Oral anti-pseudomonal antibiotics for cystic fibrosis (Review)

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ABSTRACT

Background
Pseudomonas aeruginosa is the most common bacterial pathogen causing infection in the lungs of people with CF and appropriate antibiotic therapy is vital. Antibiotics for 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 the quality of life of 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 an exacerbation of respiratory tract infection; and
(2) long-term treatment in chronic infection.

Search strategy
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 for information on relevant trials and checked reference lists of identified trials.

Most recent search: March 2007.

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

Data collection and analysis
Two authors independently selected the trials, extracted data and assessed quality. We contacted trialists to obtain missing information.

Main results
We included four trials examining exacerbations (197 participants) and two trials examining long-term therapy (85 participants). We regarded the most important outcomes as quality of life and lung function. In our analysis, we were unable to identify any statistically significant difference between oral anti-pseudomonal antibiotics and other treatments for these outcome measures for either exacerbations or long-term treatment. One of the included trials reported significantly better lung function when treating an 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.

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 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 known effectiveness 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 of great importance 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 ease of drug administration and the avoidance of hospitalisation.

We found no conclusive evidence showing an oral antibiotic regimen to be more or less effective than an alternative treatment for either exacerbations or long-term treatment of chronic infection with *P. aeruginosa.* However, the evidence available was limited as there were only 6 trials with 282 participants. Also the trials were very different in terms of design, drugs used, duration of treatment and follow up and outcome measures. Until results of adequately-powered future trials are available, treatment needs to be selected on a pragmatic basis, based upon known effectiveness against local strains and upon individual preference.

BACKGROUND

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). By 18 years of age, 80% of individuals are colonised with *P. aeruginosa* (Rajan 2002). 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, it has been suggested that there is a relationship between the onset of chronic infection and increased morbidity (Kosorok 2001; Parad 1999).

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 respiratory exacerbations; as antibiotic treatment in exacerbations of respiratory infections to relieve symptoms and restore respiratory function to baseline values.

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 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 be beneficial to the 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). 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).

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 antibi-

otics in people with CF and chronic infection with *P. aeruginosa* is discussed in a further 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 exacerbations of respiratory tract infections and as a long-term treatment in chronic infection.

OBJECTIVES

To determine the benefit or harm of oral anti-pseudomonal antibiotic therapy for people with CF who are colonised with *P. aeruginosa* in two clinical settings:
(1) treatment of an exacerbation of respiratory tract infection, and
(2) long-term treatment in chronic respiratory tract infection.

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.

Types of intervention

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 an exacerbation of respiratory tract infection, 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.

An 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 an 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 an exacerbation of respiratory tract infection
Primary outcomes
(1) Quality of life

(2) Lung function
(a) forced expiratory volume in one second (FEV_1)
(b) forced vital capacity (FVC)

Secondary outcomes
(1) Weight
(2) Time to next respiratory tract exacerbation
(3) Adverse effects of antibiotics used, e.g. deranged 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

Outcomes were measured 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.

Long-term treatment for chronic infection of P. aeruginosa
Primary outcomes
(1) Quality of life

(2) Lung function
(a) FEV_1
(b) FVC

(3) Mortality

(4) 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

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

Outcomes were measured 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.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Cystic Fibrosis and Genetic Disorders Group methods used in reviews.

Relevant trials were identified from the Group's Cystic Fibrosis Trials Register using the terms: cystic fibrosis AND antibiotic.

The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (Clinical Trials) (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.

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.

Date of the most recent search of the Group's Trials Register: March 2007.

METHODS OF THE REVIEW

Application of inclusion criteria
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 assessment of methodological quality
Two authors (TR, NJ) independently extracted the data (using a customised data extraction form) and assessed the methodological quality of the selected trials. The main evaluation of methodological quality was based on the method as described by Jüni and is outlined below (Jüni 2001). Where information was lacking, we contacted primary authors for clarification.

Generation of the allocation sequence
We graded this in each trial as:
(1) Adequate, adequate methods of randomisation included using a random number table, computer-generated lists or similar methods;
(2) Unclear, if the trial was described as randomised, but no description of the methods used to allocate participants to treatment group was described;
(3) Inadequate, inadequate methods of randomisation included alternation; the use of case record numbers; and dates of birth or day of the week.

Allocation concealment
We graded the allocation concealment in each trial as follows:
(1) Adequate, if the allocation of participants involved 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;
(2) Unclear, if the method used to conceal the allocation was not described;
(3) Inadequate, if the allocation sequence was known to, or could be deciphered by the investigators who assigned participants or if the trial was quasi-randomised (*See* 'Generation of allocation sequence' (3) above).

Blinding (or masking)
We assessed each trial with regard to the following levels of blinding:
(1) blinding of clinician (person delivering treatment) to treatment allocation;
(2) blinding of participant to treatment allocation;
(3) blinding of outcome assessor to treatment allocation.

Follow up
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 also reported on whether the investigators had performed a sample-size calculation and if they used an intention-to-treat analysis.

Data analysis
Current
We analysed the two clinical settings (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 'Statistical Analysis' consisted of data from only one or two trials.

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 these to standard deviations. We calculated a pooled estimate of treatment effect by calculating the weighted mean difference.

Two trials included in the review were cross-over in design (Jensen 1987; Wang 1988), although only one contained data (Jensen 1987). 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.

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.

We are aware that some lung function data are skewed and therefore cannnot be entered and analysed within 'Statistical Analysis'. Where this is the case we have reported the results narratively. Similarly, we also report count data narratively.

Planned

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.

When sufficient data are available, different antibiotic regimens will be analysed and compared to each other.

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.

Definitions

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 and if statistical heterogeneity between the trials had been observed, we planned to split the trials by whether or not they fulfilled our definition of chronic infection or not. However, 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.

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 (treatment failure).

DESCRIPTION OF STUDIES

Results of the search

The search identified 255 potentially eligible trials. Two authors initially assessed these trials 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. Six trials (including 282 participants) are included in the review (Hodson 1987; Jensen 1987; Richard 1997; Schaad 1997; Sheldon 1993; Wang 1988). Of these six trials, four considered the treatment of an exacerbation of respiratory tract infection (197 participants) (Hodson 1987; Jensen 1987; Richard 1997; Wang 1988) and two trials examined long-term treatment for chronic infection (85 participants) (Schaad 1997; Sheldon 1993).

Treatment of a respiratory tract exacerbation (Hodson 1987; Jensen 1987; Richard 1997; Wang 1988)

Participants

Three trials included adult participants only (Hodson 1987; Jensen 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 trialists and were able to confirm that two more

trials fulfilled our definition (Jensen 1987; Wang 1988). The remaining trial described participants as being chronically infected (Richard 1997). After contact with the trialists 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* (Richard 1997).

Interventions

Three trials compared oral with IV interventions (Hodson 1987; Richard 1997; Wang 1988) and one trial compared two oral interventions (Jensen 1987). Of the oral versus IV 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). The 14-day trial that looked at oral interventions compared oral ciprofloxacin (750 mg bd) with oral ofloxacin placebo bd versus oral ofloxacin (400 mg bd) plus oral ciprofloxacin placebo bd (Jensen 1987).

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 03).

One trial reported on quality of life (Hodson 1987). All trials reported on lung function and adverse events (Hodson 1987; Jensen 1987; Richard 1997; Wang 1988). Two trials reported on time to next respiratory tract infection (Hodson 1987; Richard 1997). All four trials reported on isolation of antibiotic-resistant strains or *P. aeruginosa* or other micro-organisms with or without antibiotic resistance (Hodson 1987; Jensen 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 two of the included trials were cross-over; one having two arms (Jensen 1987) and the other three arms (Wang 1988).

Setting

Three trials were single centre (Hodson 1987; Jensen 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* (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 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 03).

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 the frequency of infective respiratory tract infection (time span to next 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

255 trials were identified, of which 214 were excluded on the basis of title, or if this was unclear, on reading through the abstract. A further 30 trials were excluded after two authors independently assessed the full references for each trial. 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 twelve 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; 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); seven trials were on pharmacokinetics (Cipolli 2001; Davies 1987; Goldfarb 1986; Johansen 1999; Mack 1991; Smith 1997; Vitti 1975); and one trial reported on a Cox-2 inhibitor (Pukhalsky 2001).

