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Antibiotic treatment for *Burkholderia cepacia* complex in people with cystic fibrosis experiencing a pulmonary exacerbation (Review)

Horsley A, Jones AM, Lord R

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TABLE OF CONTENTS

[Intervention Review]

Antibiotic treatment for *Burkholderia cepacia* complex in people with cystic fibrosis experiencing a pulmonary exacerbation

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ABSTRACT

Background

Chronic pulmonary infection is a hallmark of lung disease in cystic fibrosis. Infections dominated by organisms of the *Burkholderia cepacia* complex, a group of at least 18 closely-related species of gram-negative bacteria, are particularly difficult to treat. These infections may be associated with a fulminant necrotising pneumonia. *Burkholderia cepacia complex* bacteria are resistant to many common antibiotics and able to acquire resistance against many more. Following patient segregation in cystic fibrosis medical care, the more virulent epidemic strains are not as frequent, and new infections are more likely to be with less virulent environmentally-acquired strains. Although evidence-based guidelines exist for treating respiratory exacerbations involving *Pseudomonas aeruginosa,* these cannot be extended to *Burkholderia cepacia* complex infections. This review, which is an update of a previous review, aims to assess the available trial evidence for the choice and application of treatments for these infections.

Objectives

To assess the effectiveness and safety of different antibiotic regimens in people with cystic fibrosis experiencing an exacerbation and chronically infected with organisms of the *Burkholderia cepacia* complex.

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.

Date of latest search: 28 August 2015.

Selection criteria

Randomised and quasi-randomised controlled trials of treatments for exacerbations of pulmonary symptoms in people with cystic fibrosis chronically infected with organisms of the *Burkholderia cepacia* complex.

Data collection and analysis

No relevant trials were identified.

Main results

No trials were included in this review.

Authors' conclusions

Burkholderia cepacia complex infections present a significant challenge for people with cystic fibrosis and their clinicians. The incidence is likely to increase as the cystic fibrosis population ages; and managing and treating these infections will become more important. There is a lack of trial evidence to guide decision making and no conclusions can be drawn from this review about the optimal antibiotic regimens for people with cystic fibrosis who have chronic *Burkholderia cepacia* complex infections. Clinicians must continue to assess each person individually, taking into account *in vitro* antibiotic susceptibility data, previous clinical responses and their own experience. Multicentre randomised clinical trials are needed to assess the effectiveness of different antibiotic regimens in people with cystic fibrosis infected with organisms of the *Burkholderia cepacia* complex.

PLAIN LANGUAGE SUMMARY

Which antibiotics are best to treat worsening symptoms in people with cystic fibrosis with persistent *Burkholderia cepacia* complex lung infection?

Review question

We looked for evidence of which antibiotics are best to treat a flare up of symptoms in people with cystic fibrosis with persistent *Burkholderia cepacia* complex lung infection.

Background

Cystic fibrosis is a common inherited condition where the lungs often become blocked with mucus. This harms the lungs' defences and often results in chronic, persistent infections that cannot be cleared by antibiotics. People with cystic fibrosis often need courses of antibiotics to reduce their symptoms (for instance cough, excess mucus and breathlessness) when these flare up or worsen. Such episodes are called exacerbations, and are usually treated with intravenous antibiotics (given through a drip into a vein). One group of bacteria that can infect the lungs of people with cystic fibrosis is called the *Burkholderia cepacia* complex. These closely-related bacteria are found widely in the environment and do not cause infections in healthy people who do not have cystic fibrosis. They are particularly hard to treat as they are resistant to many commonly-used antibiotics. Currently doctors do not know which antibiotics are best at treating these infections; which combinations of antibiotics should be used; how long the antibiotics should be used for; or whether there are additional treatments that might also help. This is an update of a previously published review.

Search date

The evidence is current to: 28 August 2015.

Study characteristics

We did not find any trials which compared groups of volunteers with exacerbations who were also infected with *Burkholderia cepacia* complex bacteria, who were given different treatments at random.

Key results

More research is needed to find out which treatments are best for improving lung function and survival and for reducing side effects and length of time spent in hospital for people infected with *Burkholderia cepacia* complex bacteria experiencing an exacerbation.

BACKGROUND

Description of the condition

Cystic fibrosis (CF) is a complex multisystem disease, caused by defects in a single gene (Ratjen 2003). It is the most common life-shortening genetic disorder in those of European descent, affecting 1 in 2500 live births in the UK and Western Europe, although it is also found in all other major ethnic groups (Bobadilla 2002). The effects in the lungs are responsible for most of the morbidity and mortality, and the hallmark of the condition is progressive and irreversible bronchiectasis and respiratory failure.

