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TABLE OF CONTENTS

[Intervention Review]

Single versus combination intravenous anti-pseudomonal antibiotic therapy for people with cystic fibrosis

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ABSTRACT

Background

Choice of antibiotic, and the use of single or combined therapy are controversial areas in the treatment of respiratory infection due to *Pseudomonas aeruginosa* in cystic fibrosis (CF). Advantages of combination therapy include wider range of modes of action, possible synergy and reduction of resistant organisms; advantages of monotherapy include lower cost, ease of administration and reduction of drug-related toxicity. Current evidence does not provide a clear answer and the use of intravenous antibiotic therapy in cystic fibrosis requires further evaluation. This is an update of a previously published review.

Objectives

To assess the effectiveness of single compared to combination intravenous anti-pseudomonal antibiotic therapy for treating people with cystic fibrosis.

Search methods

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

Most recent search of the Group's Trials Register: 14 October 2016.

Selection criteria

Randomised controlled trials (RCTs) comparing a single intravenous anti-pseudomonal antibiotic with a combination of that antibiotic plus a second anti-pseudomonal antibiotic in people with CF.

Data collection and analysis

Two authors independently assessed trial quality and extracted data.

Main results

We identified 45 trials, of which eight trials (356 participants) comparing a single anti-pseudomonal agent to a combination of the same antibiotic and one other, were included.

There was a wide variation in the individual antibiotics used in each trial. In total, the trials included seven comparisons of a beta-lactam antibiotic (penicillin-related or third generation cephalosporin) with a beta-lactam-aminoglycoside combination and three comparisons of an aminoglycoside with a beta-lactam-aminoglycoside combination. These two groups of trials were analysed as separate subgroups.

There was considerable heterogeneity amongst these trials, leading to difficulties in performing the review and interpreting the results. The meta-analysis did not demonstrate any significant differences between monotherapy and combination therapy, in terms of lung function; symptom scores; adverse effects; and bacteriological outcome measures.

These results should be interpreted cautiously. Six of the included trials were published between 1977 and 1988; these were single-centre trials with flaws in the randomisation process and small sample size. Overall, the methodological quality was poor.

Authors' conclusions

The results of this review are inconclusive. The review raises important methodological issues. There is a need for an RCT which needs to be well-designed in terms of adequate randomisation allocation, blinding, power and long-term follow up. Results need to be standardised to a consistent method of reporting, in order to validate the pooling of results from multiple trials.

PLAIN LANGUAGE SUMMARY

A comparison of single and combined intravenous drug therapy for people with cystic fibrosis infected with *Pseudomonas aeruginosa*

Review question

We reviewed the evidence about the different effects of using a single intravenous (given directly into a vein) antibiotic compared to using a combination of intravenous antibiotics in people with cystic fibrosis infected with *Pseudomonas aeruginosa*.

Background

Cystic fibrosis is a serious genetic disease that affects cells in the exocrine glands (sweat glands and others). People with cystic fibrosis have a greater risk of chronic lung infections, often due to bacteria called *Pseudomonas aeruginosa*. They receive antibiotics, either a single drug or a combination of different drugs, by injection to treat these infections. Both the choice of antibiotic and the use of single or combined therapy vary. We looked for randomised controlled trials which compared a single intravenous antibiotic with a combination of that antibiotic plus another one in people with cystic fibrosis. This is an updated version of the review.

Search date

The evidence is current to: 14 October 2016.

Study characteristics

We included eight trials with a total of 356 people. Six of these were published before 1988, were each based in a single centre and used a range of different drugs. These factors made it difficult to combine and analyse the results.

Key results

We did not find any differences between the two therapies for lung function, symptom scores, side effects or bacteriological outcome measures. We conclude that there is not enough evidence to compare the different therapies. More research is needed, particularly looking at side effects of treatment.

Quality of the evidence

Six of the included trials were quite old (published between 1977 and 1988). They did not include many people and had flaws in the way the people taking part were put into the different treatment groups. Overall, the quality of the trials' design was poor.

BACKGROUND

Description of the condition

Cystic fibrosis (CF) is the most common life-limiting inherited disorder affecting white populations, with chronic, progressive lung disease being the major cause of morbidity and shortened survival. The continuous cycle of infection and inflammation is responsible for the severe airway damage and loss of respiratory function (Cantin 1995; Konstan 1997).

Recurrent infection, in particular with *Pseudomonas aeruginosa* (*P aeruginosa*) is the main feature of the lung involvement in CF. Administration of intravenous (IV) antibiotic therapy for a period of around two weeks is standard practice for treatment of pulmonary infections in most CF centres. Some studies have shown this approach to be effective in improving sputum colony counts (Regelmann 1990). Regular, elective IV therapy, as well as other interventions such as early treatment and cohorting have been shown to have a beneficial effect on the prevalence of *P aeruginosa* (Frederiksen 1999). However, this relationship was not demonstrated in a small study by Wolter (Wolter 1999). The inconsistency of these results suggests that the use of this therapy requires further evaluation.

Description of the intervention

Currently, treatment of chronic *P aeruginosa* infection in people with CF usually involves one of the following strategies. One approach is to use IV antibiotics to treat people with CF only when they become acutely unwell, on the grounds of clinical, radiological or pulmonary function parameters (subsequently referred to as symptomatic regimen). Alternatively, chronic infection may be treated with elective IV antibiotics at regular intervals (e.g. three-monthly) (Hoiby 1993), to try to prevent long-term deterioration (subsequently referred to as elective regimen). Trials using either of these strategies will be considered for this review, if the same strategy was used for treatment and comparison groups.

Choice of antibiotic, single or combined therapy and the duration of treatment are controversial areas in the treatment of infection with IV antibiotics in CF. Current practice in the UK is variable, with one study from 1993 showed 80% choosing a combination and 20% using monotherapy (Taylor 1993). However, more recently it was reported that monotherapy is now used in only 1 out of 23 centres in the UK who replied to a postal survey (Tan 2002).

How the intervention might work

Most centres perceive dual or combination IV antibiotic therapy in CF to be more effective than single therapy. It has been suggested that a clinic policy of using monotherapy with a beta-lactam antibiotic may be responsible for the emergence of resistant strains of *P aeruginosa* (Cheng 1996). Use of a beta-lactam alone offers advantages for the individual because of ease of administration and avoidance of the need to measure aminoglycoside levels.

Why it is important to do this review

Intravenous antibiotic therapy may have contributed to improved survival among people with CF; however, the multiple use of potent and highly selective antibiotics may increase the likelihood of adverse effects and lead to the development of resistant strains of organisms (Levy 1998). This version of the review is an update of previous review versions (Elphick 2002; Elphick 2005; Elphick 2014).

OBJECTIVES

1. To assess the effectiveness of single compared to combination IV anti-pseudomonal antibiotic therapy in the treatment of people with CF.
2. To assess whether the use of combination IV anti-pseudomonal antibiotic therapy leads to an increase in adverse effects or the development of resistant strains of organisms in CF.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials. Trials in which individuals are treated according to a symptomatic or an elective regimen (see above) were included if the only difference between the treatment and comparison group is whether the participants receive single or combination antibiotic therapy. Trials where quasi-randomisation methods such as alternation were used were included, when there was sufficient evidence that the treatment and comparison groups were comparable in terms of clinical status.

Types of participants

Children and adults with defined CF diagnosed clinically and by sweat or genetic testing including all ages and all degrees of severity.

Types of interventions

Any single IV anti-pseudomonal antibiotic compared to a combination of two or more IV anti-pseudomonal antibiotics. Trials comparing a single anti-pseudomonal agent to a combination of the same antibiotic and one other anti-pseudomonal agent (drug A versus drug A plus drug B) were included. Trials which compared a single anti-pseudomonal antibiotic agent with a combination of two further anti-pseudomonal antibiotics (drug A versus drug B plus drug C) were not included.

Types of outcome measures

We aimed to assess whether a combination of IV anti-pseudomonal antibiotics is more effective than a single IV anti-pseudomonal antibiotic for the following outcomes:

1. subjective improvement;
2. clinical improvement;
3. bacteriological improvement;
4. adverse effects.

Short-term results

(i.e. at end of course of antibiotics)

Primary outcomes

1. Clinical improvement
   a. improvement in spirometric lung function (e.g. forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC))

2. Bacteriological improvement
   a. improvement in quantitative bacteriology of sputum
3. Adverse effects to antibiotics, e.g. renal and auditory impairment, serum sickness and sensitivity reactions

Secondary outcomes

1. Subjective improvement
   a. quality of life assessment, in terms of measures of the individual's well-being
2. Clinical improvement
   a. nutritional status as noted by weight gain, body mass index, z score or other indices of nutritional state
   b. additional treatment required
   c. duration of hospitalisation
   d. time to next course of IV antibiotics
   e. chest X-ray (CXR) scores
   f. improvement in symptoms
3. Bacteriological improvement
   a. Changes in inflammatory markers (in sputum or blood)

Long-term results

(measured at 6 to 12 months after course of antibiotics; if long-term outcomes are measured at other time intervals, consideration will be given to these also)

Primary outcomes

1. Clinical improvement
   a. prevention of deterioration of lung function
2. Bacteriological change
   a. development of antibiotic-resistant strains of*P aeruginosa* and other organisms
3. Adverse effects to antibiotics, e.g. renal and auditory impairment, serum sickness and sensitivity reactions

Secondary outcomes

1. Subjective improvement
   a. quality of life assessment
2. Clinical improvement
   a. number of courses of IV antibiotics in the following year

Search methods for identification of studies

Relevant trials were identified from the Group's Cystic Fibrosis Trials Register using the terms: antibiotics AND intravenous.

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

Date of the most recent search of the Group's CF Trials Register: 14 October 2016.

Data collection and analysis

Selection of studies

Two authors from different centres independently reviewed all trials to select which were to be included in the review. If disagreement arose on the suitability of a trial for inclusion in the review, the authors reached a consensus by discussion.