Studies awaiting assessment

There are currently five trials awaiting assessment (Black 1991; Kurz 1987; Postnikov 2001b; Romano 1991; Rubio 1987). We have attempted to contact the authors of these trials to clarify whether they are eligible for inclusion, but to date have received no replies. For the next update of this review we will again try and contact the authors of these trials. If we do not receive a response at this time, we will excluded these trials as we will not be able to judge them eligible for inclusion in light of the criteria of this review.

METHODOLOGICAL QUALITY

For detailed information on the methodological quality of each included trial, please refer to the 'Additional tables' section of this review (Table 02).

Treatment of a respiratory tract exacerbation (Hodson 1987; Jensen 1987; Richard 1997; Wang 1988)

Generation of the allocation sequence

One trial provided information on the randomisation of participants and this trial was graded as 'adequate' (Richard 1997). The remaining three trials were graded as 'unclear' as they failed to provide sufficient information (Hodson 1987; Jensen 1987; Wang 1988).

Allocation concealment

One trial provided information on the allocation concealment and was graded as 'adequate' (Richard 1997). The remaining three trials did not describe any method of allocation concealment and were graded as 'unclear' (Hodson 1987; Jensen 1987; Wang 1988).

Blinding

Clinicians or Persons delivering treatment

In three trials it was not possible to blind given the interventions being compared (Hodson 1987; Richard 1997; Wang 1988). In the remaining trial the blinding of persons delivering treatment was not specifically discussed, although the trial was described as "double-blind" (Jensen 1987).

Participants

In one trial which compared oral treatments the participants were blinded to the treatment group (Jensen 1987). In the remaining 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 "Additional tables" for further details (Table 02)) (Hodson 1987; Richard 1997). One further trial was described as "double-blind" although it was not specifically discussed whether the outcome assessors were blinded (Jensen 1987). The remaining trial did not provide any information on the blinding of outcome assessors (Wang 1988).

Follow-up

All four trials described withdrawals from treatment, further details can be found in the 'Additional tables' (Table 02) (Hodson 1987; Jensen 1987; Richard 1997; Wang 1988). None of the included trials specifically stated the use of an intention-to-treat anlaysis when presenting data.

Outcome reporting bias

For this review we are only reporting on time-points, for future updates of this review we will aim to examine other aspects of reporting bias.

Time-points

Please refer to an additional table for information regarding the measurement and reporting of outcome data (Table 03). In summary, only one trial reported all time-points that were measured within the trial and at follow up (Hodson 1987). A further two 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 (Jensen 1987; Richard 1997). The remaining trial is in abstract form and only reported results narratively (Wang 1988).

Sample-size calculation

None of the trials reported that they had used a sample-size calculation (Hodson 1987; Jensen 1987; Richard 1997; Wang 1988).

Long-term treatment for chronic infection of *P. aeruginosa* (Schaad 1997; Sheldon 1993)

Generation of the allocation sequence

Both trials provided information on the randomisation of participants and they were graded as 'adequate' (Schaad 1997; Sheldon 1993).

Allocation concealment

One trial provided information on the allocation concealment and was graded as 'adequate' (Sheldon 1993). The remaining trial did not describe any method of allocation concealment and was graded as 'unclear' (Wang 1988).

Blinding

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).

Follow-up

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Time-points

Please refer to an additional table for information regarding the measurement and reporting of outcome data (Table 03). 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).

Sample-size calculation

Only one trial discussed a sample-size calculation (Sheldon 1993). This trial was designed to have a power of 80% for detecting a real difference of 200 ml in the improvement of FEV1 between the groups significant at the 5% level.

RESULTS

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 respiratory tract exacerbation (Hodson 1987; Jensen 1987; Richard 1997; Wang 1988)

Of the four included trials, three compared an oral intervention to an IV intervention (Hodson 1987; Richard 1997; Wang 1988), the remaining trial compared two oral interventions (Jensen 1987).

Primary outcomes

(1) Quality of life

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

(2) Lung function

(a) FEV_1

All four trials reported this outcome. Of the three trials comparing oral and IV interventions only one reported data which we were able to enter into the 'Statistical Analysis' (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, this conflicts with the graph produced, which shows a non-significant difference (graph 01, 01). Furthermore, the trialists reported that although FEV_1 had decreased at follow up (6 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 'Statistical Analysis'.

In the other two trials comparing oral versus IV interventions, 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).

In the trial which compared two oral interventions there was no significant difference between treatments (graph 02, 01) (Jensen 1987). It was stated within the paper that a period effect was observed in that the increase in FEV_1 seen in the first treatment period was significantly higher than the increase seen during the second treatment period, regardless of the order of drug administration. The reason for this effect is unclear.

(b) FVC

All four trials reported on this outcome. Of the three trials comparing oral ciprofloxacin and IV interventions 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) (graph 01, 02). 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 'Statistical Analysis'. 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).

In the trial which compared two oral interventions there was no significant difference between treatments for this outcome (graph 02, 02) (Jensen 1987).

Secondary outcomes

(1) Weight

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

(2) Time to next respiratory tract exacerbation

Two out of the three trials comparing oral and IV interventions reported this outcome, but not in a form which allowed us to enter data into the 'Statistical Analysis' (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 1987). Richard stated that nine (out of 55) participants who had received ciprofloxacin and five (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).

In the trial which compared two oral interventions this outcome was not reported (Jensen 1987).

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

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

Three trials comparing oral and IV interventions 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 (graph 01, 03) (Hodson 1987; Richard 1997). Wang stated within the abstract that "no toxic effects were observed in any of the patients" (Wang 1988).

In the trial comparing two oral interventions there were 9 adverse events reported by the 24 participants in the ciprofloxacin group compared to 6 events from the 23 participants in the ofloxacin group (Jensen 1987). Since the trialists reported the number of adverse events as opposed to the number of people experiencing these events, we have not been able to present these data in the meta-analysis. There were seven gastro-intestinal events in the ciprofloxacin group and three in the ofloxacin group; one central nervous system event in ciprofloxacin group and three in ofloxacin group; four sensitivity reaction events in the ciprofloxacin group and three in the ofloxacin group; and one 'Other' event in the ciprofloxacin group but none of this category in the ofloxacin group. The trialists also report that the total number of reactions probably linked to treatment was eight in the ciprofloxacin group and one in the ofloxacin group, compared to five possibly linked to treatment in the ciprofloxacin group and eight in the ofloxacin group.

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

Three trials reported on this outcome (Hodson 1987; Jensen 1987; Richard 1997). Only one of the trials comparing oral and IV interventions reported data which we were able to enter into the 'Statistical Analysis' (Hodson 1987). This showed no significant difference in the number of participants who received further treatment between day 10 and 6 weeks (graph 01, 04). The remaining trial comparing an oral and IV intervention 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.

In the trial comparing two oral interventions it was reported that in 3 out of 47 courses administered (across groups) additional IV antibiotics were needed (Jensen 1987).

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

Four trials reported on this outcome (Hodson 1987; Jensen 1987; Richard 1997; Wang 1988). Hodson reported no significant difference in the isolation of antibiotic-resistant *P. aeruginosa* (graph 01, 05) or *S. aureus* (graph 01, 06) between the two groups at day 10 and at 6 weeks (Hodson 1987). Jensen reported that *P. aeruginosa* was temporarily eradicated from four participants (2 out of 24 in the ciprofloxacin group and 2 out of 23 in the ofloxacin group); however, *P. aeruginosa* reappeared in the sputum of these participants one month post treatment. A four-fold or higher increase in the minimal inhibitory concentration (MIC) was seen in 7 (out of 24) participants from the ciprofloxacin group and 3 (out of 23) from the ofloxacin group. The paper only reported resistance as being clinically significant in 1 (out of 23) participant from the ofloxacin group. Intermediate resistance was reported in 3 (out of 24) participants from the ciprofloxacin group. The paper reported diminished susceptibility in another six participants (breakdown between treatment groups not clear) (Jensen 1987). Furthermore, Jensen reported that the number of isolates of *S. aureus* declined significantly, while other pathogens that were isolated at baseline were eradicated during treatment (Jensen 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 (graph 01, 05). 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* (Schaad 1997; Sheldon 1993)

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 (graph 04, 01). However, after examining the graph produced in the 'Statistical Analysis' 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 (graph 04, 02) (Sheldon 1993). However, after examining the graph produced in the 'Statistical Analysis' 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).