The primary defect in CF is in an epithelial chloride ion channel (Riordan 1989). This is expressed throughout the body, and is involved in secretory function in a number of organs, including the lung, liver, gut, pancreas and sweat glands (Hoogeveen 1991). Defective ion transport in CF is responsible for the effects of the condition in these organs. In the lung, loss of chloride excretion and uncontrolled sodium absorption at the airway surface leads to dehydration and shrinking of the thin layer of fluid that bathes the surface of the airway (Matsui 1998). This results in defective clearance of airway mucus, retention of secretions and blockage of small airways. Bacterial infections are not cleared effectively, leading to a vicious cycle of chronic lower airway infection, inflammation and tissue destruction (Boucher 2007). The end result is progressive lung damage and decline in lung function.

Burkholderia cepacia complex (Bcc) infections in CF

Respiratory infections start early in life in CF (Rosenfeld 2001). Unlike non-CF lung infections, these tend to be persistent, sometimes involving phenotypic change in the organisms themselves (Harrison 2007). The sequence of infecting organisms also tends to follow a characteristic course, with *Staphylococcus aureus* in early life followed by *Pseudomonas aeruginosa* in later childhood or teenage years (CF Foundation 2009); although this picture has been complicated by the emergence of many new pathogens over the last two decades (Harrison 2007).

Organisms of the Bcc are a group of gram negative bacteria that comprise at least 18 closely-related species (Coenye 2001; Vanlaere 2008; Vanlaere 2009). These are phenotypically very similar and are differentiated on the basis of genetic or biochemical tests. Some of these organisms are ubiquitous in nature, commonly found in soil or water (Mahenthiralingam 2008), though for others the reservoirs remain unidentified (including *Burkholderia multivorans*, a major cause of Bcc infection in CF). Clinically, Bcc are known to be responsible for chronic pulmonary infection in CF and to be rare causes of nosocomial infections in immune-compromised individuals (Conly 1986; Pegues 1993).

Infection with Bcc organisms is particularly problematic as the organisms produce a wide variety of potential virulence factors and exhibit innate resistance to many antibiotics and disinfectants (Leitao 2010). It has been observed that Bcc are able to adhere to epithelial cells and mucin, and are also capable of invading and surviving inside airway epithelial cells and macrophages (large white blood cells, occurring principally in connective tissue and in the bloodstream, that ingest foreign particles and infectious microorganisms) (Sajjan 1995). Furthermore, Bcc form biofilms, which may protect them from both host defences and antibiotics and they have a distinct lipopolysaccharide which has also been implicated in antibiotic and antimicrobial peptide resistance (Vinion-Dubiel 2004). In addition, they secrete a number of factors, such as catalases, proteases and siderophores, which may help them to evade host defences and survive in hostile environments (Mahenthiralingam 2005). The role of individual putative virulence factors in human infection have yet to be clearly defined, and none alone is both necessary and sufficient for virulence.

Since the mid-1980s, Bcc have been increasingly identified as important pathogens in CF, with resultant increases in rates of mortality and morbidity (Tablan 1985). Currently around 3% of people with CF in the USA and UK are infected with Bcc organisms, though prevalence increases with age (CF Foundation 2009; CF Trust 2008). Although transient infection occurs, the majority of infections cannot be eradicated (De Boeck 2004). Clinical effects vary from asymptomatic carriage to a rapid and uncontrolled deterioration with septicaemia and necrotizing pneumonia (the so-called "cepacia syndrome") that usually results in early death (Isles 1984). Several studies have shown that those chronically infected with Bcc have increased mortality and morbidity (Frangolias 1999; Tablan 1987). Infection with Bcc is associated with increased requirements for intravenous antibiotics (Frangolias 1999) and outpatient attendances (Jones 2004), though this is principally in those infected with *Burkholderia cenocepacia* (*B. cenocepacia*) (Jones 2004). Some of the excess mortality and morbidity associated with *B. cenocepacia* may be due to the dominance of the ET12 strain in these studies, and may not be true of environmentally acquired *B. cenocepacia* infections. Individuals with *B. cenocepacia,* however, do appear to have poorer post lung transplant outcomes (Chaparro 2001; De Soyza 2010; Murray 2008), and most clinical units will not consider these people for lung transplantation.

