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# Continuous versus intermittent antibiotics for non-cystic fibrosis bronchiectasis (Protocol)

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[Intervention Protocol]

# Continuous versus intermittent 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 evaluate the effectiveness of continuous versus intermittent antibiotics in the treatment of adults and children with bronchiectasis.

## BACKGROUND

### Description of the condition

Bronchiectasis is a chronic airway disease characterised by abnormal destruction and dilation of the large airways, bronchi and bronchioles (Pasteur 2010). It is characterised radiologically by permanent dilation of the bronchi, and clinically by a syndrome of cough, sputum production and recurrent respiratory infections (Chalmers 2014). The pathogenesis of bronchiectasis can be explained by the vicious cycle theory, whereby an initial insult to the airway leads to bronchial wall inflammation and damage, and disordered mucociliary clearance, predisposing the patient to chronic or recurrent infection resulting in further airway damage (Cole 1986; Chalmers 2013). An understanding of this cycle of persistent bacterial colonisation, chronic inflammation of the bronchial mucosa, and progressive tissue destruction is central to the management of bronchiectasis as strategies to arrest both inflammatory and bacterial components are required to limit the progression of lung injury (Cole 1997; Pasteur 2010). Approximately half of presenting cases are idiopathic, but the most common aetiology is a previous chest infection, such as bacterial pneumonia or tuberculosis (Pasteur 2010). Diagnosis is based on identification of one or more abnormally dilated bronchi using high-resolution computed tomography (HRCT) (Chang 2010; Pasteur 2010). Bacteria most commonly isolated from the airways of patients with bronchiectasis include non-typeable*Haemophilus influenzae*, *Pseudomonas aeruginosa, Streptococcus pneumoniae, Staphylococcus aureus* and *Moraxella catarrhalis* (Foweraker 2011). Colonising pathogens such as *P aeruginosa, H influenzae* and *M catarrhalis* also commonly display antimicrobial resistance arising from intrinsic resistance mechanisms or frequent exposure to antimicrobial agents.

Approximately 29% to 70% of presenting cases are classified as idiopathic. The most commonly assigned aetiology is post-infectious bronchiectasis, a heterogenous group including patients with childhood respiratory infections like pertussis, bacterial pneumo-

nia or tuberculosis (Pasteur 2010). Diagnosis is based on identification of one or more abnormally dilated bronchi using HRCT (Chang 2010; Pasteur 2010). The main aim of therapeutic management is reduction of symptoms, such as cough, breathlessness and expectoration, reduction of the number and duration of exacerbations and improvement in quality of life (Chalmers 2015; Pasteur 2010).

Bronchiectasis was once considered a relatively rare disease but recent studies have suggested an increasing prevalence, particularly in those aged over 75 years (Weycker 2005), and higher prevalence rates in low-income and middle-income countries (Habesoglu 2011). Globally, it is estimated that prevalence in adults will increase from about 2.4 million in 2012 to over 3 million by 2020 (Polverino 2014). In the UK, point prevalence rates per 100,000 rose from 350.5 to 566.1 in women and from 301.2 to 485.5 in men over a nine-year period, reflecting an increase of more than 60% and approximately 263,000 adults living with bronchiectasis in 2013 (Quint 2016). Similarly, incidence rates per 100,000 person-years over the same period rose from 21.2 to 35.2 in women and from 18.2 to 26.9 in men, a 63% increase, with over 15,000 new cases in 2013. The prevalence per 10,000 across Europe ranges from 6.6 in Germany to 7.9 in Sweden and 36.2 in Spain (Miravitlles 2016; Ringshausen 2015).

The disease has a significant impact on children with worse quality of life in younger children and those with more frequent exacerbations (Kapur 2012). Bronchiectasis is also more common in some indigenous groups where prevalence may be as high as 16 per 1000 among southwest Alaskan children and 15 per 1000 in Australian Aboriginal and Torres Strait Islander children (Chang 2002). Furthermore, one study reported an incidence of 3.7 per 100,000 per year among New Zealand children aged under 15 years. This equates to an overall prevalence of 1 per 3000 children and 1 per 625 Pacific children (Twiss 2005). It also demonstrates that the incidence rate among children in New Zealand is almost seven times higher than those from Finland (Twiss 2005).

An improvement in diagnosis resulting from easier access to high quality CT scanners, and increased awareness of symptoms common to bronchiectasis and other lung diseases, have been cited as factors contributing to increased prevalence (Goeminne 2016).

