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Eradication therapy for *Burkholderia cepacia* complex in people with cystic fibrosis (Review)

Regan KH, Bhatt J

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[Intervention Review]

Eradication therapy for *Burkholderia cepacia* complex in people with cystic fibrosis

Kate H Regan[1], Jayesh Bhatt[2]

[1]NHS Lothian, Edinburgh, UK. [2]Paediatric Respiratory Medicine, Nottingham University Hospitals, Nottingham, UK

Contact address: Kate H Regan, NHS Lothian, Royal Infirmary of Edinburgh, 51 Little France Crescent, Edinburgh, EH16 4SA, UK. kateregan4@gmail.com.

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ABSTRACT

Background

Chronic infection with *Burkholderia cepacia* complex species remains a significant problem for clinicians treating people with cystic fibrosis. Colonisation with *Burkholderia cepacia* complex species is linked to a more rapid decline in lung function and increases morbidity and mortality. There remain no objective guidelines for strategies to eradicate *Burkholderia cepacia* complex in cystic fibrosis lung disease, as these are inherently resistant to the majority of antibiotics and there has been very little research in this area. This review aims to examine the current treatment options for people with cystic fibrosis with acute infection with *Burkholderia cepacia* complex and to identify an evidence-based strategy that is both safe and effective. This is an updated version of the review.

Objectives

To identify whether treatment of *Burkholderia cepacia* complex infections can achieve eradication, or if treatment can prevent or delay the onset of chronic infection. To establish whether following eradication, clinical outcomes are improved and if there are any adverse effects.

Search methods

We searched the Cochrane Cystic Fibrosis Trials Register, compiled from electronic database searches and handsearching of journals and conference abstract books. We also searched the reference lists of relevant articles and reviews.

Last search: 12 March 2019.

We also searched electronic clinical trials registers for the USA and Europe.

Date of last search: 12 March 2019.

Selection criteria

Randomised or quasi-randomised studies in people with cystic fibrosis of antibiotics or alternative therapeutic agents used alone or in combination, using any method of delivery and any treatment duration, to eradicate *Burkholderia cepacia* complex infections compared to another antibiotic, placebo or no treatment.

Data collection and analysis

Two authors independently assessed for inclusion in the review the eligibility of 52 studies (79 references) identified by the search of the Group's Trial Register and the other electronic searches.

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Main results

No studies looking at the eradication of *Burkholderia cepacia* complex species were identified.

Authors' conclusions

The authors have concluded that there was an extreme lack of evidence in this area of treatment management for people with cystic fibrosis. Without further comprehensive studies, it is difficult to draw conclusions about a safe and effective management strategy for *Burkholderia cepacia* complex eradication in cystic fibrosis. Thus, while the review could not offer clinicians evidence of an effective eradication protocol for *Burkholderia cepacia* complex, it has highlighted an urgent need for exploration and research in this area, specifically the need for well-designed multi-centre randomised controlled studies of a variety of (novel) antibiotic agents.

PLAIN LANGUAGE SUMMARY

Treatments to cure long-term infections with *Burkholderia cepacia* in people with cystic fibrosis

Review question

We reviewed the evidence for antibiotic treatment to cure early infection with *Burkholderia cepacia* complex in people with cystic fibrosis and prevent it becoming permanent.

Background

Cystic fibrosis is an inherited disease and people who have this disease produce large amounts of thick mucus which is difficult to clear. This mucus blocks up their lungs and digestive systems. People with cystic fibrosis suffer from lots of chest infections, which cause scarring of their airways. Eventually, they develop infections that can't be cured with antibiotics, so their lungs always contain lots of bugs, this is described as being chronically infected. One of these bugs, *Burkholderia cepacia*, causes a lot of problems for people with cystic fibrosis because it is very difficult to treat and makes their lung disease deteriorate faster than it otherwise would. This is an updated version of the review.

Search date

We last searched for any evidence on 12 March 2019.

Study characteristics

We looked for studies of treatments which could eliminate *Burkholderia cepacia* from the lungs of people with cystic fibrosis. We did not find any relevant studies. This review highlights an urgent need for more research into new ways of treating long-term *Burkholderia cepacia* infection in people with cystic fibrosis.

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BACKGROUND

Description of the condition

Cystic fibrosis (CF) is the most common autosomal recessive condition affecting people of Northern European descent (Farrell 2018), with an incidence of approximately 1 in 2500 (Ratjen 2003). A multisystem disease, CF primarily affects the lungs, pancreas and gastrointestinal (GI) tract, but in the majority of cases it is progressive lung disease that causes premature death. Frequent early bacterial infections progress to colonisation and chronic infection, resulting in an exaggerated neutrophil inflammatory response that leads to extensive lung damage (bronchiectasis), which over many years progresses to respiratory failure and death.

A mutation in an ion transporter, cystic fibrosis transmembrane conductance regulator (CFTR), results in abnormal sodium chloride exchange on the epithelia of people with CF. In the respiratory tract, it is likely that bacterial colonisation occurs because of reduced chloride secretion and increased sodium reabsorption. In the airway epithelium this leads to reduced water content of secretions as well as reduced depth of periciliary fluid, which in turn leads to the trapping of inhaled bacteria and slower clearance (Saiman 2004). There is also a growing body of evidence to suggest that the CF neutrophil displays delayed apoptosis (programmed cell death), resulting in prolonged inflammation and release of pro-inflammatory cytokines, which contributes to airway damage (Moriceau 2009; Moriceau 2010).

