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

Holland P, Jahnke N

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[Intervention Review]

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

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ABSTRACT

Background

The 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 CF 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 CF.

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: 07 October 2020.

We also searched online trials registries on 16 November 2020.

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. We assessed the certainty of the data using GRADE.

Main results

We identified 59 trials, of which we included eight trials (356 participants) comparing a single anti-pseudomonal agent to a combination of the same antibiotic and one other. 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.

There was considerable heterogeneity amongst these trials, leading to difficulties in performing the review and interpreting the results. 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 and the certainty of the evidence ranged from low to moderate.

The review did not find any differences between monotherapy and combination therapy in either the short term or in the long term for the outcomes of different lung function measures, bacteriological outcome measures, need for additional treatment, adverse effects, quality of life or symptom scores.

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, given into a vein 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: 07 October 2020.

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, bacteriological outcomes, side effects or symptom scores. We do not think that there is enough evidence to compare the different therapies properly. More research is needed, particularly looking at side effects of treatment.

Quality of the evidence

We judged the certainty of the evidence to be low to moderate. 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.

Summary of findings 1. Summary of findings: single compared with combination intravenous anti-pseudomonal antibiotic therapy for people with cystic fibrosis - short-term effects

Single compared with combination intravenous anti-pseudomonal antibiotic therapy for people with cystic fibrosis - short-term effects

Patient or population: children and adults with cystic fibrosis

Settings: inpatient or outpatient

Intervention: combination IV antibiotic therapy

Comparison: single IV antibiotic

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (trials)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Single IV antibiotic therapy	Combined IV antibiotic therapy				
Change in FEV_1 % predicted at end of antibiotic course: absolute post-treatment values Follow-up: 10 - 14 days	The mean FEV_1 (% predicted) ranged across control groups from 46% to 50.9%.	The mean FEV_1 (% predicted) in the intervention groups was 5.25% higher (9.14% lower to 19.64% higher).	MD 5.25 (95% CI -9.14 to 19.64)	93 (2)	⊕⊕⊖⊖ **low**[a,b]	3 further trials reported on this outcome, but it was not possible to include the data in our analyses. Master reported that the combination antibiotic group had a significantly higher FEV_1 % predicted after 10 days of treatment ($P < 0.05$) (Master 1997). McCarty reported a "similar improvement" in FEV_1 in both groups but no further detail (McCarty 1988). The elective trial reported higher median values for FEV_1 % predicted in the combination group at baseline and Day 14, but at Day 90 the median was higher in the single antibiotic group (Pedersen 1986).
Change in sputum *P aeruginosa* density at end of treatment (cfu/g)	The mean (SD) sputum *P aeruginosa* density was 6.9 cfu/g (15.5)	The mean sputum *P aeruginosa* density in the intervention groups was 1.60 cfu/g lower.	MD -1.60 cfu/g (95% CI -9.51 to 6.31)	76 (1)	⊕⊕⊕⊖ **moderate**[b]	2 further trials looked at bacterial concentration, but used different measures and reported within-group differences only. McLaughlin reported a significant decrease in bacterial concentration (cfu/mL) in the combination group and a non-sig-

Follow-up: 10 - 14 days	in the control group.	(9.51 cfu/g lower to 6.31 cfu/g higher).			nificant decrease in the single antibiotic group (McLaughlin 1983). McCarty reported 5/19 *P aeruginosa* isolates in the single therapy group decreased in titre by more than 10^2 cfu/mL compared to 12/19 *P aeruginosa* isolates in the combination group (McCarty 1988).
Additional treatment required	This outcome was not measured in the short term.				
Time to next course of antibiotics	This outcome was not reported in the short term.				
Adverse events during treatment Follow-up: 10 - 14 days	There were no differences between single or combination IV antibiotic therapy: • erythema at injection site, RR 0.46 (95% CI 0.09 to 2.36); • generalised rash, RR 6.16 (95% CI 0.12 to 316.67); • fever, RR 0.81 (95% CI 0.05 to 14.14); • renal impairment, RR 1.54 (95% CI 0.15 to 15.56); • auditory impairment, RR 5.86 (95% CI 0.11 to 305.44); and • proteinuria, RR 3.62 (95% CI 0.68 to 19.30).	N/A	131 (2)	⊕⊕⊖⊖ **low**[b,c]	4 further trials provided narrative information on adverse events. Master reported tinnitus in 2 participants (1 in each group) which was thought to be related to tobramycin (Master 1997). Parry reported phlebitis in 6 participants, eosinophilia in 5 participants and urticaria in 1 participant, all in the single antibiotic group (Parry 1977). The two remaining trials reported no serious adverse events or incidences of auditory problems or nephrotoxicity in either group (Costantini 1982; Pedersen 1986).
Quality of life	This outcome was not measured in the short term.				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
cfu: colony forming units; **CI**: confidence interval; **FEV_1**: forced expiratory volume in 1 second; **IV**: intravenous; **MD**: mean difference; **RR**: risk ratio; **SD**: standard deviation.

GRADE Working Group grades of evidence

High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

a. Downgraded once as there was an unclear risk of bias across some domains across the two trials. In one trial the randomisation methods weren't described adequately and both trials had a high dropout rate.
b. Downgraded once due to small sample size or low event rate, or both.
c. Downgraded once due to risk of bias within one of the included trials, particularly in the domains of sequence generation and blinding.

Summary of findings 2. Summary of findings: Single compared with combination intravenous anti-pseudomonal antibiotic therapy for people with cystic fibrosis - long-term effects

Single compared with combination intravenous anti-pseudomonal antibiotic therapy for people with cystic fibrosis - long-term effects

Patient or population: children and adults with cystic fibrosis

Settings: inpatient or outpatient

Intervention: combination IV antibiotic therapy

Comparison: single IV antibiotic

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (trials)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Single IV antibiotic therapy	Combined IV antibiotic therapy				
Change in FEV_1 (% predicted) Follow-up: 6 months	This outcome was not reported.					1 trial reported that there was no significant difference in pulmonary function tests, with mean follow-up time of 20 months; but further commented that sample size restricted statistical power (Master 1997).
Change in sputum *P aeruginosa* density at end of treatment (cfu/g)	This outcome was not reported in the long term.					

Additional treatment required	This outcome was not reported in the long term.	
Time to next course of antibiotics	This outcome was not reported in the long term.	
Adverse events during treatment Follow-up: 10 - 14 days	This outcome was not reported in the long term.	
Quality of life Follow-up: 6 months or more	1 trial reported no statistically significant difference in NIH scores between treatment groups at the long-term follow-up (mean 20 months for both groups) (Master 1997).	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
cfu: colony forming units; **CI:** confidence interval; **FEV_1**: forced expiratory volume in 1 second; **IV**: intravenous; **NIH**: National Institutes of Health.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

BACKGROUND

Description of the condition

Cystic fibrosis (CF) is the most common life-limiting inherited disorder affecting populations of Northern European descent (Farrell 2018), 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; Gibson 2003).

Recurrent infection, in particular with *Pseudomonas aeruginosa,* is the main feature of the lung involvement in CF. Antibiotic therapy may be utilised with the aim of preventing, eradicating, or controlling respiratory infections (Castellani 2018; UK CF Trust 2009).

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 intravenous (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), with the aim of preventing long-term deterioration (subsequently referred to as an 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 contentious areas in the treatment of infection with IV antibiotics in CF. Administration of IV antibiotic therapy for a period of around two weeks is standard practice for treatment of pulmonary infections in most CF centres. Current guidelines acknowledge that this is current practice, but note that evidence is lacking (Castellani 2018; UK CF Trust 2009). Treatment of *P aeruginosa* is complicated by discordance between antibiotic susceptibility pattern and clinical response (Smith 2003).

How the intervention might work

Most centres perceive dual or combination IV antibiotic therapy in CF to be more effective than single therapy. with the possibility that combination therapy may offer antibiotic synergy (Saiman 1996). 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). However, the use of a beta-lactam alone offers advantages for the individual because of ease of administration and the avoidance of aminoglycoside related toxicities (Prayle 2010).

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 (RCTs). We included trials using quasi-randomisation methods such as alternation, if there was sufficient evidence that the treatment and comparison groups were comparable in terms of clinical status at baseline.

Types of participants

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

Types of interventions

Trials of any single IV anti-pseudomonal antibiotic compared to a combination of the same IV anti-pseudomonal antibiotic plus one or more other IV anti-pseudomonal antibiotics (drug A versus drug A plus drug B). 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. Symptomatic and elective regimens (see above) were both eligible for inclusion if the only difference between the treatment and comparison group was whether the participants received single or combination antibiotic therapy.

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 clinical, bacteriological and subjective changes and in adverse events. Outcomes differed between short-term results (i.e. at end of course of antibiotics) and long-term results (measured at 6 to 12 months after course of antibiotics; if long-term outcomes are measured at other time intervals, we will also consider these).

Short-term results

Primary outcomes

1. Spirometric lung function
   a. forced expiratory volume in one second (FEV_1)
   b. forced vital capacity (FVC)
   c. other measures of lung function
2. Sputum bacteriology
   a. eradicaton of *P aeruginosa*
   b. bacterial concentration
   c. antibiotic sensitivity
3. Adverse effects to antibiotics, e.g. renal and auditory impairment, serum sickness and sensitivity reactions

Secondary outcomes

1. Quality of life (QoL) assessment

2. Nutritional status
   a. change in weight
   b. change in body mass index (BMI)
   c. change in z score
   d. other indices of nutritional status
3. Additional treatment required
4. Duration of hospitalisation
5. Time to next course of IV antibiotics
6. Clinical status
   a. chest X-ray scores
   b. other symptom scores, e.g. Schwachman score
7. Changes in inflammatory markers (in sputum or blood)

Long-term results

Primary outcomes

1. Change in lung function (prevention of deterioration of lung function)
2. 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. QoL assessment
2. Number of courses of IV antibiotics in the following year

Search methods for identification of studies

The authors did not restrict results by language or publication status.