Data extraction and management

Each author independently extracted data using standard data acquisition forms. If disagreement arose on the quality of a trial, the authors reached a consensus by discussion.

If there had been sufficient numbers of trials using quasi-randomisation methods, then the authors would have analysed this group separately.

The authors grouped data into short-term results and long-term results. They defined short-term results as those at the end of the course of antibiotics; they considered long-term results to be 6 to 12 months after the course of antibiotics. The authors will also consider other time intervals for long-term outcomes if these are reported.

For binary outcome measures the authors recorded the number of events and the number of participants for each group. For continuous outcomes, the authors recorded either the mean change from baseline for each group or mean post-treatment or intervention values and the standard deviation or standard error for each group.

Assessment of risk of bias in included studies

In order to establish a risk of bias for each trial, the authors independently assessed the methodological quality of each trial. In particular, authors examined details of the randomisation method (generation and concealment of allocation), the degree of blinding in the trial, whether intention-to-treat analyses were possible from the available data and if the investigators recorded the number of participants lost to follow up or subsequently excluded from the trial.

Measures of treatment effect

For binary outcome measures, the authors calculated a pooled estimate of the treatment effect for each outcome across trials using the Peto odds ratio with 95% confidence intervals (CIs) where appropriate. For continuous outcomes, the authors calculated a pooled estimate of treatment effect by calculating the mean difference with 95% CIs.

Unit of analysis issues

One trial included in the review was of cross-over design (Pedersen 1986). Ideally when conducting a meta-analysis combining results from cross-over trials the authors 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 they have been able to use was to treat the cross-over trial as if it was a parallel trial (assuming a correlation of zero as the most conservative estimate). Elbourne says that this approach produces conservative results as it does not take into account within-patient correlation (Elbourne 2002). Also each participant appears in both

the treatment and control group, so the two groups are not independent.

Dealing with missing data

In order to allow an intention-to-treat analysis, the authors collected data on the number of participants with each outcome event by allocated treatment group, irrespective of compliance and whether or not the participant was later thought to be ineligible or otherwise excluded from treatment or follow up.

Assessment of heterogeneity

The authors tested for heterogeneity between trial results using a standard Chi^2 test.

Data synthesis

The authors analysed the data using a fixed-effect model. In future updates, if they identify a moderate to high degree of heterogeneity, they plan to analyse the data using a random-effects model.

Subgroup analysis and investigation of heterogeneity

If there were sufficient trials, the authors planned to carry out subgroup analyses of adults separately from children; of participants on a symptomatic regimen separately from those on an elective regimen; and also of those who were colonised with *P aeruginosa* (i.e. those people with CF who are sputum positive on three consecutive occasions) separately from those who were not colonised.

Sensitivity analysis

The authors planned to perform a sensitivity analysis based on the methodological quality of the trials.

RESULTS

Description of studies

Results of the search

A total of 45 trials were identified by the searches. No trials were found through contact with pharmaceutical companies. We included eight trials in the review and excluded 37 trials.

Included studies

Eight trials (including 356 participants) were included in this review; of these three were published only as abstracts from conference proceedings (Costantini 1982; Huang 1982; Master 1997).

Seven trials were stated to be randomised controlled trials (Costantini 1982; Huang 1982; Master 1997; McCarty 1988; McLauglin 1983; Pedersen 1986; Smith 1999). The method of randomisation was stated in only one of these, in which it was described as "computer-generated" (Smith 1999). In the remaining trial, treatment was assigned as an alternate allocation with good evidence of similar groups at baseline (Parry 1977). This trial was included as a quasi-randomised trial.

In seven of the eight trials, participants were included during an exacerbation of symptoms (symptomatic regimen) in a parallel group design (Costantini 1982; Huang 1982; Master 1997; McCarty 1988; McLauglin 1983; Parry 1977; Smith 1999). In the remaining trial, participants were treated using a three-monthly elective regimen and were re-entered into the trial during consecutive courses of antibiotics in a cross-over design (Pedersen 1986). In five of the trials, evidence of *P aeruginosa* in the sputum was an inclusion requirement (Costantini 1982; Master 1997; Parry 1977; Pedersen 1986; Smith 1999); of the remaining three trials, one stated that 98% had *P aeruginosa* (McLauglin 1983).

Criteria for diagnosis of CF were stated in only one of the eight trials (Smith 1999). Sample sizes varied from 14 to 83 participants, with a total of 356 participants recruited. All trials either stated that they included both adults and children, or did not state the age range. No trial looked at the effects of single versus combination antibiotic therapy in children alone. One trial included 17 children, but included three children twice, giving a total of 20 treatment courses (McCarty 1988).

There was a wide variation in the individual antibiotics used in each trial (*see* Published notes: Description of pharmacological properties of antibiotics used). Two trials made two comparisons, therefore, in total, the eight trials included seven comparisons of a beta-lactam antibiotic (penicillin-related or third generation cephalosporin) to a beta-lactam-aminoglycoside combination and three comparisons of an aminoglycoside to a beta-lactam-aminoglycoside combination. These two groups of trials were analysed as separate subgroups.

Two trials compared two single agents with the combination of the same two antibiotics: carbenicillin versus sisomycin versus carbenicillin and sisomycin (Costantini 1982); ticarcillin versus gentamicin versus ticarcillin and gentamicin (Parry 1977). One other trial looked at an aminoglycoside as the single agent: tobramycin versus tobramycin and ceftazidime (Master 1997). Of the remaining five trials, one studied ceftazidime as the single agent (ceftazidime and tobramycin (Pedersen 1986)) and the remaining four compared an agent from the penicillin group of antibiotics: piperacillin (McCarty 1988); ticarcillin (Huang 1982); azlocillin (McLauglin 1983; Smith 1999) with a combination of that agent with tobramycin.

Outcomes were studied at the end of the treatment course in all trials. Treatment duration varied from 10 to 14 days. Three trials included a follow-up period, which varied from two to eight weeks (McLauglin 1983; Smith 1999) to six months for the cross-over trial (Pedersen 1986).

Excluded studies

A total of 37 trials were excluded. Eleven trials compared a single antibiotic agent with the existing combination of two other antibiotics (drug A versus drug B plus drug C) (Balsamo 1986; Beaudry 1980; Bosso 1988; Church 1997; De Boeck 1989; De Boeck 1999; Gold 1985; Jewett 1985; Permin 1983; Stack 1985; Wesley 1988). Fourteen trials compared different dosage regimens of the same antibiotic (Adeboyeku 2011; Al-Ansari 2006; Aminimanizani 2002; Beringer 2012; Conway 1997; Hubert 2009; Keel 2011; McCabe 2013; Prayle 2013; Noah 2010; Riethmueller 2009; Semykin 2010; Turner 2013; Whitehead 2002). One trial was excluded as it compared two single drugs (Levy 1982) and another trial as it compared two different combinations of antibiotics (Blumer 2005). One trial compared intravenous antibiotics administered in hospital compared to at home (Donati 1987) and another trial looked at an eradication regimen (Kenny 2009). Five further trials

were excluded as allocation was not by randomisation and because there were marked differences in baseline characteristics between the treatment and comparison groups (Hoogkamp 1983; Hyatt 1981; Krause 1979; Nelson 1985; Roberts 1993). Two trials were excluded as they evaluated tools to assess treatment response (Hatziagorou 2013; Kuni 1992).

One trial included 30 participants. However, 17 of these received more than one course of treatment (Padoan 1987). In total, 40 courses of treatment took place (20 in each intervention group). The trial was cross-over in design; but re-randomisation took place between courses of treatment, resulting in some participants possibly receiving two or more courses of the same treatment, or a mixture of different treatments. Since the number of participants receiving each treatment was unclear, results could not be included in the analysis of this review and therefore the trial was excluded. Individual patient data are being requested from the authors of this trial so that data from this trial may be included in future updates (Padoan 1987).

Risk of bias in included studies

In order to assess the risk of bias in the trials, the methodological quality of each trial was assessed using criteria described by Schulz (Schulz 1995). For each trial the following were assessed: concealment of allocation schedule; generation of allocation sequences; inclusion in the analysis of all randomised participants; and double-blinding.

Allocation

One trial stated that treatment was allocated to participants using a computer-generated randomisation (Smith 1999); and one trial was stratified for age and disease severity during randomisation (Master 1997). We assessed these trials as having a low risk of bias. Five trials stated that allocation was randomised, but did not specify the method of generation, so we rated the risk of bias in each of these as unclear (Costantini 1982; Huang 1982; McCarty 1988; McLauglin 1983; Pedersen 1986). One trial used alternation but does not discuss how the first participant was randomised to their treatment group and we assessed this as inadequate, thus having a high risk of bias (Parry 1977).

Four trials were assessed as adequate, Master stated that the code was only broken on completion of the study (Master 1997); another trial stated they used sequentially numbered envelopes (McCarty 1988); a further trial employed sealed envelopes prepared by pharmacy (McLauglin 1983); and the fourth trial stated central randomisation (Smith 1999). We judged these trials to have a low risk of bias. We assessed one trial as inadequate, since the investigators used alternate allocation and so we judged this to have a high risk of bias (Parry 1977). We included this trial as a quasi-randomised trial. In the remaining three trials the method of allocation concealment was unclear and so we judged these to have an unclear risk of bias (Costantini 1982; Huang 1982; Pedersen 1986).

Blinding

Five of the trials were described as double-blinded (Huang 1982; Master 1997; McLauglin 1983; Smith 1999). In each trial, saline was used for the placebo injection. We judged these trials to have a low risk of bias. One trial did not explicitly state that blinding had taken place, but did state that both interventions were given with the same volume and in the same way, so it can be assumed that there was some degree of blinding leading to a low risk of bias (Pedersen 1986). Two further trials stated that no blinding had taken place, thus we deemed these to have a potential risk of bias (McCarty 1988; Parry 1977); and in the remaining trial it was not clear whether blinding had taken place and we judge this to have an unclear risk of bias (Costantini 1982).

