Oral anti-pseudomonal antibiotics for cystic fibrosis (Review)

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[Intervention Review]

Oral anti-pseudomonal antibiotics for cystic fibrosis

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ABSTRACT

Background

Pseudomonas aeruginosa is the most common bacterial pathogen causing lung infections in people with CF and appropriate antibiotic therapy is vital. Antibiotics for pulmonary exacerbations are usually given intravenously, and for long-term treatment, via a nebuliser. Oral anti-pseudomonal antibiotics with the same efficacy and safety as intravenous or nebulised antibiotics would benefit people with CF due to ease of treatment and avoidance of hospitalisation.

Objectives

To determine the benefit or harm of oral anti-pseudomonal antibiotic therapy for people with CF, colonised with *Pseudomonas aeruginosa,* in the:

1. treatment of a pulmonary exacerbation; and

2. long-term treatment of chronic infection.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Trials Register comprising references identified from comprehensive electronic database searches and handsearches of relevant journals and abstract books of conference proceedings.

We contacted pharmaceutical companies and checked reference lists of identified trials.

Date of last search: 28 June 2013.

Selection criteria

Randomised or quasi-randomised controlled trials comparing any dose of oral anti-pseudomonal antibiotics, to other combinations of inhaled, oral or intravenous antibiotics, or to placebo or usual treatment for pulmonary exacerbations and long-term treatment.

Data collection and analysis

Two authors independently selected the trials, extracted data and assessed quality. We contacted trial authors to obtain missing information.

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Main results

We included three trials examining pulmonary exacerbations (171 participants) and two trials examining long-term therapy (85 participants). We regarded the most important outcomes as quality of life and lung function. The analysis did not identify any statistically significant difference between oral anti-pseudomonal antibiotics and other treatments for these outcome measures for either pulmonary exacerbations or long-term treatment. One of the included trials reported significantly better lung function when treating a pulmonary exacerbation with ciprofloxacin when compared with intravenous treatment; however, our analysis did not confirm this finding. We found no evidence of difference between oral anti-pseudomonal antibiotics and other treatments regarding adverse events or development of antibiotic resistance, but trials were not adequately powered to detect this. None of the studies had a low risk of bias from blinding which may have an impact particularly on subjective outcomes such as quality of life. The risk of bias for other criteria could not be clearly stated across the studies.

Authors' conclusions

We found no conclusive evidence that an oral anti-pseudomonal antibiotic regimen is more or less effective than an alternative treatment for either pulmonary exacerbations or long-term treatment of chronic infection with *P. aeruginosa*. Until results of adequately-powered future trials are available, treatment needs to be selected on a pragmatic basis, based upon any available non-RCT evidence, the clinical circumstances of the individual, the known effectiveness of drugs against local strains and upon individual preference.

PLAIN LANGUAGE SUMMARY

Oral antibiotics for treating infection with *Pseudomonas aeruginosa* in people with cystic fibrosis

Treatment of *Pseudomonas aeruginosa* (*P. aeruginosa*) lung infection is very important in managing cystic fibrosis lung disease. Oral anti-pseudomonal antibiotics which are as effective and safe as intravenous or nebulised antibiotics would improve the quality of life of people with CF due to the ease of drug administration and the avoidance of hospitalisation.

We looked for randomised controlled trials of oral antibiotics for treating infections from Pseudomonas aeruginosa. We included only five trials with 256 participants and found no conclusive evidence showing an oral antibiotic regimen to be more or less effective than an alternative treatment for either pulmonary exacerbations or long-term treatment of chronic infection with *P. aeruginosa.* However, the evidence available was limited. Also the trials were very different in terms of design, drugs used, duration of treatment and follow up and outcome measures. The risk of bias differed across studies, but we did not judge any of them to have a low risk of bias from blinding, which might affect results of subjective outcomes like quality of life. Until results of adequately-powered future trials are available, treatment needs to be selected on a practical basis, based upon any available evidence from other types of trials, the clinical circumstances of the individual, the known effectiveness of drugs against local strains and upon individual preference.

BACKGROUND

Description of the condition

A consequence of the genetic abnormality in people with cystic fibrosis (CF) is an increased susceptibility to chronic lung infections, resulting in lung damage (FitzSimmons 1996). This lung damage is progressive, ultimately leading to respiratory failure; the principal cause of CF-related mortality and morbidity (FitzSimmons 1993). By the end of the first decade of life, *Pseudomonas aeruginosa* (*P. aeruginosa*) is the predominant bacterial pathogen causing infection in the lungs of people with CF (Wang 2001). The CFF data registry reports that approximately 65% to 70% of 18 to 24 year olds have *P. aeruginosa* infection (CFF 2008). By 18 years of age, 80% of individuals are colonised with *P. aeruginosa* (Rajan 2002). In 2009 Millar reported that colonisation rates had remained stable between 1985 and 2005 at 77% to 82% (Millar 2009). Infection with *P. aeruginosa* seems to precede chronic infection (also known as colonisation) by 6 to 12 months (West 2002), and once chronic infection is established, there is evidence that mucoid strains of the isolates prevail and in progressively higher density (Burns 2001; Nixon 2001; Rosenfeld 2001). Additionally,

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it has been suggested that there is a relationship between the onset of chronic infection and increased morbidity (Kosorok 2001; Parad 1999).

Description of the intervention

Appropriate antibiotic therapy against the bacteriological pathogens in the respiratory tract is a vital component in managing CF lung disease (Ratjen 2006). Anti-pseudomonal antibiotics are used in three clinical settings (Gibson 2003): to attempt eradication of *P. aeruginosa* at first evidence of infection so as to delay chronic infection that leads to progressive lung damage; as long-term treatment in chronic infection to slow the decline in respiratory function and reduce frequency and morbidity of pulmonary exacerbations; as antibiotic treatment in pulmonary exacerbations to relieve symptoms and restore respiratory function to baseline values (Gibson 2003).

For each indication, there is a choice of antibiotics and method of administration (i.e. intravenous (IV), oral, nebulised). For long-term therapy current evidence recommends the use of nebulised antibiotics (Döring 2000). For treating moderate to severe pulmonary exacerbations, IV administration of two different classes of antibiotics is suggested to be most effective (Döring 2000). This requires IV access and hospitalisation or home care which are costly and a major inconvenience for the individual with CF.

Oral anti-pseudomonal antibiotics with the same efficacy and safety as the afore-mentioned methods would improve quality of life of people with CF due to ease of drug administration. Both nebulised and IV treatments require significantly more time compared to oral treatments. Often the administration of IV antibiotics requires hospitalisation rather than home treatment, the subject of another Cochrane Review (Asensio 2000). Furthermore, the administration of IV antibiotics may cause discomfort and is potentially a source of infection. In 1985, ciprofloxacin, now the most commonly used fluoroquinolone antibiotic for CF, was introduced as an effective oral treatment against *P. aeruginosa* (Döring 2000).

How the intervention might work

Ciprofloxacin has been shown to have excellent activity against a variety of micro-organisms found in bronchial sputum of children and adults with CF (Richard 1997; Schaad 1997).

There is concern that the wide use of oral anti-pseudomonal antibiotics has led to the emergence of resistant micro-organisms (Ball 1990), but it is not clear how great the risk is of resistant *P. aeruginosa* developing after treatment with these antibiotics or the real effect of it on the disease process. The adverse effects of these drugs have been well described, for example central nervous system effects, phototoxicity, gastrointestinal effects and joint toxicity (Ball 1986; Patterson 1991). Generally pregnancy is a contra-indication to use of these drugs, although it is difficult to know the level of risk (Schaefer 1996). In most clinical settings there are safe alternatives. Furthermore, while the risk of arthropathy in children is probably not sufficient to avoid use when there is benefit, fluoroquinolone-induced resistance remains a concern (Schaad 2007).

Why it is important to do this review

The use of oral anti-pseudomonal antibiotics to delay the onset of chronic infection with *P. aeruginosa* is covered in another Cochrane Review (Wood 2007). Evidence of the effect of macrolide antibiotics in people with CF and chronic infection with *P. aeruginosa* is discussed in another Cochrane Review (Southern 2004). We aim to assess oral anti-pseudomonal antibiotics for people with CF chronically infected with *P. aeruginosa*, both as a treatment for pulmonary exacerbations and as a long-term treatment in chronic infection.

OBJECTIVES

To determine the benefits or harms, or both, of oral anti-pseudomonal antibiotic therapy for people with CF who are colonised with *P. aeruginosa* in two clinical settings:

1. treatment of a pulmonary exacerbation: and
2. long-term treatment of chronic respiratory tract infection.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised (RCTs) and quasi-randomised trials.

Types of participants

Adults and children (with all levels of disease severity) diagnosed with CF clinically and confirmed with sweat test or genetic testing or both.

Participants to have chronic infection with *P. aeruginosa*. We arbitrarily selected the UK Cystic Fibrosis Trust's definition of chronic infection, i.e. the culture of *P. aeruginosa* on two or more occasions over a six-month period prior to the start of the trial (CF Trust 2004). A post hoc change to the review was made and we included trials in which participants were described as chronically infected, even if no further details were given.

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Types of interventions

Oral anti-pseudomonal antibiotics, given in any dose, compared with other combinations of inhaled, oral or IV antibiotics, or with placebo or with usual treatment (e.g. for long-term treatment of chronic infection, no antibiotic treatment), for:

1. treatment of a pulmonary exacerbation, one course of oral anti-pseudomonal antibiotics for less than one month;
2. long-term treatment in chronic infection, course(s) of oral anti-pseudomonal antibiotics of one month more.

A pulmonary exacerbation was regarded as an increase in symptoms requiring additional antibiotic treatment. Long-term treatment was defined as any antibiotic regimen outside the treatment of a pulmonary exacerbation with the aim of preventing exacerbation of *P. aeruginosa* infection.

Trials which evaluated oral anti-pseudomonal antibiotics for eradication of *P. aeruginosa* are the subject of another Cochrane Review (Wood 2007) and were not eligible for inclusion.

Types of outcome measures

Treatment of a pulmonary exacerbation

Primary outcomes

1. Quality of life (measured by a validated tool such as Cystic Fibrosis Questionnaire-Revised version (CFQ-R (Quittner 2009)) and Cystic Fibrosis Quality of Life Questionnaire (CFQoL (Gee 2000)))
2. Lung function
   i) forced expiratory volume in one second (FEV_1)
   ii) forced vital capacity (FVC)

Secondary outcomes

1. Weight
2. Time to next pulmonary exacerbation
3. Adverse effects of antibiotics used, e.g. abnormal liver function, diarrhoea, vomiting, renal and auditory impairment, sensitivity reactions (e.g. skin rash), bronchospasm, candidiasis
4. Frequency of need for additional antibiotic use and number of days receiving additional antibiotics
5. Isolation of antibiotic-resistant strains of *P. aeruginosa* or other micro-organisms with or without antibiotic resistance

Long-term treatment for chronic infection of *P. aeruginosa*

Primary outcomes

1. Quality of life (measured by a validated tool such as Cystic Fibrosis Questionnaire-Revised version (CFQ-R (Quittner 2009)) and Cystic Fibrosis Quality of Life Questionnaire (CFQoL (Gee 2000)))
2. Lung function
   i) FEV_1
   ii) FVC
3. Mortality

Secondary outcomes

1. Time to next pulmonary exacerbation
2. Weight, growth velocity
3. Adverse effects of antibiotics used, e.g. abnormal liver function, diarrhoea, vomiting, renal and auditory impairment, sensitivity reactions (e.g. skin rash), bronchospasm, candidiasis
4. Number of admissions to hospital and number of days spent as an inpatient
5. Frequency of need for additional courses of antibiotics and number of days receiving additional antibiotics
6. Isolation of antibiotic-resistant strains of *P. aeruginosa* or other micro-organisms with or without antibiotic resistance

Search methods for identification of studies

Electronic searches

Relevant trials were identified from the Group's Cystic Fibrosis Trials Register using the terms: antibiotics AND (pseudomonas aeruginosa OR mixed infections) AND (oral OR not stated).