Electronic searches

The authors identified relevant trials 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 website.

Date of the most recent search of the Group's CF Trials Register: 07 October 2020.

Authors also searched the following online study registries for relevant ongoing trials; please see the appendices for the search strategies (Appendix 1):

- US National Institutes of Health Ongoing Trials Register Clinicaltrials.gov (www.clinicaltrials.gov; 2000 to present);
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch; 1994 to present).

Date of latest search: 16 November 2020.

Searching other resources

The authors checked the reference lists of the identified trials for other possibly relevant trials.

Data collection and analysis

Selection of studies

Two review authors 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 review 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 (between 10 and 14 days); they considered long-term results to be six to 12 months after the course of antibiotics. The authors planned to also consider other time intervals if these are reported. In the review the review authors report data at the end of the course of antibiotics (between 10 and 14 days), at two to eight weeks and at 80 days.

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 (SD) or standard error (SE) 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 (OR) with 95% confidence intervals (CIs) where appropriate. For continuous outcomes, the authors calculated a pooled estimate of treatment effect by calculating the mean difference (MD) with 95% CIs.

Unit of analysis issues

The authors included one cross-over trial in the review (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 review 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. They planned to contact the primary investigators for clarification of data if needed.

Assessment of heterogeneity

Review authors planned to measure the inconsistency of trial results using the Chi^2 test and the I^2heterogeneity statistic to determine if variation in outcomes across trials was due to trial heterogeneity rather than chance (Higgins 2003). This Chi^2 test assesses whether observed differences in results are compatible with chance alone. A low P value (or a large Chi^2 statistic relative to its degree of freedom) provides evidence of heterogeneity of intervention effects (variation in effect estimates beyond chance). A P value of 0.10, rather than the conventional level of 0.05, is used to determine statistical significance.

The I^2statistic, as defined by Higgins (Higgins 2017), measures heterogeneity as a percentage where a value:

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

The importance of the observed value of I^2 depends on (i) magnitude and direction of effects and (ii) strength of evidence for heterogeneity (e.g. P value from the Chi^2 test, or a confidence interval for I^2).

Assessment of reporting biases

The review authors assessed selective outcome reporting as detailed above (Assessment of risk of bias in included studies). If they had been able to combine at least 10 trials, they would have assessed publication bias by generating a funnel plot (Sterne 2017).

Data synthesis

The review authors analysed the data using a fixed-effect model. If they had identified at least substantial heterogeneity (as defined above), they would have analysed the data using a random-effects model.

Subgroup analysis and investigation of heterogeneity

If the review authors had included and combined sufficient trials and identified at least substantial heterogeneity (as defined above), they 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.

While the authors were unable to conduct a formal subgroup analysis, they have presented the results of the single trial of elective treatment (reported as median and range) separately in an additional table (Pedersen 1986).

Sensitivity analysis

The review authors planned to perform a sensitivity analysis based on the methodological quality of the trials, removing any trial which had a high risk of bias in any domain.

Summary of findings and assessment of the certainty of the evidence

The authors have prepared a summary of findings table for each comparison presented in the review. They listed each population, setting, intervention and comparison and reported an illustrative risk for the experimental and control intervention. They graded the overall certainty of the body of evidence as high, moderate, low or very low using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) (Schuneman 2006). The authors based their judgements on the risk of bias within the trials, their relevance to the population of interest (indirectness), unexplained heterogeneity or inconsistency, imprecision of the results or high risk of publication bias. They downgraded the evidence once if the risk was serious and twice if the risk was deemed to be very serious and described the rationale for each judgement in footnotes to each table. For each comparison they reported the following outcomes.

1. Change in FEV_1 % predicted at end of antibiotic course
2. Change in FEV_1 % predicted at six months
3. Change in sputum *P aeruginosa* density (CFU/g) at end of antibiotic course
4. Additional treatment required
5. Time to next course of antibiotics
6. Adverse events during antibiotic course
7. QoL

RESULTS

Description of studies

Please see the tables for additional information (Characteristics of included studies; Characteristics of excluded studies).

Results of the search

The searches identified a total of 59 trials; no trials were found through contact with pharmaceutical companies. The authors included eight trials in the review and excluded 51 trials.

Included studies

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

Trial design

Seven trials were described as RCTs (Costantini 1982; Huang 1982; Master 1997; McCarty 1988; McLaughlin 1983; Pedersen 1986; Smith 1999). In the remaining trial, treatment was assigned using alternate allocation with good evidence of similar groups at baseline (Parry 1977). This trial was included as a quasi-RCT.

Seven trials of symptomatic treatment employed a parallel group design (Costantini 1982; Huang 1982; Master 1997; McCarty 1988; McLaughlin 1983; Parry 1977; Smith 1999). The remaining trial of elective treatment every three months used a cross-over design (Pedersen 1986).

Participants

In seven trials, participants were enrolled during a pulmonary exacerbation (symptomatic regimen) (Costantini 1982; Huang 1982; Master 1997; McCarty 1988; McLaughlin 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* (McLaughlin 1983).

Only one trial stated the criteria for diagnosis of CF (Smith 1999). Sample size varied from 16 participants (Huang 1982) to 83 participants (Master 1997), with a total of 356 participants recruited across all eight trials. 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). Similarly, a further two trials reported on participants with multiple admissions a higher number of admissions than participants (Costantini 1982; Master 1997).

Interventions

Treatment duration varied from 10 to 14 days. Three trials included a follow-up period, which varied from two to eight weeks (McLaughlin 1983; Smith 1999) to six months for the cross-over trial (Pedersen 1986).

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. We did not analyse these two groups of trials separately due to insufficient data.

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 (compared to ceftazidime with tobramycin (Pedersen 1986)) and the remaining four compared an agent from the penicillin group of antibiotics: piperacillin (McCarty 1988); ticarcillin (Huang 1982); azlocillin (McLaughlin 1983; Smith 1999) with a combination of that agent with tobramycin.

Outcome measures

Outcomes were studied at the end of the treatment course in all trials.

Five trials reported on lung function: mean FEV_1 % predicted and FVC % predicted at the end of the treatment course (McLaughlin 1983; Smith 1999); the mean change from baseline in FEV_1 % predicted and FVC % predicted (Master 1997); and median (range) FEV_1 % predicted and FVC % predicted at baseline, end of treatment and follow-up (Pedersen 1986). One trial measured FEV_1 and FVC, but did not specify the unit of measurement (McCarty 1988). Two trials undertook a number of other specified lung function measurements (mean RV % predicted, mean TLC % predicted, mean RV/TLC % predicted, mean PFR % predicted and mean MMEF % predicted) (McLaughlin 1983; Smith 1999). Additionally, one trial fed pulmonary function into a clinical scoring system, but did not specify the actual outcome measures or report the pulmonary function results (Huang 1982) and one trial describes performing pulmonary function tests when possible, but does not define what these were (Parry 1977).

Three trials reported on Schwachman score (McCarty 1988; McLaughlin 1983; Parry 1977); one trial reported exacerbation scores (Smith 1999); one trial reported a combination clinical score (Costantini 1982) and a further trial devised their own composite clinical score (Huang 1982).

Three trials reported on eradication of *P aeruginosa* (Costantini 1982; Huang 1982; Pedersen 1986), two trials reported on the change in *P aeruginosa* density (McCarty 1988; Smith 1999) and one trial reported on a change in sputum bacterial concentration (McLaughlin 1983). Six trials reported adverse events (Costantini 1982; Master 1997; McCarty 1988; Parry 1977; Pedersen 1986; Smith 1999).

Two trials reported of nutrition (Parry 1977; McCarty 1988). Two trials reported on hospitalisations (Huang 1982; Smith 1999) and two trials on the time to next course of antibiotics (McLaughlin 1983; Parry 1977). Three trials reported short-term changes in chest X-ray scores (Costantini 1982; Huang 1982; Parry 1977). One trial reported sputum markers of inflammation (Smith 1999) and three trials reported blood markers of inflammation (Parry 1977; Pedersen 1986; Smith 1999). Six of the eight trials examined sputum for drug sensitivity at the beginning and at the end of treatment (Costantini 1982; Huang 1982 McCarty 1988; McLaughlin 1983; Parry 1977; Pedersen 1986; Smith 1999).

One trial included longer-term results and reported no difference in pulmonary function tests or NIH scores (Master 1997).

Excluded studies

A total of 51 trials were excluded. In 11 trials a single antibiotic agent was compared with a 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). Different dosage regimens of the same antibiotic were compared in 16 trials (Adeboyeku 2011; Al-Ansari 2006; Aminimanizani 2002; Beringer 2012; Conway 1997; Hubert 2009; Keel 2011; McCabe 2013; Prayle 2016; Noah 2010; NCT01667094; NCT01694069; Riethmueller 2009; Semykin 2010; Turner 2013; Whitehead 2002). Two trials compared different durations of IV antibiotics (NCT01044719; STOP 2 2018). Three trials were excluded as they compared two single drugs (Al-Aloul 2004; Levy 1982; NCT02918409). One trial compared two IV antibiotics to those same antibiotics plus an inhaled antibiotic (Al-Aloul 2019) and one trial compared a single IV antibiotic to a combination of IV and inhaled antibiotics (NCT03066453). A further trial had a similar design but the third antibiotic in the comparator group was identified through examination of the microbiome and it was not specified how this third antibiotic was administered (CFMATTERS 2017). Similarly, one trial compared IV antibiotic treatment identified by standard testing to treatment identified from biofilm susceptibility testing (Moskowitz 2011). One trial compared an IV regimen to control (Enaud 2017) and one trial as investigators compared two different combinations of antibiotics (Blumer 2005). One trial compared IV antibiotics administered in hospital compared to at home (Donati 1987) and two trials looked at an eradication regimen (Kenny 2009; TORPEDO 2018). One trial compared oral antibiotics to IV antibiotics (Park 2018). Six 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; NCT02421120; 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 earlier versions of the review, in order to assess the risk of bias in the trials, the review authors assessed the methodological quality of each trial using the following criteria: generation of allocation sequences; concealment of allocation schedule; inclusion in the analysis of all randomised participants; and double-blinding (Schulz 1995).

