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# Once-daily versus multiple-daily dosing with intravenous aminoglycosides for cystic fibrosis (Review)

**Smyth AR, Bhatt J**

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# Once-daily versus multiple-daily dosing with intravenous aminoglycosides for cystic fibrosis

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## A B S T R A C T

**Background**

People with cystic fibrosis, who are chronically colonised with the organism *Pseudomonas aeruginosa*, often require multiple courses of intravenous aminoglycoside antibiotics for the management of pulmonary exacerbations. The properties of aminoglycosides suggest that they could be given in higher doses less often.

**Objectives**

To assess the effectiveness and safety of once-daily versus multiple-daily dosing of intravenous aminoglycoside antibiotics for the management of pulmonary exacerbations in cystic fibrosis.

**Search methods**

We searched the Cystic Fibrosis Specialist Register held at the Cochrane Cystic Fibrosis and Genetic Disorders Group's editorial base, comprising references identified from comprehensive electronic database searches, handsearching relevant journals and handsearching abstract books of conference proceedings.

Date of the most recent search: 25 November 2013.

**Selection criteria**

All randomised controlled trials, whether published or unpublished, in which once-daily dosing of aminoglycosides has been compared with multiple-daily dosing in terms of efficacy or toxicity or both, in people with cystic fibrosis.

**Data collection and analysis**

The two authors independently selected the studies to be included in the review and assessed the risk of bias of each study. Data were independently extracted by each author. Authors of the included studies were contacted for further information. As yet unpublished data were obtained for one of the included studies.

**Main results**

Fifteen studies were identified for possible inclusion in the review. Four studies reporting results from a total of 328 participants were included in this review. All studies compared once-daily dosing with thrice-daily dosing. One study had a low risk of bias for all criteria assessed; the remaining three included studies had a high risk of bias from blinding, but for other criteria were judged to have either an unclear or a low risk of bias.

There was no significant difference between treatment groups in: forced expiratory volume at one second, mean difference 0.33 (95% confidence interval -2.81 to 3.48); forced vital capacity, mean difference 0.29 (95% confidence interval -6.58 to 7.16); % weight for height, mean difference -0.82 (95% confidence interval -3.77 to 2.13); body mass index, mean difference 0.00 (95% confidence interval -0.42 to 0.42); or in the incidence of ototoxicity, relative risk 0.56 (95% confidence interval 0.04 to 7.96). The percentage change in creatinine significantly favoured once-daily treatment in children, mean difference -8.20 (95% confidence interval -15.32 to -1.08), but showed no difference in adults, mean difference 3.25 (95% confidence interval -1.82 to 8.33).

**Authors' conclusions**

Once- and three-times daily aminoglycoside antibiotics appear to be equally effective in the treatment of pulmonary exacerbations of cystic fibrosis. There is evidence of less nephrotoxicity in children.

## P L A I N   L A N G U A G E   S U M M A R Y

**Giving aminoglycoside antibiotics intravenously once daily compared to giving them several times per day in people with cystic fibrosis**

Cystic fibrosis is a serious genetic disorder which affects the lungs and the exocrine glands (sweat glands and others). Most people with cystic fibrosis develop persistent lung infections and they may receive frequent courses of intravenous antibiotics. Giving the antibiotics once per day reduces the cost and the time involved, compared to giving several doses per day. This review includes four trials with a total of 328 people. All the trials compared once-a-day dosing with three times-a-day dosing. The review found that giving the antibiotics once per day was just as good at treating lung infections in people with cystic fibrosis as giving them more frequently. The review also found that giving the antibiotics once per day appeared to be less toxic to the kidneys in children. There were no differences between the different treatments for other outcomes. While once-daily treatment can be just as effective and more convenient than three-times daily treatment, we recommend further studies to look at the long-term safety of this treatment schedule.

## B A C K G R O U N D

### Description of the condition

Cystic fibrosis (CF) is the most common serious autosomal recessive genetic disorder in the Caucasian population. It is estimated to occur in 1 in 2500 births and about one person in 25 carries the defective gene. Progressive pulmonary deterioration is the principal cause of CF-related mortality and morbidity. People with CF have an increased susceptibility to chronic lung infections, especially with *Pseudomonas aeruginosa* (*P. aeruginosa*) (Davis 1996). Most antibiotics used for treatment are administered intravenously and given for about two weeks (David 1986).

### Description of the intervention

People with CF receive frequent and repeated courses of intravenous antibiotics throughout their lifetime. The current recommendation for intravenous antibiotic treatment of pulmonary exacerbations in people colonised with *P. aeruginosa* is a combination of two antibiotics with different mechanisms of action (CF Trust 2009; Flume 2009). Combination antibiotic therapy, which has been shown to produce a synergistic effect in vitro (Weiss 1995), may limit the emergence of antibiotic resistant strains of *P. aeruginosa* (Cheng 1996). However, single versus combination intravenous antibiotic therapy in CF is the subject of another Cochrane review which found no clear evidence of benefit for combination therapy, though there was a trend to less antibiotic resistance (Elphick 2005). Previously, the majority of people with CF re-

ceived an aminoglycoside, as part of their intravenous antibiotic regimen, most commonly given in three divided doses (Tan 2002). However a recent survey of prescribing practices in the UK has shown that a once-daily regimen is usual practice in 86% of UK CF centres (Smyth 2013).

## How the intervention might work

Aminoglycosides demonstrate concentration dependent killing and the post-antibiotic effect (Spivey 1992). Concentration dependent killing means that the bactericidal action of aminoglycosides is related to the peak concentration of antibiotic achieved. Greater bactericidal effect occurs at concentrations exceeding the minimum inhibitory concentration (MIC). The post-antibiotic effect is a phenomenon in which the bactericidal action of the aminoglycoside continues even after the antibiotic has been cleared and its concentration has fallen below the MIC.

These pharmacological properties suggest that aminoglycosides could be given in higher concentrations with an extended dosing interval. There have been many randomised controlled trials (RCTs) comparing once-daily with thrice-daily aminoglycoside treatment in participants without CF and these have been the subject of a meta-analysis (Barza 1996). This study reports that once-daily dosing is as effective, and perhaps safer, than the standard thrice-daily dosing regimen. However, the results of these studies cannot be directly extrapolated to the CF population, as plasma clearance is more rapid in people with CF (de Groot 1987). Furthermore, people with CF are vulnerable to cumulative side effects from antibiotics as they receive recurrent and prolonged courses of treatment.

## Why it is important to do this review

The use of intravenous aminoglycosides is limited by their well-recognised toxicity, affecting the inner ear and the kidney. Before any change in dosing interval can be recommended, the relative toxicity of once and multiple-daily dosing must be evaluated.

Once-daily aminoglycoside dosing has major advantages to people with CF and their families, especially if they receive their antibiotics at home. In addition there are cost implications in reducing the use of consumables and the time taken to prepare and deliver antibiotics.

This is an updated version of the previously published review (Smyth 2000; Smyth 2006; Smyth 2010; Smyth 2012).

## OBJECTIVES

To assess the efficacy and safety of once-daily versus multiple-daily intravenous aminoglycoside dosing in the treatment of pulmonary exacerbations in CF. The hypotheses will be tested that once-daily intravenous aminoglycoside dosing is:

• as effective as multiple-daily dosing (as measured by the change in lung function over a course of antibiotic treatment)

• no more toxic than multiple-daily dosing (as measured by renal and auditory toxicity).

## METHODS

## Criteria for considering studies for this review

### Types of studies

RCTs, whether published or unpublished, and of parallel or crossover design. Studies using inappropriate forms of randomisation, such as alternate allocation, will not be considered. Where it is not clear, from the paper or the abstract, whether participants have been randomised appropriately, the authors will be contacted directly.

### Types of participants

People with CF, who have been diagnosed by sweat test or genetic testing or both, regardless of age or clinical severity.

### Types of interventions

Once-daily dosing compared to multiple-daily dosing of intravenous aminoglycoside antibiotics for pulmonary exacerbations in CF.

