Nebulised anti-pseudomonal antibiotics for cystic fibrosis (Review)

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ABSTRACT

Background
Persistent infection by *Pseudomonas aeruginosa* contributes to lung damage, resulting in illness and death in people with cystic fibrosis (CF). Nebulised antibiotics are commonly used to treat this infection.

Objectives
To examine the evidence that nebulised anti-pseudomonal antibiotic treatment in people with CF reduces frequency of exacerbations of infection, and improves lung function, quality of life and survival. To examine adverse effects of nebulised anti-pseudomonal antibiotic treatment.

Search strategy
Trials were identified from the Cochrane Cystic Fibrosis and Genetic Disorders Group Trials Register. Companies that marketed nebulised anti-pseudomonal antibiotics were contacted for information on unpublished trials.

Most recent search of the Group's Cystic Fibrosis Trials Register: November 2006.

Selection criteria
Trials were selected if, nebulised anti-pseudomonal antibiotics treatment was used for four weeks or more in people with CF, allocation to treatment was randomised or quasi-randomised, and there was a placebo or a no placebo control group or another nebulised antibiotic comparison.

Data collection and analysis
For the first version of this review, two authors independently selected and judged the quality of the trials to be included in the review. One author extracted data from these trials and performed all tasks for updates of the review.

Main results
The search identified 116 citations to 53 trials. Fourteen trials, with 1100 participants, met the inclusion criteria. Thirteen trials with 985 participants compared a nebulised anti-pseudomonal antibiotic with placebo or usual treatment. One of these trials accounted for 53% of the total participants; and seven of these trials used a cross-over design. Tobramycin was studied in eight trials and follow up ranged from 1 to 32 months. Lung function, measured as forced expired volume in one second (FEV_1) was better in the treated group than in control group in nine of these. Resistance to antibiotics increased more in the antibiotic treated group than in placebo group. Tinnitus and voice alteration were more frequent with tobramycin than placebo. One short-term trial of one month, with 115 participants, compared tobramycin and colistin, and showed a trend towards greater improvement in FEV_1 in the tobramycin group.

Authors' conclusions
Nebulised anti-pseudomonal antibiotic treatment improves lung function. However, more evidence, from longer duration trials, is needed to determine if this benefit is maintained as well as to determine the significance of development of antibiotic resistant organisms. There is insufficient evidence for recommendations about type of drug and dose regimens.

PLAIN LANGUAGE SUMMARY

Nebulised anti-pseudomonal antibiotic treatment improves lung function and reduces the frequency of infections in people with cystic fibrosis

Cystic fibrosis is an inherited condition which results in abnormal mucus in several parts of the body. The major complication of cystic fibrosis is lung disease. The abnormal mucus in the lung leads to infection with certain bacteria including *Pseudomonas aeruginosa*. These bacteria are impossible to eradicate by antibiotic therapy and result in permanent damage to the lungs. This review of trials found that inhaling an antibiotic to fight these bacteria helps to control this infection. However, possible adverse effects, such as an increased likelihood of acquiring drug-resistant organisms requires further research.

BACKGROUND

Cystic fibrosis (CF) is an inherited disease caused by mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene which results in abnormal ion transfer at the apical surface of epithelial cells (Rosenstein 1998). The major impact of this genetic abnormality is lung disease which is characterised by abnormal airway secretions, persistent bacterial infection and inflammation. These processes inevitably increase in severity leading to progressive impairment of lung function, respiratory failure and premature death.

The most common bacteria causing infection in older people with CF is *Pseudomonas aeruginosa* (*P. aeruginosa*) and anti-pseudomonal antibiotics are a major component of treatment. Delivery of antibiotic by inhalation of a nebulised solution is used to obtain high concentrations of antibiotic in airways to control infection with *P. aeruginosa* thus allowing use of drugs which otherwise have to be given by injection (Touw 1995). Inclusion of nebulised antibiotics as part of usual treatment was reported in about one third of participants in a trial of deoxyribonuclease (DNase) in the United States of America (Fuchs 1994) and in 48% of people attending a CF clinic in Ireland (Mulheren 1991).

A beneficial effect of nebulised anti-pseudomonal antibiotics (NAPA) on lung function, respiratory exacerbations and pseudomonal load were identified in a meta-analysis (Mukhopadhyay 1996). Additional issues of relevance around the use of nebulised antibiotics in CF include financial cost, increased time of treatment, risks of adverse effects of the drugs and an increase in the likelihood of acquisition of infection with drug-resistant organisms by long-term exposure to tobramycin and colistin which are the most frequently used drugs.

The clinical settings in which NAPA have been used are:
(1) eradication of *P. aeruginosa* in the early stages of colonisation;
(2) treatment of acute exacerbations of lung infection; and
(3) for longer-term suppression of chronic *P. aeruginosa* infection.
It is the third of these indications which is the subject of this review; the aim of treatment being to reduce lung damage associated with *P. aeruginosa* infection thereby reducing the rate of deterioration of lung function and frequency of exacerbations of infection. These outcomes should be associated with improvement in quality of life and in survival.

OBJECTIVES

To evaluate nebulised anti-pseudomonal antibiotic (NAPA) treatment of people with CF, to determine if this treatment:
(1) improves lung function;
(2) reduces frequency of exacerbations of respiratory tract infections;
(3) improves nutrition;
(4) improves quality of life;
(5) improves survival;
(6) increases frequency of antibiotic-resistant organisms;
(7) causes renal or auditory impairment;
(8) causes drug sensitivity reactions.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomised (RCTs) or quasi-randomised trials.

Types of participants

People with CF diagnosed by clinical features associated with an abnormal sweat electrolyte test or mutations of the CFTR gene or both. All ages and all levels of severity of respiratory disease were included.

Types of intervention

Treatment Group

Nebulised (synonymous with aerosolised) antibiotics with activity against *P. aeruginosa.*
Antibiotics included were aminoglycosides (gentamicin, tobramycin, amikacin), colomycin (colistin), penicillins and cephalosporins with usual activity against *P. aeruginosa.*
Antibiotics to be given for one month or more.
All doses and methods of nebulisation were included.

Trials in which an antibiotic was tested at two or more doses and trials in which two nebulised anti-pseudomonal antibiotics were compared were also selected.

Comparison Group
Nebulised placebo or to no placebo, i.e. usual treatment or another anti-pseudomonal antibiotic.
Usual treatment did not include anti-pseudomonal antibiotic therapy given orally or by intravenous injection for the duration of the trial.

Types of outcome measures

Primary outcomes
(1) Lung function measured in litre or per cent predicted
(a) forced vital capacity (FVC)
(b) forced expiratory volume in one second (FEV_1)

(2) Exacerbation of respiratory infection measured as a defined event or as the need for hospitalisation or parenteral antibiotics or both

Secondary outcomes
(3) Nutrition as measured by height and weight

(4) Quality of life

(5) Survival

(6) Antibiotic resistant *P. aeruginosa* and other organisms

(7) Adverse events
(a) renal impairment - creatinine above normal
(b) auditory impairment - impaired audiometry
(c) sensitivity reactions - bronchospasm

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

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

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

The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (Clinical Trials) (updated each new issue of *The Cochrane Library*), quarterly searches of MEDLINE, a search of EMBASE to 1995 and the prospective handsearching of two journals - *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis*. Unpublished work is identified by searching through the abstract books of three major cystic fibrosis conferences: the International Cystic Fibrosis Conference; the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference. For full details of all searching activities for the register, please see the relevant sections of the Cystic Fibrosis and Genetic Disorders Group Module.

Companies which manufacture colistin, gentamicin, tobramycin, amikacin, ceftazidime were contacted for information they had on RCTs involving these drugs delivered by a nebuliser.

Date of the most recent search of the Group's Cystic Fibrosis Trials Register: November 2006.

METHODS OF THE REVIEW

(1) Two authors (GR and MS) independently reviewed the full text of articles or abstracts identified from the search to select trials which fulfilled the inclusion criteria. They recorded reasons for excluding trials.

(2) Two authors (GR and MS) independently recorded the quality characteristics of each included trial, using the four criteria described by Schulz (Schulz 1995). This involves the rating of four features of trial design: concealment of allocation to treatment; generation of allocation sequence; inclusion in the analysis of all randomised participants; and double blinding. The ratings were adequate, inadequate, unclear for the first criterion and adequate or inadequate for the other three criteria.

The authors settled any disagreement on article selection or quality score by consensus.

(3) The authors prepared a form to record details of trial design, participant numbers and characteristics, interventions, and outcomes and one author (GR) extracted the data.

(4) Statistical analysis.
More information on the statistical methods used in this review can be found in the relevant section of the Cystic Fibrosis and Genetic Disorders Group Module. Comparisons were of all anti-pseudomonal antibiotics with placebo or usual treatment and one antibiotic compared to another. The authors compared outcome measures at one, three, six and twelve months and annually thereafter to accommodate trials of different lengths. The protocol did not exclude trials using a cross-over design. Elbourne discusses methods for meta-analysing cross-over trials (Elbourne 2002). The methods discussed rely on the data that is reported within the primary paper. The method that has been adopted within this review uses the data from the first period only, ignoring the second period data. If results of the first period were not available, the authors describe the results of the trial in the text. If possible the authors planned to perform sensitivity analyses based on methodological quality of the trials with and without quasi-randomised trials. The major potential sources of heterogeneity were the intervention, drugs, dose regimens of individual drugs (including methods of nebulisation) and severity of disease, baseline FEV_1.

DESCRIPTION OF STUDIES

The search retrieved 116 citations to 53 trials. Two trials (four citations) provide information only in abstracts and are included as awaiting assessment (Chuchalin 2005; Lenoir 2005). Fourteen trials are included in the review, including 1100 participants. No trials were found through contact with pharmaceutical companies.

(1) Nebulised antibiotic compared to placebo or usual treatment

Thirteen of the 14 trials had this comparison (Carswell 1987; Day 1988; Hodson 1981; Jensen 1987; Kun 1984; MacLusky 1989; Nathanson 1985; Ramsey 1993; Ramsey 1999; Stead 1987, Wiesemann 1998). Sample size varied from 7 to 518 participants, with a total of 963 participants enrolled. Two trials were published only as abstracts in conference proceedings (Day 1988; Nathanson 1985). There was large variation between trials in terms of design, intervention and outcome measures.

Criteria for diagnosis of CF were stated in 6 of these 13 trials (Hodson 1981; MacLusky 1989; Murphy 2004; Ramsey 1993; Ramsey 1999; Stead 1987). As participants were recruited from CF centres we accepted all twelve trials. It is unlikely that an important number of participants without CF were included. The ages of the participants seem to cover children and adults, with the youngest being less than 3 years old and the eldest being 41 years old, although an accurate age distribution is difficult to determine from the reports and is not available for the largest trial (Ramsey 1999).

There is also a wide range of disease severity as measured by baseline FEV_1, with some participants having an FEV_1 lower than 30% predicted and some over 100% predicted. However, it is not possible to know the numbers in categories of no, mild, moderate or severe impairment of lung function. Evidence of *P. aeruginosa* in sputum culture was an inclusion requirement in all trials except one, in which *P. aeruginosa* was present in 8 out of 33 participants (Kun 1984).

The pattern of respiratory disease in CF tends to be of progressive deterioration over years and with episodes of acute deterioration and some recovery. Because of these short-term fluctuations in severity, the timing of entry of participants into a trial in relation to exacerbations will probably determine outcome. In two trials, participants were recruited after a course of intravenous antibiotics against *P. aeruginosa* and lung function during the trial deteriorated in both groups (Day 1988; Jensen 1987). Four trials stated that participants were recruited at least two weeks after a course of intravenous antibiotics in an attempt to ensure a stable state (Hodson 1981; Ramsey 1993; Ramsey 1999; Stead 1987). This aspect of participant selection was not stated in the other six trials (Carswell 1987; Gibson 2003; Kun 1984; Murphy 2004; Stead 1987, Wiesemann 1998).

A cross-over design was used in seven trials with 172 participants (23% of the total participants) (Carswell 1987; Day 1988; Hodson 1981; Kun 1984; Nathanson 1985; Ramsey 1993; Stead 1987). In two of these trials, the first period could be analysed as a parallel design trial for one month (Ramsey 1993) and for the first year (Kun 1984). No trial had a washout period between treatments. Only two of the seven cross-over design trials examined for carry-over or period effects, none were found in one trial, but there were only six participants to be analysed (Carswell 1987). A carry-over effect for FEV_1 was reported in the other trial (Ramsey 1993). When tobramycin was used intermittently, an improvement in FEV_1 did not return to baseline during four weeks off treatment (Ramsey 1999). Stead reported that lung function in the saline period was higher in the participants who received it last (Stead 1987). These observations indicate a carry-over effect is likely if an inadequate washout period is used.

Seven of the ten trials were described as double-blinded (Carswell 1987; Day 1988; Hodson 1981; Jensen 1987; Nathanson 1985; Ramsey 1993; Ramsey 1999; Wiesemann 1998). In four of these trials the placebo was normal saline and it is possible that the taste of the antibiotic solution was not completely masked. In the other four double-blinded trials varying saline concentrations and addition of other chemicals (lactose or quinine or preservatives) was used to match drug and placebo solutions (Hodson 1981; Ramsey 1993; Ramsey 1999; Wiesemann 1998). In the three single-blinded trials it was stated that the investigators were unaware of generation of allocation sequence (Kun 1984; MacLusky 1989; Stead 1987). Kun used usual treatment as control (Kun 1984). Stead used 3.5% sodium chloride solution as a placebo (Stead 1987), but since then hypertonic saline has been shown to have a therapeutic effect in CF (Wark 2003).

Two trials used colistin, one million units twice daily (Day 1988; Jensen 1987). Tobramycin was used as a single agent in six trials, in a dose of 40 mg (Carswell 1987), 80 mg (MacLusky 1989; Wiesemann 1998), 600 mg (Ramsey 1993) and 300 mg (Gibson 2003; Murphy 2004; Ramsey 1999), nebulised twice daily in four trials and three times daily in two trials (MacLusky 1989; Ramsey 1993). Gentamicin was used as a single agent, 20 mg twice daily (Kun 1984) and 80 mg three times daily (Nathanson 1985). Gentamicin 80 mg was combined with carbenicillin 1.0 g twice daily in two trials (Hodson 1981; Stead 1987). Ceftazidime 1.0 g was used in one trial, as the third arm of a three-period cross-over design (Stead 1987).

The dose of drug delivered to the lung depends on a number of factors including the method of aerosol generation and delivery, the volume of solution in the nebuliser and the method of inhalation (Newman 1985). Nebulisers vary in their efficiency of aerosol generation; the nebuliser used was stated in eight trials, one of which was an ultrasonic system (Ramsey 1993). The volume of solution used was stated in eight of the ten trials which reported using jet nebulisers and varied from 1.0 ml to 5.0 ml. Some description of the compressor and airflow used to generate an aerosol was given in half the trials.

Duration of treatment was one month (Carswell 1987; Gibson 2003; Ramsey 1993), three months (Jensen 1987; Nathanson 1985), four months (Stead 1987), five months (Ramsey 1999), six months (Day 1988; Hodson 1981), 12 months (Kun 1984; Wiesemann 1998), 56 weeks (Murphy 2004) and 32 months (MacLusky 1989). The four-month trial was analysed with the three-month group and the five-month trial was analysed with the six-month group. The trial by Ramsey was a cross-over design of three months duration but one arm had two months of tobramycin and one arm had two months of placebo. Results of the first month were used as a parallel comparison (Ramsey 1993). A unique feature of two trials was the use of nebulised tobramycin intermittently, i.e. cycles of tobramycin 300 mg twice daily for four weeks, followed by four weeks off treatment for a trial duration of six months (Ramsey 1999) and 56 weeks (Murphy 2004).

The number of participants who were enrolled in the trial, but not included in analysis, varied from 2.8% (2 out of 71) (Ramsey 1993) to 65% (63 of 181) (Murphy 2004). In two trials the number of dropouts is unclear (Day 1988; Nathanson 1985). In one of the parallel group trials there was marked inequality in dropouts between the placebo group (9 out of 20) and the active treatment group (2 out of 20) (Jensen 1987).

Thirteen trials included lung function (FEV_1 and FVC) as an outcome measure. However, the time of measurement and the method of expression of results varied across the trials. Change in FEV_1 and FVC at end of treatment from baseline was the most common method, being used in five trials, expressed as change in per cent predicted in four trials (Jensen 1987; Kun 1984; Ramsey 1993; Ramsey 1999) and as change in litres in one trial (Stead 1987). Three trials compared absolute FEV_1 and FVC at the end of treatment, two as per cent predicted (Carswell 1987; Day 1988) and one in litres (Nathanson 1985). In the remaining three trials lung function result was the mean of monthly measurements for six months (Hodson 1981) and the rate of decline of predicted FEV_1 (MacLusky 1989; Murphy 2004). Five of the trials did not include standard deviations (SD) or standard errors in the results of lung function (Day 1988; Hodson 1981; Kun 1984; Nathanson 1985).

Some measurement of frequency of exacerbations of lung infection was included in eight trials. Seven trials measured number of hospital admissions (Day 1988; Hodson 1981; MacLusky 1989; Ramsey 1999; Stead 1987) or days in hospital during the trial (Kun 1984; MacLusky 1989; Murphy 2004; Ramsey 1999). Four measured the number of courses of antibiotics during the trial (Day 1988; Kun 1984; Murphy 2004; Ramsey 1999). Only one trial used a definition of pulmonary exacerbation (Ramsey 1993).

No trial used a validated quality of life instrument; seven trials reported some score of disease severity, which included symptoms, but were not consistent in their methodology (Day 1988; Jensen 1987; Kun 1984; MacLusky 1989; Nathanson 1985; Ramsey 1993; Ramsey 1999).

Sputum bacteriology for antibiotic sensitivity was reported in eight trials (Carswell 1987; Hodson 1981; Jensen 1987; Kun 1984; MacLusky 1989; Ramsey 1993; Ramsey 1999; Stead 1987).

Five trials measured renal function (Gibson 2003; MacLusky 1989; Murphy 2004; Ramsey 1993; Ramsey 1999) and six trials measured hearing as a marker of toxicity (Gibson 2003; Hodson 1981; MacLusky 1989; Murphy 2004; Ramsey 1993; Ramsey 1999).