For the current version of the review the review authors have used the Cochrane risk of bias tool judging the trials to have a low, unclear or high risk of bias (Higgins 2017).

Allocation

Generation of sequence

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

Allocation concealment

The authors assessed four trials as adequately concealing the allocation schedule leading to a low risk of bias (Master 1997; McCarty 1988; McLaughlin 1983; Smith 1999). 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 (McLaughlin 1983); and the fourth trial stated central randomisation (Smith 1999). The review authors assessed one trial as inadequately concealing the allocation schedule, since the investigators used alternate allocation, and judged this trial to have a high risk of bias (Parry 1977). In the remaining three trials the method of allocation concealment was unclear and so the reveiw authors 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 as they used saline for the placebo injection (Huang 1982; Master 1997; McLaughlin 1983; Smith 1999). The review authors 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 the review authors 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 the review authors 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 the review authors judged 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 and so a low risk of attrition bias (Costantini 1982; Huang 1982; McCarty 1988; Parry 1977). Three trials described numbers of withdrawals and reasons for these, so the review authors judged these to also have a low risk of bias (Master 1997; Pedersen 1986; Smith 1999). Master published a flow chart showing numbers randomized and included or excluded (with reasons) at each stage in paper (Master 1997). Pedersen described reasons why three participants out of a cohort of 20 withdrew (Pedersen 1986). Smith stated that 35 out of 111 participants withdrew (21 from one group) and presented the reasons for withdrawals in a table (Smith 1999).

In the remaining 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); the review authors judged this trial to have an unclear risk of bias as although 17% of participants withdrew and nearly all were from one group, the reasons do not indicate an overall direct negative or positive relationship with the intervention (McLaughlin 1983).

Selective reporting

In three trials the outcomes stated in the methods section were reported in the results section of the trial reports, so the review authors judged these to have a low risk of reporting bias (Master 1997; McLaughlin 1983; Pedersen 1986). They judged four trials to have an unclear risk of bias (Costantini 1982; Huang 1982; McCarty 1988; Smith 1999). Two trials were reported as abstracts only and since the protocols were not available and we were not able to compare the methods sections to the results sections in full reports (Costantini 1982; Huang 1982); and in two trials some clinical outcomes specified in the methods not directly reported and only summarised with brief narrative (McCarty 1988; Smith 1999). In the final trial, investigators state that "pulmonary function tests were performed when possible", but no further details or results are given, the review authors therefore judged this trial to have a high risk of bias (Parry 1977).

Other potential sources of bias

Two trials were reported as abstracts only and the review authors were unable to identify any other potential sources of bias and have judged these to have an unclear risk for this domain (Costantini 1982; Huang 1982). One trial undertook a power calculation to show an absolute difference in FEV_1 % predicted of 2%, but the sample size was not achieved, therefore the review authors judged this to have an unclear risk of bias (Master 1997).

The remaining five trials had a low risk of bias, these were published as full papers and the review authors did not identify any other potential sources of bias (McCarty 1988; McLaughlin 1983; Parry 1977; Pedersen 1986; Smith 1999).

Effects of interventions

See: **Summary of findings 1** Summary of findings: single compared with combination intravenous anti-pseudomonal antibiotic therapy for people with cystic fibrosis - short-term effects; **Summary of findings 2** Summary of findings: Single compared with combination intravenous anti-pseudomonal antibiotic therapy for people with cystic fibrosis - long-term effects

Only those primary and secondary outcomes of this review, which were reported within the eight included trials, are listed below. Only one trial included results of follow-up at over six months (Master 1997).

Single compared to combination therapy

Pooling of results was difficult because of missing data, differences in the methods of expression of the results and missing SDs. In this comparison the authors present eight trials with 356 participants (Costantini 1982; Huang 1982; Master 1997; McCarty 1988; McLaughlin 1983; Parry 1977; Pedersen 1986; Smith 1999).

Short-term results

Primary outcomes

1. Change in spirometric lung function

Although the outcome measure given in our protocol was improvement in spirometric lung function (now described as 'change' rather than improvement), no trial included these data.

Seven of the eight trials included lung function in some form 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. One trial, reported as an abstract only, fed pulmonary function into a clinical scoring system, but did not specify the actual outcome measures or report the pulmonary function results (Huang 1982). One trial states that "pulmonary function tests were performed when possible", but no further details or results are given (Parry 1977).

a. FEV_1

Two trials measured mean FEV_1 % predicted at the end of the treatment course (McLaughlin 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 and found no difference in FEV_1 % predicted between single or combination therapy at 10 to 14 days (two trials, 93 participants; low-certainty evidence) or at two to eight weeks (one trial, 41 participants) (Analysis 1.1).

One trial reported the mean absolute change in FEV_1 % predicted from baseline to 10 days, but the data were based on 44 participants with 98 admissions so we are unable to analyse these in RevMan (Master 1997). However, investigators state that the mean (SD) change with combination antibiotics of 12.8% (13.5) compared to 10.6% (8.5) with a single antibiotic was statistically significant ($P < 0.05$). By the end of the study (a minimum of 12 months) the median (range) change in FEV_1 % predicted was -2.2 (-19.3 to 8.4) in the combination group compared to -5.8 (-22.0 to 3.0) in the single antibiotic group (Master 1997)

The elective trial expressed the results for FEV_1 % predicted in terms of a median and range at baseline, end of treatment and after 90 days (Pedersen 1986). Full details are presented in the additional tables (Table 1).

One trial reported "similar improvement" in FEV_1 but did not give any further details (McCarty 1988).

b. FVC

Two trials measured mean FVC % predicted at the end of the treatment course (McLaughlin 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 and found no difference in FVC % predicted between the two treatment groups at at 10 to 14 days (two trials, 93 participants) or at two to eight weeks (one trial, 41 participants) (Analysis 1.2).

The Master trial reported the mean absolute change in FVC % predicted from baseline to 10 days, but the data were based on 44 participants with 98 admissions so we are unable to analyse these in RevMan (Master 1997). However, investigators state that FVC % predicted the mean (SD) change from baseline was significantly greater ($P < 0.05$) in the combination group, 12.1% (12.0), compared to 9.9% (9.1) in the single antibiotic group (Master 1997).

The elective trial expressed the results for FVC % predicted in terms of a median and range at baseline, end of treatment and after 90 days (Pedersen 1986). Full details are presented in the additional tables (Table 1).

McCarty also reported "similar improvement" in FVC, but did not give any further details (McCarty 1988).

c. Other measures of lung function

Two trials reported a range of other measures of lung function, but found no differences between single or combination antibiotic treatments: mean RV % predicted (Analysis 1.3); mean TLC % predicted (Analysis 1.4); mean RV/TLC % predicted (Analysis 1.5); mean PFR % predicted (Analysis 1.6); and mean MMEF % predicted (Analysis 1.7).

2. Sputum bacteriology

a. Eradication of P aeruginosa

Three trials reported on eradication of *P aeruginosa* (Costantini 1982; Huang 1982, Pedersen 1986). At up to 14 days, Huang found no difference between the single or combination antibiotic groups, but at two to eight weeks Costantini reported more cases of eradication in the single antibiotic group than the combination group, OR 10.16 (95% CI 1.44 to 71.65) (Analysis 1.8). The elective trial stated that neither treatment succeeded in eradication *P aeruginosa* from participants (Pedersen 1986).

b. Bacterial concentration

One trial reported the 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 difference between groups in the mean change in density was MD -1.60 (95% confidence interval (CI) -9.51 to 6.31) (Analysis 1.9), 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 (moderate-certainty evidence). However, on follow-up, the density of *P aeruginosa* in the sputum was similar in both groups.

One trial reported a change in sputum bacterial concentration in mean log cfu/mL, with a significant reduction in concentration of bacteria between days 1 and 10 in both combination treatment groups ($P \leq 0.01$) and a non-significant reduction in the single treatment group (P value not given) (McLaughlin 1983). At three-month follow-up, the investigators state that bacterial concentration returned to a similar level as pre-treatment. Although this data is demonstrated in a figure, the numerical values are not included in the text (McLaughlin 1983).

One trial reported 19 *P aeruginosa* isolates from each group; however, since only 17 participants were randomised in the trial the data are not independent and can not be analysed in RevMan (McCarty 1988). Investigators reported that only 5 out of 19 isolates in the single antibiotic (piperacillin) group decreased in titer by greater than 10^2 cfu/mL compared to 12 out of 19 isolates in the combination (piperacillin plus tobramycin) group (McCarty 1988).

One trial was not able to compare sputum density on days 1 and 10 as most participants were unable to expectorate on day 10 (Master 1997).

c. Antibiotic sensitivity

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 (McLaughlin 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 reported MIC values for all the isolates for ticarcillin and carbenicillin and found that the median MIC value for ticarcillin at two to six months post-treatment was same as the pre-treatment value (3.1 µg/mL), but investigators did not define antibiotic resistance (Parry 1977). 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 remaining trial states that sputum cultures were tested for antibiotic sensitivity but gives no further information (Costantini 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 (McLaughlin 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 (McLaughlin 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 (Analysis 1.10). 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.

3. Adverse events

Two trials reported analysable data for adverse events (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 (Analysis 1.11).