Where possible, a pulmonary exacerbation will be defined as four or more of the following 12 symptoms or signs: change in sputum; new or increased haemoptysis; increased cough; increased dyspnoea; malaise, fatigue or lethargy; temperature above 38º C; anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical examination of the chest; decrease in pulmonary function by 10% or more from a previously recorded value; radiographic changes indicative of a pulmonary infection (Fuchs 1994). Where there is no such definition of an exacerbation we will use the definition provided in the trial report.

### Types of outcome measures

#### Primary outcomes

1. Lung function measurements
    i) forced expiratory volume at one second ($FEV_1$)

ii) forced vital capacity (FVC)

iii) forced expiratory flow in mid expiration ($FEF_{25-75\%}$)

We compared the change in values from the start of antibiotic treatment with those taken at the end of treatment.

### Secondary outcomes

1. Nutritional status
   i) weight gain
   ii) body mass index (BMI)
   iii) z scores
2. Time to first exacerbation requiring intravenous antibiotics
3. Antibiotic resistance patterns following treatment
4. Ototoxicity (defined as an increase in auditory threshold of 20 dB or more over any frequency range)
5. Nephrotoxicity (comparison of the percentage change in creatinine over baseline)
6. Possible adverse events associated with aminoglycoside infusion (e.g. vestibular changes, tinnitus, anaphylaxis)
7. Quality of life measures (if well-validated scores are available e.g. Cystic Fibrosis Quality of Life - Revised (CFQ-R) (Quittner 2009))

## Search methods for identification of studies

### Electronic searches

Relevant studies were identified from the Group's Cystic Fibrosis Trials Register using the terms: (intravenous OR not stated) AND (tobramycin OR amikacin OR gentamicin OR netilmicin OR sisomicin OR neomycin).

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

Date of the most recent search of the Group's CF Trials Register: 25 November 2013.

## Data collection and analysis

### Selection of studies

Two authors independently selected studies for inclusion in the review. They resolved any disagreements by negotiation.

### Data extraction and management

Two authors independently extracted data and resolved any disagreements by negotiation. The authors collected data for the outcome events listed above.

### Assessment of risk of bias in included studies

Two authors assessed the risk of bias in the included studies by following the domain-based assessment as recommended in The Cochrane Handbook for Systematic Reviews of Interventions ( Higgins 2011). They assessed the following domains:

- sequence generation;
- allocation concealment;
- blinding (if it took place and who was blinded);
- incomplete outcome data;
- selective reporting;
- other sources of bias.

On the basis of these assessments, the authors attributed a high or low or unclear risk of bias for each domain to each study. For example, if the randomisation sequence was generated using random number tables or a computer, there would be a low risk of bias for this domain.

### Measures of treatment effect

For dichotomous variables (such as adverse events) the authors used risk ratio and calculated a pooled estimate of treatment effect across all studies. For continuous variables, such as lung function, the authors pooled the treatment effect across all studies, using the mean difference.

### Unit of analysis issues

When conducting a meta-analysis combining results from crossover studies we planned to use the methods recommended by Elbourne (Elbourne 2002). One of the included trials was of crossover design; however, we were not able to obtain first-arm data and have therefore only reported data from this study narratively. If full data from cross-over studies become available, the authors will use first-arm data, where possible, but only consider the efficacy outcomes.

### Dealing with missing data

If data were missing, the authors attempted to contact the study investigators for clarification.

### Assessment of heterogeneity

When sufficient studies are included in the review, the authors will test for heterogeneity between study results using the $I^2$ statistic (Higgins 2003). This measure describes the percentage of the variability in effect estimates that is due to heterogeneity rather than chance. The authors plan to use the following interpretation of the statistic:

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

### Assessment of reporting biases

The authors planned to compare original study protocols to final published papers to identify any selective reporting. If the original study protocols were not available, the authors examined the final published papers to identify any outcomes stated as being measured, but not reported in the study results.

We planned to assess publication bias by visual inspection of funnel plots, if we had been able to include and combine at least 10 studies.

### Data synthesis

We have analysed the included data using a fixed-effect model. If investigation of the studies indicates an at least substantial level of heterogeneity (over 50% using the $I^2$ statistic) among those included in an analysis, the authors will use a random-effects model.

### Subgroup analysis and investigation of heterogeneity

Furthermore, if there is a substantial or considerable level of heterogeneity (as defined above) identified and sufficient studies included in the review, the authors will perform subgroup analysis, looking at the pre-defined subgroups of children and adults.

### Sensitivity analysis

Sensitivity analysis will be undertaken if there is risk of small study effects and if sufficient studies are included in the review.

# R E S U L T S

## Description of studies

### Results of the search

Fifteen studies with publications were found by the searches. Four studies were included in the review; 10 studies were excluded from the review; one cross-over study is currently listed under 'Studies awaiting classification' while we seek first-arm data from the study investigators (Al Ansari 2006). We are aware of one study, previously listed as ongoing in this review which was a multicentre RCT of once-daily versus thrice-daily dosing of tobramycin in the USA funded by the CF Foundation, treating participants with tobramycin (12 mg/kg/day) plus the usual beta-lactam, given either once daily or thrice daily (Tureen 2001). This study failed to recruit a sufficient number of participants and was terminated without any data being made available.

Please see the PRISMA diagram illustrating the flow of studies in the review process (Figure 1).

