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TABLE OF CONTENTS

HEADER 1
ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
SUMMARY OF FINDINGS 4
BACKGROUND 8
OBJECTIVES 8
METHODS 9
RESULTS 11
Figure 1. 12
Figure 2. 15
Figure 3. 16
DISCUSSION 19
AUTHORS' CONCLUSIONS 20
ACKNOWLEDGEMENTS 20
REFERENCES 22
CHARACTERISTICS OF STUDIES 40
DATA AND ANALYSES 51
Analysis 1.1. Comparison 1 Inhaled antibiotics versus intravenous antibiotics, Outcome 1 Need for additional IV antibiotics. ... 52
Analysis 1.2. Comparison 1 Inhaled antibiotics versus intravenous antibiotics, Outcome 2 Adverse events. 52
Analysis 2.1. Comparison 2 Inhaled antibiotics plus intravenous antibiotics versus intravenous antibiotics, Outcome 1 Need for hospital admission. 53
Analysis 2.2. Comparison 2 Inhaled antibiotics plus intravenous antibiotics versus intravenous antibiotics, Outcome 2 Adverse events. 53
Analysis 2.3. Comparison 2 Inhaled antibiotics plus intravenous antibiotics versus intravenous antibiotics, Outcome 3 Development of resistant organisms. 53
WHAT'S NEW 53
CONTRIBUTIONS OF AUTHORS 54
DECLARATIONS OF INTEREST 55
SOURCES OF SUPPORT 55
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 55
INDEX TERMS 55

[Intervention Review]

Inhaled antibiotics for pulmonary exacerbations in cystic fibrosis

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ABSTRACT

Background

Cystic fibrosis is a genetic disorder in which abnormal mucus in the lungs is associated with susceptibility to persistent infection. Pulmonary exacerbations are when symptoms of infection become more severe. Antibiotics are an essential part of treatment for exacerbations and inhaled antibiotics may be used alone or in conjunction with oral antibiotics for milder exacerbations or with intravenous antibiotics for more severe infections. Inhaled antibiotics do not cause the same adverse effects as intravenous antibiotics and may prove an alternative in people with poor access to their veins. This is an update of a previously published review.

Objectives

To determine if treatment of pulmonary exacerbations with inhaled antibiotics in people with cystic fibrosis improves their quality of life, reduces time off school or work and improves their long-term survival.

Search methods

We searched the Cochrane Cystic Fibrosis Group's Cystic Fibrosis Trials Register. Date of the last search: 03 October 2018.

We searched ClinicalTrials.gov, the Australia and New Zealand Clinical Trials Registry and WHO ICTRP for relevant trials. Date of last search: 09 October 2018.

Selection criteria

Randomised controlled trials in people with cystic fibrosis with a pulmonary exacerbation in whom treatment with inhaled antibiotics was compared to placebo, standard treatment or another inhaled antibiotic for between one and four weeks.

Data collection and analysis

Two review authors independently selected eligible trials, assessed the risk of bias in each trial and extracted data. They assessed the quality of the evidence using the GRADE criteria. Authors of the included trials were contacted for more information.

Main results

Four trials with 167 participants are included in the review. Two trials (77 participants) compared inhaled antibiotics alone to intravenous antibiotics alone and two trials (90 participants) compared a combination of inhaled and intravenous antibiotics to intravenous antibiotics alone. Trials were heterogenous in design and two were only available in abstract form. Risk of bias was difficult to assess in most trials, but for all trials we judged there to be a high risk from lack of blinding and an unclear risk with regards to randomisation. Results were not fully reported and only limited data were available for analysis.

Inhaled antibiotics alone versus intravenous antibiotics alone

Only one trial (n = 18) reported a perceived improvement in lifestyle (quality of life) in both groups (very low-quality of evidence). Neither trial reported on time off work or school. Both trials measured lung function, but there was no difference reported between treatment groups (very low-quality evidence). With regards to our secondary outcomes, one trial (n = 18) reported no difference in the need for additional antibiotics and the second trial (n = 59) reported on the time to next exacerbation. In neither case was a difference between treatments identified (both very low-quality evidence). The single trial (n = 18) measuring adverse events and sputum microbiology did not observe any in either treatment group for either outcome (very low-quality evidence).

Inhaled antibiotics plus intravenous antibiotics versus intravenous antibiotics alone

Neither trial reported on quality of life or time off work or school. Both trials measured lung function, but found no difference between groups in forced expiratory volume in one second (one trial, n = 28, very low-quality evidence) or vital capacity (one trial, n = 62). Neither trial reported on the need for additional antibiotics or the time to the next exacerbation; however, one trial (n = 28) reported on hospital admissions and found no difference between groups. Both trials reported no difference between groups in adverse events (very low-quality evidence) and one trial (n = 62) reported no difference in the emergence of antibiotic-resistant organisms (very low-quality evidence).

Authors' conclusions

There is little useful high-level evidence to judge the effectiveness of inhaled antibiotics for the treatment of pulmonary exacerbations in people with cystic fibrosis. The included trials were not sufficiently powered to achieve their goals. Hence, we are unable to demonstrate whether one treatment was superior to the other or not. Further research is needed to establish whether inhaled tobramycin may be used as an alternative to intravenous tobramycin for some pulmonary exacerbations.

PLAIN LANGUAGE SUMMARY

Inhaling antibiotics to treat temporary worsening of lung infection in people with cystic fibrosis

Review question

We reviewed the evidence for inhaling antibiotics to treat exacerbations (flare ups) of lung infection in people with cystic fibrosis.

Background

Cystic fibrosis is a serious genetic disorder that results in abnormally sticky mucus in several parts of the body. In the lungs the sticky mucus can lead to repeated infection. An exacerbation makes the symptoms more severe. Antibiotics are an essential part of treatment and may be given by mouth, by needle into the blood stream or by inhaling the drug. We wanted to learn if inhaling antibiotics improved general health compared to the other methods.

This might mean that people with cystic fibrosis could avoid hospitalisation for intravenous antibiotics and some side effects. Inhaling the antibiotics would also be easier for people who have difficulty with access to their veins. This is an updated version of the review.

Search date

The evidence is current to: 09 October 2018.

Study characteristics

We found four trials with a total of 167 participants, two of which compared inhaled antibiotics alone to intravenous antibiotics alone (77 participants) and two which compared a combination of inhaled and intravenous antibiotics to intravenous antibiotics alone (90 participants) for treating exacerbations in people with cystic fibrosis. In all trials the inhaled antibiotics were compared to the same antibiotics given intravenously. The numbers of participants in each trial ranged from 18 to 62.

Key results

Inhaled antibiotics alone versus intravenous antibiotics alone

One trial (18 participants) reported a perceived improvement in lifestyle in both groups but neither trial reported on time off work or school. Both trials measured lung function, but neither reported any difference between treatment groups. One trial (18 participants) reported no difference in the need for additional antibiotics and the second trial (59 participants) reported on the time to next exacerbation - there was no difference between inhaled or intravenous antibiotics for either outcome. Only one trial (18 participants) measured adverse events and sputum microbiology, but did not find any difference between treatments for either outcome.

Inhaled antibiotics plus intravenous antibiotics versus intravenous antibiotics alone

Neither trial reported on quality of life or time off work or school. Both trials reported lung function, but found no difference between groups. Neither trial reported on the need for additional antibiotics or the time to the next exacerbation; however, one trial (28 participants) reported on hospital admissions and found no difference between groups. Both trials reported no difference between groups in adverse events and one trial (62 participants) reported no difference in the emergence of antibiotic-resistant organisms.

Quality of the evidence

We graded the quality of the evidence as very low. We had concerns since none of the trials stated how the participants were diagnosed with CF or how they defined an exacerbation. It was not possible to keep the treatment group secret from the participants as the trials compared different ways of giving the antibiotics and we thought this would likely influence some of the results. We were not sure whether the participants were put into the different groups truly at random and we do not know how this might affect the results.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Summary of findings: inhaled antibiotics compared with IV antibiotics

Inhaled antibiotics compared with IV antibiotics for pulmonary exacerbations in CF

Patient or population: children and adults with CF and an acute exacerbation

Settings: inpatient in hospital

Intervention: inhaled antibiotics

Comparison: IV antibiotics

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	IV antibiotics	Inhaled antibiotics				
Quality of life perceived change in lifestyle after treatment Follow-up: 4 weeks	There was a perceived improvement in lifestyle after treatment in both groups.			18 (1)	⊕⊖⊖⊖ **very low**[1,2]	No data provided.
Time off work or school	This outcome was not reported.					
Lung function change in FEV_1 after treatment Follow-up: 4 weeks after completion of therapy	There was improvement in FEV_1 after treatment in both groups but this was not significant.			18 (1)	⊕⊖⊖⊖ **very low**[1,2]	Not enough data to enter into analysis. A second 3-arm trial also measured lung function but the specific measurements were not described; there was no difference reported in treatment with twice-daily IV ceftazidine or once-daily inhaled ceftazidine, but both of these treatments were better than 3-times daily IV ceftazidine.

Need for additional IV or oral antibiotics Follow-up: 4 weeks after completion of therapy	No events were seen in the control group.	**RR 6.11** (0.33 to 111.71)	18 (1)	⊕⊖⊖⊖ **very low**[1,2]	Very little data reported.
Time to next pulmonary exacerbation Follow-up: 4 weeks after completion of therapy	The time to the next exacerbation was longest in the once-daily inhaled antibiotic group, less in the twice-daily IV antibiotic group, but both longer than in the group receiving IV antibiotics three-times-daily.		59 (1)	⊕⊖⊖⊖ **very low**[1,2]	Very little data reported.
Adverse events Follow-up: 4 weeks after completion of therapy	No adverse events were observed in either group.		18 (1)	⊕⊖⊖⊖ **very low**[1,2]	
Microbiology emergence of resistant organisms Follow-up: not stated	No results reported for this outcome.		59 (1)	⊕⊖⊖⊖ **very low**[1,2]	No results reported. This outcome was stated to be measured in the Shatunov trial, but no results were reported (Shatunov 2001)

*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).
CF: cystic fibrosis; **CI:** confidence interval; **FEV_1:** forced expiratory volume at 1 second; **RR:** risk ratio; **IV:** intravenous.

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

1. Downgraded twice for unclear or high risk of bias within the trial.
2. Downgraded once due to imprecision - very low participant numbers.

Summary of findings 2. Summary of findings: inhaled antibiotics plus IV antibiotics compared with IV antibiotics only

Inhaled plus IV antibiotics compared with IV antibiotics only for pulmonary exacerbation in CF

Patient or population: children and adults with pulmonary exacerbation in CF

Settings: inpatient in hospital

Intervention: inhaled antibiotics plus IV antibiotics

Comparison: IV antibiotics

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	IV antibiotics alone	IV + inhaled antibiotics				
Quality of life	This outcome was not reported.					
Time off work or school	This outcome was not reported.					
Lung function change in FEV_1 % predicted from baseline Follow-up: end of treatment (discharge from hospital which ranged from 14 days to 26 days	No significant difference was found between groups in change in FEV_1 (intervention group 6.7%, comparison group 3.9%).			28 (1)	⊕⊖⊖⊖ **very low**[1,2]	
Need for additional IV or oral antibiotics	This outcome was not reported.					
Time to next pulmonary exacerbation	This outcome was not reported.					
Adverse events moderate adverse events experienced during and after treatment Follow-up: 4 - 6 weeks after the end of treatment (2 weeks)	No reports of renal toxicity in either group. Serum creatinine levels remained at less than 1.0 mg/dL and did not increase by more than 0.5 mg/dL in any participant; no proteinuria or cylinduria observed in either group.			28 (1)	⊕⊖⊖⊖ **very low**[1,2]	No data were available for analysis so narrative text has been used. A further study reported this outcome but did not state which group the adverse events occurred in and therefore provides no evidence.
Microbiology emergence of resistant organisms	**83 per 1000**	**187 per 1000** (22 to 1000)	**RR 2.25** (0.27 to 19.04)	28 (1)	⊕⊖⊖⊖ **very low**[1,2]	

Follow-up: 1 to 2 weeks

*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).
CF: cystic fibrosis; **CI:** confidence interval; **FEV_1:** forced expiratory volume at 1 second; **RR:** risk ratio; **IV:** intravenous.

