.

Yang 2015
Yang JW, Fan LC, Lu HW, Miao XY, Mao B, Xu JF. Efficacy and safety of long-term inhaled antibiotic for patients with noncystic fibrosis bronchiectasis: a meta-analysis. Clinical Respiratory Journal 2015 Jan 26 [Epub ahead of print]. [DOI: 10.1111/crj.12278]

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Group's Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
CENTRAL (T*he Cochrane Library*)	Monthly
MEDLINE (Ovid)	Weekly
Embase (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

Bronchiectasis search

1. exp Bronchiectasis/
2. bronchiect$.mp.
3. bronchoect$.mp.
4. kartagener$.mp.
5. (ciliary adj3 dyskinesia).mp.
6. (bronchial$ adj3 dilat$).mp.
7. or/1-6

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases.

Appendix 2. Search strategy to identify relevant studies from the CAGR

#1 BRONCH:MISC1
#2 MeSH DESCRIPTOR Bronchiectasis Explode All
#3 bronchiect*
#4 #1 or #2 or #3
#5 MeSH DESCRIPTOR Anti-Bacterial Agents Explode 1
#6 antibiotic* or anti-biotic*
#7 anti-bacteri* or antibacteri*
#8 *cillin
#9 *mycin OR *micin
#10 *oxacin
#11 *tetracycline
#12 macrolide*
#13 quinolone*
#14 trimethoprim
#15 ceph*
#16 sulpha*
#17 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
#18 #4 and #17
Note: in search line #1, MISC1 denotes the field in the record where the reference has been coded for condition, in this case, bronchiectasis.

CONTRIBUTIONS OF AUTHORS

All review authors contributed to the Background section. SJM and SS contributed to the Methods section.

PG and LF will independently screen titles and abstracts for inclusion of all the studies we identify as a result of the search and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full-text study reports/publication.

PCG and LF will independently screen the full-text and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third review author (SS, SJM or JDC).

RN and LF will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreements by discussion or by involving another review author (SS, SJM or JDC).

LF, SS and SJM will complete the analyses and Results section. All review authors will contribute to the Discussion, Conclusions and remaining sections of the review.

DECLARATIONS OF INTEREST

SS is the lead applicant on a grant from Edge Hill University that provides support staff for a number of bronchiectasis reviews. She is also an editor with the Cochrane Airways Group.

LF: none known

SM: none known

RN: is Deputy Co-ordinating Editor with the Cochrane Airways Group.

PCG has received lecture fees from Novartis, Chiesi, Eurogenerics, Astra Zeneca and Boehringer and received travel accommodation from Chiesi and Novartis.

JDC has received research funding from Astrazeneca and Pfizer, and has received lecture fees or served on advisory boards for Bayer, Griffols, Astrazeneca, Pfizer, Napp and Chiesi.

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