The only adverse event in the Master trial was tinnitus, which was experienced by one participant in each group and was thought to be related to inadvertent rapid administration of tobramycin (Master 1997). The three-arm Parry trial reported adverse events which were probably drug-related for each of the single antibiotic arms (Parry 1977). In the ticarcillin arm (n = 28) phlebitis was reported by six participants, eosinophilia by five participants and urticaria by one participant; in the gentamicin arm cylinduria was reported by one participant (Parry 1977). Costantini reported there were no incidences of either auditory or nephrotoxicity (Costantini 1982).

The elective trial reported that no serious adverse events were recorded during either treatment arm (Pedersen 1986).

Secondary outcomes

2. Nutritional status

a. Change in weight

Two trials report that weight gain was similar between the two treatment groups (McCarty 1988; Parry 1977).

4. 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, Peto OR 0.30 (95% CI 0.12 to 0.73) (Smith 1999) (Analysis 1.12).

A further trial reported on the mean number of weeks that participants remained out of hospital within the three month follow-up period (McLaughlin 1983). There was no difference found between the single or combination groups (Analysis 1.13).

5. Time to next course of antibiotics

Only one trial reported the effect on the time to next course of antibiotics (McLaughlin 1983). There was no significant difference between the two groups (Analysis 1.13). A futher trial reported that time interval to next course of antibiotics did not differ significantly between treatment groups but no numerical data was provided (Parry 1977).

6. Clinical status

a. Chest x-ray scores

One trial reports that chest x-rays (assessed with Chrispin-Norman scores) only showed significant improvement in the antibiotic combination group but no numerical data was provided (Costantini 1982). One trial reported no difference between treatment groups of "percentage improvement in chest radiograph" without information regarding how this percentage was calculated (Parry 1977). One trial devised their own scoring system consisting of a combination of clinical, radiological and pulmonary function factors and reported no difference between group scores either before or after treatment (Huang 1982).

b. Other symptom scores

One trial measured mean Schwachman score (McLaughlin 1983); groups did not significantly differ at baseline and analysis of the data found no difference between groups at the end of treatment (Analysis 1.14). A second trial reporting Schwachman score described similar improvements in both groups (McCarty 1988). A further three-arm trial presented baseline Schwachmann scores in a table, but the paper does not report post-treatment values (Parry 1977).

One trial reported that the exacerbation score decreased significantly ($P < 0.001$) in each group and remained lower than the admission values at the follow-up assessment (Smith 1999). One trial devised their own scoring system consisting of a combination of clinical, radiological and pulmonary function factors and reported no difference between group scores either before or after treatment (Huang 1982). One trial reported that "clinical improvement was obtained in the 80% - 90% of patients regardless of the therapeutic regimen" according to a clinical score that included serological and clinical factors (Costantini 1982).

7. Changes in 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 (Analysis 1.15). One trial reported no difference in change of white blood cell count or sedimentation rate between treatment groups (Parry 1977). One trial reported a statistically significant decrease in white blood cell count in both treatment groups, with no difference between groups (Pedersen 1986).

Long-term results

Primary outcomes

1. Change in lung function

One trial reported that there was no significant difference in pulmonary function tests, with mean follow-up time of 20 months; but further commented that sample size restricted statistical power (Master 1997).

Secondary outcomes

1. QoL

One trial reported no statistically significant difference in NIH scores between treatment groups (Master 1997).

DISCUSSION

Choice of anti-pseudomonal antibiotic and the use of single or combined therapy are controversial areas in the treatment of respiratory infection in 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 a reduction of drug-related toxicity. From the perspective of people with CF, using 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 IV antibiotic therapy in CF requires further evaluation.

Summary of main results

This review has found eight trials that examined the effect of single compared to combination IV anti-pseudomonal antibiotic therapy, seven of these were for acute exacerbations in CF (Costantini 1982; Huang 1982; Master 1997; McCarty 1988; McLaughlin 1983; Parry 1977; Smith 1999) and one examined an elective quarterly regimen (Pedersen 1986). 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.

Short-term results

While most included trials reported on lung function, there was great variety in the tests used, the time points reported and how the results were reported. The overall results from our limited analysis (two trials, 93 participants; low-certainty evidence) showed that there was no difference between monotherapy and combination therapy (either symptomatic or elective regimen) in terms of lung function at the end of treatment for an exacerbation (McLaughlin 1983; Smith 1999). Other trials also reported similar narrative results for lung function for single and combination treatment regimens; although one symptomatic trial presented data for participants with multiple admissions and reported a greater increase in both FEV_1 % predicted and FVC % predicted with combination antibiotics compared to a single antibiotic (Master 1997). In the elective trial, the median (range) values for lung function (FEV_1 and FVC % predicted) demonstrated similar increases from baseline to 14 days which then returned to baseline levels at 90 days (Pedersen 1986).

At up to 14 days, one study (n = 25) found no difference in *P aeruginosa* eradication between the single or combination antibiotic groups (Huang 1982), but at two to eight weeks a further trial (n = 18) reported more cases of eradication in the single antibiotic group than the combination group (Costantini 1982). The elective trial stated that neither treatment succeeded in eradication *P aeruginosa* from participants (Pedersen 1986). There were no further differences in terms of bacteriological outcomes.

Five symptomatic trials and the elective trial reported adverse effects of treatment (data were available from three symptomatic trials (Master 1997; McCarty 1988; Smith 1999)), but no differences between single or combination antibiotics were identified. Two trials reported similar weight gain in both treatment groups (McCarty 1988; Parry 1977). Two trials reported on hospitalisations (Huang 1982; Smith 1999), but only one found a difference between groups (favouring combination therapy) (Smith 1999); two trials reporting the time to the next course of antibiotics found no difference between groups (McLaughlin 1983; Parry 1977). No trial reporting symptom scores found any difference between single or combination antibiotics, e.g. Schwachman scores (McCarty 1988; McLaughlin 1983), an exacerbation score (Smith 1999) and a trial-specific clinical score (Huang 1982). We found no effect on inflammatory markers or on resistant strains of *P aeruginosa*.

Long-term results

Only one trial (n = 51) reported limited long-term results (at 20 months) (Master 1997). Investigators found no difference between symptomatic single or combination antibiotic treatment in pulmonary function tests or QoL (NIH scores); but further commented that sample size restricted statistical power (Master 1997). The trial did not report any other outcomes of this review.

Overall completeness and applicability of evidence

The trials were very heterogeneous in terms of design, drugs used, duration of treatment and follow-up and outcome measures. 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 QoL scores. While there were some short-term data on resistant strains of *P aeruginosa* and side effects, there were no data for these outcomes in the long term. 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 six of the eight trials stated that they had looked for adverse effects (Costantini 1982; Master 1997; McCarty 1988; Parry 1977; Pedersen 1986; Smith 1999); therefore there may have been side effects that have not been identified. The longest follow-up in all but one trial 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.

Quality of the evidence

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. Using the GRADE framework, we downgraded the certainty of evidence for short-term effects due to risk of bias issues and small sample sizes (Summary of findings 1). There was insufficient information and data for us to carry out GRADE assessments for the long-term trials (Summary of findings 2).

The review raises some interesting methodological issues, including the difficulties of pooling results from a number of small trials that are of poor quality.

Potential biases in the review process

Comprehensive searches were undertaken and the review authors are confident that all eligible trials have been identified. For each iteration of the review, two authors have independently assessed studies and the data presented in this review, in order to minimise any potential biases or errors.

Agreements and disagreements with other studies or reviews

A review of current evidence was performed by a committee established by the Cystic Fibrosis Foundation, who agree that there is insufficient evidence to support use of either single or combination therapy; however, they recognise that standard practice is to treat with combination therapy and do not feel there is sufficient evidence to recommend changing this strategy (Flume 2008).

This version of the review is an update of previous review versions (Elphick 2002; Elphick 2005; Elphick 2014).

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 cystic fibrosis (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 review that either treatment choice is preferable or safer 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.

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; this could be particularly pertinent to children.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Costantini 1982

Study characteristics	
Methods	RCT. Duration: variable duration of course (mean (SD) 15 (3.4) days). Symptomatic regimen.

Costantini 1982 *(Continued)*

Participants	28 pulmonary exacerbations in 19 participants with CF. Age not given but stated that groups similar in age and disease severity. PsA colonised.
Interventions	Single antibiotic group 1: carbenicillin 675 mg/kg/day. Single antibiotic group 2: sisomycin 10.5 mg/kg/day. Combination antibiotic group: carbenicillin 590 mg/kg/day plus sisomycin 10 mg/kg/day.
Outcomes	CXR and symptom scores, bacteriology, development of resistant strains.
Notes	Abstract: no data. No withdrawals.

Risk of bias

Bias	Authors' judgement	Support for judgement
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.
Selective reporting (reporting bias)	Unclear risk	Not clear, only published as an abstract and protocol not available.
Other bias	Unclear risk	None identified, but limited information as only published as an abstract.

Huang 1982

Study characteristics

Methods	Double-blind RCT. Parallel design, 3-arm* Duration: 10-day course. Symptomatic regimen.
Participants	25 participants randomised. Age not stated. Mixed PsA and non-PsA.

Huang 1982 *(Continued)*

Interventions	Single antibiotic group (n = 6): ticarcillin 300 mg/kg/day. Combined antibiotic group 1 (n = 10): ticarcillin 300 mg/kg/day plus tobramycin 6 mg/kg/day. Combined antibiotic group 2 (n = 9): carbenicillin 500 mg/kg/day plus tobramycin 6 mg/kg/day.
Outcomes	Lung function, number readmitted within one month, CXR and symptom scores, bacteriology.
Notes	*originally tobramycin plus ticarcillin vs tobramycin vs carbenicillin vs placebo, but due to consent issues using placebo, ticarcillin alone substituted for placebo without breaking the code. Abstract: lung function, CXR and symptom score data not given. No withdrawals.

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.
Selective reporting (reporting bias)	Unclear risk	Not clear, only published as an abstract and protocol not available.
Other bias	Unclear risk	None identified, but limited information as only published as an abstract.