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

1. Downgraded twice due to high or unclear risk of bias in the one trial included for this outcome and possible selective reporting of some outcomes..
2. Downgraded once due to imprecision as it is a small study with a small number of participants.

BACKGROUND

Description of the condition

Pulmonary manifestations of cystic fibrosis (CF) are characterised by abnormal airway secretions associated with infection and inflammation leading to bronchiectasis. In almost all people with CF, there is an inevitable progression in the severity of lung disease resulting in more severe airway damage, progressive airflow obstruction and premature death due to respiratory failure (Gibson 2003a).

It is well-recognised that there are periodic increases in the severity of lung disease, which are referred to as pulmonary exacerbations (Elborn 2007). Exacerbations are one of the most important clinical events in the course of the disease for people with CF because of the increased symptoms, the acceleration in the rate of decline in lung function, and the need for increased treatment (de Boer 2011; Sanders 2010; Sanders 2011). Severe exacerbations have been associated with CF-related diabetes (Marshall 2005), sleep disturbances (Dobbin 2005) and may lead to reduced survival (de Boer 2011). Multiple factors play a role in the pathogenesis of pulmonary exacerbations, such as respiratory microbiome, host defences and environmental exposures (Goss 2007).

Defining pulmonary exacerbations in CF is challenging due to the variability and the subjective nature of presenting symptoms. A combination of symptoms, physical signs and laboratory findings have been used to help with diagnosis and grade severity (Gibson 2003a); the major criteria for diagnosing a pulmonary exacerbation are changes in an individual's symptoms (Goss 2007). The Fuchs criteria have been used in many clinical trials to define an exacerbation (Bilton 2011). It relies on treatment with intravenous antibiotics for four of the following respiratory signs or symptoms: new or increased haemoptysis; a change in sputum; increased cough; increased dyspnoea; fever above 38°C; fatigue; malaise; weight loss; sinus pain or pressure; change in sinus drainage; change in lung auscultation; a drop in FEV_1 of at least 10% from baseline; or new radiographic findings to identify an exacerbation state (Fuchs 1994). However, no consensus diagnostic criteria exist (BMJ 2018).

Description of the intervention

Antibacterial drugs are an essential treatment for pulmonary exacerbations. The selection of antibiotic treatment will depend on the organism(s) usually found in respiratory secretions, as well as the precipitating factor or identification of a new infection, or both. *Pseudomonas aeruginosa* is the usual organism, particularly in adults (Smyth 2006), although methicillin-resistant *Staphylococcus aureus* (MRSA) has recently emerged as an important pathogen in people with CF, with a 10-fold increase in prevalence between 1996 and 2014 (Jennings 2017).

Most inhaled antibiotics are delivered as an aerosol, generated from a nebuliser. Administration takes between five and 20 minutes, generally twice each day; the shorter delivery times reflect relatively recent developments in nebuliser technology. The nebulisers which are used to administer the antibiotics are relatively expensive and require training of the patient or caregiver to use them correctly. There are dry powder devices becoming available which should be more convenient than nebulisers. The type of nebulisers used to administer drugs in CF is the subject of a further Cochrane Review (Daniels 2013).

How the intervention might work

Treatment of exacerbations using antibiotics with activity against *P aeruginosa* reduces symptoms and improves lung function (Gold 1987; Wientzen 1980). A Cochrane Review of nebulised anti-pseudomonal antibiotics for maintenance treatment of individuals with CF and *P aeruginosa* infection have shown them to be associated with an improvement in lung function and a reduction in the frequency of exacerbations requiring additional antibiotic treatment (Smith 2018). In people with stable disease, inhaled antibiotics have been shown to reduce concentrations of *P aeruginosa* in sputum and to increase forced expiratory volume at one second (FEV_1) two weeks after onset of treatment suggesting their usefulness for treating exacerbations (Ramsey 1993).

Why it is important to do this review

In practice, inhaled antibiotics are almost certainly used to treat pulmonary exacerbations. The global frequency of such use is not known, but an article published by the Epidemiologic Study of Cystic Fibrosis (ESCF) from the USA and Canada reported that 24% of pulmonary exacerbations were treated with inhaled antibiotics (Wagener 2012). While their use has been further noted in earlier papers (Moskowitz 2008; Smyth 2008) and four articles reviewing treatment of pulmonary exacerbations mention the use of inhaled antibiotics (Flume 2009; Gibson 2003a; Smyth 2006; Smyth 2008), there are no firm recommendations and no evidence is cited. The use of inhaled antibiotics for *P aeruginosa* was recommended in the recent National Institute for Health and Care Excellence (NICE) guidance in conjunction with intravenous (IV) antibiotics in individuals experiencing new *P aeruginosa* infection to facilitate eradication; however, there is no strong evidence to support this recommendation (NICE 2017).

New inhaled antibiotics are being developed, as are devices for administering them, and these will probably increase inhaled antibiotic use for treating pulmonary exacerbations.

The use of inhaled antibiotics to treat pulmonary exacerbations has advantages compared to IV administration. Inhaled antibiotics can augment oral therapy for milder exacerbations and avoid hospitalisation and IV access. Furthermore, inhaled aminoglycosides can reduce the risk of kidney damage and loss of hearing that is associated with IV aminoglycosides. Finally, inhaled antibiotics could provide another treatment option to IV antibiotics for those individuals with difficult venous access.

Hence, there is a need to establish whether there is evidence of an effect of inhaled antibiotics for treating pulmonary exacerbations in CF.

OBJECTIVES

To determine if treatment of pulmonary exacerbations with inhaled antibiotics in people with CF improves their quality of life (QoL), reduces time off school or work and improves their long-term lung function.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials.

Types of participants

Children and adults with CF who are diagnosed with having a pulmonary exacerbation. Diagnosis of CF to be made using clinical criteria and confirmed by sweat testing or genetic analysis. A pulmonary exacerbation was taken as defined by the individual trial protocol.

Types of interventions

We will consider any inhaled antibiotic, at any dose, using any method of aerosol delivery. Duration of treatment will be between one and four weeks. The inhaled antibiotic will be administered alone or in addition to the usual treatment for pulmonary exacerbations and compared to either placebo or other antibiotic treatment.

Types of outcome measures

Primary outcomes

1. QoL (as measured by a validated tool such as CFQoL (Gee 2000) or CFQ-R (Quittner 2009))
2. Time off work or school
3. Lung function (spirometry)
   a. FEV_1 (litre or per cent (%) predicted) absolute values or change values
   b. FVC (litre or % predicted) absolute values or change values
   c. Annual change in FEV_1

Secondary outcomes

1. Need for hospital admission (in the short term (up to four weeks))
2. Need for additional antibiotics
   a. IV
   b. oral
3. Time to next pulmonary exacerbation
4. Weight (kg)
5. Adverse effects
   a. mild - resulting in no change in treatment (e.g. cough, bronchospasm)
   b. moderate - resulting in change in treatment (e.g. loss of hearing, nephrotoxicity)
   c. severe - needs hospital admission or is life-threatening (e.g. anaphylactic reactions, nephrotoxicity)
6. Microbiology
   a. emergence of new organisms
   b. emergence of resistant organisms

Search methods for identification of studies

There are no restrictions regarding language or publication status.

Electronic searches

We identified relevant trials from the Group's Cystic Fibrosis Trials Register using the terms: antibiotics AND (acute treatment OR unknown) AND (inhaled OR not stated).

The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of *The Cochrane Library*), 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's website.

Date of latest search of CF Trials Register: 03 October 2018.

We also searched for ongoing trials using ClinicalTrials.gov (using the terms cystic fibrosis AND inhaled antibiotics), the World Health Organisation International Clinical Trials Registry Platform (WHO ICTRP) (using the terms cystic fibrosis AND inhaled antibiotics) and the Australia and New Zealand Clinical Trials Registry (using the terms cystic fibrosis AND inhaled antibiotics).

Date searched: 09 October 2018.

Data collection and analysis

For any of the methods stated below, which we have not been able to undertake in this version of the review, we plan to do so if data become available for a future update.

Selection of studies

Two review authors independently screened titles and abstracts of the citations retrieved from the searches (SS and EC). The same two authors read the full text articles identified from the title and abstract screening to select trials that met the inclusion criteria (for earlier versions of the review NJ and TR, for this update two of the three authors SS and EC). Where there was disagreement between the authors on the trials selected, we attempted to reach a decision by consensus or by involving the third author to arbitrate (NR). Full text articles from the previous version of the review were not re-assessed.

Data extraction and management

Two authors recorded details of trial design, participant characteristics, interventions, quality assessment and the relevant outcome data using a customised data extraction form (for previous versions of the review NJ and TR, from 2018 SS and EC). We settled any disagreement by consensus. We have reported the following characteristics in the 'Characteristics of included studies' table where data were available from the papers:

- criteria for diagnosis of CF;
- definition of pulmonary exacerbation;
- type of infection;
- trial design;
- inhaled antibiotic and dose;

- aerosol delivery method;
- duration of treatment;
- comparison intervention;
- other treatments (e.g. IV or oral antibiotics and setting (inpatient or outpatient));and
- severity of exacerbation using baseline FEV_1 (% predicted).

We have presented separate comparisons for inhaled antibiotics alone versus IV antibiotics and for combination inhaled and IV antibiotics versus IV antibiotics alone. As planned, we have reported outcomes at up to one week, between one and two weeks, more than two weeks to three weeks, more than three weeks to four weeks. We have also considered additional follow-up data recorded at other time periods.

It is recognised that lung function is an indicator of morbidity and mortality, so, if in future we obtain data for annual change in FEV_1 we will report this as a surrogate marker for long-term survival.

Assessment of risk of bias in included studies

Two authors (for previous versions of the review NJ and TR, from 2018 SS and EC) assessed the risk of bias of the selected trials using the domain-based evaluation as described in the*Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We assessed the following domains as having either a low, unclear or high risk of bias:

1. randomisation (low risk - random number table, computer-generated lists or similar methods; unclear risk - described as randomised, but no details given; high risk - e.g. alternation, the use of case record numbers, and dates of birth or day of the week);
2. concealment of allocation (low risk - e.g. list from a central independent unit, on-site locked computer, identically appearing numbered drug bottles or containers prepared by an independent pharmacist or investigator, or sealed opaque envelopes; unclear risk - not described; high risk - if allocation sequence was known to, or could be deciphered by the investigators who assigned participants or if the trial was quasi-randomised);
3. blinding (of participants, personnel and outcome assessors);
4. incomplete outcome data (whether investigators used an intention-to-treat analysis);
5. selective outcome reporting;
6. other potential sources of bias.

We also noted whether the included trials reported any sample size calculations.

Where there was disagreement between the authors on a trial's evaluation, we reached a decision by consensus or by mediation by the contact editor. Results of the risk of bias assessment are presented in the 'Risk of bias' tables (Characteristics of included studies). The new author team did not re-assess the judgements for trials previously included in the review.

Measures of treatment effect

For binary outcome measures, we calculated a pooled estimate of the treatment effect for each outcome across trials using risk ratio (RR) and 95% confidence intervals (CIs) where appropriate.