Over the course of their lives people with CF are vulnerable to bacterial infections caused by many different species, but over the last few decades a specific subgroup of pathogens affecting the CF population has been characterised. The most troubling of these are *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Burkholderia cepacia* complex pathogens (LiPuma 2010). The *B cepacia* complex (BCC) is the collective name for a group of at least 21 closely related bacteria that have been isolated from both human infections and the natural environment (Drevinek 2010; Loveridge 2017). Although not the most commonly isolated pathogen in people with CF, affecting approximately only 2% to 4% of such people in the USA (Drevinek 2010), it is amongst the most virulent; and chronic infection has been independently associated with increased morbidity and mortality in those affected (Corey 1996). In the UK, it was reported as being responsible for 1.4% and 5.1 %of lung infections in children and adults in 2017 (CF Trust 2017). The species are grouped into 'genomovars', a term which describes different strains of *B cepacia* according to their genetic content, each of which displays independent modes of transmission and clinical effects. There are currently 21 genomovars, and while all species within the complex have been isolated from humans, two species - *B cenocepacia* (genomovar III) and *B multivorans* (genomovar II), cause between 85% and 97% of BCC infections in people with CF (Drevinek 2010). A subset of species have been shown to be transmissible from one person to another and can cause epidemics, and as a result it is important for people with CF to be segregated according to presence or absence of BCC species (LiPuma 2010; St Denis 2007). Despite the fact that many people culture genotypically distinct strains of BCC and thus it is likely that they are contracted from independent environmental sources, the majority of cases are a result of transmission from other people with CF (LiPuma 2010; Mahenthiralingam 2001; Millar-Jones 1998).

In some people, infection is transient, while others remain stable for long periods despite chronic infection (CF Trust 2004); in rare cases people with CF succumb to a rapidly progressive pneumonia known as 'cepacia syndrome' (CF Trust 2009). For most people, however, chronic BCC infection develops and causes an unpredictable decline in lung function ranging from relatively mild to rapidly deteriorating, leading to a significant increase in both time spent in hospital and mortality (CF Trust 2004; Zlosnik 2011). Furthermore, presence of BCC infection before transplant results in a significant excess in post-transplant mortality, generally caused by overwhelming BCC sepsis (CF Trust 2004). The reasons for this variable outcome are not yet fully understood, but it has been suggested that the ability of some BCC species to produce copious exomucopolysaccharides (mucoid species) is linked to a milder course than those non-mucoid species, which appear to produce a more rapid and severe decline in lung function (Zlosnik 2011). Chronic infection is usually with a single species, but super- or co-infection with additional species can occur, and in addition there is *in vitro* evidence that commonly used antibiotics, e.g. ciprofloxacin, can cause mucoid strains to become non-mucoid (LiPuma 2010; Zlosnik 2011). In summary, there is a great deal of good quality evidence from well-designed studies that shows a significant clinical deterioration as a result of BCC infections.

This review will aim to identify intervention strategies to eradicate BCC infection or prevent or delay chronicity of that infection in people with CF. There is as yet no vaccine for any of the BCC species, which is linked in part to their variability, but there have been early animal studies that suggest vaccine therapy may be possible in the future (Sokol 2000). Until such time as an effective preventive measure is developed, it is of the utmost importance to develop strategies for treating infection once it has occurred. Species of BCC, particularly *B cenocepacia*, are intrinsically resistant to aminoglycosides, most beta lactams and polymyxins and are also capable of developing *in vivo* resistance to almost any antimicrobial agent (Drevinek 2010), with some UK centres reporting pan-resistance in over 80% of isolates (Moore 2001). Resistance can be observed in all strains (Nzula 2002), but environmentally- rather than clinically-acquired infections are usually more amenable to therapy (CF Trust 2009); it has been suggested that resistance is highest in *Burkholderia dolosa* (Vermis 2003).

Description of the intervention

The increasing longevity and reduced morbidity in people with CF observed in recent years is, in major part, due to the aggressive use of appropriate antibiotics to prevent, eradicate, or control respiratory infections. Flucloxacillin prophylaxis from diagnosis until three years of age is effective in reducing the incidence of *S aureus* infection (Smyth 2003), though such an approach has been unsuccessful with *P aeruginosa* (Tramper-Stranders 2010). However, early identification and eradication of *P aeruginosa* can successfully prevent or delay chronic infection (Douglas 2009; Gibson 2003; Gibson 2007; Langton Hewer 2009; Ratjen 2001; Ratjen 2006; Taccetti 2005); and once chronic infection is established, regular nebulised antibiotics or intermittent courses of intravenous antibiotics, or both, help in maintaining lung function and reducing sputum bacterial load (CF Trust 2009). It is possible that early aggressive treatment of certain BCC species with appropriate antibiotics may delay or prevent chronic infection.

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How the intervention might work

It has been shown that chronicity develops in 94% of *B cenocepacia* infections and 50% of *B multivorans* infections despite therapy, which as previously described, represent the vast majority of BCC infections, although in some people this may be transient (Ball 2010; Etherington 2003). Strategies that have been implemented to help prevent or delay infection include segregation according to infection or strain status and emphasis on hygiene of shared equipment, which appears to be effective (CF Trust 2004).

Despite the difficulties in determining an effective therapeutic regimen for BCC, some progress has been made in identifying strategies to eradicate other troublesome CF pathogens, such as *P aeruginosa*, (Langton Hewer 2009), and it is to be hoped that the principles of this therapy may be applicable to cases of BCC infection.