**Figure 1.   Study flow diagram.**
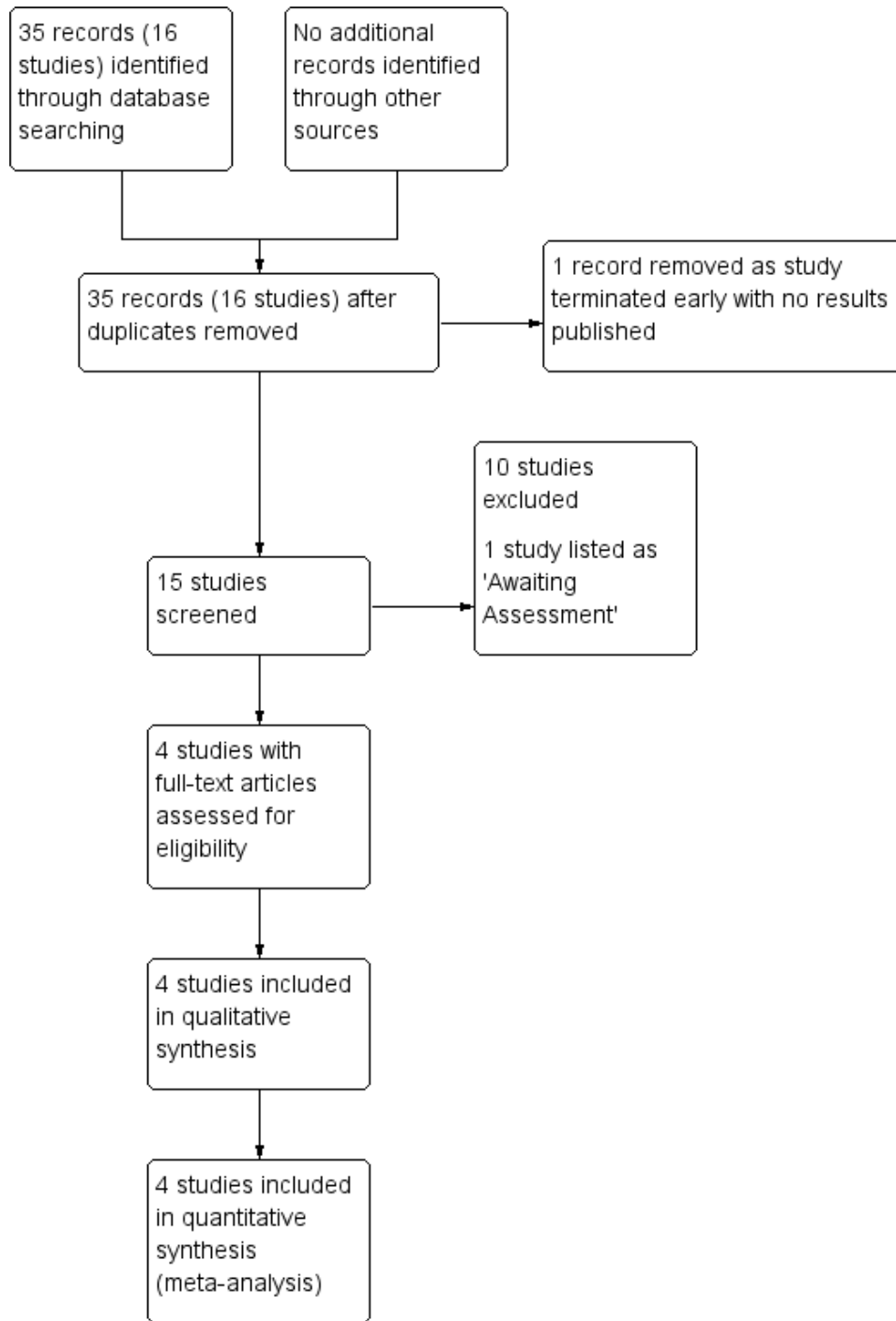
### Included studies

Four studies, with a total of 328 participants completing treatment per protocol, fulfilled the inclusion criteria for this review (Riethmueller 2009; Smyth 2005; Vic 1998; Whitehead 2002). The four studies evaluated the efficacy and toxicity of once versus thrice-daily dosing of intravenous tobramycin for a pulmonary exacerbation. One study also evaluated the use of continuous ceftazidime infusions, which is beyond the remit of this review (Riethmueller 2009). No studies were found, which compared once-daily aminoglycoside dosing with any other frequency of dosing. All studies were unblinded, apart from one (Smyth 2005). One study was cross-over in design (Riethmueller 2009), the remaining three studies were parallel (Smyth 2005; Vic 1998; Whitehead 2002). Data were recorded at the end of the treatment course with no measures of longer-term outcomes.

The first study included 22 participants: 12 in the once-daily group (8 male) age range 5.6 years to 19.3 years and 10 in the thrice-daily group (6 male) age 7.4 years to 17.2 years. (Vic 1998). The study was a randomised parallel group study but was not blinded. The total daily dose of tobramycin in each group was 15 mg/kg/day. Tobramycin was given in combination with ceftazidime, 200 mg/kg/day. Participants received 14 days of antibiotic treatment and adjuvant treatment remained unchanged. Outcome measures were calculated as mean change with standard deviation and included lung function, nutritional status and inflammatory markers measured at the start and end of treatment. An assessment of adverse effects was measured by comparing cochlear and renal indices evaluated at the start and end of treatment.

The second study studied adults (Whitehead 2002). A total of 60 participants were studied, of whom 49 completed the study: 30 in the once-daily group (16 male) age range 15 years to 47 years and 19 in the thrice-daily group (11 male) age range 16 years to 32 years. The total daily dose in each group was 10 mg/kg/day. Tobramycin was given in combination with a beta-lactam antibiotic, chosen by the clinician (either piperacillin, piperacillin/tazobactam, aztreonam, azlocillin, imipenem, meropenem or ceftazidime). Participants received 12 days of antibiotic treatment and adjuvant treatment remained unchanged. Outcome measures included lung function, nutritional status and inflammatory markers, measured at the start and end of treatment. An assessment of adverse effects was measured by comparing cochlear and renal indices evaluated at the start and end of treatment. Participant preference of treatment regimens was reported, but as this was an unblinded study, this was interpreted with caution. Intention-to-treat analysis has not been performed in this study. Of the 60 participants recruited to the study, 11 were withdrawn: four from the once-daily group and seven from the thrice-daily group. Data are missing from one participant in the thrice-daily group, leaving 18

participants on thrice-daily treatment whose data was analysed. Of those that were withdrawn, eight participants (four on each regimen) developed resistance to tobramycin, two refused to continue on thrice-daily treatment and one (in the thrice-daily group) was withdrawn when an additional drug with nephrotoxic potential was added to the treatment regimen.

The third study has now been published in full (Riethmueller 2009). There were three arms to this study:

- once-daily tobramycin with thrice-daily ceftazidime (Treatment B);
- thrice-daily tobramycin with thrice-daily ceftazidime (Treatment A); and
- once-daily tobramycin with continuous ceftazidime.

The continuous ceftazidime arm was excluded from this review. The design of the study was an open-label, cross-over with a three-month washout period. The total daily dose of tobramycin was 10 mg/kg/day. Thirty-eight participants were treated with Treatment A and Treatment B. Eight participants were lost to follow-up, three of whom were found to be colonized with resistant *P. aeruginosa* strains and were therefore switched from ceftazidime to meropenem. Therefore, 30 patients (20 female, 10 male; mean age 11.2 years, age range 1.7 to 18.1 years) ultimately received both Treatment A and Treatment B and could be analysed; 14 of these received Treatment A first and Treatment B during a subsequent course of intravenous antibiotics.

A further study, included in the review for the first time in 2006, describes the results of a large, double-blind, parallel group, randomised controlled trial of 244 participants (219 of whom completed the study per protocol) (Smyth 2005). As this was an equivalence study, analysis was per protocol. Of those who completed treatment, 107 (63 male) had once-daily treatment (age range 5.1 to 50.4 years) and 112 (68 male) had three-times daily treatment (age range 5.5 to 43.3 years). Once-daily tobramycin was compared with three-times daily dosing. A dose of 10 mg/kg/day of tobramycin was used or, if the participant had received the drug previously, the dose of tobramycin last shown to give therapeutic levels. Treatment was for 14 days and tobramycin was combined with ceftazidime 150 mg/kg/day in three divided doses. Outcome measures were calculated as adjusted mean differences for continuous variables such as $FEV_1$ and creatinine. Changes in inflammatory markers (C reactive protein), clinical score and hearing were reported. Renal function was assessed by the percentage change in creatinine over 14 days and change in concentrations of urinary N-acetyl-beta-D glucosaminidase (NAG), a proximal tubular enzyme. Time to next intravenous antibiotics was also reported.

There were insufficient data to interpret changes in the antibiotic resistance patterns of *P. aeruginosa*.

## Excluded studies

Ten studies were excluded as detailed in the table Characteristics of excluded studies. Three studies were pharmacokinetic papers (Aminimanizani 2002; Burkhardt 2006; Hamner 2006); one study used alternate allocation of treatment (Heininger 1993); one study compared monotherapy to combination therapy (Master 2001); one study was not blinded and measured efficacy on a symptom score (Powell 1983); for one study (published as an abstract) no outcome data were available and it was not clear whether the participants were randomised (Postnikov 2007); one did not include a once-daily arm of treatment (Adeboyeku 2011); the remaining two studies did not compare once-daily dosing with another dosing schedule (Winnie 1991; Wood 1996).

## Risk of bias in included studies

### Allocation

In one study the randomisation schedule was generated using a computer and stratified by centre and adult versus paediatric ( Smyth 2005). In two other studies randomisation tables were used (Vic 1998; Whitehead 2002). All three of these studies were judged to have a low risk of bias from the generation of the randomisation sequence (Smyth 2005; Vic 1998; Whitehead 2002). The fourth study was described as randomised; it was a six-centre study in which three centres randomised with three protocols and three centres randomised with two protocols, but no actual details of the randomisation process were given, so this study was therefore judged to have an unclear risk of bias (Riethmueller 2009).

In one study, central randomisation was used and the study was judged to have a low risk of bias for allocation concealment (Smyth 2005). Allocation concealment was not clear from the published account in three of the studies, hence there was an unclear risk of bias (Riethmueller 2009; Vic 1998; Whitehead 2002). Of note, one study was a six-centre study in which three centres randomised with three protocols and three centres randomised with two protocols (Riethmueller 2009).