Patient-to-patient spread of organisms may occur through social contact (LiPuma 1990). This is particularly well described for the epidemic (ET-12) strain of *B. cenocepacia,* though other epidemic strains exist, including *B. multivorans* and *B. dolosa* (Biddick 2003; Khalish 2006). The recognition of epidemic spread, and the increased mortality rates associated with the epidemic strains, has led to the policy of strict segregation in clinical units since the 1990s. As a consequence the epidemiology has altered and the most common new Bcc infection these days is with *B. multivorans* (Govan 2007), probably acquired from as-yet unidentified environmental reservoirs. Unlike *B. cenocepacia, B. multivorans* has not been associated with significant excess change in lung function or nutritional status compared to matched *Pseudomonas*-infected controls (Jones 2004; Courtney 2004). This strain has however been associated with both epidemic spread and cepacia syndrome (Govan 2007; Zahariadis 2003), and segregation policies, designed to limit the spread of the epidemic strains, are generally applied to anyone infected with any member of the Bcc. Segregation may itself cause psychological harm by excluding people from the full range of CF unit facilities (Duff 2002).

Description of the intervention

Intravenous antibiotics are given to people with CF to treat pulmonary exacerbations (CF Trust 2009; Flume 2009). Exacerbations are typically characterised by an increase in respiratory symptoms with associated deterioration in biochemical, radiological or physiological markers of disease. The precise definition of an exacerbation is contentious, often relying on clinical judgement rather than strict objective criteria, and may vary between studies. Typically, antibiotics are given for 10 to 21

days and guidelines generally recommend a combination of at least two different antibiotics (CF Trust 2009; Flume 2009). It can never be clear however, which species is responsible for the exacerbation in CF, since many (if not all) individuals are chronically infected by more than one organism, but it is common practice to choose antibiotics that are likely to be effective against the dominant bacterial species in that person. However, Bcc are innately resistant to colomycin and will often show resistance to aminoglycosides and β-lactams (Aaron 2000). Some Bcc species are even able to use penicillin G as a sole carbon source (Beckman 1979). A specific efflux pump can also confer resistance to quinolones, chloramphenicol and trimethoprim (Burns 1996). Some strains have inducible β-lactamases or dihydrofolate reductases. Multiple drug resistance is common *in vitro*, with 50% of isolates being resistant to all of 10 commonly-used antibiotics (Aaron 2000). *In vitro* treatment of Bcc cultured from individuals with CF requires multiple antibiotics, typically at least three, to offer the greatest chance of bactericidal effect (Aaron 2000).

How the intervention might work

Choice of antibiotics is dependent upon a number of factors, including drug reactions, toxicities and interactions with other medications. The best choice of antibiotics would lead to the most rapid resolution of symptoms and correction of other abnormalities (e.g. radiology, lung function and inflammatory markers) with the least toxicity. At present, there is little guidance on the most effective therapies to use in people with Bcc (CF Trust 2004).

Length of treatment is also an important factor. Shorter courses of treatment may be insufficient to treat the infection adequately, but there is an increased incidence of allergic reactions with longer antibiotic courses (Parmar 2005) and an increased risk of toxicity (e.g. ototoxicity and nephrotoxicity with aminoglycosides (Prayle 2010)), or blood dyscrasias (an imbalance in the composition of blood) with chloramphenicol.

Other factors that may determine the success of a treatment strategy include the route of administration, and whether there is additional benefit to be gained from other therapies such as recombinant dornase alfa (DNase) (Grimwood 2009) or amiloride (Middleton 2005).

It is important to recognise that when a person with CF is unwell with an exacerbation of respiratory symptoms, therapy is chosen which is both broad in spectrum and which is likely to be effective against the dominant bacterial species isolated from that individual. In all cases, however, when a person is unwell, it is unethical to withhold treatments which are widely considered to be effective. Truly placebo-controlled trials of antibiotic therapy in CF exacerbations cannot therefore be performed, and in this review we will instead consider the effects of one antibiotic regimen against another. When additional therapies are added in to a conventional regimen, then this may reasonably be compared to placebo, and we will also review any studies of this nature.

Why it is important to do this review

Since Bcc are resistant to many antibiotics, and can prove to be difficult to treat in clinical practice, it is important to review the available evidence in order to establish the optimal antibiotic therapy for treating a pulmonary exacerbation in people with CF chronically infected with Bcc organisms. This includes consideration of any factors that may impact on treatment efficacy, including the choice of antibiotics and length of treatment. Given the toxicity profiles of some of the treatments used to treat Bcc, an important part of this review is also to consider the safety profiles of different regimens.

This is an update of a previous version of this review (Horsley 2012).

OBJECTIVES

The aim of this review is to assess the effectiveness and safety of different antibiotic regimens in people with CF experiencing an exacerbation, who are chronically infected with organisms of the Bcc. This will cover only those receiving treatment for an exacerbation of pulmonary symptoms, either diagnosed by the attending clinician or by pre-defined objective criteria, but not those receiving elective eradication therapy (which is the subject of a separate Cochrane review (Regan 2014)).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised and quasi-randomised controlled trials, published or unpublished.