Non-cystic fibrosis (CF) bronchiectasis places an increasing burden on healthcare systems internationally (Redondo 2016; Chalmers 2015), with patients experiencing a high rate of exacerbations, hospital admissions and attributable mortality (Chalmers 2015). Patients colonised with *P aeruginosa* and those with a more frequent annual exacerbation rate have an accelerated decline in lung function, reduced health-related quality of life (measured using the St George's Respiratory Questionnaire, SGRQ), increased risk of hospitalisation and increased mortality risk (Evans 1996; Martinez-Garcia 2007; Wilson 1997). A history of exacerbations, and particularly severe exacerbations, low body mass index, chronic bacterial infection, low forced expiratory volume in one second ($FEV_1$ )percentage predicted, a higher proportion of affected lobes and more breathlessness are also associated with an increased risk of hospitalisation and mortality (Chalmers 2014; Rogers 2014; Seitz 2010). Average European mortality rates per 100,000 general population are estimated at 0.3 in 27 of the 28 European Union (EU) countries (ranging from 0.01 in Germany to 1.18 in the UK) and 0.2 in nine non-EU countries (ranging from 0.01 in Azerbaijan to 0.67 in Kyrgyzstan), based on 2005 to 2009 data (Gibson 2013). More recent UK figures estimate age-adjusted mortality rates to be more than twice (2.26 in women, 2.14 in men) that of the general population (Quint 2016).

Bronchiectasis care is associated with substantial resource use. A recent Spanish study reported a mean direct annual medical cost for adult patients with bronchiectasis of EUR 4671, escalating with disease severity (de la Rosa 2016). Furthermore, factors such as $FEV_1$ percentage predicted, age, *Pseudomonas* colonisation and hospitalisation may independently influence health care costs. A USA-based study reported an annual increase of USD 2319 in overall costs and USD 1607 in respiratory-related costs in patients with bronchiectasis compared with matched case-controls, attributed primarily to an increase of two outpatient visits and 1.6 respiratory-related visits per patient per year (Joish 2013).

## Description of the intervention

Antibiotics, aiming to treat bacterial infections of the respiratory tract, or to control bacterial colonisation, or both, represent a central component of the treatment of non-CF bronchiectasis, as they reduce bacterial load, inflammation and consequent tissue destruction in the airways (Chalmers 2012). Long-term prophylactic antibiotics, administered for more than three months, have proved effective for patients with frequent bronchiectasis exacerbations or those with fewer exacerbations causing significant morbidity, as they appear to decrease the frequency and severity of exacerbations, at the expense of a significant increase in the risk of emerging drug resistance (Hnin 2015). Patients taking continuous antibiotics are more than three times at risk of bacterial resistance compared to those who do not (Hnin 2015). Pathogens isolated in the sputum cultures of these patients during an exacerbation or at stable disease, such as *P aeruginosa, H influenzae or M catarrhalis* commonly display antimicrobial resistance arising from intrinsic resistance mechanisms or frequent exposure to antimicrobial agents. There is also risk of antibiotic-related adverse effects, such as hearing impairment and cardiotoxicity (Serisier 2013).

Randomised controlled trials (RCTs) have evaluated different modes of administration, namely oral, intravenous and inhaled, and different classes of antibiotics including but not limited to macrolides, quinolones or polymyxins. Two strategies for the administration of long-term antibiotics have been described: (I) continuous and (ii) intermittent administration. In contrast to continuous, intermittent refers to the repeated prophylactic admin-

istration of courses of antibiotics with predefined duration and intervals. Examples include one short course of antibiotics every month; month on and month off; or during the winter months. This review will include intermittent antibiotic therapy where administration is at predefined regular intervals over a duration of at least three weeks, and where patients are not receiving concomitant prophylactic antibiotics. We will compare continuous versus intermittent administration of long-term prophylactic antibiotics for at least three months.

### How the intervention might work

There is a strong relationship between airway bacterial infection and disease morbidity in bronchiectasis for example, patients chronically infected with *P aeruginosa* have a three-fold increase in mortality, a 6.5 times increase in hospital admission rate and an average of one additional exacerbation per patient per year, when compared to patients not chronically infected with *P aeruginosa* (Finch 2015). Other commonly isolated bacteria such as *H influenzae* and *M catarrhalis* also drive an increase in neutrophilic inflammation (Chalmers 2012) and are associated with an increased risk of severe exacerbations (Chalmers 2014). Antibiotic treatment aims to suppress neutrophilic inflammation, reduce bacterial load and thereby improve clinical outcomes (Brodt 2014). Continuous administration of antibiotic treatment is based on the assumption that chronic infection cannot be eradicated, and must therefore be continuously suppressed to prevent a return of bacterial load, increased inflammation and a recurrence of symptoms (Haworth 2014).