### Blinding

Only one study used a masked placebo and thus was judged to have a low risk of bias (Smyth 2005). Three of the four studies were unblinded to treatment regimen (Riethmueller 2009; Vic 1998; Whitehead 2002). Both review authors recognised that this may have introduced bias, but decided to include the studies in the review, whilst making this explicit.

### Incomplete outcome data

We contacted the authors of the Vic study, who informed us that no participants withdrew or were withdrawn from the study, leading to a low risk of bias (Vic 1998). A per-protocol analysis was performed as the primary analysis in another study as this was an equivalence study (Smyth 2005). This is the appropriate methodology for an equivalence study and does not increase risk of bias. Intention-to-treat analysis was not performed in two studies (Riethmueller 2009; Whitehead 2002). In the Riethmueller study there is an unclear risk of bias as a per-protocol analysis was performed of 30 of 38 participants (Riethmueller 2009). Likewise, in the Whitehead study there is an unclear risk of bias as only 49 participants were studied out of the 60 who were recruited and there is no further information on the remaining 11 participants (Whitehead 2002).

### Selective reporting

We were able to compare one study with its previously published protocol and we found no evidence of selective reporting and hence judged this study to have a low risk of bias (Smyth 2005). We were unable to compare any protocols to final publications for any of the other three included studies. We therefore judge there to be an unclear risk of bias from selective reporting in these three studies (Riethmueller 2009; Vic 1998; Whitehead 2002).

### Other potential sources of bias

We were not able to identify any other potential source of bias in the included studies.

## Effects of interventions

For each outcome measure, the number of participants differed due to incomplete data. Meta-analysis of pooled data was not possible for the nutritional status outcome measures.

### Primary outcomes

#### 1. Lung function

#### a. Mean percentage change in $FEV_1$

This result was reported in three studies with a total of 289 participants (Smyth 2005; Vic 1998; Whitehead 2002). The mean difference for change in $FEV_1$ (% predicted) was 0.33 (95% confidence interval (CI) -2.81 to 3.48). There was no significant difference between antibiotic regimens in the increment in $FEV_1$ seen with antibiotic treatment.

### b. Mean percentage change in FVC

This result was reported in two studies with a total of 70 participants (Vic 1998; Whitehead 2002). There was no significant difference between antibiotic regimens in the increment in FVC (% predicted) seen after treatment. The mean difference for change in FVC (% predicted) was 0.29 (95%CI -6.58 to 7.16).

### c. Mean percentage change in $FEF_{25-50\%}$

This result was only reported in one study with 48 participants (Whitehead 2002). Again there was no difference between regimens. The mean difference for change in $FEF_{25-50}$ (% predicted) was -1.24 (95%CI -7.78 to 5.30).

### Secondary outcomes

### 1. Nutritional status

The mean change in weight/height percentage was assessed in one study with 22 participants (Vic 1998). The mean difference for this outcome was -0.82 (95% CI -3.77 to 2.13), which suggests that the mean increase in weight/height percentage was similar in both the once-daily and thrice-daily groups.

The mean change in body mass index (BMI) was assessed in one study with 41 participants (Whitehead 2002). The mean difference for the mean change in BMI was 0.00 (95% CI -0.42 to 0.42), this suggests that the mean increase in BMI was similar in both the once-daily and thrice-daily groups.

### 2. Time to first exacerbation (requiring intravenous antibiotics) after treatment

This was available for one study (Smyth 2005). Data for the time to next course of intravenous antibiotics were available for 113 participants (56 on once daily, 57 on thrice daily). Median time was 131 days (95% CI 76 to 186) for once daily and 168 days (95% CI 34 to 302) for three-times daily treatment (P = 0·48).

### 3. Resistance patterns following treatment

None of the included studies reported this outcome.

### 4. Ototoxicity

The investigators in the Riethmueller study performed audiograms in all patients, after treatment, and found no evidence of ototoxicity in any patient (Riethmueller 2009). Audiograms were also performed in the Vic study and the results were reported but did not show any instances of ototoxicity (Vic 1998). In the Whitehead study, one participant in each group was reported as experiencing ototoxicity (Whitehead 2002). In the Smyth study no participant showed deterioration in audiograms from days 1 to 14 of treatment (Smyth 2005). Two participants (one on each regimen) reported acute dizziness and were withdrawn from the study. In both participants, symptoms resolved without treatment. Therefore, there was no significant difference in the relative risk of developing ototoxicity between once and thrice-daily dosing, risk ratio 0.56 (95% CI 0.04 to 7.96) in the four studies considered.

### 5. Nephrotoxicity

The measure of nephrotoxicity, which was pre-defined in the protocol, was the percentage increase in serum creatinine from baseline. Two studies reported this outcome (Smyth 2005; Whitehead 2002). When data from the two studies were combined, there was a non-significant trend towards a greater rise in creatinine with once-daily treatment in adults, mean difference 3.25 (95% CI -1.82 to 8.33). In contrast, in children, there was a significantly smaller rise in creatinine with once-daily treatment, mean difference -8.20 (95% CI -15.32 to -1.08). Two studies measured N-acetyl-ß-D glucosaminidase (NAG), a proximal tubular enzyme (Smyth 2005; Riethmueller 2009). This was measured at baseline and after 14 days of treatment in both studies. A significantly smaller rise (less toxicity) was seen with once daily for adults and children combined in the Smyth study (Smyth 2005). Riethmueller measured both urinary concentrations of NAG and $\alpha$-1-microglobulin (Riethmueller 2009). Both increased significantly during treatment but there was no difference between regimens. The Vic study uses creatinine clearance, lysozymuria and microglobulinuria to assess nephrotoxicity; for microglobulinuria there was a difference between groups on day 14 in favour of once-daily treatment (Vic 1998).

Therefore, using the pre-defined outcome measure of percentage change in creatinine over baseline, there was a significant difference in favour of once-daily treatment in children.

### 6. Adverse events associated with aminoglycoside infusion

None of the included studies reported this outcome.

### 7. Quality of life

None of the included studies reported this outcome.

# DISCUSSION

We set out to test the hypotheses that once-daily dosing of aminoglycosides is as effective and no more toxic than multiple-daily dosing. Four studies met the inclusion criteria for this review (a total of 320 participants contributed data). All studies used tobramycin as the aminoglycoside of choice, dosed at either 10 mg/kg/day or 15 mg/kg/day or the dose last known to give satisfactory levels.

In all studies, once-daily dosing was compared with thrice-daily dosing. Whilst the three studies used the same combination of antibiotics for all participants (Riethmueller 2009; Smyth 2005; Vic 1998), the fourth study used different beta-lactam antibiotics in combination with tobramycin (Whitehead 2002). Therefore, the individual effects of different beta-lactams in this study are unknown.

This systematic review has demonstrated no significant difference in efficacy, measured by improvement in lung function, between once-daily and thrice-daily dosing of tobramycin. The combined number of participants (289) for the outcome measure of lung function (as measured by $FEV_1$) give sufficient statistical power to demonstrate a true difference between regimens of 4% predicted, if one were present. However, evidence of no greater risk of toxicity between once-daily and thrice-daily dosing is encouraging. This systematic review has shown that the relative risk of developing ototoxicity between the two treatment groups was not significant. However, the results of studies of nephrotoxicity suggested that the rise in creatinine was significantly less in children with once-daily treatment. In adults the effect was in favour of three-times daily treatment, but was not significant. The magnitude of the change in creatinine was much less than the threshold for clinical renal impairment but could be clinically important, if the effect were cumulative with subsequent courses of treatment. Long-term safety studies (which can be open label and non-randomised) comparing the two regimens are therefore desirable. Acute renal failure has been reported in association with aminoglycoside use in CF and the prevalence is 100 times higher in children with CF than in the general population (Bertenshaw 2007). The increased risk of renal failure is associated with gentamicin use, but not with tobramycin (Smyth 2008). Chronic exposure to aminoglycosides has been shown to be associated with reduced creatinine clearance (Al Aloul 2005).

