# Antibiotic strategies for eradicating Pseudomonas aeruginosa in people with cystic fibrosis (Review)

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## ABSTRACT

**Background**
Lower respiratory tract infection with *Pseudomonas aeruginosa* (*P. aeruginosa*) occurs in most people with cystic fibrosis. Once chronic infection is established, *P. aeruginosa* is virtually impossible to eradicate and is associated with increased mortality and morbidity. Early infection may be easier to eradicate.

**Objectives**
To determine whether antibiotic treatment of early *P. aeruginosa* infection in children and adults with cystic fibrosis eradicates the organism and improves clinical and microbiological outcome.

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

Most recent search: September 2006.

**Selection criteria**
We included randomised controlled trials of people with cystic fibrosis, in whom *P. aeruginosa* had recently been isolated from respiratory secretions. We compared combinations of inhaled, oral or intravenous antibiotics with placebo or usual treatment or other combinations of inhaled, oral or intravenous antibiotics. We excluded non-randomised trials, cross-over trials, and those utilising historical controls.

**Data collection and analysis**
Both authors independently assessed selected trials, assessed methodological quality and extracted data.

**Main results**
The search identified 19 trials. Three trials (69 participants) were eligible for inclusion, two trials are ongoing. There is evidence from two trials that treatment of early *P. aeruginosa* infection with inhaled tobramycin results in microbiological eradication of the organism from respiratory secretions more often than placebo, OR 0.15 (95% CI 0.03 to 0.65) and that this effect may persist for up to 12 months. These trials were of low methodological quality.

One randomised controlled trial of oral ciprofloxacin and nebulised colisitin versus usual treatment was identified. This trial was of poor methodological quality. The results suggested treatment of early infection results in microbiological eradication of *P. aeruginosa* more often than usual treatment, after two years, OR 0.24 (95% CI 0.06 to 0.96). There is insufficient evidence to determine whether antibiotic strategies for the eradication of early *P. aeruginosa* decrease mortality or morbidity, improve quality of life, or are associated with adverse effects compared to placebo or standard treatment.

**Authors' conclusions**
We found that nebulised antibiotics, alone or in combination with oral antibiotics, were better than no treatment for early infection with *P.aeruginosa*. Eradication may be sustained in the short term. Overall, there is insufficient evidence from this review to state which antibiotic strategy should be used for the eradication of early *P. aeruginosa* infection in CF.

## PLAIN LANGUAGE SUMMARY

Nebulised (with or without oral) antibiotics for early infection with *Pseudomonas aeruginosa* in cystic fibrosis, may eradicate the organism and delay chronic infection

Cystic fibrosis blocks the airways with mucus and causes frequent respiratory infections, which may lead to death from breathing failure. A germ called *Pseudomonas aeruginosa* is a frequent cause of infection. We found that nebulised antibiotics (or a combination of nebulised and oral antibiotics) were better than no treatment in treating early infection with this germ, which was eliminated in the majority of individuals. The trials had a relatively short follow-up period and we were unable to show whether treatment made people with cystic fibrosis feel better or live longer. Further research is needed to see whether eradication improves welbeing and quality of life in people with CF.

## BACKGROUND

Cystic fibrosis (CF) is the most common life-limiting, autosomal recessively inherited disease in Caucasian populations. Although this is a multisystem disease, the primary cause of death in CF is respiratory failure resulting from chronic pulmonary infection (FitzSimmons 1993). *Pseudomonas aeruginosa* (*P. aeruginosa*) is the most frequent cause of chronic pulmonary infection beyond infancy in people with CF and once established appears to be permanent in the majority of cases (Fitzsimmons 1996). The accepted definition of chronic infection with *P. aeruginosa* in the lower respiratory tract, which will be used in this review, is the culture of *P. aeruginosa* on two or more occasions over a six month period, or a shorter period if accompanied by a sustained rise in anti-pseudomonas antibodies (Brett 1992; Høiby 1974). Other definitions have been suggested, such as the isolation of *P. aeruginosa* in more than 50% of monthly specimens (Lee 2003). The age specific prevalence of *P. aeruginosa* in pre-school children is 9%, rising to 32% for 10 to 15 year olds (UK CF Database 2003). Some authors have suggested that the use of prophylactic antistaphylococcal antibiotic therapy in early childhood may predispose to chronic *P. aeruginosa* infection (Ratjen 2001b; Stutman 2002). However, this effect was not seen in a systematic review of prophylactic antibiotic use, including over 400 participants (Smyth 2003).

In children who are too young to expectorate, cough swabs or oropharyngeal swabs are the only respiratory specimens which can be easily obtained. These do not reliably predict the presence of *P. aeruginosa* in the lower respiratory tract (Armstrong 1996; Rosenfeld 1999), whereas sputum cultures have been shown to accurately reflect lower respiratory tract organisms in expectorating children and adults (Iacocca 1963; Thomassen 1984). Most people with CF have chronic infection with *P. aeruginosa* by early adulthood (Döring 2000) although prior to chronic infection, *P. aeruginosa* is often isolated intermittently from lower respiratory tract specimens. This may represent transient colonies of *P. aeruginosa* within the lower respiratory tract or alternatively it may reflect the difficulties in accurately detecting *P. aeruginosa* in the lungs of young people with CF (Burns 2001).The quantity and type of *P. aeruginosa* present in the lower respiratory tract changes as infection becomes established. *P. aeruginosa* has two major strains - mucoid and non-mucoid. Following first isolation there is a progressive increase in the density of *P. aeruginosa* colonies in the lower respiratory tract (Rosenfeld 2001). Initial isolates are often non-mucoid strains, however as infection progresses mucoid strains prevail. *P. aeruginosa* provokes an inflammatory response of the lower respiratory tract (Muhlebach 1999) and there is a marked step up in this inflammatory response as the number of *P. aeruginosa* colonies increases (Armstrong 1996).

The presence of *P. aeruginosa* in respiratory secretions is a major predictor of mortality in children with CF (Emerson 2002). Individuals with CF infected with *P. aeruginosa* also suffer greater morbidity with a more rapid deterioration in lung function (Emerson 2002; Pamukcu 1995) and a more rapid decline in chest radiograph score (Kosorok 2001), poor growth, reduced quality of life, increased hospitalisation and increased need for antibiotic treatment (Ballmann 1998; Nixon 2001; Winnie 1991). Some trials suggest there is a temporal relationship between the onset of chronic infection and increased morbidity (Abman 1991; Hudson 1993; Kosorok 2001; Parad 1999), whilst others do not support these findings (Kerem 1990; Rosenfeld 2001). On balance, there seems to be good evidence from well-designed non-experimental studies that clinical state deteriorates after first isolation of *P. aeruginosa*.

It has been suggested that antibiotic treatment against *P. aeruginosa* given at the time of first isolation may prevent or delay chronic infection (Frederiksen 1997). Other strategies which have the potential to prevent or delay infection of the lower respiratory tract with *P. aeruginosa* include avoidance of contact with people who carry *P. aeruginosa* (UK CF Trust 2004) and the development of vaccines against *P. aeruginosa* (Keogan 2002). Uncontrolled series have indicated that a variety of anti-pseudomonal antibiotics either singly (Littlewood 1985; Ratjen 2001a) or in combination (Vazquez 1993) at first isolation may delay the onset of chronic infection. A trial using historical controls suggested that oral ciprofloxacin and nebulised colistin are effective in delaying or preventing chronic infection (Frederiksen 1997). An uncontrolled pilot study of intravenous therapy suggested that intravenous treatment alone was

less effective in delaying the onset of chronic infection (Steinkamp 1989). There is also evidence supporting eradication therapy from long-term observational studies of chronic infection with *P. aeruginosa* in CF clinics such as the study reported by Lee (Lee 2004).