The principal of intermittent treatment is that with continuous exposure to antibiotics, bacteria become resistant and treatment may lose its effectiveness (Chalmers 2015). On the contrary, intermittent administration of antibiotics might remove or limit the antibiotic selection pressure and, consequently, prevent the development of resistance. While data are lacking on the impact of intermittent versus continuous administration of antibiotics on the development of antibiotic resistance among patients with bronchiectasis, there is ample indirect evidence. Characteristically, in a large retrospective analysis of mechanically-ventilated patients with nosocomial infections, it was demonstrated that an interval of at least 20 days between serial courses of antibiotics is associated with a 24% reduction in development of resistance (Hui 2013).

An additional advantage of intermittent antibiotic administration is a reduced treatment burden to patients and that continuous administration may result in more side effects as a result of higher cumulative exposure of the patient to antibiotics.

### Why it is important to do this review

While long-term antibiotic treatments given both orally and via inhalation are part of the standard care for patients with bronchiectasis (Chalmers 2015), there is no agreement on the optimal method of delivery of antibiotic therapies. It is common practice to administer both oral and inhaled antibiotics daily (Altenburg 2013; Haworth 2014), on alternate days (Wong 2012), month on and month off (Barker 2014) or during the winter months where patients may experience more exacerbations. International guidelines are unable to comment on which method of antibiotic administration is most effective or is associated with the lowest rates of adverse events or antibiotic resistance. A European Respiratory Society/European Bronchiectasis Network (EMBARC) task force produced 22 consensus recommendations for future research into bronchiectasis, including "Studies should evaluate whether cyclic or continuous administration of long-term antibiotics is superior both in terms of clinical efficacy and the emergence of resistance" (Aliberti 2016). As this was determined to be an important clinical question by both patients and physicians, this systematic review aims to evaluate the current evidence for continuous vs intermittent administration of antibiotic treatment in bronchiectasis.

## OBJECTIVES

To evaluate the effectiveness of continuous versus intermittent antibiotics in the treatment of adults and children with bronchiectasis.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We will include randomised controlled trials (RCTs) and cluster-randomised trials . We will also include cross-over studies, but will only use data from the first pre-cross-over phase to eliminate potentially irreversible carry-over effects (e.g. antibiotic resistance). We will include studies reported as full-text, those published as abstract only, and unpublished data.

#### Types of participants

We will include adults and children (< 18 years) diagnosed with bronchiectasis by bronchography, or computed tomography who report daily signs or symptoms, such as cough, sputum production, or those with recurrent episodes of chest infections. Studies will be excluded if participants had received a diagnosis of cystic fibrosis (CF) or active allergic bronchopulmonary aspergillosis. Data on children and adults will be analysed separately.

### Types of interventions

We will compare continuous versus intermittent administration of long-term prophylactic antibiotics of at least three months duration. The delivery method should be the same in all study groups, e.g. nebulised versus nebulised, in order to isolate the effect of the antibiotic rather than the delivery device.

We will consider intermittent administration of antibiotics, provided there are predefined regular intervals of antibiotic administration followed by a duration of at least three weeks when participants do not receive prophylactic antibiotics (e.g. one short course of antibiotics every month; month on and month off; or during the winter months).

### Types of outcome measures

#### Primary outcomes

1. Exacerbations (frequency, proportion with one or more, duration, time to next exacerbation) (defined using study authors' criteria).
2. Antibiotic resistance, defined as either the presence of antibiotic resistance after the administration of antibiotics for at least three months, or the development of antibiotic resistance within at least three months of antibiotic administration. We will only evaluate resistance to the antibiotic(s) being investigated.
3. Serious adverse events.