When comparing once-daily and multiple-daily dosing, the expectation may be that the new treatment (once-daily dosing) is better than the standard (thrice-daily dosing). In fact, it is more likely that the new treatment will match the efficacy of the standard treatment but have advantages perhaps in safety, convenience and cost. Therefore, the most useful comparison of once-daily and multiple-daily dosing is one using the methodology for an equivalence study, as suggested in a paper by Jones (Jones 1996). The TOPIC study employed this study design (Smyth 2005).

Finally, in a chronic disorder such as CF, long-term measures of health status are important. There was found to be no difference in time to next exacerbation in one study (Smyth 2005). Any differences in long-term benefits of improved lung function and nutritional status between the two groups is unknown. Further longitudinal studies are desirable measuring: cumulative effect on renal function; cumulative ototoxic effect; time to the next pulmonary exacerbation; quality of life and longitudinal changes in the antibiotic sensitivity of *P. aeruginosa*.

# AUTHORS' CONCLUSIONS

## Implications for practice

This review has demonstrated no difference in efficacy between the two treatment regimens, although once daily appears less nephrotoxic in children. Once-daily aminoglycoside treatment for pulmonary exacerbations of CF may be adopted as it is more convenient for people with CF. For further details of once-daily aminoglycoside treatment the authors would like to refer readers to the document "Antibiotic Treatment for Cystic Fibrosis" (CF Trust 2009).

## Implications for research

Long-term safety studies of once-daily treatment are desirable.

# ACKNOWLEDGEMENTS

# REFERENCES

## References to studies included in this review

**Riethmueller 2009** *{published data only}*

* Riethmueller J, Ballmann M, Schroeter TW, Franke P, von Butler R, Claass A, et al.Tobramycin once- vs thrice-daily for elective intravenous antipseudomonal therapy in pediatric cystic fibrosis patients. *Infection* 2009;**37**(5): 424–31. [CFGD Register: PI154f]

Riethmueller J, Busch A, Franke P, Ziebach R, von Butler R, Stern M. Pharmacodynamic variation of intravenous antibiotic treatment with ceftazidime and tobramycin in CF-patients is equally effective [abstract]. 13th International Cystic Fibrosis Congress; 2000 June 4-8; Stockholm, Sweden. 2000:166.

Riethmueller J, Franke P, Schroeter TW, Claass A, Busch A, Ziebach R, et al.Optimized intravenous antibiotic treatment with ceftazidime (thrice-daily vs. continuous) and tobramycin (thrice vs. once-daily) in CF patients [abstract]. Abstracts of the 24th European Cystic Fibrosis Conference; 2001 June 6-9; Vienna, Austria. 2001:P192.

Riethmueller J, Junge S, Schroeter TW, Kuemmerer K, Franke P, Ballmann M, et al.Continuous vs thrice-daily ceftazidime for elective intravenous antipseudomonal therapy in cystic fibrosis. *Infection* 2009;**37**(5):418–23. [CFGD Register: PI154e]

Schroeter T, Eggert P, Riethmueller J, Stern M, Claass A. Acute-phase nephrotoxicity of tobramycin in CF patients: a prospective randomized trial of once- versus thrice-daily dosing. *Pediatric Pulmonology* 2002;**34**(Suppl 24):289.

Schroeter TW, Eggert P, Riethmueller J, Stern M, Claass A. A prospective randomized trial on the nephrotoxicity of thrice-daily versus once-daily tobramycin in cystic fibrosis patients [abstract]. Abstracts of the 24th European Cystic Fibrosis Conference; 2001 June 6-9; Vienna, Austria. 2001: P190.

**Smyth 2005** *{published data only}*

Mulheran M, Hyman-Taylor P, Tan KH, Lewis S, Stableforth D, Knox A, et al.Absence of cochleotoxicity measured by standard and high-frequency pure tone audiometry in a trial of once- versus three-times-daily tobramycin in cystic fibrosis patients. *Antimicrobial Agents and Chemotherapy* 2006;**50**(7):2293–9.

Smyth A, Docherty C, Govan J, Tan K, Hyman-Taylor P, Stableforth D, et al.Once daily tobramycin achieves cidal levels against Pseudomonas aeruginosa in patients with cystic fibrosis [abstract]. *Thorax* 2001;**56**(Suppl 3):iii84.

* Smyth A, Tan K H-V, Hyman-Taylor P, Mulheran M, Lewis S, Stableforth D, et al.Once vs. three times daily regimens of tobramycin treatment for pulmonary exacerbations of cystic fibrosis - the TOPIC study: a randomised controlled trial. *Lancet* 2005;**365**(9459): 573–8.

Smyth A, Tan K, Hyman-Taylor P, Mulheran M, Lewis S, Stableforth D, et al.A randomised controlled trial of once vs three times daily tobramycin for pulmonary exacerbations

of cystic fibrosis [abstract]. Pediatric Pulmonology. 2003, issue Suppl 25:292.

Touw DJ, Knox AJ, Smyth A. Population pharmacokinetics (PK) of tobramycin administered thrice daily (TD) and once daily (OD) in children and adults with CF [abstract]. *Journal of Cystic Fibrosis* 2007;**6**(Suppl 1):S16.

Touw DJ, Knox AJ, Smyth A. Population pharmacokinetics of tobramycin administered thrice daily and once daily in children and adults with cystic fibrosis. *Journal of Cystic Fibrosis* 2007;**6**(5):327–33.

VandenBussche HL, Klepser ME. Single daily tobramycin dosing in cystic fibrosis: is it better for the patients or the bugs [comment]. *Lancet* 2005;**365**:547–8.

**Vic 1998** *{published data only}*

Canis F, Trivier D, Vic P, Ategbo S, Turck D, Husson MO. Comparison of the pharmacokinetics of tobramycin administered in a single daily dose or in three doses in cystic fibrosis [Comparaison de la pharmacocinetique de la tobramycine administree en dose unique journaliere ou en trois doses dans la mucoviscidose]. *Pathologie-biologie* 1998; **46**(6):449–51.

* Vic P, Ategbo S, Turck D, Husson MO, Launay V, Loeuille GA, et al.Efficacy, tolerance, and pharmacokinetics of once daily tobramycin for pseudomonas exacerbations in cystic fibrosis. *Archives of Disease in Childhood* 1998;**78**(6):536–9.

Vic P, Ategbo S, Turck D, Husson MO, Launay V, Loueille GA, et al.Efficacy, tolerance and pharmokinetics of once-daily (OD) versus thrice-daily (TD) Tobramycine (TBM) for Pseudomonas aeruginosa (PA) pulmonary exacerbations [abstract]. *Pediatric Pulmonology* 1996;**22**(Suppl 13):293.

**Whitehead 2002** *{published and unpublished data}*

Watson A, Whitehead A, Conway SP, Etherington C. Efficacy and safety of once daily tobramycin in treating acute respiratory exacerbations in adult patients [abstract]. *Pediatric Pulmonology* 1999;**28**(Suppl 19):262–3.

* Whitehead A, Conway SP, Etherington C, Caldwell NA, Setchfield N, Bogle S. Once-daily tobramycin in the treatment of adult patients with cystic fibrosis. *European Respiratory Journal* 2002;**19**(2):303–9.

Whitehead A, Conway SP, Etherington C, Dave J. Efficacy and safety of once daily tobramycin in treating acute respiratory exacerbations in adult patients [abstract]. *The Netherlands Journal of Medicine* 1999;**54**(Suppl):S36–37.

## References to studies excluded from this review

**Adeboyeku 2011** *{published data only}*

Adeboyeku D, Jones AL, Hodson ME. Twice vs three-times daily antibiotics in the treatment of pulmonary exacerbations of cystic fibrosis. *Journal of Cystic Fibrosis* 2011;**10**(1):25–30. [CFGD Register: PI243]

**Aminimanizani 2002** *{published data only}*

* Aminimanizani A, Beringer PM, Kang J, Tsang L, Jelliffe RW, Shapiro BJ. Distribution and elimination of tobramycin administered in single or multiple daily doses in

adult patients with cystic fibrosis. *Journal of Antimicrobial Chemotherapy* 2002;**50**(4):553–9.

