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Antibiotic therapy for chronic infection with Burkholderia cepacia complex in people with cystic fibrosis (Protocol)

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Antibiotic therapy for chronic infection with Burkholderia cepacia complex in people with cystic fibrosis

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A B S T R A C T

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

The objective of this review is to assess the effects of long-term oral and inhaled antibiotic therapy targeted against chronic BCC lung infections in people with CF. The primary objective is to assess the efficacy of treatments in terms of improvements in lung function and reductions in exacerbation rate. Secondary objectives include quantifying adverse events, mortality and changes in quality of life associated with treatment.

B A C K G R O U N D

Description of the condition

Cystic fibrosis (CF) is a common life-threatening inherited disease affecting over 10,000 people in the UK, 35,000 in Europe and 30,000 in the USA (CFF 2016; CF Trust 2014; Farrell 2008). There have been significant improvements in CF survival since the 1930s when 70% of those with CF died in infancy, to a current median predicted survival of 43.5 years (CF Trust 2014). Early CF deaths are now rare: over 95% of children with CF enter adulthood and those born in this century can expect to survive into at least their sixth decade. Recent predictions are that the number of CF adults will increase by 78% by 2025 (Burgel 2015).

In CF, the genetic autosomal-recessive defect in the CFTR protein causes abnormal salt and water movements across mucus-producing cell surfaces. This results in thick mucus leading to a combination of infection and inflammation with subsequent local organ damage, which is most apparent in the lungs and pancreas, but affects many other organs. In the lungs the hallmarks of disease are chronic airway inflammation and chronic infection with difficult to treat pathogens, such as *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Burkholderia cepacia* complex (BCC). Chronic airway infection is associated with a progressive loss of lung function, which is the primary cause of death in people with CF (Corey 1997).

BCC is comprised of a group of over 20 closely related species with a cumulative annual prevalence in people with CF of 3% to 5%; *Burkholderia cenocepacia* and *Burkholderia multivorans* account for 85% to 97% of BCC infections (CFF 2016; CF Trust 2017; Drevinek 2010; Mahenthiralingam 2002; Vandamme 2011). These two pathogens are associated with poor outcomes including accelerated pulmonary decline, a necrotizing pneumo-

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nia known as 'cepacia syndrome' and a higher mortality rate (Aris 2001; Mahenthiralingam 2002; Zlosnik 2015). *B cenocepacia* is the more pathogenic of the two, with an increased likelihood of chronic infection and reduced survival compared to *B multivorans* (Jones 2004; Mahenthiralingam 2001). Acquisition is often from environmental sources, but clonal transmission of epidemic strains has been extensively reported, particularly for *B cenocepacia*, and hence infection control and segregation measures are required to prevent cross-infection (Ledson 1998; LiPuma 2010; Zlosnik 2015).

Resistance to aminoglycosides, to most beta-lactams as well as to polymyxins is common within BCC and some species have the ability to develop resistance to any agent resulting in pan-resistant strains (CF Trust 2017; Drevinek 2010; Mahenthiralingam 2002). Therefore, the clinical management of chronic BCC infection in CF poses a challenge to clinicians.

Description of the intervention

Long-term antibiotics are one of the mainstays of treatment in people with CF with chronic infection. Administration is usually via the inhaled or oral route and aims to reduce the bacterial burden in sputum. Inhaled antibiotics allow rapid deposition of high concentrations of antibiotic direct to the site of action and hence represent an attractive strategy. In those with *P aeruginosa* infection, colistimethate, tobramycin and aztreonam have all demonstrated clinical benefit (Gibson 2003; McCoy 2008; Retsch-Bogart 2008; Ryan 2011). The low systemic absorption associated with inhaled antibiotics can help avoid some of the side-effects seen with intravenous antibiotics used in acute infection (Weber 1995).

Oral antibiotics are quick and convenient to take, but may not be able to deliver as high a concentration to the lung as inhaled formulations. Nevertheless, oral macrolide therapy has been shown to be effective in CF with a recent Cochrane Review demonstrating a reduction in pulmonary exacerbations and improved respiratory function after six months treatment of azithromycin (Southern 2012).

How the intervention might work

Long-term antibiotic therapy targeted towards *P aeruginosa* infections has been associated with improved clinical outcomes in people with CF and both inhaled and oral antibiotic therapies are recommended in that cohort (NICE 2017). There is no clear guidance on whether treatments targeted towards BCC are effective, but inhaled antibiotics may theoretically overcome traditional resistance breakpoints due the 100-fold increased concentrations achieved in the lung. Hence antimicrobial agents, with little or no activity against BCC at systemically achievable concentrations, may still exert bactericidal effects when inhaled into the lungs (Ramsey 1999).