Other outcome measures used infrequently were death, chest X-ray score, blood antibiotic levels, quantitative bacterial count in sputum, blood levels of inflammatory parameters and weight.

Searches of the Group's CF Trials Register identified 30 citations that report data from a trial, first fully published in 1999 (Ramsey 1999). This trial is widely known as the 'TOBI' trial from the trade name of the preservative-free formulation of tobramycin used in the trial (Ramsey 1999). A report of this trial by Burns is published in full and provides information on the effect of tobramycin treatment on isolation of drug resistant organisms (Burns 1999). Birnbaum published another report of this trial describing an analysis of the effect of tobramycin on hospitalisation and home intravenous antibiotic use. These particular data are only published as an abstract and the results are not currently in a form which can be included within the review (Birnbaum 1998).

(a) Individual drugs versus placebo

It was planned to consider the effectiveness of anti-pseudomonal antibiotics by aggregating data from all drugs together in comparison to placebo or usual treatment. It was also planned to compare individual antibiotics to placebo or usual treatment if there were sufficient trials. The following is a description of trials involving individual antibiotics.

(i) Colistin

Two trials with 54 participants compared colistin to placebo, using a dose of one million units twice daily for three months (Jensen 1987) and for six months (Day 1988). One trial has little detail in the abstract, which is the only form of publication available, and it is of cross-over design (Day 1988). The other reported improvement in clinical score and inflammatory parameters, which are not outcome measures for this review (Jensen 1987). Lung function was measured over three months (see 'Results'). There was a large inequality in the number of participants excluded from analysis; 9 out of 20 in the control group and 2 out of 20 in the colistin group (Jensen 1987).

(ii) Tobramycin

Seven trials compared tobramycin to placebo or usual treatment in doses varying from 40 mg twice daily to 600 mg three times daily and duration of the trials varying from 1 month to 33 months (Carswell 1987; Gibson 2003; MacLusky 1989; Murphy 2004; Ramsey 1993; Ramsey 1999; Wiesemann 1998). Sixty one per cent of participants were in one high quality trial (Ramsey 1999).

(iii) Gentamicin

Two trials used gentamicin as a single agent, 20 mg twice daily for 12 months (Kun 1984) and 80 mg three times daily for three months (Nathanson 1985), both using a cross-over design.

(iv) Ceftazidime
Only one trial used this drug, one gram twice daily, as the third arm of a three-way cross-over trial without a washout period (Stead 1987).

(v) Gentamicin and carbenicillin
Two trials of cross-over design with 38 participants tested this combination (Hodson 1981; Stead 1987).

(2) Nebulised anti-pseudomonal antibiotics compared
Two of the trials reported on this comparison (Hodson 2002; Stead 1987). Ceftazidine was compared to a combination of gentamicin and carbenicillin as well as a saline placebo in a three period cross-over trial (Stead 1987). Tobramycin was compared to colistin in 115 participants in a 28-day parallel group trial (Hodson 2002). This was accepted as one month duration and included. Lung function was the primary outcome measure.

METHODOLOGICAL QUALITY

Lack of information in the reports of the trials made it difficult to rate using the criteria described by Jüni (Jüni 2001). *See* Addtional table 'Quality Assessment' for information from each of the reports on these criteria (Table 01). One trial has been included in both comparison groups (Stead 1987).

Nebulised antibiotic compared to placebo or to usual treatment
Thirteen trials reported on this comparison (Carswell 1987; Day 1988; Gibson 2003; Hodson 1981; Jensen 1987; Kun 1984; MacLusky 1989; Murphy 2004; Nathanson 1985; Ramsey 1993; Ramsey 1999; Stead 1987; Wiesemann 1998).

(1) Generation of allocation sequences
Eight trials stated that allocation was randomised and so is probably adequate (Carswell 1987; Gibson 2003; Hodson 1981; Jensen 1987; Murphy 2004; Ramsey 1993; Ramsey 1999; Stead 1987). In three trials the method may be inadequate (Kun 1984; MacLusky 1989; Wiesemann 1998). In two trials the method was not stated (Day 1988; Nathanson 1985).

(2) Concealment of treatment allocation schedule
Two trials, using alternate participants, were rated inadequate (Kun 1984; MacLusky 1989). The other eleven trials were rated as unclear.

(3) Blinding
Nine trials reported the trial to be double-blinded without specifying who was unaware of treatment (Carswell 1987; Day 1988; Gibson 2003; Hodson 1981; Jensen 1987; Nathanson 1985; Ramsey 1993; Ramsey 1999; Wiesemann 1998). Trials that reported double blinding may not have achieved this because of the taste of antibiotic solutions; two trials reported using quinine to attempt to mask nebulised solutions adequately (Ramsey 1993; Ramsey 1999) and one used the tobramycin preservative solution to saline as the placebo (Wiesemann 1998). One trial was 'single' blind (MacLusky 1989). One trial was not blind (Murphy 2004). Blinding was not mentioned in two reports (Kun 1984; Stead 1987).

(4) Participant attrition
The number of participants enrolled but not analysed was not stated in two trials (Day 1988; Nathanson 1985). The percentage of participants enrolled that were not available for analysis varied from 0% to 46%. Use of intention-to-treat analysis was stated in three trials (Gibson 2003; Ramsey 1993; Ramsey 1999).

Nebulised anti-pseudomonal antibiotics compared
Two trials reported on this comparison (Hodson 2002; Stead 1987).

(1) Generation of allocation sequences
The treatment sequence in the cross-over design used a 'latin square' method (Stead 1987). The method of allocation in other trial was unclear (Hodson 2002).

(2) Concealment of treatment allocation schedule
This was unclear in both trial reports.

(3) Double blinding
This was not used.

(4) Participant attrition
The dropout rates were 6% and 28%

Two trials (Gibson 2003; Murphy 2004) had early termination for benefit which may overestimate benefit (Montori 2005).

RESULTS

The outcomes reported for each study are tabulated in the additional tables (Table 02). Not all outcomes reported have results that can be analysed. Pooling of results for analysis is not possible for most outcomes because of differences in trial duration, methods of measuring and expressing results of the outcome and because of missing estimates of variance. A major problem was the high proportion of cross-over trials, 7 out of 14 included trials. There must be doubt about the suitability of this design for trials of antibiotic treatment in people with cystic fibrosis (see 'Discussion'). Despite this doubt they are included in the description of results. They are excluded from meta-analyses unless the first period parallel group comparison was available.

Nebulised anti-pseudomonal antibiotics compared to placebo
Primary outcomes
(1) Effect on Lung Function

One study measured lung function (parameters not specified) and stated in results that there was significant difference between tobramycin and placebo groups (Wiesemann 1998).

(a) FEV_1

A result for FEV_1 was present in ten reports but at several different times and in several different units. Six of these ten trials were of cross-over design and the results were not included in the tables, apart from two trials from which results are available from the first period (Kun 1984; Ramsey 1993). Jensen presented results as change in FEV_1 (% predicted) at three months and as the absolute FEV_1 (% predicted) at one, two, and three months; and all were included in the tables (Jensen 1987). Ramsey reported change in FEV_1 (% predicted) at five months in a table without variance estimate (Ramsey 1999). In eight of these trials the FEV_1 in the treatment group was better than in the control group; in six of the eight trials the difference was reported as statistically significant. In the trial without results, it was stated in the abstract that FEV_1 at end of trial was better in the treatment group (Day 1988).

In one trial of 72 participants, the difference in per cent change in FEV_1 (% predicted) after one month of treatment was weighted mean difference (WMD) 9.69% (95% confidence interval (CI) 4.93 to 14.45) (Ramsey 1993). In a further trial of 27 participants, after three months of treatment the WMD was 6.00% (95% CI -1.07 to 13.07) (Jensen 1987). Another trial showed an increase in FEV_1 of 12% predicted in the tobramycin group after five months ($P < 0.001$, no variance measure) (Ramsey 1999). In a trial by Kun, the units for change in FEV_1 after 12 months of treatment are not clear (Kun 1984). Rate of lung function decline was the primary endpoint in two trials (MacLusky 1989; Murphy 2004) In one the difference in rate of change of FEV_1, as % predicted per year, was WMD 7.80 (95% CI 3.29 to 12.31) (MacLusky 1989). In the other no difference was found but only 57% of participants had the minimum number of measurements (Murphy 2004). In the Jensen trial, the mean FEV_1 after one and three months of treatment were not statistically different (Jensen 1987).

(b) FVC

FVC was reported in nine trials; however, these results were measured at several different times and in several different units. Six of these nine trials were of cross-over design. In eight of these nine trials the FVC in the treatment group was better than in the control group; in six of the eight trials the difference was reported as statistically significant (Day 1988; Hodson 1981; Jensen 1987; MacLusky 1989; Ramsey 1993; Ramsey 1999).

The difference in per cent change in FVC (% predicted), after one month of treatment in one trial of 69 participants was WMD 6.17% (95% CI 1.35 to 10.99) (Ramsey 1993). In a further trial of 29 participants, after three months, the WMD was 11.00% (95% CI 1.94 to 20.06) (Jensen 1987). The mean change in FVC (% predicted) measured at five months showed an 8% increase in the treatment group compared to a 1% decline in the placebo group ($P < 0.05$), there was no variance estimate stated (Ramsey 1999). The difference in rate of change of FVC, as % predicted per year, was WMD 5.40 (95% CI 0.86 to 9.94) (MacLusky 1989).

(2) Effect on exacerbation of respiratory infection

(a) Hospital admissions

Hospital admission was measured in seven trials (Day 1988; Hodson 1981; Kun 1984; MacLusky 1989; Murphy 2004; Ramsey 1999; Stead 1987). It was reported in different scores and at different times. Three trials were cross-over in design; Day reported hospital admissions were 'similar', Stead reported four of five hospital admissions were during the four-month placebo period and Hodson reported three hospital admissions during treatment period and seven during placebo period (Day 1988; Hodson 1981; Stead 1987).

Odds ratios (OR) for one or more hospital admissions during treatment were 0.72 (95% CI 0.51 to 1.03) at six months (Ramsey 1999), 0.51 (95% CI 0.25 to 1.05) (Murphy 2004) and 0.63 (95%CI 0.14 to 2.89) at 32 months (MacLusky 1989). In the latter trial the total admissions during the 32 months were 14 from 15 participants in the treatment group and 21 from 12 participants in the control group (MacLusky 1989).

The mean number of days in hospital was lower in the treated group than the control group in three trials with 576 participants (Kun 1984; MacLusky 1989; Ramsey 1999). For the MacLusky trial the WMD was estimable over 32 months, WMD -3.20 (95% CI -9.05 to 2.65), control was 13.5 days and antibiotic was 10.3 days (MacLusky 1989). For the other trials, variances were not provided, but the results were control 8.1 days and antibiotic 5.1 days in six months (Ramsey 1999), control 26 days and antibiotic 15 days over 12 months (Kun 1984). The number of annualized days in hospital was similar for treatment (4.6 days per year) and control (4.5 days per year) (Murphy 2004).

(b) Courses of intravenous antibiotics

Courses of intravenous antibiotics were measured in three trials (Kun 1984; Ramsey 1993; Ramsey 1999). It was reported in different scores and at different times. In one trial it was a score of oral and intravenous antibiotic use of uncertain validity with no significant difference after 12 months (Kun 1984). Another trial found no difference in the frequency of oral or intravenous antibiotic use during the first month of a cross-over designed trial (Ramsey 1993). There was a significant reduction in the number of participants receiving one or more courses of intravenous anti-pseudomonal antibiotics in a six-month trial of 520 participants; OR 0.60 (95% CI 0.42 to 0.84) (Ramsey 1999). Oral antibiotic use was stated to be similar during colistin and placebo treatment periods in a cross-over designed trial with 14 participants (Day 1988). The need for intravenous antibiotics was the cause of withdrawal from the study in 2 of 11 participants using placebo and none of those taking tobramycin (Wiesemann 1998).

(c) Pulmonary exacerbations

In the one trial which used a definition of pulmonary exacerbation, there were similar rates during the first month of the trial; 14% (5 out of 36) in the tobramycin group and 6% (2 out of 35) in the control group, OR 2.66 (95% CI 0.48 to 14.74) (Ramsey 1993).

Secondary outcomes

(3) Effect on nutrition

(a) Weight

Three studies with 48 participants reported this outcome (Day 1988; Gibson 2003; Stead 1987). Two reported an increase in weight with antibiotic treatment (Day 1988; Stead 1987). Both were cross-over design and results are not available for meta-analysis. In the other trial no significant difference in weight was found after one or two months nebulised antibiotic treatment (Gibson 2003).

(4) Quality of Life

No validated score was used in any trial.

(5) Survival

Five deaths were reported in two parallel group trials of 547 participants with no deaths reported during treatment with nebulised antibiotic (MacLusky 1989; Ramsey 1999). The difference was not statistically significant in either trial. Also, Kun reported 2 deaths in 33 participants from a cross-over design trial. These deaths occurred at three and six months after changing from gentamicin to the saline mixture (Kun 1984).

(6) Sputum microbiology

(a) Antibiotic-resistant *P. aeruginosa*

Ten trials examined sputum for drug sensitivity but little detail of results was usually reported. Also interpretation is difficult in the six trials using a cross-over design (Carswell 1987; Hodson 1981; Kun 1984; Nathanson 1985; Ramsey 1993; Stead 1987). Carswell found aminoglycoside resistance developed in three of five participants who had sensitive organisms on entry to the trial (Carswell 1987). Gentamicin resistance developed in 3 out of 25 participants during the period on gentamicin and 2 out of 25 participants during the period on placebo (Kun 1984). During four months of tobramycin and placebo treatment 14% of participants developed tobramycin resistant organisms without apparent difference between antibiotic and placebo groups (Ramsey 1993). There was no information on gentamicin resistance in two trials (Hodson 1981; Nathanson 1985). Two cross-over designed trials used combinations of drugs. Hodson reported only transient resistance to carbenicillin in 2 out of 17 participants (Hodson 1981). Stead reported partial resistance to ceftazidime in 1 out of 13 participants and to carbenicillin in 2 out of 13 participants (Stead 1987).

Two parallel group designed trials provided quantitative comparative information for tobramycin (MacLusky 1989; Ramsey 1999). Both used a minimum inhibitory concentration (MIC) greater than 16 mg per ml to define resistance. In one trial the proportion of isolates of *P. aeruginosa* resistant to tobramycin increased from 13% to 23% in the tobramycin group and decreased from 10% to 8% in the control group between Week 0 and Week 24 of the trial; the OR for frequency of tobramycin resistance at end of trial was 3.35 (95% CI 1.88 to 5.95) (Burns 1999; Ramsey 1999). MacLusky found this developed in 4 out of 14 participants (28.5%) in the tobramycin group and in none of the 12 participants in the control group in the sputum collected during the first 24 months of the trial, OR 10.71 (95% CI 0.52 to 222.81) (MacLusky 1989). A trial in a small number of young children reported no difference in tobramycin susceptibility after one month of treatment (Gibson 2003).

One of two trials testing colistin reported no change in MIC to colistin during the three-month trial (Jensen 1987).

(b) Other tobramycin-resistant organisms

Six cross-over design trials indicated sputum was cultured during the trial (Carswell 1987; Hodson 1981; Kun 1984; Nathanson 1985; Ramsey 1993; Stead 1987). There is little information on results other than a statement that no new pathogens were isolated during the trial. In one of these cross-over trials there were new isolates of *Burkoholderia cepacia* (*B. cepacia*) in three participants and of *Stenotrophomonas maltophilia* (*S. maltophilia*) in 10 participants; it is difficult to know how many of the participants from the 71 enrolled had this sputum examination (Ramsey 1993).

B. cepacia isolation was reported from two parallel group trials (MacLusky 1989; Ramsey 1999). No significant differences were found. A subsequent report on the Ramsay trial indicated there were intermittent isolates of *B. cepacia* (two in the tobramycin group and three in the placebo group), but none of the isolates of *B. cepacia* were persistent, i.e. not present on all three sputum specimens during the six-month trial (Burns 1999).

Persistent isolates of *S. maltophilia* and *Alcaligenes xylosoxidans* (*A. xylosoxidans*) were also uncommon although intermittent isolates were more frequent in the trial that reported this detail (Burns 1999). Intermittent isolates in tobramycin and placebo groups for *S. maltophilia* were 14.7% and 21.8% respectively and for *A. xylosoxidans* were 7.4% and 9.2% respectively.

No new pathogens were found in a trial using colistin (Jensen 1987).

(7) Adverse events

(a) Renal impairment

Five trials measured renal function (serum creatinine) and found no significant evidence of persistent renal impairment (Gibson 2003; MacLusky 1989; Murphy 2004; Ramsey 1993; Ramsey 1999). In the largest trial nine people in both the tobramycin group (300 mg twice daily) and the placebo group had transient increases of 50% or more in the creatinine level (Ramsey 1999).

(b) Auditory impairment

Five trials measured audiometry and three stated that no abnormality was found (Gibson 2003; Hodson 1981; Murphy 2004;

Ramsey 1993; Ramsey 1999). MacLusky found a change in hearing in one participant, attributed to auditory polyp, presumably no other abnormality in either group (MacLusky 1989). Ramsey reported tinnitus more frequently in the tobramycin-treated group (8 out of 258) than in the placebo group (0 out of 262), OR 17.81 (95% CI 1.02 to 310.26) (Ramsey 1999).

(c) Bronchospasm
One trial with 520 participants measured FEV_1 response to an inhalation of the nebulised solutions, at first dose and at Week 20 (Ramsey 1999). Thirty minutes after the first dose median FEV_1 fell in both groups, tobramycin -1.8% (range -34.4 to 22.1) and placebo -2.6% (range -43.6 to 34.1). Results at Week 20 were similar. MacLusky reported that three participants complained of dyspnea after inhaling tobramycin but had a negative challenge and continued the trial (MacLusky 1989). Stead reported one participant with transient chest tightness with gentamicin (Stead 1987).