#### Secondary outcomes

1. Health-related quality of life using measures validated in a clinical setting (e.g. SGRQ, LCQ, QoL-B).
2. Hospital admissions due to exacerbations (frequency, duration) (defined using study authors' criteria).
3. Mortality (we will extract and report whether mortality is defined as all-cause or bronchiectasis-related in the individual studies).
4. Sputum volume and colour.
5. Symptoms (cough, dyspnoea, wheeze).
6. Lung function measured as forced expiratory volume in one second ($FEV_1$) (litres or percent of predicted).
7. Exercise capacity (e.g. 6MWD).
8. Adverse events/side effects.

We will use the definitions from Edwards 2000 and Hansen 2015 for serious adverse events and adverse events as follows:

1. Serious adverse events are those that result in death or life-threatening events; requirement for hospitalisation or prolongation of existing hospitalisation; persistent or significant disability; or congenital anomalies, or are events that are considered medically important.
2. Adverse events are any untoward occurrence that may present while a patient is taking a drug but which does not necessarily have a causal relation to the treatment. They are undetectable by the patient; usually identified by laboratory tests (e.g. biochemical, haematological, immunological, radiological, pathological tests) or by clinical investigations (e.g. gastrointestinal endoscopy, cardiac catheterisation).

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

## Search methods for identification of studies

### Electronic searches

We will identify studies from the Cochrane Airways Trials Register, which is maintained by the Information Specialist for the Group. The Cochrane Airways Trials Register contains studies identified from several sources:

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), through the Cochrane Register of Studies Online (crso.cochrane.org);
2. Weekly searches of MEDLINE Ovid SP 1946 to date;
3. Weekly searches of Embase Ovid SP 1974 to date;
4. Monthly searches of PsycINFO Ovid SP;
5. Monthly searches of CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature);
6. Monthly searches of AMED EBSCO (Allied and Complementary Medicine); and
7. Handsearches of the proceedings of major respiratory conferences.

Studies contained in the Trials Register are identified through search strategies based on the scope of Cochrane Airways. Details of these strategies, as well as a list of handsearched conference proceedings, are in Appendix 1. See Appendix 2 for search terms used to identify studies for this review.

We will search the following trials registries:

1. USA National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov)
2. World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch)

We will search the Cochrane Airways Trials Register and additional sources from inception to present, with 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 (AM and TD) 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 (AM and TD) 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 review author (JC). 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 (TD) 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: 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 (TD 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 review author (JC). One review author (TD) will transfer data into the Review Manager file (Review Manager 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 (LF) will spot-check study characteristics for accuracy against the study report.

### Assessment of risk of bias in included studies

Two review authors (LF and TD) 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 (SM). 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 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, and continuous data as mean differences or standardised mean differences. We will enter data presented as a scale with a consistent direction of effect. We will undertake meta-analyses only when this is meaningful (i.e. when treatments, participants and the underlying clinical question are similar enough for pooling to make sense).

We will narratively describe skewed data reported as medians and interquartile ranges.

When multiple trial arms are reported in a single trial, 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 halve the control group to avoid double-counting.

### Unit of analysis issues

In all included studies, the unit of analysis will be the participant. In terms of exacerbation rates and hospitalisation rates, we plan to focus on the number of events experienced by the participant during the trial and to analyse the results using rate ratios if possible. We will use adjusted data if it is available (e.g. rate ratios from

Poisson regression models, or mean differences from ANOVA or results from cluster randomised studies adjusted for cluster effect) as first choice, followed by change scores and final scores as last choice.

### 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 conduct meta-analyses when the population, interventions, outcomes and study designs are similar. In presence of substantial heterogeneity (> 50%), we will report outcomes in the text, giving direction and size of the effect along with the strength of the evidence (risk of bias). We envisage that antibiotic studies will vary by population, design, and outcomes, therefore meta-analysis using a random-effects model would be most appropriate. However, where there are few studies or the effects of interventions across studies are not randomly distributed (e.g. with publication bias), the estimates from a random-effects model may be unreliable or biased. It is likely that this review will only include a small number of low-powered studies, therefore we will use a fixed-effect model, reported with 95% confidence intervals (CI), and evaluate the impact of model choice using a sensitivity analysis. We will synthesise and report dichotomous and continuous data separately for each outcome (e.g. exacerbation/no exacerbation or exacerbation duration). Where end-of-study point estimates and change from baseline scores are reported, we will analyse these separately. Furthermore, we will use standardised mean difference (SMD) when outcomes are measured using different scales (e.g. health-related quality of life measures). We will also use standard deviation (SD) of baseline for SMD analyses.