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*), quarterly searches of MEDLINE, a search of EMBASE to 1995 and the prospective handsearching of two journals - *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis*. Unpublished work is identified by searching the abstract books of three major cystic fibrosis conferences: the International Cystic Fibrosis Conference; the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference. For full details of all searching activities for the register, please see the relevant sections of the Cystic Fibrosis and Genetic Disorders Group Module.

Date of the most recent search of the Group's Cystic Fibrosis Trials Register: 28 June 2013.

Searching other resources

We contacted pharmaceutical companies that manufacture oral anti-pseudomonal antibiotics for any information on any relevant trials. We also checked the reference lists of all trials to identify further relevant trials.

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Data collection and analysis

We included an arbitrary definition of chronic infection in the 'Types of participants' section. However, several trials, whilst stating that participants were chronically infected (as described below in the 'Description of studies' section) did not completely fulfil our definition. However, we did not feel that it was appropriate to exclude these trials on these grounds. Therefore, we subsequently made a post hoc change to the protocol to enable us to include these trials, i.e. we included trials in which participants were described as chronically infected, even if no further details were given.
Furthermore, we have regarded the development of antibiotic resistance as a result of therapy (a resistant strain that emerges soon after and in relation to antibiotic treatment) separately to a strain which is there at baseline and which does not respond to antibiotic treatment, i.e. persists.

Selection of studies

Two authors (TR, NJ) independently applied the inclusion criteria to all potential trials. We performed this without blinding. There was no discrepancy between authors in trial selection.

Data extraction and management

Two authors (TR, NJ) independently extracted the data using a customised data extraction form. Where information was lacking, we contacted primary authors for clarification.
For treatment of a pulmonary exacerbation, we measured outcomes at less than a week, one to two weeks, more than two weeks to three weeks, more than three weeks to four weeks. We also considered additional follow-up data recorded at other time periods.
For long-term treatment for chronic infection of *P. aeruginosa*, we measured outcomes at one month, up to three months, up to six months, up to twelve months and then annually thereafter. For future updates, if outcome data are recorded at other time periods, we will consider examining these as well.

Assessment of risk of bias in included studies

Two authors (TR, NJ) assessed each trial using a simple form and followed the domain-based evaluation as described in the *Cochrane Handbook for Systematic Reviews of Interventions 5.0* (Higgins 2008).
We assessed the following domains as having either a low, unclear or high risk of bias.

1. Randomisation ('Low risk' - random number table, computer-generated lists or similar methods; 'Unclear risk' - described as randomised, but no details given; 'High risk' - e.g. alternation, the use of case record numbers, and dates of birth or day of the week).
2. Concealment of allocation ('Low risk' - e.g. list from a central independent unit, on-site locked computer, identically appearing numbered drug bottles or containers prepared by an independent pharmacist or investigator, or sealed opaque envelopes; 'Unclear risk' - not described; 'High risk' - if allocation sequence was known to, or could be deciphered by the investigators who assigned participants or if the trial was quasi-randomised).
3. Blinding (of participants, personnel and outcome assessors) ('Low risk' - e.g. there was no blinding, but we judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding, or at least outcome assessors were blinded; 'Unclear risk' - not described; 'High risk' - e.g. no or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding, or blinding was attempted, but likely to have been broken).
4. Incomplete outcome data (Whether investigators used an intention-to-treat analysis) ('Low risk' - e.g. no missing data, or missing data have been imputed using appropriate methods; 'Unclear risk' - e.g. insufficient reporting of attrition/exclusions; 'High risk' - e.g. reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups).
5. Selective outcome reporting ('Low risk' - e.g. the study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; 'Unclear risk' - e.g. insufficient information to permit judgement; 'High risk' - e.g. not all of the study's pre-specified primary outcomes have been reported).
6. Other potential sources of bias ('Low risk' - the study appears to be free of other sources of bias; 'Unclear risk' - e.g. insufficient information to assess whether an important risk of bias exists; 'High risk' - e.g. had a potential source of bias related to the specific study design used, or had extreme baseline imbalance).

We also reported on whether the investigators had performed a sample-size calculation.
We compared assessments and resolved any inconsistencies by discussion.

Measures of treatment effect

For binary outcome measures, in order to allow an intention-to-treat analysis, we sought data on the number of participants with each outcome event, by allocated treated group, irrespective of compliance and whether or not the individual was later thought to be ineligible or otherwise excluded from treatment or follow up.
We calculated a pooled estimate of the treatment effect for each outcome across trials using relative risk where appropriate.
For continuous outcomes, we recorded either mean relative change from baseline for each group or mean post-treatment or post-intervention values and standard deviation. If standard errors had been reported (and if it were possible) we planned to convert

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these to standard deviations. We calculated a pooled estimate of treatment effect by calculating the weighted mean difference. We are aware that some lung function data are skewed and therefore cannot be entered and analysed within 'Statistical Analysis'. Where this is the case we have reported the results narratively.
We have also reported count data narratively.

Unit of analysis issues

One of the trials included in the review was cross-over in design, but the abstract did not contain any data for analysis (Wang 1988). Ideally when conducting a meta-analysis combining results from cross-over trials we would have liked to use the inverse variance methods that are recommended by Elbourne (Elbourne 2002). However, due to restrictions on the data that were available from the included trial, the only method that we have been able to use was to treat the cross-over trial as if it was a parallel trial (assuming a correlation of zero as the most conservative estimate). Elbourne says that this approach produces conservative results as it does not take into account within-patient correlation (Elbourne 2002). Also each participant appears in both the treatment and control group, so the two groups are not independent.

Dealing with missing data

We assessed whether the numbers and reasons for dropouts and withdrawals in all intervention groups were described or if it was specified that there were no dropouts or withdrawals. We contacted trial authors of five trials for clarification on any missing information, and following correspondence, these have all been excluded from the review (Black 1991; Kurz 1987; Postnikov 2001b; Romano 1991; Rubio 1987).

Assessment of heterogeneity

When sufficient trials are included in the review, we plan to perform a sensitivity analysis based on the methodological quality of the trials, including and excluding quasi-randomized trials. We plan to assess the degree of heterogeneity between trials using the I^2 statistic (Higgins 2003). This measure describes the percentage of total variation across studies that are due to heterogeneity rather than by chance (Higgins 2003). The values of I^2 lie between 0% and 100%, and a simplified categorization of heterogeneity that we plan to use is of low (I^2 value of 25%), moderate (I^2 value of 50%), and high (I^2 value of 75%) (Higgins 2003). If we find significant heterogeneity (over 50%), we will investigate the possible causes further by performing subgroup analyses based on the methodological quality of the included trials and the condition of the individuals (i.e. severity of disease, duration and type of treatment e.g. single or combined treatment). If no significant heterogeneity is identified, we will compute pooled estimates of the treatment effect for each outcome under a fixed effect model.

Assessment of reporting biases

In the 'Characteristics of included studies' table we have reported when measurements were taken by the primary investigators during the trial, what measurements were reported within the published paper and what data we reported in the review.
Within the review we have not reported baseline data. We have reported end of treatment data in line with the time-frames which we pre-specified in the protocol and additionally have included follow-up data from one of the short-term trials (Hodson 1987). Since this is longitudinal data we accept that we have treated these data as independent, although in reality they are not.
When a sufficient number of trials are included, we will attempt to assess whether our review is subject to publication bias by using a funnel plot. If asymmetry is detected, causes other than publication bias will be explored.

Data synthesis

We analysed the two clinical settings (pulmonary exacerbations and long-term treatment of chronic infection) separately. We were only able to analyse data from five of the six included trials. Most of the outcome measures included in the meta-analysis (Data and analyses) consisted of data from only one or two trials.

Subgroup analysis and investigation of heterogeneity

If we had been able to include sufficient number of trials, we planned to split the trials by whether or not they fulfilled our definition of chronic infection or not. There were insufficient trials to do this, but this planned subgroup analysis will be carried out if sufficient trials are included in a future update of this review. When sufficient data are available, different antibiotic regimens will be analysed and compared to each other.

RESULTS

Description of studies

Results of the search

Two authors initially assessed the trials identified in the searches for eligibility on the grounds of trial design, i.e. whether the trials were RCTs or quasi-randomised controlled trials, and also according to whether participants were stated to be chronically infected with *P. aeruginosa*. The authors then further assessed the trials remaining after this initial evaluation according the the criteria stated above. Five trials (including 256 participants) are included in the review (Hodson 1987; Richard 1997; Schaad 1997; Sheldon 1993;

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Wang 1988). Of these five trials, three considered the treatment of a pulmonary exacerbation (171 participants) (Hodson 1987; Richard 1997; Wang 1988) and two trials examined long-term treatment for chronic infection (85 participants) (Schaad 1997; Sheldon 1993).
A total of 39 trials are listed as excluded.

Included studies

Treatment of a pulmonary exacerbation

Three trials reported on this comparison (Hodson 1987; Richard 1997; Wang 1988).

Participants

Two trials included adult participants only (Hodson 1987; Wang 1988) and one trial included children only (Richard 1997).
It was difficult to establish that all participants in these trials had chronic infection with *P. aeruginosa*. On first reading only one trial clearly fulfilled our definition of 'chronic infection', as described in the 'Types of Participants' section (Hodson 1987). We then contacted trial authors and were able to confirm that one more trial fulfilled our definition (Wang 1988). The remaining trial described participants as being chronically infected (Richard 1997). After contact with the trial authors it was confirmed that the participants enrolled were "chronically colonised with *P. aeruginosa*, suffering from an acute bronchopulmonary exacerbation caused by *P. aeruginosa* as confirmed by sputum culture". The trial authors confirmed that the all participants did have more than just one positive sputum culture of *P. aeruginosa* (Richard 1997).

Interventions

Three trials compared oral with IV interventions (Hodson 1987; Richard 1997; Wang 1988). Of these trials, one 10-day trial compared oral ciprofloxacin (500 mg three times daily (tds)) versus IV azlocillin (5 g tds) plus gentamicin (80 mg tds) (Hodson 1987); one 14-day trial compared oral ciprofloxacin (15 mg/kg twice daily (bd)) with IV ceftazidine (50 mg/kg tds) plus tobramycin (3 mg/kg tds) (Richard 1997); one three-arm trial ,with treatment periods of 14 days, compared oral ciprofloxacin (750 mg bd) with IV tobramycin plus ticarcillin versus IV tobramycin plus azlocillin (Wang 1988).

Outcomes

Please refer to the 'Review-specified outcomes reported in included trials' table in 'Additional tables' for the outcomes reported in each trial (Table 1).
One trial reported on quality of life (Hodson 1987). All trials reported on lung function and adverse events (Hodson 1987; Richard 1997; Wang 1988). Two trials reported on time to next respiratory tract infection (Hodson 1987; Richard 1997). All three trials reported on isolation of antibiotic-resistant strains of *P. aeruginosa* or other micro-organisms with or without antibiotic resistance (Hodson 1987; Richard 1997; Wang 1988). No trials reported on weight; the frequency of need for additional courses of antibiotics and number of days receiving additional antibiotics.

Design

Two of the included trials were parallel in design (Hodson 1987; Richard 1997) and one of the included trials was cross-over; having three arms (Wang 1988).

Setting

Two trials were single centre (Hodson 1987; Wang 1988) and one was multicentre carried out in 15 centres in 9 countries (France, Germany, Greece, Hungary, Israel, Italy, Portugal, South Africa and Switzerland) (Richard 1997).