Incomplete outcome data

An intention-to-treat analysis was not stated in any of the included trials. In four, however, there appeared to be no withdrawals (Costantini 1982; Huang 1982; McCarty 1988; Parry 1977). In one trial, seven of the 41 participants did not complete the trial, six from the single therapy group and one from the combination group (reasons given) (McLauglin 1983) and another described reasons why three participants out of a cohort of 20 withdrew (Pedersen 1986). One trial published a flow chart showing numbers randomized and included or excluded (with reasons) at each stage in paper (Master 1997). A further trial gave the numbers and reasons for withdrawals in a table (Smith 1999).

Effects of interventions

Only those primary and secondary outcomes of this review, which were reported within the included studies, are listed below. No trial included follow up for longer than six months.

Single compared to combination therapy

Pooling of results was difficult because of missing data, differences in method of expression of the results and missing standard deviations.

Primary outcomes

1. Clinical improvement

a. Effect on lung function

Seven of the eight trials included lung function as an outcome measure. However, there was great variety between the trials in the tests used, the time at measurement and the method of expression of the results.

Although the outcome measure given in our protocol was improvement in spirometric lung function, no trial included these data. Two trials measured mean FEV_1 and FVC at the end of the treatment course, expressed as per cent predicted (McLauglin 1983; Smith 1999). These trials were randomised and gave baseline data, clearly stating that there was no significant difference between the single and combination treatment groups at baseline. We therefore analysed these outcomes.

One trial did compare mean change in FEV_1 and FVC, expressed as per cent predicted, but did not include standard deviations (SD) in the results, so we could not include the data (Master 1997). No data were given in a further three trials (Huang 1982; McCarty 1988; Parry 1977) and one trial expressed the results in terms of a median and range (Pedersen 1986).

There were no significant differences between the single and combination treatment groups in the lung function parameters, which we were able to include.

b. Effect on clinical scores

Measures of change in clinical status were used in most trials. In all but two, either no data or measure of variance were given. One trial measured mean Schwachman score at the end of treatment (McLauglin 1983). This was a randomised trial with no significant difference between the groups at baseline. There was no significant difference between single and combination groups for this parameter.

2. Bacteriological improvement

a. Effect on sputum bacteriology

One trial reported change in sputum *P aeruginosa* density in colony forming units per gram (cfu/g) (Smith 1999). This trial showed a significant decrease in *P aeruginosa* density in both treatment groups, at the end of treatment, with a greater decrease in the combination group. The mean difference in the mean change in density was -1.60 (95% confidence interval (CI) -9.51 to 6.31), i.e. the mean decrease in *P aeruginosa* density was 1.6 cfu/g greater in the combination treatment group than for the single treatment group. However, on follow up, the density of *P aeruginosa* in the sputum was similar in both groups.

3. Effect on adverse events

Three trials reported adverse events (Master 1997; McCarty 1988; Smith 1999). The most commonly reported were: local erythema at the injection site; generalised rash; fever; renal impairment and proteinuria; auditory impairment; and hypersensitivity reaction, with no differences found between treatment groups.

Secondary outcomes

2. Clinical improvement

c. Hospitalisation

Two trials measured the number of participants readmitted to hospital within given time periods of one month (Huang 1982) and 80 days (Smith 1999). Huang found no significant difference between the two groups (Huang 1982). The results from the Smith trial favoured combination therapy with a Peto odds ratio of 0.30 (95% CI 0.12 to 0.73) (Smith 1999).

d. Effect on time to next course of antibiotics

Only one trial reported the effect on the time to next course of antibiotics (McLauglin 1983). There was no significant difference between the two groups.

3. Bacteriological improvement

a. Effect on inflammatory markers

One trial reported blood or sputum markers of inflammation (Smith 1999). This trial reported mean white blood cell (WBC) count at the end of the antibiotic course and involved treatment groups with similar baseline characteristics. There was no significant difference between the groups.

b. Effect on antibiotic resistant strains of P aeruginosa

Six of the eight trials examined sputum for drug sensitivity at the beginning of the trial; five of these defined sensitivity in terms of minimum inhibitory concentration (MIC). One trial found that the disc diffusion method did not identify resistant strains (Smith 1999). The trials varied in their definitions of resistance, e.g. resistance to tobramycin was defined as MIC greater than 8 µg/ml in one trial (McLauglin 1983) and as MIC greater than 32 µg/ml in another (Master 1997). No trial used antibiotic sensitivity in their entry criteria. In one trial, the bacteria were clearly sensitive to the antibiotics used (Pedersen 1986). This trial gave mean MIC values at baseline and the end of the treatment course and found no significant change. Parry stated MIC values for all the isolates for ticarcillin and carbenicillin, but did not define antibiotic resistance (Parry 1977). This trial found that the median MIC value for ticarcillin at the end of treatment was same as the pre-treatment value (3.1 µg/ml). One further trial stated that there was no significant difference between the single and combination groups at the beginning of the treatment period, and that emergence of resistance was not seen with any isolate (McCarty 1988). The two remaining trials gave the number or per cent of bacterial sensitivity, but did not comment on whether the two groups were significantly different at baseline (Costantini 1982; Huang 1982).

In the two trials included in the analysis, the number of participants developing resistant strains of *P aeruginosa* at baseline, end of treatment and follow up at between two and eight weeks was reported (McLauglin 1983; Smith 1999). For completeness, we have shown each of these analyses on the forest plot, as well as the difference between baseline and follow up in two of the trials. The second trial could not be represented in the latter analysis, as the total numbers of participants changed from baseline to follow up (Smith 1999). McLaughlin classified bacteria as resistant to tobramycin if the MIC was greater than 8 µg/ml and to azlocillin if the MIC was greater than 125 µg/ml (McLauglin 1983). Smith defined resistance to tobramycin if the MIC was greater than 8 µg/ml and for azlocillin, if the MIC was greater than 100 µg/ml (Smith 1999).

The result of the analysis showed that the difference between the single and combination therapy groups was not significant at baseline or at the end of the treatment course. At two to eight weeks follow up, both trials individually showed an increase in the number of participants with resistant strains of *P aeruginosa* with single therapy, but the aggregated results showed that the difference was not significant. However, the aggregation of the studies at follow up included a relatively small number of participants, with a total of 40 participants in each group. Calculation of the difference between the numbers of participants with resistant strains from baseline to two to eight weeks post-treatment also favoured combination treatment, although the difference was not significant.

Symptomatic compared to elective regimen

One trial studied outcomes at the end of an elective course of antibiotics and again after a second course three months later, using a cross-over design (Pedersen 1986). Results were expressed as median and range in all outcomes and therefore meta-analysis using RevMan within this review was not possible.

Beta-lactam versus beta-lactam-aminoglycoside combination compared to aminoglycoside versus beta-lactam-aminoglycoside combination

Insufficient data on outcome measures were given in all of the three comparisons of aminoglycoside with aminoglycoside-beta-lactam combination therapy and therefore meta-analysis using RevMan within this review was not possible (Costantini 1982; Master 1997; Parry 1977).

DISCUSSION

Choice of anti-pseudomonal antibiotic and the use of single or combined therapy are controversial areas in the treatment of respiratory infection in cystic fibrosis (CF). Current practice is variable. Advantages of combination therapy include a wider range of modes of action, possible synergy and reduction of resistant organisms; whereas advantages of monotherapy include lower cost and reduction of drug-related toxicity. From the perspective of the individual with CF, the use of a beta-lactam alone offers such advantages as ease of administration and no requirement for blood sampling to measure aminoglycoside levels. Current evidence does not provide a clear answer and, therefore, the use of intravenous (IV) antibiotic therapy in CF requires further evaluation.

This review has found eight trials that examined the effect of single compared to combination IV anti-pseudomonal antibiotic therapy for acute exacerbations in CF. There was considerable heterogeneity amongst these trials, which led to difficulties in performing the review and interpreting the results. We were unable to perform adequate meta-analysis for most outcome measures. The overall results showed that there was no significant difference between monotherapy and combination therapy in terms of clinical outcome measures, such as lung function and symptom scores, or in terms of bacteriological outcomes.

These results should be interpreted with caution. All but two of the included trials were published between 1977 and 1988; these were single-centre trials with flaws in the randomisation process. Furthermore, the sample sizes were too small to have the power to detect a difference between the two groups. Three of the eight trials were not published as full papers. Overall, the methodological quality was poor: only one trial was considered to have adequate randomisation allocation and concealment (Smith 1999); only four were double-blinded; and none stated any intention-to-treat analysis. The review raises some interesting methodological issues, including the difficulties of pooling results from a number of small trials that are of poor quality.

The trials were very heterogeneous in terms of design, drugs used, duration of treatment and follow up and outcome measures. The combinations of antibiotics in each trial were different and therefore we aggregated the two groups according to the class of antibiotics: beta-lactams and aminoglycosides. Inconsistencies in expression of results and statistical reporting made meta-analysis impossible in most cases and individual patient data would need to be collected from authors to clarify these issues. It was disappointing that only four trials included data that were possible to analyse. Most of the outcome measures analysed included data from only one or two trials. Due to the small number of trials, it was not possible to examine for effects of trial quality, type of antibiotic or treatment regimen using sensitivity and subgroup analyses.

In our protocol we stated that we would like to compare the differences between adults and children. This was not possible, as no trial looked at children alone. No trial looked specifically at quality of life scores. There were no long-term outcome measures such as the development of resistant bacterial strains or side effects, such as ototoxicity to aminoglycosides. This may be relevant particularly to children, in whom there is emerging evidence of ototoxicity due to chronic use of aminoglycosides (Katbamna 1998; Mulherin 1991). Only four trials stated that they had looked for adverse effects; therefore there may have been side effects that have not been identified. The longest follow up in this systematic review was six months, but the majority of trials did not have any follow up after the acute course of antibiotics. Potential problems with development of drug-resistant bacteria, which may shorten long-term survival, may not be detected in trials of such short duration covered by this review.