(d) Other
There was an increase in voice alteration in two studies using tobramycin 300 mg twice daily, OR 2.64 (95% CI 1.53 to 4.55) (Murphy 2004; Ramsey 1999). There were reports of one or two cases of rash, bad taste and burning sensation of tongue. Two cross-over trials reported an episode of pneumothorax in each (Hodson 1981; Stead 1987). The best estimate of the risk of pneumothorax was from 5 episodes in 520 participants, OR 0.25 (95% CI 0.03 to 2.26), favouring tobramycin (Ramsey 1999). In that trial the risk for hemoptysis with tobramycin was an OR of 0.82 (95% CI 0.56 to 1.19) (Ramsey 1999).

Individual drugs versus placebo
There was no subgroup analysis by any of the individual drugs or combinations because of the small number of trials, different duration of these trials, different methods of expressing results of outcomes and absence of variance in results.

Nebulised anti-pseudomonal antibiotics compared
Tobramycin (300 mg of preservative free solution twice daily) versus colistin (1 million units twice daily)
Primary outcome
(1) Effect on lung function
(a) FEV_1
The mean % change in FEV_1 (measured as % predicted) from baseline was 6.7% (SD = 15.1) in the tobramycin group and 0.37%, (SD = 18.8) in the colistin group; WMD 6.33 (95% CI -0.04 to 12.70). Baseline FEV_1 was higher in the colistin group, 59.4% predicted, compared to the tobramycin group, 55.4% predicted (Hodson 2002).

Secondary outcomes
(6) Sputum microbiology
The frequency of tobramycin *P. aeruginosa* MIC greater than 4 μg/ml changed from 38% participants at baseline to 49% after 28 days in the tobramycin treated group and was unchanged in the colistin treated group at 55% (Hodson 2002).

(7) Adverse events
In this four week trial there were no reports of pneumothorax, hemoptysis or renal impairment. Increases in cough or in sputum and dyspnea were reported as adverse events. In other trials these symptoms were part of definition of a respiratory exacerbation (Ramsey 1993) or an indication for hospitalisation and intravenous antibiotics (MacLusky 1989). Pharyngitis was more common with tobramycin, OR 2.99 (95% CI 0.73 to 12.21). Regarding bronchospasm, there were similar falls in FEV_1, measured 30 minutes after treatment with tobramycin and colistin at commencement of the trial (Hodson 2002).

Ceftazidime versus combined gentamicin and carbenicillin (Stead 1987).
Primary outcome
(1) Effect on lung function
This was done as part of a three-arm cross-over designed trial. Lung function and weight were stated to be similar in both groups at the end of treatment (Stead 1987).

DISCUSSION

This review has found 14 trials that examined the effect of any NAPA treatment as long-term (i.e. 1 to 32 months) therapy in people with CF. There were 13 trials that compared antibiotic(s) to placebo or usual treatment. There was important heterogeneity amongst these trials which led to difficulties in performing the review and interpreting results. Despite these difficulties the review found evidence that NAPA improved lung function and reduced frequency of exacerbations of respiratory infection in these people with CF. Furthermore, there was no evidence of clinically important adverse effects during the trials. There were two trials that compared two antibiotics, but these do not provide sufficient evidence to make firm recommendations about whether one drug is superior. Overall the most studied NAPA is tobramycin.

It is unlikely that any trials of NAPA, particularly good quality trials, have not been identified and included. The search strategy was thorough. The selection of trials for inclusion in the review from those found in the search strategy has favoured inclusion rather than exclusion. For example quasi-randomised trials and trials in which the criteria for diagnosis of CF were not explicitly stated were included.

The temporal sequence of the trials is interesting. The report by Hodson was the first report of use in CF and renewed interest in inhaled antibiotic therapy (Hodson 1981). Seven trials were then published between 1984 and 1989; these were all small sample size, single centre trials with important problems in trial design (Carswell 1987; Day 1988; Jensen 1987; Kun 1984; MacLusky 1989; Nathanson 1985; Stead 1987). Furthermore the doses of

antibiotic used in these trials was relatively small and probably determined by the size of the ampoule for intravenous therapy e.g. doses of gentamicin or tobramycin from 20 mg to 80 mg. In vitro data suggested much higher doses would be needed to ensure bacterial killing. This led to the trial using 600 mg of tobramycin three times daily which needed an ultrasonic nebuliser for drug delivery, an inconvenient and costly program (Ramsey 1993). The next development was production of a preservative free tobramycin in a dose of 300 mg in 5 ml solution and able to be delivered by jet nebuliser (Hodson 2002Ramsey 1999). These last two trials were multicentre with larger numbers of participants and were performed at a time when there was more critical examination of trial design in trials involving people with CF and they were of higher quality. There were three trials in children with early isolation of *P. aeruginosa* or persistant isolation but with mild impairment of lung function (Gibson 2003; Murphy 2004; Wiesemann 1998).

Two design features that are problems for trials of nebulised antibiotics in CF are cross-over periods and double blinding. Cross-over design for antibiotic therapy in CF is probably inappropriate. Firstly, the clinical course of lung disease in CF is unstable with a frequent pattern of progressive deterioration and exacerbations causing further temporary deterioration. Secondly, an effective antibiotic treatment may have a carry-over effect. Thirdly, treatment of exacerbations with antibiotics and more physiotherapy and other treatment will cause an improvement in lung function that is likely to persist with time, with potential for carry-over benefit.

Blinding is important for these trials but care is needed to mask the taste of antibiotic solutions and this may not have been achieved in a number of trials using normal saline for placebo. Another possible bias is selection bias from the reporting of results. For example, reporting results only at the final time point and in selecting which parameter of lung function to report.

This review also raises issues about the methodology for performing and analysing systematic reviews. One is the level of rigour in selecting trials. We included 'quasi-randomised' trials and, included all drugs with anti-pseudomonal activity rather than a single agent (or combination). The number of trials is relatively small hence it is not possible to examine for the effect of trial quality, type of antibiotic, etc. by using sensitivity and subgroup analyses. The trials are very heterogeneous in terms of design, drug type, dose and delivery, duration of treatment and outcome measures. This reduces the validity of pooling results. Despite this there was reasonable consistency in finding some improvement in lung function although it is impossible to know the consistency in the size of this improvement.

The sample of trials gives an example for the debate on the relative validity of pooling results from a number of small trials with results that are prone to error or the results from a single large well-designed trial. In this review one trial contributed 54% of all participants in the 13 trials comparing nebulised antibiotic versus placebo and was well-designed (Ramsey 1999).

Statistical analysis was limited by variation in reporting results of lung function and by imprecise definition and lack of reporting of exacerbations of respiratory infection. Totals for measures of lung function can not be calculated because of trials of different durations. All information from the Ramsey trial could not be used because of the different periods of tobramycin and placebo treatment (Ramsey 1993).

The benefits shown in this review support the use of NAPA treatment but some caution in application to patient care is needed. CF is a chronic disorder without cure and causing premature death, therefore the important outcomes of long-term treatments are length of life, quality of life and independence. Eight trials were of one to six months duration which could be regarded as too short to determine if any benefit was maintained and if adverse effects developed. Unfortunately the longest trials rated low in quality and results may be biased.

The effect on quality of life could not be ascertained and there were only a small number of deaths during these trials. The most frequently measured outcomes were lung function, hospitalisation and antibiotic use, which can be considered reasonable surrogates for survival and quality of life. Nebulised therapy is time-consuming and this will have a negative impact on the quality of life and the independence of people with CF.

Important adverse effects were not common in these trials. However, there are potential problems with development of drug-resistant *P. aeruginosa* or acquisition of other relatively antibiotic-resistant bacteria such as *B. cepacia* and *S. maltophilia*. Infection with these organisms may reduce survival and not be detected in trials of short duration covered by this review. It was difficult to know acceptability of treatment. For example, bronchospasm has been reported to occur relatively frequently in some case series and is a probable cause of intolerance of NAPA, however, it was reported infrequently in the participants in this review.

AUTHORS' CONCLUSIONS

Implications for practice

The practice of prescribing nebulised antibiotics for treatment of chronic *P. aeruginosa* infection in people with cystic fibrosis is widespread. Drugs used are usually tobramycin or colistin. Treatment is often long-term i.e. years.

This review is restricted to randomised trials designed to test the benefit of these drugs. As described there is some evidence that nebulised antibiotic treatment of *P. aeruginosa* infection is of some benefit in terms of improvement in lung function and reduction in exacerbations of respiratory infection. In addition there do not seem to be severe or frequent adverse effects.

However, the findings of this review raise some issues to consider when prescribing this treatment long-term:
(1) there is little or no evidence of benefit in survival, quality of life or independence;
(2) the level of benefit is uncertain as most trials are small and prone to error and reporting is such that pooled analysis is not possible;
(3) the major evidence for benefit is use for up to six months, hence uncertainty about any longer-term benefit remains;
(4) there is no adequate RCT evidence to support the use of colistin;
(5) the optimal dose regimen for tobramycin is not established;
(6) no conclusion on the optimum method of aerosol generation and delivery can be made from this review; and
(7) harm of treatment may be underestimated from short-term RCTs, particularly the risk of antibiotic-resistant pathogens emerging with long-term use.

Implications for research

It is likely that NAPA will be increasingly used for the long-term treatment of people with CF who are troubled by complications attributable to chronic *P. aeruginosa* infection.

This review raises some questions that need to be answered by more RCTs. These trials need to be designed to overcome methodological problems found in many of the trials examined in this review. These problems can be resolved by adequate generation of allocation sequence, not using a cross-over design, careful blinding of treatments and obtaining complete follow up of participants. A review of the literature would be improved by more consistent reporting of lung function test results and care with defining exacerbations of respiratory tract infection in terms of hospitalisation and of antibiotic use. There should be information on the effect of long-term use on quality of life and survival.

Some specific issues which should be the objectives of trials are:
(1) to compare colistin (including different doses) with placebo to determine effectiveness;
(2) to determine the optimum dose, daily frequency of administration and frequency of treatment with tobramycin;
(3) to compare antibiotics for benefits and harm. There should be a longer term comparison of tobramycin and colistin, and perhaps combinations;
(4) to determine adverse effects of longer-term use, particularly on the frequency and impact of drug resistance organisms. This evidence will come from cohort and surveillance trials.

NOTES

Information on previous updates of the review

Review update: February 2006

The search of the Group's Cystic Fibrosis Trials Register to September 2005 identified 32 new citations of 16 trials:

ADDITIONAL CITATIONS TO ALREADY EXCLUDED TRIALS
Chua 1990 (1 additional citation added)
Dodd 1997 (1 additional citation added)
Frederiksen 1997 (1 additional citation added)
Alothman 2002 (1 additional citation added)

ADDITIONAL CITATIONS TO ALREADY INCLUDED TRIALS
Ramsey 1999 (10 additional citations added)
Hodson 2002 (2 additional citations added)
These additional reports of results from these two included trials did not add new results to the review compared to the reports already included. These citations either reported results already included in this review, or included outcomes that were not in the protocol for this review; or reported sub-group analyses, or results from open-label extension.

NEWLY EXCLUDED
Adeboyeku 2001(1 citation)
Geborek 2003 (1 citation)
Geller 2004 (2 citations)
Gullliver 2003 (1 citation)
Ledson 1998 (2 citations)
Pradal 2002 (1 citation)
Wainwright 2002 (1 citation)
Westerman 2003 (2 citations)

NEWLY INCLUDED:
Gibson 2003 (2 citations)
Murphy 2004 (3 citations)
Wiesemann 1998 (2 citations)

Methodological quality of included studies
This section has been revised by using a new method to classify quality criteria, describing the criteria for individual studies in a table and summarising the results in the text. The results of this quality assessment has not been used for study selection or in analysis.

Results
The inclusion of three studies has not significantly changed the results. Gibson 2003 reported only adverse effects, the primary outcome of the study was density of Pseudomonas aeruginosa, which was not an outcome of this review. Murphy 2004 added some results to respiratory tract exacerbations (hospitalisation, antibiotic use), lung function, adverse events. Wiesemann 1998 studied people with CF and early acquisition of Pseudomonas. The primary outcome was time to eradication of Pseudomonas; lung function was measured and reported as not different without numbers.

Review update: May 2003

There has been an extensive rewrite of the review in the May 2003 update by Gerard Ryan. This reflects:

(1) inclusion of new trial (Hodson 2002), which is a comparison of two nebulised anti-pseudomonal antibiotics (tobramycin and colistin);
(2) revision of inclusion of cross-over trials. The seven trials using this study design are included in the review. Elbourne 2000 has discussed issues of pooling results in meta-analysis. Results from these trials were included in tables of results in previous versions of this review. This is invalid. Therefore, results are not entered into RevMan unless there are data from the first period and considered as a parallel group study. This has reduced the number of tables and graphs;
(3) removal of totals from tables of studies of different duration. This has changed estimates of size of effect for "effect on exacerbation of respiratory infection".

The search carried out on the Collaborative Review Group (CRG) Cystic Fibrosis Controlled Trials Register found 13 references as potential trials for inclusion in this update of the review. Two were not considered further (case series and not Pseudomonas aeruginosa). One was selected for inclusion (Hodson 2002). Seven were further analyses of the trial reported and already included as Ramsay 1999. The other three were single dose studies. GR selected trials and extracted data for this update.

Abstract: selection criteria and results changed.
Criteria: edited according to style policy of CRG.
Description of studies: new headings for single antibiotics versus placebo and for antibiotics compared.
Methodological quality of included studies: new heading for antibiotics compared.
Results: new heading for antibiotics compared. Results of cross-over design described in text but not used for quantitative estimate of effect. The totals that included trials of different durations were removed.
Discussion: altered discussion on selection criteria and on place of cross-over design trials in this review.
Comparisons: results taken from cross-over trials removed from tables. Totals removed from analyses of trials of different duration.

POTENTIAL CONFLICT OF INTEREST

None known.

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REFERENCES

References to studies included in this review

Carswell 1987 *{published data only}*
Carswell F, Ward C, Cook DA, Speller DCE. A controlled trial of nebulized aminoglycoside and oral flucloxacillin versus placebo in the out-patient management of children with cystic fibrosis. *British Journal of Diseases of the Chest* 1987;**81**(4):356–60.

Day 1988 *{unpublished data only}*
Day AJ, Williams J, McKeown C, Bruton A, Weller PH. Evaluation of inhaled colomycin in children with cystic fibrosis [abstract]. Proceedings of the 10th International Cystic Fibrosis Congress; 1988 March 5-10; Sydney. 1988:106.

Gibson 2003 *{published data only}*
Gibson RL, Emerson J, McNamara S. A randomized controlled trial of inhaled tobramycin in young children with cystic fibrosis: eradication of Pseudomonas from the lower airway. *Pediatric Pulmonology* 2002;**S24**:300.

Gibson RL, Emerson J, McNamara S, Burns JL, Rosenfeld M, Yunker A, et al. Online Supplement to 'Significant microbiological effect of inhaled tobramycin in young children with cystic fibrosis'. [online]. *American Journal of Respiratory and Critical Care Medicine* 2003;**167**(6):841 Online.

* Gibson RL, Emerson J, McNamara S, Burns JL, Rosenfeld M, Yunker A, et al. Significant microbiological effect of inhaled tobramycin in young children with cystic fibrosis. *American Journal of Respiratory and Critical Care Medicine* 2003;**167**(6):841–9.

Hodson 1981 *{published data only}*

Hodson ME, Penketh ARL, Batten JC. Aerosol carbenicillin and gentamicin treatment of Pseudomonas aeruginosa infection in patients with cystic fibrosis. *Lancet* 1981;**2**(8256):1127–9.

Hodson 2002 *{published and unpublished data}*

Govan JR. Insights into cystic fibrosis microbiology from the European tobramycin trial in cystic fibrosis. *Journal of Cystic Fibrosis* 2002; **1**(Suppl 2):203–8.

Hodson ME, Gallagher CG. New clinical evidence from the European tobramycin trial in cystic fibrosis. *Journal of Cystic Fibrosis* 2002; **1**(Suppl 2):S199–S202.

* Hodson ME, Gallagher CG, Govan JRW. A randomised clinical trial of nebulised tobramycin or colistin in cystic fibrosis. *European Respiratory Journal* 2002;**20**(3):658–64.

Hodson ME, Gallagher CG, Govan JRW, PL TNDS 101 Clinical Trial Group. Randomised UK / Eire clinical trial of the efficacy and safety of tobramycin 300 mg/5 ml nebuliser solution or nebulised colistin in CF patients [abstract]. *Pediatric Pulmonology* 2000;**20**: 248–9.

Hodson ME, Gallagher CG, Govan JRW, the PL-TNDS-101 Clinical Trial Group. Randomised UK/Eire clinical trial of the efficacy and safety of tobramycin 300 mg/5 mL nebuliser solution or nebulised colistin [abstract]. Proceedings of the 13th International Cystic Fibrosis Congress; 2000 June 4-8; Stockholm. 2000:145.

Jensen 1987 *{published data only}*

Jensen T, Pederson SS, Garne S, Heilmann C, Hoiby N, Koch C. Colistin inhalation therapy in cystic fibrosis patients with chronic Pseudomonas aeruginosa lung infection. *Journal of Antimicrobial Chemotherapy* 1987;**19**(6):831–8.

Kun 1984 *{published data only}*

Kun P, Landau LI, Phelan PD. Nebulized gentamicin in children and adolescents with cystic fibrosis. *Australian Paediatric Journal* 1984; **20**(1):43–5.

MacLusky 1989 *{published data only}*

MacLusky IB, Gold R, Corey M, Levison H. Long-term effects of inhaled tobramycin in patients with cystic fibrosis colonized with pseudomonas aeruginosa. *Pediatric Pulmonology* 1989;**7**(1):42–8.

Murphy 2004 *{published data only}*

Anbar RD, Yu X, Colin AA. Reduction of pulmonary hospitalizations during a randomized, controlled, open-label study of tobramycin solution for inhalation in young CF patients with mild lung disease [abstract]. *Pediatric Pulmonology* 2003;**Suppl 25**:296.

Colin AA, Anbar RD, Yu X. Reduction in pulmonary hospitalizations during a randomized, controlled, open-label study of tobramycin solution for inhalation in young CF patients with mild lung disease [abstract]. *Journal of Cystic Fibrosis* 2003;**2**(Suppl 1):S22.