Master 1997

Study characteristics

Methods	Double-blind RCT. Parallel trial. Duration: 10-day course. Symptomatic regimen.
Participants	51 participants randomised (combination n = 22, single n = 29). Combination (tobramycin and ceftazidime) group: 21 participants with 51 admissions assessed; mean (SD) age 16 (7) years. Single (tobramycin) group: 23 participants with 47 admissions assessed; mean (SD) age 14 (5) years.

Master 1997 *(Continued)*

	12 participants in the combination (tobramycin and ceftazidime) group and 9 participants in the single (tobramycin) group were eligible for long-term assessment (at lease 2 admissions in 12 months). Participants in both groups experienced an average of 3.1 and 3.0 admissions, respectively, for IV antibiotic treatment during the study period.
Interventions	Single antibiotic group: tobramycin once daily (9 mg/kg/dose). Combination antibiotic group: tobramycin once daily (3 mg/kg/dose) plus ceftazidime 50 mg/kg/dose 8-hourly. Participants given 6 syringes/day, in the combination group these were 3 each of tobramycin and ceftazidime, in the single group these were a single syringe of tobramycin and 5 syringes of sodium chloride (placebo).
Outcomes	Lung function, adverse events.
Notes	Full paper. Exclusion criteria stated. The trial was halted for a period of 3 months when one of the trial participants committed suicide by utilizing a trial syringe to administer a lethal substance. The trial was recommenced after the coroner's finding that this was an unrelated death. During this time of suspension, there were 14 admissions of participants 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 trial.
Blinding (performance bias and detection bias) All outcomes	Low risk	Medical staff, nursing staff and participants were blinded to the treatment. Participants given 6 syringes/day, in the combination group these were 3 each of tobramycin and ceftazidime, in the single group these were a single syringe of tobramycin and 5 syringes of sodium chloride (placebo).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Flow chart showing numbers randomized and included/excluded (with reasons) at each stage in paper.
Selective reporting (reporting bias)	Low risk	Outcomes stated in the methods section were reported in the results section.
Other bias	Unclear risk	Power calculation undertaken to show an absolute difference in FEV_1 % predicted of 2%, but sample size not achieved.

McCarty 1988

Study characteristics

Methods	RCT. Parallel design (but 3 participants treated on more than one occasion - see below).

McCarty 1988 *(Continued)*

	Duration: minimum of 10 days. Symptomatic regimen.
Participants	17 participants experiencing a pulmonary exacerbation. 3 participants treated on more than one occasion (2 initially in piperacillin group and several months later randomised to combination group; 1 participant enrolled 2x in piperacillin group). 20 data sets. Age, range: 2 to 12 years. Mixed PsA and non-PsA.
Interventions	Single antibiotic group (n = 8): piperacillin 600 mg/kg/day. Combination antibiotic group (n = 9): piperacillin plus tobramycin 8 to 10 mg/kg/day. All participants also received intense chest physiotherapy and nutritional support.
Outcomes	Lung function, weight, symptom scores (Schwachman scale), adverse events, bacteriology.
Notes	No data for lung function, weight or symptom scores. No withdrawals.

Risk of bias

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	No details on blinding specified, not double-blind.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Clear explanation of participants in groups, no drop outs occurred.
Selective reporting (reporting bias)	Unclear risk	Some clinical outcomes specified in the methods not directly reported and only summarised with a single narrative sentence.
Other bias	Low risk	None identified.

McLaughlin 1983

Study characteristics

Methods	Double-blind RCT. Duration: 10 days with follow-up after approximately 4 weeks. Symptomatic regimen.

McLaughlin 1983 *(Continued)*

	No ITT analysis.
Participants	60 participants originally enrolled and 51 completed. Age, mean (SD): 21 (5) years. PsA in 98%. Schwachman score, mean (SD), range: 60 (14), 36 - 83. Age and Schwachman score similar across groups.
Interventions	Single antibiotic group (n = 16): azlocillin 300 mg/kg/day in 6 divided doses plus placebo (0.85% NaCl) in 3 divided doses. Combination antibiotic group 1 (n = 17): ticarcillin 300 mg/kg/day in 6 divided doses plus plus tobramycin 6 mg/kg/day in 3 divided doses. Combination antibiotic group 2 (n = 18): azlocillin 300 mg/kg/day in 6 divided doses plus tobramycin 6 mg/kg per day in 3 divided doses. All participants also received chest physiotherapy.
Outcomes	Lung function, symptom scores, development of resistant strains, time to next course.
Notes	Only data from the single antibiotic group and the azlocillin plus tobramycin group are presented in the review. 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	9 participants withdrew: 3 participants withdrawn for drug-related complications (1 participant from single antibiotic group for haemoptysis; and 1 each from single antibiotic and ticarcillin plus tobramycin combination group for urticarial rash); 3 participants (1 from each group) discharged improved before completion of antibiotic course; 3 participants from single antibiotic group 3 withdrawn due to incomplete outcome data.
Selective reporting (reporting bias)	Low risk	Outcomes specified in methods reported in results.
Other bias	Low risk	None identified.

Parry 1977

Study characteristics	
Methods	Quasi-RCT (alternate allocation). Parallel trial. Duration: 14 days. Symptomatic regimen.
Participants	28 participants, but some enrolled on multiple occasions giving 42 courses/data sets. Total cohort: 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. This was a control group from the same study period not part of the alternate allocation.
Interventions	Single group 1; ticarcillin 300 mg/kg/day, 4-hourly. Single group 2: gentamicin 3 - 4 mg/kg/day (adults), 4 - 7 mg/kg/day (children). Combination group: ticarcillin 300 mg/kg/day, 4-hourly plus gentamicin 3 - 4 mg/kg/day (adults), 4 - 7 mg/kg/day (children). All participants also received chest physiotherapy, bronchial drainage and aerosol therapy with mucolytics.
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. No withdrawals.

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.

Parry 1977 *(Continued)*

Selective reporting (reporting bias)	High risk	Paper states that "pulmonary function tests were performed when possible", but no further details or results are given.
Other bias	Low risk	None identified.

Pedersen 1986

Study characteristics	
Methods	RCT. Cross-over design - 3 months in between treatment arms. Duration: 14-day course. Elective regimen.
Participants	20 participants; 3 drop outs, 17 completed trial. Age, mean: 12.6 years. Gender split: 10 male, 10 female. PsA colonised.
Interventions	Single antibiotic: ceftazidime 150 mg/kg/day, 8-hourly. Combination antibiotic: ceftazidime plus tobramycin 10 mg/kg/day, 8-hourly.
Outcomes	Lung function, inflammatory markers, development of resistant strains.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
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. NJ: described as an open study - so I interpret this to mean no blinding??
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).
Selective reporting (reporting bias)	Low risk	Outcomes stated in the methods section reported in the results.
Other bias	Low risk	None identified.

Smith 1999

Study characteristics	
Methods	Double-blind RCT. Parallel trial. Duration: 12 - 14 days (but maximum duration of 31 days) with follow-up 2 to 8 weeks later. Symptomatic regimen.
Participants	111 participants enrolled, 35 withdrawn. Total cohort (n = 76); mean (range) age 16.3 years (6 - 18 years); 37 male, 39 female; PsA colonised. Single group (azlocillin) (n = 33): mean (SD) age 16.07 (7.4) years; 19 male, 14 female. Combination group (azlocillin plus tobramycin) (n = 43): mean (SD) age 16.53 (6.9) years; 18 male, 25 female.
Interventions	Single group: azlocillin 450 mg/kg/day, 4-hourly plus placebo (5% dextrose in water), 6-hourly. Combination group: azlocillin plus tobramycin 240 mg/m^2/day, 6-hourly.
Outcomes	Lung function, time to next admission, symptom scores, adverse events, bacteriology, inflammatory markers, resistant strains.
Notes	No data for symptom scores only narrative.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation balance by FVC and centre.
Allocation concealment (selection bias)	Low risk	Code generated by research pharmacist at the core centre.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and clinicians blinded, serum concentrations monitored by unblinded 3rd party (research pharmacist).
Incomplete outcome data (attrition bias) All outcomes	Low risk	35 out of 111 participants withdrawn (21 from azlocillin group), reasons given in a table. SS: should this be unclear or high risk because more than 15% dropped out?
Selective reporting (reporting bias)	Unclear risk	Outcomes described in the methods are reported in the results, but some just brief narrative statements.
Other bias	Low risk	None identified.

CBC: complete blood count
CF: cystic fibrosis
CXR: chest x-ray
ITT: intention-to-treat
PsA: *Pseudomonas aeruginosa*
RCT: randomised controlled trial

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-Aloul 2004	Comparison of two single IV antibiotics, not single vs combination.
Al-Aloul 2019	No single IV AB arm, both groups got two IV AB treatments and one group additionally got fosfomycin.
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).
CFMATTERS 2017	Comparison of 2 antibiotics with the same 2 antibiotics plus a 3rd microbiome-derived antibiotic treatment.
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.
Enaud 2017	Comparison of IV antibiotics and control, not single vs combination IV regimen.
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.

Study	Reason for exclusion
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.
McCabe 2013	Not a comparison of single vs combination antibiotics; evaluation of a twice-daily tobramycin regimen.
Moskowitz 2011	Comparison of IV antibiotics using standard vs biofilm susceptibility testing of P. aeruginosa sputum isolates.
NCT01044719	Comparison of duration of antibiotic treatment not comparing single vs combination antibiotics.
NCT01667094	Comparison of intermittent vs continuous IV regimens, not a comparison of single vs combination antibiotics.
NCT01694069	Comparison of timing of administration of the same IV antibiotic combination, not single vs combination.
NCT02421120	Comparison of IV antibiotics, but not randomised.
NCT02918409	Comparison of 2 single antibiotics.
NCT03066453	Single IV vs combination IV antibiotics plus nebulised antibiotic.
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.
Park 2018	Comparison of oral vs IV antibiotics for treating MRSA not *Pseudomonas aeruginosa*.
Permin 1983	Comparison of single agent compared with 2 other antibiotics (i.e. drug A vs drug B plus drug C).
Prayle 2016	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).
STOP 2 2018	Comparison of duration of antibiotic treatment not comparing single vs combination antibiotics.