There are differences in the approach to detection and management of first isolation of *P. aeruginosa*. Some CF centres advocate frequent microbiological surveillance with attempts to eradicate *P. aeruginosa* when it first appears in the lung (Döring 2000) whereas others treat only when clinical or radiological signs of pulmonary infection are present (Ramsey 1996). There is evidence that, when *P. aeruginosa* is cleared from respiratory secretions it is not simply suppressed because, when infection recurs, this is with a genetically distinct organism in most cases (Munck 2001). It is uncertain whether eradication strategies result in increased survival or improved quality of life for CF sufferers. The cost-effectiveness of these strategies remains undetermined.

## OBJECTIVES

To determine whether antibiotic treatment of early *P. aeruginosa* infection in children and adults with CF alters clinical and microbiological outcome when compared to usual treatment.

To test the hypotheses that antibiotics against *P. aeruginosa*, given at the time of first isolation, reduces CF-related mortality; improves quality of life; improves pulmonary function; nutritional status; and reduces the need for subsequent hospitalisation and consumption of antibiotics. To investigate whether these antibiotics prevent or delay the onset of chronic infection of the lower respiratory tract with *P. aeruginosa*; increase the incidence of isolates of other micro-organisms from the lower respiratory tract; and are associated with adverse effects which are either important to the individual with CF or have long-term sequelae.

## CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

### Types of studies

Randomised controlled trials.

### Types of participants

Children and adults with CF, diagnosed clinically and by sweat or genetic testing (or both) with a first positive microbiological isolate of *P. aeruginosa* from a lower respiratory tract specimen. Participants should be enrolled into a trial within two months from first isolation of *P. aeruginosa*. People with CF of all ages and disease severity will be included, however participants with evidence of past *P. aeruginosa* isolation or raised specific antibody titres to *P. aeruginosa* will be excluded from analysis.

### Types of intervention

Combinations of inhaled, oral or intravenous antibiotics with the aim of eradicating first pulmonary isolates of *P. aeruginosa* compared with placebo or usual treatment (or both) or other combinations of inhaled, oral or intravenous antibiotics.

### Types of outcome measures

***Primary outcomes***

(1) Eradication of *P. aeruginosa* from the lower respiratory tract as defined by:
(a) no isolation of *P. aeruginosa* from bronchoalveolar lavage (BAL), sputum or oropharyngeal cultures at 1, 2, 3, 6,12 and 24 months after commencement of therapy;
(b) time to next isolation of *P. aeruginosa* from BAL, sputum or oropharyngeal cultures.

***Secondary outcomes***

(2) Mortality
(3) Quality of life assessment
(4) Spirometric lung function (e.g. forced expiratory volume in one second ($FEV_1$) and forced vital capacity (FVC)) expressed as percentage predicted values for age, sex and height

(5) Growth and nutritional status as measured by weight, height (children), body mass index or z score

(6) Frequency of respiratory exacerbations as defined by:
(a) frequency of infective pulmonary exacerbations expressed as the number of exacerbations per patient year
(b) time to next course of IV antibiotics from commencement of therapy
(c) days in hospital expressed as days in hospital per patient year
(d) days of antibiotic usage expressed as days of antibiotic usage per patient year

(7) Isolation of other micro-organisms from the lower respiratory tract expressed as the number of positive cultures per patient year

(8) Adverse effects to antibiotics, e.g. renal and auditory impairment, serum sickness and sensitivity reactions

***Additional outcomes which have arisen during the review***

(9) Time to chronic infection (defined as the presence of *P. aeruginosa* in each monthly sputum sample for six consecutive months or the presence of precipitating antibodies to *P. aeruginosa* or both)

(10) Clinical and radiological scores

Outcome data were grouped into those measured at one, three, six, twelve months and annually thereafter. In addition, we previously stated that if outcome data were recorded at other time periods as well, that we would also consider examining these data. Data at two months for some outcomes were reported, and we have included these data within the review.

## 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 pseudomonas.

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 T*he Cochrane Library*), quarterly searches of MEDLINE, a search of EMBASE to 1995 and the prospective handsearching of two journals - *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis*. Unpublished work is identified by searching the abstract books of three major CF 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 Trials Register, please see the relevant sections of the Cystic Fibrosis and Genetic Disorders Group Module.

Date of the most recent search of the Group's trials register: September 2006.

## METHODS OF THE REVIEW

The two authors (DW, AS) independently selected the trials to be included in the review. Each author independently assessed the methodological quality of each trial, based on the method described by Schulz (Schulz 1995). In particular, authors examined details of the randomisation method, method of allocation concealment, the degree of blinding in the trial, whether intention-to-treat analyses were possible from the available data, and if the number of participants lost to follow up, or subsequently excluded from the trial, were recorded. Each author independently extracted data using standard data acquisition forms. Where there was disagreement on the suitability of a trial for inclusion in the review, or on its quality, the authors reached a consensus by discussion.

For binary outcome measures, in order to allow an intention-to-treat analysis, we sought data on the number of participants with each outcome event, by allocated treated group, irrespective of compliance and whether or not the participant was later thought to be ineligible or otherwise excluded from treatment or follow up. In trials where outcome data were unavailable for participants who had been randomised, we performed an available case analysis. This available case analysis included data on only those participants whose results are known, using as a denominator the total number of people who completed the trial for the particular outcome in question. We calculated a pooled estimate of the treatment effect for each outcome across trials, (the odds ratio or the ratio of the odds of an outcome among treatment allocated participants to the corresponding odds among controls). When data were incomplete, we imputed the missing data to provide best case and worst case scenarios, in order to show the range of possible results for the combined analysis (see graphs 01,06; 01,07; 01,08). The best case scenario analysis is based on the assumption that all the missing data points represented beneficial clinical outcomes, whereas the worst case analysis assumes that all missing data points had a negative clinical outcome.

For continuous outcomes, in order to allow an intention-to-treat analysis, we sought outcome data by allocated treated group, irrespective of compliance and whether or not the participant was later thought to be ineligible or otherwise excluded from treatment or follow up. We recorded either mean change from baseline for each group or mean post-treatment or intervention values and standard deviation. We calculated a pooled estimate of treatment effect by calculating the weighted mean difference. We have reported longitudinal data as individual time points. We realise that this method ignores any correlation between the participants; however, we have been unable to analyse these data using more appropriate methods as we do not have the correlation co-efficient for these data. If in the future, we are able to obtain the correlation co-efficient, we will analyse these data more appropriately.

For future updates of this review, for time-to-event data, such as time to next *P. aeruginosa* infection or time to chronic infection, we will attempt to obtain individual patient data (IPD). We will use these IPD to provide estimates of the log hazard ratio and its standard error and plan to combine time-to-event data from trials in a meta-analysis. We will assess heterogeneity using the $I^2$ statistic (Higgins 2003). If we find evidence of clinical heterogeneity in the included trials, we plan to perform a random effects analysis. In this version of the review, time-to-event data were not available, but binary data were presented on clearance of *P. aeruginosa* from BAL, sputum or oropharyngeal cultures and occurrence of chronic infection with *P. aeruginosa* at multiple time points. Therefore, we calculated the odds ratio (or odds of an outcome among treatment allocated participants to the corresponding odds among controls) at each time point separately, thus ignoring the correlation between time points.

Cross-over trials are not eligible for inclusion within this review. The natural history of infection with *P. aeruginosa* in CF comprises an initial infection with the organism in planktonic form followed by chronic infection by the *P. aeruginosa* biofilm. In the planktonic form, the organism can be eradicated with antibiotics. However, once a biofilm has formed, eradication is not possible. In a cross-over trial, comparing active treatment with placebo, the group receiving the active treatment after placebo will therefore be at a disadvantage compared with those receiving active treatment first. The *P. aeruginosa* may form a biofilm during placebo treatment and so it could not be eradicated during the active treatment phase. Hence, a cross-over trial is an inappropriate design and cross-over trials have not been included in this review.

