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Head-to-head trials of antibiotics for non-cystic fibrosis bronchiectasis (Protocol)

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[Intervention Protocol]

Head-to-head trials of 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 comparative effects of different antibiotics in the treatment of adults and children with non-cystic fibrosis bronchiectasis.

BACKGROUND

Description of the condition

Bronchiectasis is characterised by abnormal dilation of the airways that is associated with a pathological mechanism of progressive airway destruction, due to the 'vicious cycle' of recurrent bacterial infection, inflammatory mediator release, airway damage and subsequent further infection (Cole 1986). The airways show chronic inflammation with various features, including loss of ciliated epithelium and mucous gland hypertrophy. Bacterial colonisation is facilitated by this loss of an integral epithelial structure (host defence) which, in turn, triggers further immune responses and a continuation of the inflammatory process. An understanding of this cycle 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. Typically microbiology for bronchiectasis patients includes *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis* and, importantly, *Pseudomonas aeruginosa*, though the microbiological profile differs between adults and children with *Pseudomonas* more common in adults and prevalent in only 0% to 6% of children. *Pseudomonas* colonisation often occurs later in the natural progression of the condition and may infer a worse prognosis in terms of symptoms, exacerbations and loss of lung function (Evans 1996). In severe cases, the cycle of lung infection may lead to repeated hospitalisation, chronic respiratory failure and death.

Most adult cases of bronchiectasis are either idiopathic or due to a previous severe lung infection. However, treatable causes, such as immune-deficiency, allergic bronchopulmonary aspergillosis, mycobacterial infection and recurrent aspiration may be identified in a minority of cases (Pasteur 2010; Goeminne 2012; Wilson 2013). One study found a proportion of cases were associated with chronic obstructive pulmonary disease (COPD) and connective tissue dis-

eases (Loni 2015). Underlying causes can be determined in up to 70% of paediatric cases (Eastham 2004; Twiss 2005). Diagnosis is based on a combination of clinical symptoms and high-resolution computerised tomography (HRCT) that show one or more abnormally dilated bronchi (Chang 2010; Pasteur 2010). Symptoms may include chronic productive cough, wheeze and breathlessness, together with recurrent lower respiratory tract infections. Colonisation with *P. aeruginosa* and frequent exacerbations are associated with accelerated decline in lung function (Evans 1996; Martínez García 2007), and, along with impaired exercise capacity and respiratory symptoms, reduced quality of life and hospitalisations (Wilson 1997; Finch 2015).

Management of bronchiectasis requires careful attention to sputum clearance, bronchodilator therapy, and the prescription of antibiotics (Welsh 2015). In the short term, the main aim is to reduce microbial load in order to reduce the severity and frequency of exacerbations, thereby ameliorating symptoms and improving quality of life (Pasteur 2010), with the longer-term aim of breaking the infection cycle, slowing the decline in lung function and reducing mortality rates. Antibiotics have traditionally been reserved for the treatment of acute infection/exacerbation although there is possibly a role for prophylactic strategies in some cases. Latterly the use of macrolides has attracted further interest and trials have explored their prescription in bronchiectasis patients (Wu 2014).

Global prevalence estimates are unclear because of variable diagnostic strategies (Weycker 2005), and higher prevalence rates in low and middle income countries (Habesoglu 2011). 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 nine-year period in the USA (Seitz 2010). Higher prevalence rates were associated with people over 60 years of age and women, and varied by ethnicity (Chang 2003; Seitz 2012). Recent data from a UK study suggests that incidence and prevalence may be higher than previously estimated (Quint 2016). Over a nine-year period to 2013, point prevalence rates per 100,000 rose from 350.5 to 566.1 in women and from 301.2 to 485.5 in men. This reflects an increase of more than 60% with almost 263,000 adults living with bronchiectasis in 2013. Similarly, the incidence rates per 100,000 person-years rose from 21.2 to 35.2 in women and from 18.2 to 26.9 in men. Representing an approximate increase in new cases of 63% to over 15,000 in 2013. Bronchiectasis is also associated with higher age-adjusted mortality rates, with estimates 2.26 times higher in women and 2.14 times higher in men compared to the general population (Quint 2016). The disease has a significant impact on paediatric populations where quality of life is worse for younger children and those with a more frequent annual exacerbation rate (Kapur 2012). Global prevalence estimates are variable, ranging from conservative estimates of 17.2 in the North-East of England (Eastham 2004), to 33.5 in New Zealand (Twiss 2005), per 100,000 children under 15 years. Rates may be higher in children from indigenous populations, with estimates of 1 per 625 (160 per 100,000) in children from the pacific islands (Twiss 2005), 15 per 1000 (1500 per 100,000) in native central Australian Aborginal children, and 16 per 1000 (1600 per 100,000) in native Alaksan children (Singleton 2000; Chang 2002).

The economic burden of bronchiectasis may be considerable but little data is available. Data collected in 2001 in the USA reported an additional 2.0 days in hospital, 6.1 more outpatient encounters and 27.2 more days of antibiotic therapy associated with bronchiectasis (Weycker 2005). Estimates of the overall additional annual costs of bronchiectasis range from USD 5681 to USD 7827, based on data collected between 2001 and 2009 (Weycker 2005; Seitz 2010; Joish 2013).