Long-term treatment for chronic infection of *P. aeruginosa*

Two trials reported on this comparison (Schaad 1997; Sheldon 1993).

Participants

One trial included adult participants only (Sheldon 1993) and one trial included both adults and children (Schaad 1997).
Again, it was difficult to establish whether all participants in these trials had chronic infection with*P. aeruginosa*. One trial described participants as being chronically infected (Schaad 1997). After contact with the trialists of the Schaad paper, it was confirmed that the participants enrolled were "chronically colonised with *P. aeruginosa*, suffering from an acute bronchopulmonary exacerbation caused by *P. aeruginosa* as confirmed by sputum culture". The trialists confirmed that the all participants did have more than just one positive sputum culture of *P. aeruginosa* (Schaad 1997). The Sheldon paper reported that "Chronic infection implied isolation of *P.aeruginosa* from at least four sputum samples over the previous two years" (Sheldon 1993). Additionally, it was reported in the Sheldon paper that there was a difference in lung function between the groups at baseline; participants in the ciprofloxacin group started with worse lung function than those in the placebo group (Sheldon 1993).

Interventions

Two trials were included that examined long-term treatment of chronic infection. One three-month trial compared oral ciprofloxacin (30 mg/kg/day) versus oral ciprofloxacin (30 mg/kg/day) plus amikacin inhalation therapy (500 mg/day). Ciprofloxacin was

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given in two doses to a maximum of 1.5 g/day (Schaad 1997). It should be noted, however, that there was a 14-day intensive hospital therapy with IV antibiotics and inhalation therapy prior to the randomisation for the oral antibiotic trial. A further 12-month trial compared oral ciprofloxacin (500 mg tds) to identical placebo for 10 days every three months for four courses of treatment (Sheldon 1993).

Outcomes

Please refer to the 'Review-specified outcomes reported in included trials' table in 'Additional tables' for a clear representation of the relevant outcomes reported in each trial (Table 1).

One trial reported on quality of life (Sheldon 1993). Both trials reported on: lung function; adverse events; weight, growth velocity; and isolation of antibiotic-resistant strains or *P. aeruginosa* or other micro-organisms with or without antibiotic resistance (Schaad 1997; Sheldon 1993). Neither trial reported on time to next pulmonary exacerbation determined clinically or radiologically or both that cannot be attributed to concurrent isolates of other organisms. One trial reported on the number of admissions to hospital and number of days spent as an inpatient and on the frequency of need for additional courses of antibiotics and number of days receiving additional antibiotics (Sheldon 1993).

Design

Both of the included trials were parallel in design (Schaad 1997; Sheldon 1993).

Setting

Both of the included trials were single centre (Schaad 1997; Sheldon 1993).

Excluded studies

A total of 39 trials were excluded. The reasons for exclusion were as follows: seven trials were found not be RCTs or quasi-randomised (Denning 1977; Kapranov 1995; Ordonez 2001a; Pirzada 1999; Postnikov 2001a; Scully 1987; Strandvik 1989); in thirteen trials not all participants were colonised or infected with *P.aeruginosa* (Bosso 1987; Bosso 1989; Equi 2002; Harrison 1985; Knight 1979; Loening-Baucke 1979; Nolan 1982; Owen 1991; Postnikov 2001b; Shapera 1981; Stutman 1987; Weaver 1994; Wolter 2002); three trials were reporting on macrolides, which we did not consider to be anti-pseudomonal antibiotics (Anstead 2001; Saiman 2003; Sriram 2003); one trial assessed combined oral and inhaled therapy (no oral therapy alone) (Treggiari 2011); eight trials were on pharmacokinetics (Cipolli 2001; Davies 1987; Goldfarb 1986; Johansen 1999; Mack 1991; Pai 2006; Smith 1997; Vitti 1975); one trial reported on a Cox-2 inhibitor (Pukhalsky 2001); one trial reporting on chronic infection did not meet the criteria for treatment duration (Jensen 1987); and one trial compared a combination of oral and inhaled antibiotics for three weeks or three months (Frederiksen 2003). For four trials we were not able to clarify eligibility after two attempted contacts with the authors (Black 1991; Kurz 1987; Romano 1991; Rubio 1987).

Risk of bias in included studies

For detailed information on the risk of bias of each included trial, please refer to the risk of bias tables attached to the 'Characteristics of included studies' section of this review. A summary is also presented in the figures (Figure 1). There are three trials reporting on the treatment of a pulmonary exacerbation (Hodson 1987; Richard 1997; Wang 1988). There are two trials reporting on long-term treatment (Schaad 1997; Sheldon 1993).

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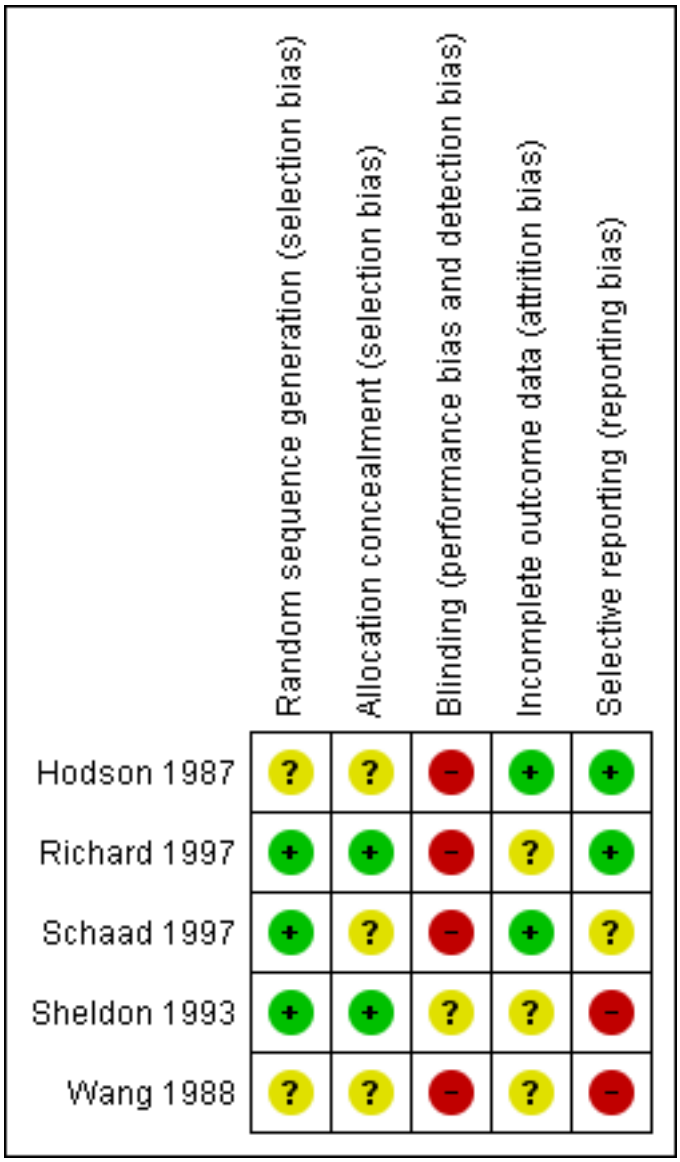
Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



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Allocation

Treatment of a pulmonary exacerbation

Generation of the allocation sequence

One trial provided information on the randomisation of participants and we assessed this trial as having a low risk of bias (Richard 1997). We judged the remaining two trials as 'unclear' as they failed to provide sufficient information (Hodson 1987; Wang 1988).

Allocation concealment

One trial provided information on the allocation concealment and was judged to have a low risk of bias (Richard 1997). The remaining two trials did not describe any method of allocation concealment and were assessed as 'unclear' (Hodson 1987; Wang 1988).

Long-term treatment for chronic infection of *P. aeruginosa*

Generation of the allocation sequence

Both trials provided information on the randomisation of participants and they were judged to have a low risk of bias (Schaad 1997; Sheldon 1993).

Allocation concealment

One trial provided information on the allocation concealment and was thought to have a low risk of bias (Sheldon 1993). The remaining trial did not describe any method of allocation concealment and we assessed this as 'unclear' (Schaad 1997).

Blinding

Treatment of a pulmonary exacerbation

Clinicians or Persons delivering treatment

In three trials it was not possible to blind participants or clinicians given the interventions being compared, which means there is a potential risk of bias (Hodson 1987; Richard 1997; Wang 1988).

Participants

In all three trials it was not possible to blind given the interventions being compared (Hodson 1987; Richard 1997; Wang 1988).

Outcome assessor

Two trials reported that outcome assessors were blinded with regards to specific outcomes (see the 'Risk of bias' tables in Characteristics of included studies for further details) (Hodson 1987; Richard 1997). The remaining trial did not provide any information on the blinding of outcome assessors (Wang 1988).

Long-term treatment for chronic infection of *P. aeruginosa*

Clinicians or Persons delivering treatment

In one trial it was reported that the person delivering the treatment was blinded to the treatment group (Sheldon 1993). In the remaining trial it was not possible to blind given the interventions being compared (Schaad 1997).

Participants

In one trial which compared oral treatments the participants were blinded to the treatment group (Sheldon 1993). In the remaining trial it was not possible to blind given the interventions being compared (Schaad 1997).

Outcome assessor

One trial was described as "double-blind" although it was not specifically discussed whether the outcome assessors were blinded (Sheldon 1993). The remaining trial did not provide any information on the blinding of outcome assessors (Schaad 1997).

Incomplete outcome data

Treatment of a pulmonary exacerbation

All three trials in this setting described withdrawals from treatment, further details can be found in the 'Risk of bias' tables in Characteristics of included studies (Hodson 1987; Richard 1997; Wang 1988). None of the included trials specifically stated the use of an intention-to-treat analysis when presenting data.

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Long-term treatment for chronic infection of *P. aeruginosa*

Both trials described withdrawals from treatment, further details can be found in the 'Risk of bias' tables in Characteristics of included studies (Schaad 1997; Sheldon 1993). Neither of the included trials specifically stated the use of an intention-to-treat analysis when presenting data.

Selective reporting

Please refer to an additional table for information regarding the measurement and reporting of outcome data (Table 1).

Treatment of a pulmonary exacerbation

In summary, only one trial reported all time-points that were measured within the trial and at follow up (Hodson 1987). A further trial did not report on one of the time-points that was stated as having been measured, this was between baseline and end of treatment (Richard 1997). The remaining trial is in abstract form and only reported results narratively (Wang 1988).

Long-term treatment for chronic infection of *P. aeruginosa*

In summary, both trials did not report on one of the time-points that was stated as having been measured and in both cases these were between baseline and end of treatment (Schaad 1997; Sheldon 1993).

For the Schaad trial, we note that the investigators, while stating that lung function was measured at clinic visits, did not report on FEV_1 (generally regarded as the standard lung function measurement and reported within most published trials in this area) (Schaad 1997).

Effects of interventions

Where the results entered into the 'Statistical Analysis' conflict with the results reported within the paper, we have reported both sets of results.

Treatment of a pulmonary exacerbation

All three trials included in this setting compared an oral intervention to an IV intervention (Hodson 1987; Richard 1997; Wang 1988).

Primary outcomes

1. Quality of life

This outcome was not reported on by any of the included trials (Hodson 1987; Richard 1997; Wang 1988).

2. Lung function

a. FEV_1

All three trials reported this outcome. Only one reported data which we were able to enter into Data and analyses (Hodson 1987). This paper reported that at end of treatment (day 10), FEV_1 improved significantly more in the ciprofloxacin group compared to the azlocillin + gentamicin group ($P < 0.05$). However, we note that this result conflicts with the graph produced, which shows a non-significant difference; we are unable to explain this difference from the information provided (Analysis 1.1). Furthermore, the trial authors reported that although FEV_1 had decreased at follow up (six weeks) it was still significantly better in the oral ciprofloxacin group ($P < 0.001$). These data are skewed and therefore have not been entered into the data tables.