## DESCRIPTION OF STUDIES

A total of 19 trials were identified by our search. Of these trials three met our inclusion criteria (Gibson 2003; Valerius 1991; Wiesemann 1998). These three trials were parallel in design and enrolled a total of 69 participants. No cross-over trials were identified.

The Gibson trial was a randomised, double-blind, placebo-controlled, parallel-group, multicentre trial (Gibson 2003). There were a total of 21 participants (11 males) were included, from nine centres in North America. Participants were aged six months to six years with microbiological evidence of recent onset of persistent *P. aeruginosa* infection of the lower airways. Participants were randomised to receive either tobramycin solution for inhalation (TSI) (300 mg twice-daily, for 28 days at home) or to placebo inhalations. Randomisation was stratified for age and participating centre. The planned sample size was 98 participants. The randomisation was stopped early after an interim analysis by the 'Data Monitoring Committee', which was performed because of poor accrual. This analysis showed a statistically significant treatment effect. All randomised participants completed the trial. The primary outcome measure was eradication of *P. aeruginosa* from lower respiratory tract specimens, with oropharyngeal cultures measured at entry and on days 14, 28, 42 and 56. Bronchoscopic BAL fluid for culture was obtained from the same lobar segment on trial entry as well as day 28. Other measured outcomes included nutritional status, modified Shwachman score and monitoring for adverse clinical and microbiological effects.

The Valerius trial was a randomised, placebo-controlled, parallel-group, single-centre trial (Valerius 1991). There were a total of 26 participants (13 males), from one Danish CF Centre, with evidence of recent onset of persistent *P. aeruginosa* infection of the lower airways. Participants were randomised, without stratification, to receive either treatment with ciprofloxacin 250 mg to 750 mg (according to body weight) twice-daily and inhalation of colistin 1MU twice-daily for three weeks at entry to the trial (and each time *P. aeruginosa* was subsequently isolated from monthly sputum samples) or to no (standard) treatment. The end point was chronic infection with *P. aeruginosa* and results were expressed as time-to-chronic infection (defined as presence of *P. aeruginosa* in monthly sputum samples for six consecutive months or the development of precipitating serum antibodies against *P. aeruginosa*) or both. There were no withdrawals during the trial period.

The Wiesemann trial was a randomised, double-blind, placebo-controlled, parallel-group, multicentre trial (Wiesemann 1998). There were a total of 22 participants (9 males) from five German paediatric CF centres, aged 4 to 18 years with microbiological evidence of recent onset of persistent *P. aeruginosa* infection. Individuals with raised titres to anti-pseudomonal antibodies were excluded from the trial. Participants were randomised to receive either aerosolised tobramycin parenteral preparation (Eli Lilly, Bad Homburg Germany) (80 mg) or placebo containing the same preservatives to be inhaled twice-daily for 12 months. Eight participants (two from the treatment group and six from the placebo group) failed to complete the trial. These withdrawals were prompted by a variety of reasons, including: unwillingness to do daily inhalations; need for intravenous treatment; cough during inhalations; lack of the expected effect of treatment on cough and sputum production. The primary outcome was time to clearance of *P. aeruginosa* from the lower airways with monthly sputum or oropharyngeal swabs during the trial period

Trials with no control group were excluded (Heinzl 2002; Littlewood 1985; Ratjen 2001a; Steinkamp 1989; Taccetti 2005), as were trials which used historical controls (Frederiksen 1997; Vazquez 1993; Taccetti 2005) and those which were observational in nature (Ballmann 1998). Likewise, we excluded trials designed to evaluate a diagnostic technique for *P. aeruginosa* (Brett 1992; Wainwright 2002) and those which evaluated symptomatic rather than eradication treatment (Church 1997; Schaad 1997). No cross-over trials were identified.

Fourteen trials were excluded: one trial was excluded as it was not randomised (Gibson 2007); four trials were excluded as they did not have a control group (Heinzl 2002; Littlewood 1985; Ratjen 2001a; Steinkamp 1989); four trials were excluded as they used historical controls (Frederiksen 1997; Griese 2002; Taccetti 2005; Vazquez 1993); one trial was excluded because it was an observational study (Ballmann 1998); two trials were excluded as they were designed to evaluate a diagnostic technique for P. aeruginosa (Brett 1992; Wainwright 2002); and two trials were excluded as they evaluated symptomatic rather than eradication treatment (Church 1997; Schaad 1997).

Two trials were identified which are still ongoing (Ramsey 2005; Ratjen 2006). Further details of these can be found in the table 'Characteristics of ongoing studies'. Data from these trials will be included in a future update of this review once they have been published.

## METHODOLOGICAL QUALITY

Methodological quality was assessed using the criteria described by Schulz (Schulz 1995). Briefly, these criteria evaluate concealment of treatment allocation schedule, generation of allocation sequence, blinding and whether analysis was by intention-to-treat.

The three trials were reported as randomised controlled trials; in two, the method of generation of allocation sequence was not stated (Gibson 2003; Valerius 1991). In the third the allocation sequence was generated using a coin flip (Wiesemann 1998). There is no information as to who was responsible for the coin flip or what controls were in place to ensure validity of the result of the coin flip.

None of the trials reported how allocation was concealed (Gibson 2003; Valerius 1991; Wiesemann 1998).

Two trials were reported as double blind trials (Gibson 2003; Wiesemann 1998). Gibson did not provide any details regarding who was blinded or the method of blinding (Gibson 2003). Wiesemann reported that participants were blinded by providing a placebo inhalation with a similar taste to the treatment inhalation, but it is not clear whether the clinicians administering the treatment were blinded to treatment allocation (Wiesemann 1998).The remaining trial did not utilise blinding (Valerius 1991).

Two trials were analysed on an intention-to-treat basis (Gibson 2003; Valerius 1991); both reported data on all participants who were randomised. There were no dropouts reported in either trial. In one trial, five participants withdrew from the trial after randomisation (Wiesemann 1998). Only baseline data at entry to this trial were presented for these participants and to date we have been unable to obtain further outcome data. The trial was therefore analysed on an available case basis (Wiesemann 1998).

Please see further information in the 'Additional tables' section of the review (Table 01).

## RESULTS

**Tobramycin (inhaled) versus placebo** (two trials including 43 participants (Gibson 2003; Wiesemann 1998))

***Primary outcome***

*(1) Eradication of P. aeruginosa from the lower respiratory tract as defined by:*

(a) Clearance of *P. aeruginosa* from BAL, sputum or oropharyngeal cultures at 1, 2, 3, 6, 12 and 24 months after commencement of therapy

We did not combine these two trials in a formal analysis of this outcome, as results were not available for all the participants in the Wiesemann trial, thereby precluding an intention-to-treat analysis. An available case analysis of the data presented in the Wiesemann trial showed that, when combined with the data from the Gibson trial, there was a reduction in the odds of a positive culture in the treatment group compared to the placebo group at one month, odds ratio (OR) 0.06 (95% confidence interval (CI) 0.01 to 0.33); and two months, OR 0.15 (95% CI 0.03 to 0.65) (Gibson 2003; Wiesemann 1998). A sensitivity analysis following imputation of the missing data to provide best case and worst case scenarios for the combined analysis showed a range of possible results. The best case scenario showed a reduction in the odds of a positive culture of *P. aeruginosa* in the treatment group at both one month, OR 0.06 (95% CI 0.01 to 0.30); and two months, OR 0.14 (95% CI 0.03 to 0.60). In the worst case scenario the odds of a positive culture was reduced at one month, OR 0.08 (95% CI 0.02 to 0.38); but was not statistically significant at two months, OR 0.18 (95% CI 0.04 to 0.73). Wiesemann was able to demonstrate a statistically significant reduction in the odds of a positive culture from the lower respiratory tract specimen after six months, OR 0.06 (95%CI 0.00 to 0.92); and twelve months of treatment, OR 0.02 (95 % CI 0.00 to 0.67) (Wiesemann 1998).