Types of participants

Individuals with CF, of any age, diagnosed on the basis of clinical evidence of CF-lung disease and either genotype analysis or sweat testing, or both. Participants were also required to have evidence of pulmonary infection with organisms of the *Burkholderia cepacia* complex (Bcc), defined as at least two positive sputum or broncho-alveolar lavage microbiology specimens within the last six months, grown on specialist media and confirmed by conventional molecular and microbiological techniques (see below).

The nature of the techniques used to identify and type Bcc have changed over time, and early studies may not have had access to current technology. Early studies were considered if Bcc infection was identified by culture on Bcc-specific selective media and confirmed by a national or regional reference laboratory. For studies published after 2010 however, the techniques used to identify Bcc were required to be consistent with published microbiological guidelines, and appropriate molecular techniques (e.g. *recA* sequencing, species specific polymerase chain reaction (PCR) or *recA* PCR and restriction fragment length polymorphism) should have been employed to confirm species identification (CF Trust 2010).

Finally, participants should have been receiving therapy for an exacerbation of CF-lung disease, defined on the basis of a combination of changes in clinical criteria, lung function and radiology. There is no universally accepted consensus as to what constitutes an exacerbation in CF. Studies will not be excluded based upon the definition of exacerbation, which could be diagnosed by the attending clinician or by pre-defined objective criteria, providing that the defining criteria are explicit and consistent and that the intent was treatment of new symptoms rather than eradication of existing infection.

Types of interventions

Any antibiotic treatment regimen for treating an exacerbation of CF-lung disease compared to placebo or different antibiotic regimen, regardless of frequency of administration, treatment duration, route of delivery or use of additional therapies (e.g. DNase, amiloride etc).

Types of outcome measures

Primary outcomes

1. Lung function
   a. change in absolute values for forced expiratory volume in one second (FEV_1)
   b. change in per cent predicted values for FEV_1
2. Survival (measured as hazard ratios)
3. Adverse events, classified as:
   a. mild (transient and treatment continued, e.g. rash, nausea);
   b. moderate (necessitating discontinuation of treatment, e.g. reversible renal or hepatic impairment);
   c. severe (life threatening or seriously debilitating, e.g. aplastic anaemia, permanent hearing loss or renal impairment)

Secondary outcomes

1. Number of days in hospital
2. Time to next exacerbation (*post hoc* change)
3. Nutritional markers
   a. weight (kg)
   b. body mass index (BMI)
4. Acquisition or eradication of other significant CF pathogens
5. Changes in inflammatory markers
   a. serum samples
   b. sputum or bronchoalveolar lavage (BAL) samples
6. Quality of life (QoL) (as measured by a valid disease-specific QoL tool (Gee 2000; Quittner 2009))

Search methods for identification of studies

Electronic searches

We identified relevant trials from the Group's Cystic Fibrosis Trials Register using the following terms: 'antibiotics AND burkholderia cepacia' and also 'antibiotics AND mixed infections AND (acute treatment [pulmonary exacerbations] 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 was 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 sections of the Cystic Fibrosis and Genetic Disorders Group Module.

Date of the latest search of the Cystic Fibrosis Trials Register: 28 August 2015.

Searching other resources

For the initial review we contacted experts in the field to enquire if they are aware of unpublished trial data. We invited manufacturers of antimicrobial agents known to be of use in the treatment of Bcc infections to submit data from unpublished trials. This will not be repeated in any subsequent updates. If any trials are identified in the future, we will assess the bibliographic references of these for additional trial reports.

Data collection and analysis

Selection of studies

In both the initial review and subsequent update all authors independently selected trials (published both as abstracts or full papers) to be included in the review. We reviewed abstracts initially to exclude obviously irrelevant trials; we then reviewed the full text of the remaining trials separately. We will repeat the same process at future updates of this review. We plan to resolve any disagreement through discussion and if necessary seek arbitration from an independent third party.

Data extraction and management

We were not able to include any trials in this initial version of the review; however, if we include trials in future updates of the review, we will proceed as detailed below.

All authors will independently extract data from included trials and enter these onto data extraction sheets for analysis using the review software 'Review Manager' (RevMan 2011). All authors will independently make the decision on whether trials are sufficiently similar in design and quality to be pooled; we will resolve any disagreement through discussion. It may be necessary to perform several different meta-analyses, depending on the types of trials and recorded outcome measures available. If outcome measures differ in the way they are reported (e.g. FEV_1 versus per cent predicted FEV_1, survival at different time points), we will contact the primary investigators for raw data to be used in the meta-analysis. We will consider different modes of drug delivery separately. If there are differences between trials in the length of treatment, we will report data at two weeks, four weeks and three months, but will consider presenting data at other time-points as appropriate.