(3) Mortality
One trial reported on this outcome and there was no significant difference found between the groups (graph 04, 06) (Sheldon 1993). However, the trial was not adequately powered to detect a difference between groups in this outcome.

(4) Frequency of infective respiratory tract exacerbation (time span to next exacerbation) determined clinically or radiologically or both that cannot be attributed to concurrent isolates of other organisms.
Neither trial reported on this outcome (Schaad 1997; Sheldon 1993).

Secondary outcomes
(1) 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) (graph 04, 03). 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).

(2) Adverse effects of antibiotics used, e.g. diarrhoea, vomiting, renal and auditory impairment, sensitivity reactions (e.g. skin rash), bronchospasm, candidiasis.
In the 'Statistical Analysis', 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 (graph 04, 08) (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 trialists 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.

(3) 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 'Statistical Analysis'.

(4) 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) (graph 04, 07).

(5) Isolation of antibiotic-resistant strains or 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 (graph 03, 01) (Schaad 1997). The trialists 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 (graph 04, 09) (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 (graph 04, 10) (Sheldon 1993).

DISCUSSION

Current standard treatment for an 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; four trials of treatment of respiratory tract exacerbations and two trials of long-term treatment for chronic infection of the respiratory tract.

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 trialists to clarify these issues; however, given the age of the trials it is unlikely that this would be possible. It was disappointing that only five trials included data which we were able to analyse. Most of the outcome measures included in the 'Statistical Analysis' 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).

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 an exacerbation with oral ciprofloxacin compared to a combination of IV azlocillin and gentamicin (Hodson 1987). The consensus for standard treatment of an exacerbation is the use of intravenous antibiotics, but we were unable to identify any evidence from RCTs for this. The trial comparing oral ciprofloxacin to oral ofloxacin showed no significant difference in terms of lung function and adverse events between the drug treatments (although we have no information as to whether this was sufficiently powered to detect a difference) (Jensen 1987). If this is so, then in cases of drug intolerance it may be appropriate to exchange one drug for another with no loss of treatment effect. However, since drug intolerance to quinolones is usually due to a class effect, exchanging one quinolone for another may not help. 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.

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.

In summary, we were unable to present any conclusive evidence to show that an oral anti-pseudomonal antibiotic regimen (alone or in combination with another therapy) is more or less effective than any other drug regimen in treating an 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*.

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 known effectiveness against local strains and upon individual preference.

Implications for research

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 compare oral treatment with current standard therapies for both acute exacerbations and long-term treatment of

chronic infection. Adequately-powered trials should have clearly defined outcome measures which are important to people with CF and their carers; these outcome measures could be established in advance through liaison with consumer groups. Trialists should employ standard definitions for trial eligibility (e.g. chronic infection) and report results fully in a standardised and consistent method which should be appropriate to the data. These factors will facilitate the pooling of results from multiple trials in a future update of this systematic review.

POTENTIAL CONFLICT OF INTEREST

None known.

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* *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	**Hodson 1987**
Methods	RCT (generation of allocation sequence & allocation concelament 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 (5g) plus gentamicin (80mg) both given intravenously or ciprofloxacin (500mg) 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*.
Notes	Time-points used in the review: day 10 and follow up at 6 weeks.
Allocation concealment	B – Unclear

Study	**Jensen 1987**
Methods	Double-blind RCT (generation of allocation sequence & allocation concelament both graded as 'unclear'). Cross-over design. Single centre.
Participants	26 people entered the study. 14 in initial ciprofloxacin group and 12 in initial ofloxacin group. 24 received ciprofloxacin and 23 received ofloxacin. Adults with CF with chronic broncho-pulmonary P. aeruginosa infection. Excluded if had acute respiratory failure, renal or hepatic failure, pregnant or breastfeeding women. Disease status: Chronic broncho-pulmonary P. aeruginosa infection of 9 years mean duration (3 to 20 years). Mean age: 23 years; range 18 to 36 years. Sex: 11 males, 9 females in each group. Country: Denmark.
Interventions	Each treatment given for 14 days bd. 3-month washout. CPX (750mg) with ofloxacin placebo or ofloxacin (400mg) plus CPX placebo. Tablets containing drug or placebo were identical. Time-points when measurements were taken during the trial: day 1, 8, 15. Time-points reported in the trial: day 1, day 8 (for some outcomes only) and day 15.
Outcomes	Clinical score of severity of infection FVC (% of normal values for the same sex, height and age)* FEV1 (% of normal values for the same sex, height and age)* Bacteriological examination of sputum samples Measurement of acute phase response Screen of adverse reactions * Sputum samples

Characteristics of included studies (*Continued*)

Notes	Time-points used in the review: day 15. Authors confirmed that 'colonisation' met the criteria of the review. Follow up was for 3 months but only for microbiological outcomes. Data were obtained (in both treatment periods) on day 1 (at start of treatment), day 8 and day 15. In addition, sputum samples were obtained approximately 3 months after completing both treatment periods. The trialists reported data from day 1 and day 15. We have included data from day 15 in the review.
Allocation concealment	B – Unclear

Study	**Richard 1997**
Methods	RCT (generation of allocation sequence & allocation concelament 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. 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 (15mg/kg bd, maximum dose, 1500 mg/day) versus IV ceftazidine plus tobramycin (50mg/kg tds, 3mg/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 FEV1 (% 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) 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.
Allocation concealment	A – Adequate

Characteristics of included studies (*Continued*)

Study	**Schaad 1997**
Methods	RCT (generation of allocation sequence graded as adequate & allocation concelament 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 <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/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.
Allocation concealment	B – Unclear

Study	**Sheldon 1993**
Methods	Double-blind RCT (generation of allocation sequence & allocation concelament both graded as 'adequate'). Parallel design. Single centre.
Participants	40 randomised. 31 completed the trial.

Characteristics of included studies (*Continued*)

	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 age (sd) of 15 participants in the active treatment group: 28.3 years (6.06 years) Mean age (sd) 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 FEV1* FVC* Oxygen saturation 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.
Allocation concealment	A – Adequate

Study	**Wang 1988**
Methods	RCT (generation of allocation sequence & allocation concelament 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).
Allocation concealment	B – Unclear

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
tds: three times a day
*: indicates an outcome used in the review

Characteristics of excluded studies

Study	Reason for exclusion
Anstead 2001	Macrolide (azithromycin) is not a conventional anti-pseudomonal drug.
Bosso 1987	Not all participants colonised or infected with P. aeruginosa.
Bosso 1989	Participants not colonised with P. aeruginosa.
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.
Goldfarb 1986	A pharmacokinetic trial administering 3 single variable doses.
Harrison 1985	Not all participants were colonised with P. aeruginosa.
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.
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.
Pirzada 1999	Not randomised. Case-control study.
Postnikov 2001a	Not an RCT or quasi-randomised.
Pukhalsky 2001	Cox-2 inhibitor. Not looking at an oral anti-pseudomonal.
Saiman 2003	Macrolide (azithromycin) is not a conventional anti-pseudomonal drug.

Characteristics of excluded studies (*Continued*)

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.
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

ADDITIONAL TABLES

Table 01. Trials awaiting assessment

Trial	Reason listed
Black 1991	Queried how the participants were assigned to treatment groups and whether participants were colonised with Pseudomonas aeruginosa as per the definition used in the review. Stated within the paper that "People who have cultured PA in their sputum".
Kurz 1987	Queried the definition of "Chronic infection". Stated within the paper that "PA was identified in sputum over a period of months".
Postnikov 2001	Queried how the participants were assigned to treatment groups and whether participants were colonised with Pseudomonas aeruginosa as per the definition used in the review.
Romano 1991	Queried how the participants were assigned to treatment groups and whether participants were colonised with Pseudomonas aeruginosa as per the definition used in the review.
Rubio 1987	Queried how the participants were assigned to treatment groups and whether participants were colonised as per the definition used in the review.