(b) Time to next isolation of *P. aeruginosa* from BAL, sputum or oropharyngeal cultures

Neither trial assessed or reported on this outcome.

(c) Time to chronic infection (defined as the presence of *P. aeruginosa* in each monthly sputum sample for six consecutive months or the presence of precipitating antibodies to *P. aeruginosa* or both)

Neither trial assessed or reported on this outcome.

***Secondary Outcomes***

*(2) Mortality*

Mortality was not included as an outcome in either trial. There were no reported deaths during any of the trial periods.

*(3) QOL assessment*

Neither trial assessed or reported on this outcome.

*(4) Spirometric lung function*

Wiesemann reported no change in spirometric pulmonary function during or after the treatment period, but no data were given (Wiesemann 1998). Gibson did not assess or report on spirometric lung function (Gibson 2003).

*(5) Growth and nutritional status*

The trial by Gibson was the only one to present data on weight (Gibson 2003). They found no significant difference between the two groups in the change in weight from baseline (measured at trial entry) and subsequent weights measured at one month, WMD 0.20 (95% CI -0.28 to 0.68) and two months, WMD 0.10 (95% CI -0.38 to 0.58).

*(6) Frequency of respiratory exacerbations*

Neither trial assessed or reported on this outcome.

*(7) Isolation of other micro-organisms*

Gibson reported no changes in the prevalence of other micro-organisms, including multi-resistant organisms, cultured from respiratory secretions (Gibson 2003). Wiesemann did not collect data on this outcome (Wiesemann 1998).

*(8) Adverse effects to antibiotics*

Gibson reported cough in association with inhalation in 7 out of 8 participants in the treatment group and in 12 out of 13 in the placebo group, OR 0.58 (95% CI 0.03 to 10.86) (Gibson 2003). There was no evidence of a difference in serum creatinine levels or auditory threshold between the groups, however the numbers of participants was small (Gibson 2003). Wiesemann reported one withdrawal from the placebo group because of cough, however the authors did not report on the presence or absence of cough in other participants (Wiesemann 1998).

***Additional outcomes which have arisen during the review***

*(9) Time to chronic infection (defined as the presence of P. aeruginosa in each monthly sputum sample for six consecutive months or the presence of precipitating antibodies to P. aeruginosa or both)*
Neither trial assessed or reported on this outcome.

*(10) Clinical and radiological scores*
Only the Gibson trial reported modified Shwachmann scores (Gibson 2003). These were recorded at one month and two months from enrolment and were expressed as both mean scores with standard deviations and mean change from baseline with standard deviations. There was no significant differences between the two groups in changes in either mean scores or modified Schwachman scores from baseline at either one month, WMD 1.30 (95% CI -2.36 to 4.96) or two months, WMD 3.80 (95% CI -0.22 to 7.82) (Gibson 2003).

**Ciprofloxacin and colistin versus control** (one trial including 26 participants (Valerius 1991)).
***Primary outcome***
*(1) Eradication of P. aeruginosa from the lower respiratory tract as defined by:*
(a) No isolation of *P. aeruginosa* from BAL, sputum or oropharyngeal cultures at 1, 2, 3, 6, 12 and 24 months after commencement of therapy
The included trial did not report on this outcome.

(b) Time to next isolation of *P. aeruginosa* from BAL, sputum or oropharyngeal cultures
The included trial did not report on this outcome.

***Secondary Outcomes***
*(2) Mortality*
The included trial did not report on this outcome.

*(3) Quality of life*
The included trial did not report on this outcome.

*(4) Spirometric lung function*
The included trial did not report on this outcome.

*(5) Growth and nutritional status*
The included trial did not report on this outcome.

*(6) Frequency of respiratory exacerbations*
The included trial did not report on this outcome.

*(7) Isolation of other micro-organisms*
The included trial did not report on this outcome.

*(8) Adverse effects to antibiotics*
Valerius did not describe cough specifically but reported that there were no adverse effects in either group (Valerius 1991).

***Additional outcomes which have arisen during the review***
*(9) Time to chronic infection (defined as the presence of P. aeruginosa in each monthly sputum sample for six consecutive months or the presence of precipitating antibodies to P. aeruginosa or both)*
In the Valerius trial, from the data provided, it was possible to calculate the proportion of participants in each group who were defined as chronically colonised with *P. aeruginosa* from respiratory secretions at 3, 6, 12 and 24 month time points (Valerius 1991). The odds of being chronically infected with *P. aeruginosa* was reduced in the treatment group compared to the placebo group after 24 months, OR 0.12 (95% CI 0.02 to 0.79). No significant difference was detected between the two groups at the other time points. No other trials used this outcome measure to express their findings.

*(10) Clinical and radiological scores*
The included trial did not report on this outcome.

## DISCUSSION

Our review includes three trials of antibiotic strategies for the eradication of *P. aeruginosa* infection in CF, with data from 69 participants. The quality of the trials was variable with important deficiencies identified in each trial. An early interim analysis was performed due to slow accrual in one trial (Gibson 2003). This trial was stopped early because of evidence of significant treatment effect. It has been suggested that the results of randomised controlled trials stopped early for benefit should be interpreted with caution particularly when the number of events is small (Montori 2005).

Cumulative data from 43 participants in two of the three included trials indicate that *P. aeruginosa* was more frequently eradicated from the respiratory secretions in the participants receiving antibiotics than from those receiving placebo (Gibson 2003; Wiesemann 1998). This reduction in the number of isolates of *P. aeruginosa* was noted at both one month and two months, after the start of treatment. The accuracy of the analysis was hampered by incomplete follow-up of a number of participants in one of the trials. The absence of these data has complicated the combined analysis of the two trials that compare inhaled tobramycin with placebo; one trial was analysed on an intention to treat basis and another on an available case basis with a sensitivity analysis. A sensitivity analysis based on best and worst case scenarios demonstrated similar results to the available case analysis. The available case analysis revealed a reduction in the odds of a positive culture for *P. aeruginosa* in the group treated with tobramycin inhalation when compared to the odds in the placebo group at both one and two months from the start of treatment. The trial by Valerius suggests that the onset of chronic infection with *P. aeruginosa*, is delayed in those individuals who have received antibiotic therapy compared to those receiving no therapy (Valerius 1991). There was some evidence from the trials by Valerius and Wiesemann that this effect may persist for up to 24 months (Valerius 1991; Wiesemann 1998). There was evidence for no difference in adverse events or the isolation of other micro-organisms associated with antibiotic treatment, aimed at eradicating *P. aeruginosa* from the respiratory

tract. These results should be interpreted with caution for a number of reasons.

The relationship between the presence of *P. aeruginosa* in secretions from the upper respiratory tract and the isolation of *P. aeruginosa* from the lower respiratory tract is inconsistent. Reporting of the presence of organisms in respiratory secretions is difficult to standardise, dependent on the sampling methods used and on the number of samples taken. The trials included in this review used a heterogeneous mix of methods to sample respiratory secretions from both the lower and upper respiratory tracts. No two trials used the same methods and more than one method was used in two trials. There was no subgroup analysis based on sampling method in any of the trials, probably owing to relatively small numbers of participants in individual trials. Wiesemann used a combination of oropharyngeal swabs and sputum samples, whereas Gibson used oropharyngeal swabs and bronchoscopic bronchoalveolar lavage fluid (Gibson 2003; Wiesemann 1998). Armstrong has shown that the results of oropharyngeal specimens are poorly predictive of the presence of organisms in the lower respiratory tract (Armstrong 1996). Valerius relied on sputum samples which can be of poor quality in younger children (Valerius 1991).