In the other two trials, Richard stated that the mean changes in FEV_1 at the end of treatment were ciprofloxacin (7.4%) and ceftazidine + tobramycin (7.5%) ($P = 0.97$) (Richard 1997). In the abstract, Wang briefly mentioned this outcome, but did not present any specific results (Wang 1988).

b. FVC

All three trials reported on this outcome. Again, only one reported data which we were able to enter into the analysis (Hodson 1987). There was no significant difference between FVC at end of treatment (day 10) (Analysis 1.2). However, the trialists stated that at six weeks FVC had decreased but was still significantly improved in the oral ciprofloxacin group ($P < 0.005$), these data are skewed and therefore have not been entered into the data tables. The Richard trial reported that mean changes in FVC at the end of treatment were oral (9.3%) and IV therapy (7.7%) ($P = 0.60$) (Richard 1997). In the abstract, Wang briefly mentioned this outcome, but did not present any specific results (Wang 1988).

Secondary outcomes

1. Weight

This outcome was not reported on by any of the included trials (Hodson 1987; Richard 1997; Wang 1988).

2. Time to next pulmonary exacerbation

Two out of the three trials reported this outcome, but not in a form which allowed us to enter data into the data tables (Hodson 1987; Richard 1997). Hodson stated that there was no significant difference between the groups in the number of participants who received further treatment between day 10 and 6 weeks (Hodson

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1987). Richard stated that 9 (out of 55) participants who had received ciprofloxacin and 5 (out of 53) who had received parenteral therapy suffered a further acute exacerbation between 9 and 30 days after the end of therapy (Richard 1997).

3. Adverse effects of antibiotics used, e.g. diarrhoea, vomiting, renal and auditory impairment, sensitivity reactions (e.g. skin rash), bronchospasm, candidiasis.

In the data tables, we have grouped adverse effects into gastrointestinal, central nervous system, musculoskeletal, sensitivity reactions and others.
All three trials reported on this outcome (Hodson 1987; Richard 1997; Wang 1988). Hodson and Richard reported details of the adverse events occurring in their respective trials. When pooled in a meta-analysis none of these events reached statistical significance (Analysis 1.3) (Hodson 1987; Richard 1997). Wang stated within the abstract that "no toxic effects were observed in any of the patients" (Wang 1988).

4. Frequency of need for additional antibiotic use and number of days receiving additional antibiotics

Two trials reported on this outcome (Hodson 1987; Richard 1997). Only one of the trials reported data which we were able to enter into the data tables (Hodson 1987). This showed no significant difference in the number of participants who received further treatment between day 10 and 6 weeks (Analysis 1.4). The remaining trial reported data "between 9 and 30 days after the end of therapy", due to the structured time periods defined in the protocol, we were not able to enter these data into a meta-analysis (Richard 1997). During this time period it was reported that six participants in the ciprofloxacin group and three in the ofloxacin group were given additional antibiotics for new acute exacerbations.

5. Isolation of antibiotic-resistant strains of *P. aeruginosa* or other micro-organisms with or without antibiotic resistance

Three trials reported on this outcome (Hodson 1987; Richard 1997; Wang 1988). Hodson reported no significant difference in the isolation of antibiotic-resistant *P. aeruginosa* (Analysis 1.5) or *S. aureus* (Analysis 1.6) between the two groups at day 10 and at 6 weeks (Hodson 1987). Richard reported that, at day 14, resistant strains ("persistence") were found in 72% of the oral ciprofloxacin group and 33% of the IV group (Analysis 1.5). However, in the long term the IV group encountered a higher rate of recurrent infection with *P. aeruginosa*. Neither antibiotic therapy affected the resistant strains (Richard 1997). In the Wang trial weekly sputum cultures did not reveal any emergence or resistance to ciprofloxacin (Wang 1988).

Long-term treatment for chronic infection of P. aeruginosa

Of the two included trials, one compared an oral intervention to placebo (Sheldon 1993) and the other compared an oral intervention to oral + inhaled therapy (Schaad 1997).

Primary outcomes

1. Quality of life

This outcome was not reported on by either of the included trials (Schaad 1997; Sheldon 1993).

2. Lung function

a. FEV_1

Only the trial comparing oral ciprofloxacin with placebo reported on this outcome (Sheldon 1993). There was no significant difference between treatment groups at the end of therapy (Analysis 3.1). However, after examining the graph produced, there are indications that data are skewed and so results should be interpreted with caution. Furthermore, it should be noted that participants in the ciprofloxacin group started with lower lung function than those in the placebo group.

b. FVC

Both trials reported on this outcome. The trial comparing oral ciprofloxacin with placebo reported no significant difference between treatment groups at the end of therapy (Analysis 3.2) (Sheldon 1993). However, after examining the graph produced, there are indications that data are skewed and so results should be interpreted with caution. The oral ciprofloxacin versus oral ciprofloxacin + inhaled amikacin trial reported geometric means and ranges which cannot be entered into a meta-analysis (Schaad 1997). In the paper, mean change in FVC (% predicted) at three months was reported as 67% (range 35% to 123%) in the ciprofloxacin group, compared to 55% (range 28% to 119%) in the combined group. The authors also stated that the improvements in FVC attained during IV therapy (the pre-therapy before the start of the oral antibiotic trial, as discussed in the Description of studies section) gradually deteriorated during oral therapy (Schaad 1997).

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3. Mortality

Only Sheldon reported on this outcome; there was one death (n = 20) in the treatment group and one death in the placebo group (n = 20) (Analysis 3.3) (Sheldon 1993). However, the trial was not adequately powered to detect a difference between groups in this outcome.

Secondary outcomes

1. Time to next pulmonary exacerbation

Neither trial reported on this outcome (Schaad 1997; Sheldon 1993).

2. Weight, growth velocity

Both trials reported on this outcome. The trial comparing oral ciprofloxacin with placebo found no significant differences between the groups for weight (Sheldon 1993) (Analysis 3.4). The oral ciprofloxacin versus oral ciprofloxacin + inhaled amikacin trial reported geometric means and ranges which cannot be entered into a meta-analysis (Schaad 1997). In the paper, mean change in height at three months was reported as 146.7 cm (range 103 cm to 187 cm) in the ciprofloxacin alone group, compared to 147.2 cm (range 103 cm to 180 cm) in the combined group. The authors further stated that growth curves revealed unchanged increase of the height measured by stadiometer along the individual percentile (Schaad 1997).

3. Adverse effects of antibiotics used, e.g. diarrhoea, vomiting, renal and auditory impairment, sensitivity reactions (e.g. skin rash), bronchospasm, candidiasis

In the data tables, we have grouped adverse effects into gastro-intestinal, central nervous system, musculoskeletal, sensitivity reactions and others.

Both trials reported on this outcome. The trial comparing oral ciprofloxacin with placebo found no significant differences between the groups for the gastro-intestinal events (Analysis 3.5) (Sheldon 1993). The oral ciprofloxacin versus oral ciprofloxacin + inhaled amikacin trial reported that five participants in each group experienced adverse events but only reported details on the number of events, not on the number of participants experiencing these events, therefore these data cannot be entered into a meta-analysis (Schaad 1997). The trial authors reported that there were a total of five events for five participants in the ciprofloxacin group and ten events for five participants in the combined group. These were split as follows: one gastro-intestinal event in the ciprofloxacin group and four in the combined group; one central nervous system event in the ciprofloxacin group and four in the combined group; one musculoskeletal event in each of the treatment groups; and two 'Other' events in the ciprofloxacin group and one in the combined group (Schaad 1997). We note that neither trial was of sufficient duration to detect any skeletal adverse events.

4. Number of admissions to hospital and number of days spent as an inpatient

One trial reported on this outcome (Sheldon 1993). Participants in the ciprofloxacin group experienced a mean (SD) 7.50 (10.32) number of days in hospital compared to participants in the placebo group who experienced a mean (SD) 6.75 (14.29) number of days in hospital. These count data cannot be entered into the data tables.

5. Frequency of need for additional courses of antibiotics and number of days receiving additional antibiotics

One trial reported on this outcome and there was no significant difference found between the groups (Sheldon 1993) (Analysis 3.6).

6. Isolation of antibiotic-resistant strains of *P. aeruginosa* or other micro-organisms with or without antibiotic resistance

Both trials reported on this outcome. At the end of three months, Schaad reported a total of seven incidences of antibiotic-resistant strains of *P. aeruginosa*; however, there was no significant difference between the oral ciprofloxacin versus oral ciprofloxacin + inhaled amikacin treatment groups (Analysis 2.1) (Schaad 1997). The trial authors reported that at routine follow up, 10 to 15 weeks later, all 7 isolates reversed to ciprofloxacin-susceptible strains of *P. aeruginosa* (Schaad 1997). The Sheldon trial reported a total of 15 incidences of antibiotic-resistant strains of *P. aeruginosa*; however, there was no significant difference between the treatment groups at 12 months (Analysis 3.7) (Sheldon 1993). Sheldon also reported transient resistance to ciprofloxacin in four participants in the treatment group and two participants in the placebo group (Sheldon 1993). Furthermore, Sheldon also reported that *S. aureus* was persistently isolated from four participants in the treatment group and six participants in the placebo group during the trial (Analysis 3.8) (Sheldon 1993).

DISCUSSION

Current standard treatment for a pulmonary exacerbation of cystic fibrosis-lung disease is intravenous administration of two different classes of antibiotics (Döring 2000). Standard long-term treatment is to use nebulised antibiotics (Döring 2000). There may be significant advantages of oral treatment for people with cystic fibrosis compared to an intravenous or inhaled drug regimen. We identified six trials which were eligible for inclusion in the review;

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four trials of treatment of pulmonary exacerbations and two trials of long-term treatment for chronic infection of the respiratory tract.

Summary of main results

In summary, we were unable to find sufficient evidence of benefits and harms to provide guidance on the use of an oral anti-pseudomonal antibiotic regimen (alone or in combination with another therapy) in treating a pulmonary exacerbation. Likewise, we were unable to present any conclusive evidence to show that an oral antibiotic regimen (alone or in combination with another therapy) is more or less effective than any other drug regimen for long-term treatment of chronic infection with *P. aeruginosa*.

No sufficient data were established to validate the concern surrounding emergence of antibiotic resistance as a result of widespread and long-term use of oral anti-pseudomonal antibiotics. Similarly, no differences in frequency or severity of adverse effects of antibiotics were found. However, the trials were not adequately powered to detect these differences and may not have been of sufficient duration to detect long-term adverse events.

Quality of the evidence

All of the trials were published at least 10 years ago and did not always report outcome measures which clinicians and consumers currently perceive to be important. The trials were very heterogeneous in terms of design, drugs used, duration of treatment and follow up and outcome measures. We used an arbitrary definition of chronic infection (CF Trust 2004); however, several trials, whilst stating that participants were chronically infected did not define this term clearly and consistently. After correspondence with several authors to clarify definitions of chronic infection, we were able to make a post hoc change to the review and include trials which we initially thought would be excluded. Furthermore, inconsistencies in expression of results and statistical reporting (for example different measures of lung function were reported in a variety of ways) made meta-analysis impossible in most cases. We would need to collect individual patient data from the trial authors to clarify these issues; however, given the age of the trials it is unlikely that this would be possible. It was disappointing that only four trials included data which we were able to analyse. Most of the outcome measures included in the data tables consisted of data from only one or two trials. An insufficient number of trials and lack of data presented within the included trials meant we were unable to use sensitivity and subgroup analyses to examine for effects of methodological quality of trials, the condition of the individuals (i.e. severity of disease), duration of treatment or type of treatment (e.g. single or combined treatment).