AUTHORS' CONCLUSIONS

Implications for practice

The results of this review, regarding the benefits and risks of single versus combination anti-pseudomonal antibiotic therapy in terms of lung function and clinical outcome in people with CF, are inconclusive. In particular, side effects of treatment have not been investigated to a sufficient level, and therefore it is not possible to conclude from this trial that either treatment choice is safe compared to the other. All the trials included in the review looked at different antibiotics, both as a single anti-pseudomonal agent and in combination therapy and therefore the drug(s) of choice remains uncertain.

Implications for research

This systematic review raises important questions regarding the use of antibiotic combinations for acute exacerbations in CF, which need to be answered by further randomised controlled trials. These trials need to be designed to overcome the methodological issues highlighted by this review, such as randomisation allocation, blinding, adequate power and long-term follow up. There is a particular need to compare the effects of single anti-pseudomonal therapy versus a combination of anti-pseudomonal antibiotics in terms of long-term toxicity and the development of drug-resistant organisms. An observational cohort study, co-ordinated through national databases, of centres whose practice is either monotherapy or combination therapy may give useful information on a large number of participants for these outcomes. Results need to be standardised to a consistent method of reporting, for example, mean and SD change in FEV_1 and FVC expressed as % predicted in order to validate the pooling of results from multiple trials.

This could be particularly pertinent to children, in view of the emergence of long-term side effects such as ototoxicity with cumulative use of aminoglycoside antibiotics. It would be important to address this issue within a trial.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Costantini 1982

Methods	No withdrawals, symptomatic regimen.
Participants	28 participants randomised. PsA colonised, age not stated.
Interventions	Carbenicillin 675 mg/kg/day vs sisomycin 10.5 mg/kg/day vs carbenicillin 590 mg/kg/day plus sisomycin. Variable duration of course.
Outcomes	CXR and symptom scores, bacteriology, development of resistant strains.
Notes	Abstract: no data.

Risk of bias

Bias	Authors' judgement	Support for judgement

Costantini 1982 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Randomly assigned, but no further details given.
Allocation concealment (selection bias)	Unclear risk	Not directly discussed, but referred to as a controlled clinical trial.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not discussed, but appears to be no withdrawals.

Huang 1982

Methods	Double-blind trial, no withdrawals, symptomatic regimen. Parallel trial.
Participants	16 participants randomised. Mixed PsA and non-PsA, age not stated.
Interventions	Ticarcillin 300 mg/kg/day vs ticarcillin plus tobramycin 6 mg/kg/day. 10-day course.
Outcomes	Lung function, number readmitted within one month, CXR and symptom scores, bacteriology.
Notes	Abstract: Lung function, CXR and symptom score data not given.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Mentions randomisation code, but no details given of how it was generated.
Allocation concealment (selection bias)	Unclear risk	Mentions randomisation code, but no details of how this may have been concealed.
Blinding (performance bias and detection bias) All outcomes	Low risk	Stated as double-blind, but no further details given.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not discussed, but appears to be no drop outs or withdrawals.

Master 1997

Methods	Double-blind trial, symptomatic regimen. Parallel trial.
Participants	83 participants randomised. PsA colonised, age not stated. 51 participants randomized, of these, 21 in the tobramycin and ceftazidime group (51 admissions assessed) and 23 in the tobramycin group (47 admissions assessed). 12 participants in the tobramycin and ceftazidime group and 9 participants in the tobramycin group were eligible for long-term assess-

Master 1997 *(Continued)*

	ment. Participants in both groups experienced an average of 3.1 and 3.0 admissions, respectively, for IV antibiotic treatment during the study period. Tobramycin and ceftazidime group: mean (SD) age 16 (7) years Tobramycin group: mean (SD) age 14 (5) years
Interventions	Tobramycin 24-hourly vs tobramycin and ceftazidime 8-hourly. 10-day course.
Outcomes	Lung function, adverse events.
Notes	Full paper. Exclusion criteria stated. The study was halted for a period of 3 months when one of the study patients committed suicide by utilizing a study syringe to administer a lethal substance. The study was recommenced after the coroner's finding that this was an unrelated death. During this time of study suspension, there were 14 admissions of patients previously enrolled. Data from these admissions were not included.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was stratified for age and disease severity.
Allocation concealment (selection bias)	Low risk	The treatment code was broken only at the completion of the study.
Blinding (performance bias and detection bias) All outcomes	Low risk	Medical staff, nursing staff and participants were blinded to the treatment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Flow chart showing numbers randomized and included/excluded (with reasons) at each stage in paper.

McCarty 1988

Methods	Not double blind, no withdrawals, symptomatic regimen.
Participants	17 participants treated (8 in piperacillin group, 9 in piperacillin plus tobramycin group); 3 participants treated on more than one occasion (2 initially in piperacillin group and several months later randomised to other group; 1 participant enrolled 2x in piperacillin group). 20 data sets. Mixed PsA and non-PsA, aged 2 to 12 years.
Interventions	Piperacillin 600 mg/kg/day vs piperacillin plus tobramycin 8 to 10 mg/kg/day, minimum duration 10 days.
Outcomes	Lung function, weight, symptom scores, adverse events, bacteriology.
Notes	No data for lung function, weight and symptom scores.

Risk of bias

McCarty 1988 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Treatment randomly assigned, no further details.
Allocation concealment (selection bias)	Low risk	Used sequentially numbered envelopes.
Blinding (performance bias and detection bias) All outcomes	High risk	Not double-blind.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Clear explanation of participants in groups, no drop outs occurred.

McLauglin 1983

Methods	Double-blind trial, symptomatic regimen.
Participants	41 participants randomised (11 years and older), 34 completed. No ITT analysis. Mean age 21 years. PsA in 98%.
Interventions	Azlocillin 300 mg/kg/day, 4-hourly plus placebo vs azlocillin plus tobramycin 6 mg/kg/day, 8-hourly. 10-day course. Group 1: azlocillin 300 mg/kg/day in 6 divided doses plus tobramycin (6 mg/kg per day) in 3 divided doses. Group 2:azlocillin 300 mg/kg/day in 6 divided doses plus placebo (0.85% NaCl) in 3 divided doses.
Outcomes	Lung function, symptom scores, development of resistant strains, time to next course.
Notes	Participants were white, of various socioeconomic backgrounds and lived in New England. Exclusion criteria stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants randomly selected, but no further details given.
Allocation concealment (selection bias)	Low risk	Hospital pharmacist used consecutively numbered sealed envelopes.
Blinding (performance bias and detection bias) All outcomes	Low risk	Neither participants or clinicians knew which regimen they were receiving.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2 participants in azlocillin plus placebo group withdrawn due to suspected drug-related complications; 2 participants discharged improved before completion of antibiotic course; 3 withdrawn due to incomplete outcome data.

Parry 1977

Methods	Not double blind, alternate allocation, no withdrawals, symptomatic regimen. Parallel trial.
Participants	21 male, 21 female, mean age 15.1 years. PsA colonised. 14 participants in each of 3 treatment groups. Group 1 (ticarcillin): 8 male, 6 female; mean (range) age 16.1 (2 - 30) years Group 2 (ticarcillin & gentamicin): 7 males, 7 females: mean (range) age 16.4 (4 - 30) years Group 3 (gentamicin):6 males, 8 females; mean (range) 12.9 (5 - 31) years
Interventions	Ticarcillin 300 mg/kg/day, 4-hourly vs gentamicin 3 - 4 mg/kg/day (adults), 4 - 7 mg/kg/day (children) vs combination. Variable length of course.
Outcomes	Lung function, bacteriology, adverse events, CBC, sedimentation rate, urinalysis, serum electrolytes, blood urea nitrogen, creatinine, liver function tests, chest radiographs, blood gas determinations, sputum cultures, change in cough, weight.
Notes	No data available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No discussion of how first participant was assigned to which treatment group.
Allocation concealment (selection bias)	High risk	Alternation.
Blinding (performance bias and detection bias) All outcomes	High risk	Drugs administered in different ways so clinicians and participants couldn't be blinded, no discussion of blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No drop outs or withdrawals.

Pedersen 1986

Methods	Not double blind, elective regimen, crossover - 3 months in between treatment arms.
Participants	20 participants (10 male, 10 female), mean age 12.6 years. PsA colonised. 3 drop outs, 17 completed trial.
Interventions	Ceftazidime 150 mg/kg/day, 8-hourly vs ceftazidime plus tobramycin 10 mg/kg/day, 8-hourly, 14-day course.
Outcomes	Lung function, inflammatory markers, development of resistant strains.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Pedersen 1986 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Described as randomised, but no details of method given.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Low risk	Both interventions given with same volume and in same way.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 participants excluded - reasons given (bacteriological resistance developed between treatment arms in 2 participants and a 3rd withdrew on first day of 2nd treatment arm due to nausea).

Smith 1999

Methods	Double-blind, computer-generated randomisation, symptomatic regimen. Parallel trial.
Participants	37 male, 39 female, mean age 16.3 years. 111 participants enrolled, 35 withdrawn. 76 participants in total aged 6 - 18 years. PsA colonised. Group 1 (azlocillin): 33 participants (19 male) mean (SD) age 16.07 (7.4) years Group 2 (azlocillin & tobramycin): 43 participants (18 male) mean (SD) age 16.53 (6.9) years
Interventions	Azlocillin 450 mg/kg/day, 4-hourly plus placebo vs azlocillin plus tobramycin 240 mg/m2/day, 6-hourly, 14 days course.
Outcomes	Lung function, time to next admission, symptom scores, adverse events, bacteriology, inflammatory markers, resistant strains.
Notes	No data for symptom scores.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation balance by FVC and center.
Allocation concealment (selection bias)	Low risk	Code generated by research pharmacist at the core center.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and clinicians blinded, serum concentrations monitored by un-blinded 3rd party (research pharmacist).
Incomplete outcome data (attrition bias) All outcomes	Low risk	35 participants withdrawn (21 from azlocillin group), reasons given in a table.