The aim of antibiotic therapy for early *P. aeruginosa* infection in CF should be both eradication of the micro-organism and improvement in (or slowing in the rate of decline of) clinical parameters, whilst minimising adverse effects and the isolation of new micro-organisms. If *P. aeruginosa* is successfully eradicated, but there is no measurable clinical benefit then, either *P. aeruginosa* is less important than many clinicians believe it to be, or (which is more likely) current measures of clinical status are not sufficiently sensitive to small but important changes in the condition of an individual with CF.

There are differences in the type and dose of drug administered to the treatment groups in the two trials where nebulised tobramycin was compared to placebo. Wiesemann utilised tobramycin nebulised parenteral preparation (injectable solution) at a low dose (80 mg twice daily) for a long duration (12 months) (Wiesemann 1998); whereas Gibson used tobramycin solution for inhalation (TSI, TOBI) at a high dose (300 mg twice daily) for a short duration (28 days) (Gibson 2003). This is a potential source of heterogeneity between the trials. It is of interest that significant heterogeneity was detected between the trials at the one month time point but this was not detected at the two month time point.

No deaths were reported during the trial periods. The participants were young children with CF and mortality is low in this group of individuals. Eradication of isolates of *P. aeruginosa* is easiest in people with CF with recent onset of *P. aeruginosa* infection of the respiratory tract, in particular in those who have non-mucoid isolates of *P. aeruginosa* as they seem particularly susceptible to antibiotic therapy. As onset of *P. aeruginosa* infection in people with CF is usually in mid-childhood these results should not be extrapolated to older individuals or those with established *P. aeruginosa* infection of the lower respiratory tract.

## AUTHORS' CONCLUSIONS

### Implications for practice

Significantly more children with CF show clearance of *P. aeruginosa* from their respiratory secretions two months after commencing antibiotic therapy aimed at eradication of the organism from their lower respiratory tract when compared to placebo. This effect may last for several months. This review has not established any improvement in clinical outcome measures following treatment. However, the small numbers of participants in the eligible trials mean that this review may have insufficient statistical power to detect changes in these clinical outcomes. There was no significant difference in the rate of common adverse effects nor in the isolation of micro-organisms other than *P. aeruginosa*.

We found that nebulised antibiotics (or a combination of nebulised and oral antibiotics) were better than no treatment in treating early infection with *P.aeruginosa*, which was eliminated in the majority of individuals. Eradication may be sustained in the short term. We were unable to determine whether there is an associated clinical benefit to people with CF. Overall, there is insufficient evidence from this review to state which antibiotic strategy should be used, for the eradication of early *P. aeruginosa* infection in CF.

### Implications for research

There is an urgent need for well-designed and executed trials, which are specifically designed to examine the hypothesis: that antibiotic treatment of early *P. aeruginosa* infection will prevent or delay chronic infection, and result in appreciable clinical benefit to patients, without causing them harm. This requires well-designed, multicentre, double-blind, randomised controlled trials enrolling adequate numbers of participants to ensure the trial has sufficient power. Eradication treatment is part of routine clinical practice in many CF centres and clinical trials comparing alternative eradication regimens may be preferable for pragmatic reasons. Consideration should be given to appropriate outcome measures particularly spirometric lung function and nutritional status and duration of follow up, Long-term follow-up trials with careful clinical and bacteriological surveillance are required.

## POTENTIAL CONFLICT OF INTEREST

Dr Smyth has received financial support from Forest Laboratories and Profile Pharma (both companies market a nebulised colistin product) and from Chiron (manufacturers of the TOBI® brand of nebulised tobramycin).

## ACKNOWLEDGEMENTS

Hazel Bunn assisted in formulation of the review protocol.

## SOURCES OF SUPPORT

### External sources of support

- No sources of support supplied

### Internal sources of support

- No sources of support supplied

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EPIC Study. Ongoing study December 2004.

**Ratjen 2006**
ELITE Study. Ongoing study Recruitment completed in December 2005 with a follow-up period of 27 months.

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* *Indicates the major publication for the study*

## TABLES

### Characteristics of included studies

| Study | Gibson 2003 |
|---|---|
| Methods | Randomised, double-blind, placebo-controlled, parallel, multicentre trial.<br>Randomisation was stratified by study centre and age (=/<36 months; > 36 months). |
| Participants | 21 participants aged 6 months to 6 years (males: females = 11:10) with a recent positive oropharyngeal culture and isolation of P. aeruginosa from bronchoalveolar lavage at study entry. |
| Interventions | Tobramycin solution for inhalation (300 mg twice daily for 28 days) versus placebo inhalations. |
| Outcomes | Eradication of P. aeruginosa, nutritional status, modified Shwachman score, adverse effects. |

| | |
|---|---|
| Notes | Oropharyngeal cultures performed at entry and on days 14, 28,42 and 56 of the study. BAL from the same lobar segment on entry and day 28. |
| Allocation concealment | B – Unclear |

| **Study** | **Valerius 1991** |
|---|---|
| Methods | Randomised, placebo-controlled, parallel, single centre trial.<br>Randomly allocated without stratification. |
| Participants | 26 participants aged 2 to 9 years (males: females = 13:13) with a recent positive culture who have never received anti-pseudomonal therapy. |
| Interventions | Oral ciprofloxacin (250 - 750 mg) twice-daily and inhaled colistin (1 mill. IU) for 3 weeks at entry and each time Pseudomonas isolated or no anti-pseudomonas chemotherapy. Length of trial: 27 months. |
| Outcomes | Time to chronic colonisation with Pseudomonas (defined as the presence of P. aeruginosa in monthly routine sputum specimens for 6 consecutive months and/or the development of precipitating serum antibodies against P. aeruginosa). |
| Notes | No published information on randomisation method or allocation concealment.<br>Monthly sputum samples. |
| Allocation concealment | B – Unclear |

| **Study** | **Wiesemann 1998** |
|---|---|
| Methods | Randomised, double-blind, placebo-controlled, parallel, multicentre trial.<br>Randomisation performed by flipping a coin. |
| Participants | 22 children age 4-18 years (males: females = 9:13) with P. aeruginosa-negative throat swabs of sputum cultures for > 1 year and negative serum antibody titers were eligible. |
| Interventions | Nebulised tobramycin 80 mg or placebo inhaled twice-daily for 2 years. |
| Outcomes | Time to clearance of pseudomonas from the lower airway. |
| Notes | Generation of randomisation sequence by coin flip.<br>Monthly sputum or oropharyngeal swabs during trial period. |
| Allocation concealment | B – Unclear |

P. aeruginosa: Pseudomonas aeruginosa

## Characteristics of excluded studies

| **Study** | **Reason for exclusion** |
|---|---|
| Ballmann 1998 | Eradication treatment not used. Observational study. |
| Brett 1992 | Randomised to treatment on the basis of IgG levels and clinical indications compared to therapy based on clinical indications alone. |
| Church 1997 | Symptomatic treatment not eradication. |
| Frederiksen 1997 | Historical control group. |
| Gibson 2007 | Not randomised and with no allocation concealment. |
| Griese 2002 | Case control study. |
| Heinzl 2002 | No control group. |
| Littlewood 1985 | No control group. |
| Ratjen 2001a | No control group. |
| Schaad 1997 | Symptomatic treatment not eradication. |