Assessment of risk of bias in included studies

All authors will independently assess the risk of bias for each included trial using the Cochrane risk of bias tool (Higgins 2011a). We will use this to generate a risk of bias table for each trial and assess the risk of bias as high, low or unclear. In particular, we will examine the following potential sources of bias: the process of randomisation; the degree of blinding in the trial; completeness of outcome data; selective outcome reporting and any other potential sources of bias.

Measures of treatment effect

We plan to pool trials of similar design and with similar outcomes and analyse data using the RevMan software (RevMan 2011). For binary outcome measures we will calculate a pooled estimate of treatment effect for each outcome using the pooled odds ratio (OR) and 95% confidence intervals (CIs).

For continuous outcomes, we will use either mean change over the course of therapy, or mean post-treatment values, and standard deviation (SD) to calculate a pooled estimate of the treatment effect across trials by calculating the mean difference (MD) and 95% CIs.

We plan to compare survival data using hazard ratios (HR). We will combine adverse event data regardless of length of treatment and compare using risk ratios.

Unit of analysis issues

Because of the nature of the intervention and predicted length of therapy, all participants are likely to be receiving some form of active therapy. We do not consider cross-over trials of an additional therapy during the course of a single treatment episode to be an appropriate trial design because of both the short-term effects of the other therapies and the anticipated length of treatment. We will consider cross-over trials that randomised to different interventions during separate exacerbation episodes if the washout period between exacerbations was appropriate (minimum four weeks).

Dealing with missing data

We will perform an intention-to-treat analysis. In cases of missing data, we will contact the trial primary investigators to provide this, wherever possible. If individual participant data are not available, and SDs are not quoted, we plan to estimate these as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b).

Assessment of heterogeneity

We plan to assess heterogeneity between comparable trials by inspection of forest plots and application of the I^2 statistic, which describes the percentage of total variation across trials that is caused by heterogeneity rather than by chance (Higgins 2003). The importance of the observed value of I^2 depends on both the magnitude and direction of effects and on the strength of evidence for heterogeneity, represented by the CIs for I^2. We will base our assessment of the level of heterogeneity on the following cut offs for I^2, taking into account the CIs:

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

We will calculate CIs for the I^2 values after taking statistical advice and according to the methods described by Higgins (Higgins 2002).

Assessment of reporting biases

Wherever possible, we will obtain the original trial protocols for comparison with the published papers to ensure that all outcomes are reported. If it is not possible to obtain the trial protocols, we will scrutinise the 'Methods' section of the published paper(s) to ensure full reporting of all measured variables. If negative data are not fully reported, we will contact the primary investigators for these data. If there are a sufficient number of comparable trials, we will explore these for reporting bias using a funnel plot. We will also assess publication bias by looking for evidence of conference presentations not followed by subsequent journal publications.

Data synthesis

We plan to use a fixed-effect model to analyse data from trials. If there is evidence of substantial heterogeneity (I^2 is greater than 50%), we will use a random-effects analysis and compare the two analyses. If the results of the random-effects analysis are different, we will review the trials to identify sources of heterogeneity.

Subgroup analysis and investigation of heterogeneity

If we identify substantial heterogeneity (I^2 greater than 50%), we plan to explore this further. In the first instance, we will check data to ensure accurate recording and entry. Where there are sufficient data to permit it (minimum of 10 trials), we then plan to use subgroup analysis to examine the causes of heterogeneity. In particular, this will include a comparison of different age groups (up to 16 years and 16 years and older), lung function severity (expressed as FEV_1 per cent predicted: less than 40%; 40% to 60%; 60% to 80%; and over 80%), species of Bcc (*cenocepacia* or *multivorans* or other), and presence of significant co-morbidities (diabetes, CF-related liver disease, BMI below 18).

Sensitivity analysis

If there are sufficient comparable trials to permit it, we will perform the following sensitivity analyses: excluding and including trials with a high risk of bias (in any of the five key domains); and analysis using a fixed-effect versus a random-effects model.