Tsang L, Aminimanizani A, Beringer PM, Jelliffe R, Shapiro B. Pharmacokinetics of once-daily tobramycin in adult cystic fibrosis patients [abstract]. *Pediatric Pulmonology* 2000;**30**(Suppl 20):284.

**Burkhardt 2006** *{published data only}*
Burkhardt O, Lehmann C, Madabushi R, Kumar V, Derendorf H, Welte T. Once-daily tobramycin in cystic fibrosis: better for clinical outcome than thrice-daily tobramycin but more resistance development?. *Journal of Antimicrobial Chemotherapy* 2006;**58**(4):822–9.

**Hamner 2006** *{published data only}*
Hamner JR, Poppy A, Ebaugh S, Reiter PD, Pan Z, Wagener J, Sagel S. Pharmacokinetics and safety of once-daily tobramycin in children with cystic fibrosis. *Pediatric Pulmonology* 2006;**41**(S29):326.

**Heininger 1993** *{published data only}*
Heininger U, Bowing B, Stehr K, Solbach W. Aminoglycosides in patients with mucoviscidosis and pulmonary exacerbation. Comparison of once or three times daily administration [Aminoglykoside bei Patienten mit Mukoviszidose und pulmonaler Exazerbation: Vergleich von Einmal– und Dreimalgabe]. *Klinische Padiatrie* 1993; **205**(1):18–22.

**Master 2001** *{published data only}*
Master V, Martin AJ, Holmes M, Roberts G, Coulthard K, Kennedy D, et al.Once daily tobramycin monotherapy versus conventional antibiotic therapy for the treatment of pseudomonal pulmonary exacerbations in cystic fibrosis patients [abstract]. *European Respiratory Journal* 1997;**10** (Suppl 25):162s.
* Master V, Roberts GW, Coulthard KP, Baghurst PA, Martin A, Roberts ME, et al.Efficacy of Once-daily Tobramycin Monotherapy for Acute Pulmonary Exacerbations of Cystic Fibrosis: A Preliminary Study. *Pediatric Pulmonology* 2001;**31**(5):367–76.

**Postnikov 2007** *{published data only}*
Postnikov SS, Semykin SY, Polikarpova SV, Dubovik LG, Gracheva LA, Sagatelyan RM. A prospective trial on the efficacy and tolerability of twice-daily dosing (TDD) versus once-daily dosing (ODD) amikacin in cystic fibrosis patients [abstract]. *Journal of Cystic Fibrosis* 2007;**6**(Suppl 1):S34.

**Powell 1983** *{published data only}*
Powell SH, Stern RC, Thompson WL. Safety of once daily therapy with high-dose tobramycin [abstract]. 20th Annual Meeting Cystic Fibrosis Club Abstracts; 1979 May 1; Atlanta, Georgia. 1979.
* Powell SH, Thompson WL, Luthe MA, Stern RC, Grossniklaus DA, Bloxham DD, et al.Once-daily vs. continuous aminoglycoside dosing: efficacy and toxicity in animal and clinical studies of gentamicin, netilmicin, and tobramycin. *Journal of Infectious Diseases* 1983;**147**(5): 918–32.

**Winnie 1991** *{published data only}*
Winnie GB, Cooper JA, Witson J, Cowan RG, Mayer D, Lepow M. Comparison of 6 and 8 hourly tobramycin dosing intervals in treatment of pulmonary exacerbations in cystic fibrosis patients. *Pediatric Infectious Disease Journal* 1991;**10**(5):381–6.

**Wood 1996** *{published data only}*
Wood PJ, Ioannides Demos LL, Li SC, Williams TJ, Hickey B, Spicer WJ, et al.Minimisation of aminoglycoside toxicity in patients with cystic fibrosis. *Thorax* 1996;**51**(4):369–73.

## References to studies awaiting assessment

**Al Ansari 2006** *{published data only}*
Al Ansari NA, Foweraker J, Mackeown D, Bilton D. Evaluation of once daily tobramycin versus the traditional three times daily for the treatment of acute pulmonary exacerbations in adult cystic fibrosis patients [abstract]. *Qatar Medical Journal* 2006;**15**(1):34–8. [CFGD Register: PI173b; MEDLINE: 97294575]

## Additional references

**Al Aloul 2005**
Al Aloul M, Miller H, Alapati S, Stockton PA, Ledson MJ, Walshaw MJ. Renal impairment in cystic fibrosis patients due to repeated intravenous aminoglycoside use. *Pediatric Pulmonology* 2005;**39**(1):15–20.

**Barza 1996**
Barza M, Ioannidis JPA, Cappelleri JC, Lau J. Single or multiple daily dosing of aminoglycosides: a meta-analysis. *BMJ* 1996;**312**(7027):338–45.

**Bertenshaw 2007**
Bertenshaw C, Watson AR, Lewis S, Smyth A. Survey of acute renal failure in patients with cystic fibrosis in the UK. *Thorax* 2007;**62**(6):541–5.

**CF Trust 2009**
UK Cystic Fibrosis Trust Antibiotic Group. Antibiotic treatment for cystic fibrosis. Report of the UK Cystic Fibrosis Trust Antibiotic Group 2009.

**Cheng 1996**
Cheng K, Smyth RL, Govan JR, Doherty C, Winstanley C, Denning N, et al.Spread of beta-lactam-resistant Pseudomonas aeruginosa in a cystic fibrosis clinic. *Lancet* 1996;**348**(9028):639–42.

**David 1986**
David TJ. Intravenous antibiotics at home in children with cystic fibrosis. *Journal of the Royal Society of Medicine* 1986; **82**:130–1.

**Davis 1996**
Davis PB, Drumm M, Konstan MW. Cystic fibrosis. *American Journal of Respiratory and Critical Care Medicine* 1996;**154**(5):1229–56.

**de Groot 1987**
de Groot R, Smith AL. Antibiotic pharmacokinetics in cystic fibrosis. Differences and clinical significance. *Clinical Pharmacokinetics* 1987;**13**(4):228–53.

**Elbourne 2002**

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

**Elphick 2005**

Elphick H, Tan A. Single versus combination intravenous antibiotic therapy for people with cystic fibrosis. *Cochrane Database of Systematic Reviews* 2005, Issue 2. [DOI: 10.1002/14651858.CD002007.pub2]

**Flume 2009**

Flume PA, Mogayzel PJ Jr, Robinson KA, Goss CH, Rosenblatt RL, Kuhn RJ, et al.Cystic fibrosis pulmonary guidelines. Treatment of pulmonary exacerbations. *American Journal of Respiratory and Critical Care Medicine* 2009;**180**(9):802–8. [DOI: 10.1164/rccm.200812-1845PP]

**Fuchs 1994**

Fuchs HJ, Borowitz DS, Christiansen DH. Effect of aerosolised recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. *New England Journal of Medicine* 1994;**331**(10):637–42.

**Higgins 2003**

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327** (7414):557–60.

**Higgins 2011**

Higgins JPT, Altman DG (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

**Jones 1996**

Jones B, Jarvis P, Lewis JA, Ebbutt AF. Trials to assess equivalence: the importance of rigorous methods. *BMJ* 1996;**313**(7048):36–9.

**Quittner 2009**

Quittner AL, Modi AC, Wainwright C, Otto K, Kirihara J, Montgomery AB. Determination of the minimal clinically important difference scores for the Cystic Fibrosis Questionnaire-Revised respiratory symptom scale in two populations of patients with cystic fibrosis and chronic Pseudomonas aeruginosa airway infection. *Chest* 2009;**135** (6):1610–8.

**Smyth 2008**

Smyth A, Lewis S, Bertenshaw C, Choonara I, McGaw J, Watson A. Case-control study of acute renal failure in patients with cystic fibrosis in the UK. *Thorax* 2008;**63**(6): 532–5.