**Characteristics of excluded studies** (*Continued*)

| | |
|---|---|
| Steinkamp 1989 | No control group. |
| Taccetti 2005 | Primary outcome did not have a control group. Historical controls utilised for other outcomes. No randomisation. |
| Vazquez 1993 | Historical control group. |
| Wainwright 2002 | Randomised to therapy directed by the results of bronchoalveolar lavage compared to therapy based on clinical indications or upper respiratory samples. |

## Characteristics of ongoing studies

| **Study** | **Ramsey 2005** |
|---|---|
| Trial name or title | EPIC Study |
| Participants | 300 participants with CF free of P. aeruginosa |
| Interventions | Culture based versus cycled therapy with high dose nebulised tobramycin with or without oral ciprofloxacin |
| Outcomes | Primary outcome is time to first exacerbation requiring intravenous therapy and proportion of positive cultures in each group |
| Starting date | December 2004 |
| Contact information | bonnie.ramsey@seattlechildrens.org |
| Notes | |

| **Study** | **Ratjen 2006** |
|---|---|
| Trial name or title | ELITE Study |
| Participants | 121 participants with CF free of P. aeruginosa |
| Interventions | 28 days versus 56 days of high dose nebulised tobramycin |
| Outcomes | Primary outcome is duration of eradication of P. aeruginosa defined as time to next isolate |
| Starting date | Recruitment completed in December 2005 with a follow-up period of 27 months |
| Contact information | felix.ratjen@sickkids.ca |
| Notes | |

## ADDITIONAL TABLES

### Table 01. Methodological quality of included studies (assessed using Schulz criteria)

| **Trial** | **Allocation conceal't** | **Randomisation** | **Blinding** | **Type of analysis** |
|---|---|---|---|---|
| Gibson 2003 | Method not stated. | Randomisation method not stated. Stratified by trial centre and age (36 months or less and more than 36 months). | Yes. Stated as double blind, although not clear how this was achieved. | Intention-to-treat .Enrolement was discontinued due to an interim analysis, precipitated by poor accrual of participants, which showed a statistically significant microbiological effect of |

**Table 01. Methodological quality of included studies (assessed using Schulz criteria) (*Continued*)**

| Trial | Allocation conceal't | Randomisation | Blinding | Type of analysis |
|---|---|---|---|---|
| | | | | treatment. All participants who enrolled completed the trial. |
| Wiesmann 1998 | Placebo inhalation designed to taste similar to treatment | Randomisation was by flipping a coin for pairs of participants. | Yes. Stated as double blind, although not clear how this was achieved. | Available case analysis. 2/11 patients withdrew from treatment group. 5/11 patients withdrew from placebo group. |
| Valerius 1991 | Method not stated. | Randomisation method not stated. | No. No blinding of allocation. | Intention-to-treat. |

## ANALYSES

### Comparison 01. Inhaled tobramycin versus placebo

| Outcome title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 01 Positive respiratory culture for P. aeruginosa (Gibson 2003) | | | Odds Ratio (Fixed) 95% CI | Totals not selected |
| 02 Positive respiratory culture for P. aeruginosa (Wiesemann 1998) | | | Odds Ratio (Fixed) 95% CI | Totals not selected |
| 03 Positive respiratory culture for P. aeruginosa (combined available case analysis) | | | Odds Ratio (Fixed) 95% CI | Subtotals only |
| 04 Positive respiratory culture for P. aeuginosa (combined) - best case | | | Odds Ratio (Fixed) 95% CI | Subtotals only |
| 05 Positive respiratory culture for P. aeruginosa (combined) - worst case | | | Odds Ratio (Fixed) 95% CI | Subtotals only |
| 06 Change in weight from baseline | | | Weighted Mean Difference (Fixed) 95% CI | Totals not selected |
| 07 Adverse events | | | Odds Ratio (Fixed) 95% CI | Totals not selected |
| 08 Change in modified Shwachmann score from baseline | | | Weighted Mean Difference (Fixed) 95% CI | Totals not selected |

### Comparison 02. Oral ciprofloxacin and inhaled colistin versus no treatment

| Outcome title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 01 Proportion colonised with P. aeruginosa | | | Odds Ratio (Fixed) 95% CI | Totals not selected |

## INDEX TERMS

**Medical Subject Headings (MeSH)**

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

**MeSH check words**

Child; Humans

## COVER SHEET

| | |
|---|---|
| **Title** | Antibiotic strategies for eradicating Pseudomonas aeruginosa in people with cystic fibrosis |
| **Authors** | Wood DM, Smyth AR |
| **Contribution of author(s)** | Damian Wood wrote the first draft of the review. Both Damian Wood and Alan Smyth edited it to produce the final version. Both Damian Wood and Alan Smyth have worked on the updated version of the review.<br>Damian Wood acts as guarantor of the review. |
| **Issue protocol first published** | 2003/2 |
| **Review first published** | 2006/1 |
| **Date of most recent amendment** | 13 November 2007 |
| **Date of most recent SUBSTANTIVE amendment** | 15 November 2005 |
| **What's New** | Review update: November 2007<br>The search identified four new trials; two of which have been excluded (Gibson 2007; Griese 2002); and two of which are still ongoing (Ramsey 2005; Ratjen 2006).<br>The review authors have addressed some comments from the CFGD Group's medical statistician within this update. |
| **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** | 11 September 2006 |
| **Date authors' conclusions section amended** | Information not supplied by author |
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**Editorial group** Cochrane Cystic Fibrosis and Genetic Disorders Group

**Editorial group code** HM-CF

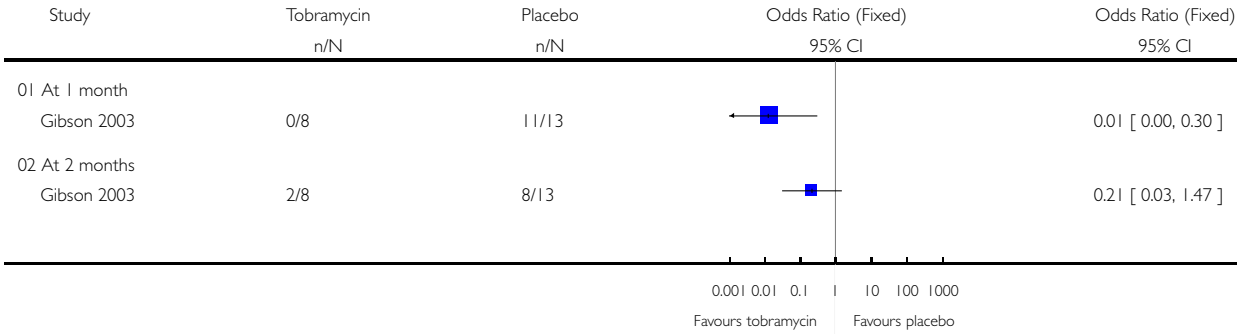
## GRAPHS AND OTHER TABLES

### Analysis 01.01. Comparison 01 Inhaled tobramycin versus placebo, Outcome 01 Positive respiratory culture for P. aeruginosa (Gibson 2003)

Review: Antibiotic strategies for eradicating Pseudomonas aeruginosa in people with cystic fibrosis

Comparison: 01 Inhaled tobramycin versus placebo

Outcome: 01 Positive respiratory culture for P. aeruginosa (Gibson 2003)



## Analysis 01.02. Comparison 01 Inhaled tobramycin versus placebo, Outcome 02 Positive respiratory culture for P. aeruginosa (Wiesemann 1998)

Review: Antibiotic strategies for eradicating Pseudomonas aeruginosa in people with cystic fibrosis