Why it is important to do this review

The outcome of BCC infection in people with CF is variable, but generally results in an increase in morbidity and mortality related to a decline in lung function. The epidemiology of these infections seems to be changing and treatment of these infections is challenging because of the inherent antibiotic resistance. There is no real consensus on the best way to treat these infections and as yet no standard treatment regimens for eradication. Successful eradication would hopefully reduce decline in lung function, and therefore morbidity and mortality, and improve quality of life. It is important to systematically analyse the evidence available in order to try and find a strategy that may help alleviate the burden of disease currently caused by BCC infections in people with CF. This is an updated version of the review (Regan 2012; Regan 2014; Regan 2016).

OBJECTIVES

To identify whether early, aggressive therapy of BCC infections is able to achieve eradication after initial acquisition or prevent or delay onset of chronic infection and whether this improves clinical outcome measures such as lung function, nutritional status, clinical scores and mortality.

To determine whether these therapies are linked to any adverse effects or cause an increase the isolates of other species in the lower respiratory tract.

To assess any evidence of superiority between different therapies or therapeutic regimens with respect to cost-effectiveness or clinical outcome.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised controlled studies.

Types of participants

Any person with a clinical diagnosis of CF that has been confirmed by sweat testing or genetic analysis, or both, who acquires a new infection or a re-infection with BCC. People of all ages and disease severity will be included.

Types of interventions

Any antibiotic or antibiotic adjuvant therapy used alone or in combination to eradicate BCC infection. Treatments may be compared to an alternative antimicrobial agent, a placebo or no treatment, (excluding the participant's usual therapeutic regimen). The mode of delivery of the intervention may be inhaled, oral or intravenous and there is no limit to the duration of therapy or dosage used.

Types of outcome measures

Primary outcomes

1. Eradication (i.e. no BCC positive cultures from bronchoalveolar lavage (BAL), sputum or oropharyngeal aspirate for a period of 12 months over a minimum of six samples)
2. Length of time remaining infection free (post-eradication therapy)

Secondary outcomes

1. Spirometric lung function, expressed as a per cent predicted based on age, sex and height
   a. forced expiratory volume at one second (FEV_1)
   b. forced vital capacity (FVC)
2. Growth and nutritional status
   a. body mass index (BMI) z score
   b. weight z score
   c. height (in children only) z score
3. Mortality
4. Quality of life (QoL) assessment (measured using all instruments, validated or not, e.g. the Cystic Fibrosis Questionnaire-Revised version (CFQ-R) (Quittner 2009) and the Cystic Fibrosis Quality of Life Questionnaire (CFQoL) (Gee 2000))
5. Adverse events of the eradication treatment used (as classified by the review authors), including microbiological sequelae (i.e. does eradication of *B cepacia* result in alternative colonisation?) and drug interactions or hypersensitivity reactions:
   a. mild: resulted in no change to treatment, e.g. mild sensitivity reactions
   b. moderate: resulted in a change in treatment, e.g. renal or auditory impairment
   c. severe: required hospital admission or is life-threatening, e.g. anaphylaxis

Search methods for identification of studies

Studies are eligible for inclusion in the review irrespective of publication status (e.g. abstract or online trial report) or language.

Electronic searches

We identified relevant studies from the Group's CF Trials Register using the terms: *Burkholderia cepacia* OR (mixed infections AND (eradication OR unknown)).

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

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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 sections of the Cochrane Cystic Fibrosis and Genetic Disorders Group website..

Date of the last search: 12 March 2019.

We searched a number of online trials registries as detailed in the appendices (Appendix 1).

Date of the last search: 12 March 2019.

Searching other resources

In addition to our search of the Group's CF Trials Register, we would also have handsearched the reference list of any study that we included. If, in future updates of the review, we identify any relevant papers in the reference lists of included studies, we will contact the authors for further information. To the best of our knowledge, there are no novel anti-BCC antimicrobial agents on that market at the current time, so we did not approach any manufacturers of antibiotics.

Data collection and analysis

Selection of studies

The two authors (KR, JB) independently applied the selection criteria to determine the studies to be included in the review. There was no disagreement between the authors. Where it was unclear which pathogens participants were colonised with, the authors contacted the relevant authors to find out if any participants had BCC species.

Data extraction and management

Both authors planned to extract data independently from any included studies using standard data acquisition forms. If there had been any disagreements on the risk of bias or suitability of a study, they planned to reach a consensus by discussion. The authors planned to extract information on the mode of delivery of drug treatment. If data become available in future, they will initially combine all data in the analysis and later undertake a subgroup analysis by mode of delivery (see below).

With cases of *P aeruginosa,* infection is defined as chronic when more than 50% of months, when samples had been taken, were *P aeruginosa*-culture positive and intermittent when 50% or less of months, when samples had been taken, were *P aeruginosa*-culture positive, People with CF are considered free of infection if no growth of *P aeruginosa* has been identified during the previous 12 months if they were previously *P aeruginosa*-culture positive or if *P aeruginosa* has never been cultured from sputum or a cough swab (Lee 2003). In accordance with this, the authors classified chronic infection as BCC cultured from more than 50% samples over 12 months; initial infection as those with a first isolation of BCC; and recent infection as those with less than 12 months history of BCC isolation. In future versions of this review, in those studies where this information is not included, the review authors will contact the study authors to seek this additional information.