If other types of data are included in future updates of the review, we will analyse these as follows. For continuous outcomes, we will record either mean relative change from baseline for each group or mean post-treatment or post-intervention values and the standard deviation (SD). If the papers report standard errors (SE) (and if it is possible) we will convert these to SDs. We will present a pooled estimate of treatment effect by calculating the mean difference and 95% CIs. If we become aware that some data are skewed and therefore we are not able to enter and analyse these within RevMan, we will report these narratively (RevMan 2014).

We will analyse any count data using a rate ratio (or narratively if this is not possible).

For any time-to-event outcomes included in the review, we plan to obtain a mixture of logrank and Cox model estimates from the trials; we aim to combine all results using the generic inverse variance method as we hope to be able to convert the logrank estimates into log hazard ratios and SEs as detailed in the*Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We will analyse longitudinal data using the most appropriate method available (Jones 2009).

Unit of analysis issues

An important factor in the validity of cross-over trials is that the severity of the disease is stable, so that disease status at the start point of each period is similar. This is very unlikely to be the case for pulmonary exacerbations in CF and therefore we will only include first-arm data from any eligible cross-over trials; where these data are unavailable we have excluded these trials from the review.

Dealing with missing data

Where possible, we have reported the numbers and reasons for dropouts and withdrawals in all intervention groups. We have also stated whether the papers specify that there were no dropouts or withdrawals. We have contacted authors for clarification on some missing information.

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

Assessment of heterogeneity

If sufficient data had been available, we planned to assess the degree of heterogeneity between trials through visual examination of the combined data presented in the forest plots, and by considering the I^2 statistic (Higgins 2003) together with Chi^2 values (Deeks 2011) and their confidence intervals. The I^2 statistic is a measure which describes the percentage of total variation across trials that are due to heterogeneity rather than by chance (Higgins 2003). The values of I^2 lie between 0% and 100%, and a simplified categorization of heterogeneity that we plan to use is of low (I^2 value of approximately 25%), moderate (I^2 value of approximately 50%), and high (I^2 value of approximately 75%) (Higgins 2003).

Assessment of reporting biases

In the tables below, we reported when the primary investigators took measurements during the trial, what measurements were

reported within the published paper and what data we report in the review (Characteristics of included studies). For the two full papers included, we compared the methods sections to the results sections to identify any potential selective reporting. We also used knowledge of the clinical background to identify standard outcome measures that are used, but may not have been reported by the investigators. We further attempted to assess the impact of the reporting of several surrogate outcomes that are not directly relevant.

If, in future updates, we are able to include a sufficient number of trials, we will attempt to assess whether our review is subject to publication bias by using a funnel plot. If asymmetry is detected, causes other than publication bias will be explored.

Data synthesis

If, in future updates of this review, we identify moderate to high levels of heterogeneity (as defined above), we will present pooled estimates of the treatment effect using a random-effects model. If this level of heterogeneity is not identified, we will compute pooled estimates of the treatment effect for each outcome under a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

In future, if we find moderate to high heterogeneity (over 50%) and a sufficient number of trials are included, we will investigate the possible causes further by performing subgroup analyses based on the the dose and the inhaled antibiotic, the pathogen causing the exacerbation, the severity of the pulmonary exacerbation, the severity of respiratory disease prior to the exacerbation (FEV_1 % predicted*), age of participants (children versus adults) and the duration and setting of treatment.

We plan to use the definitions of disease severity presented by the American Thoracic Society (Pellegrino 2005):

Degree of severity	FEV_1 % predicted
Mild	over 70%
Moderate	60% to 69%
Moderately severe	50% to 59%
Severe	35% to 49%
Very severe	less than 35%

Sensitivity analysis

If we are able to include a sufficient number of trials in a future update of the review, we plan to perform a sensitivity analysis based on the risk of bias of the trials (e.g. including and excluding trials assessed as having a high risk of bias).

Summary of findings

In accordance with current Cochrane guidance we have included a summary of findings table for each comparison in the review. The two comparisons are as follows:

1. inhaled antibiotics compared to IV antibiotics;
2. an inhaled antibiotic in addition to IV antibiotics compared to IV antibiotics.

We have selected the following seven outcomes, which we consider to be the most important, to include in the tables.

1. QoL (as measured by a validated tool such as CFQoL (Gee 2000) or CFQ-R (Quittner 2009))
2. Time off work or school
3. Lung function (spirometry)
4. Need for additional antibiotics (IV or oral)
5. Time to next pulmonary exacerbation
6. Adverse events
7. Microbiology - emergence of new or resistant strains

We used the GRADE approach to assess the quality of the evidence for each outcome based on the risk of bias within the trials, relevance to our population of interest (indirectness), unexplained heterogeneity or inconsistency, imprecision of the results or high risk of publication bias. We downgraded the evidence once if the risk was serious and twice if the risk was deemed to be very serious.

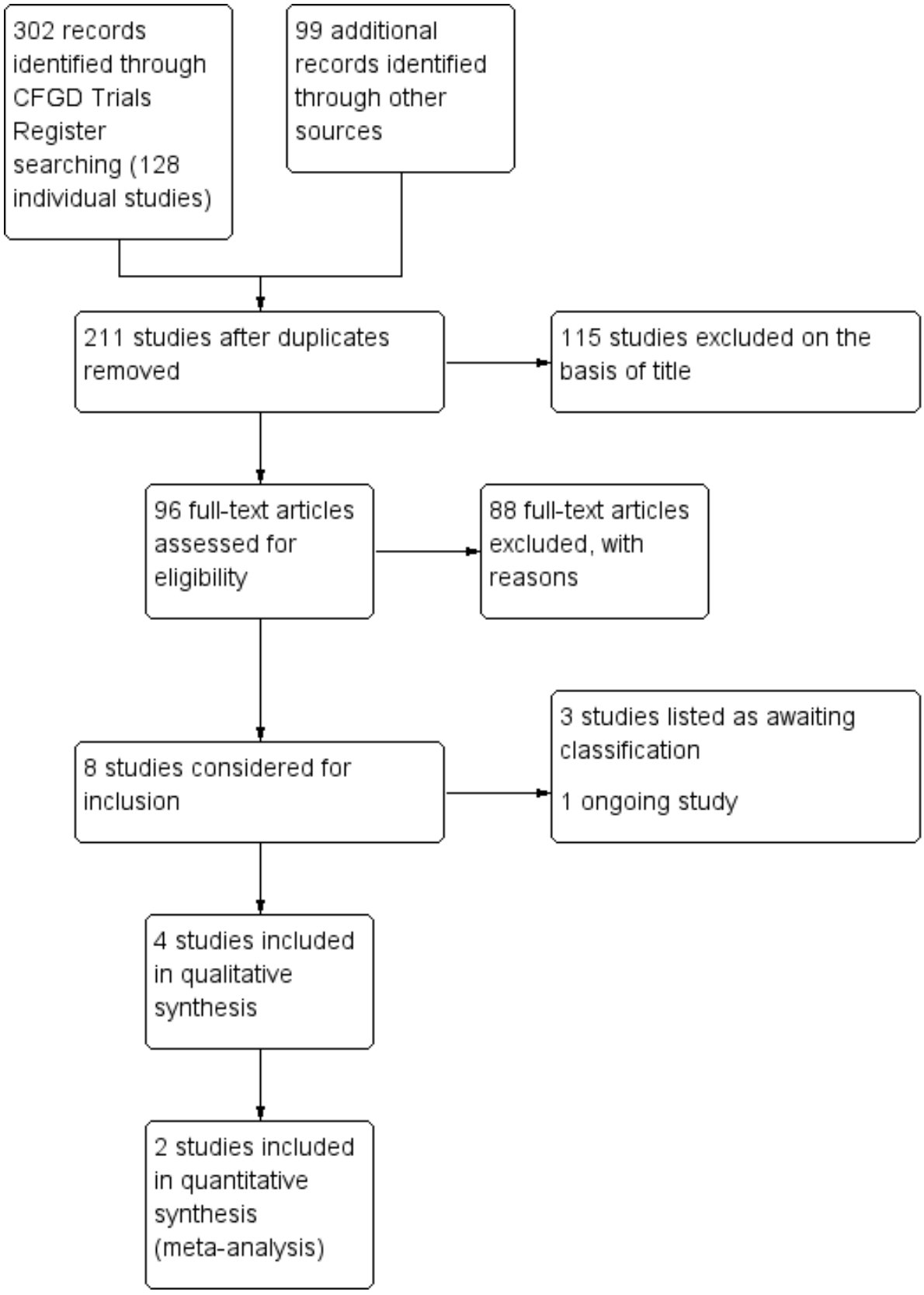
RESULTS

Description of studies

Results of the search

The searches identified a total of 211 separate trials for consideration. We included four trials in the review with a total of 167 participants and excluded 203 trials (115 on the basis of title alone, and 88 which are listed in 'Excluded studies'). One trial was previously listed in ongoing trials (Soulsby 2010) and is now listed in Studies awaiting classification. This trial is now complete and we have obtained study data from the author. However, it is a small, cross-over trial for which separate first-arm data have not yet been provided. We have contacted the author again (18 April 2018) for additional information and we will include this in a future update, if these data become available.Two further trials are currently awaiting classification (Postnikov 2007; Semykin 2010) and one new trial is listed in Ongoing studies. A flow chart showing the process of trial selection is presented in the figures (Figure 1).

Figure 1. PRISMA flow diagram



Included studies

Inhaled antibiotics alone versus IV antibiotics

Trial design

Two trials (77 participants) of parallel design were included in the review (Cooper 1985; Shatunov 2001). Duration of treatment was described as 14 days in one trial (Shatunov 2001) and not stated in the second trial (Cooper 1985). One trial specifically stated that participants were admitted to hospital for pulmonary exacerbations and treated as inpatients (Cooper 1985). In the remaining trial it is not clear if participants were treated as inpatients or outpatients (Shatunov 2001).

Participants

The number of participants in each trial was 18 (Cooper 1985) and 59 (Shatunov 2001). Neither trial defined their criteria for the diagnosis of CF or gave a definition for a pulmonary exacerbation. One trial reports "pseudomonal-related" pulmonary deterioration (Cooper 1985), and the second trial describes participants as being chronically colonised or infected with *P aeruginosa* and having pulmonary exacerbations (Shatunov 2001).

Interventions

Both trials compared inhaled antibiotic treatment to the same antibiotics given intravenously (Cooper 1985; Shatunov 2001). The drugs used by inhalation were tobramycin and carbenicillin (Cooper 1985) and ceftazidime (Shatunov 2001).

Study ID	Active treatment	Comparator treatment(s)
Cooper 1985	Inhaled tobramycin + inhaled carbenicillin (dose not specified)	IV ticarcillin + IV tobramycin (dose not specified)
Shatunov 2001	Inhaled ceftazidime (1500 mg 1x daily)	IV ceftazidime (150 mg/kg/day in 3 divided doses) or IV ceftazidime (150 mg/kg/day in 2 divided doses)

Outcomes

Both trials reported on lung function; FEV_1 was reported in one trial (Cooper 1985) and the second trial described measuring "ventilation parameters and peakflowmetry" (Shatunov 2001). Other reported outcomes were the time until the next pulmonary exacerbation (Shatunov 2001), adverse effects (Cooper 1985), microbiological outcomes (Shatunov 2001), QoL (Cooper 1985) and need for additional IV antibiotics (Cooper 1985).

Both trials stated explicitly that they had measured outcomes at baseline and end of treatment (Cooper 1985; Shatunov 2001).

