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Dual antibiotics for non-cystic fibrosis bronchiectasis (Protocol)

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TABLE OF CONTENTS

[Intervention Protocol]

Dual 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 effects of dual antibiotics for treatment of adults and children with non-cystic fibrosis bronchiectasis.

BACKGROUND

Description of the condition

Non-cystic fibrosis bronchiectasis is a persistent respiratory condition associated with progressive destruction of the airways due to a 'vicious cycle' of recurrent bacterial infection, pulmonary inflammation and consequent structural damage (Cole 1997; Pasteur 2010). The pathological process of bronchiectasis leads to disruption of the normal epithelial barrier, which consequently allows inhaled pathogens to both colonise the airways and cause clinical episodes of infection (Cole 1986). In severe cases, this cycle of infection may lead to repeated hospitalisation, chronic respiratory failure and death. An understanding of the cycle is central to the management of bronchiectasis, as strategies to arrest both inflammatory and bacterial components are required to limit progression of lung injury. Approximately half of presenting cases are idiopathic, but the most common cause 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 on high-resolution computerised tomography (HRCT) with characteristic symptoms including breathlessness, chronic productive cough and recurrent lower respiratory tract infection (Chang 2010; Pasteur 2010). Patients colonised with *Pseudomonas aeruginosa* and those with a frequent annual exacerbation rate have an accelerated decline in lung function, reduced health-related quality of life (measured on St George's Respiratory Questionnaire), increased risk of hospitalisation and increased mortality risk (Evans 1996; Martinez Garcia 2007; Wilson 1997). Low forced expiratory volume in one second (FEV_1) % predicted, a higher proportion of affected lobes and increased breathlessness are associated with increased risks of hospitalisation and mortality (Chalmers 2014; Martinez Garcia 2014; Seitz 2010). Bacteria most commonly associated with infective exacerbations include *non-typeable Haemophilus influenzae*,*Pseudomonas aeruginosa, Streptococcus pneumoniae, Staphylococcus aureus* and*Moraxella catarrhalis* (Foweraker 2011). The microbiological profile differs between adults and children, and *Pseudomonas* is more common among adults. *Pseudomonas* is resistant to many oral antibiotics and is very difficult to eradicate, but it is prevalent in only 0 to 6%

of children. Colonising pathogens such as *Pseudomonas, H influenzae* and *M catarrhalis* also commonly display antimicrobial resistance as the result of frequent exposure to antimicrobial agents. The main aims of therapeutic management include preservation of lung function; reduction in symptoms, such as cough, breathlessness and expectoration; reduction in the number and duration of exacerbations; and improvement in quality of life (Lavery 2005; Pasteur 2010).

Global prevalence estimates are confounded by variable diagnostic strategies (Weycker 2005) and higher prevalence rates in developing countries (Habesoglu 2011), but the global burden of bronchiectasis is increasing, with mortality rates rising by 3% per year between 2001 and 2007 in England and Wales (Roberts 2010), and hospitalisations increasing by 3% per year over a nine-year period in the United States (Seitz 2010). Both Roberts 2010 and Seitz 2012 reported higher prevalence rates among women and in people over 60 years of age. More recent studies suggest that prevalence may be increasing more rapidly than was previously estimated. In Germany in 2013, prevalence was estimated at 67 cases per 100,000 general population (Ringshausen 2015). In the UK, from 2004 to 2013, incidence rates rose by approximately 63%, with an increase from 21.2 to 35.2 in women and from 18.2 to 26.9 in men, per 100,000 person-years (Quint 2016). Similarly, point prevalence rose from 350.5 to 566.1 in women and from 301.2 to 485.5 in men, per 100,000 head of population, with approximately 262,900 adults in the UK living with bronchiectasis in 2013. The disease has a significant impact on paediatric populations; younger children and those with more frequent exacerbations experience worse quality of life (Kapur 2012a). Bronchiectasis is more common in some ethnic groups, for example, southwest Alaskan children (16:1000) and Australian aborigine children (15:1000) (Chang 2002). Furthermore, one study reported an incidence of 3.7 per 10000 per year among children younger than 15 years old in New Zealand. This equates to a prevalence of 1:3000 children overall and 1:625 in Pacific children () (Twiss 2005). It also demonstrates that the incidence rate among children in New Zealand is almost seven times higher than among those in Finland (Twiss 2005). Average mortality rates per 100,000 general population in Europe are estimated at 0.3 in 27 of the 28 EU countries (ranging from 0.01 in Germany to 1.18 in the UK) and at 0.2 in nine non-EU countries (ranging from 0.01 in Azerbaijan to 0.67 in Kyrgyzstan), on the basis of 2005 to 2009 data (European Lung White Book 2013). More recent UK figures estimate that age-adjusted mortality rates are 2.26 times higher in women and 2.14 times higher in men compared with the general population (Quint 2016).