Study	Reason for exclusion
TORPEDO 2018	An eradication trial comparing oral antibiotics plus inhaled antibiotics to IV antibiotics plus inhaled antibiotics - so not a comparison of single or combination IV antibiotics.
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
IV: intravenous
vs: versus

DATA AND ANALYSES

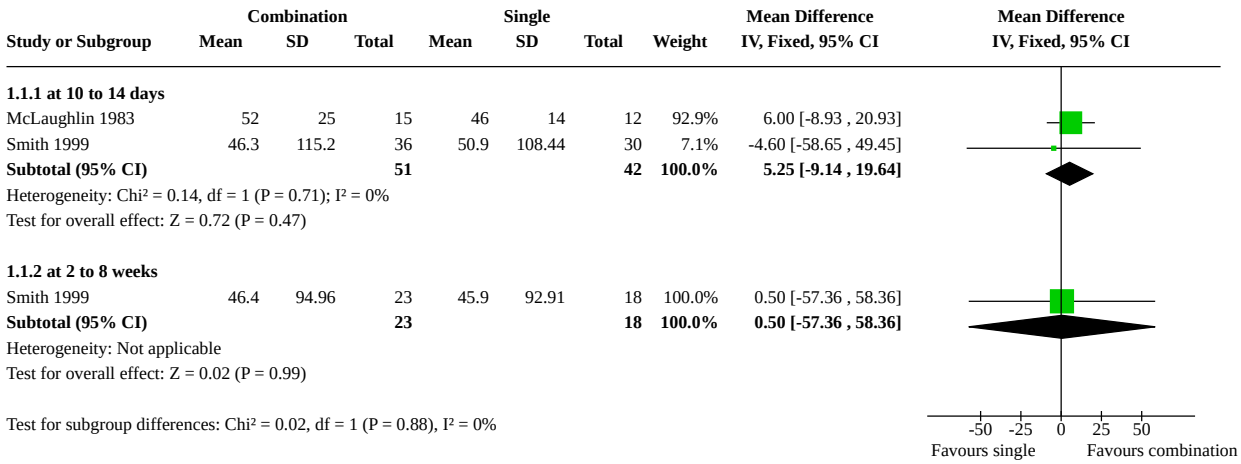
Comparison 1. Single versus combination antibiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 FEV_1 % predicted (mean absolute values at end of course)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1.1 at 10 to 14 days	2	93	Mean Difference (IV, Fixed, 95% CI)	5.25 [-9.14, 19.64]
1.1.2 at 2 to 8 weeks	1	41	Mean Difference (IV, Fixed, 95% CI)	0.50 [-57.36, 58.36]
1.2 Mean FVC at end of course (% pred)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.2.1 at 10 to 14 days	2	93	Mean Difference (IV, Fixed, 95% CI)	1.84 [-11.44, 15.12]
1.2.2 at 2 to 8 weeks	1	41	Mean Difference (IV, Fixed, 95% CI)	6.90 [-50.50, 64.30]
1.3 Mean RV at end of course (% pred)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.3.1 at 10 to 14 days	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.4 Mean TLC at end of course (% pred)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.4.1 at 10 to 14 days	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.5 Mean RV/TLC at end of course (% pred)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.5.1 at 10 to 14 days	1	64	Mean Difference (IV, Fixed, 95% CI)	-1.40 [-40.68, 37.88]
1.5.2 At 2 to 8 weeks	1	40	Mean Difference (IV, Fixed, 95% CI)	-5.20 [-54.27, 43.87]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.6 Mean PFR at end of course (% pred)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.6.1 at 10 to 14 days	2	91	Mean Difference (IV, Fixed, 95% CI)	3.21 [-11.49, 17.91]
1.6.2 At 2 to 8 weeks	1	40	Mean Difference (IV, Fixed, 95% CI)	2.30 [-60.90, 65.50]
1.7 Mean MMEF at end of course (% pred)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.7.1 at 10 to 14 days	2	91	Mean Difference (IV, Fixed, 95% CI)	7.17 [-8.22, 22.55]
1.7.2 At 2 to 8 weeks	1	40	Mean Difference (IV, Fixed, 95% CI)	-1.90 [-73.27, 69.47]
1.8 Number of Pseudomonas isolates eradicated at end of course	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.8.1 at 10 to 14 days	1	16	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.34 [0.51, 78.02]
1.8.2 2 to 8 weeks	1	18	Peto Odds Ratio (Peto, Fixed, 95% CI)	10.16 [1.44, 71.65]
1.9 Mean change Pseudomonas density in cfu/g at end of course	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.9.1 at 10 to 14 days	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.10 Number resistant strains of Pseudomonas aeruginosa	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.10.1 at baseline	2	140	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.83 [0.38, 1.82]
1.10.2 at 10 to 14 days	2	99	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.44 [0.94, 6.32]
1.10.3 at 2 to 8 weeks	2	76	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.44 [0.17, 1.14]
1.10.4 Difference from baseline at 2 to 8 weeks	1	29	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.27 [0.06, 1.18]
1.11 Number adverse events	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.11.1 local erythema / irritation	2	131	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.46 [0.09, 2.36]
1.11.2 generalised rash	1	20	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.16 [0.12, 316.67]

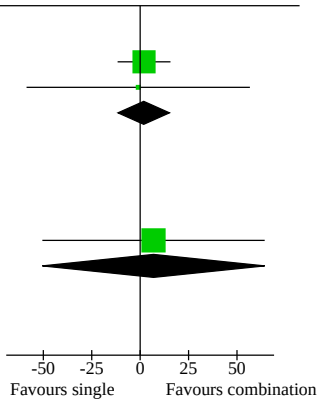
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.11.3 fever	1	20	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.81 [0.05, 14.14]
1.11.4 renal impairment (increased creatinine by 50%)	1	80	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.54 [0.15, 15.56]
1.11.5 auditory impairment	1	76	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.86 [0.11, 305.44]
1.11.6 proteinuria	1	63	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.62 [0.68, 19.30]
1.12 Number readmitted to hospital	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.12.1 at 2 to 8 weeks	1	16	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.01, 1.30]
1.12.2 in 80 days	1	76	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.30 [0.12, 0.73]
1.13 Mean time to next course of antibiotics (weeks)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.14 Mean Schwachman score at end of course	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.15 Mean WBC count at end of course	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.15.1 at 10 to 14 days	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1: Single versus combination antibiotics, Outcome 1: FEV_1 % predicted (mean absolute values at end of course)



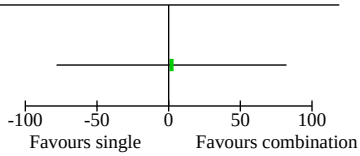
Analysis 1.2. Comparison 1: Single versus combination antibiotics, Outcome 2: Mean FVC at end of course (% pred)

Study or Subgroup	Combination Mean	SD	Total	Single Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.2.1 at 10 to 14 days								
McLaughlin 1983	71	24	15	69	11	12	94.7%	2.00 [-11.65 , 15.65]
Smith 1999	72.7	122.4	36	73.7	116.1	30	5.3%	-1.00 [-58.66 , 56.66]
Subtotal (95% CI)			**51**			**42**	**100.0%**	**1.84 [-11.44 , 15.12]**
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%								
Test for overall effect: Z = 0.27 (P = 0.79)								
1.2.2 at 2 to 8 weeks								
Smith 1999	70.5	108.87	23	63.6	78.49	18	100.0%	6.90 [-50.50 , 64.30]
Subtotal (95% CI)			**23**			**18**	**100.0%**	**6.90 [-50.50 , 64.30]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.24 (P = 0.81)								
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.87), I² = 0%								



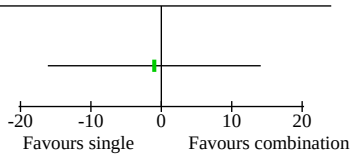
Analysis 1.3. Comparison 1: Single versus combination antibiotics, Outcome 3: Mean RV at end of course (% pred)

Study or Subgroup	Combination Mean	SD	Total	Single Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.3.1 at 10 to 14 days							
McLaughlin 1983	281	126	15	279	86	12	2.00 [-78.21 , 82.21]



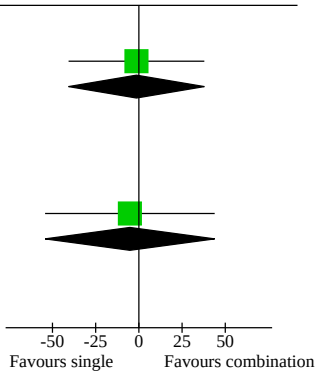
Analysis 1.4. Comparison 1: Single versus combination antibiotics, Outcome 4: Mean TLC at end of course (% pred)

Study or Subgroup	Combination Mean	SD	Total	Single Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.4.1 at 10 to 14 days							
McLaughlin 1983	117	21	15	118	19	12	-1.00 [-16.12 , 14.12]



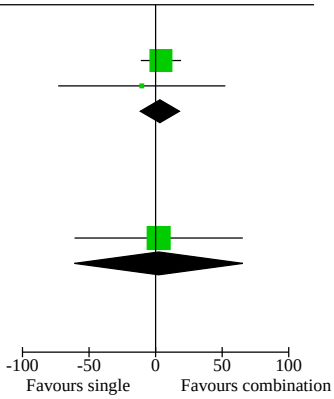
Analysis 1.5. Comparison 1: Single versus combination antibiotics, Outcome 5: Mean RV/TLC at end of course (% pred)