Inhaled antibiotics plus IV antibiotics versus IV antibiotics alone

Trial design

Two trials (90 participants) of parallel design were included in the review (Schaad 1987; Stephens 1983). Duration of treatment in both was described as 14 days or two weeks (Schaad 1987; Stephens 1983) and both trials specifically state that participants were admitted to hospital for pulmonary exacerbations and treated as inpatients (Schaad 1987; Stephens 1983).

Participants

The number of participants in each trial were 62 (Schaad 1987) and 28 (Stephens 1983). Neither trial defined their criteria for the diagnosis of CF or gave a definition for a pulmonary exacerbation. One trial gave baseline FEV_1 data to indicate the severity of the exacerbation (Stephens 1983). With regards to the pathogen causing the pulmonary exacerbation, there are no consistent inclusion criteria. In one trial the isolation of*P aeruginosa* from sputum was a definite inclusion criteria (Schaad 1987). The second trial does not discuss possible causes of infection, although it is stated within the trial report that at baseline sputum colony counts of *P aeruginosa* were comparable between treatment and control groups (Stephens 1983).

Interventions

Both trials compared the addition of an inhaled antibiotic to an IV combination therapy that included the same drug given intravenously (Schaad 1987; Stephens 1983). The inhaled antibiotics were amikacin (Schaad 1987) and tobramycin (Stephens 1983).

Study ID	Active treatment	Comparator treatment(s)
Schaad 1987	Inhaled amikacin (100 mg 2x daily) + IV ceftazidime (250 mg/kg/day in 4 divided doses) + IV amikacin (33 mg/kg/day in 3 divided doses)	IV ceftazidime (250 mg/kg/day in 4 divided doses) + IV amikacin (33 mg/kg/day in 3 divided doses)
Stephens 1983	Inhaled tobramycin (80 mg) mixed with salbutamol (1 mL) plus buffering nebulising solution (2 ml) 3x daily + IV tobramycin (10	IV tobramycin (10 mg/kg/day in 3 divided doses) + IV ticarcillin (300 mg/kg/day in 4 divided doses)

mg/kg/day in 3 divided doses) + IV ticarcillin (300 mg/kg/day in 4 divided doses)

Outcomes

Both trials reported on lung function; FEV_1 was reported in one trial (Stephens 1983) and the second trial measured lung volumes and airway resistance during quiet breathing (Schaad 1987). Other reported outcomes were the time until the next pulmonary exacerbation (Stephens 1983), adverse effects (Schaad 1987; Stephens 1983) and microbiological outcomes (Schaad 1987; Stephens 1983), weight (Schaad 1987; Stephens 1983) and need for hospital admission (Stephens 1983).

Both trials stated explicitly that they had measured outcomes at baseline and end of treatment; and one further reported follow-up data at four to six weeks after end of treatment (Schaad 1987).

Excluded studies

A total of 115 trials were excluded on the basis of title alone, further details of these trials are not presented. Papers were obtained for the remaining identified trials and a total of 88 are listed in the review as excluded trials; reasons for exclusion are given in the tables (Characteristics of excluded studies). Most trials were excluded as they were in people with chronic disease (n = 45); some trials stated that participants were clinically stable (n = 9) or that they were undergoing maintenance treatment (n = 4); and two trials were single-dose trials. Seven trials looked at eradication treatment and two at prophylaxis. Two trials looked at the correct intervention in the correct population, but were of cross-over design and first-arm data were not available. In two trials, the intervention was not an inhaled antibiotic. In the remaining 15 trials participants were not included if they had pulmonary exacerbations.

Studies awaiting classification

There are three trials awaiting classification (Postnikov 2007; Semykin 2010; Soulsby 2010).

One trial is a two-arm cross-over trial which lasted two weeks and recruited 15 children aged between seven and 17 years of age (Postnikov 2007). Participants received either once-daily or twice-daily amikacin at a dose of between 15 mg/kg/day and 20 mg/kg/day in combination with ceftazidime or meropenem. The investigators planned to report on lung function, microbiology and adverse events at baseline and at day 14. It is currently not clear from the abstract whether the amikacin was inhaled or IV (Postnikov 2007).

One trial is a three arm of parallel trial in 108 participants aged between four and 17 years with chronic *P aeruginosa* infection experiencing an exacerbation. Treatments compared were twice-daily TOBI® 300 mg or twice-daily Bramitob® 300 mg (both in combination with IV ceftazidime and oral ciprofloxacin) versus IV cefepime plus IV amikacin versus IV meropemem plus IV amikacin. Investigators measured clinical symptoms, lung function and microbiology. To date this trial has only been published as an abstract (Semykin 2010).

The third trial currently awaiting classification is an open-label cross-over RCT in 24 people older than six years of age and with chronic *P aeruginosa* infection experiencing an exacerbation. Investigators compared IV tobramycin at the dose they received on their last admission (usually 7 - 10 mg/kg) once daily for 14 days versus inhaled tobramycin at a dose of 300 mg twice daily for 14 days. Outcomes include lung function, time to next exacerbation, adverse events (renal function and antibiotic resistance), weight and QoL (Soulsby 2010).

Ongoing studies

One cross-over trial is ongoing (Prevotat 2018). Investigators are recruiting participants of at least eight years of age with chronic *P aeruginosa* infection experiencing an exacerbation. The treatment comparison is a 'short cure' (14 days of IV Nebcin plus five days of IV tobramycin followed by nine days of inhaled tobramycin (Tobi Inhalant Product) 300 mg twice daily) versus 'standard' treatment (14 days IV Nebcin plus 14 days of IV tobramycin).

Risk of bias in included studies

Summary figures for the risk of bias are presented in the figures (Figure 2; Figure 3).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

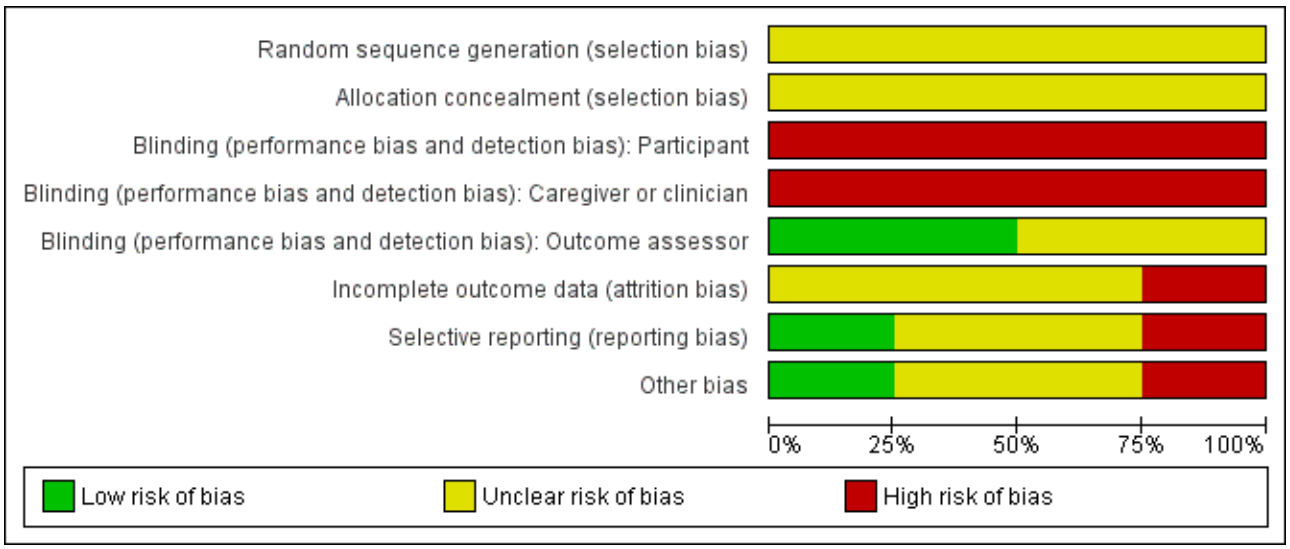
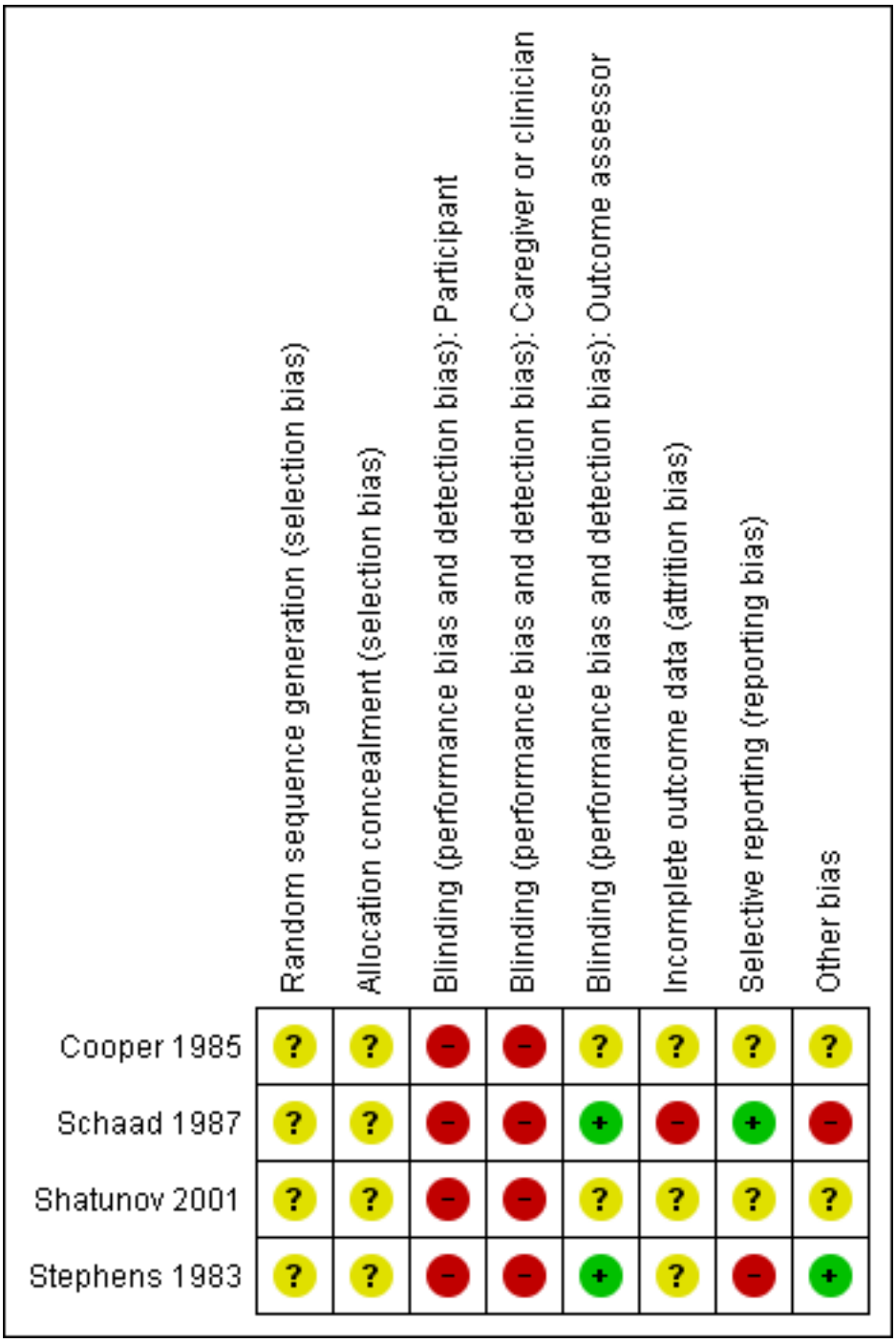


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Generation of sequence

All of the trials were judged to have an unclear risk of bias. Three of the trials described participants as being randomly allocated to groups but gave no description of the randomisation process (Cooper 1985; Schaad 1987; Stephens 1983). One trial stated that participants were "divided into three groups" but again, no details of the process were given (Shatunov 2001).