In cases where participants are infected with multiple species, the review authors still planned to utilise data on eradication of *B. cepacia* as it remains clinically relevant since people with CF are often colonised with multiple species.

If data become available for future versions of this review, the authors plan to group data relating to the outcomes measured according to the time elapsed from baseline. Standard clinical practice is to take a sample at the end of any eradication therapy and thereafter at any routine clinical encounter and upon exacerbation. Thus the review authors will group data according to samples taken at: post-eradication therapy; up to three months; up to six months; up to nine months; up to one year; and over one year. In those cases where eradication is defined differently than above, the authors will discuss the alternative definition and decide whether it is comparable to their own or whether they should exclude the study from statistical analysis.

Assessment of risk of bias in included studies

Both authors planned to independently determine the risk of bias using the Cochrane Collaboration's tool for assessing risk of bias as detailed in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The authors aimed to examine the following from reported data for each included study: randomisation process; method of allocation concealment; degree of blinding; completeness of outcome data and whether intention-to-treat analyses were possible; and selective reporting.

If any studies are included in future updates of the review, where the authors view the description and methods of randomisation and allocation concealment to be adequate, they will consider this to be a low risk of bias and where methods are inadequate, a high risk of bias. If the methods are not sufficiently described, they will consider this to constitute an unclear risk of bias. The greater the degree of blinding in the intervention, the lower the risk of bias that the authors will attribute to the study, (e.g. a double-blinded study has a lower risk of bias than a single-blinded study). Where study investigators properly account for withdrawals from studies and these are of similar quantity across groups, the authors will judge the study to be at low risk of bias. However, where the authors deem that investigators inadequately justify withdrawals or their number are unevenly distributed between groups, the review authors will consider the study to be at high risk of bias. If the authors identify any evidence of selective outcome reporting as described in 'Assessment of reporting biases' below, they will consider the study to be at high risk of bias, if they find no evidence of selective reporting , they will consider the study to be at a low risk of bias.

In future, where there is disagreement over any aspect of the risk of bias for a given study, the authors will reach a consensus by discussion.

Measures of treatment effect

The absence of data available within the scope of this review has prevented the application of the methodology described below to the current version, but should any data become available in the future, we intend to use this protocol to analyse data.

The wide range of outcome measures the authors hope to assess in this review will produce data of distinct types and they will therefore assess these by different measures. They plan to collect data on all participants regardless of compliance or later decisions by study authors about suitability for inclusion in the results.

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For binary (dichotomous) data, they will identify the number of participants with each outcome event by allocated treatment group, and will use these data to calculate the odds ratio (OR) and 95% confidence intervals (CIs). For continuous data, the authors will separate outcome data (means and standard deviations (SDs)) according to allocated treatment group and calculate the mean difference (MD) and 95% CIs for each group. If outcomes are measured using different units of measurement, they will calculate the standardised mean difference (SMD). For time-to-event data, they plan to calculate the hazard ratio (HR) and 95% CIs according to the outcomes for each of the groups in the study.

Unit of analysis issues

The authors' inclusion criteria for studies in the review do not permit the use of cross-over studies or cluster-randomised studies. For a highly variable and chronic condition like CF, a cross-over study design is not appropriate as baseline values at the start of the second treatment arm are likely to be significantly different from those at the start of the first. Cluster-randomised studies present a unit of analysis issue, unless data are analysed only at the level of the group rather than an individual level. Furthermore, individuals in the same cluster tend to be more similar to one another than to individuals in other clusters, which represents a risk of bias. When analysing the data, the unit of analysis will be the individual and not the number of episodes of a given event (e.g. infection or adverse reaction).

Dealing with missing data

In future versions of this review, in those studies where data on outcome measures are not available for all participants enrolled in the studies, the authors will perform an available-case analysis using the available data. Where all randomised participants are accounted for they will perform an intention-to-treat (ITT) analysis.

Assessment of heterogeneity

In the event that data are available on this subject in future versions of this review, where sufficient studies are available, the authors will assess statistical heterogeneity using the I^2 statistic (Higgins 2003). They will consider I^2 values of under 25% to be of low heterogeneity; those between 26% and 50% to be moderate heterogeneity; those between 51% and 75% to be substantial heterogeneity; and those over 75% to be considerable heterogeneity. Their analysis will use 95% CIs, which should be sufficient for the number of participants they are likely to be considering, and they will perform a Chi^2 test. The Chi^2 analysis will allow the authors to determine whether any differences in results between studies are a result of chance. They will use the test to compare the statistical heterogeneity of studies in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions*, and will also use it in the visual assessment of forest plots (Deeks 2011).

Assessment of reporting biases

The authors plan to assess reporting bias by comparing the published outcome measures with those outcomes mentioned in the description of the methods within the published papers. In the event that important outcome measures have not been accounted for, they will contact the authors for information about both the missing data and the original study protocol. In accordance with guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2011), they will use the funnel plot tool to assess the publication bias of each study to be included.

Data synthesis

When data are available, the authors will use a fixed-effect model to analyse the data from the included studies where possible. However, if they detect at least substantial statistical heterogeneity using the I^2 statistic (over 50%), they will apply a random-effects model.

Subgroup analysis and investigation of heterogeneity

Where sufficient evidence is available (minimum 10 studies for meta-analysis - not achieved with this version of the review) the authors will investigate the effects of:

- dosage;
- duration of treatment, e.g. up to 14 days, up to one month, up to three months, up to six months, up to 12 months;
- antibiotic therapies used alone or when delivered in combination with adjuvant therapies;
- mode of delivery, e.g. inhaled and oral agents versus intravenous delivery.