Description of the intervention

Bronchiectasis is characterised by daily coughing, sputum expectoration and recurrent respiratory infection. Serial infections often culminate in bacterial colonisation with dilatation and inflammation of the airways. Whilst abnormalities may be pan-lobar (i.e. throughout both lungs), infection may be limited to a single lung lobe or manifest in a patchy distribution. Antibiotics are used to reduce bacterial burden, to tackle the cycle of infection and tissue damage (Cole 1984; Pasteur 2010). They may be administered short-term (less than four weeks) to treat acute exacerbations or for longer ($\geq$ 4 weeks). Longer durations of antibiotics are used for pathogen eradication, suppression of bacterial load or for anti-inflammatory properties (e.g. macrolides). Several routes of administration are available including: oral, inhaled and parenteral routes, with analysis of sputum bacteriology informing the specific choice of antibiotic. Prescribing is also informed by clinical context as well as bacteriology and sputum purulence is considered a reliable indicator of the need for treatment (Hill 1988). Antibiotics may therefore be prescribed before the results of sputum bacteriology are obtained. Antibiotics are a frontline therapy for the management of bacterial load in bronchiectasis but their use is tempered with the need for considered use in the face of adverse effects and increasing concerns over antibiotic resistance (Pasteur 2010).

How the intervention might work

A range of antibiotic strategies have been used to reduce bacterial load and re-infection rates in people with bronchiectasis, including short-term prescriptions for acute exacerbations and longer-term prophylactic use in patients with frequent exacerbations where chronic sputum purulence is a common feature (Evans 2003; Chalmers 2012). Longer-term use of antibiotics is not currently recommended as part of routine treatment (Valery 2012; Wu 2014), but may be considered for patients with frequent exacerbations (three or more per year requiring antibiotic therapy)

(Pasteur 2010). Antibiotic choice is usually guided by sputum microbiology and patterns of local antibiotic resistance but treatment is often started empirically with a broad spectrum oral or intravenous antibiotic until the specific pathogen has been isolated. If there is more than one positive culture an antibiotic is selected to cover both. However, dual therapy is likely where monotherapy will not suffice, such as with *Pseudomonas* spp, a common pathogen in bronchiectasis. Macrolide antibiotics may additionally be prescribed for their potential anti-inflammatory properties as well as antibacterial effects.

Why it is important to do this review

Evidence for the effectiveness of a range of treatment strategies in bronchiectasis is limited by the number and quality of clinical trials, including those on antibiotics, and the need for evidence on head-to-head comparisons of antibiotics have been highlighted as a key priority (Welsh 2015). The comparative cost-effectiveness of within-class antibiotics, e.g. from different manufacturers, is unclear but this type of evidence could be used to inform choice of antibiotic, particularly in developing countries where use of cheaper antibiotics may be more prevalent compared to developed countries.

Therefore this Cochrane Review will include studies that directly compare the effectiveness of two or more antibiotics, as well as consider issues relating to duration of treatment and mode of delivery. We will endeavour to draw together existing evidence comparing their effectiveness for non-cystic fibrosis bronchiectasis against key outcomes identified by Welsh 2015. We are conducting this as a Cochrane Review employing established methodology in accordance with the recent evaluation of these standards versus alternative approaches (Page 2016). This Cochrane Review is being conducted alongside four other closely-related reviews: *Macrolide antibiotics for non-cystic fibrosis bronchiectasis (*Kelly 2016*)* ;*Dual antibiotics for non-cystic fibrosis bronchiectasis (*Felix 2017a*); Oral versus inhaled antibiotics for non-cystic fibrosis bronchiectasis (*Spencer 2017*); and* Continuous versus intermittent antibiotics for *non-cystic* bronchiectasis (Felix 2017b). .

OBJECTIVES

To evaluate the comparative effects of different 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 articles, those published as abstracts only and unpublished data.

Types of participants

We will include adults and children (less than 18 years of age) diagnosed with bronchiectasis by bronchography or high-resolution computed tomography who report daily signs/symptoms, such as cough, sputum production, haemoptysis or those with recurrent episodes of chest infections. We will exclude studies if patients have been receiving continuous or high-dose antibiotics in the four weeks before the start of the study, if they have a diagnosis of traction bronchiectasis due to pulmonary fibrosis or if they have received a diagnosis of cystic fibrosis.

Types of interventions

We will include studies that compare one antibiotic with another where they are administered by the same delivery method, e.g. nebulised vs nebulised, in order to isolate the effect of the antibiotic rather than the delivery device. We will consider short-term use (less than four weeks) for treating acute exacerbations and longer-term use as a prophylactic ($\geq$ four weeks) separately. Also we will analyse generational comparisons (e.g. 3rd vs 4th generation fluoroquinolones) separately from between-class comparisons (e.g. penicillin vs fluoroquinolones).

Types of outcome measures

Primary outcomes

We will include the following primary outcomes.

1. Exacerbation, e.g. frequency during follow-up or time to first exacerbation.
2. Serious adverse events, defined according to Hansen 2015.