**Smyth 2013**

Smyth AR, Campbell EL. Prescribing practices for intravenous aminoglycosides in UK Cystic Fibrosis clinics: A questionnaire survey. Journal of Cystic Fibrosis 2013 Dec [epub ahead of print]. [DOI: 10.1016/j.jcf.2013.11.007]

**Spivey 1992**

Spivey JM. The post antibiotic effect. *Clinical Pharmacy* 1992;**11**(10):865–75.

**Tan 2002**

Tan KH, Hyman-Taylor P, Mulheran M, Knox A, Smyth A. Lack of concordance in the use and monitoring of intravenous aminoglycosides in UK cystic fibrosis centres. *Pediatric Pulmonology* 2002;**33**(2):165.

**Tureen 2001**

Tureen J. Once Daily Intravenous Aminoglycoside Treatment Study. US Cystic Fibrosis Foundation. Planned to be published 2001/2002, terminated.

**Weiss 1995**

Weiss K, Lapointe JR. Routine susceptibility testing of four antibiotic combinations for improvement of laboratory guide to therapy of cystic fibrosis infections caused by pseudomonas aeruginosa. *Antimicrobial Agents and Chemotherapy* 1995;**39**(11):2411–4.

## References to other published versions of this review

**Smyth 2000**

Smyth A, Tan K, Bunn H. Once-daily versus multiple-daily dosing with intravenous aminoglycosides for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2000, Issue 4. [DOI: 10.1002/14651858.CD002009]

**Smyth 2006**

Smyth AR, Bhatt J. Once-daily versus multiple-daily dosing with intravenous aminoglycosides for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2006, Issue 3. [DOI: 10.1002/14651858.CD002009.pub2]

**Smyth 2010**

Smyth AR, Bhatt J. Once-daily versus multiple-daily dosing with intravenous aminoglycosides for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2010, Issue 1. [DOI: 10.1002/14651858.CD002009.pub3]

**Smyth 2012**

Smyth AR, Bhatt J. Once-daily versus multiple-daily dosing with intravenous aminoglycosides for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2012, Issue 2. [DOI: 10.1002/14651858.CD002009.pub4]

* *Indicates the major publication for the study*

# CHARACTERISTICS OF STUDIES

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

**Riethmueller 2009**

| Methods | 6 centre study: 3 centres randomised with 3 protocols and 3 centres with 2 protocols. Cross-over design. |
|---|---|
| Participants | 80 participants with CF.<br>38 completed all 3 arms. |
| Interventions | Once-daily dosing (10 mg/kg/day) versus thrice-daily dosing (10 mg/kg/day) of tobramycin.<br>2-week cycle.<br>Combination therapy with ceftazidime (200 mg/kg/day). |
| Outcomes | Lung function: $FEV_1$ and FVC.<br>Weight (kg).<br>Ototoxicity.<br>Nephrotoxicity: NAG and $\alpha$-1-microglobulin. |
| Notes | |

*Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Described as randomised but no details in paper. |
| Allocation concealment (selection bias) | Unclear risk | Not described. |
| Blinding (performance bias and detection bias)<br>All outcomes | High risk | Unblinded. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | No intention-to-treat analysis. 38 out of 67 completed all 3 arms of the study - data not included on other participants |
| Selective reporting (reporting bias) | Low risk | Published protocol compared to final paper. |
| Other bias | Low risk | Publication bias not identified. |

**Smyth 2005**

| Methods | 21 centres in the UK. Central randomisation, stratified by centre and adult versus paediatric.<br>Parallel design. |
|---|---|
| Participants | Per protocol analysis (n = 219).<br>Once daily n = 107 (63 male); age range 5.1 to 50.4 years.<br>Thrice daily n = 112 (68 male); age range 5.5 to 43.3 years.<br>Pulmonary exacerbation defined. |
| Interventions | Once-daily dosing (10 mg/kg/day ) versus thrice-daily dosing (10 mg/kg/day) of tobramycin or dose last shown to give therapeutic levels.<br>14 days of treatment.<br>Combination therapy with ceftazidime. |
| Outcomes | Lung function: $FEV_1$ and FVC.<br>Weight (kg).<br>Ototoxicity.<br>Nephrotoxicity: serum creatinine & urine NAG. |
| Notes | |

*Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Central randomisation, using a computer generated list (permuted blocks of 6), stratified by centre and adult versus paediatric |
| Allocation concealment (selection bias) | Low risk | Adequate, allocation performed centrally. |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | Placebo masked. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | A per-protocol analysis was performed as the primary analysis as this was an equivalence study. A CONSORT flow diagram is included, giving details of participants screened (n = 569), those enrolled (n = 244) and those who did not complete the study *per protocol* (n = 25). |
| Selective reporting (reporting bias) | Low risk | Published protocol compared to final paper. |
| Other bias | Low risk | No reporting or publication bias. |

**Vic 1998**

| Methods | Randomisation table used. Parallel design. |
|---|---|
| Participants | 22 participants with diagnosis of CF. Once daily: n = 12 (8 male); age range 5.6 - 19.3 years. Thrice daily: n = 10 (6 male); age range 7.4 - 17.2 years. Pulmonary exacerbation defined. |
| Interventions | Once-daily dosing (15 mg/kg/day) versus thrice-daily dosing (15 mg/kg/day) of tobramycin. 14 days of treatment. Combination therapy with ceftazidime (200 mg/kg/day). |
| Outcomes | Lung function: $FEV_1$ and FVC. Weight/Height %. Ototoxicity. Nephrotoxicity: creatinine clearance; lysozymuria; B2-microglobulinuria; 24 hour proteinuria |
| Notes | |

*Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Randomisation table used. |
| Allocation concealment (selection bias) | Unclear risk | No details in the published paper. |
| Blinding (performance bias and detection bias) All outcomes | High risk | Unblinded. |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | No intention-to-treat analysis, authors confirmed no withdrawals from the study |
| Selective reporting (reporting bias) | Unclear risk | Protocol not published in advance. |
| Other bias | Low risk | No publication bias. |

**Whitehead 2002**

| Methods | Randomisation table used. Parallel design. |
|---|---|
| Participants | 60 participants with diagnosis of CF. 49 studied: |

**Whitehead 2002** (*Continued*)

| | |
|---|---|
| | Once daily: n = 30 (16 male); age range 15 to 47 years.<br>Thrice daily: n = 19 (11 male); age range 16 to 32 years.<br>Pulmonary exacerbation defined. |
| Interventions | Once-daily dosing (10 mg/kg/day ) versus thrice-daily dosing (10 mg/kg/day) of to-bramycin.<br>12 days of treatment.<br>Combination therapy with beta-lactam. |
| Outcomes | Lung function: $FEV_1$, FVC, $FEF_{25-75\%}$.<br>Body mass index.<br>Ototoxicity.<br>Nephrotoxicity: serum creatinine.<br>Clinical score.<br>White cell count (% neutrophils).<br>C-reactive protein.<br>Participant preference. |
| Notes | |

*Risk of bias*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Randomisation table used. |
| Allocation concealment (selection bias) | Unclear risk | Not described in the published paper. |
| Blinding (performance bias and detection bias)<br>All outcomes | High risk | Unblinded. |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | No intention-to-treat analysis. 60 recruited, 49 studied. No data given on the remaining 11 |
| Selective reporting (reporting bias) | Unclear risk | Protocol not published in advance. |
| Other bias | Low risk | No publication bias. |

CF: cystic fibrosis
$FEV_1$: forced expiratory volume at one second
$FEF_{25-75\%}$: forced mid-expiratory flow FVC: forced vital capacity
NAG: N-acetyl-beta-D glucosaminidase
vs: versus