Table 02. Methodological quality of included trials

Trial	Gen Allocation Seq	Allocation Conceal't	Blinding	Follow up	Outcome report bias	Sample-size calc
Hodson 1987	Grade: unclear. Described as "randomly allocated" but no further information on the methods used was provided.	Grade: unclear. Method not described.	Clinician/person delivering treatment: not possible (oral vs IV). Participants: not possible (oral vs IV). Outcome assessor: not discussed other than for lung function, which was tested by an assessor not involved in the trial.	Withdrawals described. Data recorded for all 40 participants on days 1 and 10, but only 15 in each group were evaluated at 6 weeks. 4 participants who had received azlocillin/gentamicin had to be admitted during this period and were treated again with IV chemotherapy; 1 participant died. 32 participants completed diary cards. Sputum weights were available for 19 participants in each group. 1 participant who had received azlocillin/gentamicin and 2 (including the one who died within 6 weeks) who had received CPX had died 3 months after the start of the treatment. All these patients had very severe lung disease before entry into the trial. Intention-to-treat analysis: not stated.	Time-points data measured: day 1, day 10, 6 weeks. On each of the 10 days of treatment temperature, max PEF and sputum weight were recorded. Time-points data reported in paper: day 1, day 10, 6 weeks Time-points included in review: day 10, 6 weeks	Not discussed.
Jensen 1987	Grade: unclear. Described as	Grade: unclear. Method not described.	Participants: yes. Described as "double-	Withdrawals described. All patients completed	Time-points data measured: day 1, day 8,	Not discussed.

Table 02. Methodological quality of included trials (*Continued*)

Trial	Gen Allocation Seq	Allocation Conceal't	Blinding	Follow up	Outcome report bias	Sample-size calc
	"Consecutive patients were randomly assigned" but no further information on the methods used was provided.		blind" but no further information provided on who else was blinded.	treatment period 1 and 21 completed both treatment periods. Two participants receiving CPX and 1 receiving ofloxacin in period 1 failed to complete the trial owing to treatment failure. Another 2 participants, 1 in each drug group, refused to continue the study after period 1. So 11 participants who started on CPX and 10 who started on ofloxacin completed both trial periods. Intention-to-treat analysis: not stated.	day 15 Time-points data reported in paper: day 1, day 15 Time-points included in review: day 15	
Richard 1997	Grade: adequate. Authors confirmed assignment was based on the random code generated at the Institute of Biometry of Bayer AG, Wuppertal, Germany.	Grade: adequate. Author confirmed sealed envelope for each participant specifying individual drug schedule to be opened after enrolment.	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)).	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. Intention-to-treat analysis: no.	Time-points data measured: baseline, days 5-7, day 14 and at follow up (day 20-30). Time-points data reported in paper: baseline, day 14 and at follow-up (day 20-30) Time-points included in review: day 14	Not discussed.
Schadd 1997	Grade: adequate. Authors confirmed that	Grade: unclear. Method not described.	Clinician/person delivering treatment:	Withdrawals described. 22 to CPX and	Time-points data measured: baseline, 6	Not discussed.

Table 02. Methodological quality of included trials (*Continued*)

Trial	Gen Allocation Seq	Allocation Conceal't	Blinding	Follow up	Outcome report bias	Sample-size calc
	a computer-generated randomisation list was used and strictly adhered to.		not possible (oral vs oral plus inhaled). Participants: not possible (oral vs oral plus inhaled) Outcome assessor: no information provided.	23 to CPX with inhaled amikacin. One participant randomised to treatment with CPX was excluded from the efficacy evaluation because the baseline culture had been negative for PA. Two participants discontinued treatment with oral CPX plus inhaled amikacin: 1 because of abdominal pain, tiredness and loss of concentration, after three weeks of therapy; and the other, at 4 weeks because of subjective breathlessness after amikacin therapy inhalation. Intention-to-treat analysis: not clear.	weeks and at 3 months (randomised section) Time-points data reported in paper: baseline and at 3 months (randomised section) Time-points included in review: 3 months (randomised section)	
Sheldon 1993	Grade: adequate. 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	Grade: adequate. Treatment courses were prepared by Bayer, none of the staff involved with the trial had knowledge of the treatment allocated to each participant.	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	Withdrawals 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	Time-points data measured: Baseline and every 3 months for clinical assessment (up to 12 months). At each 3-month visit participants' clinical symptoms, signs, weight and drug history were recorded. Lung function data recorded. During	The trial had a power of 80% for detecting a real difference of 200 ml in the improvement of FEV1 between the groups significant at the 5% level.

Table 02. Methodological quality of included trials (*Continued*)

Trial	Gen Allocation Seq	Allocation Conceal't	Blinding	Follow up	Outcome report bias	Sample-size calc
	the start of the trial in blocks of 4: 2 each for treatment and placebo.		to each patient".	withdrawn for the following reasons: poor compliance (2), death (1), desire to become pregnant (1).	each 10-day course patients were asked to complete a diary card listing their symptoms, sputum vol and PEF. Sputum samples were cultured at the start and finish of each course of tablets. Time-points data reported in paper: baseline and 12 months Time-points included in review: 12 months	
Wang 1988	Grade: unclear. Described as "were placed at random on 1 of 3 regimens".	Grade: unclear. Method not described.	Clinician/person delivering treatment: not possible (oral vs IV). Participants: not possible (oral vs IV) Outcome assessor: no information provided.	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.	Time-points data measured: before, at week 1 and after completion of treatment Time-points data reported in paper: narrative reporting (no data) Time-points included in review: narrative reporting (no data)	Not discussed.

Table 03. Review-specified outcomes reported in included trials

Trial	Quality of life	FEV1 & FVC	Mortality	Time to next RTE	Weight	Adverse effects	Additional ABs	AB-resistant strains	Hospital admissions
Hodson 1987	Breathlessness, wheeziness, treatment preference.	FEV1 & 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. aerugnosa-resistant strains measured at day 1, day 10 and 6 weeks.	
Jensen 1987		FEV1 and FVC at day 1, 8 and 15.				Gastrointestinal,			
Richard 1997		FEV1 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 exacerbations.	Bacteriologic outcome 48 hours before treatment and at the end of treatment (day 14) and at follow up (day 20-30).	
Schaad 1997		FVC at baseline, 6 weeks (although not presented) and 3 months			Measured, no data presented.	Gastrointestinal, nervous system, others.		P. aerugnosa-resistant strains measured at the end of treatment (3 months).	
Sheldon 1993	Days off work and breathlessness.	FEV1 and FVC assessed at baseline and every 3 months. Data reported at baseline	Within 12 months.		Measured at baseline and every 3 months. Data reported from baseline and 12	Gastrointestinal.	Further IV treatment reported up to 12 months.	P. aerugnosa-resistant strains measured at the end of treatment (12	Reported mean number of days in hospital at end of 12 months.