Concealment of allocation

None of the included trials discuss allocation concealment and hence were judged to have an unclear risk of bias (Cooper 1985; Schaad 1987; Shatunov 2001; Stephens 1983).

Blinding

The risk of bias from blinding of participants, of caregivers or clinicians and of outcome assessors was assessed separately. Given that the interventions being compared were either inhaled

antibiotics or a combination of inhaled and IV antibiotics versus IV antibiotics and there were no placebo interventions, it was not possible to blind either the participants or the caregivers to the treatment arm. This has resulted in all trials being judged to have a high risk of bias for blinding in the groups 'Participant' and 'Caregiver or clinician'. Given that the majority of the outcomes in this review are not subjective, it is unclear how this risk of bias will impact on the results. However, the blinding of outcomes assessors would have been possible. Two trials report that outcome assessors were blinded to the treatment group (Schaad 1987; Stephens 1983). Schaad reports that clinical evaluations, radiographs and sputum analysis were all assessed by individuals who had no knowledge of treatment group (Schaad 1987). Stephens only reports that the technician performing the lung function tests was not aware of the treatment group and does not give any details for other outcomes (Stephens 1983). We have judged these two trials to have a low risk of bias (Schaad 1987; Stephens 1983). The remaining two trials did not discuss blinding of outcome assessors and are judged to have an unclear risk of bias (Cooper 1985; Shatunov 2001).

Incomplete outcome data

Three trials were judged to have an unclear risk of bias as withdrawals were not discussed (Cooper 1985; Shatunov 2001; Stephens 1983).

We regarded the trial by Schaad to have a high risk of bias, this was because not all outcomes were reported for all of the participants, and reasons for this were not given (Schaad 1987).

Selective reporting

Two of the included trials were only published as abstracts and so it is not clear from the available information if all the outcomes that were planned to be measured were indeed reported (Cooper 1985; Shatunov 2001). We therefore judged both of these trials to have an unclear risk of bias.

Two trials have been published as full papers (Schaad 1987; Stephens 1983). The Stephens paper explicitly states that FVC would be measured, but no data were reported on this outcome. Also, outcomes were measured on days 1, 5 and 12, but the table in the paper only presents clinical status data for the start and end of treatment (Stephens 1983). It is unclear whether the trial investigators have selectively reported data by time-point. The Schaad paper appears to be consistent between those outcomes stated as being measured and those mentioned in the results section, giving this a low risk of bias (Schaad 1987).

We would also like to note that for the outcome 'Time to next pulmonary exacerbation' the trial where this was reported presented data in a manner which did not allow us to undertake our planned analysis (hazard ratios), which we regard as a potential form of selective reporting (Shatunov 2001).

Other potential sources of bias

We judged one trial as having a high risk of bias for this section (Schaad 1987). Schaad reports that 13 participants enrolled twice and six participants participated three times (Schaad 1987).

For one trial we did not identify any other potential source of bias, and was thus judged as having a low risk of bias (Stephens 1983).

The remaining two trials were both only published in abstract form and so, due to limited information, we were not able to identify any other potential sources of bias; we have therefore judged these to have an unclear risk of bias (Cooper 1985; Shatunov 2001).

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings: inhaled antibiotics compared with IV antibiotics; **Summary of findings 2** Summary of findings: inhaled antibiotics plus IV antibiotics compared with IV antibiotics only

In the summary of findings tables, the quality of the evidence has been graded for pre-defined outcomes (see above) and definitions of these gradings provided.

Inhaled antibiotics alone versus IV antibiotics

Two trials (n = 77) reported on this comparison (Cooper 1985; Shatunov 2001) and results are summarised in the tables (Summary of findings for the main comparison).

Primary outcomes

1. QoL

One abstract stated 'perceived improvement in lifestyle' as an outcome in the trial; however, no results were reported (Cooper 1985). The quality of this evidence was deemed to be very low.

2. Time off work or school

Neither trial reported on this outcome.

3. Lung function

Both trials stated that lung function was an outcome measure. One trial did not specify which 'ventilatory parameters' were measured (Shatunov 2001). The abstract reports no difference in treatment with twice-daily IV ceftazidine or once-daily inhaled ceftazidine, but that both of these treatment regimens were better than treatment with three-times daily IV ceftazidine ($P < 0.05$) (Shatunov 2001).

a. FEV_1

Cooper reported FEV_1 % predicted was 42% before treatment and 55% post-treatment in the inhaled tobramycin and carbenicillin group and 39% before treatment and 52% after treatment in the IV antibiotic group (same combination of drugs given intravenously); there was no statistically significant difference in FEV_1 at end of treatment between treatment or control. There was insufficient information for meta-analysis (Cooper 1985).

The GRADE evidence for this outcome was deemed to be very low (Summary of findings for the main comparison).

b. FVC

Only Cooper reported the mean FVC % predicted at the end of treatment. In the group on inhaled antibiotics (n = 8) this was 73% predicted compared to 68% predicted in the group receiving the same antibiotics intravenously (n = 10) (Cooper 1985).

c. Annual change in FEV_1

Neither trial reported on this outcome.

Secondary outcomes

1. Need for hospital admission

Neither trial reported on this outcome.

2. Need for additional antibiotics

a. IV

One trial reported that two participants from the inhaled group needed additional IV antibiotics, RR 6.11 (95% CI 0.33 to 111.71) (Analysis 1.1) (Cooper 1985). The GRADE evidence was again deemed to be very low.

b. oral

Neither trial reported on the need for additional oral antibiotics.

3. Time to next pulmonary exacerbation

Only one trial reported information on the time to the next pulmonary exacerbation, but not in a format that allowed a meta-analysis (Shatunov 2001). Our original planned analysis was not possible as this trial did not report hazard ratios.

Shatunov reported that the time to next exacerbation was maximal in the once-daily inhaled antibiotic group, less in the twice-daily IV antibiotic group, but both longer than in the group receiving IV antibiotics three-times-daily (Shatunov 2001).

4. Weight

Neither trial reported on weight.

5. Adverse effects

a. Mild

Neither trial reported on this outcome.

b. Moderate

Cooper monitored renal and auditory changes and reported no adverse effects in either the inhaled or the IV antibiotic groups (Cooper 1985).

c. Severe

Neither trial reported on this outcome.

6. Microbiology

Both trials measured this outcome (Cooper 1985; Shatunov 2001). Cooper stated that there were no adverse effects seen in sputum microbiology (Cooper 1985).

a. Emergence of new organisms

No trials reported on the emergence of new organisms.

b. Emergence of resistant organisms

This outcome was stated to be measured in the Shatunov trial, but no results were reported (Shatunov 2001).

Inhaled antibiotics plus IV antibiotics versus IV antibiotics alone

Two trials reported on this comparison (n = 90) (Schaad 1987; Stephens 1983). Due to multiple enrolments in the Schaad trial, data were reported on episodes, rather than on participants (therefore not independent), and thus data cannot be entered into the meta-analysis for any of the outcomes listed below (Schaad 1987). Results are summarised in the tables (Summary of findings 2).

Primary outcomes

1. QoL

Neither trial reported on this outcome.

2. Time off work or school

Neither trial reported on this outcome.

3. Lung function

Both trials stated that lung function was an outcome measure (Schaad 1987; Stephens 1983).

a. FEV_1

One trial reported the change from baseline in FEV_1 % predicted, but there was insufficient information for meta-analysis (Stephens 1983). There was a 6.7% change in the group receiving the combination of inhaled and IV antibiotics and a 3.9% change in the IV antibiotics only group; the difference between groups was described as not statistically significant.

The GRADE evidence for this outcome was deemed to be very low.

b. FVC

Neither trial reported FVC, but Schaad reported results of vital capacity (VC) measured during quiet breathing (Schaad 1987). At the end of the two-week treatment, the mean (SD) VC % predicted for the inhaled amikacin plus IV amikacin and ceftazidine group (n = 30) was 57% (16%) and for the group (n = 24) given both drugs IV was 62% (16%). At follow-up four to six weeks later, the inhaled plus IV group (n = 12) had a mean (SD) VC % predicted of 51% (20%) and the IV alone group (n = 14) of 57% (17%).

c. Annual change in FEV_1

Neither trial reported on this outcome.

Secondary outcomes

1. Need for hospital admission

One trial reported on the need for hospital admission (Stephens 1983); the results were not statistically significant, RR 1.50 (95% CI 0.15 to 14.68) (Analysis 2.1).

2. Need for additional antibiotics

Neither trial reported on the need for either additional IV or additional oral antibiotics.

3. Time to next pulmonary exacerbation

Neither trial reported on this outcome.

4. Weight

Both trials reported data for weight, although we were not able to enter data from either trial into a meta-analysis (Schaad 1987; Stephens 1983).

Schaad reported on weight as degree of underweight (%) at the end of treatment and at follow-up (Schaad 1987). At the end of treatment Schadd reported in the IV plus inhaled group (n = 43) a

mean (SD) % of underweight as 13.1% (7.1%) compared to the IV alone group (n = 44) where mean (SD) was 13.5% (7.3%). At follow-up (four to six weeks), in the IV plus inhaled group (n = 36) the mean (SD) % of underweight was 14.8% (7.7%) compared to the IV alone group where the mean (SD) was 14.9% (7.8%) (Schaad 1987).

Stephens reported that the mean change in weight for the inhaled group (n = 16) was 1.7 and in the control group (n = 12) was 2.2 (Stephens 1983). The units of weight were not specified and no variance measures were reported. It was reported within the paper that the difference was not significant.

5. Adverse effects

a. Mild

One trial reported mild adverse events, but we are not able to present these in the analysis (Schaad 1987). Schaad reported mild adverse effects but did not state in which of the treatment groups these events had occurred (Schaad 1987). Phlebitis was reported in five participants (6%) and urticarial rash in a further four (5%) participants. Furthermore Schaad reported no significant changes in blood urea nitrogen, creatinine and urine analysis (Schaad 1987).

b. Moderate

Both trials reported on moderate adverse events (Schaad 1987; Stephens 1983).

Schaad reported on moderate adverse events, but as before did not break these down by treatment group precluding inclusion in the analysis (Schaad 1987). Pre- and post-treatment audiograms were undertaken in 81 (93%) out of 87 participants and interpreted as unchanged in all. While a more than three-fold increase in aspartate transaminase (SGOT) and alanine aminotransferase (SGPT) activities were noted in five out of 87 participants at end of therapy, this was not the case at follow-up. Further transient haematologic abnormalities were noted in eight participants as follows: four developed eosinophilia; three developed neutropenia; and one developed thrombocytopenia (Schaad 1987).

Stephens reported that there were no reports of renal toxicity in either group (Analysis 2.2). Furthermore, serum creatinine levels remained at less than 1.0 mg/dL and did not increase by more than 0.5 mg/dL in any participant; no proteinuria or cylinduria observed in either group (Stephens 1983). The GRADE assessment for moderate adverse events was very low.

c. Severe

Schaad reported that there were no significant adverse events observed in either group (Schaad 1987).