Furthermore, macrolides have no in vitro bactericidal effect against *P aeruginosa*, yet appear to produce marked clinical improvements. This is most likely secondary to an anti-inflammatory effect with attenuated cytokine production and reductions in neutrophil elastase reported in a number of studies (Bell 2005; Wales 1999). Hence, despite BCC often demonstrating in vitro resistance to many of the antimicrobial agents available for chronic use in CF, there is hope that the principles of treatment and agents used in chronic *P aeruginosa* infection are relevant in BCC infection.

Why it is important to do this review

Chronic infection with BCC is associated with poorer clinical outcomes in people with CF. The inherent antibiotic resistance in these species makes the treatment of chronic infection challenging for clinicians. This review aims to assess the current evidence with regards to antibiotic treatment options for people with CF who are chronically infected with BCC to identify evidence-based strategies.

Strategies will primarily be assessed in terms of their ability to preserve or improve pulmonary function and to reduce acute pulmonary exacerbations.

O B J E C T I V E S

The objective of this review is to assess the effects of long-term oral and inhaled antibiotic therapy targeted against chronic BCC lung infections in people with CF. The primary objective is to assess the efficacy of treatments in terms of improvements in lung function and reductions in exacerbation rate. Secondary objectives include quantifying adverse events, mortality and changes in quality of life associated with treatment.

M E T H O D S

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (including cross-over trials) will be considered for inclusion in this review.

Types of participants

Adults and children with CF (confirmed by either a positive sweat test or the identification of two pathogenic CFTR mutations) and chronic BCC infection (defined as a positive respiratory culture

growth of BCC within the last six months and BCC growth in more than 50% of all respiratory cultures in the last 12 months) (Lee 2003).

Types of interventions

Long-term (defined as a period of eight weeks or more) antibiotics (all agents, doses and regimens) via either the inhaled or oral route*. Trials will be included if there is comparison against no treatment, placebo, another antibiotic agent, another mode of delivery, or another dose or regimen of the same antibiotic.

*Antibiotics administered via oral and inhaled route will be analysed and presented separately.

Types of outcome measures

Primary outcomes

1. Lung function
   i) Forced expiratory volume in one second (FEV_1)
      a) Absolute change in volumes, % predicted or both
      b) Relative change in volumes, % predicted or both
2. Pulmonary exacerbations
   i) Time to next exacerbation
   ii) Hospitalisations
   iii) Exacerbation rate
   iv) IV antibiotic use
3. Adverse events
   i) Proportion of participants who had to withdraw or change therapy
      a) mild: transient event, no treatment change, e.g. rash, nausea, diarrhoea
      b) moderate: treatment discontinued, e.g. nephrotoxicity, ototoxicity, hepatitis, visual impairment
      c) severe: causing hospitalisation or death

Secondary outcomes

1. Mortality
2. Quality of life (QoL)
   i) Validated QoL score (e.g. CFQ-R, CRISS score)
3. BCC culture
   i) Sputum density of BCC
4. Changes in inflammatory markers
   i) Sputum or bronchoalveolar lavage (BAL) samples
   ii) Serum or blood

Search methods for identification of studies

We will formulate a comprehensive search strategy in an attempt to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress).

Electronic searches

The Cochrane Cystic Fibrosis and Genetic Disorders Group's Information Specialist will conduct a systematic search of the Group's Cystic Fibrosis Trials Register for relevant trials using the following terms:cystic fibrosis and (burkholderia OR cepacia).

The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of the Cochrane Library), weekly searches of MEDLINE, a search of Embase to 1995 and the prospective handsearching of two journals - *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis*. Unpublished work is identified by searching the abstract books of three major cystic fibrosis conferences: the International Cystic Fibrosis Conference; the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference. For full details of all searching activities for the register, please see the relevant section of the Cochrane Cystic Fibrosis and Genetic Disorders Group's website.

We will search the following trials registries:
- the World Health Organization (WHO) International Clinical Trials Registry Platform (www.who.int/ trialsearch)
- Clinicaltrials.gov (www.clinicaltrials.gov)

See an appendix for details of the searches (Appendix 1).

Searching other resources

We will check the references of included trials and any relevant systematic reviews identified for further references to relevant trials.

Data collection and analysis

Selection of studies

Two review authors (FF, DN) will independently select trials to be included in the review. Where there is disagreement on the suitability of a trial for inclusion, all three review authors will attempt to reach a consensus decision after discussion.