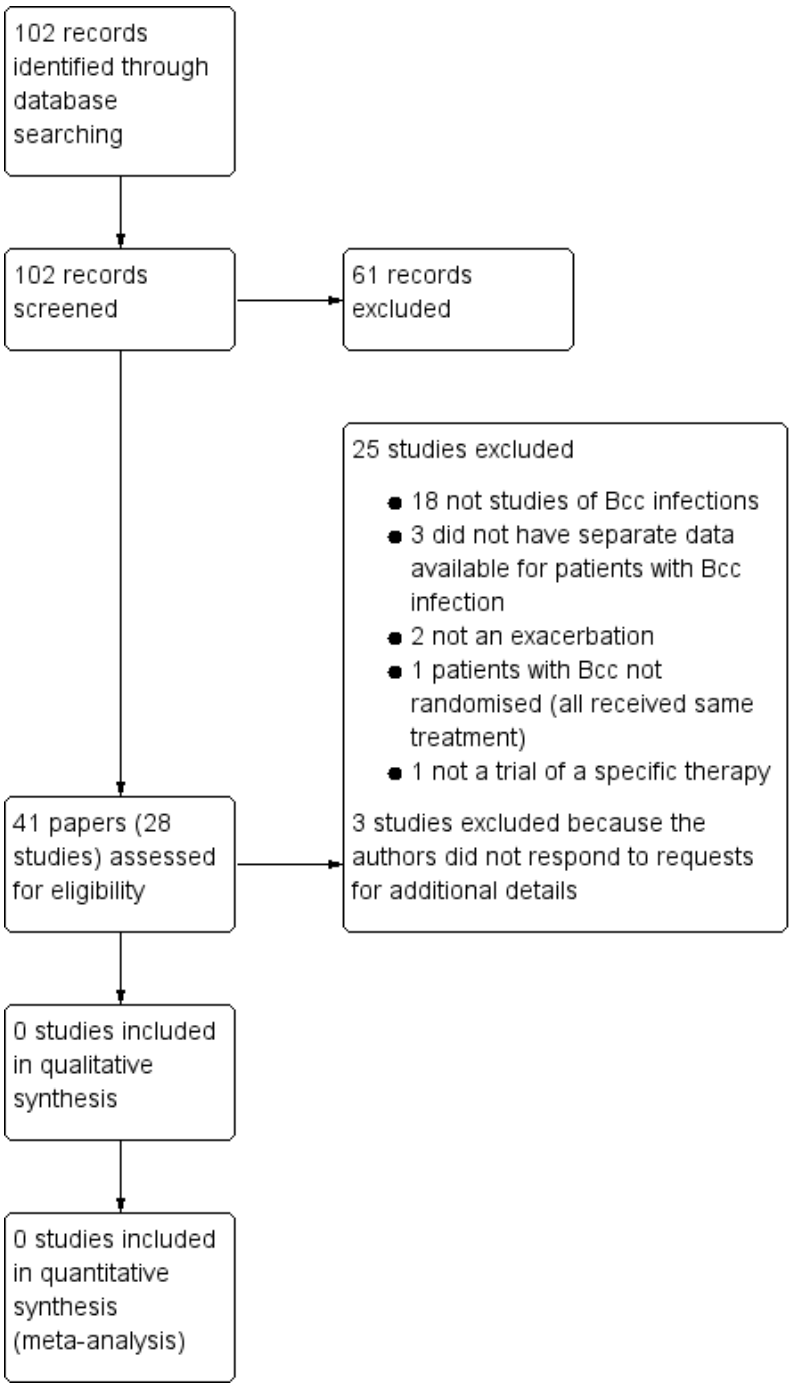
RESULTS

Description of studies

Results of the search

Searching of databases, for both the initial review and update, identified 102 records. After the exclusion of 61 references, we retrieved a total of 41 references to 28 trials (Figure 1). In six cases, we previously contacted the authors for further details, where the trials have reported the inclusion of participants with "*Pseudomonas cepacia*" (as Bcc organisms were originally designated). We have received replies for three of these trials, all of which have subsequently been excluded as separate data are not available for participants with Bcc infections (Bosso 1987; Bosso 1988; Gold 1987). There was no response for the other three remaining trials and these have now also been excluded (Conway 1996a; Reed 1987c; Reed 1987c). On the initial review one unpublished trial was listed as 'Awaiting classification'; this trial has now been excluded (Tullis 2014).

Figure 1. Study flow diagram. Please note: some studies had more than one reason for exclusion. All are included here, although only the major reason is described in the text.



Included studies

We did not identify any trials for inclusion in this review.

Excluded studies

All retrieved trials were excluded. The majority of these (n = 18) reported exclusively on treatment for chronic infection with *Pseudomonas aeruginosa*. Three trials did not have separate data available for participants chronically infected with Bcc organisms (Bosso 1987; Bosso 1988; Gold 1987). One trial was not randomised (Blumer 2003). We were only able to identify three randomised trials of Bcc-specific interventions, none of which met the inclusion criteria. In two trials, the treatment was only given to individuals with stable disease (Ledson 2002; Tullis 2014) and in a third the intervention was not a specific therapy regimen, but related to the use of bacterial cultures to select antibiotics (Aaron 2005). For three studies the authors were contacted but did not reply therefore they have been excluded (Conway 1996; Reed 1987a; Reed 1987b).