Secondary outcomes

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

1. Frequency of hospitalisations due to exacerbations of bronchiectasis.
2. Response rates as defined by study authors (e.g. diary cards of physician global assessment).
3. Sputum volume and purulence.
4. Measures of lung function (e.g. forced expiratory volume in one second (FEV_1)).
5. Systemic markers of infection (e.g. leucocyte count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)).

6. Adverse events (e.g. cardiac arrhythmias, gastrointestinal symptoms, hearing impairment).
7. Deaths, all-cause and respiratory, which we will analyse and report separately.
8. Emergence of resistance to antibiotics.
9. Exercise capacity (e.g. Six-Minute Walk Distance (6MWD)).
10. Quality of life (e.g. St George Respiratory Questionnaire (SGRQ) or QoL-B).

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

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 Cochrane Airways Group. The CAGR 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 World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) 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 reference lists of all primary studies and review articles for additional references. We will search relevant manufacturers' websites for trial information.

We will search for errata or retractions from included studies published in full-text on PubMed (www.ncbi.nlm.nih.gov/pubmed) and report the date that we perform this.

Data collection and analysis

Selection of studies

Two review authors, ES and LF, will independently screen all titles and abstracts of all studies we identify from the literature search and will code them as either 'retrieve' (eligible or potentially eligible/unclear studies) or 'do not retrieve'. We will retrieve the full-text study reports/publications of all articles in the 'retrieve' category. Two review authors, ES and LF, will independently screen the full-text articles 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 or SJM). We will identify and exclude duplicates and will 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 we will pilot on at least one study that we include in the review. One review author, LF, will extract study characteristics from included studies. We will extract the following study characteristics.

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 trial and notable conflicts of interest of trial authors.

Two review authors, AK and LF, will independently extract outcome data from the included studies. We will note in the 'Characteristics of included studies' table if an included trial did not report outcome data in a usable way. We will resolve any disagreements by consensus or by consulting a third review author (SS or SJM). One review author, LF, will transfer data into Review Manager 5 (RevMan 5) (Review Manager 2014). We will double-check that LF has entered data correctly by comparing the data presented in the systematic review with the study reports. A second review author, AK, will spot-check the study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (AK and LF) will independently assess the risk of bias for each included 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 and 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.
7. Other bias.

We will grade each potential source of bias as either high, low or unclear and will provide a quote from the study report together with a justification for our judgment 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 trial author, 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 report 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 either mean difference or standardised mean difference values. We will enter data presented as a scale with a consistent direction of effect.

We will undertake meta-analyses only where this is meaningful i.e. if the 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.

Where a single trial has multiple trial arms, we will include only the relevant trial arms. If two comparisons (e.g. drug A versus drug B and drug C versus drug B) are combined in the same meta-analysis, we will halve the comparison group to avoid double-counting.

Unit of analysis issues

In all included studies the unit of analysis will be the participant. We will analyse exacerbation rates as rate ratios if the data are available.

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 abstract only). Where this is not possible and we believe that the missing data may have introduced serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis**.**

Assessment of heterogeneity

We will use the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identify substantial heterogeneity, i.e. when I^2 is greater than 50% (Deeks 2011)„ we will report it and explore possible cause 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 fixed-effect model for meta-analysis and will perform a sensitivity analysis with a random-effects model.

'Summary of findings' table

We will create a 'Summary of findings' table using the following primary and secondary outcomes; exacerbations serious adverse events, response rates, deaths and quality of life. We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes. We will use methods and recommendations described in Section 8.5 (Higgins 2011) and Chapter 12 (Schünemann 2011)of the *Cochrane Handbook for Systematic Reviews of Interventions* using GRADEpro software (GRADEpro GDT 2016). We will justify all decisions to downgrade or upgrade the quality of studies using footnotes and we will make comments to aid the reader's understanding of the Cochrane Review where necessary.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses.

1. Adults vs children.
2. Dose or schedule, or both.
3. Duration (prophylactic antibiotics).
4. Type of antibiotic.

We will use the following outcomes in subgroup analyses.

1. Exacerbation duration (short-term therapy).
2. Exacerbation frequency (long-term therapy).
3. Hospitalisation.
4. Adverse events.

We will use the formal test for subgroup interactions in RevMan 5 (Review Manager 2014).

Sensitivity analysis

We plan to evaluate the impact of methodological study quality by removing studies at high or unclear risk of bias according to the following risk of bias domains: random sequence generation and allocation concealment. We will use a fixed-effect model as well as a random-effects model as part of our sensitivity analysis.

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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	Search frequency
CENTRAL (the Cochrane Library)	Monthly
MEDLINE (Ovid)	Weekly
EMBASE (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly

(*Continued*)

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 trials 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, bronchiectasis]

CONTRIBUTIONS OF AUTHORS

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

DECLARATIONS OF INTEREST

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

AK: none known

SM: none known

LF: none known

ES: none known

PM: received lecture fees and conference accommodation/fees from industry unrelated to the current review.

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- The authors declare that no external funding was received for this systematic review, Other.