Description of the intervention

The lungs of patients with non-cystic fibrosis bronchiectasis are commonly colonised by bacteria, and treatment with antibiotics can help to decrease bacterial load while reducing systemic inflammation (Kapur 2012). Antibiotics are used to reduce bacterial burden and to tackle the cycle of infection and lung damage, consequently helping to reduce the impact and frequency of chest infection and the frequency and duration of hospital admissions while also reducing mortality (Cole 1986; Pasteur 2010). Antibiotics can be administered on a short-term (< 4 weeks) or longer-term (≥ 4 weeks) basis via various modes, including oral, inhaled and intravenous routes, with specific choice of antibiotic informed by analysis of sputum bacteriology. Antibiotics serve as front-line therapy for management of bacterial load, but their use is weighed against potential adverse effects and increasing concerns about antibiotic resistance (Pasteur 2010).

'Combination' or 'dual' antibiotic therapy for non-cystic fibrosis bronchiectasis is defined as the combination of two or more antibiotics, rather than use of a single antibiotic (monotherapy), irrespective of the route of administration or the duration of therapy. Dual antibiotic therapy is commonly administered therapeutically over a short duration (up to four weeks), rather than prophylactically for prevention, and is commonly used to treat patients with acute exacerbations whose lungs are colonised by multiple strains of bacteria with different patterns of antibiotic resistance, when monotherapy is unlikely to be effective. Dual therapy may also be used when the clinician is concerned about increasing the risk of antibiotic resistance, for example, when antibiotics have been prescribed frequently or for a prolonged duration. British Thoracic Society guidelines recommend the use of combination antibiotics when patients present with multiple pathogens (Pasteur 2010).

How the intervention might work

Chronic bacterial airway colonisation commonly occurs in patients with non-cystic fibrosis bronchiectasis; high bacterial load is associated with increased inflammation and symptoms and worse quality of life (McShane 2013). It has been hypothesised that inflammation contributes to progression of non-cystic fibrosis bronchiectasis, and evidence suggests that the presence of bacteria in the airways promotes inflammation (Haworth 2014). Bronchiectatic airways are commonly colonised by multiple bacteria or different strains of the same bacteria, some of which may not be positively cultured in the laboratory. Bacterial load can be reduced through treatment with systemic antibiotics (Rubin 2014), and various antibiotic strategies have been used to reduce bacterial load and reinfection, including short-term (< 4 weeks) therapy for acute exacerbations and longer-term (≥ 4 weeks) prophylactic therapy for frequent exacerbations characterised by chronic sputum purulence (Chalmers 2012; Evans 2003). Although longer-term antibiotics are not recommended for routine treatment (Valery 2012; Wu 2014), they may be considered for treatment of patients with frequent exacerbations (three or more per year requiring antibiotic therapy) (Pasteur 2010). Dual antibiotic therapy for exacerbations could reduce bacterial load and levels of inflammation, consequently improving clinically mean-

ingful outcomes, such as length of exacerbation, frequency of exacerbation, disease progression and mortality.

Why it is important to do this review

The benefits and risks of dual antibiotics given for management of acute exacerbations and for prophylaxis are currently unclear. It is important to weigh the benefits of dual antibiotics in terms of bacterial eradication and suppression of bacterial load against the risks of enhanced antibiotic resistance and exposure to side effects associated with multiple antibiotic therapy.

This review aims to summarise available evidence on the use of dual antibiotics for patients with bronchiectasis to inform clinical practice and future research needs. This review is being conducted alongside two other, closely related reviews: *Macrolide antibiotics for non-cystic fibrosis bronchiectasis* and *Head-to-head trials of antibiotics for non-cystic fibrosis bronchiectasis*.

OBJECTIVES

To evaluate the effects of dual antibiotics for 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 paediatric participants with a clinical diagnosis of bronchiectasis confirmed by plain film chest radiograph or HRCT. We will exclude studies in which participants were receiving continuous or high-dose antibiotics immediately before the study began or had received a diagnosis of cystic fibrosis (CF), sarcoidosis or active allergic bronchopulmonary aspergillosis.

Types of interventions

The main aim of this review is to compare the effectiveness of combined antibiotics versus monotherapy. As a secondary aim, we will compare the effectiveness of one combination of antibiotics versus another. We will include studies comparing dual antibiotics versus a single antibiotic, provided that both arms include a common route of administration. . We will analyse short-course (< 4 weeks) and long-term (≥ 4 weeks) dual antibiotics separately. This review will focus on comparisons of antimicrobial agents and will exclude comparisons of macrolides owing to their anti-inflammatory properties. Potential comparison groups for dual therapy versus monotherapy include the following.