Data extraction and management

Each author will independently extract data using standardised data collection forms. If there are any disagreements over the suitability of trials for inclusion in the review, we will aim to reach a consensus after discussion between all three review authors. We plan to compare outcome measures at eight weeks to three months, over three months to six months and over six months to one year. However, if we identify trials with outcome data at alternative time-points, we will also consider these. We will analyse oral and inhaled antibiotics separately.

Assessment of risk of bias in included studies

Each review author will independently assess trials following the domain-based evaluation as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). Briefly, a judgement of 'low risk', 'high risk' or 'unclear risk' of bias will be made for each of the seven domains in the Cochrane tool which.are listed below.

- Random sequence generation
- Allocation concealment
- Blinding of participant personnel
- Blinding of outcome assessment
- Incomplete outcome data
- Selective reporting
- Other sources of bias

If there are any disagreements between the three review authors, then we aim to reach a consensus by discussion.

Measures of treatment effect

For continuous outcomes, such as change in lung function and time to next exacerbation, we will calculate the mean difference (MD) with corresponding 95% confidence intervals (CI) to measure treatment effect. If trials report multiple variations of a similar outcome, we will calculate the standardized mean difference (SMD) and corresponding 95% CIs.

For dichotomous outcomes such as mortality, we will calculate odds ratios (OR) and corresponding CIs.

Unit of analysis issues

Given the long-term nature of the interventions we are investigating in this review, it is unlikely that we will identify any eligible cross-over trials; however, should we identify these, we will include data from such trials should the duration of treatment meet the inclusion criteria and if the relevant information, as described by Elbourne is available (Elbourne 2002). We aim to treat the trials as parallel trials and pool the intervention arms to be compared against the control arms, or alternatively perform analysis on the first period only. We will choose the method of analysis dependent on the information available.

Dealing with missing data

We will assess for missing data in reported results and report the percentage of participants from whom no outcome data were obtained on the data collection form. Unless there is reason to suspect data are not missing at random, we will include data on only those whose results are known in the analysis and use the total participants with complete data as the denominator rather than the total number of participants (Higgins 2011b).

Assessment of heterogeneity

We will assess heterogeneity of inconsistencies across trials using the I^2 statistic. We will interpret the I^2 statistic based on the thresholds of heterogeneity set out by Higgins (Higgins 2003):

- 0% to 40%: might not be important;
- 30% to 60%: may represent evidence of moderate heterogeneity;
- 50% to 90%: may represent evidence of substantial heterogeneity;
- 75% to 100%:may represent evidence of considerable heterogeneity.

Assessment of reporting biases

If we are able to include a sufficient number of trials (10 or more as recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a)), we will attempt to assess whether our review is subject to publication bias by using a funnel plot. If we detect asymmetry, we will explore causes other than publication bias.

Data synthesis

We will assess whether trials are clinically similar enough to combine into a meta-analysis, and if so, will assess for heterogeneity as set out above. If there is substantial heterogeneity (higher than 50%), we will undertake a random-effects meta-analysis, otherwise, we will use a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

We will conduct a subgroup analysis of outcomes in included trials for *B cenocepacia* and *B multivorans*.

Where it is reported, we will record outcome effects adjusted for the intermittent use of acute antibiotics during the trial period and we will conduct a subgroup analysis using these reported outcomes if there are sufficient data available.

Sensitivity analysis

If there are sufficient trials included (10 or more) we will review the validity of our conclusions in a sensitivity analysis. Firstly, we will carry out a sensitivity analysis to assess the influence of a high risk of bias in any domain on our results and conclusions. Secondly, if a fixed-effect model is used in an analysis, a random-effects model will also be tested, and vice-versa.

Summary of findings table

We will prepare summary of findings tables for each comparison included in the review, when, within each comparison, there is at least one included trial of any antibiotic therapy targeting chronic

BCC infection. We will include reported changes in the primary outcomes FEV_1 (changes in relative % predicted or volumes or both), time to next exacerbation and hospitalisations, mortality and adverse events (mild, moderate and severe). We will list population, setting, intervention and comparison and report an illustrative risk for the experimental and control intervention with MDs re-expressed as ORs if required (Schünemann 2011b). The grade of overall quality will be given using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) with comments (Schunemann 2006).

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* Indicates the major publication for the study

APPENDICES

Appendix 1. Search strategies - trial registries

Registry	Search terms
WHO ICTRP	Search terms: burkholderia OR cepacia Study type: interventional studies Condition: cystic fibrosis Phase: any
ClinicalTrials.gov	Condition: cystic fibrosis Intervention: antibiotic OR antimicrobial Phase: any

CONTRIBUTIONS OF AUTHORS

FF conceived the review and designed the protocol with input and advice from DN. MS provided advice regarding statistical methods.

DECLARATIONS OF INTEREST

All authors: none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK.

This systematic review was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group.