Agreements and disagreements with other studies or reviews

We regarded the most important outcomes as quality of life and clinical improvement. In our analysis, we unable to present any significant results for these outcome measures for any of the comparisons, either for exacerbation or maintenance treatment. However, in her primary paper Hodson reported significant results for lung function when treating a pulmonary exacerbation with oral ciprofloxacin compared to a combination of IV azlocillin and gentamicin (Hodson 1987). The consensus for standard treatment of a pulmonary exacerbation is the use of intravenous antibiotics, but we were unable to identify any evidence from RCTs for this. For long-term maintenance treatment, standard care consists of nebulised antibiotics; we were unable to demonstrate any evidence from RCTs that this is more effective than oral treatment.

AUTHORS' CONCLUSIONS

Implications for practice

We found no evidence from RCTs that oral anti-pseudomonal antibiotics, alone or in combination with another therapy, are any more or less effective in treating acute pulmonary infectious exacerbations or for long-term treatment of chronic infection in people with CF than other therapies. Until results of adequately-powered future trials are available, treatment needs to be selected on a pragmatic basis, based upon any available non-RCT evidence, the clinical circumstances of the individual, the known effectiveness of drugs against local strains and upon individual preference.

Implications for research

The effectiveness of oral antibiotics for treatment of lung infection in people with CF who have chronic Ps aeruginosa infection is an important question for people with CF. The evidence from available RCTs is insufficient to answer the question. Unfortunately, as far as we are aware, there have been no RCTs of this intervention since 1998, and this highlights the need for further research. Future trials should be designed to adequately compare oral treatment with current standard therapies for both acute pulmonary exacerbations and long-term treatment of chronic infection. This review gives limited evidence of the frequency and variance of outcome measures to plan sample size. In order to enable future pooling of data, trial authors should endeavour to use standard methods and definitions to report on outcomes which are important to people with CF and their carers, such as quality of life, pulmonary exacerbations, antibiotic resistance; all of which are reasonably widely accepted in CF literature.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

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

Hodson 1987

Methods	RCT (generation of allocation sequence & allocation concealment both graded as 'unclear'). Parallel design. Single centre.
Participants	40 admitted with acute exacerbations of pulmonary symptoms associated with isolation of *P. aeruginosa* from sputum. 20 randomly allocated to each group. Aged 16 and over, diagnosed with CF and had grown *P. aeruginosa* consistently in their sputum for at least 6 months, were admitted to hospital with an exacerbation of pulmonary symptoms. All had chronic bronchopulmonary infection, malabsorption, and a sodium concentration in sweat of more than 70mmol/l The *P. aeruginosa* isolated in sputum had to be sensitive to CPX, azlocillin and gentamicin. Excluded if had abnormal renal or hepatic function, previous adverse reactions to drugs in trial, were pregnant or taking theophyllines Mean age: 23 years; range: 18 to 35 years. Sex: 11 males, 9 females in each group. Country: UK.
Interventions	Each treatment given 3 times a day for 10 days. Azlocillin (5 g) plus gentamicin (80 mg) both given intravenously or ciprofloxacin (500 mg) given orally Time-points when measurements were taken during the trial: day 1 (for all 40 participants), day 10 (for all 40 participants), 6 weeks (for 30 participants (15 in each group) . On each of the 10 days of treatment temperature, max PEF and sputum weight were recorded. Time-points reported in the trial: day 1, day 10, 6 weeks.
Outcomes	Sputum cultured and sensitivities for any isolates assessed by standard disc methods. Sputum weight PEF FEV1* FVC* Blood and liver function tests. Temperature Scores on diary cards: breathing; sputum colour and volume; whether chest felt wheezy or better/same/worse as day 1*. Any side-effects noted (gastro-intestinal, nervous system, others)*. CPX participants asked whether they preferred oral to IV treatment. Additional IV treatment required*. Isolation of antibiotic-resistant strains*. Death within 3 months post-treatment. Any treatment with IV anti-pseudomonal drugs within 3 months post-treatment*

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Hodson 1987 (*Continued*)

Notes	Time-points used in the review: day 10 and follow up at 6 weeks Sample-size calculation not discussed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as "randomly allocated" but no further information on the methods used
Allocation concealment (selection bias)	Unclear risk	Method not described.
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible to blind participants or clinicians given the interventions being compared Reported that lung function was tested by an assessor not involved in the trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis: not stated. Data recorded for all 40 participants on days 1 and 10, but only 15 in each group evaluated at 6 weeks Some withdrawals described: 4 participants receiving azlocillin/gentamicin admitted and treated again with IV chemotherapy. 32 out of 40 participants completed diary cards. Sputum weight available for 38 out of 40 participants (19 in each group). 3 deaths by 3 months after start of treatment (1 azlocillin/gentamicin; 2 CPX) , all had very severe lung disease at start of trial
Selective reporting (reporting bias)	Low risk	Study protocol not available, however, all outcomes listed as being measured at clinic visits were described in full in the results section of the paper

Richard 1997

Methods	RCT (generation of allocation sequence & allocation concealment both graded as 'adequate'). Parallel design. Multi centre (15 centres in 9 countries).
Participants	108 people randomised (55 to oral CPX and 53 to parenteral combination therapy) Minimum age of 5 years and whose growth was not completed, hospitalised between May 1993 and April 1995, for treatment of an exacerbation of pulmonary infection.

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Richard 1997 (*Continued*)

	Treatment was confined to those who were infected with *P. aeruginosa* and microbiologically susceptible to CPX and at least 1 of the comparison drugs. Those people with advanced CF were excluded (Shwachman score < or = 40), so were those with previous or current joint abnormality, CF arthropathy, myasthenia or a history of allergy to quinolones, beta-lactams or aminoglycosides Mean age in CPX group: 10.2 years; in combination therapy group: 11.00 years. Age across groups ranged from 5 to 17 years Sex: 59 males, 49 females in each group. CPX group (32 males, 23 females); combination therapy group (27 males, 26 females) Country: 9 countries.
Interventions	Each treatment given for 14 days. Oral CPX (15 mg/kg bd, maximum dose, 1500 mg/day) versus IV ceftazidine plus tobramycin (50 mg/kg tds, 3 mg/kg tds, respectively). The dosage was adjusted to achieve to achieve peak plasma concentrations between 6 & 12 mg/l and trough values <2 mg/l Time-points when measurements were taken during the trial: at baseline, at 5 to 7 days, at 14 days and at follow up (20 to 30 days). Time-points reported in the trial: baseline, day 14 and follow up (day 20 to 30) data
Outcomes	Shwachman score Chest radiographs (using Chrispin-Norman score) Severity of acute exacerbations was assessed by a modified acute change clinical score system FEV_1 (% of predicted value for height)* FVC (% of predicted value for height)* Baseline sputum samples were taken 48 hr before treatment. Bacteriologic outcome at the end of treatment and at follow up. Physical examination of the joints (knees, hips, shoulders) assessed four times* MRI evaluation Laboratory assessments (Days 5 to 7, chemistry) and at the end of therapy (all) and at follow-up (haematology) Adverse events Additional antibiotics for new acute exacerbations*
Notes	Time-points used in the review: day 14 and at follow up (20 to 30 days) Authors confirmed colonisation according to our criteria.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Authors confirmed assignment was based on random code generated at the Institute of Biometry of Bayer AG, Wuppertal, Germany
Allocation concealment (selection bias)	Low risk	Authors confirmed sealed envelope for each participant specifying individual drug schedule to be opened after enrolment

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Richard 1997 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	High risk	Clinician/person delivering treatment: not possible (oral vs IV). Participants: not possible (oral vs IV) Outcome assessor: yes (chest radiographs, ultrasound documents, MRI pictures, physical examination of joints undertaken by a specialist (usually a physiotherapist))
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intention-to-treat analysis: no. Withdrawals described. 4 participants on CPX not evaluated - 3 dropped out (1 withdrawal of consent, 1 recognition of previous joint disorder, 1 pneumothorax) and clinician reported indeterminate response in 1 participant
Selective reporting (reporting bias)	Low risk	Study protocol not available, however, all outcomes listed as being measured at clinic visits were described in full in the results section of the paper

Schaad 1997

Methods	RCT (generation of allocation sequence graded as adequate & allocation concealment graded as 'unclear'). Parallel design. Single centre.
Participants	45 people randomised. 24 male and 21 female. 22 were randomly assigned to maintenance treatment with CPX alone and 23 received CPX with amikacin. 1 female excluded from CPX group after baseline culture showed no *P. aeruginosa*. Participants admitted because of deterioration in their condition were eligible for inclusion provided that *P. aeruginosa* was confirmed as the dominant pathogen by sputum culture. Those with advanced stage illness (bernese score, < or = 10) were excluded from entering the study, as were those with impaired cardiac, renal or liver function, hearing or balance disorders or any disease of the skeleton Age range: 8 to 25 years. 28 participants < 15 years. CPX group mean age 13.4 years (range 4 to 25 years with 13 aged < 15 years). In CPX plus amikacin group mean age 14 years (range 5 to 26 years, with 15 aged < 15 years) Country: Switzerland
Interventions	Pre-treatment began with an intensive, 2-week hospital course of IV ceftazidime (300 mg/kg/day) and amikacin (36 mg/kg/day). Ceftazidime was given in 4 doses to a maximum of 12 g/day and amikacin was given in 3 doses to a maximum of 1.5 mg/kg/day. Each antibiotic was administered as a separate 5 minute IV injection. In all participants IV therapy was supplemented by twice daily inhalation of amikacin (500 mg in 2 ml) administered using a nebuliser. Patients who responded to hospital treatment were randomised to a 3-month period of outpatient therapy with oral ciprofloxacin (30 mg/kg/

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	day) either alone or in combination with supplemental amikacin inhalation therapy (500 mg/kg/day). CPX was given in 2 doses to a maximum dose of 1.5 g/day. Physiotherapy tds when participants were in hospital and bd thereafter. Inhaled salbutamol (2 ml in 0. 9% saline) was administered by nebuliser immediately after each physiotherapy session, and nebulised amikacin was always administered after physiotherapy Time-points when measurements were taken during the trial: baseline; 6 weeks; and at 3 months (randomised section). Time-points reported in the trial: baseline; and 3 months.
Outcomes	Participants were assessed at the start and end of hospital therapy (pre-randomisation) and after 6 weeks and 3 months of outpatient treatment At each assessment: sputum samples were taken for bacteriologic examination; lung function (respiratory rate, forced vital capacity*; residual volume; and airway resistance); weight and height*; adverse events were recorded as free text*. Blood and urine samples were taken for routine haematology, clinical chemistry and urinalysis tests; Strains of isolated *P. aeruginosa* were tested for antibiotic susceptibility*; Changes in clinical symptoms were scored at the end of maintenance therapy as "improved or "unchanged" compared with the end of hospital therapy, or as "clinical failure"
Notes	Time-points used in the review: 3 months.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Authors confirmed that a computer-generated randomisation list was used and strictly adhered to
Allocation concealment (selection bias)	Unclear risk	Method not described.
Blinding (performance bias and detection bias) All outcomes	High risk	Clinician/person delivering treatment: not possible (oral vs oral plus inhaled). Participants: not possible (oral vs oral plus inhaled) Outcome assessor: no information provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis: not clear. Withdrawals described. CPX group: 1 participant in the CPX group was excluded because the baseline culture had been negative for PA. CPX plus inhaled amikacin: 2 participants

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		discontinued treatment; 1 (after 3 weeks of therapy) because of abdominal pain, tiredness and loss of concentration; and the other (at 4 weeks) because of subjective breathlessness after amikacin therapy inhalation
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available. The methods section of the paper states that lung function was measured at each assessment and the following were reported in a table for baseline, end of oral and end of IV therapy: respiratory rate, vital capacity, residual volume and airway resistance. One of the standard lung function measurements, FEV_1, is not mentioned and it is not clear if this was not measured at each assessment or if the authors have selectively reported this outcome