6. Microbiology

Both trials reported on this outcome (Schaad 1987; Stephens 1983).

a. Emergence of new organisms

Neither trial reported on the emergence of new organisms.

b. Emergence of resistant organisms

Schaad reported that at the end of treatment, two out of 39 strains were resistant to ceftazidime and two were resistant to amikacin in the group using inhaled amikacin combined with IV amikacin and ceftazidime. In the group treated with the same IV antibiotics, three out of 39 strains were resistant to ceftazidime and one to amikacin (Schaad 1987). Stephens reported that there was no difference in the rate of *P aeruginosa* isolates being resistant to inhaled tobramycin, RR 2.25 (95% CI 0.27 to 19.04) (Analysis 2.3) (Stephens 1983). The GRADE assessment found the evidence to be of very low quality.

DISCUSSION

Pulmonary exacerbations associated with chronic *P aeruginosa* infection are well recognised in people with CF, although there is no agreed definition and pathophysiology is not well understood. Exacerbations are associated with both short- and long-term effects on health (Sanders 2010). The usual treatment of exacerbations is a combination of two antibiotics delivered intravenously and more airway clearance for two to three weeks, frequently in hospital (Flume 2009; Gibson 2003a). In some instances oral antibiotic treatment (ciprofloxacin) is the first antibiotic used. There has been limited research on the effect of inhaled antibiotics for treatment of pulmonary exacerbations in people with CF. The rationale to undertake these trials is to provide people with CF with therapeutic options that are less invasive and potentially less toxic but equally effective as compared to other treatment options (e.g. IV antibiotics).

Summary of main results

We identified four RCTs with 167 participants from our search of the literature. Two trials compared inhaled antibiotics alone to IV antibiotics alone (n = 77), while two compared a combination of inhaled and IV antibiotics to IV antibiotics alone (n = 90). Outcome measures of interest were either not reported or reported in a style that was not suitable for meta-analysis. It is of note that in the two trials that reported data for FEV_1 (one from each comparison), no differences were found between the groups. In one of the trials comparing inhaled antibiotics alone to IV antibiotics alone the time to the next exacerbation was not found to be different (Shatunov 2001). No significant adverse events were reported in any of the trials in either comparison. Larger trials are needed to confirm these findings.

Overall completeness and applicability of evidence

Two of the included trials used inhaled tobramycin (one of these combined it with inhaled carbenicillin and the second with IV tobramycin and IV ticarcillin) which is the most commonly-used inhaled antibiotic. The dose used was not stated in one of these trials. Trials were varied in design and specific intervention and comparator, making meta-analyses of the results not appropriate.

The trials included in this review were designed to show that inhaled antibiotics are equally as effective as other treatment options. Such equivalence trials require large numbers of participants to ensure confidence in the results. The included trials all had a small sample size, which would make them prone to a Type II error, indeed in the two trials which provided data on lung function there were only 41 participants and a difference could have been missed.

The only trials we were able to include in the review were relatively old and in a fast-moving area of treatment development it brings into question the applicability of any results to the current domain. Our primary outcome was change in QoL, but this was only

measured in one of the four trials and the quality of the evidence was very low.

There is currently one ongoing trial which is recruiting participants; we will report on this trial at the next update of the review (Prevotat 2018).

Quality of the evidence

The overall quality of the evidence was either low or very low across all outcomes reported in the trials included in both comparisons. The risk of bias was unclear overall for all of the trials, largely due to the fact there was a lack of information provided (two trials were only published in abstract form). Given the obvious inability to blind participants and caregivers to mode of delivery (IV versus inhaled) there is a potential risk of bias for subjective outcomes, such as QoL (our primary outcome). However, given the lack of data included in the review for subjective outcomes, this potential risk of bias currently has no bearing on our conclusions.

We also downgraded the evidence because of low participant numbers within the trials causing imprecision.

Potential biases in the review process

Although few trials were identified, we are confident that all eligible trials have been identified by the comprehensive search undertaken.

We have contacted authors for clarification on some missing information. However, we have received no additional unpublished data. We are unable to comment on the potential risk of bias this poses.

Given the limited data available there is a low risk of bias due to data handling errors.

Agreements and disagreements with other studies or reviews

Our findings concur with those published in the American CF pulmonary guidelines, in that these also highlight a lack of evidence for the use of inhaled antibiotics during the treatment of a pulmonary exacerbation (Flume 2009). In the UK, CF Trust guidelines state that there is no evidence that inhaled antibiotics are suitable alternatives to IV antibiotics for pulmonary exacerbations, or that there is clinical benefit when used in addition to IV antibiotics in this setting (CF Trust 2009). Most recently, the newly published NICE guidelines recommend the use of inhaled antibiotics in conjunction with oral antibiotics for mild exacerbations but there is little evidence to support this (NICE 2017).

AUTHORS' CONCLUSIONS

Implications for practice

The evidence of benefit to people with cystic fibrosis (CF) from use of inhaled antibiotics as long-term suppression of respiratory infection suggests there might also be benefit for treatment of exacerbations (Smith 2018). The evidence is strongest for inhaled tobramycin. A number of authors have advocated the use of inhaled antibiotics to treat exacerbations without citing evidence of effect (Gibson 2003a; Moskowitz 2008). This review has found no high level evidence to inform the use of inhaled antibiotics for exacerbations. There were only four trials comparing inhaled antibiotics (either alone or in combination with intravenous (IV) antibiotics) with IV antibiotics for exacerbations and these were inadequate for a valid analysis.

When considering the use of antibiotics to treat pulmonary exacerbations, there are situations when IV antibiotic therapy is challenging, e.g. where IV access is difficult; where an admission or home treatment with IV antibiotics cannot be arranged for social reasons; or where the clinician wants to avoid the adverse effects of systemic therapy. An inhaled aminoglycoside may be useful when an IV aminoglycoside is contra-indicated because of renal impairment or a risk of drug-induced hearing loss. In such circumstances an oral quinolone (such as ciprofloxacin) and a nebulised antibiotic may be an alternative strategy (Smyth 2008). However, evidence for the effectiveness of these strategies is absent.

Implications for research

Consumer input into this review has highlighted how important this topic is to people with CF and how disappointing it is that the included trials reported outcomes that were not relevant to people with CF. Early detection and treatment of pulmonary exacerbations is central to CF care and other options for antibiotic delivery in these circumstances (apart from IV treatment) should be evaluated. However, we were only able to identify a single ongoing trial of nebulised antibiotics for the management of pulmonary exacerbations (Prevotat 2018).

One of the difficulties when describing the effects of treatments for exacerbations is the lack of a consensus definition of what constitutes a mild, moderate or severe exacerbation. Research would benefit from a move towards such a consensus definition.

Randomised controlled trials are required in order to answer the following questions in people with CF experiencing pulmonary exacerbations.

1. For mild pulmonary exacerbations, does inhaled tobramycin (or another inhaled antibiotic) added to oral ciprofloxacin improve outcomes compared to ciprofloxacin alone? The outcomes of interest are rate of return to health (quality of life, time off work or school), lung function (e.g. forced expiratory volume in one second (FEV_1)), weight, need for a rescue course of IV antibiotics and time to next exacerbation. Safety outcomes (such as known adverse effects of tobramycin) should also be studied.
2. For more severe pulmonary exacerbations, is inhaled tobramycin as effective as IV tobramycin when either one is added to other IV antibiotics?

We feel it is important that outcomes such as quality of life or time off work or school are recorded.

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opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Cooper 1985

Methods	Randomised controlled trial. Parallel design. Single centre in Canada. Duration: 4 weeks.
Participants	18 participants who had CF (method of CF diagnosis not stated) and acute pseudomonas-related pulmonary deterioration (no definition given) requiring intensive treatment and admission to hospital. Inhaled group: n = 8; IV group: n = 10. Age and sex of participants not stated.
Interventions	High-dose inhaled: carbenicillin and tobramycin. High-dose IV: ticarcillin and tobramycin.
Outcomes	QoL, lung function (FEV_1, FVC), need for additional IV antibiotics, adverse effects.
Notes	Single abstract only published. Mean values given for lung function data, but no SDs. Sample size calculation not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Abstract states 'randomly allocated', no details of method given.
Allocation concealment (selection bias)	Unclear risk	Not discussed.

Cooper 1985 *(Continued)*

Blinding (performance bias and detection bias) Participant	High risk	Not possible, inhaled versus IV treatment.
Blinding (performance bias and detection bias) Caregiver or clinician	High risk	Not possible, inhaled versus IV treatment.
Blinding (performance bias and detection bias) Outcome assessor	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Appear to be no withdrawals.
Selective reporting (reporting bias)	Unclear risk	No access to protocol, this is only an abstract so no complete methods and results sections to compare.
Other bias	Unclear risk	Not clear, only abstract with limited information.

Schaad 1987

Methods	Randomised controlled trial. Parallel design. Single centre in Switzerland (Berne). Duration: 2 weeks (average 15 days).
Participants	Participants with CF (no information on how CF diagnosed) admitted for exacerbation of pulmonary symptoms (no further details given). Inclusion criteria: isolation of Pa from sputum on admission; absence of life-threatening illness, renal or hepatic failure and history of drug allergy; at least 6 months since last hospital admission. 87 data sets (62 participants, but 87 episodes - 13 enrolled twice (possibly in different arms) and 6 enrolled 3 times). Mean age 15 years, range 3 - 24 years. Baseline data not presented: “two therapy groups comparable in sex, age, clinical/radiographic score and IV anti-pseudomonal therapy”.
Interventions	**IV alone**: ceftazidime (250 mg/kg/day in 4 divided doses) plus amikacin (33 mg/kg/day in 3 divided doses) administered over 5 min. **IV + inhaled**: ceftazidime (250 mg/kg/day in 4 divided doses) plus amikacin (33 mg/kg/day in 3 divided doses) administered over 5 min plus aerosolized amikacin (1x 100 mg vial amikacin sulphate in 2 ml aqueous solution) 2x daily via Pari Jet nebuliser after chest physio. IV (ceftazidime plus amikacin) (44 episodes) versus IV (ceftazidime plus amikacin) plus inhaled amikacin (43 episodes).
Outcomes	Lung function (VC, RV, FRC and airway resistance), weight, adverse effects, microbiology, serum and sputum concentrations, radiologic score, clinical or radiographic score, erythrocyte sedimentation rate, leukocytes, band neutrophils.

Schaad 1987 *(Continued)*

	Reported at baseline, end of therapy (2 weeks) and 4 - 6 weeks later.
Notes	States on page 600 “87 were randomly allocated..” but on page 601 “62 patients were admitted to the study and received 87 course of therapy by random assignment. 13 patients were enrolled twice, 6 participated 3 times”. Number of participants analysed differs for different outcomes, but at end of therapy ranges from 54 to 87, at follow-up 26 to 68. Sample size calculation not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Paper states “87 patients randomly allocated ...” but not details given of method.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) Participant	High risk	Not possible, comparison of IV versus IV + inhaled antibiotics.
Blinding (performance bias and detection bias) Caregiver or clinician	High risk	Not possible, comparison of IV versus IV + inhaled antibiotics.
Blinding (performance bias and detection bias) Outcome assessor	Low risk	Paper states: - “ clinical evaluations done by the same investigator (JWK) who was not aware of the type of anti-microbial therapy” - “radiographs graded ... by a pediatric radiologist who had no knowledge of a patient’s treatment” - “Sputum studies ... processed by the Institute of Microbiology, University of Berne for culture and antibiotic susceptibility testing, by the Pulmonary Division Laboratory, University of Berne for microscopic analysis and by the Division of Paediatric Infectious Diseases, University of Geneva, for measurement of elastolytic activity and total protein concentration.”
Incomplete outcome data (attrition bias) All outcomes	High risk	All 87 courses completed (62 participants; 13 enrolled twice and 6 enrolled 3 times), but not all outcomes reported for all of the participants, and reason for this not given. Only 68 participants available for follow-up (IV = 32; IV + inhaled = 36) not sure if any of these were multiple enrolments. Number of participants analysed differs for different outcomes, but at end of therapy ranges from 54 to 87, at follow-up 26 to 68.
Selective reporting (reporting bias)	Low risk	Consistency between outcomes stated as being measured and those mentioned in the results section.
Other bias	High risk	Some participants appear in trial on multiple counts: States on page 601 "62 patients were admitted to the study and received 87 course of therapy by random assignment. 13 patients were enrolled twice, six participated 3 times".