Comparison: 01 Inhaled tobramycin versus placebo

Outcome: 02 Positive respiratory culture for P. aeruginosa (Wiesemann 1998)

| Study | Tobramycin n/N | Placebo n/N | Odds Ratio (Fixed) 95% CI | Odds Ratio (Fixed) 95% CI |
|---|---|---|---|---|
| 01 At 1 month | | | | |
| Wiesemann 1998 | 3/8 | 7/9 | | 0.17 [ 0.02, 1.44 ] |
| 02 At 2 months | | | | |
| Wiesemann 1998 | 2/8 | 7/9 | | 0.10 [ 0.01, 0.90 ] |
| 03 At 3 months | | | | |
| Wiesemann 1998 | 2/8 | 4/7 | | 0.25 [ 0.03, 2.24 ] |
| 04 At 6 months | | | | |
| Wiesemann 1998 | 1/9 | 4/6 | | 0.06 [ 0.00, 0.92 ] |
| 05 At 12 months | | | | |
| Wiesemann 1998 | 1/8 | 4/4 | | 0.02 [ 0.00, 0.67 ] |


## Analysis 01.03. Comparison 01 Inhaled tobramycin versus placebo, Outcome 03 Positive respiratory culture for P. aeruginosa (combined available case analysis)

Review: Antibiotic strategies for eradicating Pseudomonas aeruginosa in people with cystic fibrosis

Comparison: 01 Inhaled tobramycin versus placebo

Outcome: 03 Positive respiratory culture for P. aeruginosa (combined available case analysis)

| Study | Tobramycin n/N | Placebo n/N | Odds Ratio (Fixed) 95% CI | Weight (%) | Odds Ratio (Fixed) 95% CI |
|---|---|---|---|---|---|
| 01 At 1 month | | | | | |
| Gibson 2003 | 0/8 | 11/13 | | 67.4 | 0.01 [ 0.00, 0.30 ] |
| Wiesemann 1998 | 3/8 | 7/9 | | 32.6 | 0.17 [ 0.02, 1.44 ] |
| Subtotal (95% CI) | 16 | 22 | | 100.0 | 0.06 [ 0.01, 0.33 ] |
| Total events: 3 (Tobramycin), 18 (Placebo) | | | | | |
| Test for heterogeneity chi-square=1.82 df=1 p=0.18 $I^2$ =45.0% | | | | | |
| Test for overall effect z=3.32 p=0.0009 | | | | | |
| 02 At 2 months | | | | | |
| Gibson 2003 | 2/8 | 7/9 | | 51.9 | 0.10 [ 0.01, 0.90 ] |
| Wiesemann 1998 | 2/8 | 8/13 | | 48.1 | 0.21 [ 0.03, 1.47 ] |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| Study | Tobramycin n/N | Placebo n/N | Odds Ratio (Fixed) 95% CI | Weight (%) | Odds Ratio (Fixed) 95% CI |
|---|---|---|---|---|---|
| Subtotal (95% CI) | 16 | 22 | | 100.0 | 0.15 [ 0.03, 0.65 ] |
| Total events: 4 (Tobramycin), 15 (Placebo) | | | | | |
| Test for heterogeneity chi-square=0.27 df=1 p=0.61 $I^2$ =0.0% | | | | | |
| Test for overall effect z=2.54 p=0.01 | | | | | |


## Analysis 01.04. Comparison 01 Inhaled tobramycin versus placebo, Outcome 04 Positive respiratory culture for P. aeuginosa (combined) - best case

Review: Antibiotic strategies for eradicating Pseudomonas aeruginosa in people with cystic fibrosis

Comparison: 01 Inhaled tobramycin versus placebo

Outcome: 04 Positive respiratory culture for P. aeuginosa (combined) - best case

| Study | Tobramycin n/N | Placebo n/N | Odds Ratio (Fixed) 95% CI | Weight (%) | Odds Ratio (Fixed) 95% CI |
|---|---|---|---|---|---|
| 01 At 1 month | | | | | |
| Gibson 2003 | 0/8 | 11/13 | | 64.6 | 0.01 [ 0.00, 0.30 ] |
| Wiesemann 1998 | 3/9 | 7/9 | | 35.4 | 0.14 [ 0.02, 1.16 ] |
| Subtotal (95% CI) | 17 | 22 | | 100.0 | 0.06 [ 0.01, 0.30 ] |
| Total events: 3 (Tobramycin), 18 (Placebo) | | | | | |
| Test for heterogeneity chi-square=1.58 df=1 p=0.21 $I^2$ =36.8% | | | | | |
| Test for overall effect z=3.42 p=0.0006 | | | | | |
| 02 At 2 months | | | | | |
| Gibson 2003 | 2/8 | 8/13 | | 45.6 | 0.21 [ 0.03, 1.47 ] |
| Wiesemann 1998 | 2/9 | 7/9 | | 54.4 | 0.08 [ 0.01, 0.75 ] |
| Subtotal (95% CI) | 17 | 22 | | 100.0 | 0.14 [ 0.03, 0.60 ] |
| Total events: 4 (Tobramycin), 15 (Placebo) | | | | | |
| Test for heterogeneity chi-square=0.39 df=1 p=0.53 $I^2$ =0.0% | | | | | |
| Test for overall effect z=2.65 p=0.008 | | | | | |
| 03 At 3 months | | | | | |
| Wiesemann 1998 | 2/9 | 6/9 | | 100.0 | 0.14 [ 0.02, 1.16 ] |
| Subtotal (95% CI) | 9 | 9 | | 100.0 | 0.14 [ 0.02, 1.16 ] |
| Total events: 2 (Tobramycin), 6 (Placebo) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect z=1.82 p=0.07 | | | | | |
| 04 At 6 months | | | | | |