CBC: complete blood count
CXR: chest x-ray
ITT: intention-to-treat
PsA: *Pseudomonas aeruginosa*

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

Study	Reason for exclusion
Adeboyeku 2011	Comparison of twice daily vs three times daily antibiotics, not single vs combination.
Al-Ansari 2006	Comparison of once vs multiple daily dosing, not single vs combination.
Aminimanizani 2002	Comparison of single vs multiple daily dosing, not single vs combination.
Balsamo 1986	Comparison of single agent compared with 2 other antibiotics (i.e. drug A vs drug B plus drug C).
Beaudry 1980	Comparison of single agent compared with 2 other antibiotics (i.e. drug A vs drug B plus drug C).
Beringer 2012	Not a comparison of single vs combination antibiotics; a comparison of a single intravenous dose of an antibiotic and multiple oral doses of the same antibiotic.
Blumer 2005	Comparison of two combination regimens.
Bosso 1988	Comparison of single agent compared with 2 other antibiotics (i.e. drug A vs drug B plus drug C).
Church 1997	Comparison of single agent compared with 2 other antibiotics (i.e. drug A vs drug B plus drug C).
Conway 1997	Comparison of colistin with multiple antibiotic combinations.
De Boeck 1989	Comparison of single agent compared with 2 other antibiotics (i.e. drug A vs drug B plus drug C).
De Boeck 1999	Comparison of single agent compared with 2 other antibiotics (i.e. drug A vs drug B plus drug C).
Donati 1987	Home vs hospital therapy, not single vs combination.
Gold 1985	Comparison of single agent compared with 2 other antibiotics (i.e. drug A vs drug B plus drug C).
Hatziagorou 2013	Not a comparison of a single vs combination antibiotics; evaluation of tool to assess treatment response in children.
Hoogkamp 1983	Non-randomised study: first 7 participants allocated to single treatment; next 7 to combination treatment with marked differences in baseline characteristics.
Hubert 2009	Comparison of intermittent vs continuous infusions, not single vs combination.
Hyatt 1981	Comparison of anti-staphylococcal drug (oxacillin) vs oxacillin plus 2 anti-pseudomonal drugs.
Jewett 1985	Comparison of single agent compared with 2 other antibiotics (i.e. drug A vs drug B plus drug C).
Keel 2011	Not a comparison of a single vs combination antibiotic; comparison of intravenous and oral versions of the same agent.
Kenny 2009	Study of eradication of *Pseudomonas aeruginosa*, not a comparison of single vs combination.
Krause 1979	Pseudo-randomised study. Treatment and comparison groups were not sufficiently similar at baseline.
Kuni 1992	Not a comparison of single vs combination antibiotics.
Levy 1982	Comparison of 2 single agents.

Study	Reason for exclusion
McCabe 2013	Not a comparison of single vs combination antibiotics; evaluation of a twice-daily tobramycin regimen.
Nelson 1985	Review article on single vs combination antibiotic treatment, i.e. not an RCT.
Noah 2010	Inhaled vs systemic antibiotics.
Padoan 1987	Reported number of courses of treatment instead of number of people included. Some participants may have been counted twice or included in both treatment group therefore analysis unclear.
Permin 1983	Comparison of single agent compared with 2 other antibiotics (i.e. drug A vs drug B plus drug C).
Prayle 2013	Not a comparison of single vs combination antibiotics; comparison of morning vs evening intravenous tobramycin.
Riethmueller 2009	Continuous vs intermittent infusions.
Roberts 1993	Randomisation method unclear - participants appeared to have been randomised to single or combination therapy each morning using a cross-over method.
Semykin 2010	Not a comparison of single vs combination antibiotics; trial of inhaled tobramycin therapy.
Stack 1985	Comparison of single agent compared with two other antibiotics (i.e. drug A vs drug B plus drug C).
Turner 2013	Not a comparison of single vs combination antibiotics; study of continuous vs intermittent infusion piperacillin-tazobactam.
Wesley 1988	Comparison of single agent compared with 2 other antibiotics (i.e. drug A vs drug B plus drug C).
Whitehead 2002	Efficacy of once daily tobramycin, not a comparison of single vs combination agents.

CXR: chest X-ray
vs: versus

DATA AND ANALYSES

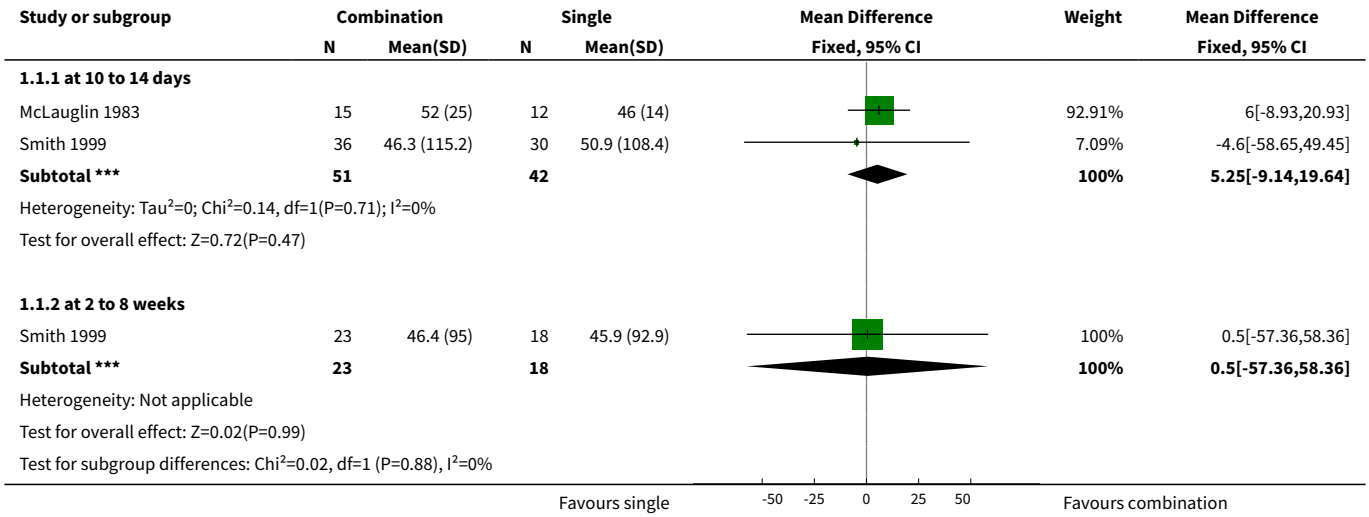
Comparison 1. Single versus combination, symptomatic regimen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean FEV_1 at end of course (% pred)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 at 10 to 14 days	2	93	Mean Difference (IV, Fixed, 95% CI)	5.25 [-9.14, 19.64]
1.2 at 2 to 8 weeks	1	41	Mean Difference (IV, Fixed, 95% CI)	0.5 [-57.36, 58.36]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2 Mean FVC at end of course (% pred)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 at 10 to 14 days	2	93	Mean Difference (IV, Fixed, 95% CI)	1.84 [-11.44, 15.12]
2.2 at 2 to 8 weeks	1	41	Mean Difference (IV, Fixed, 95% CI)	6.90 [-50.50, 64.30]
3 Mean RV at end of course (% pred)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Mean TLC at end of course (% pred)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5 Mean RV/TLC at end of course (% pred)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 at 2 weeks	1	64	Mean Difference (IV, Fixed, 95% CI)	-1.40 [-40.68, 37.88]
5.2 At 2 to 8 weeks	1	40	Mean Difference (IV, Fixed, 95% CI)	-5.20 [-54.27, 43.87]
6 Mean PFR at end of course (% pred)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 at 10 to 14 days	2	91	Mean Difference (IV, Fixed, 95% CI)	3.21 [-11.49, 17.91]
6.2 At 2 to 8 weeks	1	40	Mean Difference (IV, Fixed, 95% CI)	2.30 [-60.90, 65.50]
7 Mean MMEF at end of course (% pred)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 at 10 to 14 days	2	91	Mean Difference (IV, Fixed, 95% CI)	7.17 [-8.22, 22.55]
7.2 At 2 to 8 weeks	1	40	Mean Difference (IV, Fixed, 95% CI)	-1.90 [-73.27, 69.47]
8 Mean Schwachman score at end of course	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9 Number of Pseudomonas isolates eradi-cated at end of course	3	72	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.63 [2.12, 14.94]
10 Mean change Pseudomonas density in cfu/g at end of course	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11 Number adverse events	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only