Risk of bias in included studies

We did not identify any trials for inclusion in this review.

Effects of interventions

We did not identify any trials for inclusion in this review.

DISCUSSION

Despite the recognition of the clinical importance of *Burkholderia cepacia complex* (Bcc) infections in cystic fibrosis (CF) for over 25 years now, there have been no randomised trials to systematically evaluate the optimum treatment of exacerbations. Historically, there are several factors which may have contributed to this. Some of the antibiotics now commonly employed in these infections were not available when the importance of the Bcc infections was first recognised. In addition, the epidemiology has changed from one of a transmissible and virulent infection to one of sporadic but infrequent new acquisitions (Govan 2007). Although a small proportion of new Bcc infections may be cleared, either spontaneously or with antibiotics, the majority become chronic (Horsley 2011). With time, and with an ageing CF population, the challenges posed by managing exacerbations in individuals infected with Bcc will therefore not only persist but may even increase.

The small numbers of randomised trials in CF have understandably focused on treating individuals chronically infected with *Pseudomonas aeruginosa,* since this infection is both common and known to be associated with accelerated decline in lung function (Emerson 2002). The differences between the two organisms mean that outcomes from these trials cannot be applied to people with Bcc infections. We reviewed many of these trials, however, in the hope that they might also contain data on outcomes in individuals additionally infected with organisms of the Bcc. Unfortunately, where such infections were reported, the data were not analysed separately for the different infecting organisms. These studies are now at least 16 years old (and the majority much older). The antibiotic regimens were not specifically tailored to treating people with Bcc infections, and would not be likely to be considered for current management of exacerbations. We have been able to identify only three randomised trials targeted at people with Bcc infections, none of which met the the inclusion criteria for this review. The first of these was an assessment in people with stable disease (Ledson 2002) and the second was not a trial of a specific therapy, but rather of an approach to selecting the optimal treatment regimen (Aaron 2005). The third trial, not included in the previous version of this review, was a trial of inhaled aztreonam but again in people with stable disease (Tullis 2014).

AUTHORS' CONCLUSIONS

Implications for practice

We did not identify any randomised trials of therapies for treating exacerbations in people with CF chronically infected with Bcc, which could be included. No conclusions can be drawn about the optimal antibiotic regimens for people with CF with chronic Bcc infections and clinicians must continue to assess each person individually, taking into account *in vitro* antibiotic susceptibility data, previous clinical responses and their own experience.

Implications for research

Currently very little is known about how Bcc infections in CF respond to antibiotics *in vivo* and a number of important questions remain unanswered. There is a need for multicentre randomised clinical trials to assess the effectiveness of different antibiotic regimens in people with CF infected with organisms of the Bcc and identify: the optimum antibiotic regimen(s); the length of treatment; the incidence of adverse effects; the effects of additional therapies; and long-term outcome data. Trials should explore these and other aspects of exacerbation therapies in people with CF chronically infected with Bcc. The most important primary outcome measures are those which reflect improvement in lung function and survival, and reduction in adverse events. Important secondary outcome measures include length of hospital stay, quality of life, nutritional status and measure of inflammation.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the kind assistance provided by Nikki Jahnke in preparing this review.

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Blumer 2003 *{published data only}*

Blumer JL, Minkwitz M, Saiman L, San Gabriel P, Iaconis J, Melnick D. Meropenem (MEM) compared with ceftazidime (CAZ) in combination with tobramycin (TOB) for treatment of acute pulmonary exacerbations (APE) in patients with cystic fibrosis (CF) infected with Pseudomonas aeruginosa (PA) or Burkholderia cepacia (BC) [abstract]. *Pediatric Pulmonology* 2003;**36**(Suppl 25):294. [CFGD Register: PI179]