Shatunov 2001

Methods	Parallel design. Single centre in Russia. Duration: 2 weeks.
Participants	59 children with CF infected with *P aeruginosa* and in a period of moderate pulmonary exacerbation (no further information provided). Not clear how many in each intervention group. Age range 5 - 15 years, gender split not described. Method of CF diagnosis not stated.
Interventions	3 groups: A: ceftazidime 150 mg/kg/day IV every 8 hours. B: ceftazidime 150 mg/kg/day IV every 12 hours. C: ceftazidime inhalation 1500 mg once daily via Pari28® and Portaneb® jet nebulisers.
Outcomes	Peakflowmetry (but not clear which lung function tests used), oxygen saturation, chest X-ray, time to next pulmonary exacerbation, duration of *P aeruginosa* eradication, emergence of new or resistant organisms. Measured at baseline and end of treatment.
Notes	Abstract only. No data presented to enter into meta-analysis. Sample size calculation not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Abstract states ‘divided into 3 groups’ but does not state 'randomised' or describe process. Authors contacted and awaiting response.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) Participant	High risk	Not possible: IV twice-daily versus IV 3-times-daily versus inhaled.
Blinding (performance bias and detection bias) Caregiver or clinician	High risk	Not possible: IV twice-daily versus IV 3-times-daily versus inhaled once-daily.
Blinding (performance bias and detection bias) Outcome assessor	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not clear if all randomised participants were treated or if there were any withdrawals.
Selective reporting (reporting bias)	Unclear risk	Abstract only - results described in general terms only.

Shatunov 2001 *(Continued)*

		States: Ventilation parameters, peak-flowmetry, oxygen saturation, chest X-ray, sputum bacteriology were done before and after. Sputum and serum samples for CTZ concentrations were collected after the first administration and for steady-state concentrations. Frequency and duration of *P aeruginosa* eradication and time until next exacerbation were analysed too.
Other bias	Unclear risk	Not clear, only abstract with limited information.

Stephens 1983

Methods	Randomised controlled trial. Parallel design. Single centre in Canada. Duration: 14 days.
Participants	28 people with CF (no information on how CF diagnosed) admitted to hospital for treatment of pulmonary exacerbation. IV + inhaled group: n = 16; IV alone group: n = 12. Age: IV + inhaled: mean (SD) 15.3 (3.5) years; IV: mean (SD) 15.1 (4.7) years. Age range for both groups 7 - 22 years. Gender: IV + inhaled: 9 males, 7 females; IV: 9 males, 3 females. Clinical status: admitted to hospital for treatment of exacerbation (no definition given). Groups comparable in age and details listed below. Mean (SD) Schwachman score: IV + inhaled: 53.4 (9.5); IV: 55.4 (9.0). Mean (SD) FEV_1 % predicted: IV + inhaled: 64.3 (11.8); IV: 72.2 (10.9). Mean (SD) FEF_{25-75} % predicted: IV + inhaled: 30.6 (26.5); IV: 36.6 (21.0). Mean (SD) $\log_{10}$ sputum colony count of *P aeruginosa*: IV + inhaled: 6.9 (1.6); IV: (7.4 (1.2).
Interventions	**IV + inhaled**: IV (tobramycin 10 mg/kg/day in 3 divided doses plus ticarcillin 300 mg/kg/day in 4 divided doses, each dose infused over 30 minutes) *plus* 80 mg aerosolized tobramycin mixed with 1 ml salbutamol and 2 ml buffering nebulising solution 3x daily via a Bennet twin jet nebulizer. **IV alone**: tobramycin 10 mg/kg/day in 3 divided doses plus ticarcillin 300 mg/kg/day in 4 divided doses, each dose infused over 30 minutes.
Outcomes	FEV_1, FVC, FEF_{25-75}, need for hospital admission, weight, adverse effects, emergence of resistant organisms, serum concentrations, sleeping pulse and respiratory rates, temperature, Schwachman score, sputum culture, antimicrobial sensitivities. Data reported at start of trial and discharge from hospital (25 participants discharged after 14 days, 2 from treatment and 1 from control group discharged at 21 to 26 days). Serum concentrations for adjustment of IV tobramycin measured on days 1, 5 and 12 - day 5 not reported in paper.
Notes	All *P aeruginosa* strains sensitive to ≤8 µg/ml tobramycin and ≤100 µg/ml ticarcillin. For FEV_1 and weight, paper reports means, but no SDs, so data can not be entered into RevMan. Paper also reports that "Eradication of Pa transient and all children re-colonized within 1 to 2 months after discharge."

Stephens 1983 *(Continued)*

Sample size calculation not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Paper states "allocated randomly to either the control or treatment groups" but process not described.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) Participant	High risk	Not possible, IV + inhaled versus IV alone.
Blinding (performance bias and detection bias) Caregiver or clinician	High risk	Not possible, IV + inhaled versus IV alone.
Blinding (performance bias and detection bias) Outcome assessor	Low risk	For lung function tests paper states "technician performing the tests was not aware of the treatment", but no details given for other outcome measures.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Appear to be no withdrawals.
Selective reporting (reporting bias)	High risk	Data for FVC not reported. Furthermore, paper states that "Serum concentrations were obtained prior to and 30 minutes after completion of the 30-min infusion. Serum concentrations of tobramycin and ticarcillin were measured on day 1, 5 and 12. Sleeping pulse & respiratory rates recorded daily and body temp (oral) 4 times a day. Schwachman score, quantitative sputum culture & antimicrobial sensitivities pulmonary function tests were performed at entry and at end of 2 weeks of treatment. Sputum obtained prior to 1st morning dose of inhaled tobramycin." Table 2 in the paper reports these clinical status data for start and at end of treatment, but no data are given for day 5 - unclear if this is selectively reported or not.
Other bias	Low risk	No other bias identified.

BMI: body mass index
CF: cystic fibrosis
FEF_{25-75}: mid-expiratory flow
FEV_1: forced expiratory volume at one second
FRC: functional residual capacity
FVC: forced vital capacity
IV: intravenous
P aeruginosa: *Pseudomonas aeruginosa*
PEG: percutaneous endoscopic gastrostomy
QoL: quality of life
RV: residual volume
SD: standard deviation
VC: vital capacity

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

Study	Reason for exclusion
Adeboyeku 2002	Not pulmonary exacerbation.
Al-Aloul 2004	Cross-over trial. First-arm data unavailable.
Alothman 2002	Not pulmonary exacerbation.
Bresnik 2008	Not pulmonary exacerbation.
Bruinenberg 2008	Chronic infection.
Carswell 1987	Chronic infection.
Chua 1990	Not pulmonary exacerbation.
Chuchalin 2007	Chronic infection.
Clancy 2013	Chronic infection.
Coates 2011	Trial of nebuliser device in patients with stable disease.
Colin 2003	Chronic infection.
Dasenbrook 2015	Chronic infection
Davies 2004	Chronic infection.
Day 1988	Chronic infection. Duration of treatment longer than 4 weeks
Dodd 1997	Participants clinically stable.
Dodd 1998	Not pulmonary exacerbation.
Dorkin 2011	Chronic infection.
Einarsson 2017	Wrong intervention - not inhaled antibiotics
Eisenberg 1997	Study of nebuliser, participants do not appear to have Pex, single administration of each intervention.
Elborn 2015	Clinically stable people with CF with chronic *P. aeruginosa*.
Flume 2014	Chronic infection
Flume 2015a	Chronic infection
Flume 2016	Chronic infection in stable patients
Frederiksen 1997	Maintenance treatment.
Geborek 2003	Cross-over trial. First-arm data unavailable.
Geller 2004	Single dose study of inhaled antibiotic.

Study	Reason for exclusion
Geller 2007	Participants clinically stable.
Geller 2011	Patients clinically stable.
Gibson 2003b	Chronic infection.
Gibson 2004	Patients clinically stable.
Goss 2009	Chronic infection.
Griffith 2008	Patients clinically stable.
Gulliver 2003	Not pulmonary exacerbation.
Herrmann 2017	Chronic infection. Duration of intervention longer than 4 weeks
Hodson 2002	Chronic infection.
Huls 2000	Not pulmonary exacerbation.
Jenkins 1985	Chronic infection.
Jensen 1987	Chronic infection.
Kapranov 1995	Wrong intervention. Not an inhaled antibiotic
Kenny 2009	Eradication, not pulmonary exacerbation.
Konstan 2010	Chronic infection.
Konstan 2011	Chronic infection.
Kun 1984	Not pulmonary exacerbation.
Ledson 2002	Chronic infection.
Lenoir 2007	Chronic infection.
Mainz 2014	Not pulmonary exacerbation, pulmonary exacerbation given as reason for exclusion from trial.
Mazurek 2011	Chronic infection.
McCoy 2008	Chronic infection.
Nasr 2006	Participants had chronic disease, treatment for 28 days.
Nathanson 1985	Chronic infection.
Nikolaizik 1996	Chronic infection.
Nikolaizik 2005	Chronic infection.
Nikonova 2010	Chronic infection.

Study	Reason for exclusion
Noah 2010	Patients clinically stable.
Nolan 1982	Prophylaxis, not pulmonary exacerbation.
Novartis 2010	Eradication, not pulmonary exacerbation.
Oermann 2009	Chronic infection
Poli 2005	Chronic infection.
Proesmans 2013	Eradication, not pulmonary exacerbation.
Ramsey 1993	Maintenance treatment.
Ramsey 1999	Chronic infection.
Ratjen 2010	Eradication, not pulmonary exacerbation.
Regelmann 1990	Stable disease.
Retsch-Bogart 2007	Chronic infection.
Retsch-Bogart 2008	Chronic infection.
Rietschel 2009	Chronic infection.
Rosenfeld 2006	Not pulmonary exacerbation.
Ruddy 2013	Participants had chronic disease, treatment for 28 days.
Schaad 1997	Maintenance treatment.
Schelstraete 2009	Eradication, not pulmonary exacerbation.
Schuster 2013	Maintenance treatment.
Smith 1994	Not pulmonary exacerbation.
Stass 2008	Single-dose pharmacokinetic trial, not pulmonary exacerbation.
Stass 2009	Chronic infection
Stead 1987	Chronic infection.
Stroobant 1985	Not pulmonary exacerbation.
Taccetti 2012	Eradication, not pulmonary exacerbation.
Tramper-Stranders 2009	Prophylaxis.
Trapnell 2010	Chronic infection.
Treggiari 2011	Chronic infection.
Tullis 2014	Not pulmonary exacerbation, trial duration up to 48 weeks.

Study	Reason for exclusion
Valerius 1991	Chronic infection.
Wainwright 2002	Eradication, not pulmonary exacerbation.
Wainwright 2011	Chronic infection.
Westerman 2003	Chronic infection.
Westerman 2005	Chronic disease.
Wiesemann 1998	Chronic infection.
Yasmin 1974	Not pulmonary exacerbation.