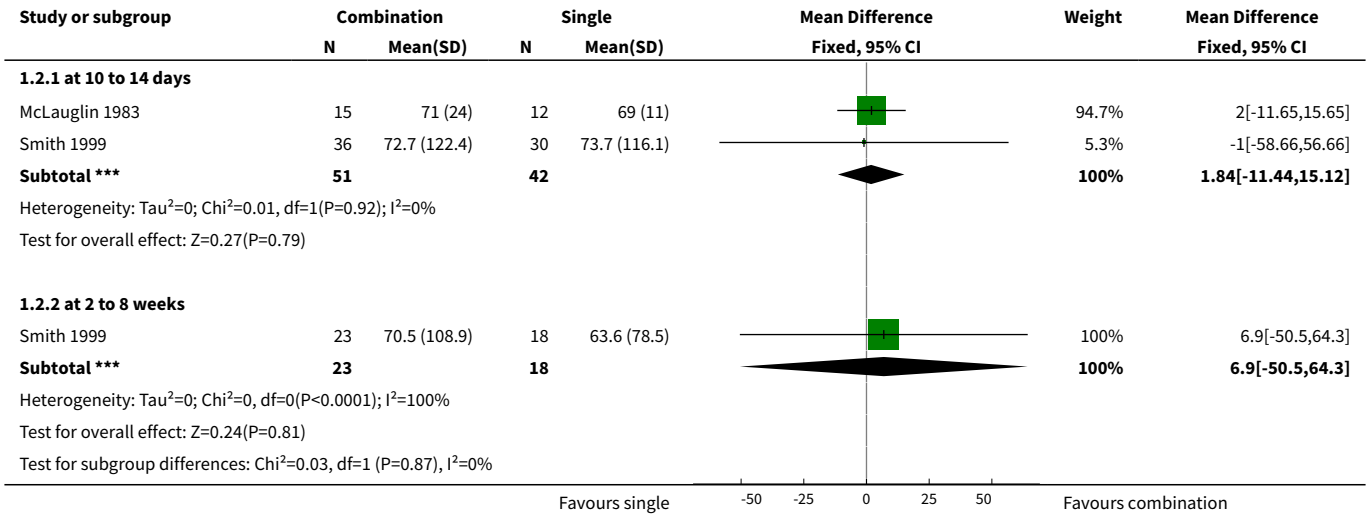
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 local erythema / irritation	2	131	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.46 [0.09, 2.36]
11.2 generalised rash	1	20	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.16 [0.12, 316.67]
11.3 fever	1	20	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.81 [0.05, 14.14]
11.4 renal impairment (increased creatinine by 50%)	1	80	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.54 [0.15, 15.56]
11.5 auditory impairment	1	76	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.86 [0.11, 305.44]
11.6 proteinuria	1	63	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.62 [0.68, 19.30]
12 Number readmitted	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
12.1 in 1 month	1	16	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.01, 1.30]
12.2 in 80 days	1	76	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.30 [0.12, 0.73]
13 Mean time to next course of antibiotics (weeks)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
14 Mean WBC count at end of course	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
15 Number resistant strains	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
15.1 at baseline	2	140	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.83 [0.38, 1.82]
15.2 at end of course	2	99	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.44 [0.94, 6.32]
15.3 at 2 to 8 weeks	2	76	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.44 [0.17, 1.14]
15.4 Difference between baseline and 2 to 8 weeks	1	29	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.27 [0.06, 1.18]

Analysis 1.1. Comparison 1 Single versus combination, symptomatic regimen, Outcome 1 Mean FEV_1 at end of course (% pred).



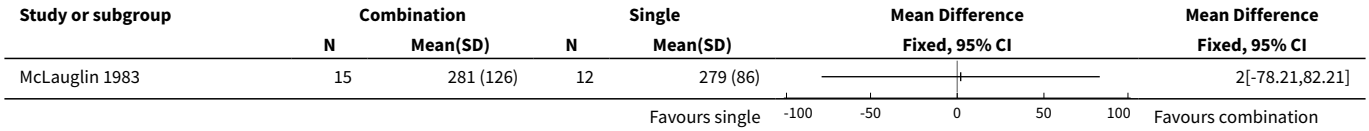
Study or subgroup	Combination N	Combination Mean(SD)	Single N	Single Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.1.1 at 10 to 14 days							
McLauglin 1983	15	52 (25)	12	46 (14)		92.91%	6[-8.93,20.93]
Smith 1999	36	46.3 (115.2)	30	50.9 (108.4)		7.09%	-4.6[-58.65,49.45]
Subtotal ***	**51**		**42**			**100%**	**5.25[-9.14,19.64]**
Heterogeneity: Tau^2=0; Chi^2=0.14, df=1(P=0.71); I^2=0%							
Test for overall effect: Z=0.72(P=0.47)							
1.1.2 at 2 to 8 weeks							
Smith 1999	23	46.4 (95)	18	45.9 (92.9)		100%	0.5[-57.36,58.36]
Subtotal ***	**23**		**18**			**100%**	**0.5[-57.36,58.36]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.02(P=0.99)							
Test for subgroup differences: Chi^2=0.02, df=1 (P=0.88), I^2=0%							

Analysis 1.2. Comparison 1 Single versus combination, symptomatic regimen, Outcome 2 Mean FVC at end of course (% pred).



Study or subgroup	Combination N	Combination Mean(SD)	Single N	Single Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.2.1 at 10 to 14 days							
McLauglin 1983	15	71 (24)	12	69 (11)		94.7%	2[-11.65,15.65]
Smith 1999	36	72.7 (122.4)	30	73.7 (116.1)		5.3%	-1[-58.66,56.66]
Subtotal ***	**51**		**42**			**100%**	**1.84[-11.44,15.12]**
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.92); I^2=0%							
Test for overall effect: Z=0.27(P=0.79)							
1.2.2 at 2 to 8 weeks							
Smith 1999	23	70.5 (108.9)	18	63.6 (78.5)		100%	6.9[-50.5,64.3]
Subtotal ***	**23**		**18**			**100%**	**6.9[-50.5,64.3]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%							
Test for overall effect: Z=0.24(P=0.81)							
Test for subgroup differences: Chi^2=0.03, df=1 (P=0.87), I^2=0%							

Analysis 1.3. Comparison 1 Single versus combination, symptomatic regimen, Outcome 3 Mean RV at end of course (% pred).



Study or subgroup	Combination N	Combination Mean(SD)	Single N	Single Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
McLauglin 1983	15	281 (126)	12	279 (86)		2[-78.21,82.21]

Analysis 1.4. Comparison 1 Single versus combination, symptomatic regimen, Outcome 4 Mean TLC at end of course (% pred).

Study or subgroup	Combination N	Combination Mean(SD)	Single N	Single Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
McLaughlin 1983	15	117 (21)	12	118 (19)		-1[-16.12,14.12]

Favours single -20 -10 0 10 20 Favours combination

Analysis 1.5. Comparison 1 Single versus combination, symptomatic regimen, Outcome 5 Mean RV/TLC at end of course (% pred).

Study or subgroup	Combination N	Combination Mean(SD)	Single N	Single Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.5.1 at 2 weeks							
Smith 1999	35	42.7 (88.2)	29	44.1 (72.2)		100%	-1.4[-40.68,37.88]
Subtotal ***	**35**		**29**			**100%**	**-1.4[-40.68,37.88]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.07(P=0.94)							
1.5.2 At 2 to 8 weeks							
Smith 1999	22	45.9 (73.6)	18	51.1 (82.7)		100%	-5.2[-54.27,43.87]
Subtotal ***	**22**		**18**			**100%**	**-5.2[-54.27,43.87]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.21(P=0.84)							
Test for subgroup differences: Chi^2=0.01, df=1 (P=0.91), I^2=0%							

Favours single -50 -25 0 25 50 Favours combination

Analysis 1.6. Comparison 1 Single versus combination, symptomatic regimen, Outcome 6 Mean PFR at end of course (% pred).

Study or subgroup	Combination N	Combination Mean(SD)	Single N	Single Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.6.1 at 10 to 14 days							
McLaughlin 1983	15	67 (21)	12	63 (19)		94.52%	4[-11.12,19.12]
Smith 1999	35	54.7 (117.7)	29	65.1 (135.2)		5.48%	-10.4[-73.18,52.38]
Subtotal ***	**50**		**41**			**100%**	**3.21[-11.49,17.91]**
Heterogeneity: Tau^2=0; Chi^2=0.19, df=1(P=0.66); I^2=0%							
Test for overall effect: Z=0.43(P=0.67)							
1.6.2 At 2 to 8 weeks							
Smith 1999	22	61.9 (106.5)	18	59.6 (97.2)		100%	2.3[-60.9,65.5]
Subtotal ***	**22**		**18**			**100%**	**2.3[-60.9,65.5]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.07(P=0.94)							
Test for subgroup differences: Chi^2=0, df=1 (P=0.98), I^2=0%							

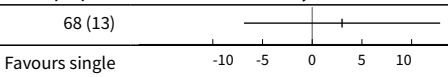
Favours single -100 -50 0 50 100 Favours combination

Analysis 1.7. Comparison 1 Single versus combination, symptomatic regimen, Outcome 7 Mean MMEF at end of course (% pred).

Study or subgroup	Combination N	Combination Mean(SD)	Single N	Single Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.7.1 at 10 to 14 days							
McLauglin 1983	15	30 (27)	12	22 (14)		94.88%	8[-7.79,23.79]
Smith 1999	35	25.2 (111.8)	29	33.5 (156.7)		5.12%	-8.3[-76.31,59.71]
Subtotal ***	**50**		**41**			**100%**	**7.17[-8.22,22.55]**
Heterogeneity: Tau^2=0; Chi^2=0.21, df=1(P=0.65); I^2=0%							
Test for overall effect: Z=0.91(P=0.36)							
1.7.2 At 2 to 8 weeks							
Smith 1999	22	25.8 (94.8)	18	27.7 (128.6)		100%	-1.9[-73.27,69.47]
Subtotal ***	**22**		**18**			**100%**	**-1.9[-73.27,69.47]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.05(P=0.96)							
Test for subgroup differences: Chi^2=0.06, df=1 (P=0.81), I^2=0%							

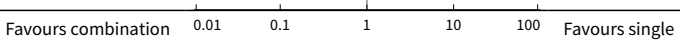
Analysis 1.8. Comparison 1 Single versus combination, symptomatic regimen, Outcome 8 Mean Schwachman score at end of course.

Study or subgroup	Combination N	Combination Mean(SD)	Single N	Single Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
McLauglin 1983	15	71 (13)	12	68 (13)		3[-6.87,12.87]



Analysis 1.9. Comparison 1 Single versus combination, symptomatic regimen, Outcome 9 Number of Pseudomonas isolates eradicated at end of course.