* Murphy TD, Anbar RD, Lester LA, Nasr SZ, Nickerson B, VanDevanter DR, et al. Treatment with tobramycin solution for inhalation reduces hospitalizations in young CF subjects with mild lung disease. *Pediatric Pulmonology* 2004;**38**(4):314–20.

Nathanson 1985 *{unpublished data only}*

Nathanson I, Cropp GJA, Li P, Neter P. Effectiveness of aerosolized gentamicin in cystic fibrosis (CF) [abstract]. Cystic Fibrosis Club Abstracts; 1985. 1985; Vol. 28:145.

Ramsey 1993 *{published data only}*

Fiel SB. Aerosol delivery of antibiotics to the lower airways of patients with cystic fibrosis. *Chest* 1995;**107**(Suppl 2):61S–64S.

Ramsey BW, Dorkin HL, Eisenberg JD, Gibson RL, Harwood IR, Kravitz RM, et al. Efficacy of aerosolized tobramycin in patients with cystic fibrosis. *New England Journal of Medicine* 1993;**328**(24):1740–6.

Ramsey 1999 *{published data only}*

Birnbaum HG, Greenberg P, Finkelstein S, Berndt E, Otto KL, Montgomery AB, et al. Economic analysis of hospitalization and home IV anti-pseudomonal antibiotic use in CF patients on tobramycin solution for inhalation (TOBI) [abstract]. *Pediatric Pulmonology* 1998;**Suppl 17**:273.

Bowman CM. The long-term use of inhaled tobramycin in patients with cystic fibrosis. *Journal of Cystic Fibrosis* 2002;**1**(Suppl 2):S194–8.

Burns JL, Van Dalfsen JM, Shawar RM, Otto KL, Garber RL, Quan JM, et al. Effect of chronic intermittent administration of inhaled tobramycin on respiratory microbial flora in patients with cystic fibrosis. *Journal of Infectious Diseases* 1999;**179**(5):1190–6.

Enger C, Rothman K, Kylstra JW. Mortality rates during two years of treatment with intermittent inhaled tobramycin (TOBI) in CF [abstract]. *Pediatric Pulmonology* 1999;**Suppl 19**:339–40.

Fiel S, VanDevanter DR, Yu X. Effect of tobramycin solution for inhalation on pulmonary function decline rates in exacerbating and stable CF patients [abstract]. Abstracts of the 24th European Cystic Fibrosis Conference; 2001 June 6-9; Vienna. 2001:P195.

Fiel SB. Long term effect of tobramycin solution for inhalation on reduction of hospitalization of CF patients [abstract]. *European Respiratory Journal* 2000;**16**(Suppl 31):1545.

Geller DE, Pitlick WH, Nardella PA, Tracewell WG, Ramsey BW. Pharmacokinetics and bioavailability of aerosolized tobramycin in cystic fibrosis. *Chest* 2002;**122**(1):219–26.

Graff GR, Gordon DC, Van Dalfsen, Burns JL. Epidemiology of Stenotrophomonas maltophilia culture in cystic fibrosis (CF) patients during the tobramycin solution for inhalation (TOBI) study [abstract]. *Pediatric Pulmonology* 2000;**Suppl 20**:283.

Hazinski TA. Intermitent administration of inhaled tobramycin in patients with cystic fibrosis [comment]. *Journal of Pediatrics* 1999; **135**(1):130.

Klystra JW, Bowman CM, Meyer U, Montgomery AB, Schaeffler B, Stewart P, et al. Who benefits more? An age-stratified analysis of lung function and weight gain in CF patients using inhaled tobramycin [abstract]. *The Netherlands Journal of Medicine* 1999;**54**:S83.

Konstan MW, VanDevanter DR. Peripheral white blood cell count as a surrogate marker for progression of lung disease in cystic fibrosis [abstract]. *Pediatric Pulmonology* 2001;**Suppl 22**:305.

LeLorier J, Perreault S, Birnbaum H, Greenberg P, Sheehy O. Savings in direct medical costs from the use of tobramycin solution for inhalation in patients with cystic fibrosis. *Clinical Therapeutics* 2000; **22**(1):140–51.

LiPuma JJ. Microbiological and immunologic considerations with aerosolized drug delivery. *Chest* 2001;**120**(Suppl 3):118S–23S.

MacLeod DL, Nelson LE, Shawar RM, Lin BB, Lockwood LG, Dirks JE, et al. Aminoglycoside-resistance mechanisms for cystic fibrosis Pseudomonas aeruginosa isolates are unchanged by long-term, intermittent, inhaled tobramycin treatment. *Journal of Infectious Diseases* 2000;**181**(3):1180–4.

Moss R, Klystra JW, Montgomery AB, Gibson R. Who benefits more? An analysis of FEV1 and weight in adolescents (age 13 - <18) CF patients using inhaled tobramycin (TOBI) [abstract]. *Pediatric Pulmonology* 1999;**Suppl 19**:243.

Moss RB. Administration of aerosolized antibiotics in cystic fibrosis patients. *Chest* 2001;**120**(Suppl 3):107S–13S.

Moss RB. Long-term benefits of inhaled tobramycin in adolescent patients with cystic fibrosis. *Chest* 2002;**121**(1):55–63.

Nickerson B, Montgomery AB, Klystra JW, Ramsey BW. Safety and effectiveness of 2 years of treatment with intermittent inhaled tobramycin in CF patients [abstract]. *Pediatric Pulmonology* 1999; **Suppl 19**:243–4.

Otto KL, Montgomery AB, Lin A, Ramsey BW. Seasonality of hospitalisations for pulmonary exacerbations and lower respiratory tract infections in phase III tobramycin solution for inhalation trials [abstract]. *Pediatric Pulmonology* 1998;**4**(Suppl 17):273.

Quan JM, Vasiljev M, Schaeffler B, Phelps C, Burrington C, Meyer U. Treatment for exacerbation only does not arrest progressive lung function decline in CF [abstract]. *The Netherlands Journal of Medicine* 1999;**54**:S84.

Quittner A, Gordon D, Yu X. Convergence of quality of life assessments and clinical outcomes in patients enrolled in the tobramycin solution for inhalation (TSI) trials [abstract]. Abstracts of the 24th European Cystic Fibrosis Conference; 2001 June 6-9; Vienna. 2001: P326.

Quittner AL, Buu A. Effects of tobramycin solution for inhalation on global ratings of quality of life in patients with cystic fibrosis and Pseudomonas aeruginosa infection. *Pediatric Pulmonology* 2002;**33** (4):269–76.

Quittner AL, Buu A, Gordon D. Longitudinal changes in global ratings of quality of life for patients in the tobramycin solution for inhalation (TSI) trials [abstract]. *Pediatric Pulmonology* 2001;**Suppl 22**:349.

Ramsey B, Burns J, Smith A. Safety and efficacy of tobramycin solution for inhalation in patients with cystic fibrosis: the results of two phase III placebo controlled clinical trial [abstract]. *Pediatric Pulmonology* 1997;**Suppl 14**:137–8.

Ramsey BW, Bowman MC, Montgomery AB, Smith AR, TOBI Study Group. Design of Phase 3 aerosolized tobramycin studies for chronic intermittent therapy [abstract]. Proceedings of the 21st European Cystic Fibrosis Conference; 1997 June 1-6; Davos. 1997:144.

Ramsey BW, Bowman MC, Vasiljev-K M, Smith AR, TOBI Study Group. Results of Phase 3 aerosolized tobramycin studies for chronic intermittent therapy [abstract]. Proceedings of the 21st European Cystic Fibrosis Conference; 1997 June 1-6; Davos. 1997:144.

* Ramsey BW, Pepe MS, Quan JM, Otto KL, Montgomery AB, Williams Warren J, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. *New England Journal of Medicine* 1999;**340**(1):23–30.

Rosenfeld M, Emerson J, Williams-Warren J, Pepe M, Smith A, Montgomery AB, et al. Defining a pulmonary exacerbation in cystic fibrosis. *Journal of Pediatrics* 2001;**139**(3):359–65.

Taylor CJ. Nebulised high dose Tobramycin (TOBI) in adolescents with cystic fibrosis [abstract]. *Pediatric Pulmonology* 2001;**Suppl 22**: 291.

VanDevanter D, Hou K, Yu X. Effect of tobramycin solution for inhalation (TOBI) on long term rates of lung function decline in Pseudomonas aeruginosa-infected cystic fibrosis (CF) patients with mild to moderate lung disease [abstract]. *Pediatric Pulmonology* 2000; **Suppl 20**:298.

VanDevanter DR, Yu X, Konstan MW. Effect of tobramycin solution for inhalation on circulating white blood cell counts in exacerbating and stable CF patients [abstract]. Abstracts of the 24th European Cystic Fibrosis Conference; 2001 June 6-9; Vienna. 2001:P172.

Stead 1987 *{published data only}*

* Stead RJ, Hodson ME, Batten JC. Inhaled ceftazidime compared with gentamicin and carbenicillin in older patients with cystic fibrosis infected with Pseudomonas aeruginosa. *British Journal of Diseases of the Chest* 1987;**81**(3):272–9.

Stead RJ, Hodson ME, Batten JC. Nebulised cefazidime compared with gentamicin and carbenicillin in adults with cystic fibrosis infected with Pseudomonas aeruginosa [abstract]. Proceedings of the 13th Annual Meeting of the European Working Group for Cystic Fibrosis; 1985 Nov 3-8; Jerusalem. 1985; Vol. 2:51.

Wiesemann 1998 *{published data only}*

Ratjen F, Steinkamp G, Doring G, Bauernfeind A, Wiesemann HG, Von Der Hardt H. Prevention of chronic Pseudomonas aeruginosa infection by early inhalation therapy with tobramycin [abstract]. *Pediatric Pulmonology* 1994;**Suppl 10**:250.

* Wiesemann HG, Steinkamp G, Ratjen F, Bauernfeind A, Przyklenk B, Doring G, et al. Placebo-controlled, double-blind, randomized study of aerosolized tobramycin for early treatment of Pseudomonas aeruginosa colonization in cystic fibrosis. *Pediatric Pulmonology* 1998; **25**:88–92.

References to studies excluded from this review

Adeboyeku 2001

Adeboyeku DU, Agent P, Jackson V, Hodson M. A double blind randomised study to compare the safety and tolerance of differing concentrations of nebulised colistin administered using HaloLite in cystic fibrosis (CF) patients [abstract]. *2001* Pediatric Pulmonology; **Suppl 22**:288.

Al-Aloul 2004

Al-Aloul M, Miller H, Browning P, Ledson MJ, Walshaw MJ. A randomised cross over trial of TOBI® vs IV tobramycin in acute pulmonary exacerbations in CF [abstract]. *Pediatric Pulmonology* 2004; **38**(Suppl 27):249.

Alothman 2000

Alothman GA, Alsaadi MM, Ho BL, Ho SL, Dupuis A, Corey M, et al. Evaluation of bronchial constriction in children with cystic fibrosis after inhaling two different preparations of tobramycin. *Chest* 2002; **122**(3):930–4.

Alothman GA, Coates Al, Corey M, Dupuis A, Ho SL, Ho BL, et al. In cystic fibrosis (CF) patients, does the inhalation of an intravenous tobramycin preparation result in more bronchospasm than a preservative free tobramycin preparation? [abstract]. *Pediatric Pulmonology* 2000;**Suppl 20**:298–9.

Alothman 2005

Alothman GA, Ho B, Alsaadi MM, Ho SL, O'Drowsky L, Louca E, et al. Bronchial constriction and inhaled colistin in cystic fibrosis. *Chest* 2005;**127**(2):522–9.

App 2000

App EM, Huls G, Bittner-Dersch P, Stolz S, Lindemann H, Matthys H. Impared lung function influences the serum concentration of inhaled drugs in cystic fibrosis [abstract]. *Pediatric Pulmonology* 2000; **Suppl 20**:279–80.

Huls G, App EM, Bittner-Dersch, Stolz S, Lindemann H. Impaired lung function influences the serum concentration of inhaled drugs in cystic fibrosis [abstract]. Proceedings of the 13th International Cystic Fibrosis Congress; 2000 June 4-8; Stockholm. 2000:177.

Chua 1990

Chua H, Collis G, Souef P. Bronchial response of children with cystic fibrosis to nebulised antibiotics [abstract]. *Australian and New Zealand Journal of Medicine* 1990;**20**:537.

* Chua HL, Collis GG, Le Souef PN. Bronchial response to nebulised antibiotics in children with cystic fibrosis. *European Respiratory Journal* 1990;**3**(10):1114–6.

Cooper 1985

Cooper DM, Harris M, Mitchell I. Comparison of intravenous and inhalation antibiotic therapy in acute pulmonary deterioration in cystic fibrosis. *American Review of Respiratory Disease* 1985;**131**:A242.

Dodd 1997

Dodd M, Maddison J, Abbott J, Webb AK. The effect of the tonicity of nebulised colistin on lung function in adults with cystic fibrosis [abstract]. Proceedings of the 18th European Cystic Fibrosis Conference; 1993 May 21-26; Madrid. 1993:121.

* Dodd ME, Abbott J, Maddison J, Moorcroft AJ, Webb AK. Effect of tonicity of nebulised colistin on chest tightness and pulmonary function in adults with cystic fibrosis. *Thorax* 1997;**52**(7):656–8.

Dodd ME, Maddison J, Abbot J, Webb AR. The effect of the tonicity of nebulised colistin on chest tightness and lung function in adults with cystic fibrosis [abstract]. *European Respiratory Journal* 1993;**6** (Suppl 17):515s.

Eisenberg 1997

Eisenberg J, Pepe M, Williams-Warren J, Vasiliev M, Montgomery AB, Smith AL, et al. A comparison of peak sputum tobramycin concentration in patients with cystic fibrosis using jet and ultrasonic nebulizer systems. *Chest* 1997;**111**:955–62.

Franz 1985

Franz MN, Spohn WA, Ronald PM. Evaluation of tobramycin aerosol therapy in cystic fibrosis [abstract]. Cystic Fibrosis Club Abstracts; 1985. 1985; Vol. 26:143.

Frederiksen 1997

Frederiksen B, Hansen A, Koch C, Hoiby N. Delay of recurrence of Pseudomonas aeruginosa in patients with cystic fibrosis with inhaled colistin and oral ciproxin; a comparison between 3 weeks and 3 months of treatment. *Pediatric Pulmonology* 1997;**Supp 14**:288.

Frederiksen B, Pressler T, Koch C, Hoiby N. Endpoints for evaluating early anti-pseudomonal treatment: changes in pseudomonas prevalence and in pulmonary function [abstract]. *Pediatric Pulmonology* 2003;**Suppl 25**:334.

Geborek 2003

Geborek A, Hjelte L, Lindblad A, Mared L, Eriksson L, Johannesson M, et al. Cross-over study of TOBI® vs. intravenous tobramycin in combination treatment of pulmonary exacerbations in cystic fibrosis patients [abstract]. *Journal of Cystic Fibrosis* 2003;**Suppl 1**:S22.

Geller 2004

Geller DE, Rodriguez CA, Howenstine M, Murphy T, Voter K, Nickerson B, et al. The effects of doubling concentration of tobramycin solution for inhalation on pharmacokinetics (PK), safety and delivery time in patients with cystic fibrosis (CF) [abstract]. *American Journal of American Journal of Respiratory and Critical Care Medicine* 2004; **169**(7):A391.

Rosenfeld M, Geller DE, Rodriguez CA, Howenstine M, Konstan M, Ordonez C, et al. Serum pharmacokinetics of two preparations of tobramycin solution for inhalation in young cystic fibrosis patients [abstract]. *American Journal of Respiratory and Critical Care Medicine* 2004;**169**(7):A386.

Gibson 2006

Burns JL, Stapp J, Lofland D, AI Phase 2 Study Group. Microbiology results from a phase 2 clinical study of aztreonam lysinate for inhalation (AI): a new inhaled antibiotic to treat CF patients with Pseudomonas aeruginosa (PA) [abstract]. *Journal of Cystic Fibrosis* 2005; **4 Suppl**:S55.

Gibson RL, Retsch-Bogart G, Ahrens R, Clancy J, Daines C, Milla C, et al. Safety and tolerability of aztreonam for inhalation (AI) in cystic fibrosis patients [abstract]. *Pediatric Pulmonology* 2004;**38**(Suppl 27): 253.

* Gibson RL, Retsch-Bogart GZ, Oermann C, Milla C, Pilewski J, Daines C, et al. Microbiology, safety, and pharmacokinetics of aztreonam lysinate for inhalation in patients with cystic fibrosis. *Pediatric Pulmonology* 2006;**41**(7):656–65.

Retsch-Bogart GZ, Gibson RL, AI Phase 2 Study Group. A phase 2 study of aztreonam lysinate for inhalation to treat cystic fibrosis patients with Pseudomonas aeruginosa infection [abstract]. American Thoracic Society International Conference; 2005 May 20-25; San Diego, USA. 2005:A576.

Gulliver 2003

Gulliver T, Wilson S, Williams G, Harris M, Cooper D. Nebulized tobramycin (intravenous solution) is tolerated without inducing cough and wheeze in cystic fibrosis patients [abstract]. Proceedings of

the Thoracic Society of Australia & New Zealand Annual Scientific Meeting; 2003 April 4-9; Adelaide, Australia. 2003:Abst#P139.

Jenkins 1985

Jenkins SG, Kelly WC, Mason WG, Peele JD, Cruse MA, Coludro EO, et al. Aerosolized amikacin administration to cystic fibrosis patients chronically infected with Pseudomonas aeruginosa [abstract]. Cystic Fibrosis Club Abstracts; 1985. 1985; Vol. 28:147.

Knowles 1988

Knowles NE, Hallberg TK, Colombe JL. Efficacy of aerosolized antibiotics combined with intravenous treatment of cystic fibrosis pulmonary exacerbation [abstract]. Pediatric Pulmonology. 1998; Vol. Suppl 2, issue 1:120.

Ledson 2002

Ledson MJ, Gallagher MJ, Cowperthwaite C, Robinson M, Convery RP, Walshaw MJ. A randomised double blind placebo controlled crossover trial of nebulised taurolidine in adult CF patients colonised with B cepacia [abstract]. Proceedings of the 22nd European CF Conference; 1998 June 13-19; Berlin, Germany. 1998:120.