CF: cystic fibrosis
P. aeruginosa: *Pseudomonas aeruginosa*

Characteristics of studies awaiting assessment *[ordered by study ID]*

Postnikov 2007

Methods	2-arm cross-over design. Duration: 14 days.
Participants	15 children with CF aged 7 - 17 years.
Interventions	Twice-daily versus once-daily amikacin. Dose: 15 mg/kg/day - 20 mg/kg/day in combination with ceftazidime or meropenem.
Outcomes	Lung function (FVC, FEV_1), *P aeruginosa* colonies, nephrotoxicity, ototoxicity, serum levels of amikacin. Measured on day 1 and day 14.
Notes	Not clear if inhaled or IV.

Semykin 2010

Methods	Randomised controlled trial. 3-arm parallel design.
Participants	108 participants with chronic *P aeruginosa.* Age range: 4 - 17 years.
Interventions	Group A: (n = 32, age range 4-16 years) TOBI® (n = 16) 300 mg bid or Bramitob® (n = 16) 300 mg bid + IV ceftazidime plus oral ciprofloxacin. Group B: (n = 39, age range 6 - 17 years) IV cefepime + IV amikacin. Group C: (n = 37, age 4 - 17 years) IV meropemem + IV amikacin.

Semykin 2010 *(Continued)*

Outcomes	Clinical symptoms, lung function (FVC, FEV_1), sputum *P aeruginosa* density.
Notes	

Soulsby 2010

Methods	Randomised controlled trial. Randomisation order generation using the toss of a coin. No blinding. Open (masking not used). Phase IV trial.
Participants	Diagnosed with CF. Chronically colonised with *P aeruginosa.* Exacerbation of a lung infection. Male and female. Minimum age: 6 years old. Target sample size: 24.
Interventions	IV tobramycin at the dose they received on their last admission (usually 7 - 10 mg/kg) once daily for 14 days versus inhaled tobramycin at a dose of 300 mg twice daily for 14 days. Cross-over to other treatment arm at next admission (at least 6 weeks apart).
Outcomes	**Primary outcomes** 1. FEV_1 % predicted (measured at admission, on last day of treatment (day 14) and next clinical appointment - usually 6 weeks after end of treatment). 2. Time to next admission for an exacerbation (measured in weeks). 3. Change in renal function (measured on day 1 and 8 using blood samples also measured using urine samples on day 1, 14 and at next clinic visit - usually 6 weeks after end of treatment). **Secondary outcomes** 1. Weight measured (measured at admission, on last day of treatment (day 14) and next clinical appointment - usually 6 weeks after end of treatment). 2. QoL questionnaire (measured at day 1 and 14). 3. Antibiotic resistance to *P aeruginosa* using sputum samples (day 1, 14 and next clinical appointment - usually 6 weeks after end of treatment).
Notes	Funding source: The Society of Hospital Pharmacists of Australia, PO Box 1774, Collingwood, VIC 3066, Australia. We have no first-arm data for this small cross over trial; author contacted to see if we can obtain the data we need to include it.

FEV_1: forced expiratory volume at 1 second
FVC: forced vital capacity
IV: intravenous
P aeruginosa: *Pseudomonas aeruginosa*
QoL: quality of life

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

Prevotat 2018

Trial name or title	Evaluation of short antibiotic combination courses followed by aerosols in cystic fibrosis (TOBRAMUC).
Methods	Randomised cross-over trial.
Participants	Estimated enrolment: 97 participants. **Inclusion criteria:** 8 years and older; CF confirmed by sweat or genetic test; clinical signs of an exacerbation (increased cough, sputum (abundance, purulence), fever, anorexia, weight loss and FEV_1) or acute exacerbations (defined at the clinician's discretion); $FEV_1 \geq 25$ %; *P aeruginosa* chronic carriers; received at least 1 IV course of antibiotics in the year prior to inclusion.
Interventions	Intervention group (short cure): 14 days IV Nebcin plus 5 days of IV tobramycin followed by 9 days of inhaled tobramycin (Tobi Inhalant Product) 300 mg 2x daily. Control group (standard): 14 days IV Nebcin plus 14 days of IV tobramycin.
Outcomes	**Primary outcome** FEV_1 (up to 18 months post treatment) measure of dyspnoea. **Secondary outcomes** FEV_1 (change from baseline at day 16 or day 22) measure of dyspnoea. Visual analogue scale (change from baseline at day 16 or day 22) measure of dyspnoea, condition of patient, bronchial congestion. Number of participants with bronchial congestion (change from baseline at day 16 or day 22). Sputum sample culture (change from baseline at day 16 or day 22) (a descriptive analysis of *P aeruginosa*, and the other bacteria in the bacterial flora of sputum). Time to first exacerbation post treatment (up to 18 months). Number of pulmonary exacerbations and those leading to hospitalisation (up to 18 months post treatment).
Starting date	13 June 2017
Contact information	Anne Prévotat, MD anne.prevotat@chru-lille.fr
Notes	

CF: cystic fibrosis
FEV_1: forced expiratory volume at 1 second
IV: intravenous
P aeruginosa: *Pseudomonas aeruginosa*

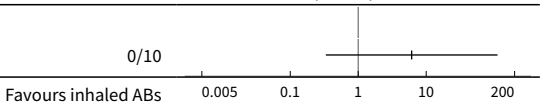
DATA AND ANALYSES

Comparison 1. Inhaled antibiotics versus intravenous antibiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Need for additional IV antibiotics	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 At 1 to 2 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Renal toxicity	1	18	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

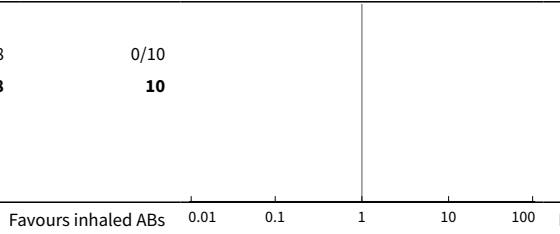
Analysis 1.1. Comparison 1 Inhaled antibiotics versus intravenous antibiotics, Outcome 1 Need for additional IV antibiotics.

Study or subgroup	Inhaled ABs n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
1.1.1 At 1 to 2 weeks				
Cooper 1985	2/8	0/10		6.11[0.33,111.71]



Analysis 1.2. Comparison 1 Inhaled antibiotics versus intravenous antibiotics, Outcome 2 Adverse events.

Study or subgroup	Inhaled ABs n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Renal toxicity					
Cooper 1985	0/8	0/10			Not estimable
Subtotal (95% CI)	**8**	**10**			**Not estimable**
Total events: 0 (Inhaled ABs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



Comparison 2. Inhaled antibiotics plus intravenous antibiotics versus intravenous antibiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Need for hospital admission	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 At 1 to 2 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Renal toxicity	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Development of resistant organisms	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 At 1 to 2 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 Inhaled antibiotics plus intravenous antibiotics versus intravenous antibiotics, Outcome 1 Need for hospital admission.

Study or subgroup	Inhaled ABs n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
2.1.1 At 1 to 2 weeks				
Stephens 1983	2/16	1/12		1.5[0.15,14.68]

Favours inhaled ABs 0.01 0.1 1 10 100 Favours control

Analysis 2.2. Comparison 2 Inhaled antibiotics plus intravenous antibiotics versus intravenous antibiotics, Outcome 2 Adverse events.

Study or subgroup	Inhaled ABs n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.1 Renal toxicity					
Stephens 1983	0/16	0/12			Not estimable
Subtotal (95% CI)	**16**	**12**			**Not estimable**
Total events: 0 (Inhaled ABs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Favours inhaled ABs 0.01 0.1 1 10 100 Favours control

Analysis 2.3. Comparison 2 Inhaled antibiotics plus intravenous antibiotics versus intravenous antibiotics, Outcome 3 Development of resistant organisms.

Study or subgroup	Inhaled ABs n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
2.3.1 At 1 to 2 weeks				
Stephens 1983	3/16	1/12		2.25[0.27,19.04]

Favours inhaled ABs 0.01 0.1 1 10 100 Favours control

WHAT'S NEW

Date	Event	Description
22 October 2018	New search has been performed	143 references to 40 trials were identified in the searches.

Date	Event	Description
		We excluded 25 references immediately on title and did not list these in the review. **Excluded studies** We identified 85 additional references to 25 trials previously listed as excluded in the review (Al-Aloul 2004; Clancy 2013; Coates 2011; Dorkin 2011; Elborn 2015; Geller 2011; Goss 2009; Griffith 2008; Konstan 2010; Konstan 2011; Mainz 2014; Mazurek 2011; McCoy 2008; Noah 2010; Proesmans 2013; Ratjen 2010; Retsch-Bogart 2007; Rietschel 2009; Schuster 2013; Stass 2008; Taccetti 2012; Tramper-Stranders 2009; Trapnell 2010; Treggiari 2011; Wainwright 2002). We identified 13 new trials (30 references) which we have listed as excluded studies (Dasenbrook 2015; Day 1988; Einarsson 2017; Eisenberg 1997; Elborn 2015; Flume 2014; Flume 2015a; Flume 2016; Geller 2004; Herrmann 2017; Kapranov 1995; Nasr 2006; Ruddy 2013). **Ongoing studies** One trial was identified from clinicaltrials.gov, but is at the recruitment stage so has been listed as an ongoing study (Prevotat 2018). **Studies awaiting classification** One trial, originally listed as ongoing, has now been completed; but it is a cross-over trial and no first-arm data are currently available. The author has been contacted and we have moved the trial to awaiting classification pending a response (Soulsby 2010). One reference to one newly identified trial is listed as awaiting classification (Postnikov 2007). The 'Plain language summary' has been updated in accordance with the latest guidelines and summary of findings tables added.
22 October 2018	New citation required but conclusions have not changed	The previous author team have stepped down and a new review team has taken this review on.

CONTRIBUTIONS OF AUTHORS

Up to 2018

Gerard Ryan conceived the protocol and all three authors worked on drafting the protocol.

NIkki Jahnke and Tracey Remmington undertook trial selection and data extraction. Nikki Janke entered data and with Gerard Ryan drafted the first version of the review. All authors worked on finalising the review following peer reviewer comments and editorial input.

From 2018

Sherie Smith and Edward Charbek undertook trial selection and data extraction. Nicola Rowbotham arbitrated on discrepancies in inclusion decisions and added clinical expertise.

All authors contributed to updating the text of the review.

DECLARATIONS OF INTEREST

No conflicts of interest were reported by Sherie Smith or Ed Charbek

Nicola J Rowbotham is an NIHR academic clinical fellow. She has received non-financial support (travel and accommodation) for conference attendance from TEVA.

Previous author team

Dr Gerard Ryan received funds for research for a multicentre industry-sponsored trial of aztreonam. Dr Ryan worked in a CF centre that contributed participants to the trial with funding going to the Lung Institute of Western Australia (LIWA) for research staff. No funding went to the CF centre.

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External sources

- National Institute for Health Research, UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Unit of analysis issues

Previously we proposed excluding all cross-over trials from this review. However, on revisiting the issue of the inclusion of such trials, all three authors agreed that the inclusion of first-arm data from these trials would be appropriate.

Summary of findings tables have been included in line with updated Cochrane guidance.

INDEX TERMS

Medical Subject Headings (MeSH)

*Pseudomonas aeruginosa; Administration, Inhalation; Amikacin [administration & dosage]; Anti-Bacterial Agents [*administration & dosage]; Carbenicillin [administration & dosage]; Ceftazidime [administration & dosage]; Cystic Fibrosis [*complications] [microbiology]; Disease Progression; Forced Expiratory Volume; Injections, Intravenous; Pseudomonas Infections [*drug therapy]; Randomized Controlled Trials as Topic; Respiratory Tract Infections [drug therapy] [microbiology]; Ticarcillin [administration & dosage]; Tobramycin [administration & dosage]

MeSH check words

Humans