Study or subgroup	Combination n/N	Single n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Costantini 1982	6/11	0/7		24.99%	10.16[1.44,71.65]
Huang 1982	3/10	0/6		15.13%	6.34[0.51,78.02]
McCarty 1988	12/19	5/19		59.88%	4.27[1.21,15.07]
Total (95% CI)	**40**	**32**		**100%**	**5.63[2.12,14.94]**
Total events: 21 (Combination), 5 (Single)					
Heterogeneity: Tau^2=0; Chi^2=0.54, df=2(P=0.76); I^2=0%					
Test for overall effect: Z=3.47(P=0)					



Analysis 1.10. Comparison 1 Single versus combination, symptomatic regimen, Outcome 10 Mean change Pseudomonas density in cfu/g at end of course.

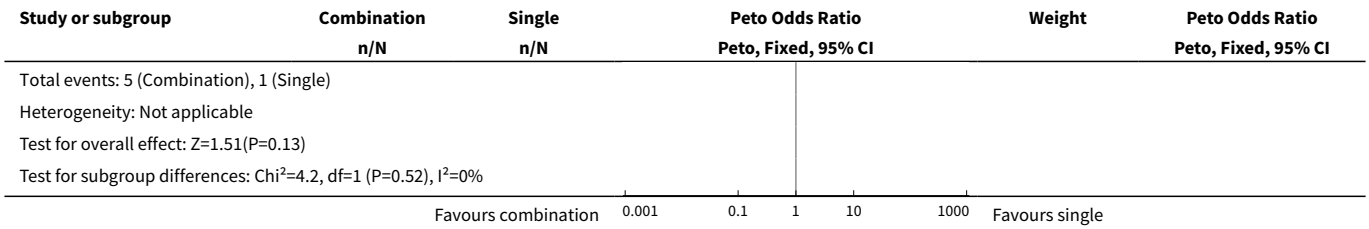
Study or subgroup	Combination N	Combination Mean(SD)	Single N	Single Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Smith 1999	43	5.3 (19.7)	33	6.9 (15.5)		-1.6[-9.51,6.31]

Favours single -10 -5 0 5 10 Favours combination

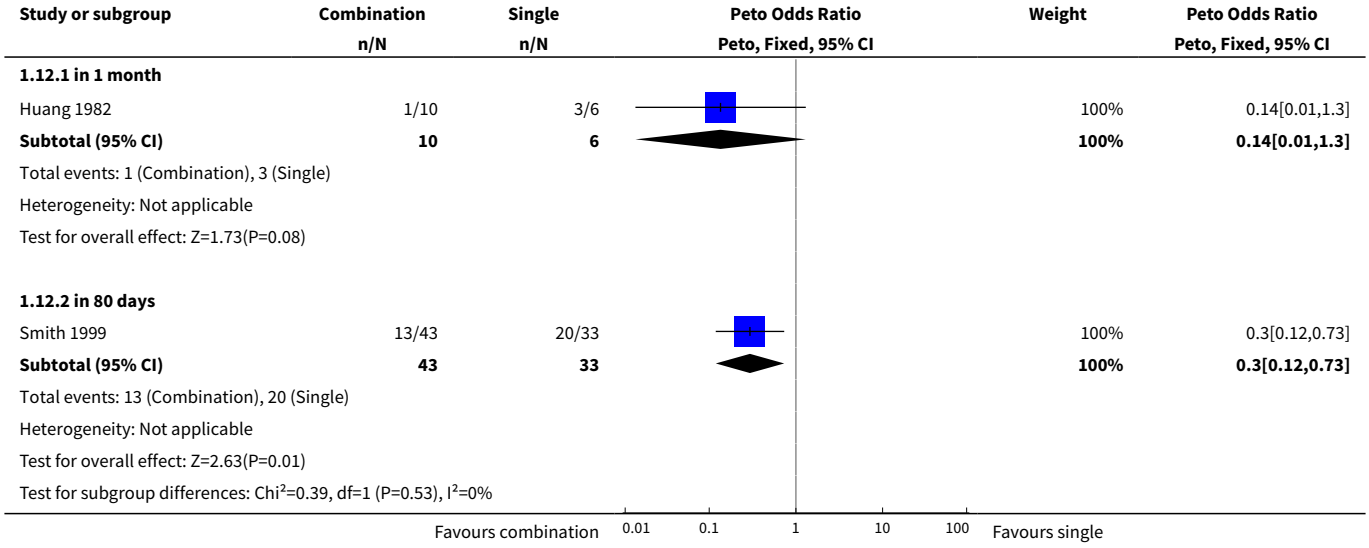
Analysis 1.11. Comparison 1 Single versus combination, symptomatic regimen, Outcome 11 Number adverse events.

Study or subgroup	Combination n/N	Single n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.11.1 local erythema / irritation					
McCarty 1988	0/11	1/9		17.06%	0.11[0,5.57]
Smith 1999	2/57	3/54		82.94%	0.62[0.1,3.72]
Subtotal (95% CI)	**68**	**63**		**100%**	**0.46[0.09,2.36]**
Total events: 2 (Combination), 4 (Single)					
Heterogeneity: Tau^2=0; Chi^2=0.63, df=1(P=0.43); I^2=0%					
Test for overall effect: Z=0.93(P=0.35)					
1.11.2 generalised rash					
McCarty 1988	1/11	0/9		100%	6.16[0.12,316.67]
Subtotal (95% CI)	**11**	**9**		**100%**	**6.16[0.12,316.67]**
Total events: 1 (Combination), 0 (Single)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.9(P=0.37)					
1.11.3 fever					
McCarty 1988	1/11	1/9		100%	0.81[0.05,14.14]
Subtotal (95% CI)	**11**	**9**		**100%**	**0.81[0.05,14.14]**
Total events: 1 (Combination), 1 (Single)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.15(P=0.88)					
1.11.4 renal impairment (increased creatinine by 50%)					
Smith 1999	2/45	1/35		100%	1.54[0.15,15.56]
Subtotal (95% CI)	**45**	**35**		**100%**	**1.54[0.15,15.56]**
Total events: 2 (Combination), 1 (Single)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.37(P=0.71)					
1.11.5 auditory impairment					
Smith 1999	1/43	0/33		100%	5.86[0.11,305.44]
Subtotal (95% CI)	**43**	**33**		**100%**	**5.86[0.11,305.44]**
Total events: 1 (Combination), 0 (Single)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.88(P=0.38)					
1.11.6 proteinuria					
Smith 1999	5/34	1/29		100%	3.62[0.68,19.3]
Subtotal (95% CI)	**34**	**29**		**100%**	**3.62[0.68,19.3]**

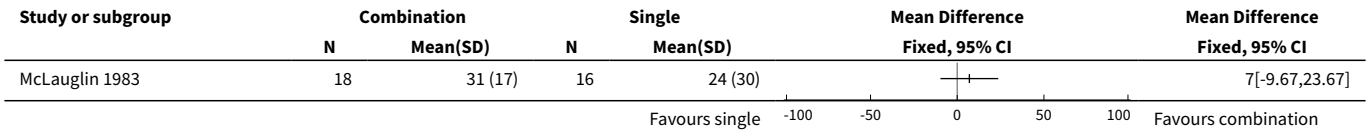
Favours combination 0.001 0.1 1 10 1000 Favours single



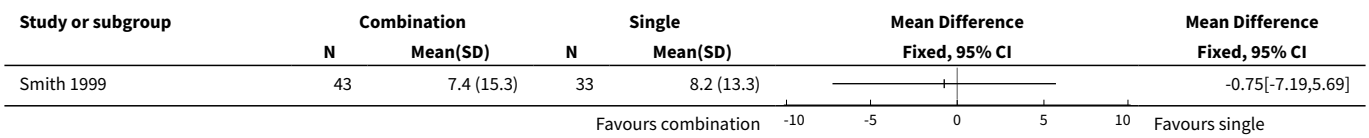
Analysis 1.12. Comparison 1 Single versus combination, symptomatic regimen, Outcome 12 Number readmitted.



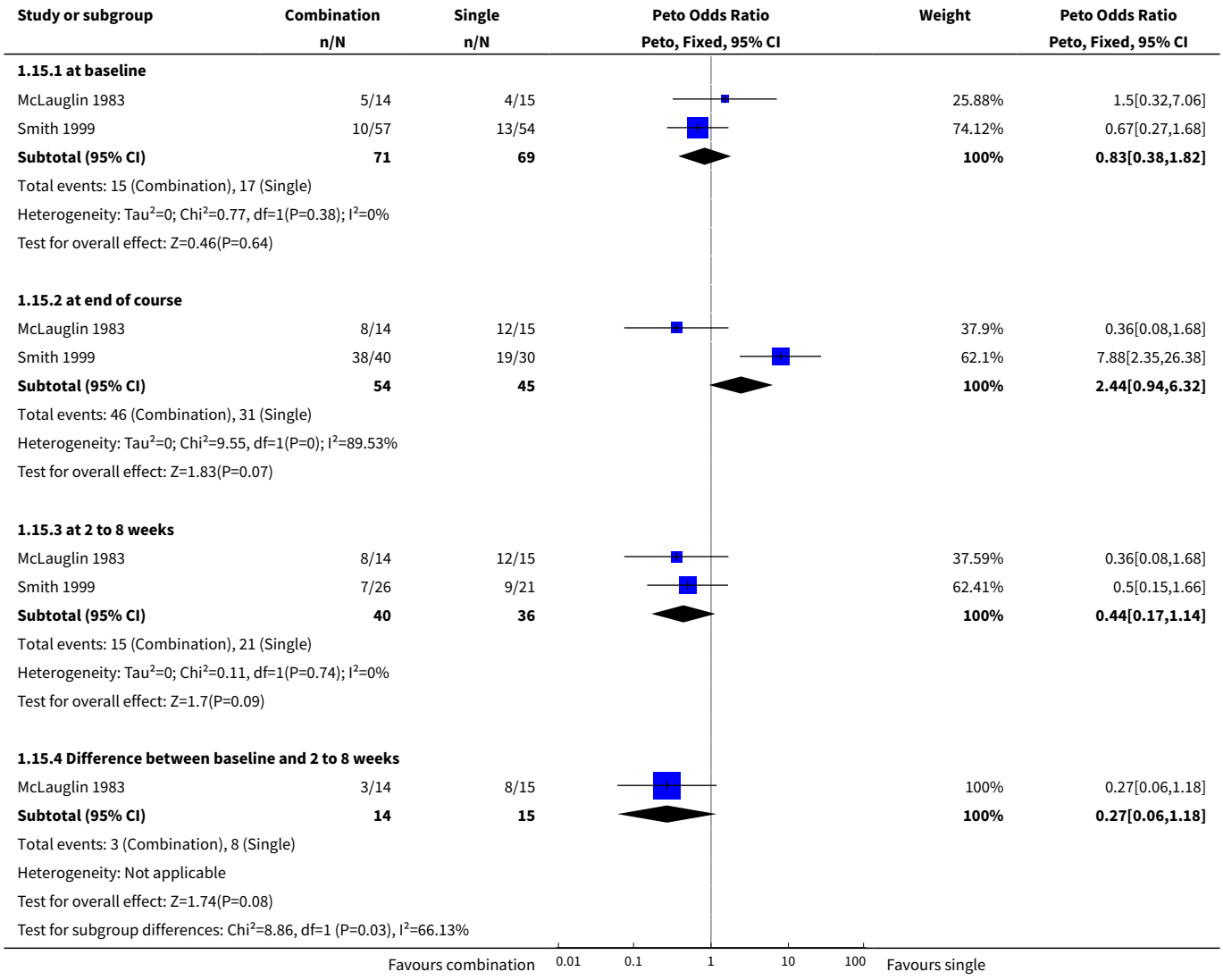
Analysis 1.13. Comparison 1 Single versus combination, symptomatic regimen, Outcome 13 Mean time to next course of antibiotics (weeks).