We will achieve this by categorising participants into the related subgroups and performing meta-analyses on each of these subgroups.

Sensitivity analysis

The authors will test the robustness of their results using sensitivity analyses relating to:

- fixed-effect versus random-effects analysis;
- multicentre versus single-centre studies.

Summary of findings tables

We will construct a summary of findings table for each comparison included in the review using the GRADEpro software. We will consider the following outcomes:

1. eradication of BCC;
2. length of time remaining infection free (post eradication therapy);
3. FEV_1 (change from baseline);
4. BMI;
5. mortality;
6. QoL; and
7. adverse events.

Using the GRADE approach, described in Chapter 12 of *the Cochrane Handbook of Systematic Review for Interventions* (Schünemann 2011), we will classify the body of evidence as high, moderate, low or very low. Where we judge the evidence not to be high quality, we will describe the rationale for this judgement in footnotes to the table.

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RESULTS

Description of studies

Results of the search

Searches of the CFGD Group's CF Trials Register identified 50 studies (77 references) and two studies (one reference each) were identified by an additional electronic search (NCT00298922; Uluer 2013). None of these met the inclusion criteria for the review (see Excluded studies).

This process is graphically represented in a study flow diagram (Figure 1).

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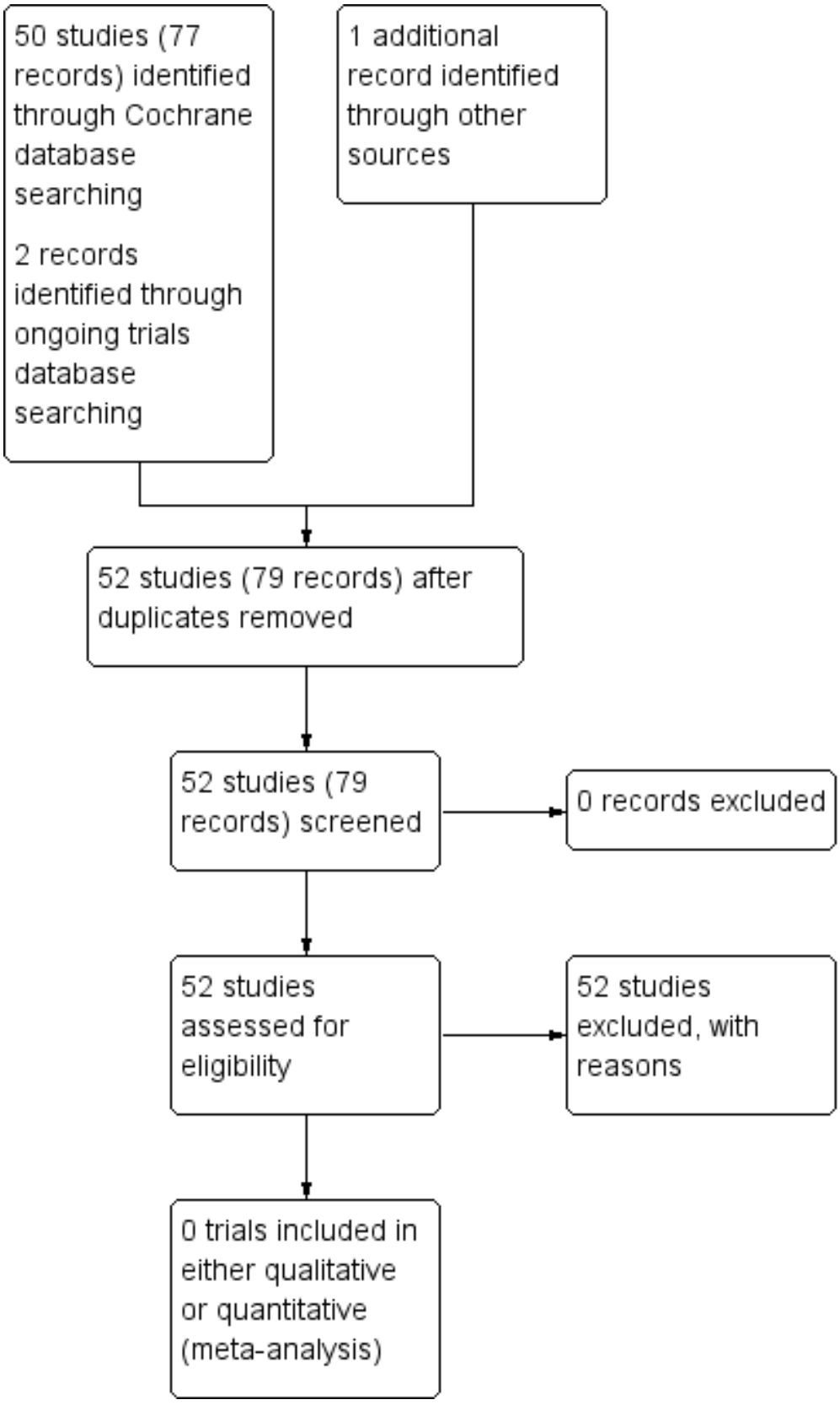
Figure 1. Study flow diagram.



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Included studies

No studies were eligible for inclusion in this review.