Study or Subgroup	Combination Mean	SD	Total	Single Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.5.1 at 10 to 14 days								
Smith 1999	42.7	88.15	35	44.1	72.16	29	100.0%	-1.40 [-40.68 , 37.88]
Subtotal (95% CI)			**35**			**29**	**100.0%**	**-1.40 [-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	45.9	73.64	22	51.1	82.73	18	100.0%	-5.20 [-54.27 , 43.87]
Subtotal (95% CI)			**22**			**18**	**100.0%**	**-5.20 [-54.27 , 43.87]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.21 (P = 0.84)								
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.91), I² = 0%								



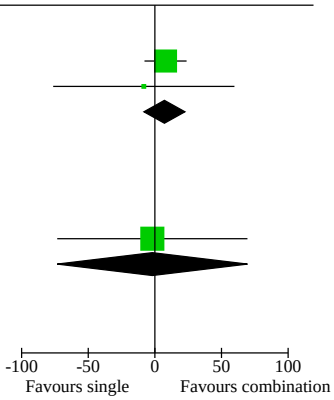
Analysis 1.6. Comparison 1: Single versus combination antibiotics, Outcome 6: Mean PFR at end of course (% pred)

Study or Subgroup	Combination Mean	SD	Total	Single Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.6.1 at 10 to 14 days								
McLaughlin 1983	67	21	15	63	19	12	94.5%	4.00 [-11.12 , 19.12]
Smith 1999	54.7	117.73	35	65.1	135.17	29	5.5%	-10.40 [-73.18 , 52.38]
Subtotal (95% CI)			**50**			**41**	**100.0%**	**3.21 [-11.49 , 17.91]**
Heterogeneity: Chi² = 0.19, df = 1 (P = 0.66); I² = 0%								
Test for overall effect: Z = 0.43 (P = 0.67)								
1.6.2 At 2 to 8 weeks								
Smith 1999	61.9	106.47	22	59.6	97.16	18	100.0%	2.30 [-60.90 , 65.50]
Subtotal (95% CI)			**22**			**18**	**100.0%**	**2.30 [-60.90 , 65.50]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.07 (P = 0.94)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.98), I² = 0%								



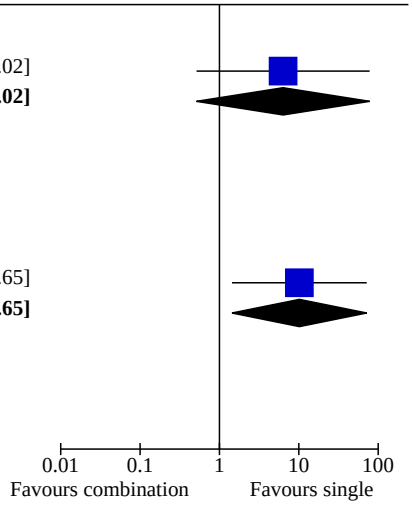
Analysis 1.7. Comparison 1: Single versus combination antibiotics, Outcome 7: Mean MMEF at end of course (% pred)

Study or Subgroup	Combination Mean	SD	Total	Single Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.7.1 at 10 to 14 days								
McLaughlin 1983	30	27	15	22	14	12	94.9%	8.00 [-7.79 , 23.79]
Smith 1999	25.2	111.81	35	33.5	156.7	29	5.1%	-8.30 [-76.31 , 59.71]
Subtotal (95% CI)			**50**			**41**	**100.0%**	**7.17 [-8.22 , 22.55]**
Heterogeneity: Chi² = 0.21, df = 1 (P = 0.65); I² = 0%								
Test for overall effect: Z = 0.91 (P = 0.36)								
1.7.2 At 2 to 8 weeks								
Smith 1999	25.8	94.75	22	27.7	128.55	18	100.0%	-1.90 [-73.27 , 69.47]
Subtotal (95% CI)			**22**			**18**	**100.0%**	**-1.90 [-73.27 , 69.47]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.05 (P = 0.96)								
Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.81), I² = 0%								



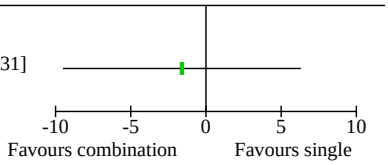
Analysis 1.8. Comparison 1: Single versus combination antibiotics, Outcome 8: Number of Pseudomonas isolates eradicated at end of course

Study or Subgroup	Combination Events	Combination Total	Single Events	Single Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.8.1 at 10 to 14 days						
Huang 1982	3	10	0	6	100.0%	6.34 [0.51 , 78.02]
Subtotal (95% CI)		**10**		**6**	**100.0%**	**6.34 [0.51 , 78.02]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.44 (P = 0.15)						
1.8.2 2 to 8 weeks						
Costantini 1982	6	11	0	7	100.0%	10.16 [1.44 , 71.65]
Subtotal (95% CI)		**11**		**7**	**100.0%**	**10.16 [1.44 , 71.65]**
Total events:	6		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.33 (P = 0.02)						
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.77), I² = 0%						



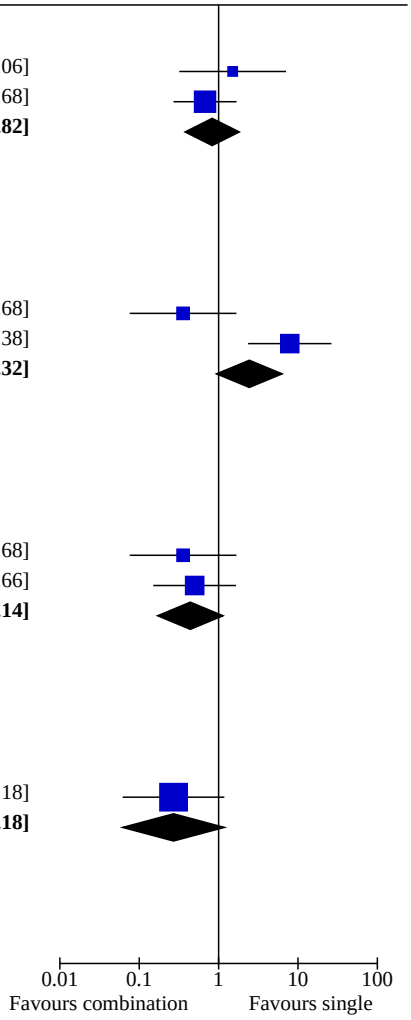
Analysis 1.9. Comparison 1: Single versus combination antibiotics, Outcome 9: Mean change Pseudomonas density in cfu/g at end of course

Study or Subgroup	Combination Mean	Combination SD	Combination Total	Single Mean	Single SD	Single Total	Mean Difference IV, Fixed, 95% CI
1.9.1 at 10 to 14 days							
Smith 1999	5.3	19.67	43	6.9	15.5	33	-1.60 [-9.51 , 6.31]



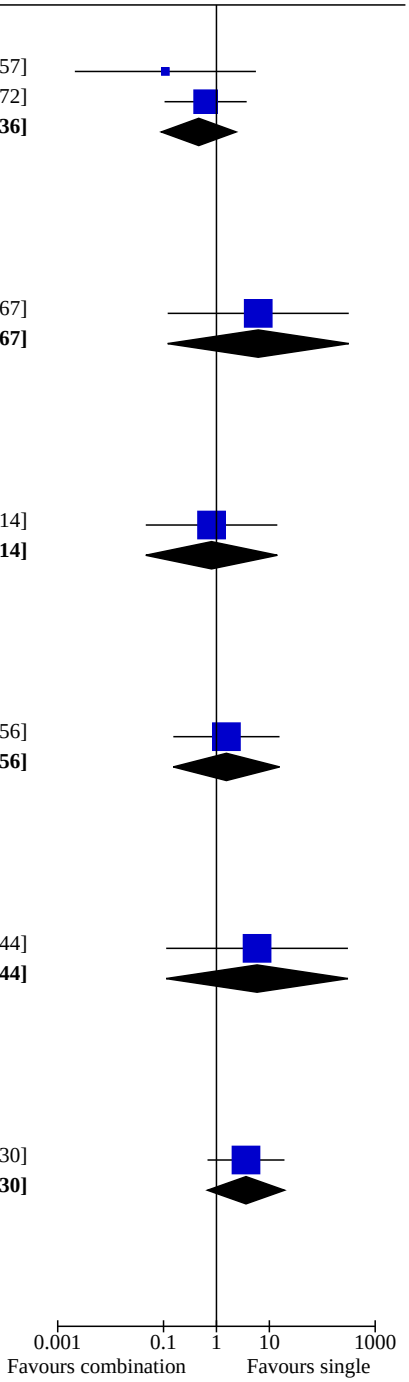
Analysis 1.10. Comparison 1: Single versus combination antibiotics, Outcome 10: Number resistant strains of Pseudomonas aeruginosa

Study or Subgroup	Combination Events	Combination Total	Single Events	Single Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.10.1 at baseline						
McLaughlin 1983	5	14	4	15	25.9%	1.50 [0.32 , 7.06]
Smith 1999	10	57	13	54	74.1%	0.67 [0.27 , 1.68]
Subtotal (95% CI)		**71**		**69**	**100.0%**	**0.83 [0.38 , 1.82]**
Total events:	15		17			
Heterogeneity: Chi² = 0.77, df = 1 (P = 0.38); I² = 0%						
Test for overall effect: Z = 0.46 (P = 0.64)						
1.10.2 at 10 to 14 days						
McLaughlin 1983	8	14	12	15	37.9%	0.36 [0.08 , 1.68]
Smith 1999	38	40	19	30	62.1%	7.88 [2.35 , 26.38]
Subtotal (95% CI)		**54**		**45**	**100.0%**	**2.44 [0.94 , 6.32]**
Total events:	46		31			
Heterogeneity: Chi² = 9.55, df = 1 (P = 0.002); I² = 90%						
Test for overall effect: Z = 1.83 (P = 0.07)						
1.10.3 at 2 to 8 weeks						
McLaughlin 1983	8	14	12	15	37.6%	0.36 [0.08 , 1.68]
Smith 1999	7	26	9	21	62.4%	0.50 [0.15 , 1.66]
Subtotal (95% CI)		**40**		**36**	**100.0%**	**0.44 [0.17 , 1.14]**
Total events:	15		21			
Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² = 0%						
Test for overall effect: Z = 1.70 (P = 0.09)						
1.10.4 Difference from baseline at 2 to 8 weeks						
McLaughlin 1983	3	14	8	15	100.0%	0.27 [0.06 , 1.18]
Subtotal (95% CI)		**14**		**15**	**100.0%**	**0.27 [0.06 , 1.18]**
Total events:	3		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.74 (P = 0.08)						
Test for subgroup differences: Chi² = 8.86, df = 3 (P = 0.03), I² = 66.1%						