Analysis 1.14. Comparison 1 Single versus combination, symptomatic regimen, Outcome 14 Mean WBC count at end of course.



Analysis 1.15. Comparison 1 Single versus combination, symptomatic regimen, Outcome 15 Number resistant strains.



WHAT'S NEW

Date	Event	Description
14 October 2016	New search has been performed	A search of the Cystic Fibrosis and Genetic Disorders Review Group's Cystic Fibrosis Trials Register identified three new references that were potentially eligible for inclusion in the review. One reference was an additional reference to an already excluded trial (Blumer 2005); the remaining two references to two trials were also excluded (Prayle 2013; Turner 2013).
14 October 2016	New citation required but conclusions have not changed	Dr Alison Scott has replaced Nikki Jahnke on the review team. The review title has been amended to reflect that the therapies included focus on anti-pseudomonal antibiotics.

Date	Event	Description
		No new data were added to the review at this update, therefore our conclusions remain the same.

HISTORY

Protocol first published: Issue 2, 2000
Review first published: Issue 1, 2001

Date	Event	Description
29 April 2014	New citation required but conclusions have not changed	The previous co-author, Dr Anton Tan, has stepped down and a new co-author, Nikki Jahnke, has joined the review team. No new references have been added to this review, hence the conclusions remain the same.
29 April 2014	New search has been performed	A search of the Cystic Fibrosis and Genetic Disorders Cystic Fibrosis Trials Register identified seven references to six potentially eligible studies all of which were excluded from the review (Beringer 2012; Blumer 2005; Hatziagorou 2013; Keel 2011; McCabe 2013; Semykin 2010).
17 October 2012	Amended	Contact details updated.
3 November 2011	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register identified 15 new references potentially eligible for inclusion in this review. However, none of the references were suitable for inclusion in the review.
15 September 2009	New search has been performed	A search of the Group's Cystic Fibrosis Register identified no new references which were potentially eligible for inclusion in this review.
11 November 2008	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register identified no new references eligible for inclusion in this review.
11 November 2008	Amended	Converted to new review format.
20 February 2008	Amended	The 'Plain Language Summary' has been updated in line with latest guidance from The Cochrane Collaboration.
20 February 2008	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register identified no new references eligible for inclusion in this review.
21 February 2007	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register identified no new references eligible for inclusion in this review.
15 February 2006	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register identified no new references.
9 February 2005	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register identified no new references. One previously included trial has now been excluded from the review (Padoan 1987). In this trial a total of 40 courses of treatment

Date	Event	Description
		took place (20 in each intervention group). The trial was cross-over in design, however, re-randomisation took place between courses of treatment, resulting in some participants possibly receiving two or more courses of the same treatment, or a mixture of different treatments. Since the number of participants receiving each treatment was unclear, results could not be included in the analysis of this review and therefore the trial was excluded.
9 February 2005	New citation required and conclusions have changed	Substantive amendment
13 November 2002	New search has been performed	Excluded Studies: One additional study has been added - Krause 1979 . An additional reference to the Nelson 1985 study has also been included.

CONTRIBUTIONS OF AUTHORS

Dr. Anton Tan assisted in the assessment of trial quality and extraction of data up until 2013.

Dr. Heather Elphick performed the updates and acts as guarantor of the review. Dr Alison Scott joined the author team as a co-author from the update in 2016.

DECLARATIONS OF INTEREST

Dr Heather Elphick has no interests to declare.

Dr Alison Scott has no interests to declare.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK.

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

NOTES

Description of the pharmacological properties of the antibiotics used in the studies included in the review (Kucers 1997).

1. Beta-Lactams

a. Carbenicillin

Carbenicillin is a semisynthetic penicillin derived from the penicillin nucleus 6 APA and can only be administered parenterally. Its most important feature is its activity against *Pseudomonas aeruginosa* due to its ability to penetrate the outer cell membrane of the bacteria and is less susceptible than other beta-lactam antibiotics to at least one beta-lactamase produced by *Pseudomonas aeruginosa*. It is also active against other gram positive and negative aerobic organisms including *Staphylococcus aureus* and *Haemophilus influenzae*. Principal side effects include hypersensitivity, drug fever and rarely convulsions and effects on platelet function.

b. Ticarcillin

Ticarcillin is very similar to carbenicillin but is at least twice as active against *Pseudomonas aeruginosa*. It has now replaced carbenicillin for clinical use. As ticarcillin is used in a lower dosage than carbenicillin, it causes fewer side effects, but can be associated with eosinophilia and urticaria.

c. Piperacillin

Piperacillin and azlocillin are semisynthetic penicillins, referred to as 'newer anti-pseudomonal penicillins' and are considerably more active in vitro than carbenicillin and ticarcillin against *Pseudomonas aeruginosa* due to their ability to pass through the layers of the cell envelope to reach the enzyme penicillin-binding protein PBP3, which is responsible for septum formation during bacterial growth and cell division. Piperacillin is not however clinically superior and development of resistant strains have been observed. Piperacillin also has activity against *Burkholderia cepacia*, *Haemophilus influenzae*, *Staphylococcus aureus* and other gram negative organisms. Main side effects are similar to those of carbenicillin.

d. Azlocillin

Azlocillin is a ureido-penicillin and is similar to piperacillin in its activity against *Pseudomonas aeruginosa* and acts synergistically with aminoglycosides. Azlocillin-resistant *Pseudomonas aeruginosa* strains are uncommon. It has some activity against *Haemophilus influenzae*.

e. Ceftazidime

Ceftazidime is a third generation cephalosporin, resistant to the usual beta-lactamases of most gram negative bacteria and its activity against *Pseudomonas aeruginosa* is one of its most important properties. Ceftazidime-resistant strains have been described. Ceftazidime can only be administered parenterally and acts in a similar way to penicillin G on the bacterial cell wall and shows an affinity for PBP3. Ceftazidime has low toxicity with a low incidence of hypersensitivity, eosinophilia and reversible elevations in liver enzymes.

2. Aminoglycosides

a. Gentamicin

Gentamicin is an aminoglycoside antibiotic which has particular activity against gram-negative organisms. Its usefulness has decreased since the mid-1970s because of the emergence of bacterial resistance. Gentamicin inhibits bacterial growth by inhibiting protein synthesis in a manner similar to streptomycin. It probably also interacts with the cell envelope of some gram-negative bacilli such as *Pseudomonas aeruginosa*, resulting in lysis of the cell. Gentamicin has also been shown to inhibit the activity of the extracellular proteases secreted by *Pseudomonas aeruginosa*, enzymes which contribute to pathogenicity. The major side effects seen with gentamicin are ototoxicity in the form of both cochlear and vestibular toxicity with high prolonged serum levels of the drug and nephrotoxicity due to damage to the proximal tubules, characterised by excretion of casts, oliguria, proteinuria and elevated urea and creatinine. Other side effects include neuromuscular blockade, hypersensitivity reactions and haematological effects.

b. Tobramycin

Tobramycin is an aminoglycoside antibiotic with a similar mode of action to gentamicin but its advantages include greater intrinsic activity against *Pseudomonas aeruginosa*, activity against some gentamicin-resistant strains and lesser nephrotoxicity and therefore is often used in preference to gentamicin. The efficacy and safety of tobramycin given as a once-daily infusion in cystic fibrosis are currently under evaluation.

c. Sisomycin

Sisomycin is another aminoglycoside with similar antimicrobial spectrum to gentamicin. Sisomycin is more active than gentamicin, but less active than tobramycin against *Pseudomonas aeruginosa*. It has had limited clinical trials and has been available commercially in Europe but not in the UK, USA or Australia. The toxicity is about the same as that of gentamicin.

INDEX TERMS

Medical Subject Headings (MeSH)

Aminoglycosides [administration & dosage]; Anti-Bacterial Agents [*administration & dosage]; Bacterial Infections [*drug therapy]; Cephalosporins [administration & dosage]; Cystic Fibrosis [*complications]; Drug Therapy, Combination [methods]; Injections, Intravenous; Pseudomonas Infections [*drug therapy]; Pseudomonas aeruginosa; Randomized Controlled Trials as Topic; Respiratory Tract Infections [*drug therapy]; beta-Lactams [administration & dosage]

MeSH check words

Humans