Excluded studies

A total of 52 studies were excluded from the review for a number of reasons and full details are available in the tables 'Characteristics of excluded studies'. Where it was unclear which pathogens participants were colonised with, we contacted the relevant authors to find out if any participants had BCC species. Three studies specifically included participants infected with BCC: two of these were excluded as although they looked at eradication of BCC species, they were of cross-over design (Ledson 2002; Rye 2015); while a further study was excluded as it recruited participants with chronic BCC infection where eradication is not possible (Tullis 2014). Six studies were excluded as they looked at treatment for *P aeruginosa* (Adeboyeku 2001; Carswell 1987; Huang 1982; Kapranov 1995; Knight 1979; Loening-Bauke 1979). In a further 10 studies no pathogen was specified (Chua 1990; Conway 1996; Cooper 1985; Heininger 1993; Nathanson 1985; Postnikov 2001a; Romano 1991; Romano 1992; Salh 1992; Stutman 1987). One study was focused on reducing early pulmonary infections in CF, not including BCC (Singh 2013), and a further study had no participants infected with BCC (Frederiksen 2006). The most common reason for exclusion was that studies examined pharmacokinetics or safety issues of antibiotic therapy; 19 studies were excluded for this reason (Davis 1987; Degg 1996; Dodd 1997; Geller 2004; Goldfarb 1986; Griffith 2008; Gulliver 2003; Hodges 2014; Huls 2000; Kruger 2001; Labiris 2004; Pai 2006; Postnikov 2000; Postnikov 2001; Prayle 2016, Roberts 1993; Rosenfeld 2006; Smith 1997; Wood 1996). Two studies examined the role of zinc supplementation in reducing frequency of pulmonary exacerbations in CF (Khorasani 2009; Sharma 2016). Five studies were excluded as they specifically looked at the effects of treatment in relation to the mode of delivery: three studies looked at the effects of home intravenous antibiotic treatment (Amelina 2000; Hjelte 1988; Ramstrom 2000); one study looked at the efficacy of delivery of a nebulised antibiotic (Keller 2010); and one study looked at the effect of pancreatic enzymes on the absorption of oral antibiotics (Vitti 1975). One study was excluded as it had an open-label design and did not have a control group (Uluer 2013). One study considered compliance to a treatment regimen (Dodd 1998) and one study looked at the development of a scoring system for the efficacy of antibiotic regimens (Huang 1979). The remaining study was not able to enrol the intended sample size and initial attempts to get it published were unsuccessful and hence the investigators did not persist (NCT00298922).

Risk of bias in included studies

No studies were included in the review.

Effects of interventions

No studies were included in the review.

DISCUSSION

Summary of main results

For this review, we could not find any study that met the inclusion criteria of any antibiotic or antibiotic adjuvant therapy used alone or in combination to eradicate BCC infection which was compared to an alternative antimicrobial agent, a placebo or no treatment, (excluding the participant's usual therapeutic regimen).

Overall completeness and applicability of evidence

From a selection of studies, the Ledson study was the only one that was a randomised controlled trial of eradication therapy for BCC in CF (Ledson 2002). However, it was of cross-over design, comparing nebulised taurolidine (an antibiotic to which BCC has displayed in vitro sensitivity) to 0.9% saline as a placebo, and hence excluded from the review.

As we were unable to identify any studies for inclusion in this review, we were not able to address our aim of establishing options for BCC eradication in people who are infected with BCC and no data were available on attempts to delay or prevent chronic infection as no such studies were identified. The lack of suitable studies also meant that we were unable to compare treatment options and assess any differences in efficacy or adverse events.

Quality of the evidence

There was no evidence identified for this review.

Potential biases in the review process

While every possible effort has been made by the authors to limit bias in the review process, there remains the possibility of sources of bias. While comprehensive searches have been performed, it is possible that relevant studies were missed or that studies have been undertaken and results of these have not been published.

Agreements and disagreements with other studies or reviews

The Ledson study is in many ways representative of the albeit small pool of evidence available on eradication of BCC in CF. In this cross-over study, the eradication of BCC was not achieved in any participant, and there was no improvement in either FEV_1 or FVC. It is likely that, as with *P aeruginosa*, eradication is most likely to be successful if attempted at first detection, rather than once chronic infection has become established, and thus these results cannot reliably be extrapolated to people with a first isolation of BCC in their sputum, when they may be more susceptible to eradication strategies. Despite the lack of efficacy in this study, the lack of adverse events indicates that nebulised taurolidine may be a viable treatment on a case-to-case basis where specific colonising organisms are known to be sensitive. The specificity of BCC infection is such that there are almost no data on BCC from other conditions, since it is rarely encountered outside the context of CF and chronic granulomatous disease (a very rare disorder of the immune system). The evidence which is available, most of which is in the form of individual case reports or small, non-randomised or non-blinded studies, rarely reports successful eradication of BCC from the CF airways. This is due to both the difficulties of accessing a severely diseased airway and also the inherent resistance of BCC species themselves. Other evidence on eradication has not been systematically reviewed to the best of our knowledge due to the nature of the reports.

Consensus documents acknowledge the lack of high quality evidence in this area, but do make recommendations for the treatment of BCC (CF Trust 2009) which are summarised as follows:

- antimicrobial therapy should be directed by in vitro sensitivities where available;

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- combination therapy should be used for treatment of BCC exacerbations and "cepacia syndrome";
- the routine use of synergy testing to guide therapy of BCC cannot be recommended at this time;
- the use of eradication therapy for all new growths of BCC should be considered.