* Ledson MJ, Gallagher MJ, Robinson M, Cowperthwaite C, Willets T, Hart CA, Walshaw MJ. A randomized double-blinded placebo-controlled crossover trial of nebulized taurolidine in adult cystic fibrosis patients infected with Burkholderia cepacia. *Journal of Aerosol Medicine* 2002;**15**(1):51–7.

Nizolaizik 1996

Nizolaizik WH, Jenni JV, Schoni MH. Bronchial constriction after nebulized tobramycin preparations and saline in patients with cystic fibrosis. *European Journal of Pediatrics* 1996;**155**:608–11.

Nolan 1982

Nolan G, McIvor P, Levison H, Fleming PC, Corey M, Gold R. Antibiotic prophylaxis in cystic fibrosis: inhaled cephaloridine as an adjunct to oral cloxacillin. *Journal of Pediatrics* 1982;**101**(4):626–30.

Poli 2005

Poli G, Acerbi D, Pennini R, Soliani Raschini A, Bianco F, et al. Clinical pharmacology study of a new tobramycin solution for nebulisation [abstract]. *Journal of Cystic Fibrosis* 2006;**5 Suppl**:S43.

Poli G, Acerbi D, Pennini R, Soliani Raschini A, Corrado M, Eichler HG, Eichler I. Clinical pharmacology study of a new tobramycin solution for nebulisation [abstract]. *European Respiratory Journal* 2005; **26**(suppl 49):729s.

Pradal 2002

Pradal U, Casotti V, Delmarco A, Nicolis E, Livraghi A, Conese M, et al. Effects of gentamicin on ion transport, MRNA and protein CFTR expression in patients with R1162X: A double blind placebo controlled study [abstract]. *Pediatric Pulmonology* 2002;**Suppl 24**: 263.

Ramsey 2005

Ramsey B. TOBI use in infants and children with early Pseudomonas Aeruginosa infection - duration of effect and epic update [abstract]. *Pediatric Pulmonology* 2005;**40**(Suppl 28):146.

Ratjen 2006

Ratjen F, Munck A, Campello V. Inhaled tobramycin nebuliser solution for treatment of early Pseudomonas aeruginosa infection: first results from the Elite study [abstract]. *Pediatric Pulmonlogy* 2006;**41** (Suppl 29):318.

Ratjen F, Munck A, Campello V. Safety of inhaled tobramycin nebuliser solution for treatment of early pseudomonas aeruginosa infection: first results from the ELITE study [abstract]. *Journal of Cystic Fibrosis* 2006;**5 Suppl**:S22.

Schaad 1987

Schaad UB, Wedgwood-Krucko J, Suter S, Kraemer R. Efficacy of inhaled amikacin as adjunct to intravenous combination therapy (ceftazidime and amikacin) in cystic fibrosis. *Journal of Pediatrics* 1987;**111**(4):599–605.

Schaad 1997

Schaad UB, Wedgwood J, Reuderberg A, Kraemer R, Hampel B. Ciprofloxacin as antipseudomonal treatment in patients with cystic fibrosis. *Pediatric Infectious Disease Journal* 1997;**16**(1):106–11.

Smith 1989

Smith AL, Ramsey BW, Hedges DL, Hack B, Williams-Warren J, Weber A, et al. Safety of aerosol tobramycin administration for three months to patients with cystic fibrosis. *Pediatric Pulmonology* 1989; **7**:265–71.

Steinkamp 1989

Gappa M, Steinkamp G, Tummler B, Von Der Hardt H. Long-term tobramycin aerosos therapy of chronic Pseudomonas aeruginosa infection in patients with cystic fibrosis. *Scandinavian Journal of Gastroenterology* 1988;**23**(Suppl 143):74–6.

Steinkamp G, Tummler B, Gappa M, Albus A, Potel J, Doring G, et al. Long-term tobramycin aerosol therapy in cystic fibrosis. *Pediatric Pulmonology* 1989;**6**:91–8.

Stephens 1983

Stephens D, Garey D, Isles A, Levison H, Gold R. Efficacy of inhaled tobramycin in the treatment of pulmonary exacerbations in children with cystic fibrosis. *Pediatric Infectious Disease Journal* 1983;**2**(3): 209–11.

Stroobant 1985

Heaf DP, Tyson S, Dinwiddie R, Matthew D. A comparison of inhaled therapies in children with cystic fibrosis [abstract]. Proceedings of the 9th International Cystic Fibrosis Congress; 1984 June 9-15; Brighton, England. 1984:274.

* Stroobant J, Heaf DP, Tyson S, Matthew DJ. Effect of inhaled azlocillin, mistabron and combination therapy in children with cystic fibrosis. *Pediatric Research* 1985;**19**:1099.

Stroobant J, Heaf DP, Tyson S, Matthew DJ. Effect of inhaled azlocillin, mistabron and combination therapy in children with cystic fibrosis [abstract]. Proceedings of the 13th Annual Meeting of European Working Group for Cystic Fibrosis; 1985 Nov 3-8; Jerusalem. 1985:47.

Valerius 1991

Valerius NH, Koch C, Hoiby N. Prevention of chronic colonization with Pseudomonas aeruginosa in patients with CF by early treatment with ciprofloxacin and colistin aerosol inhalations [abstract]. *Pediatric Pulmonology* 1990;**Suppl 5**:219.

* Valerius NH, Koch C, Hoiby N. Prevention of chronic Pseudomonas aeruginosa colonisation in cystic fibrosis by early treatment. *Lancet* 1991;**338**(8769):725–6.

Wainwright 2002

Wainwright CE, Carlin J, Cooper P, Byrnes C, Whitehead B, Martin J, et al. Early infection with pseudomonas aeruginosa can be cleared in

young children with cystic fibrosis [abstract]. *Pediatric Pulmonology* 2002;**Suppl 24**:300–1.

Wall 1984

Wall MA, Steinbach S, McNamara M, Terry AB. Prophylactic inhaled antibiotics in cystic fibrosis [abstract]. 25th Annual Meeting Cystic Fibrosis Club Abstracts;1984; San Jose. 1984:35.

Wall MA, Terry AB, Eisenberg J, McNamara M, Cohen R. Inhaled antibiotics in cystic fibrosis [letter]. *Lancet* 1983;**1**(8337):1325.

Wang 1984

Wang CI, Roldan MA, Aufderheide M, Sehgal S. The effect of tobramycin aerosol to pulmonary infection from Pseudomonas aeruginosa in patients with cystic fibrosis [abstract]. 25th Annual Meeting Cystic Fibrosis Club Abstracts;1984; San Jose. 1984:159.

Westerman 2003

* Westerman EM, Le Brun PP, Touw DJ, Frijlink HW, Heijerman HG. Effect of nebulized colistin sulphate and colistin sulphomethate on lung function in patients with cystic fibrosis: a pilot study. *Journal of Cystic Fibrosis* 2004;**3**(1):23–8.

Westerman EM, Le Brun PPH, Frijlink HW, Heijerman HGM. Effect of nebulised colistin sulphate and colistin sulphomethate on lung function in patients with cystic fibrosis [abstract]. *Journal of Cystic Fibrosis* 2003;**2**(Suppl 1):S55.

Westerman 2005

Westerman EM, de Boer AH, Le Brun PPH, Touw DJ, Frijlink HW, Heijerman HGM. Colistin dry powder inhalation in cystic fibrosis: novel Twincer® inhaler compared to nebulization: a pilot study [abstract]. *Journal of Cystic Fibrosis* 2005;**4**(Suppl 1):S64.

Yasmin 1974

Yasmin N, Laraya-Cuasay LR, Mueller S, Liberi P, Braverman S, Capitanio M, et al. A critical evaluation of antibiotic aerosol in patients with cystic fibrosis [abstract]. Proceedings of the 15th Annual Meeting of Cystic Fibrosis Club; 1974. 1974.

References to studies awaiting assessment

Chuchalin 2005

* Chuchalin A, Gyurkovics K, Mazurek H, Varoli G, Monici Preti P. Long-term administration of aerosolised tobramycin in patients with cystic fibrosis [abstract]. *European Respiratory Journal* 2005;**26**(suppl 49):619s.

Chuchalin A, Gyurkovics K, Mazurek HVG, Monici Preti PA. Long-term administration of nebulised tobramycin in patients with cystic fibrosis [abstract]. *Journal of Cystic Fibrosis* 2006;**5 Suppl**:S42.

Lenoir 2005

Lenoir G, Aryayev N, Varoli G, Monici Preti P. Aerosolized tobramycin in the treatment of patients with cystic fibrosis and pseudomonas aeruginosa infection [abstract]. *Journal of Cystic Fibrosis* 2006;**5 Suppl**:S42.

* Lenoir G, Aryayev N, Varoli G, Monici Preti P. Highly concentrated aerosolized tobramycin in the treatment of patients with cystic fibrosis and Pseudomonas aeruginosa infection [abstract]. *European Respiratory Journal* 2005;**26**(suppl 49):620s.

Additional references

Birnbaum 1998

Birnbaum HG, Greenberg P, Finkelstein S, Berndt E, Otto KL, Montgomery AB, et al. Economic analysis of hospitalization and home IV anti-pseudomonal antibiotic use in CF patients on tobramycin solution for inhalation (TOBI) [abstract]. *Pediatric Pulmonology* 1998;**Suppl 17**:273.

Burns 1999

Burns JL, Van Dalfsen JM, Shawar RM, Otto KL, Garber RL, Quan JM, et al. Effect of chronic intermittent administration of inhaled tobramycin on respiratory microbial flora in patients with cystic fibrosis. *Journal of Infectious Diseases* 1999;**179**(5):1190–6.

Elbourne 2002

Elbourne DR, Altman DG, Higgins JPT, Curtin F, Worthington HV, Vail A. Meta-analysis involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2002;**31**(1):140–9.

Fuchs 1994

Fuchs HJ, Borowitz DS, Christiansen DH, Morris EM, Nash ML, Rasmey BW, et al. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. The Pulmozyme Study Group. *New England Journal of Medicine* 1994;**331**(10):637–42.

Jüni 2001

Jüni P, Altman DG, Egger M. Assessing the equality of controlled clinical trials. *BMJ* 2001;**323**(7303):42–6.

Montori 2005

Montori VM, Devereaux PJ, Adhakiri NKJ, et al. Randomized trials stopped early for benefit. *JAMA* 2005;**294**(17):2203–9.

Mukhopadhyay 1996

Mukhopadhyay S, Singh M, Cater JI, Ogston S, Franklin M, Olver RE. Nebulised antipseudomonal antibiotic therapy in cystic fibrosis: a meta-analysis of benefits and risks. *Thorax* 1996;**51**(4):364–8.

Mulheren 1991

Mulheren D, Ward K, Coffey M, Koogam MT, Fitzgerald M. Cystic fibrosis in adolescents and adults. *Irish Medical Journal* 1991;**84**:121–4.

Newman 1985

Newman SP. Aerosol deposition considerations in inhalational therapy. *Chest* 1985;**88**(2Suppl):152S–60S.

Rosenstein 1998

Rosenstein BJ, Zeitlin PL. Cystic Fibrosis. *Lancet* 1998;**351**(9098):277–82.

Schulz 1995

Schulz K, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**(5):408–12.

Touw 1995

Touw DJ, Brimicombe RW, Hodson ME, Heijerman HGM, Bakker W. Inhalation of antibiotics in cystic fibrosis. *European Respiratory Journal* 1995;**8**(9):1594–604.

Wark 2003

Wark P, McDonald V. Nebulised hypertonic saline for cystic fibrosis (Cochrane Review). *Cochrane Database of Systematic Reviews* 2003, Issue 3. Art. No.: CD001506. DOI: 10.1002/14651858.CD001506.pub2.

References to other published versions of this review

Ryan 1999

Ryan G, Mukhopadhyay S, Singh M. Nebulised anti-pseudomonal antibiotics for cystic fibrosis (Cochrane Review). *Cochrane Database of Systematic Reviews* 1999, Issue 3. Art. No.: CD001021. DOI: 10.1002/14651858.CD001021.

** Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	**Carswell 1987**
Methods	Allocation method not stated. Cross-over design. Double blinded. Placebo control.
Participants	9 participants. Age range 7 - 16 years. Diagnostic criteria for CF not stated. All had P. aeruginosa on sputum culture. FEV1 at end of placebo about 15% - 85% predicted.
Interventions	Nebulised tobramycin (gentamicin one participant) 40 mg twice daily for 4 weeks. All taking flucloxacillin 25 mg/kg/dose twice daily for trial. Saline placebo.
Outcomes	Lung function (FEV1, FVC, PEF), sputum culture and sensitivity.
Notes	Bard nebuliser with 1.0 ml solution. Three subjects withdrew and six analysed. FEV1 result 'after at least three weeks of therapy' in figure only. Sponsor Eli Lily and Beecham Research.
Allocation concealment	B – Unclear

Study	**Day 1988**
Methods	Allocation method not stated. Cross-over design. Double-blinded. Placebo control.
Participants	14 participants (seven males). Age range 5 - 16 years. Criteria for diagnosis of CF not stated. All colonised with P. aeruginosa. Baseline FEV1 range 30% - 106% predicted.
Interventions	Colomycin 1 million units or saline twice daily for 6 months.
Outcomes	Lung function (FEV1 and FVC), exacerbations (antibiotic use and hospital admissions), symptom score and weight.
Notes	Nebuliser (type not stated) with 2.0 ml solution. Dropout rate not stated. FEV1 result not stated.
Allocation concealment	B – Unclear

Study	**Gibson 2003**
Methods	Random allocation.

	Parallel group. Double blinded.
Participants	21 participants (11 males) age range 6 months - 6 years. Positive P. aeruginosa culture.
Interventions	Tobramycin 300mg or placebo twice daily for 28 days.
Outcomes	Density of P. aeruginosa on BAL culture. Adverse effects. Weight.
Notes	Method of nebulisation not stated. Early termination, 21 of planned 98 randomised. Sponsors NIH, FDA, Chiron Corporation.
Allocation concealment	B – Unclear

Study	**Hodson 1981**
Methods	Random allocation. Cross-over design. Double blinded. Placebo control.
Participants	20 participants (11 males). Age range 15 - 42 years. Criteria for diagnosis of CF were clinical features and elevated sweat sodium. All with P. aeruginosa in sputum culture.
Interventions	Carbenicillin 1 g and gentamicin 80mg or hypertonic saline and lactose placebo twice daily for 6 months.
Outcomes	Lung function (FEV1, FVC, PEFR), exacerbations of infection (courses of intravenous antibiotics), sputum culture and sensitivity, audiogram.
Notes	Bird nebuliser. Four dropouts (intervention uncertain). No baseline clinical features. Lung function result only as mean (no SD) of six measurements during treatment. Sponsor Beecham and Roussel Laboratories.
Allocation concealment	B – Unclear

Study	**Hodson 2002**
Methods	Random allocation. Parallel groups. Open label.
Participants	143 people screened, 17 screening failures, 126 randomised, 11 withdrew before treatment, 115 treated (males 45% of total). Age range 7 - 50 years. Exclusion included any anti-pseudomonal antibiotics within the previous 14 days. Criteria for diagnosis abnormal sweat electrolytes, gene mutation.
Interventions	Tobramycin 300 mg in 5 ml twice daily. Colistin 1MU in 3 ml. Duration 28 days. Saline twice daily.
Outcomes	Lung function (FEV1). Sputum culture for P. aeruginosa, density and MIC. Adverse effects.
Notes	Pari LC plus (tobramycin) or Ventstream (colistin) nebuliser with CR50 compressor. Seven withdrew from treatment. Sponsor Pathogenesis Limited.
Allocation concealment	B – Unclear

Study	**Jensen 1987**
Methods	Random allocation. Parallel groups. Double-blinded. Placebo control.

Characteristics of included studies (*Continued*)

Participants	40 (20 males) participants. Age range 7 - 35 years. Diagnostic criteria for CF not stated. Chronic P. aeruginosa infection. Mean baseline FEV1 71% (SD 25) and 79% (SD 29) predicted in two treatment groups.
Interventions	Colistin (1 million units) or normal saline, twice daily for 3 months.
Outcomes	Lung function (FEV1 and FVC), clinical score, sputum culture and sensitivity, blood tests (ESR, WCC).
Notes	Raindrop nebuliser with 3.0ml of solution. Dropouts; two from colistin group and nine from placebo group. FEV1 result (% predicted) at end of treatment and as change from baseline.
Allocation concealment	B – Unclear

Study	**Kun 1984**
Methods	Allocation by alternating patients in three severity groups. Cross-over design. Single-blinded (observer). Usual treatment control.
Participants	33 participants. Age range 7.8 - 16 years. Criteria for diagnosis not stated. P. aeruginosa in sputum culture in 12 (gentamicin) or 9 (control) at start of treatment. Baseline FEV1 29% to 105% predicted.
Interventions	Gentamicin 20 mg twice daily after physiotherapy or no nebulised therapy after physiotherapy for 12 months.
Outcomes	Lung function (FEV1), exacerbation (hospital days and antibiotic use), sputum culture, symptom score.
Notes	Bennett twinjet nebuliser. 4 dropouts. FEV1 result as % predicted change from baseline (no SD). Sponsor Essex Laboratories.
Allocation concealment	C – Inadequate

Study	**MacLusky 1989**
Methods	Allocation by coin toss for first subject and alternate subjects. Parallel group. Single-blinded (investigator). Placebo control.
Participants	28 participants (14 male). Age range 7 - 24 years. Criteria for CF chronic lung disease, pancreatic insufficiency and elevated sweat chloride. All had P. aeruginosa in sputum culture. Mean baseline FEV1 78% (SD 21) and 70% (SD 22) predicted in treatment groups.
Interventions	Tobramycin 80 mg or normal saline twice daily for mean duration of study of 30 months (saline control) and 33 months (tobramycin).
Outcomes	Lung function (FEV1 and FVC), clinical scores, sputum culture and sensitivity (24 months), exacerbations (hospitalization for respiratory deterioration), ototoxicity and renal toxicity.
Notes	Hodson 1730 or Intec 3010 nebulizer with 2 ml of solution. 1 participant excluded from analysis. Lung function expressed as rate of decline of FEV1 as % predicted/year. Sponsor Canadian CFF.
Allocation concealment	C – Inadequate

Study	**Murphy 2004**
Methods	Randomised.