Sheldon 1993

Methods	Double-blind RCT (generation of allocation sequence & allocation concealment both graded as 'adequate'). Parallel design. Single centre.
Participants	40 randomised. 31 completed the trial. Eligible if over 18 years of age and chronically infected with *P. aeruginosa*. Participants were excluded from the trial if they had *P. aeruginosa* resistant to CPX in their sputum culture immediately prior to entering the trial, renal insufficiency, an intention to become pregnant, current treatment with theophyllines or a past history of poor compliance Mean (SD) age of 15 participants in the active treatment group: 28.3 years (6.06 years) Mean (SD) age of 16 participants in the placebo group: 24.9 years (5.15 years) Sex: active treatment group: 13 males, 2 females; placebo group: 10 males, 6 females Country: UK
Interventions	CPX (500 mg) tds or an identical placebo for 10 days every 3 months for 4 courses Time-points when measurements were taken during the trial: baseline; every 3 months up to 12 months. Time-points reported in the trial: baseline; day 10 (every 3 months) for MIC only; final assessment
Outcomes	At each visit the participants' clinical symptoms, signs, weight and drug history were recorded*. PEF FEV_1* FVC* Oxygen saturation

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	Diary card completed listing details of symptoms, sputum volume and PEF. Breathlessness was graded by the participants using a 3-point scale*. Sputum volume was recorded using a 5-point scale. Sputum samples were cultured at the start and finish (day 10) of each course of tablets. Sputum specimens were collected at each outpatient visit and at the end of each treatment period. Susceptibility of isolates of *P. aeruginosa* were stored for analysis of MIC at the end of the trial period. Mortality Adverse effects*
Notes	Time-points used in the review: 12 months. In this trial, participants in the ciprofloxacin group started with worse lung function than those in the placebo group The trial had a power of 80% for detecting a real difference of 200 ml in the improvement of FEV_1 between the groups significant at the 5% level.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	On enrolment into the trial participants were given consecutive trial numbers, which corresponded to the treatment group randomised before the study. Randomisation of treatment courses was arranged prior to the start of the trial in blocks of 4: 2 each for treatment and placebo
Allocation concealment (selection bias)	Low risk	Treatment courses were prepared by Bayer, none of the staff involved with the trial had knowledge of the treatment allocated to each participant
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Clinician/person delivering treatment: yes Participants: yes Outcome assessor: unclear (see below). Described as double-blinded "None of the staff involved in the study had knowledge of the treatment allocated to each patient"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	9 withdrawals, all described. 5 participants receiving CPX were withdrawn for the following reasons: poor compliance (2), heart-lung transplant (1), death (1), nausea & anorexia (1) 4 participants receiving placebo were withdrawn for the following reasons: poor compliance (2), death (1), desire to become

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Sheldon 1993 (*Continued*)

		pregnant (1)
Selective reporting (reporting bias)	High risk	Study protocol not available. All outcomes listed as being measured at clinic visits were described in full in the results section of the paper for baseline and 12 months. However, no data were presented for intermediate clinic visits

Wang 1988

Methods	RCT (generation of allocation sequence & allocation concealment both graded as 'unclear'). 3-way cross-over design. Single centre.
Participants	23 people randomised. CF adults over 18 years of age with an exacerbation of pulmonary infection. Moderately severe disease, treated during exacerbation of pulmonary infection Age: "young CF adults over 18 years of age". Country: USA.
Interventions	Each treatment given for 2 weeks. CPX 750 mg bd versus IV tobramycin plus ticarcillin versus IV tobramycin plus azlocillin Time-points when measurements were taken during the trial: before, at week 1 and after completion of treatment. Time-points reported in the trial: no data reported. Narrative "...after completion…"
Outcomes	Laboratory tests (before and after completion of treatments) Chest X-rays Pulmonary function tests* Toxic effects* Sputum cultures (weekly)
Notes	Time-points used in the review: no specific data reported. Pilot (abstract only).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as "were placed at random on 1 of 3 regimens".
Allocation concealment (selection bias)	Unclear risk	Method not described.
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding not possible for clinicians or participants as the comparison was oral versus IV antibiotics.

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Wang 1988 (*Continued*)

		Outcome assessor: not discussed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals: Described as "16 patients received 17 courses of CPX (with 1 receiving CPX twice). All but 1 then went on to receive IV tobramycin plus ticarcillin. Similarly, 4 out of 16 also went on to receive IV tobramycin and azlocillin. The remaining 7 in regimen 3 received tobramycin plus ticarcillin on other admissions" Intention-to-treat analysis: unclear.
Selective reporting (reporting bias)	High risk	Abstract states data measured: baseline, at week 1 and after completion of treatment. However, paper reports narratively with no data

bd: twice daily
CF: cystic fibrosis
CPX: ciprofloxacin
ESR: erythrocyte sedimentation rate
FEV1: forced expiratory volume in 1 second
FVC: forced vital capacity
IV: intravenous
MIC: minimum inhibitory concentration
MRI: magnetic resonance imaging
PEF: peak expiratory flow
P. aeruginosa: *Pseudomonas aeruginosa*
RCT: randomised controlled trial
SD: standard deviation
tds: three times a day
*: indicates an outcome used in the review

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

Study	Reason for exclusion
Anstead 2001	Macrolide (azithromycin) is not a conventional anti-pseudomonal drug
Black 1991	Eligibility for inclusion not clear. Contacted author team on two occasions for clarification of eligibility. No response received
Bosso 1987	Not all participants colonised or infected with *P. aeruginosa*.
Bosso 1989	Participants not colonised with *P. aeruginosa*.

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(*Continued*)

Cipolli 2001	Pharmacokinetic study, no relevant outcomes.
Davies 1987	Pharmacokinetic study, no relevant outcomes. Colonisation unclear
Denning 1977	Not an RCT or quasi-randomised.
Equi 2002	Not all participants colonised with *P. aeruginosa*.
Frederiksen 2003	A study of a combination of oral and inhaled antibiotic for three weeks compared to three months - no arm where participants received only oral antibiotics
Goldfarb 1986	A pharmacokinetic trial administering 3 single variable doses
Harrison 1985	Not all participants were colonised with *P. aeruginosa*.
Jensen 1987	The participants did not have a pulmonary exacerbation, nor were they treated for more than one month (the eligibility criteria for inclusion in long-term treatment for chronic disease comparison)
Johansen 1999	Those participants colonised with *P. aeruginosa* were only part of a pharmacokinetic study - not part of the clinical trial
Kapranov 1995	Not an RCT or quasi-randomised.
Knight 1979	Participants not colonised with *P. aeruginosa*.
Kurz 1987	Eligibility for inclusion not clear. Contacted author team on two occasions for clarification of eligibility. No response received
Loening-Baucke 1979	Broad spectrum of disease severity. Not all colonised with *P. aeruginosa*.
Mack 1991	Pharmacokinetic study, no relevant outcomes.
Nolan 1982	Not all participants colonised.
Ordonez 2001a	Not an RCT or quasi-randomised.
Owen 1991	Not colonised - recruiting newborns.
Pai 2006	Pharmacokinetic study regarding interaction of levofloxacin with calcium carbonate
Pirzada 1999	Not randomised. Case-control study.
Postnikov 2001a	Not an RCT or quasi-randomised.
Postnikov 2001b	Not all participants colonised with *P. aeruginosa*.
Pukhalsky 2001	Cox-2 inhibitor. Not looking at an oral anti-pseudomonal.

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(*Continued)*

Romano 1991	Eligibility for inclusion not clear. Contacted author team on two occasions for clarification of eligibility. No response received
Rubio 1987	Unclear if colonisation was a prerequisite for trial entry. Unable to clarify with trial authors
Saiman 2003	Macrolide (azithromycin) is not a conventional anti-pseudomonal drug
Scully 1987	Not an RCT or quasi-randomised.
Shapera 1981	Not all participants colonised.
Smith 1997	Pharmacokinetic study.
Sriram 2003	Macrolide (azithromycin) is not a conventional anti-pseudomonal drug
Strandvik 1989	Trialists 'intended' to treat participants in a random fashion, but actual process not clear. 20 participants were recruited of which 8 received each treatment. Data presented for courses of treatment, rather than for each participant
Stutman 1987	Not all participants infected or colonised with *P. aeruginosa*.
Treggiari 2011	Trial looks at combined oral and inhaled therapy (no oral therapy alone)
Vitti 1975	Pharmacological study looking at Interaction of enzyme supplement with antibiotics
Weaver 1994	Not colonised - recruiting newborns.
Wolter 2002	Participants not all infected with *P. aeruginosa* and treatment drug was a macrolide.

P.aeruginosa: *Pseudomonas aeruginosa*
RCT: Randomised controlled trial

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DATA AND ANALYSES

Comparison 1. Pulmonary exacerbation - oral versus IV antibiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV_1 ml (mean change)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 At more than 1 week and up to 2 weeks	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 FVC ml (mean change)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 At more than 1 week and up to 2 weeks	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Adverse events	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Gastro-intestinal	2	148	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.53, 2.03]
3.2 Central nervous system	2	148	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.14, 3.43]
3.3 Musculoskeletal	1	108	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.19, 2.15]
3.4 Sensitivity reactions	1	108	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.06, 15.01]
3.5 Others	2	148	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.05, 2.01]
4 Frequency of need for additional antibiotic use	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Isolation of antibiotic-resistant strains - *P. aeruginosa*	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 At more than 1 week and up to 2 weeks	2	137	Risk Ratio (M-H, Fixed, 95% CI)	1.91 [1.26, 2.91]
5.2 Follow-up data at more than 3 weeks and up to 4 weeks	1	97	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.93, 1.42]
5.3 Follow-up data at 6 weeks	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.58]
6 Isolation of antibiotic-resistant strains - *S. aureus*	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 2. Long-term treatment - oral versus oral and inhaled antibiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Isolation of antibiotic-resistant strains - *P. aeruginosa*	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 At more than 1 month and up to 3 months	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

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Comparison 3. Long-term treatment - oral versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean FEV_1 at end of course (L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 >6 months and up to 12 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Mean FVC at end of course (L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 >6 months and up to 12 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Mortality	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Weight (kg)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 > 6 months and up to 12 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 Gastro-intestinal	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Participants needing additional IV courses	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 Isolation of antibiotic-resistant strains - *P. aeruginosa*	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8 Isolation of antibiotic-resistant strains - *S. aureus*	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

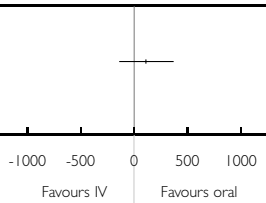
Analysis 1.1. Comparison 1 Pulmonary exacerbation - oral versus IV antibiotics, Outcome 1 FEV1 ml (mean change).

Review: Oral anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 1 Pulmonary exacerbation - oral versus IV antibiotics

Outcome: 1 FEV_1 ml (mean change)

Study or subgroup	Oral N	Mean(SD)	IV N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 At more than 1 week and up to 2 weeks						
Hodson 1987	20	532 (456)	20	418 (358)		114.00 [-140.08, 368.08]



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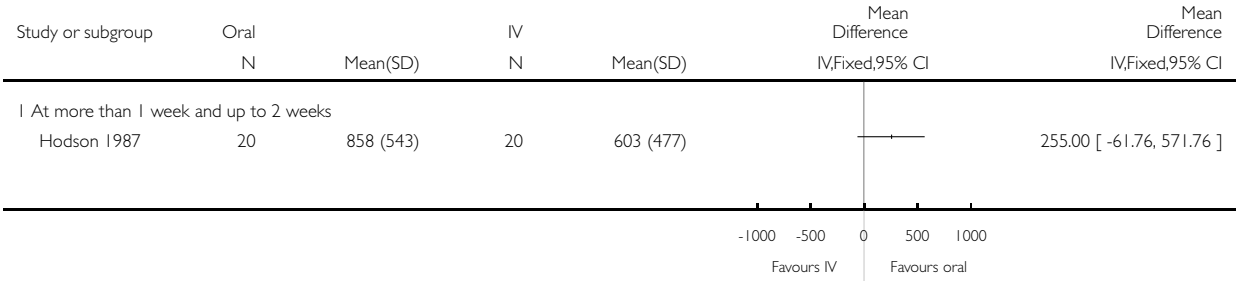
Analysis 1.2. Comparison 1 Pulmonary exacerbation - oral versus IV antibiotics, Outcome 2 FVC ml (mean change).