1. Oral dual therapy versus oral monotherapy.
2. Intravenous dual therapy versus intravenous monotherapy.
3. Oral + inhaled dual therapy versus oral monotherapy.
4. Oral + intravenous dual therapy versus oral monotherapy.
5. Inhaled + intravenous dual therapy versus inhaled monotherapy.
6. Inhaled + oral dual therapy versus inhaled monotherapy.
7. Intravenous + inhaled dual therapy versus intravenous monotherapy.
8. Intravenous + oral dual therapy versus inhaled monotherapy.

We will include studies comparing one combination of antibiotics versus another if they compare different classes of antibiotics in combination or different administration routes of agents from the same class (e.g. IV cephalosporin + IV aminoglycoside vs IV cephalosporin + inhaled aminoglycoside).

Types of outcome measures

Primary outcomes

1. Successful treatment of exacerbation
2. Length of exacerbation
3. Length of hospitalisation
4. Time to next exacerbation
5. Frequency of exacerbations
6. Serious adverse event

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. Systemic markers of infection (e.g. leucocyte count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR))
5. Adverse events (e.g. cardiac arrhythmias, GI symptoms, hearing impairment, nephrotoxicity)

6. Deaths
7. Emergence of resistance to antibiotics
8. Exercise capacity (e.g. Six-Minute Walk Distance (6MWD))
9. Quality of life (e.g. St George's Respiratory Questionnaire (SGRQ))
10. Adverse events/side effects

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

Search methods for identification of studies

Electronic searches

We will identify studies from the Cochrane Airways Group 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, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Allied and Complementary Medicine Database (AMED) and PsycINFO, and by handsearching of respiratory journals and meeting abstracts (please see Appendix 1 for details). We will search all records in the CAGR using the search strategy presented in Appendix 2.

We will also conduct a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization (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 and 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 will report within the review the date this was done.

Data collection and analysis

Selection of studies

Two review authors (LF and SG) will independently screen titles and abstracts of all studies that we identify for possible inclusion as a result of the search and will code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve full-text study reports/publications, and two review authors (LF and SG) will independently screen them to identify studies for inclusion, and to identify ineligible studies and record reasons for their exclusion. We will resolve disagreements 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 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram and 'Characteristics of excluded studies' table (Moher 2009).

Data extraction and management

We will use a data collection form that has been piloted on at least one study in the review to record study characteristics and outcome data.. One review author (RA) 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 locations, study setting, withdrawals, date of study.
2. Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria, exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications, excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, time points reported.
5. Notes: funding for trial, notable conflicts of interest of trial authors.

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

Assessment of risk of bias in included studies

Two review authors (LF and RA) 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 disagreements by discussion or by consultation with another review author (SS or SJM). We will assess 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 high, low or unclear and will provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We will summarise risk of bias judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes when necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different from risk of bias for a patient-reported pain scale). When information on risk of bias is related 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 risk of bias for studies that contributed to those outcomes.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and will report 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 vs placebo and drug B vs 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 admission 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.

Dealing with missing data

We will contact investigators or study sponsors to verify key study characteristics and to obtain missing numerical outcome data when possible (e.g. when a study is identified as abstract only). When this is not possible, and the missing data are thought to introduce serious bias, we will perform a sensitivity analysis to explore the impact of including such studies in the overall assessment of results.

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 this and will explore possible causes by performing prespecified subgroup analyses.

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 will perform a sensitivity analysis using a fixed-effect model.

'Summary of findings' table

We will create a 'Summary of findings' table using the following primary and secondary outcomes: exacerbations, hospitalisations, 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 studies that contributed data to the meta-analyses for prespecified outcomes. We will adhere to methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and will use GRADEpro software (GRADEpro GDT). We will justify all decisions to downgrade or upgrade the quality of studies by using footnotes, and we will make comments to aid the reader's understanding of the review when necessary.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses.

1. Duration: short (< 4 weeks) and longer (≥ 4 weeks).
2. Type of antibiotic: aminoglycosides, beta-lactams, chloramphenicol, fluoroquinolones, macrolides, tetracyclines.
3. Children versus adults.
4. *Pseudomonas* colonisation versus no *P seudomonas* colonisation.

We will use the following outcomes in subgroup analyses.

1. Exacerbations.
2. Hospitalisations.
3. Serious adverse events.

We will use the formal test for subgroup interactions provided in Review Manager (RevMan 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: random sequence generation and allocation concealment.

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* *Indicates the major publication for the study*

APPENDICES

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

Electronic searches: core databases

Database	Frequency of search
MEDLINE (Ovid)	Weekly
Embase (Ovid)	Weekly
CENTRAL (the Cochrane Library)	Monthly
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. (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 (Lefebvre 2011) were 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 review authors contributed to the Background section. SJM and SS contributed to the Methods section.

HH will search trial registries, SG and LF will conduct screenings, RA and LF will extract data and complete the risk of bias assessment, LF will undertake data analysis and all review authors will contribute to writing of the report.

DECLARATIONS OF INTEREST

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