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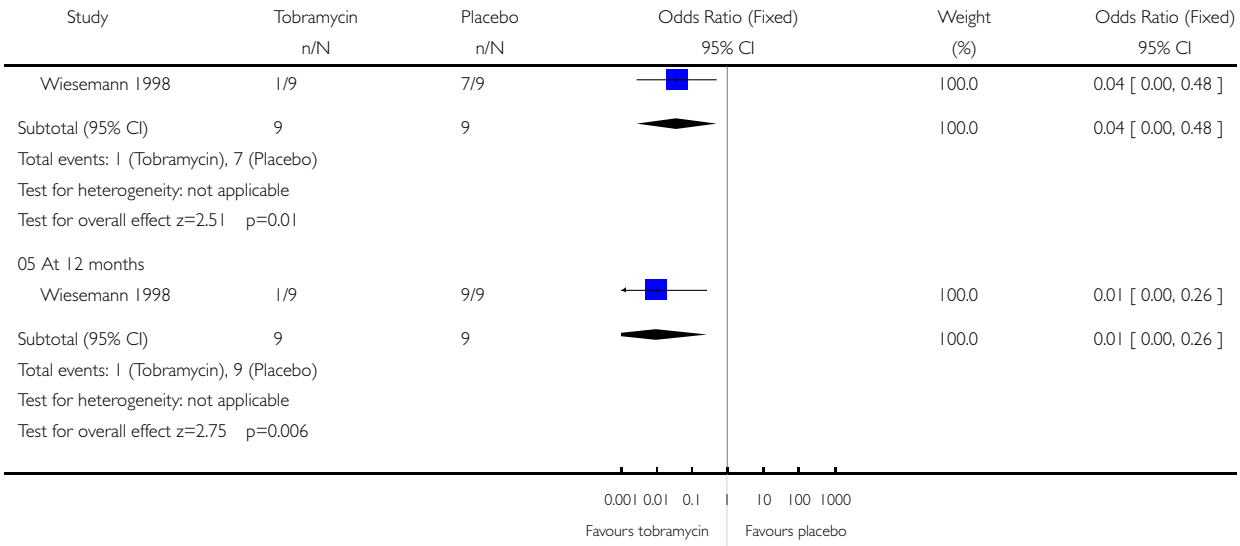
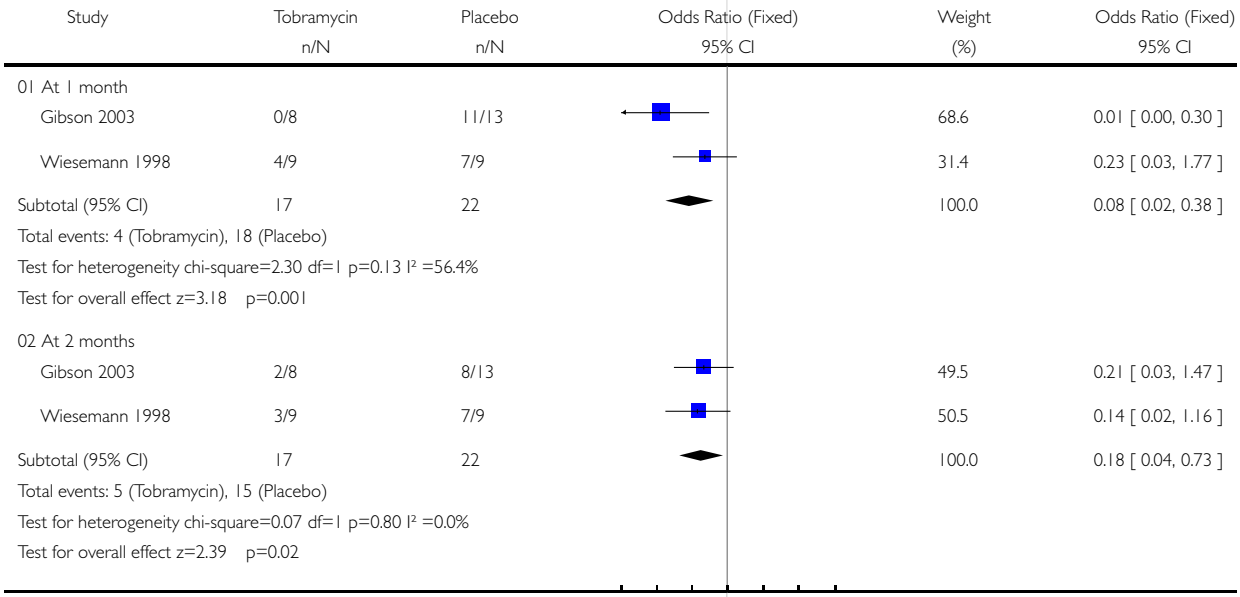



**Analysis 01.05. Comparison 01 Inhaled tobramycin versus placebo, Outcome 05 Positive respiratory culture for P. aeruginosa (combined) - worst case**

Review: Antibiotic strategies for eradicating Pseudomonas aeruginosa in people with cystic fibrosis

Comparison: 01 Inhaled tobramycin versus placebo

Outcome: 05 Positive respiratory culture for P. aeruginosa (combined) - worst case

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| Study | Tobramycin n/N | Placebo n/N | Odds Ratio (Fixed) 95% CI | Weight (%) | Odds Ratio (Fixed) 95% CI |
|---|---|---|---|---|---|
| 03 At 3 months | | | | | |
| Wiesemann 1998 | 2/9 | 4/9 | | 100.0 | 0.36 [ 0.05, 2.77 ] |
| Subtotal (95% CI) | 9 | 9 | | 100.0 | 0.36 [ 0.05, 2.77 ] |
| Total events: 2 (Tobramycin), 4 (Placebo) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect z=0.98 p=0.3 | | | | | |
| 04 At 6 months | | | | | |
| Wiesemann 1998 | 1/9 | 4/9 | | 100.0 | 0.16 [ 0.01, 1.83 ] |
| Subtotal (95% CI) | 9 | 9 | | 100.0 | 0.16 [ 0.01, 1.83 ] |
| Total events: 1 (Tobramycin), 4 (Placebo) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect z=1.48 p=0.1 | | | | | |
| 05 At 12 months | | | | | |
| Wiesemann 1998 | 2/9 | 4/9 | | 100.0 | 0.36 [ 0.05, 2.77 ] |
| Subtotal (95% CI) | 9 | 9 | | 100.0 | 0.36 [ 0.05, 2.77 ] |
| Total events: 2 (Tobramycin), 4 (Placebo) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect z=0.98 p=0.3 | | | | | |

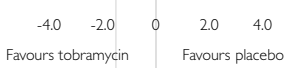

### Analysis 01.06. Comparison 01 Inhaled tobramycin versus placebo, Outcome 06 Change in weight from baseline

Review: Antibiotic strategies for eradicating Pseudomonas aeruginosa in people with cystic fibrosis

Comparison: 01 Inhaled tobramycin versus placebo

Outcome: 06 Change in weight from baseline

| Study | Tobramycin N | Tobramycin Mean(SD) | Placebo N | Placebo Mean(SD) | Weighted Mean Difference (Fixed) 95% CI | Weighted Mean Difference (Fixed) 95% CI |
|---|---|---|---|---|---|---|
| 01 At 1 month | | | | | | |
| Gibson 2003 | 8 | 0.30 (0.50) | 13 | 0.10 (0.60) | | 0.20 [ -0.28, 0.68 ] |
| 02 At 2 months | | | | | | |
| Gibson 2003 | 8 | 0.40 (0.50) | 13 | 0.30 (0.60) | | 0.10 [ -0.38, 0.58 ] |



### Analysis 01.07. Comparison 01 Inhaled tobramycin versus placebo, Outcome 07 Adverse events

Review: Antibiotic strategies for eradicating Pseudomonas aeruginosa in people with cystic fibrosis

Comparison: 01 Inhaled tobramycin versus placebo

Outcome: 07 Adverse events

| Study | Tobramycin n/N | Placebo n/N | Odds Ratio (Fixed) 95% CI | Odds Ratio (Fixed) 95% CI |
|---|---|---|---|---|
| 01 Cough | | | | |
| Gibson 2003 | 7/8 | 12/13 | | 0.58 [ 0.03, 10.86 ] |


### Analysis 01.08. Comparison 01 Inhaled tobramycin versus placebo, Outcome 08 Change in modified Shwachmann score from baseline

Review: Antibiotic strategies for eradicating Pseudomonas aeruginosa in people with cystic fibrosis

Comparison: 01 Inhaled tobramycin versus placebo

Outcome: 08 Change in modified Shwachmann score from baseline

| Study | Tobramycin N | Tobramycin Mean(SD) | Placebo N | Placebo Mean(SD) | Weighted Mean Difference (Fixed) 95% CI | Weighted Mean Difference (Fixed) 95% CI |
|---|---|---|---|---|---|---|
| 01 At 1 month | | | | | | |
| Gibson 2003 | 8 | 0.50 (2.40) | 13 | -0.80 (6.00) | | 1.30 [ -2.36, 4.96 ] |
| 02 At 2 months | | | | | | |
| Gibson 2003 | 8 | 2.40 (3.40) | 13 | -1.40 (6.00) | | 3.80 [ -0.22, 7.82 ] |

## Analysis 02.01. Comparison 02 Oral ciprofloxacin and inhaled colistin versus no treatment, Outcome 01 Proportion colonised with P. aeruginosa

Review: Antibiotic strategies for eradicating Pseudomonas aeruginosa in people with cystic fibrosis

Comparison: 02 Oral ciprofloxacin and inhaled colistin versus no treatment

Outcome: 01 Proportion colonised with P. aeruginosa