### 'Summary of findings' table

We will create a 'Summary of findings' table using the following outcomes: exacerbations, antibiotic resistance, serious adverse events, hospitalisations, mortality, symptoms 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. Mode of delivery (e.g. oral, nebulised).
2. Antibiotic class (e.g. macrolide).
3. Duration participants colonised with *P aeruginosa.*
4. Specifically for the outcome antibiotic resistance, we will carry out subgroup analyses according to the definition of antibiotic resistance (presence versus development of antibiotic resistance after the administration of antibiotics for at least three months).

We will use the following outcomes in subgroup analyses:

1. Exacerbations.
2. Antibiotic resistance.
3. Serious adverse events.

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

### Sensitivity analysis

We plan to evaluate the impact of methodological quality by using the following domains to remove studies at high or unclear risk of bias:

1. Random sequence generation.
2. Allocation concealment.

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

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* *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 (the Cochrane Library) | Monthly |
| MEDLINE (Ovid) | Weekly |
| Embase (Ovid) | Weekly |
| PsycINFO (Ovid) | Monthly |

(*Continued*)

| | |
|---|---|
| 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 studies for the CAGR**

**Condition search**

1. exp Asthma/
2. asthma$.mp.
3. (antiasthma$ or anti-asthma$).mp.
4. Respiratory Sounds/
5. wheez$.mp.
6. Bronchial Spasm/
7. bronchospas$.mp.
8. (bronch$ adj3 spasm$).mp.
9. bronchoconstrict$.mp.
10. exp Bronchoconstriction/
11. (bronch$ adj3 constrict$).mp.
12. Bronchial Hyperreactivity/
13. Respiratory Hypersensitivity/
14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.
15. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp.

16. or/1-15
17. exp Aspergillosis, Allergic Bronchopulmonary/
18. lung diseases, fungal/
19. aspergillosis/
20. 18 and 19
21. (bronchopulmonar$ adj3 aspergillosis).mp.
22. 17 or 20 or 21
23. 16 or 22
24. Lung Diseases, Obstructive/
25. exp Pulmonary Disease, Chronic Obstructive/
26. emphysema$.mp.
27. (chronic$ adj3 bronchiti$).mp.
28. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.
29. COPD.mp.
30. COAD.mp.
31. COBD.mp.
32. AECB.mp.
33. or/24-32
34. exp Bronchiectasis/
35. bronchiect$.mp.
36. bronchoect$.mp.
37. kartagener$.mp.
38. (ciliary adj3 dyskinesia).mp.
39. (bronchial$ adj3 dilat$).mp.
40. or/34-39
41. exp Sleep Apnea Syndromes/
42. (sleep$ adj3 (apnea$ or apnoea$)).mp.
43. (hypopnoea$ or hypopnoea$).mp.
44. OSA.mp.
45. SHS.mp.
46. OSAHS.mp.
47. or/41-46
48. Lung Diseases, Interstitial/
49. Pulmonary Fibrosis/
50. Sarcoidosis, Pulmonary/
51. (interstitial$ adj3 (lung$ or disease$ or pneumon$)).mp.
52. ((pulmonary$ or lung$ or alveoli$) adj3 (fibros$ or fibrot$)).mp.
53. ((pulmonary$ or lung$) adj3 (sarcoid$ or granulom$)).mp.
54. or/48-53
55. 23 or 33 or 40 or 47 or 54

### Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomised 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 studies 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
*[In search line #1, MISC1 denotes the field in the record where the reference has been coded for condition, in this case, bronchiectais]*

## CONTRIBUTIONS OF AUTHORS

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

## DECLARATIONS OF INTEREST

J Chalmers: part of the EMBARC group that set research priorities in bronchiectasis. He also receives grant support from Pfizer, AstraZeneca and GlaxoSmithKline. In addition, he is part of an innovative medicines initiative consortium that includes Novartis and Basilea. He has participated in advisory boards for BayerHealthCare, Chiesi and Raptor Pharmaceuticals. He has received fees for speaking from Napp, AstraZeneca, BI and Pfizer. None of these conflicts of interest are related to the work of this review and are unrelated to the topic of the review.

T Donovan: none known.

L Felix: none known.

A Mathioudakis: none known.

S Milan: none known.

S Spencer: named co-investigator on a study conducted to develop a series of reviews on bronchiectasis.

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### Internal sources

- Edge Hill University, UK.

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### External sources

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Evidence to guide care in adults and children with asthma, 13/89/14