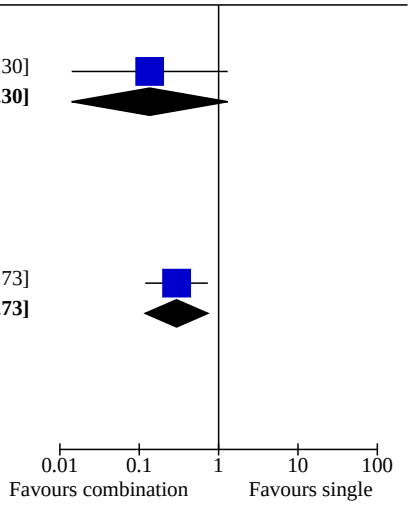
Analysis 1.11. Comparison 1: Single versus combination antibiotics, Outcome 11: Number adverse events

Study or Subgroup	Combination Events	Combination Total	Single Events	Single Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.11.1 local erythema / irritation						
McCarty 1988	0	11	1	9	17.1%	0.11 [0.00 , 5.57]
Smith 1999	2	57	3	54	82.9%	0.62 [0.10 , 3.72]
Subtotal (95% CI)		**68**		**63**	**100.0%**	**0.46 [0.09 , 2.36]**
Total events:	2		4			
Heterogeneity: Chi² = 0.63, df = 1 (P = 0.43); I² = 0%						
Test for overall effect: Z = 0.93 (P = 0.35)						
1.11.2 generalised rash						
McCarty 1988	1	11	0	9	100.0%	6.16 [0.12 , 316.67]
Subtotal (95% CI)		**11**		**9**	**100.0%**	**6.16 [0.12 , 316.67]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.90 (P = 0.37)						
1.11.3 fever						
McCarty 1988	1	11	1	9	100.0%	0.81 [0.05 , 14.14]
Subtotal (95% CI)		**11**		**9**	**100.0%**	**0.81 [0.05 , 14.14]**
Total events:	1		1			
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	100.0%	1.54 [0.15 , 15.56]
Subtotal (95% CI)		**45**		**35**	**100.0%**	**1.54 [0.15 , 15.56]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.37 (P = 0.71)						
1.11.5 auditory impairment						
Smith 1999	1	43	0	33	100.0%	5.86 [0.11 , 305.44]
Subtotal (95% CI)		**43**		**33**	**100.0%**	**5.86 [0.11 , 305.44]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.88 (P = 0.38)						
1.11.6 proteinuria						
Smith 1999	5	34	1	29	100.0%	3.62 [0.68 , 19.30]
Subtotal (95% CI)		**34**		**29**	**100.0%**	**3.62 [0.68 , 19.30]**
Total events:	5		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.51 (P = 0.13)						
Test for subgroup differences: Chi² = 4.20, df = 5 (P = 0.52), I² = 0%						



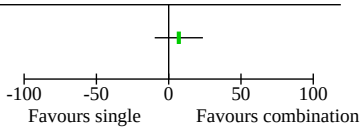
Analysis 1.12. Comparison 1: Single versus combination antibiotics, Outcome 12: Number readmitted to hospital

Study or Subgroup	Combination Events	Combination Total	Single Events	Single Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.12.1 at 2 to 8 weeks						
Huang 1982	1	10	3	6	100.0%	0.14 [0.01 , 1.30]
Subtotal (95% CI)		**10**		**6**	**100.0%**	**0.14 [0.01 , 1.30]**
Total events:	1		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.73 (P = 0.08)						
1.12.2 in 80 days						
Smith 1999	13	43	20	33	100.0%	0.30 [0.12 , 0.73]
Subtotal (95% CI)		**43**		**33**	**100.0%**	**0.30 [0.12 , 0.73]**
Total events:	13		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.63 (P = 0.009)						
Test for subgroup differences: Chi² = 0.39, df = 1 (P = 0.53), I² = 0%						



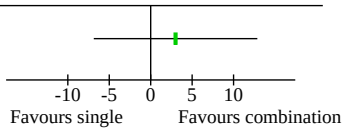
Analysis 1.13. Comparison 1: Single versus combination antibiotics, Outcome 13: Mean time to next course of antibiotics (weeks)

Study or Subgroup	Combination Mean	Combination SD	Combination Total	Single Mean	Single SD	Single Total	Mean Difference IV, Fixed, 95% CI
McLaughlin 1983	31	17	18	24	30	16	7.00 [-9.67 , 23.67]



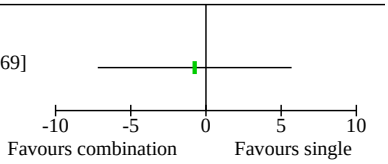
Analysis 1.14. Comparison 1: Single versus combination antibiotics, Outcome 14: Mean Schwachman score at end of course

Study or Subgroup	Combination Mean	Combination SD	Combination Total	Single Mean	Single SD	Single Total	Mean Difference IV, Fixed, 95% CI
McLaughlin 1983	71	13	15	68	13	12	3.00 [-6.87 , 12.87]



Analysis 1.15. Comparison 1: Single versus combination antibiotics, Outcome 15: Mean WBC count at end of course

Study or Subgroup	Combination Mean	Combination SD	Combination Total	Single Mean	Single SD	Single Total	Mean Difference IV, Fixed, 95% CI
1.15.1 at 10 to 14 days							
Smith 1999	7.43	15.34	43	8.18	13.27	33	-0.75 [-7.19 , 5.69]



ADDITIONAL TABLES

Table 1. Lung function results (median (range)) from Pedersen 1986

Time point	Outcome	Combination antibiotics	Single antibiotic
Day 1	FEV_1 % predicted	56 (35 to 74)	53 (33 to 68)
	FVC % predicted	57 (39 to 79)	54 (38 to 67)
Day 14	FEV_1 % predicted	69 (56 to 83)	66 (52 to 81)
	FVC % predicted	72 (60 to 85)	64 (53 to 83)
Day 90	FEV_1 % predicted	53 (27 to 70)	55 (33 to 75)
	FVC % predicted	67 (33 to 76)	59 (45 to 80)

FEV_1: forced expiratory volume at 1 second
FVC: forced vital capacity

APPENDICES

Appendix 1. Electronic search strategies

Database	Search strategy	Date searched
US National Institutes of Health Ongoing Trials Register Clinicaltrials.gov (www.clinicaltrials.gov)	[Advanced Search] CONDITION/ DISEASE: Cystic Fibrosis OTHER TERMS: (Antibiotic OR antibacterial) AND intravenous AND (Pseudomonas aeruginosa OR P. aeruginosa) STUDY TYPE: Interventional Studies	16 November 2020
World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch)	[Advanced Search Form] TITLE: antibiotics OR antibacterial CONDITION: cystic fibrosis INTERVENTION: intravenous OR IV RECRUITMENT STATUS: All	database unavailable due to Covid-19 pandemic

WHAT'S NEW

Date	Event	Description
30 June 2021	Review declared as stable	Due to a lack of research in this area, this review will no longer be updated.

HISTORY

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

Date	Event	Description
12 April 2021	New citation required but conclusions have not changed	Two new authors have updated this review after the previous author team stepped down. The review's conclusions remain the same.
12 April 2021	New search has been performed	A search of the Cystic Fibrosis and Genetic Disorders Review Group's Cystic Fibrosis Trials Register identified 24 references that were potentially eligible for inclusion in the review and searches of online trials registries identified a further three references to three studies. Three references were single additional references to already excluded studies (Gold 1985; Hubert 2009; Prayle 2016). 13 new studies (29 references) were excluded (Al-Aloul 2004; Al-Aloul 2019; CFMATTERS 2017; Moskowitz 2011; NCT01044719; NCT01667094; NCT01694069; NCT02421120; NCT02918409; NCT03066453; Park 2018; STOP 2 2018; TORPEDO 2018). We have added two new summary of findings tables to this updated review.
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. No new data were added to the review at this update, therefore our conclusions remain the same.
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 2016; Turner 2013).
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

Date	Event	Description
		(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	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.
20 February 2008	Amended	The 'Plain Language Summary' has been updated in line with latest guidance from The Cochrane Collaboration.
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 citation required and conclusions have changed	Substantive amendment
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 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.
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

Current review version

Dr Poppy Holland updated the additional searches, checked the previously included trials and drafted the text of the review.

Nikki Jahnke helped draft the text of the review.

Previous versions of the review

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 Poppy Holland has no potential conflict of interest to declare.

Nikki Jahnke has no potential conflict of interest to declare.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- National Institute for Health Research, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For this 2021 update of the review, in our outcome measures we have replace the term 'improvement' with 'change' to reflect that changes may not always be improvements. For this update we have also added two new summaryof findnigs tables.

It was noted that a previous review team had additionally reported on clinical scores and antibiotic resistance after the outcomes in the original protocol were published. We agree that these are important clinical outcomes and should be included in the review.

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

MeSH check words

Adult; Child; Humans