Bosso 1987 *{published data only}*

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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
Aaron 2005	Not an assessment of a specific treatment regimen.
Blumer 2003	Participants with Bcc not randomised, all given same treatment.
Bosso 1987	Separate data not available for participants with Bcc infection - confirmed by trial authors.
Bosso 1988	Separate data not available for participants with Bcc infection - confirmed by trial authors.
Carswell 1987	Not a trial of participants with Bcc infections.
Conway 1996	Not clear if participants had Bcc infections and no answer from trial authors after contact.
Cooper 1985	Not a trial of participants with Bcc infections.
Gold 1987	Separate data not available for participants with Bcc infection - confirmed by trial authors.
Heiniger 1993	Not a trial of participants with Bcc infections.
Hoogkamp-Korstanje 1983	Not a trial of participants with Bcc infections.
Huang 1979	Not a trial of participants with Bcc infections.
Huang 1982	Not a trial of participants with Bcc infections.
Ivanov 1997	Not a trial of participants with Bcc infections.
Kapranov 1995	Not a trial of participants with Bcc infections.
Knight 1979	Not a trial of participants with Bcc infections. Assessed stable participants only, not those being treated for an exacerbation.
Knowles 1988	Not a trial of participants with Bcc infections.
Krause 1979	Not a trial of participants with Bcc infections.
Ledson 2002	Assessed stable participants only, not those being treated for an exacerbation.
Loenig-Baucke 1978	Not a trial of participants with Bcc infections. Assessed stable participants only, not those being treated for an exacerbation.

Study	Reason for exclusion
Nathanson 1985	Not a trial of participants with Bcc infections.
Powell1983	Not a trial of participants with Bcc infections.
Reed 1987a	Not clear if participants had Bcc infections and no answer from trial authors after contact.
Reed 1987b	Not clear if participants had Bcc infections and no answer from trial authors after contact.
Rubio 1987	Not a trial of participants with Bcc infections.
Salh 1992	Not a trial of participants with Bcc infections.
Tullis 2014	Not a trial of a regimen for acute exacerbations
Wang 1988	Not a trial of participants with Bcc infections.
Wesley 1988	Not a trial of participants with Bcc infections.

Bcc: *Burkholderia cepacia* complex

WHAT'S NEW

Date	Event	Description
6 January 2016	New search has been performed	A search of the Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Register identified 21 references potentially eligible for inclusion in the review. Of these we retrieved a total of seven papers, all for the same study, which had previously been listed as 'Awaiting classification' (Tullis 2014). This was then excluded as it was not a therapy for an acute exacerbation.
6 January 2016	New citation required but conclusions have not changed	A new author (Dr R Lord) has joined the review team. No additional studies have been included in the review and our conclusions remain the same.

CONTRIBUTIONS OF AUTHORS

Roles and responsibilities	
TASK	**WHO WILL UNDERTAKE THE TASK?**
Protocol stage: draft the protocol	Alex Horsley (AH)
Review stage: select which trials to include (2 + 1 arbiter)	AH & Andrew Jones (AJ)
Review stage: extract data from trials (2 people)	AH & AJ
Review stage: enter data into RevMan	AH

Review stage: carry out the analysis	AH
Review stage: interpret the analysis	AH & AJ
Review stage: draft the final review	AH & AJ
Update stage: update the review	AH, AJ and RL

DECLARATIONS OF INTEREST

AH declares that his institution has received money from Celtaxys Pharmaceuticals (consultancy), Vertex Pharamceuticals (grant to host a one day CF conference in Manchester in 2016) and Markedsmodingsfonden (grant from Danish Government to assist in improving the clinical utility of the Innocor multiple breath washout system; funds supported research nurse to use the system and feedback on how to improve usability). AH has applied to the UK CF Trust as part of two Strategic Research Consortium bids (money payable to his institution) both of which are multi-centre collaborative efforts to address different areas of CF care, unrelated to the current review. He has personally received an honorarium from Gilead Pharmaceuticals for presenting at the Expert Viewpoints in CF meeting, 2014 and received royalties from Oxford University Press from the sale of Oxford Respiratory Medicine Library Handbook on Cystic Fibrosis, published March 2015 (2nd edition).

AJ declares the receipt of funds for advisory board work for Gilead Pharmaceuticals. His institution has received contributions from Forest Pharmaceuticals and Gilead Pharmaceuticals for AH to travel to conferences. He has participated in a multicentre project evaluating clinical outcome of use of nebulised aztreonam (sponsored by Gilead Sciences) and in January 2015 he spoke at the national Irish CF Meeting (meeting and AJ travel to there sponsored by Gilead). AJ further declares sponsorship from Forest Pharmaceuticals for the CF Centre's annual away day team meeting and an annual meeting with regional paediatric teams (which he helps organise and run). Vertex Pharmaceuticals provided an unrestricted educational grant to his institution to fund a one-day CF meeting in Manchester in 2016.

RL declares no known conflict of interest.

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Internal sources

- University Hospitals South Manchester, UK.
- University of Manchester, UK.

External sources

- National Institute for Health Research Clinician Scientist Award, UK.

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  The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.
- National Institute for Health Research, UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

An additional secondary outcome measure has been added to those stated in the protocol (time to next exacerbation), for analysis in future updates of this review. This is a clinically valid endpoint that was overlooked in the initial protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Humans