AUTHORS' CONCLUSIONS

Implications for practice

No studies were identified which met the reviews's inclusion criteria and hence there is insufficient evidence from the literature to determine an effective strategy for the eradication of *Burkholderia cepacia* complex (BCC) species from adults with cystic fibrosis (CF).

Implications for research

This review highlights a clear lack of reliable evidence on which to base management decisions for people with CF, either chronically or newly infected with BCC species, despite a wealth of knowledge on the adverse long-term effects of BCC infection. There is a need for well-designed, randomised, multi-centre studies of a variety of eradication strategies, based on in vitro studies of sensitivity or individual case reports of successful eradication, that will allow the examination of the effects of different agents on BCC infection and provide sufficient participants to ensure the studies have adequate power. In order for progress to be made more rapidly in this field, it may be appropriate for studies to address a number of alternative regimens in order for successful therapies to be identified sooner. Such studies should be specifically designed to address the issue of eradicating BCC species from people with CF while minimising adverse effects and preventing harmful changes in airway colonisation. Of particular interest would be randomised studies examining aggressive management at first isolation of BCC, as it is now standard practice to delay or prevent onset of chronicity of *Pseudomonas aeruginosa* infection in CF in most centres. Such strategies may be the only realistic hope of eradication during a potential window of susceptibility before infection is established and in the absence of novel antimicrobial agents to which BCC is sensitive. Outcome measurements for these studies should focus on clinically relevant parameters including improvements in forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC), body mass index (BMI) and nutritional status as well as the primary measure of reduction in bacterial colonisation assessed by airway secretions. These outcome measures offer good clinical evidence as to the general health of a person with CF, and can thus indicate the relevance of any alterations in colonisation. Furthermore, evidence from people with both CF and non-CF bronchiectasis suggests that while, in the short term, eradication of chronic airway pathogens is difficult, longer-term regimens (up to 12 months) can often prove effective. This is something that should be considered when designing studies, and it may be that effects on colony counts are not seen until a number of months after the initiation of therapy.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Adeboyeku 2001	Study of safety and tolerability of an eradication protocol for *P. aeruginosa*.
Amelina 2000	Study of effects of home IVs for exacerbations of CF bronchiectasis on lung function and QoL in CF.
Carswell 1987	Study of eradication protocols for *P. aeruginosa* colonisation.
Chua 1990	Assessment of bronchial responsiveness to nebulised antibiotics, pathogen not specified.
Conway 1996	Assessment of different combinations of IV antibiotics in the treatment of exacerbations of CF bronchiectasis, pathogen not specified.
Cooper 1985	Assessment of different combinations of IV antibiotics in the treatment of exacerbations of CF bronchiectasis, pathogen not specified.
Davis 1987	Study of the pharmacokinetics of ciprofloxacin in people with CF, pathogen not specified.
Degg 1996	Evaluation of the ototoxic effects of gentamicin on people with CF, pathogen not specified.
Dodd 1997	Study of the correlation between tonicity and adverse effects of nebulised colistin in CF, pathogen not specified.
Dodd 1998	Discussion of the discrepancy between patient-reported and objectively assessed non-compliance in clinical studies, neither drug or pathogen specified.

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Study	Reason for exclusion
Frederiksen 2006	No participants infected with BCC in study.
Geller 2004	Pharmacokinetics, safety and efficacy of nebulised tobramycin in CF, pathogen not specified.
Goldfarb 1986	Pharmacokinetics of single dose oral ciprofloxacin in people with CF, pathogen not specified.
Griffith 2008	Pharmacokinetics of single dose nebulised levofloxacin in people with CF, pathogen not specified.
Gulliver 2003	Study of tolerance of nebulised tobramycin in people with CF, pathogen not specified.
Heininger 1993	Comparison of different dose regimens of aminoglycosides in exacerbations of CF bronchiectasis, pathogen not specified.
Hjelte 1988	Study of QoL for people with CF with home versus inpatient IV antibiotics for exacerbations.
Hodges 2014	Pharmacokinetic study.
Huang 1979	Study of a novel scoring system for assessing the efficacy of IV antibiotic regimens in exacerbations of CF bronchiectasis.
Huang 1982	Strategy for eradication of *P. aeruginosa*.
Huls 2000	Study of the effects of lung function on serum concentrations of antibiotics, pathogen not specified.
Kapranov 1995	Strategy for eradication of *P. aeruginosa*.
Keller 2010	Investigation of the efficacy of delivery of a novel therapeutic preparation of nebulised tobramycin, pathogen not specified.
Khorasani 2009	Study examined the role of zinc supplementation in reducing frequency of pulmonary exacerbations in CF.
Knight 1979	Eradication strategy for *P. aeruginosa*.
Kruger 2001	Report of ototoxicity of IV tobramycin in people with CF, pathogen not specified.
Labiris 2004	Investigation of whether inhalation of preservatives from IV tobramycin preparations causes airway inflammation in CF, pathogen not specified.
Ledson 2002	Cross-over study of *B. cepacia* therapy, study design not eligible.
Loening-Bauke 1979	Comparison of long-term options for eradication of *P. aeruginosa*.
Nathanson 1985	Study of efficacy of nebulised gentamicin in CF, pathogen not specified.
NCT00298922	Due to delays in starting related to getting placebo, the investigators were not able to enrol the intended sample size. The study was negative but was underpowered. Initial attempts to get it published were unsuccessful and hence the investigators did not persist.
Pai 2006	Pharmacokinetics of levofloxacin in adults with CF, pathogen not specified.
Postnikov 2000	Study of tolerance and efficacy of pefloxacin as a prophylaxis and treatment of severe infections in children with CF and aplastic anaemia, pathogen not specified.