	Parallel group. Open label. Stratified by age and sex.
Participants	184 participants (52% male). Age 6 - 15 years. Two or more cultures of P. aeruginosa.
Interventions	Tobramycin 300mg twice daily, alternating 4 weekly cycles for 56 weeks.
Outcomes	Lung function, hospitalisation, antibiotic use.
Notes	Method of nebulisation not stated. Early termination. 63 of 181 randomised participants completed 56 weeks. Sponsor Chiron Corporation.
Allocation concealment	B – Unclear

Study	**Nathanson 1985**
Methods	Allocation method not stated. Cross-over design. Double-blinded. Placebo control.
Participants	Seven participants. Mean age 15.6 years, SD 5.7 years. Diagnostic criteria for CF not stated. All with P. aeruginosa in sputum culture sensitive to gentamicin.
Interventions	Gentamicin 80 mg or saline 3 times daily for 3 months.
Outcomes	Lung function (FEV1, FVC), sputum culture, NIH clinical score, sputum and blood gentamicin level.
Notes	Nebuliser type not stated, 2 ml volume. No dropouts reported. FEV1 result, in litre, no SD, probably end of study. Sponsor Schering.
Allocation concealment	B – Unclear

Study	**Ramsey 1993**
Methods	Random allocation. Three period cross-over design. Double blinded. Placebo control.
Participants	71 participants (37 male). Mean age 17.7 years, SD 1.25 years and 16.6 years, SD 1.24 years of two groups. CF diagnosed by sweat test. Sputum culture of P. aeruginosa susceptible to tobramycin. Mean baseline FEV1 55% (SE 3.7) and 60% (SE 3.2) predicted in two treatment arms.
Interventions	Tobramycin 600 mg or 0.5 normal saline 3 times daily for 28 days, then cross-over for two 28-day periods.
Outcomes	Lung function (FEV1 and FVC), exacerbations of infection, sputum bacteriology and sensitivity, ototoxicity, nephrotoxicity, clinical score.
Notes	Ultrasonic (Ultraneb 100/99) nebuliser with 30 ml solution and 200 inhalations. 5 withdrew from study. Results of first 28 day parallel group comparison used for review, FEV1 % predicted change from baseline. Sponsor CFF.
Allocation concealment	A – Adequate

Study	**Ramsey 1999**
Methods	Random allocation. Parallel groups. Double blinded.

Characteristics of included studies (*Continued*)

	Placebo control.
Participants	520 participants (54% male). Age from six years, 54% 18 years or older. Criteria for CF were CFF clinical practice guidelines. All infected with P. aeruginosa. Baseline FEV1 25-75% predicted.
Interventions	Tobramycin 300 mg or 0.225 normal saline and 1.25 mg quinine twice daily for three 28-day on-off cycles.
Outcomes	Lung function (FEV1 and FVC), exacerbations (hospitalization or intravenous antibiotics), sputum P. aeruginosa colony count, renal toxicity, ototoxicity.
Notes	Pari LC plus nebuliser with 5 ml of solution and Pulmo-aide compressor. 56 participants did not complete the study. FEV1 result as change from baseline as % predicted. Support NIH, CFF, FDA. Patent holders.
Allocation concealment	A – Adequate

Study	**Stead 1987**
Methods	Random allocation. Three period cross-over design. Partially blinded. Placebo control.
Participants	18 participants (12 male). Age range 13 - 41 years. Criteria for diagnosis of CF were clinical features and sweat sodium more than 70 mmol/litre. All had P. aeruginosa on sputum culture. Mean baseline FEV1 1.29 (0.53) litre.
Interventions	Ceftazidime 1 g or placebo (3.5% saline) twice daily for 4 months.
Outcomes	Lung function (FEV1, FVC, PEF), exacerbations (admission to hospital for intravenous antibiotics), sputum bacteriology, sputum volume, and participant preference.
Notes	DeVilbiss nebuliser with 2 ml to 4 ml of solution. Five participants did not complete study. FEV1 (litre) result at end of treatment. 2 arms used for this comparison. Sponsor Glaxo Group Research Limited.
Allocation concealment	B – Unclear

Study	**Wiesemann 1998**
Methods	Random allocation. Performed in groups of two by flipping a coin.
Participants	22 participants (13 male). Age > 4 years, mean 11.4 and 9.8 in two groups.
Interventions	Tobramycin 80mg or placebo (saline with same preservatives) twice daily for 12 months.
Outcomes	Eradication of PA, lung function, inflamatory parameters.
Notes	Pari Boy jet nebuliser, 4 ml of solution. 66% of participants completed. No results of lung function reported
Allocation concealment	B – Unclear

BAL: Bronchoalveolar lavage
CFF: Cystic Fibrosis Foundation
ESR: erythrocyte sedimentation rate
FDA: Food and drug administration
FEV1: forced expiratory volume in one second
FVC: forced vital capacity
NIH: National Institutes of Health
P. aeruginosa: Pseudomonas aeruginosa
PEF: peak expiratory flow
PEFR: peak expiratory flow rate
SD: standard deviation
SE: standard error

Characteristics of excluded studies

Study	Reason for exclusion
Adeboyeku 2001	Single dose study.
Al-Aloul 2004	Duration less than one month.
Alothman 2000	Single dose study. Outcome adverse effect.
Alothman 2005	Duration less than one month.
App 2000	Single dose study. Outcome tobramycin level.
Chua 1990	Duration less than 1 month, single dose only.
Cooper 1985	Comparison of inhaled (nebulised) with intravenous antibiotics in hospital. Duration of treatment not stated.
Dodd 1997	Duration less than 1 month. Single inhalation of colistin solution of 3 levels of tonicity to determine effect on FEV1 and symptoms.
Eisenberg 1997	Duration less than 1 month. A single inhalation of tobramycin by 3 nebuliser systems to determine amount delivered to the lung measured by sputum and serum concentrations.
Franz 1985	Case series, no placebo or usual treatment control.
Frederiksen 1997	Concurrent anti-pseudomonal antibiotic therapy with ciprofloxacin. A trial to compare the effect of colistin and ciprofloxacin given for 3 weeks or for 3 months.
Geborek 2003	Duration less than one month. Trial in respiratory tract exacerbations.
Geller 2004	Duration less than one month. Outcome measure (pharmacokinetics and bioavailability of tobramycin) not in protocol.
Gibson 2006	Duration less than one month.
Gulliver 2003	Duration less than one month, single dose study of tobramycin.
Jenkins 1985	Duration of treatment less than 1 month. A randomised, placebo control, cross-over trial of aerosol amikacin 500 mg twice daily for 3 weeks.
Knowles 1988	Duration of treatment less than 1 month. Aerosol tobramycin and pipericillin added to intravenous antibiotics compared to intravenous antibiotics alone for the hospital treatment of pulmonary exacerbations.
Ledson 2002	Not anti-pseudomonal antibiotic treatment.
Nizolaizik 1996	Not a RCT. Duration less than 1 month.
Nolan 1982	Cephaloridine not an anti-pseudomonal antibiotic. Problems with quality of the trial were that allocation to inhaled cephaloridine was not concealed (alternate participants after random allocation of the first participant in each of strata based on age, sex and FEV1) and the trial was not blinded.
Poli 2005	Duration less than one month.
Pradal 2002	Treatment not nebulised, duration < 1 month. Outcomes not in protocol.
Ramsey 2005	Trial investigating treatment of early colonisation with and eradication of Pseudomonas aeruginosa infection.
Ratjen 2006	Trial objective is to estimate duration of eradication of Pseudomonas aeruginosa after treatment.
Schaad 1987	Duration less than 1 month. A comparison of 2 weeks of nebulised amikacin (100 mg twice daily) added to intravenous amikacin and ceftazidime with intravenous antibiotics alone for treatment of acute pulmonary exacerbations in CF.
Schaad 1997	Concurrent anti-pseudomonal antibiotic therapy. A comparison of ciprofloxacin and nebulised amikacin (500 mg daily) with ciprofloxacin alone for 3 months.
Smith 1989	No placebo or usual treatment control. Case series to monitor for toxic effects of aerosolised tobramycin, using 600 mg 3 times a day for 12 weeks.

Characteristics of excluded studies (*Continued*)

Steinkamp 1989	No placebo or usual treatment control. An open non-controlled study comparing before-after treatment effect of a course of nebulised tobramycin 80 mg twice daily.
Stephens 1983	Duration less than 1 month. Trial was a comparison of intravenous (tobramycin and ticarcillin) and inhaled (tobramycin) antibiotics with intravenous antibiotics alone for treatment of acute pulmonary exacerbations.
Stroobant 1985	Anti-pseudomonal antibiotic (azlocillin) compared to mistabron, a mucolytic.
Valerius 1991	Concurrent anti-pseudomonal treatment. A comparison of the effect of 3 week courses of nebulised colistin and oral ciprofloxacin compared to no anti-pseudomonal antibiotic treatment on isolation rate of P. aeruginosa.
Wainwright 2002	Randomised to bronchoscopy not to treatment outcome.
Wall 1984	No placebo or usual treatment control. An open label, uncontrolled trial with before - after comparison of effect of nebulised tobramycin and ticarcillin.
Wang 1984	No placebo or usual treatment control.
Westerman 2003	Duration less than 1 month, single dose study.
Westerman 2005	Duration less than 1 month, single dose study.
Yasmin 1974	Duration less than 1 month (2 weeks) and control group received intravenous antibiotic treatment.

FEV1: forced expired volume in one second.
RCT: randomised controlled trial
P. aeruginosa: Pseudomonas aeruginosa

ADDITIONAL TABLES

Table 01. Quality Assessment

Study ID	Gen allocation seq	Concel alloc'n seq	Blinding	Patient attrition
Carswell 1987	Randomised. Cross-over.	Not stated. Randomisation by pharmacy department	Double-blind.	6/9 completed. Attrition rate 33%
Day 1988	Not stated. Cross-over.	Not stated.	Double-blind.	Not stated.
Gibson 2003	Randomised. Stratified by age and sex	Not stated. Multi-centre.	Double blind	Early termination of trial. ITT. 21/21 analysed.
Hodson 1981	Randomised. Cross-over.	Not stated.	Double-blind.	17/20 completed. Attrition rate 15%.
Hodson 2002	Randomised. Startified by age groups in each centre.	Not stated. Multi-centre.	No.	ITT stated. 94% completed. Attrition rate 6%.
Jensen 1987	Randomised.	Not stated.	Double-blind.	29/40 completed. Attrition rate 28%.
Kun 1984	First participant in each severity group by chance then alternating. Cross-over.	Not stated.	Not stated.	29/33 analysed. Attrition rate 12%.
MacLusky 1989	First participant in 6 strata (age, sex) assigned by coin toss and then alternation. Randomly assigned by	Not stated - randomisation and allocation performed by study nurse.	Participants aware. Study physicians blinded.	15/28 completed. Attrition rate 46%.

Table 01. Quality Assessment (*Continued*)

Study ID	Gen allocation seq	Concel alloc'n seq	Blinding	Patient attrition
	study nurse.			
Murphy 2004	Randomised	Not stated. Multi-centre	Open label.	Early termination of trial. 63/181 randomised completed 56 weeks. Attrition rate 65%.
Nathanson 1985	Not stated. Cross-over.	Not stated.	Double-blind.	Not stated.
Ramsey 1993	Randomised. Cross-over 3 period. Stratified FEV1groups in each centre.	Not stated. Multi-centre.	Double-blind (quinine).	ITT stated with random exclusion to match numbers for cross-over analysis. 66/71 completed. Attrition rate 6%.
Ramsey 1999	Randomised. Stratified by 7 criteria.	Not stated. Multi-centre.	Double-blind (quinine).	ITT stated. 90% completed. Attrition rate 10%.
Stead 1987	Randomised. Cross-over - 3 period . Latin-square design.	One arm open; otherwise blinded for participants and investigators.	None stated.	13/18 completed. Attrition rate 28%.
Wiesemann 1998	Randomised (flipping a coin)	Not stated	Double-blind	14/22 completed. Attrition rate 36%

Table 02. Outcome measures reported in studies

Study	Lung function - FEV1	Exacerbations	Quality of life	Survival	AB resist. orgs.	AEs	Primary outcome
Carswell 1987 XO	FEV1 % predicted End of study				Pseudomonas aeruginosa resistance		Not stated
Day 1988 XO	FEV1 % predicted End of study	Hospitalisation Oral antibiotic use					Not stated
Gibson 2003					Pseudomonas aeruginosa resistance Other organisms	AEs Renal function Auditory function	Change in BAL Pseudomonas aeruginosa density
Hodson 1981 XO	FEV1 litres Mean of 6 measurements over 6 months	Hospitalisation			Pseudomonas aeruginosa resistance	Audiometry	Not stated
Hodson 2002	FEV1 %				Pseudomonas	AEs	FEV1

Table 02. Outcome measures reported in studies (*Continued*)

Study	Lung function - FEV1	Exacerbations	Quality of life	Survival	AB resist. orgs.	AEs	Primary outcome
	predicted Change at 1 month				aeruginosa MIC Other organisms	Renal function Airway reactivity	
Jensen 1987	FEV1 % predicted % change at 3 months				Pseudomonas aeruginosa MIC Other organisms	AEs	Not stated
Kun 1984 XO	FEV1 % predicted Change at 12 months	Hospital days Antibiotic usage score		Deaths reported			Not stated
MacLusky 1989	FEV1 % predicted Annual rate of decline	Hospitalisation - admitted - admissions - days		Deaths reported	Pseudomonas aeruginosa resistance Other organisms	Renal function Audiometry	FEV1 - rate of decline
Murphy 2004	FEV1 % predicted Rate of decline	Hospitalisation - admitted - admissions - days Antibiotic use				AEs Renal function Audiometry	FEV1 - rate of decline
Nathanson 1985 XO	FEV1 litres End of study				Pseudomonas aeruginosa resistance		Not stated
Ramsey 1983 XO	FEV1 % predicted Change at 1 month	Exacerbation defined Antibiotic use			Pseudomonas aeruginosa resistance Other organisms	Renal function Audiometry Vestibular function	FEV1
Ramsey 1999	FEV1 % predicted Change at Week 20	Hospitalisation IV antibiotic use			Pseudomonas aeruginosa resistance Other organisms	AEs Renal function Audiometry Airway reactivity	FEV1 Sputum Pseudomonas aeruginosa density
Stead 1987 XO	FEV1 End of 4 month period	Hospitalisation			Pseudomonas aeruginosa resistance		Not stated
Wiesemann 1998	Lung function parameters						Time to converion of

Table 02. Outcome measures reported in studies (*Continued*)

Study	Lung function - FEV1	Exacerba-tions	Quality of life	Survival	AB resist. orgs.	AEs	Primary outcome
	not specified						respiratory cultures to Ps aeruginosa negative

ANALYSES

Comparison 01. Nebulised anti-pseudomonal antibiotic versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Mean per cent change in FEV1 (% predicted)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
02 Mean FEV1 at end of treatment (% predicted)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
03 Rate of change of FEV1 (% predicted per year)	1	27	Weighted Mean Difference (Fixed) 95% CI	7.80 [3.29, 12.31]
04 Mean per cent change in FVC (% predicted)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
05 Mean FVC at end of treatment (% predicted)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
06 Rate of change of FVC (% predicted per year)	1	27	Weighted Mean Difference (Fixed) 95% CI	5.40 [0.86, 9.94]
07 Frequency of one or more hospital admissions			Odds Ratio (Fixed) 95% CI	Subtotals only
08 Hospital admissions, mean number of days in hospital			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
09 Frequency of one or more courses of oral or intravenous antibiotics			Odds Ratio (Fixed) 95% CI	Subtotals only
10 Frequency of one or more courses of intravenous antibiotics			Odds Ratio (Fixed) 95% CI	Subtotals only
11 Exacerbation of respiratory infection	1	71	Odds Ratio (Fixed) 95% CI	2.66 [0.48, 14.74]
12 Weight - change (kg)	2	42	Weighted Mean Difference (Fixed) 95% CI	0.15 [-0.19, 0.49]
13 Deaths			Odds Ratio (Fixed) 95% CI	Subtotals only
14 Frequency of tobramycin resistant P. aeruginosa at end of study			Odds Ratio (Fixed) 95% CI	Subtotals only
15 Frequency of new isolates of drug resistant organisms			Odds Ratio (Fixed) 95% CI	Subtotals only
16 Number experiencing adverse event at end of study			Odds Ratio (Fixed) 95% CI	Subtotals only

Comparison 02. Nebulised antibiotics compared

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Mean per cent change in FEV1 (% predicted)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
02 Number experiencing adverse events by end of study			Odds Ratio (Fixed) 95% CI	Subtotals only
03 FEV1 change after single treatment	1	113	Weighted Mean Difference (Fixed) 95% CI	-0.62 [-3.84, 2.60]

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Inhalation; Administration, Intranasal; Aerosols; Anti-Bacterial Agents [*administration & dosage]; Cystic Fibrosis [*complications; drug therapy]; Nebulizers and Vaporizers; Pseudomonas aeruginosa; Pseudomonas Infections [etiology; *prevention & control]; Randomized Controlled Trials; Respiratory Tract Infections [etiology; *prevention & control]

MeSH check words

Humans

COVER SHEET

Title	Nebulised anti-pseudomonal antibiotics for cystic fibrosis
Authors	Ryan G, Mukhopadhyay S, Singh M
Contribution of author(s)	Somnath Mukhopadhyay developed the protocol. Meenu Singh selected studies and assessed study quality. Gerard Ryan was involved in all aspects of the review. Gerard Ryan completed the updates and acts as guarantor of the review.
Issue protocol first published	1998/1
Review first published	1999/3
Date of most recent amendment	21 February 2007
Date of most recent SUBSTANTIVE amendment	17 May 2003
What's New	Review update: February 2007 The search of the Group's Cystic Fibrosis Trials Register to September 2006 identified 18 new citations to 11 trials: ADDITIONAL CITATIONS TO ALREADY INCLUDED TRIALS Gibson 2003 (1 citation added) Ramsey 1999 (1 citation added) Results for weight, a secondary outcome, is now reported for the Gibson 2003 citation and is included. NEW TRIALS Two trials have been published as abstracts and have been added to the section 'Awating Assessment' until the full papers have been published. Chuchalin 2005 (2 citations) Lenoir 2005 (2 citations) The remaining 12 citations to 7 trials have been excluded.

Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	23 November 2006
Date authors' conclusions section amended	Information not supplied by author
Contact address	Dr Gerard Ryan Department of Respiratory Medicine Sir Charles Gairdner Hospital Ground Floor B Block Verdun Street Nedlands Western Australia 6009 AUSTRALIA E-mail: gerard.ryan@health.wa.gov.au Tel: +61 8 9346 3333 Fax: +61 8 9346 3606
DOI	10.1002/14651858.CD001021
Cochrane Library number	CD001021
Editorial group	Cochrane Cystic Fibrosis and Genetic Disorders Group
Editorial group code	HM-CF

GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Nebulised anti-pseudomonal antibiotic versus placebo, Outcome 01 Mean per cent change in FEV1 (% predicted)

Review: Nebulised anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 01 Nebulised anti-pseudomonal antibiotic versus placebo

Outcome: 01 Mean per cent change in FEV1 (% predicted)

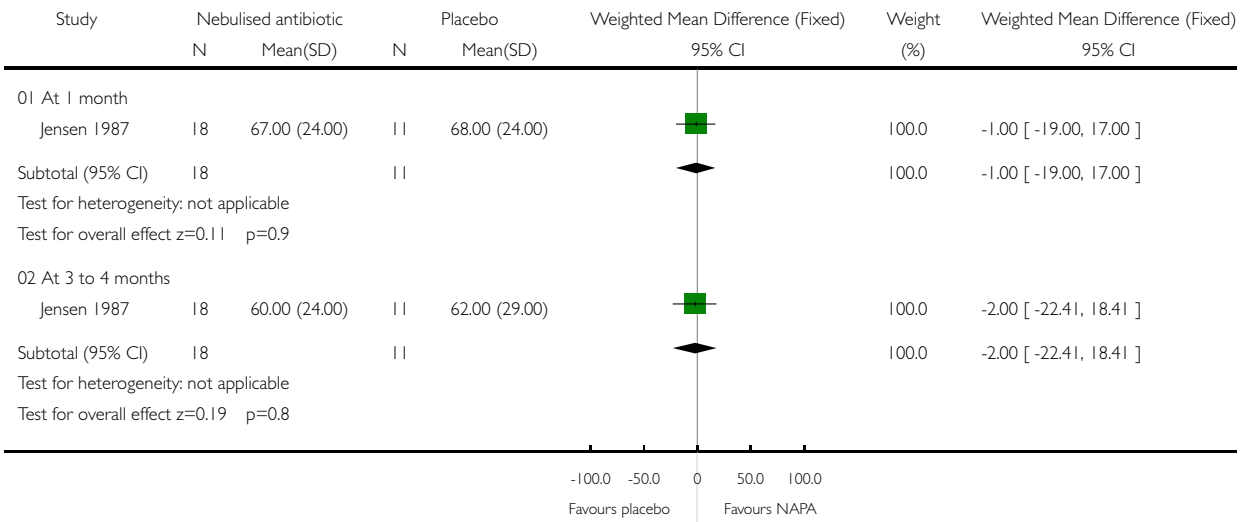
Study	Nebulised antibiotic N	Nebulised antibiotic Mean(SD)	Placebo N	Placebo Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 At 1 month							
Ramsey 1993	36	3.72 (9.90)	36	-5.97 (10.68)		100.0	9.69 [4.93, 14.45]
Subtotal (95% CI)	36		36			100.0	9.69 [4.93, 14.45]
Test for heterogeneity: not applicable							
Test for overall effect z=3.99 p=0.00007							
02 At 3 to 4 months							
Jensen 1987	18	-11.00 (6.00)	11	-17.00 (11.00)		100.0	6.00 [-1.07, 13.07]
Subtotal (95% CI)	18		11			100.0	6.00 [-1.07, 13.07]
Test for heterogeneity: not applicable							
Test for overall effect z=1.66 p=0.1							

Analysis 01.02. Comparison 01 Nebulised anti-pseudomonal antibiotic versus placebo, Outcome 02 Mean FEV1 at end of treatment (% predicted)

Review: Nebulised anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 01 Nebulised anti-pseudomonal antibiotic versus placebo

Outcome: 02 Mean FEV1 at end of treatment (% predicted)

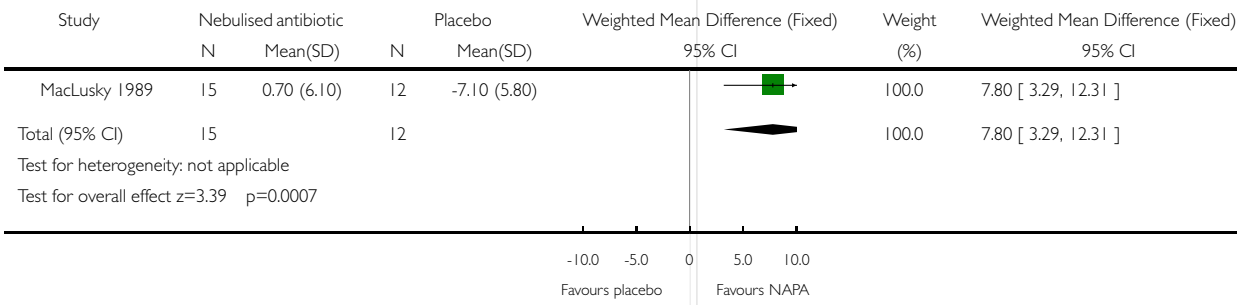


Analysis 01.03. Comparison 01 Nebulised anti-pseudomonal antibiotic versus placebo, Outcome 03 Rate of change of FEV1 (% predicted per year)

Review: Nebulised anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 01 Nebulised anti-pseudomonal antibiotic versus placebo

Outcome: 03 Rate of change of FEV1 (% predicted per year)

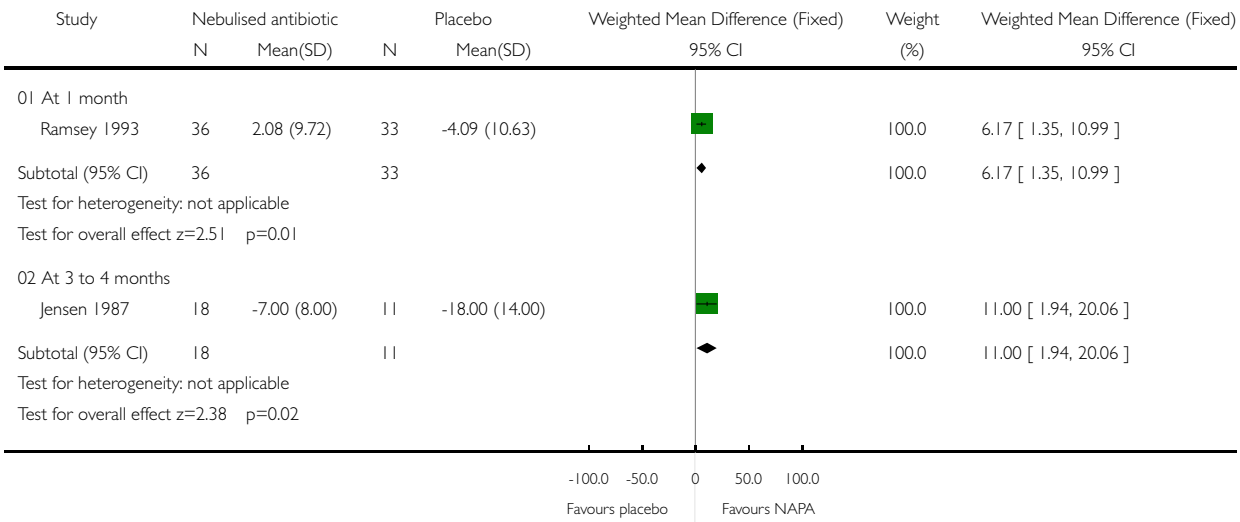


Analysis 01.04. Comparison 01 Nebulised anti-pseudomonal antibiotic versus placebo, Outcome 04 Mean per cent change in FVC (% predicted)

Review: Nebulised anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 01 Nebulised anti-pseudomonal antibiotic versus placebo

Outcome: 04 Mean per cent change in FVC (% predicted)

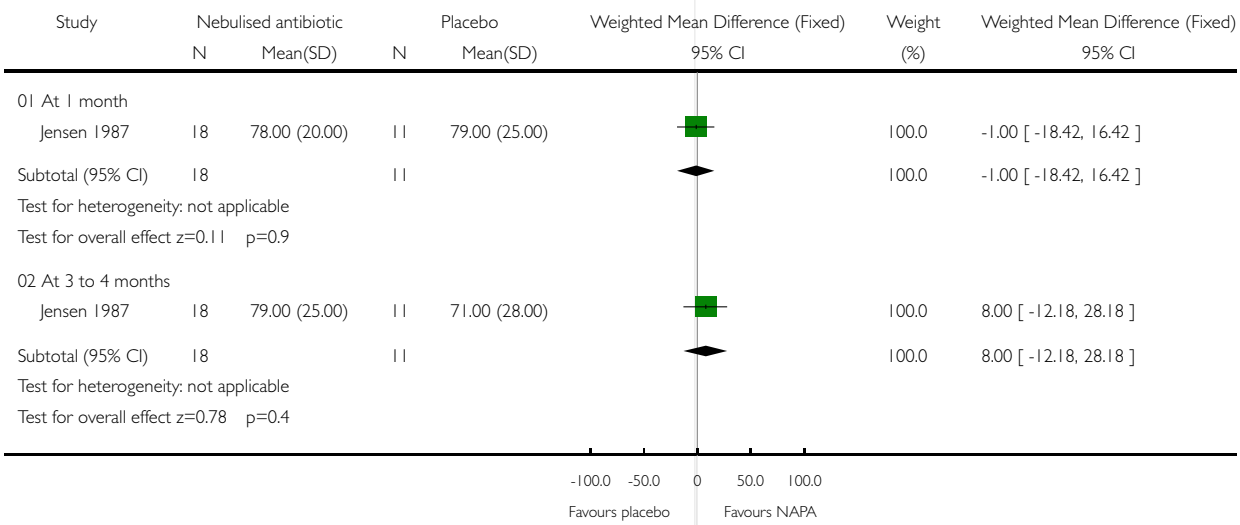


Analysis 01.05. Comparison 01 Nebulised anti-pseudomonal antibiotic versus placebo, Outcome 05 Mean FVC at end of treatment (% predicted)

Review: Nebulised anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 01 Nebulised anti-pseudomonal antibiotic versus placebo

Outcome: 05 Mean FVC at end of treatment (% predicted)

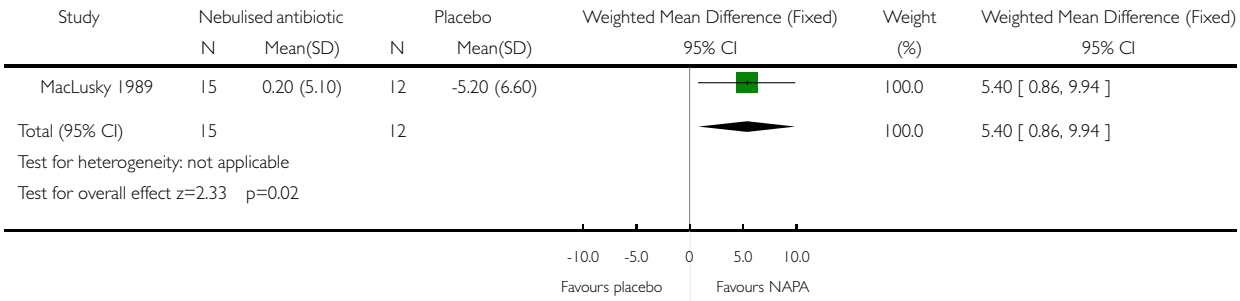


Analysis 01.06. Comparison 01 Nebulised anti-pseudomonal antibiotic versus placebo, Outcome 06 Rate of change of FVC (% predicted per year)

Review: Nebulised anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 01 Nebulised anti-pseudomonal antibiotic versus placebo

Outcome: 06 Rate of change of FVC (% predicted per year)

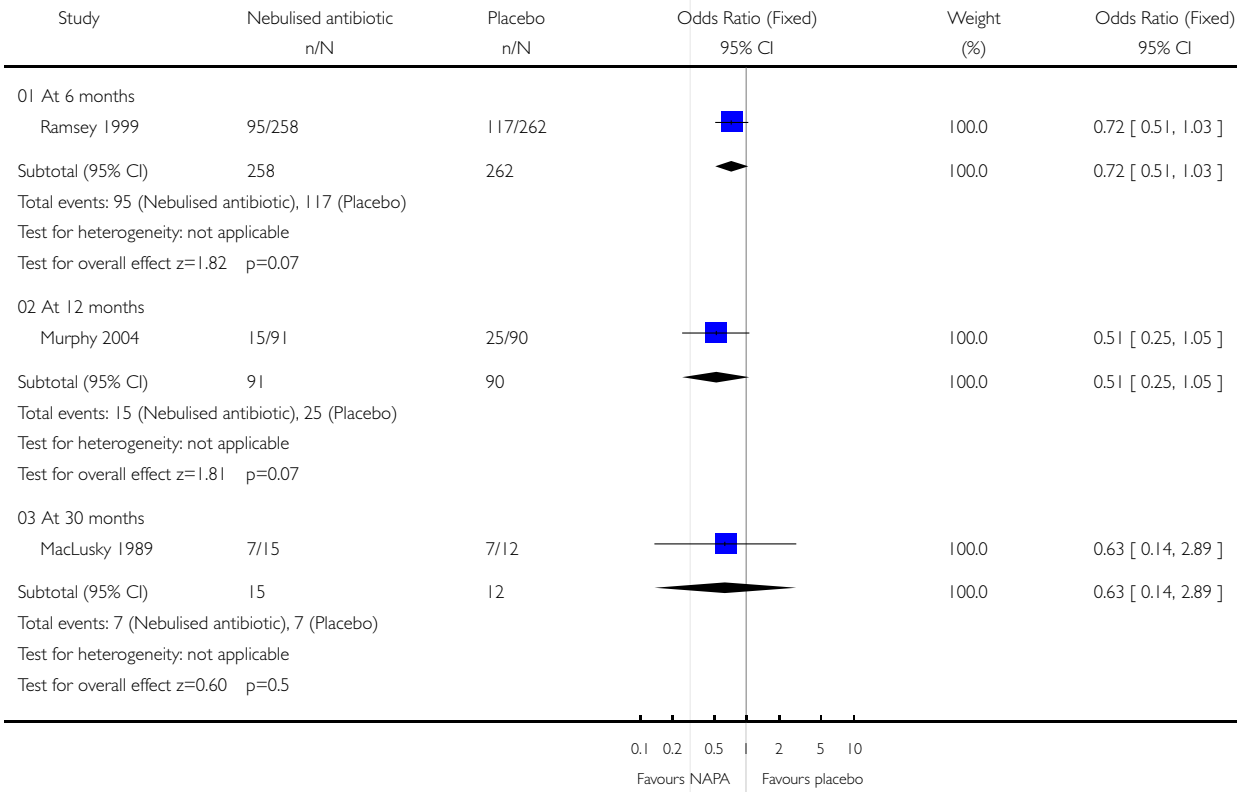


Analysis 01.07. Comparison 01 Nebulised anti-pseudomonal antibiotic versus placebo, Outcome 07 Frequency of one or more hospital admissions

Review: Nebulised anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 01 Nebulised anti-pseudomonal antibiotic versus placebo

Outcome: 07 Frequency of one or more hospital admissions

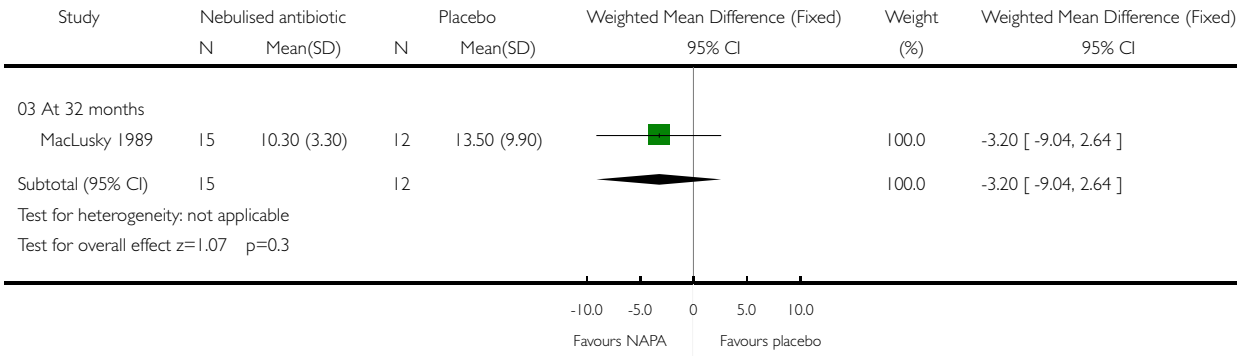


Analysis 01.08. Comparison 01 Nebulised anti-pseudomonal antibiotic versus placebo, Outcome 08 Hospital admissions, mean number of days in hospital

Review: Nebulised anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 01 Nebulised anti-pseudomonal antibiotic versus placebo