Table 03. Review-specified outcomes reported in included trials (*Continued*)

Trial	Quality of life	FEV1 & FVC	Mortality	Time to next RTE	Weight	Adverse effects	Additional ABs	AB-resistant strains	Hospital admissions
		and 12 months.			months.			months).	
Wang 1988									

ANALYSES

Comparison 01. Exacerbation - oral versus IV antibiotics

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 FEV1 ml (mean change)			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
02 FVC ml (mean change)			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
03 Adverse events			Relative Risk (Fixed) 95% CI	Subtotals only
04 Frequency of need for additional antibiotic use			Relative Risk (Fixed) 95% CI	Totals not selected
05 Isolation of antibiotic-resistant strains - P. aeruginosa			Relative Risk (Fixed) 95% CI	Subtotals only
06 Isolation of antibiotic-resistant strains - S. aureus			Relative Risk (Fixed) 95% CI	Totals not selected

Comparison 02. Exacerbation - oral versus oral

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 FEV1% predicted (mean change)			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
02 FVC % predicted (mean change)			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
03 Adverse events			Relative Risk (Fixed) 95% CI	Totals not selected

Comparison 03. Long-term treatment - oral versus oral and inhaled antibiotics

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Isolation of antibiotic-resistant strains - P. aeruginosa			Relative Risk (Fixed) 95% CI	Totals not selected

Comparison 04. Long-term treatment - oral versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Mean FEV1 at end of course (L)			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
02 Mean FVC at end of course (L)			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
03 Mortality			Relative Risk (Fixed) 95% CI	Totals not selected
04 Weight (kg)			Weighted Mean Difference (Fixed) 95% CI	Totals not selected

05 Adverse events	Relative Risk (Fixed) 95% CI	Totals not selected
06 Participants needing additional IV courses	Relative Risk (Fixed) 95% CI	Totals not selected
07 Isolation of antibiotic-resistant strains - P. aeruginosa	Relative Risk (Fixed) 95% CI	Totals not selected
08 Isolation of antibiotic-resistant strains - S. aureus	Relative Risk (Fixed) 95% CI	Totals not selected

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Adult; Child; Humans

COVER SHEET

Title	Oral anti-pseudomonal antibiotics for cystic fibrosis
Authors	Remmington T, Jahnke N, Harkensee C
Contribution of author(s)	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. REVIEW 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.
Issue protocol first published	2005/3
Review first published	2007/3
Date of most recent amendment	21 May 2007
Date of most recent SUBSTANTIVE amendment	18 May 2007
What's New	November 2006 The term colonisation has been replaced with more suitable term 'chronic infection'.
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	31 March 2007
Date authors' conclusions section amended	Information not supplied by author

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Editorial group Cochrane Cystic Fibrosis and Genetic Disorders Group

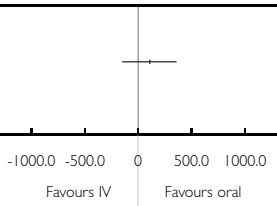
Editorial group code HM-CF

GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Exacerbation - oral versus IV antibiotics, Outcome 01 FEV1 ml (mean change)

Review: Oral anti-pseudomonal antibiotics for cystic fibrosis
Comparison: 01 Exacerbation - oral versus IV antibiotics
Outcome: 01 FEV1 ml (mean change)

Study	Oral N	Oral Mean(SD)	IV N	IV Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weighted Mean Difference (Fixed) 95% CI
01 At more than 1 week and up to 2 weeks						
Hodson 1987	20	532.00 (456.00)	20	418.00 (358.00)		114.00 [-140.08, 368.08]

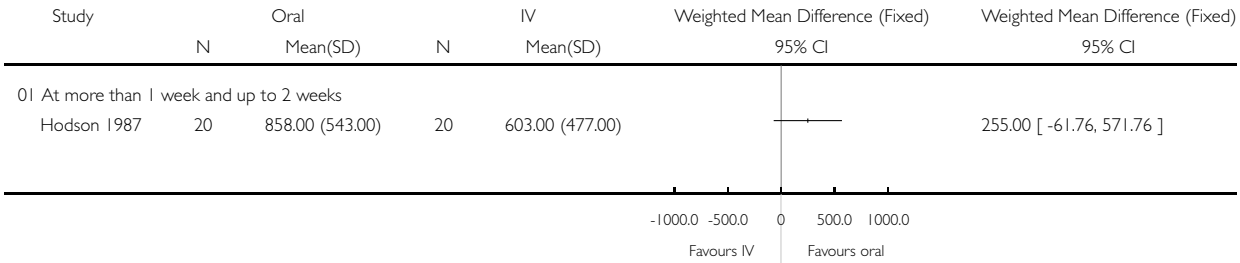


Analysis 01.02. Comparison 01 Exacerbation - oral versus IV antibiotics, Outcome 02 FVC ml (mean change)

Review: Oral anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 01 Exacerbation - oral versus IV antibiotics

Outcome: 02 FVC ml (mean change)

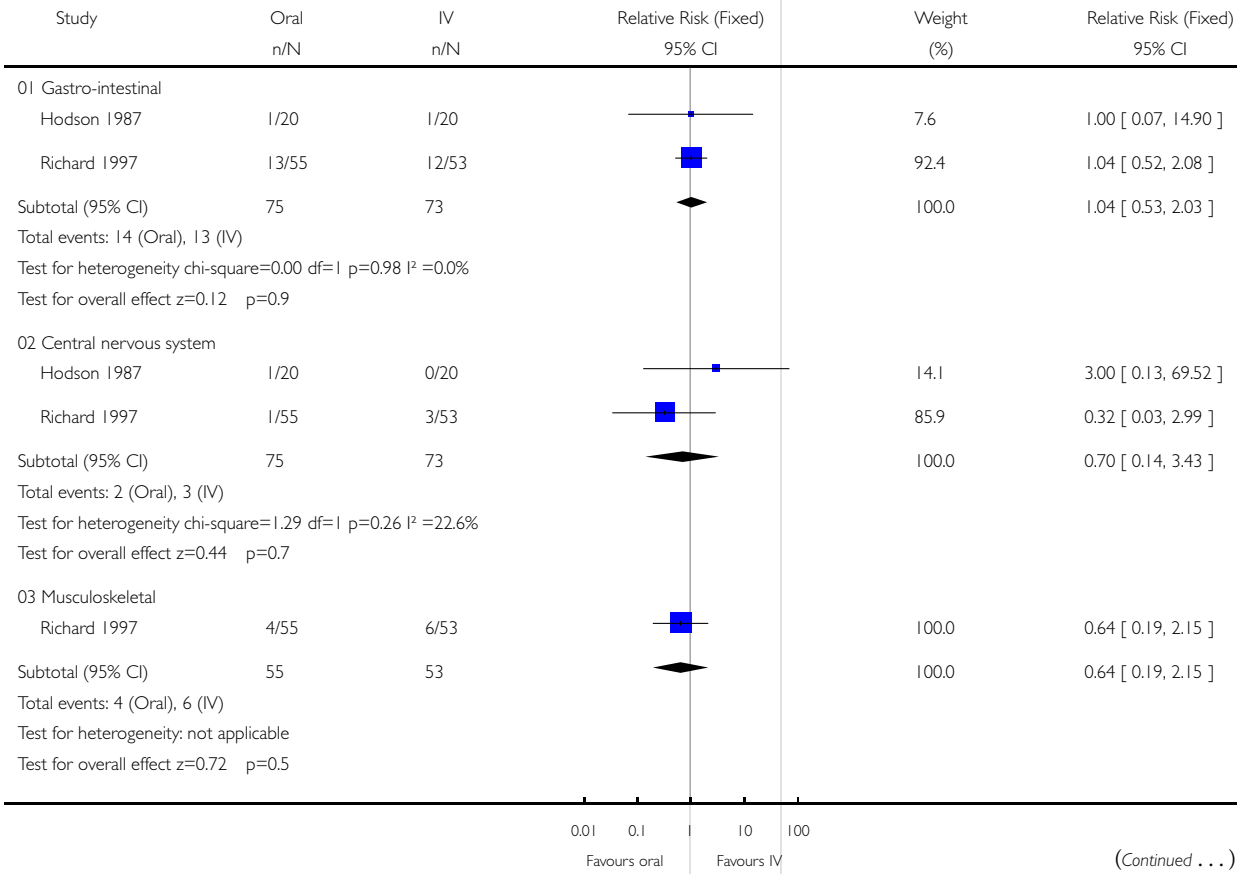


Analysis 01.03. Comparison 01 Exacerbation - oral versus IV antibiotics, Outcome 03 Adverse events

Review: Oral anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 01 Exacerbation - oral versus IV antibiotics