Review: Oral anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 1 Pulmonary exacerbation - oral versus IV antibiotics

Outcome: 2 FVC ml (mean change)

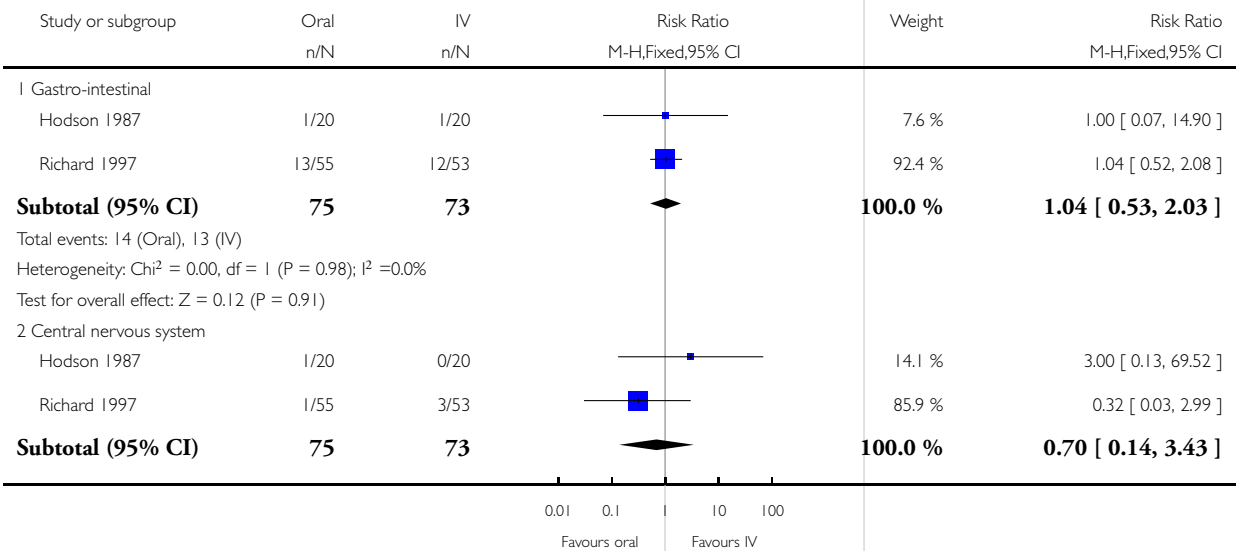


Analysis 1.3. Comparison 1 Pulmonary exacerbation - oral versus IV antibiotics, Outcome 3 Adverse events.

Review: Oral anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 1 Pulmonary exacerbation - oral versus IV antibiotics

Outcome: 3 Adverse events



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Study or subgroup	Oral n/N	IV n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 2 (Oral), 3 (IV)					
Heterogeneity: Chi² = 1.29, df = 1 (P = 0.26); I² =23%					
Test for overall effect: Z = 0.44 (P = 0.66)					
3 Musculoskeletal					
Richard 1997	4/55	6/53		100.0 %	0.64 [0.19, 2.15]
Subtotal (95% CI)	**55**	**53**		**100.0 %**	**0.64 [0.19, 2.15]**
Total events: 4 (Oral), 6 (IV)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.72 (P = 0.47)					
4 Sensitivity reactions					
Richard 1997	1/55	1/53		100.0 %	0.96 [0.06, 15.01]
Subtotal (95% CI)	**55**	**53**		**100.0 %**	**0.96 [0.06, 15.01]**
Total events: 1 (Oral), 1 (IV)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.03 (P = 0.98)					
5 Others					
Hodson 1987	1/20	1/20		21.9 %	1.00 [0.07, 14.90]
Richard 1997	0/55	3/53		78.1 %	0.14 [0.01, 2.60]
Subtotal (95% CI)	**75**	**73**		**100.0 %**	**0.33 [0.05, 2.01]**
Total events: 1 (Oral), 4 (IV)					
Heterogeneity: Chi² = 0.99, df = 1 (P = 0.32); I² =0.0%					
Test for overall effect: Z = 1.21 (P = 0.23)					

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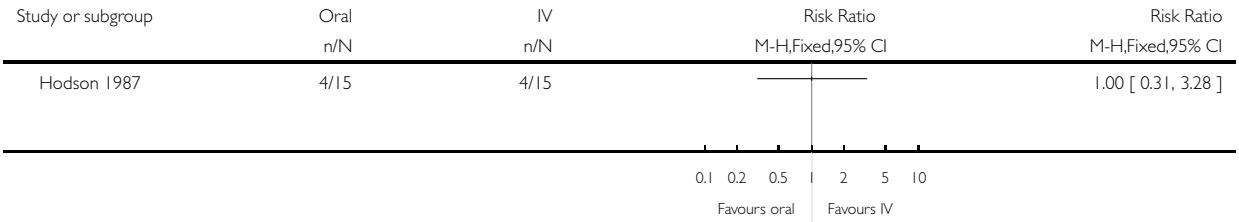
Analysis 1.4. Comparison 1 Pulmonary exacerbation - oral versus IV antibiotics, Outcome 4 Frequency of need for additional antibiotic use.

Review: Oral anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 1 Pulmonary exacerbation - oral versus IV antibiotics

Outcome: 4 Frequency of need for additional antibiotic use

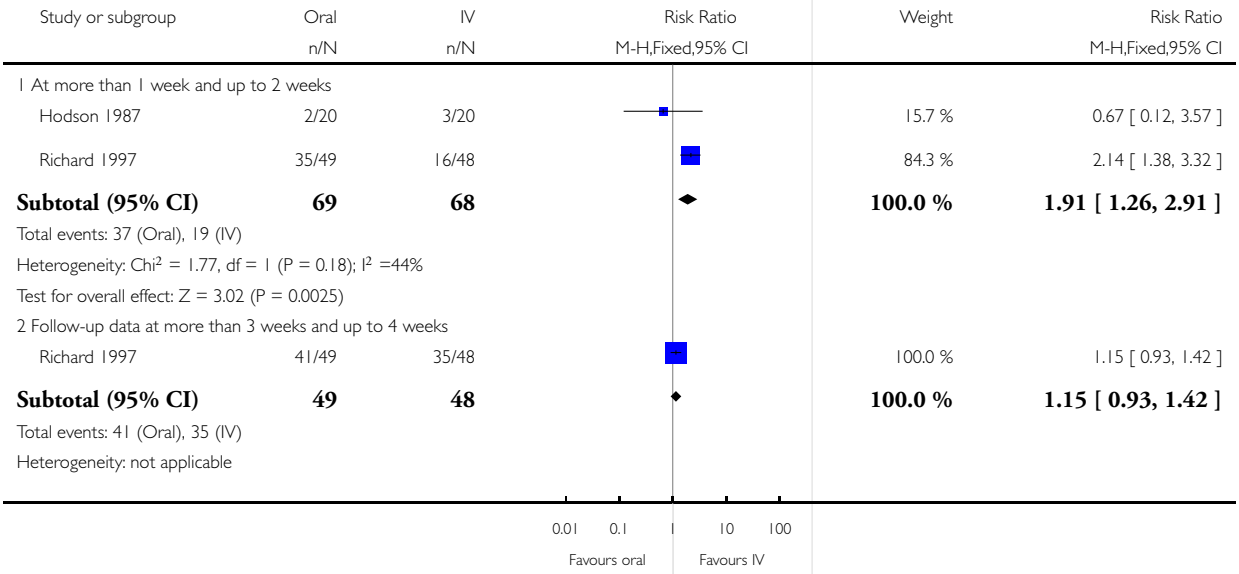


Analysis 1.5. Comparison 1 Pulmonary exacerbation - oral versus IV antibiotics, Outcome 5 Isolation of antibiotic-resistant strains - P. aeruginosa.

Review: Oral anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 1 Pulmonary exacerbation - oral versus IV antibiotics

Outcome: 5 Isolation of antibiotic-resistant strains - *P. aeruginosa*



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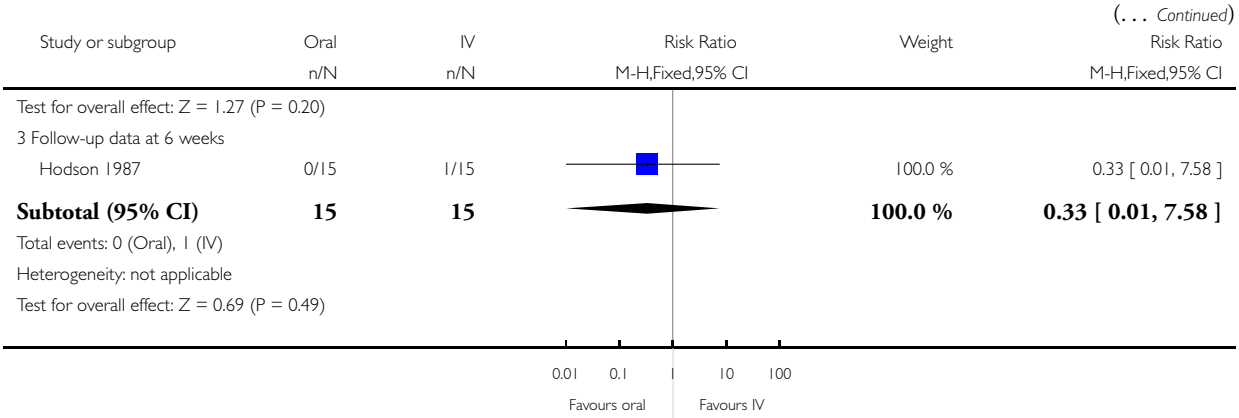
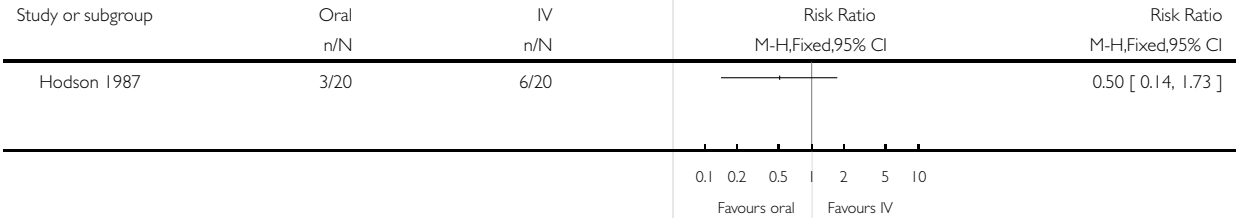


Analysis 1.6. Comparison 1 Pulmonary exacerbation - oral versus IV antibiotics, Outcome 6 Isolation of antibiotic-resistant strains - S. aureus.