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Study	Reason for exclusion
Postnikov 2001	Study of safety of fluoroquinolones in children, pathogen not specified.
Postnikov 2001a	Comparison of growth rates of children with CF either treated or not treated with ciprofloxacin, pathogen not specified.
Prayle 2016	Pharmacokinetic study.
Ramstrom 2000	Study of the effects of altered methods of preparation of home IV antibiotic therapies in CF.
Roberts 1993	Study of interactions of tobramycin and ticarcillin in CF, pathogen not specified.
Romano 1991	Non-blinded study of ofloxacin for people with CF requiring long-term antibiotics with 'sensitive' sputum culture (pathogens unknown).
Romano 1992	Non-blinded study of ofloxacin for people with CF requiring long-term antibiotics with 'sensitive' sputum culture (pathogens unknown).
Rosenfeld 2006	Study of accumulation of nebulised tobramycin in respiratory secretions, pathogen not specified.
Rye 2015	Cross-over study of *B. cepacia* therapy, study design not eligible.
Salh 1992	Study of antibiotic regimens for treatment of CF bronchiectasis exacerbations, pathogen not specified.
Sharma 2016	Study examined the role of zinc supplementation in reducing frequency of pulmonary exacerbations in CF.
Singh 2013	Study focused on reducing early pulmonary infections in CF, not including BCC.
Smith 1997	Study of the uses of salivary ciprofloxacin concentrations in people with CF, pathogen not specified.
Stutman 1987	Comparison of different dose regimens of oral ciprofloxacin in chronically infected people with CF, pathogen not specified.
Tullis 2014	RCT of treatment for people with chronic *B. cepacia* infection.
Uluer 2013	Open-label design with no control group; treatment offered to all people with CF with *Burkholderia dolosa*.
Vitti 1975	Study of effectiveness of pancreatic enzyme supplements on absorption of oral antibiotics in CF.
Wood 1996	Study of minimisation of aminoglycoside toxicity in CF.

B. cepacia: Burkholderia cepacia
CF: cystic fibrosis
IV: intravenous
P aeruginosa: Pseudomonas aeruginosa
QoL: quality of life
RCT: randomised controlled trial

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APPENDICES

Appendix 1. Additional electronic searches

Database	Search terms	Date of latest search
European Union Clinical Trials Register (www.clinicaltrialsregister.eu)	"cystic fibrosis" AND "*Burkholderia cepacia*"	12 March 2019
ClinicalTrials.gov (clinicaltrials.gov)	"cystic fibrosis" AND "*Burkholderia cepacia*"	12 March 2019
WHO ICTRP (apps.who.int/trialsearch/)	"cystic fibrosis" AND "*Burkholderia cepacia*"	12 March 2019
UK Clinical Trials Gateway (www.ukctg.nihr.ac.uk/).	"cystic fibrosis" AND "*Burkholderia cepacia*"	12 March 2019

WHAT'S NEW

Date	Event	Description
18 March 2019	New search has been performed	A search of the Cystic Fibrosis and Genetic Disorders Review Group's Cystic Fibrosis Trials Register identified seven new references for potential inclusion in the review. All seven were additional references to the already excluded studies (Griffith 2008; Prayle 2016; Rye 2015; Tullis 2014). Two potential new references were identified from searches of online trial registries and were also excluded (NCT00298922; Uluer 2013).
18 March 2019	New citation required but conclusions have not changed	No new studies or data were included in this updated review, hence our conclusions remain the same.

HISTORY

Protocol first published: Issue 5, 2012
Review first published: Issue 10, 2014

Date	Event	Description
1 November 2016	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Trials Register identified nine references to seven studies potentially eligible for inclusion in this review. These were assessed by the authors and unfortunately none were eligible for inclusion. Two studies previously listed as awaiting classification have now been excluded (NCT00298922; Uluer 2013).

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Date	Event	Description
1 November 2016	New citation required but conclusions have not changed	No new data have been included in this updated review, hence there are no changes to the conclusions.

CONTRIBUTIONS OF AUTHORS

Roles and responsibilities	
TASK	**WHO WILL UNDERTAKE THE TASK?**
Protocol stage: draft the protocol	Kate Regan
Review stage: select which studies to include (2 + 1 arbiter)	Kate Regan & Jayesh Bhatt
Review stage: extract data from studies (2 people)	Kate Regan & Jayesh Bhatt
Review stage: enter data into RevMan	Kate Regan
Review stage: carry out the analysis	Kate Regan
Review stage: interpret the analysis	Kate Regan & Jayesh Bhatt
Review stage: draft the final review	Kate Regan & Jayesh Bhatt
Update stage: update the review	Kate Regan & Jayesh Bhatt

DECLARATIONS OF INTEREST

Kate Regan declares no conflict of interest.

Jayesh Bhatt has received lecture fees from Vertex Pharmaceuticals Inc. for a talk on pulmonary exacerbations in cystic fibrosis; Vertext do not produce any drugs relevant to this review.

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Internal sources

- No sources of support supplied

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- National Institute for Health Research, UK.

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INDEX TERMS

Medical Subject Headings (MeSH)

*Burkholderia cepacia complex; Anti-Bacterial Agents [*therapeutic use]; Burkholderia Infections [*drug therapy]; Cystic Fibrosis [*microbiology]; Disease Eradication

MeSH check words

Humans

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