Outcome: 03 Adverse events



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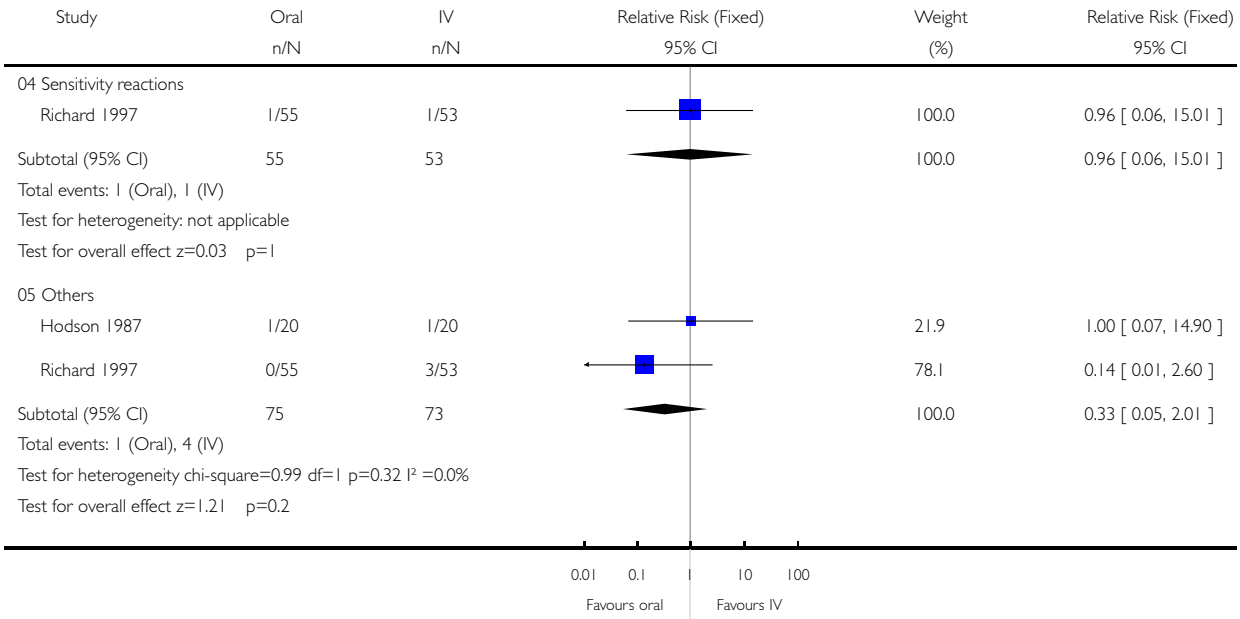
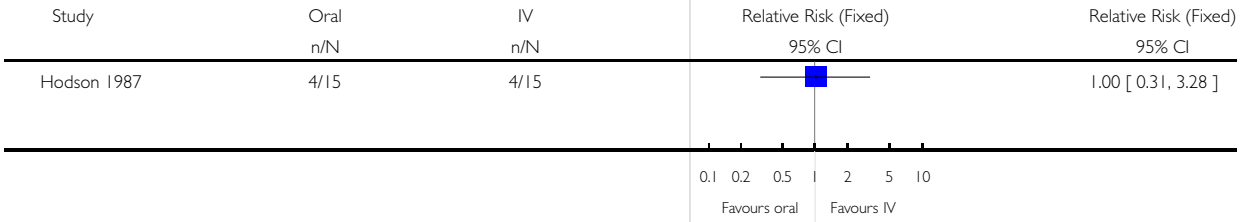


Analysis 01.04. Comparison 01 Exacerbation - oral versus IV antibiotics, Outcome 04 Frequency of need for additional antibiotic use

Review: Oral anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 01 Exacerbation - oral versus IV antibiotics

Outcome: 04 Frequency of need for additional antibiotic use

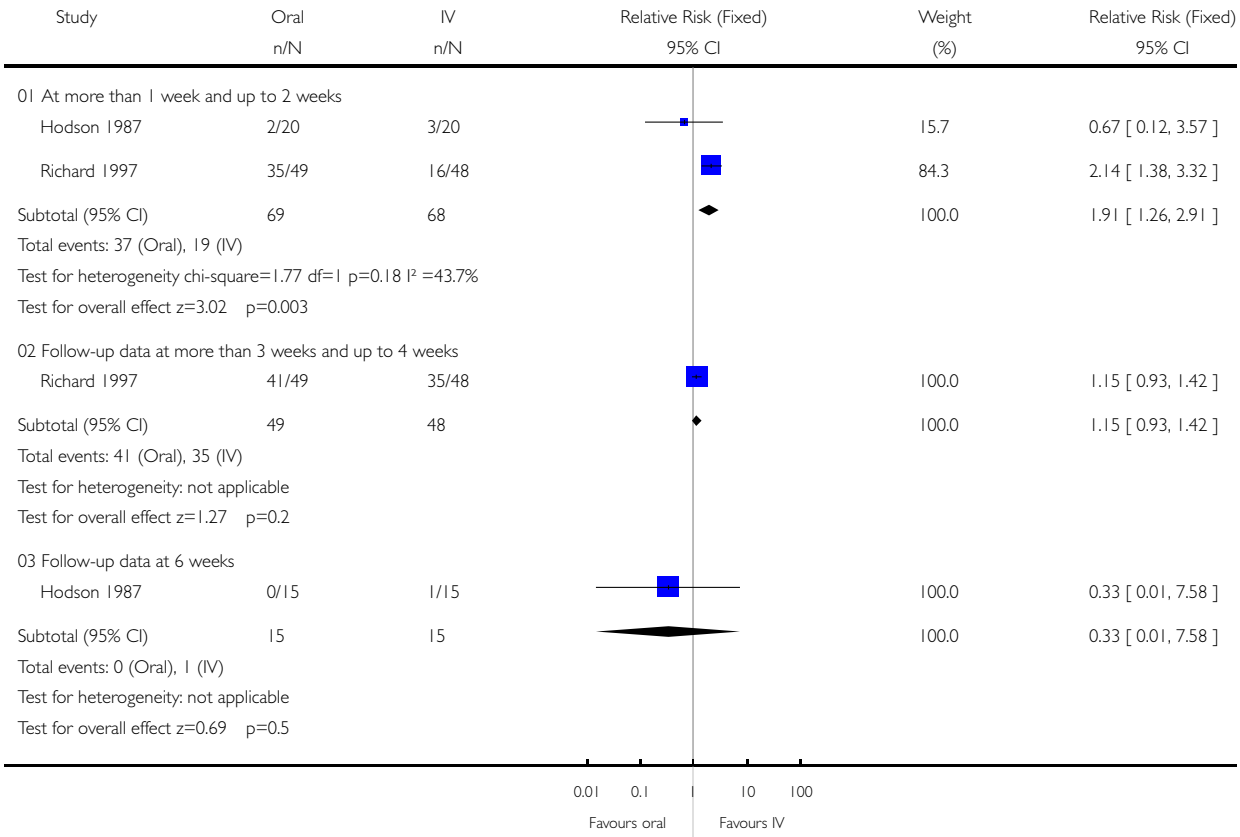


Analysis 01.05. Comparison 01 Exacerbation - oral versus IV antibiotics, Outcome 05 Isolation of antibiotic-resistant strains - P. aeruginosa

Review: Oral anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 01 Exacerbation - oral versus IV antibiotics

Outcome: 05 Isolation of antibiotic-resistant strains - P. aeruginosa

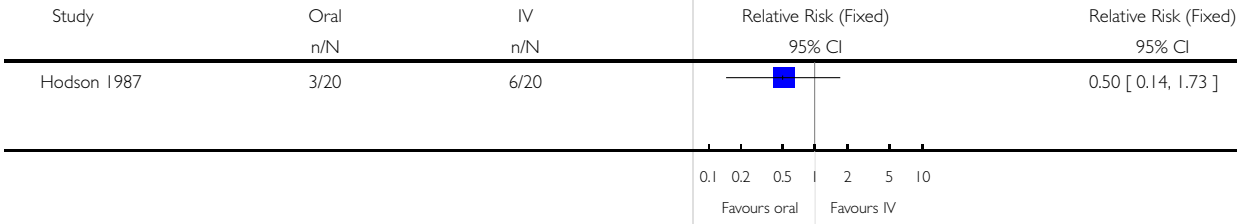


Analysis 01.06. Comparison 01 Exacerbation - oral versus IV antibiotics, Outcome 06 Isolation of antibiotic-resistant strains - S. aureus