Outcome: 08 Hospital admissions, mean number of days in hospital

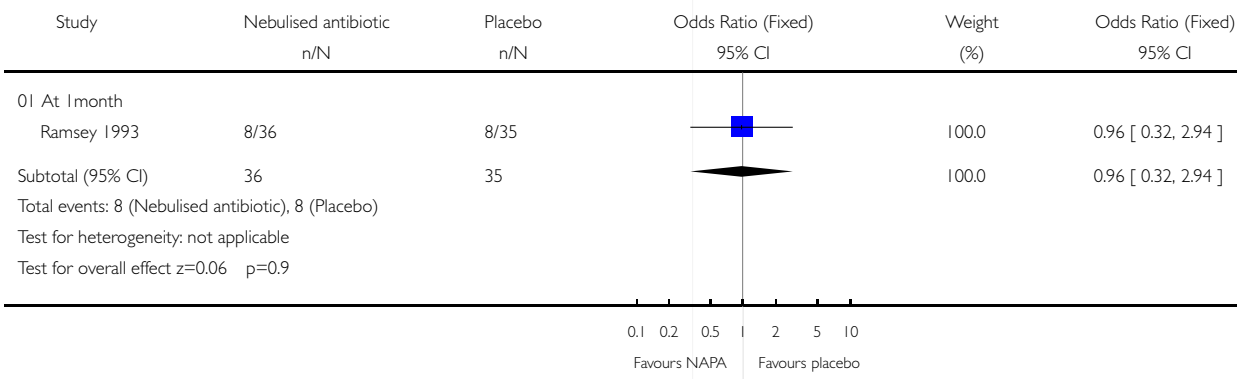


Analysis 01.09. Comparison 01 Nebulised anti-pseudomonal antibiotic versus placebo, Outcome 09 Frequency of one or more courses of oral or intravenous antibiotics

Review: Nebulised anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 01 Nebulised anti-pseudomonal antibiotic versus placebo

Outcome: 09 Frequency of one or more courses of oral or intravenous antibiotics



Analysis 01.10. Comparison 01 Nebulised anti-pseudomonal antibiotic versus placebo, Outcome 10 Frequency of one or more courses of intravenous antibiotics

Review: Nebulised anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 01 Nebulised anti-pseudomonal antibiotic versus placebo

Outcome: 10 Frequency of one or more courses of intravenous antibiotics

Study	Nebulised antibiotic n/N	Placebo n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
01 At 1 month					
Ramsey 1993	8/36	8/35		100.0	0.96 [0.32, 2.94]
Subtotal (95% CI)	36	35		100.0	0.96 [0.32, 2.94]
Total events: 8 (Nebulised antibiotic), 8 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.06 p=0.9					
02 At 6 months					
Ramsey 1999	100/258	135/262		100.0	0.60 [0.42, 0.84]
Subtotal (95% CI)	258	262		100.0	0.60 [0.42, 0.84]
Total events: 100 (Nebulised antibiotic), 135 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.92 p=0.004					
03 At 12 months					
Murphy 2004	16/91	24/90		100.0	0.59 [0.29, 1.20]
Subtotal (95% CI)	91	90		100.0	0.59 [0.29, 1.20]
Total events: 16 (Nebulised antibiotic), 24 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.46 p=0.1					

Analysis 01.11. Comparison 01 Nebulised anti-pseudomonal antibiotic versus placebo, Outcome 11 Exacerbation of respiratory infection

Review: Nebulised anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 01 Nebulised anti-pseudomonal antibiotic versus placebo

Outcome: 11 Exacerbation of respiratory infection

Study	Nebulised antibiotic n/N	Placebo n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
Ramsey 1993	5/36	2/35		100.0	2.66 [0.48, 14.74]
Total (95% CI)	36	35		100.0	2.66 [0.48, 14.74]
Total events: 5 (Nebulised antibiotic), 2 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.12 p=0.3					

Analysis 01.12. Comparison 01 Nebulised anti-pseudomonal antibiotic versus placebo, Outcome 12 Weight - change (kg)

Review: Nebulised anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 01 Nebulised anti-pseudomonal antibiotic versus placebo

Outcome: 12 Weight - change (kg)

Study	Tobramycin N	Tobramycin Mean(SD)	Placebo N	Placebo Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 At 1 month							
Gibson 2003	8	0.30 (0.50)	13	0.10 (0.60)		50.0	0.20 [-0.28, 0.68]
Subtotal (95% CI)	8		13			50.0	0.20 [-0.28, 0.68]
Test for heterogeneity: not applicable							
Test for overall effect z=0.82 p=0.4							
02 At 2 months							
Gibson 2003	8	0.40 (0.50)	13	0.30 (0.60)		50.0	0.10 [-0.38, 0.58]
Subtotal (95% CI)	8		13			50.0	0.10 [-0.38, 0.58]
Test for heterogeneity: not applicable							
Test for overall effect z=0.41 p=0.7							
Total (95% CI)	16		26			100.0	0.15 [-0.19, 0.49]
Test for heterogeneity chi-square=0.08 df=1 p=0.77 I^2 =0.0%							
Test for overall effect z=0.87 p=0.4							

Analysis 01.13. Comparison 01 Nebulised anti-pseudomonal antibiotic versus placebo, Outcome 13 Deaths

Review: Nebulised anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 01 Nebulised anti-pseudomonal antibiotic versus placebo

Outcome: 13 Deaths

Study	Nebulised antibiotic n/N	Placebo n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
01 At 6 months					
Ramsey 1999	0/258	4/262		100.0	0.11 [0.01, 2.07]
Subtotal (95% CI)	258	262		100.0	0.11 [0.01, 2.07]
Total events: 0 (Nebulised antibiotic), 4 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.47 p=0.1					
03 At 30 months					
MacLusky 1989	0/15	1/12		100.0	0.25 [0.01, 6.64]
Subtotal (95% CI)	15	12		100.0	0.25 [0.01, 6.64]
Total events: 0 (Nebulised antibiotic), 1 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.83 p=0.4					

Analysis 01.14. Comparison 01 Nebulised anti-pseudomonal antibiotic versus placebo, Outcome 14 Frequency of tobramycin resistant P. aeruginosa at end of study

Review: Nebulised anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 01 Nebulised anti-pseudomonal antibiotic versus placebo

Outcome: 14 Frequency of tobramycin resistant P. aeruginosa at end of study

Study	Nebulised antibiotic n/N	Placebo n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
01 At 6 months					
Ramsey 1999	51/222	18/220		100.0	3.35 [1.88, 5.95]
Subtotal (95% CI)	222	220		100.0	3.35 [1.88, 5.95]
Total events: 51 (Nebulised antibiotic), 18 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=4.12 p=0.00004					
02 At 24 months					
MacLusky 1989	4/14	0/12		100.0	10.71 [0.52, 222.81]
Subtotal (95% CI)	14	12		100.0	10.71 [0.52, 222.81]
Total events: 4 (Nebulised antibiotic), 0 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.53 p=0.1					

Analysis 01.15. Comparison 01 Nebulised anti-pseudomonal antibiotic versus placebo, Outcome 15 Frequency of new isolates of drug resistant organisms

Review: Nebulised anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 01 Nebulised anti-pseudomonal antibiotic versus placebo

Outcome: 15 Frequency of new isolates of drug resistant organisms

Study	Nebulised antibiotic n/N	Placebo n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
01 Burkholderia cepacia					
MacLusky 1989	1/9	3/7		100.0	0.17 [0.01, 2.16]
× Ramsey 1999	0/258	0/262		0.0	Not estimable
Subtotal (95% CI)	267	269		100.0	0.17 [0.01, 2.16]
Total events: 1 (Nebulised antibiotic), 3 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.37 p=0.2					
02 Stenotrophomonas maltophilia					
Ramsey 1999	3/258	1/262		100.0	3.07 [0.32, 29.71]
Subtotal (95% CI)	258	262		100.0	3.07 [0.32, 29.71]

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Study	Nebulised antibiotic n/N	Placebo n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
Total events: 3 (Nebulised antibiotic), 1 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.97 p=0.3					
03 Alcaligenes xylosoxidans					
Ramsey 1999	1/258	1/262		100.0	1.02 [0.06, 16.32]
Subtotal (95% CI)	258	262		100.0	1.02 [0.06, 16.32]
Total events: 1 (Nebulised antibiotic), 1 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.01 p=1					
04 Asperillus species					
Ramsey 1999	43/258	20/262		100.0	2.42 [1.38, 4.24]
Subtotal (95% CI)	258	262		100.0	2.42 [1.38, 4.24]
Total events: 43 (Nebulised antibiotic), 20 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=3.09 p=0.002					

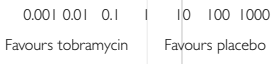
Analysis 01.16. Comparison 01 Nebulised anti-pseudomonal antibiotic versus placebo, Outcome 16 Number experiencing adverse event at end of study

Review: Nebulised anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 01 Nebulised anti-pseudomonal antibiotic versus placebo

Outcome: 16 Number experiencing adverse event at end of study

Study	Tobramycin n/N	Placebo n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
01 Impaired hearing					
× MacLusky 1989	0/15	0/12		0.0	Not estimable
× Ramsey 1999	0/152	0/148		0.0	Not estimable
Subtotal (95% CI)	167	160		0.0	Not estimable
Total events: 0 (Tobramycin), 0 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
02 Tinnitus					
Ramsey 1999	8/258	0/262		100.0	17.81 [1.02, 310.26]
Subtotal (95% CI)	258	262		100.0	17.81 [1.02, 310.26]



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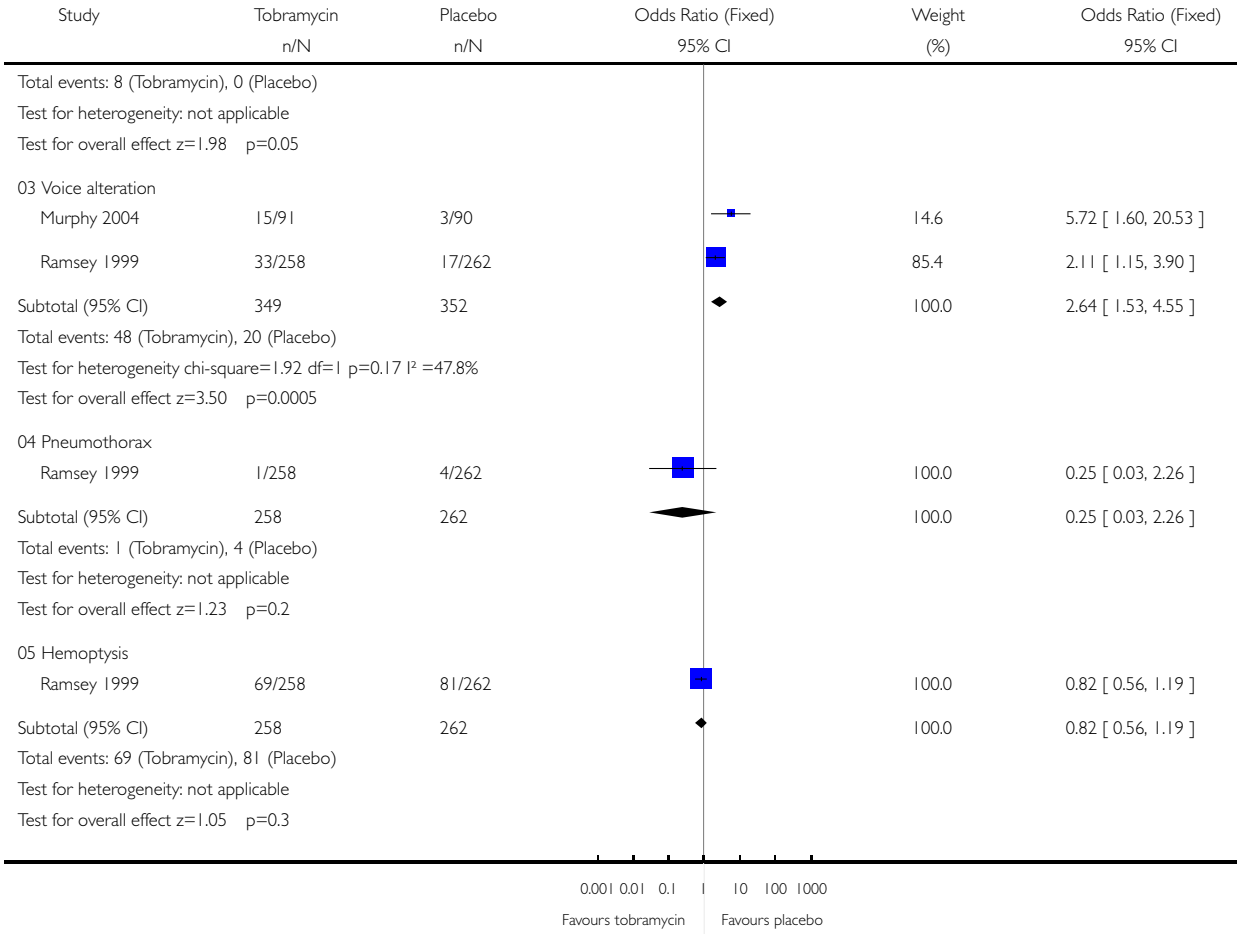
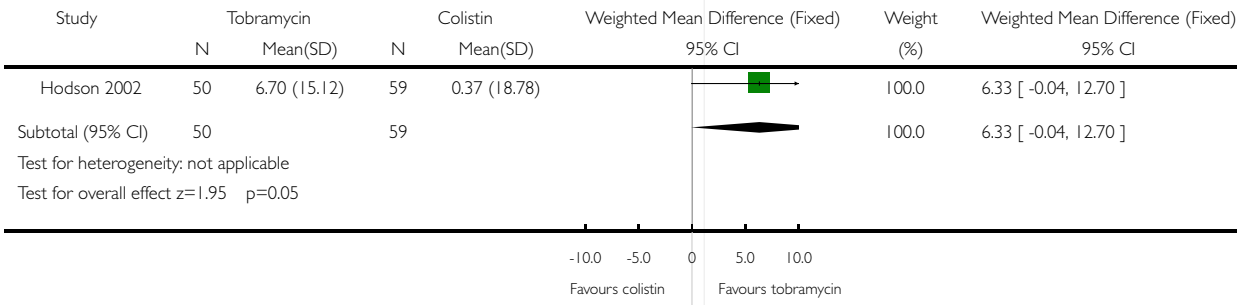


Analysis 02.01. Comparison 02 Nebulised antibiotics compared, Outcome 01 Mean per cent change in FEV1 (% predicted)

Review: Nebulised anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 02 Nebulised antibiotics compared

Outcome: 01 Mean per cent change in FEV1 (% predicted)

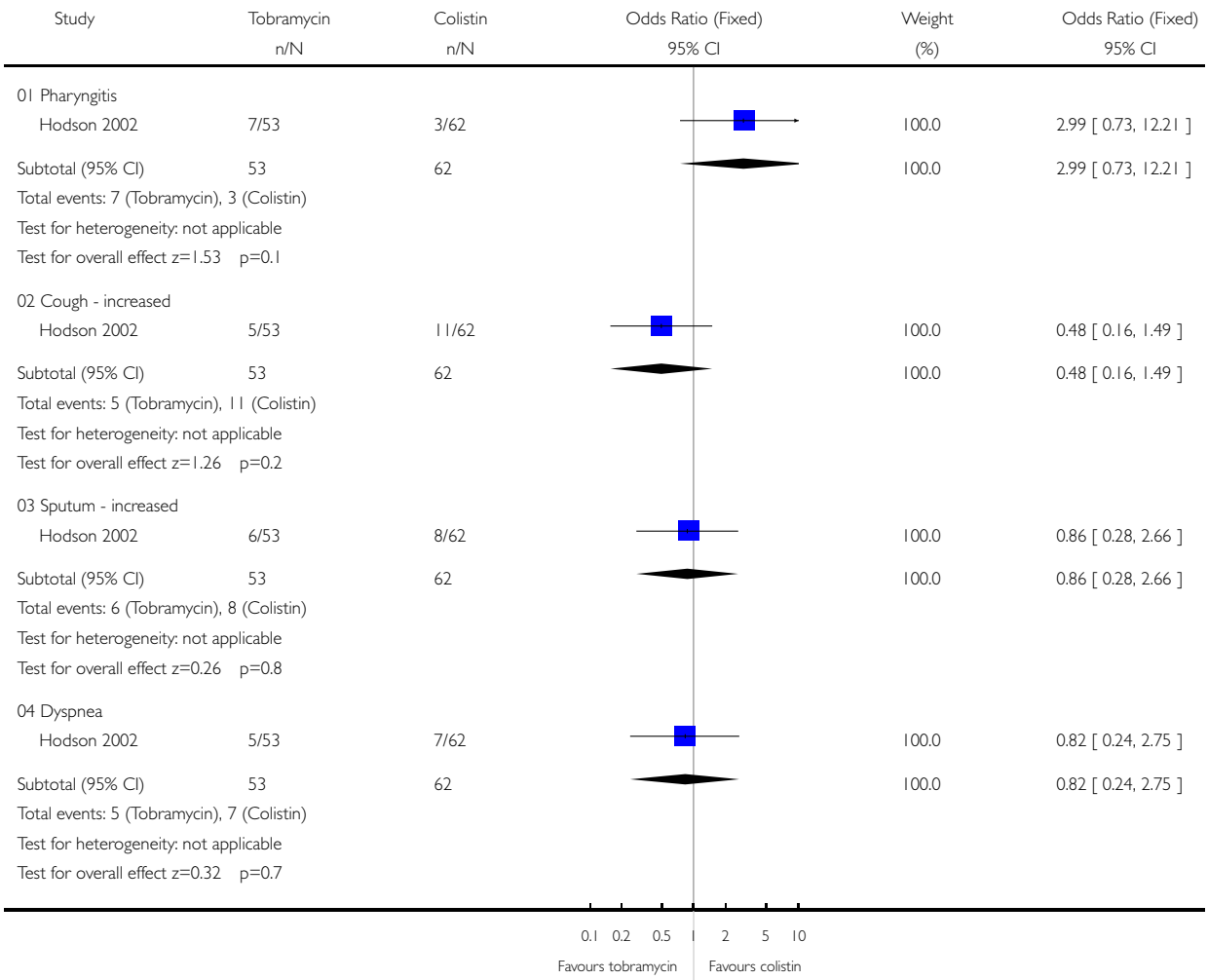


Analysis 02.02. Comparison 02 Nebulised antibiotics compared, Outcome 02 Number experiencing adverse events by end of study

Review: Nebulised anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 02 Nebulised antibiotics compared

Outcome: 02 Number experiencing adverse events by end of study



Analysis 02.03. Comparison 02 Nebulised antibiotics compared, Outcome 03 FEV1 change after single treatment

Review: Nebulised anti-pseudomonal antibiotics for cystic fibrosis

Comparison: 02 Nebulised antibiotics compared

Outcome: 03 FEV1 change after single treatment