Review: Oral anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 1 Pulmonary exacerbation - oral versus IV antibiotics

Outcome: 6 Isolation of antibiotic-resistant strains - *S. aureus*



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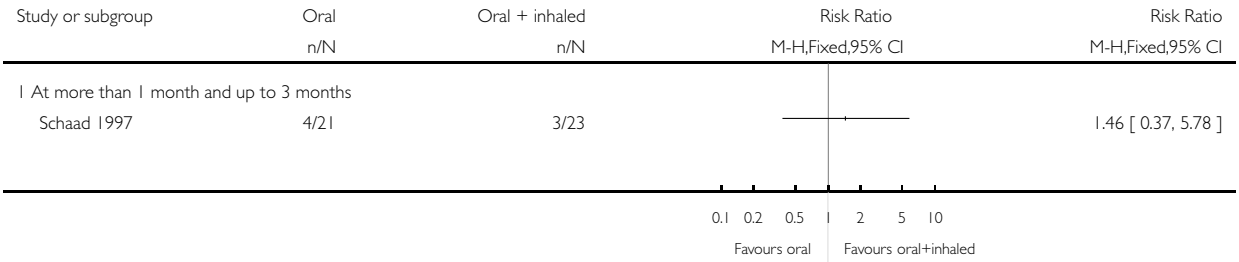
Analysis 2.1. Comparison 2 Long-term treatment - oral versus oral and inhaled antibiotics, Outcome 1 Isolation of antibiotic-resistant strains - P. aeruginosa.

Review: Oral anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 2 Long-term treatment - oral versus oral and inhaled antibiotics

Outcome: 1 Isolation of antibiotic-resistant strains - *P. aeruginosa*

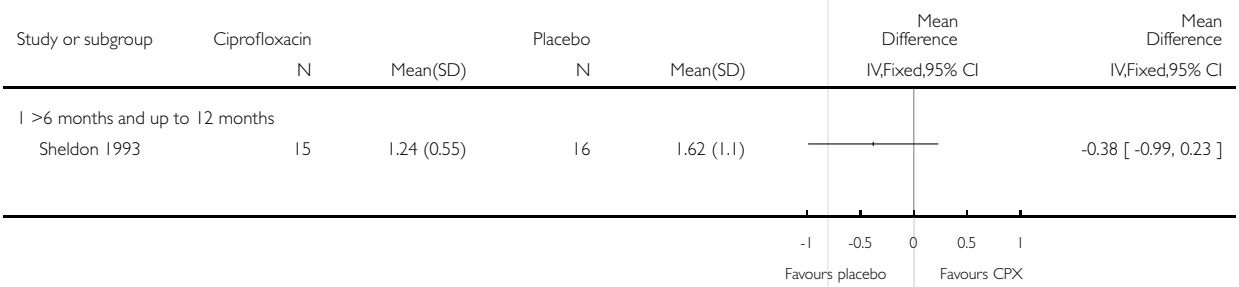


Analysis 3.1. Comparison 3 Long-term treatment - oral versus placebo, Outcome 1 Mean FEV1 at end of course (L).

Review: Oral anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 3 Long-term treatment - oral versus placebo

Outcome: 1 Mean FEV_1 at end of course (L)



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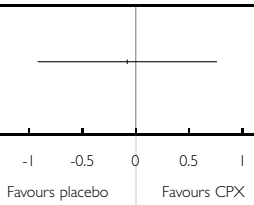
Analysis 3.2. Comparison 3 Long-term treatment - oral versus placebo, Outcome 2 Mean FVC at end of course (L).

Review: Oral anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 3 Long-term treatment - oral versus placebo

Outcome: 2 Mean FVC at end of course (L)

Study or subgroup	Ciprofloxacin N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 >6 months and up to 12 months						
Sheldon 1993	15	2.75 (0.86)	16	2.83 (1.46)		-0.08 [-0.92, 0.76]



Analysis 3.3. Comparison 3 Long-term treatment - oral versus placebo, Outcome 3 Mortality.

Review: Oral anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 3 Long-term treatment - oral versus placebo

Outcome: 3 Mortality

Study or subgroup	Ciprofloxacin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Sheldon 1993	1/20	1/20		1.00 [0.07, 14.90]

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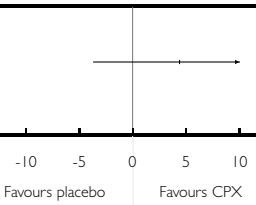
Analysis 3.4. Comparison 3 Long-term treatment - oral versus placebo, Outcome 4 Weight (kg).

Review: Oral anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 3 Long-term treatment - oral versus placebo

Outcome: 4 Weight (kg)

Study or subgroup	Ciprofloxacin N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 > 6 months and up to 12 months						
Sheldon 1993	15	55.7 (11.4)	16	51.3 (11.6)		4.40 [-3.70, 12.50]



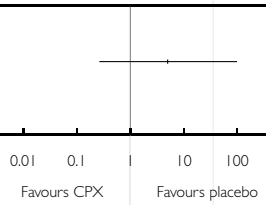
Analysis 3.5. Comparison 3 Long-term treatment - oral versus placebo, Outcome 5 Adverse events.

Review: Oral anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 3 Long-term treatment - oral versus placebo

Outcome: 5 Adverse events

Study or subgroup	Ciprofloxacin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Gastro-intestinal				
Sheldon 1993	2/20	0/20		5.00 [0.26, 98.00]



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Analysis 3.6. Comparison 3 Long-term treatment - oral versus placebo, Outcome 6 Participants needing additional IV courses.

Review: Oral anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 3 Long-term treatment - oral versus placebo

Outcome: 6 Participants needing additional IV courses

Study or subgroup	Ciprofloxacin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Sheldon 1993	5/15	6/16		0.89 [0.34, 2.31]

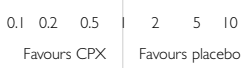
Analysis 3.7. Comparison 3 Long-term treatment - oral versus placebo, Outcome 7 Isolation of antibiotic-resistant strains - P. aeruginosa.

Review: Oral anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 3 Long-term treatment - oral versus placebo

Outcome: 7 Isolation of antibiotic-resistant strains - *P. aeruginosa*

Study or subgroup	Ciprofloxacin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Sheldon 1993	10/15	5/16		2.13 [0.95, 4.80]



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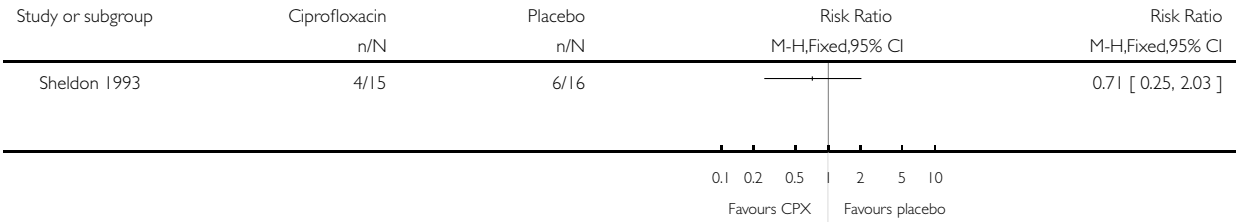
Analysis 3.8. Comparison 3 Long-term treatment - oral versus placebo, Outcome 8 Isolation of antibiotic-resistant strains - S. aureus.

Review: Oral anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 3 Long-term treatment - oral versus placebo

Outcome: 8 Isolation of antibiotic-resistant strains - *S. aureus*



ADDITIONAL TABLES

Table 1. Review-specified outcomes reported in included trials

Trial	Quality of life	FEV_1 & FVC	Mortality	Time to next pulmonary exacerbation	Weight	Adverse effects	Additional ABs	AB-resistant strains	Hospital admissions
Hodson 1987		FEV_1 & FVC at day 1, day 10 & 6 weeks.	Within 3 months post-treatment.	Measured, but only at follow up.		Gastrointestinal, nervous system and other.	Further IV treatment reported between day 10 and 6 weeks.	*P. aeruginosa*-resistant strains measured at day 1, day 10 and 6 weeks.	
Richard 1997		FEV_1 and FVC at baseline, 5-7 days, 14 days and at follow up at 20-30 days		Measured and presented combined data over 9 to 30 days.		Gastrointestinal, musculoskeletal and other.	Additional antibiotics for new acute pulmonary exacerbations	Bacteriologic outcome 48 hours before treatment and at the end of treatment (day 14) and at follow up (day 20 - 30)	

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Table 1. Review-specified outcomes reported in included trials (*Continued*)

Schaad 1997		FVC at baseline, 6 weeks (although not presented) and 3 months			Measured, no data presented.	Gastrointestinal, nervous system, others.		*P. aeruginosa*-resistant strains measured at the end of treatment (3 months)	
Sheldon 1993		FEV_1 and FVC assessed at baseline and every 3 months. Data reported at baseline and 12 months	Within 12 months.		Measured at baseline and every 3 months. Data reported from baseline and 12 months	Gastrointestinal.	Further IV treatment reported up to 12 months.	*P. aeruginosa*-resistant strains measured at the end of treatment (12 months)	Reported mean number of days in hospital at end of 12 months
Wang 1988									

FEV_1: forced expiratory volume at one second
FVC: forced vital capacity
IV: intravenous
P. aeruginosa: *Pseudomonas aeruginosa*

WHAT'S NEW

Last assessed as up-to-date: 16 October 2013.

Date	Event	Description
16 October 2013	New citation required but conclusions have not changed	None of the new references identified were eligible for inclusion in this review, hence the conclusions of the review remain the same
16 October 2013	New search has been performed	There are no new trials added to the 'Included studies' section of the review. However, three trials have been added to the 'Excluded studies' section (Frederiksen 2003; Rubio 1987; Treggiari 2011).

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HISTORY

Protocol first published: Issue 3, 2005

Review first published: Issue 3, 2007

Date	Event	Description
6 October 2010	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register identified 35 potentially eligible new references, of which one has been listed under Excluded studies (Pai 2006). One trial previously listed under Studies awaiting classification has been excluded following correspondence with the trial author (Postnikov 2001b). Three trials previously listed under Studies awaiting classification have been excluded following no response from two attempted contacts with each author team (Black 1991; Kurz 1987; Romano 1991). A previously included trial has now been excluded (Jensen 1987). While treatment duration was only 14 days, on closer examination of the paper, we noted that the participants did not have a pulmonary exacerbation, but also, given that they were not treated for more than one month they were not eligible for inclusion in the comparison for long-term treatment for chronic disease
3 April 2008	New search has been performed	Search of the Group's Cystic Fibrosis Trials Register identified five new trials, however, none were eligible for inclusion in this review
3 April 2008	Amended	Converted to new review format.
18 May 2007	New citation required and conclusions have changed	Review first published.

CONTRIBUTIONS OF AUTHORS

Protocol

Tracey Remmington took the lead on the write up of the protocol with significant input on all draft stages from Nikki Jahnke. Christian Harkensee commented on several draft versions.

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Review & updates

Tracey Remmington and Nikki Jahnke independently selected trials and extracted data for inclusion in the review. Each then worked together in inputting the data and drafting the text and should be regarded as joint first authors on the review. Christian Harkensee advised on some clinical aspects of the review and commented on several draft versions.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- UK Cystic Fibrosis Trust, UK.
- Department of Health, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

November 2006: The term colonisation has been replaced with more suitable term 'chronic infection'.

September 2010: Following editorial advice, the previously listed fourth primary outcome for the comparison 'Long-term treatment for chronic infection of *P. aeruginosa*' has been amended from 'Frequency of infective respiratory tract exacerbation (time to next exacerbation) determined clinically or radiologically or both that cannot be attributed to concurrent isolates of other organisms' to 'Time to next pulmonary exacerbation'. This outcome has also been moved from 'Primary outcomes' to 'Secondary outcomes' in line with current CFGD Group policy regarding the maximum number of primary outcomes which should be listed within a review.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [*therapeutic use]; Cystic Fibrosis [*complications; microbiology]; Pseudomonas Infections [*drug therapy]; Pseudomonas aeruginosa; Randomized Controlled Trials as Topic; Respiratory Tract Infections [*drug therapy; microbiology]; Treatment Outcome

MeSH check words

Adult; Child; Humans

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