Review: Oral anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 01 Exacerbation - oral versus IV antibiotics

Outcome: 06 Isolation of antibiotic-resistant strains - S. aureus

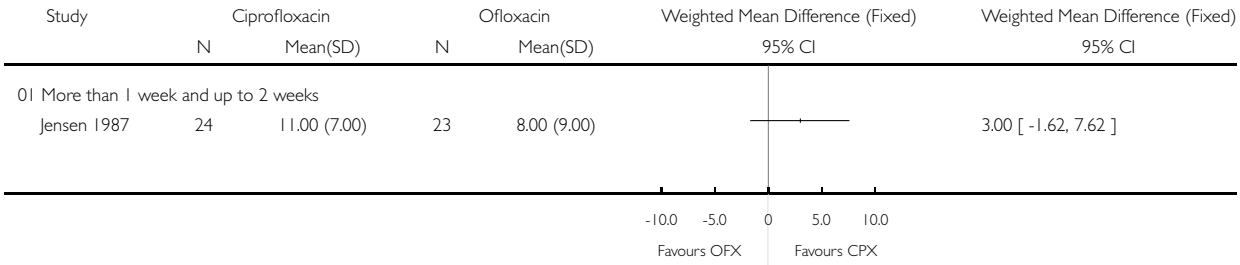


Analysis 02.01. Comparison 02 Exacerbation - oral versus oral, Outcome 01 FEV1% predicted (mean change)

Review: Oral anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 02 Exacerbation - oral versus oral

Outcome: 01 FEV1% predicted (mean change)

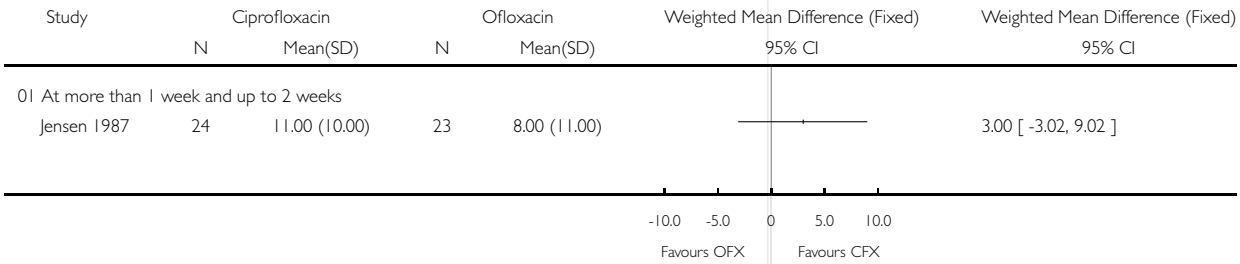


Analysis 02.02. Comparison 02 Exacerbation - oral versus oral, Outcome 02 FVC % predicted (mean change)

Review: Oral anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 02 Exacerbation - oral versus oral

Outcome: 02 FVC % predicted (mean change)

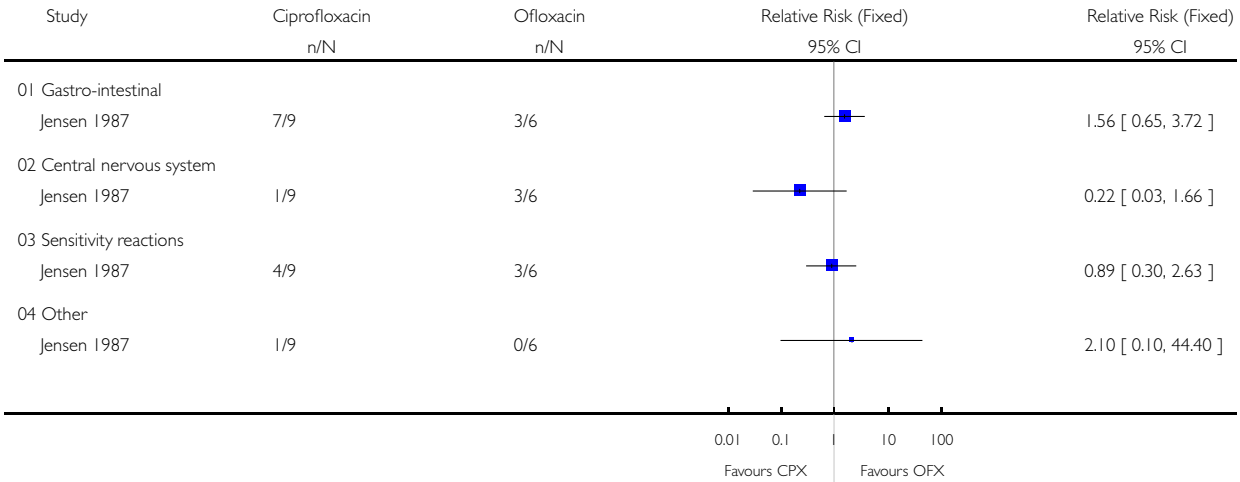


Analysis 02.03. Comparison 02 Exacerbation - oral versus oral, Outcome 03 Adverse events

Review: Oral anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 02 Exacerbation - oral versus oral

Outcome: 03 Adverse events

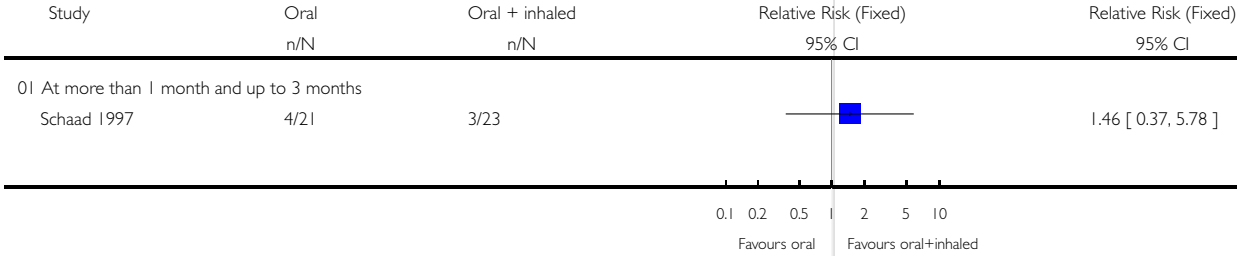


Analysis 03.01. Comparison 03 Long-term treatment - oral versus oral and inhaled antibiotics, Outcome 01 Isolation of antibiotic-resistant strains - P. aeruginosa

Review: Oral anti-pseudomonal antibiotics for cystic fibrosis

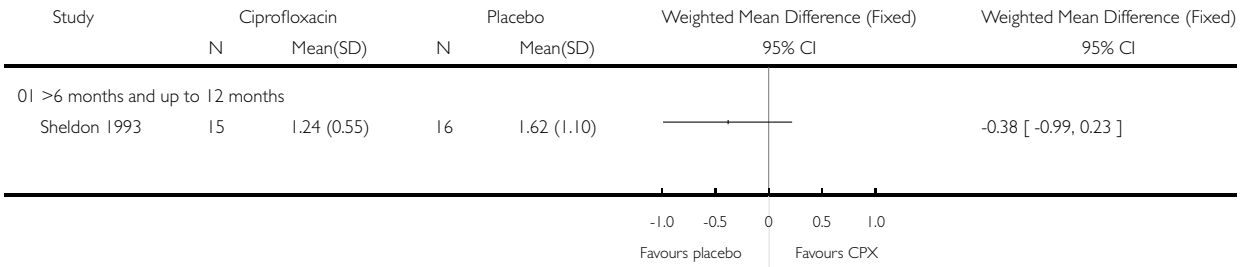
Comparison: 03 Long-term treatment - oral versus oral and inhaled antibiotics

Outcome: 01 Isolation of antibiotic-resistant strains - P. aeruginosa



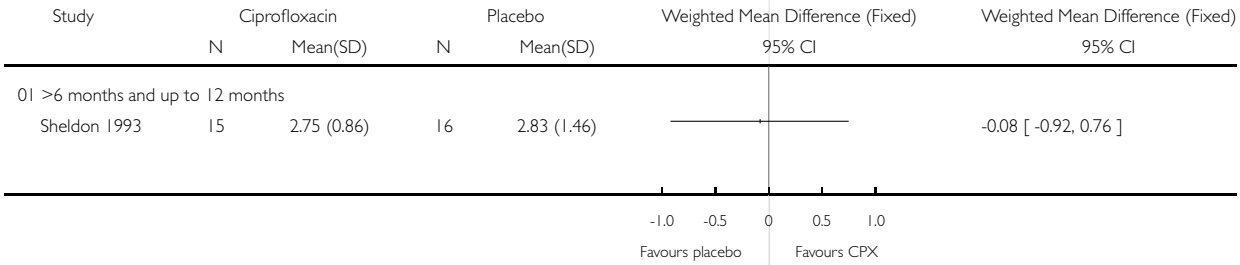
Analysis 04.01. Comparison 04 Long-term treatment - oral versus placebo, Outcome 01 Mean FEV1 at end of course (L)

Review: Oral anti-pseudomonal antibiotics for cystic fibrosis
Comparison: 04 Long-term treatment - oral versus placebo
Outcome: 01 Mean FEV1 at end of course (L)



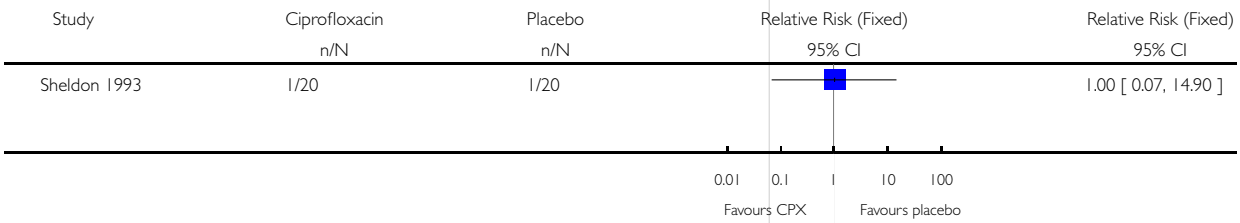
Analysis 04.02. Comparison 04 Long-term treatment - oral versus placebo, Outcome 02 Mean FVC at end of course (L)

Review: Oral anti-pseudomonal antibiotics for cystic fibrosis
Comparison: 04 Long-term treatment - oral versus placebo
Outcome: 02 Mean FVC at end of course (L)



Analysis 04.03. Comparison 04 Long-term treatment - oral versus placebo, Outcome 03 Mortality

Review: Oral anti-pseudomonal antibiotics for cystic fibrosis
Comparison: 04 Long-term treatment - oral versus placebo
Outcome: 03 Mortality

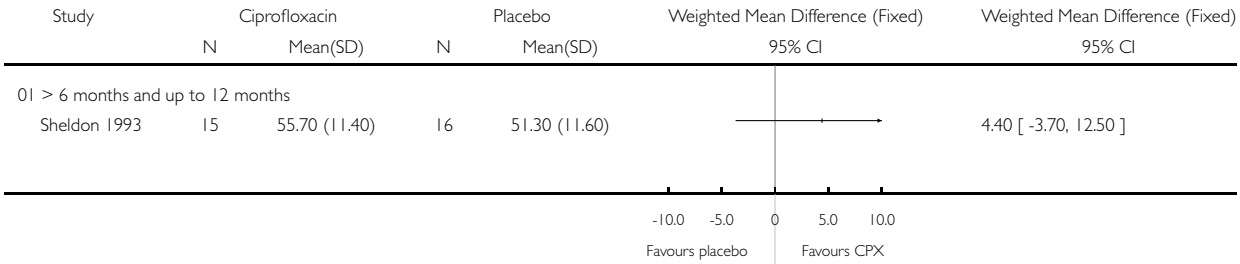


Analysis 04.04. Comparison 04 Long-term treatment - oral versus placebo, Outcome 04 Weight (kg)

Review: Oral anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 04 Long-term treatment - oral versus placebo

Outcome: 04 Weight (kg)

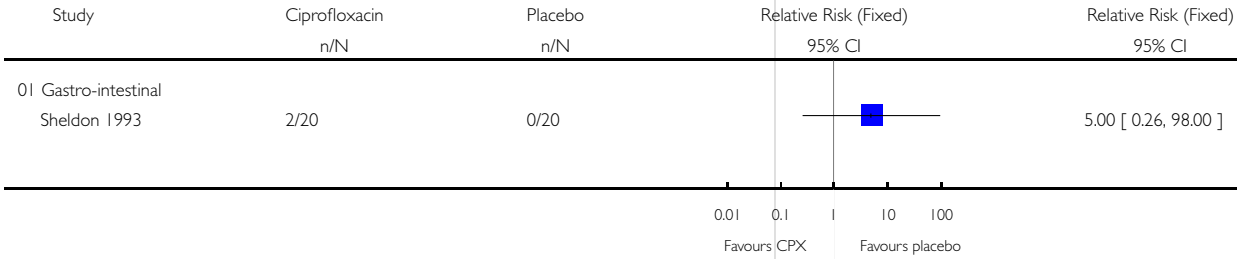


Analysis 04.05. Comparison 04 Long-term treatment - oral versus placebo, Outcome 05 Adverse events

Review: Oral anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 04 Long-term treatment - oral versus placebo

Outcome: 05 Adverse events

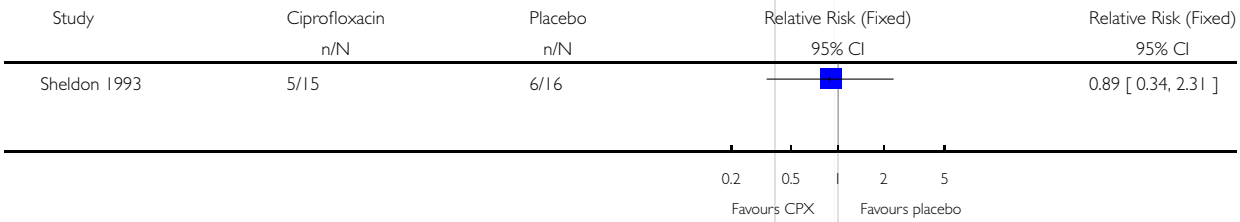


Analysis 04.06. Comparison 04 Long-term treatment - oral versus placebo, Outcome 06 Participants needing additional IV courses

Review: Oral anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 04 Long-term treatment - oral versus placebo

Outcome: 06 Participants needing additional IV courses

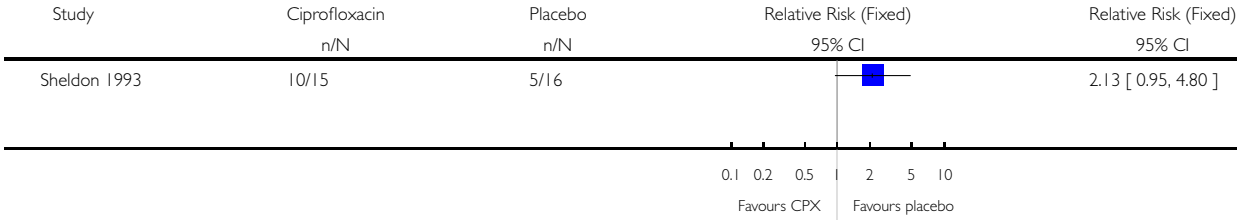


Analysis 04.07. Comparison 04 Long-term treatment - oral versus placebo, Outcome 07 Isolation of antibiotic-resistant strains - P. aeruginosa

Review: Oral anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 04 Long-term treatment - oral versus placebo

Outcome: 07 Isolation of antibiotic-resistant strains - P. aeruginosa



Analysis 04.08. Comparison 04 Long-term treatment - oral versus placebo, Outcome 08 Isolation of antibiotic-resistant strains - S. aureus

Review: Oral anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 04 Long-term treatment - oral versus placebo

Outcome: 08 Isolation of antibiotic-resistant strains - S. aureus