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

| Study | Reason for exclusion |
|---|---|
| Adeboyeku 2011 | No once-daily arm. |
| Aminimanizani 2002 | A pharmacokinetic paper. |
| Burkhardt 2006 | A pharmacokinetic paper. |
| Hamner 2006 | A pharmacokinetic paper. |
| Heininger 1993 | Alternate allocation of treatment. |
| Master 2001 | Trial of monotherapy versus combination therapy. |
| Postnikov 2007 | Unclear whether randomised. Abstract only. No outcome data. No response from authors for further information |
| Powell 1983 | Unblinded trial with efficacy measured on a symptom score. |
| Winnie 1991 | Comparison of tds versus qds tobramycin dosing. |
| Wood 1996 | Comparison of bds versus tds tobramycin dosing. |

bds: twice daily
qds: four times daily
tds: thrice daily

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

**Al Ansari 2006**

| | |
|---|---|
| Methods | Cross-over RCT. |
| Participants | Adults with CF. |
| Interventions | Once- versus thrice-daily dosing of tobramycin for pulmonary exacerbations |
| Outcomes | $FEV_1$ at day 7. |
| Notes | Authors have been approached for first-arm data. |

CF: cystic fibrosis
$FEV_1$: forced expiratory volume at one second

RCT: randomised controlled trial

# DATA AND ANALYSES

## Comparison 1. Once-daily dosing of intravenous aminoglycoside antibiotics versus multiple-daily dosing

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
| --- | --- | --- | --- | --- |
| 1 Mean percentage change in $FEV_1$ | 3 | 289 | Mean Difference (IV, Fixed, 95% CI) | 0.33 [-2.81, 3.48] |
| 2 Mean percentage change in FVC | 2 | 70 | Mean Difference (IV, Fixed, 95% CI) | 0.29 [-6.58, 7.16] |
| 3 Mean change in $FEF_{25-75}$ | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 4 Mean change in weight/height % | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 5 Mean change in body mass index | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 6 Development of ototoxicity (after treatment) | 3 | 266 | Risk Ratio (M-H, Fixed, 95% CI) | 0.56 [0.04, 7.96] |
| 7 Percentage change in creatinine with treatment | 2 | 245 | Mean Difference (IV, Fixed, 95% CI) | -0.61 [-4.74, 3.52] |
| 7.1 Percentage change in creatinine with treatment - adults | 2 | 131 | Mean Difference (IV, Fixed, 95% CI) | 3.25 [-1.82, 8.33] |
| 7.2 Percentage change in creatinine with treatment - children | 1 | 114 | Mean Difference (IV, Fixed, 95% CI) | -8.2 [-15.32, -1.08] |

## Analysis 1.1. Comparison 1 Once-daily dosing of intravenous aminoglycoside antibiotics versus multiple-daily dosing, Outcome 1 Mean percentage change in FEV1.

Review: Once-daily versus multiple-daily dosing with intravenous aminoglycosides for cystic fibrosis

Comparison: 1 Once-daily dosing of intravenous aminoglycoside antibiotics versus multiple-daily dosing

Outcome: 1 Mean percentage change in $FEV_1$

| Study or subgroup | Once-daily N | Mean(SD)[% pred.] | Thrice-daily N | Mean(SD)[% pred.] | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Vic 1998 | 12 | 14 (15.3) | 10 | 14.9 (16) | | 5.7 % | -0.90 [ -14.06, 12.26 ] |
| Whitehead 2002 | 30 | 10.1 (12.3) | 18 | 9.66 (11.3) | | 21.2 % | 0.44 [ -6.39, 7.27 ] |
| Smyth 2005 | 107 | 10.4 (13.8) | 112 | 10 (14) | | 73.0 % | 0.40 [ -3.28, 4.08 ] |
| **Total (95% CI)** | **149** | | **140** | | | **100.0 %** | **0.33 [ -2.81, 3.48 ]** |

Heterogeneity: Chi² = 0.04, df = 2 (P = 0.98); I² =0.0%

Test for overall effect: Z = 0.21 (P = 0.84)

Test for subgroup differences: Not applicable

-10   -5   0   5   10

Favours thrice-daily   Favours once-daily
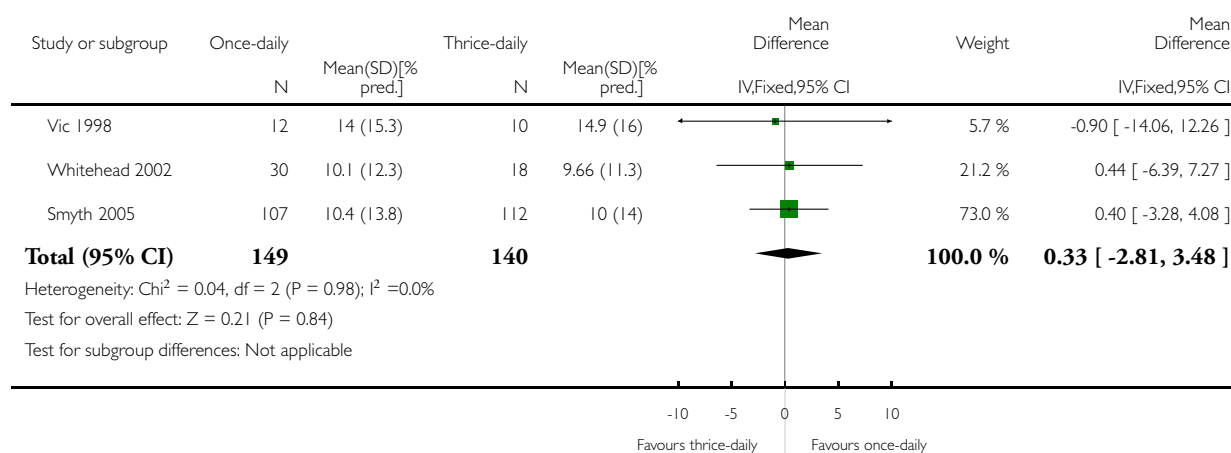
**Analysis 1.2. Comparison 1 Once-daily dosing of intravenous aminoglycoside antibiotics versus multiple-daily dosing, Outcome 2 Mean percentage change in FVC.**

| Study or subgroup | Once-daily | | Thrice-daily | | Mean Difference | Weight | Mean Difference |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD)[% pred.] | N | Mean(SD)[% pred.] | IV,Fixed,95% CI | | IV,Fixed,95% CI |
| Vic 1998 | 12 | 10.5 (13) | 10 | 13.8 (15) | | 33.6 % | -3.30 [ -15.15, 8.55 ] |
| Whitehead 2002 | 30 | 14.3 (14.8) | 18 | 12.2 (14.2) | | 66.4 % | 2.10 [ -6.33, 10.53 ] |
| **Total (95% CI)** | **42** | | **28** | | | **100.0 %** | **0.29 [ -6.58, 7.16 ]** |

Heterogeneity: Chi² = 0.53, df = 1 (P = 0.47); I² =0.0%

Test for overall effect: Z = 0.08 (P = 0.93)

Test for subgroup differences: Not applicable

```
        -10    -5    0    5    10
   Favours thrice-daily    Favours once-daily
```

## Analysis 1.3.   Comparison 1 Once-daily dosing of intravenous aminoglycoside antibiotics versus multiple-daily dosing, Outcome 3 Mean change in FEF25-75.

| Study or subgroup | Once-daily | | Thrice-daily | | Mean Difference | Mean Difference |
|---|---|---|---|---|---|---|
| | N | Mean(SD)[% pred.] | N | Mean(SD)[% pred.] | IV,Fixed,95% CI | IV,Fixed,95% CI |
| Whitehead 2002 | 30 | 5.15 (12.1) | 18 | 6.39 (10.6) | | -1.24 [ -7.78, 5.30 ] |

-10   -5   0   5   10

Favours thrice-daily        Favours once-daily

## Analysis 1.4.   Comparison 1 Once-daily dosing of intravenous aminoglycoside antibiotics versus multiple-daily dosing, Outcome 4 Mean change in weight/height %.

| Study or subgroup | Once-daily | | Thrice-daily | | Mean Difference | Mean Difference |
|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | IV,Fixed,95% CI |
| Vic 1998 | 12 | 3.14 (4.35) | 10 | 3.96 (2.63) | | -0.82 [ -3.77, 2.13 ] |

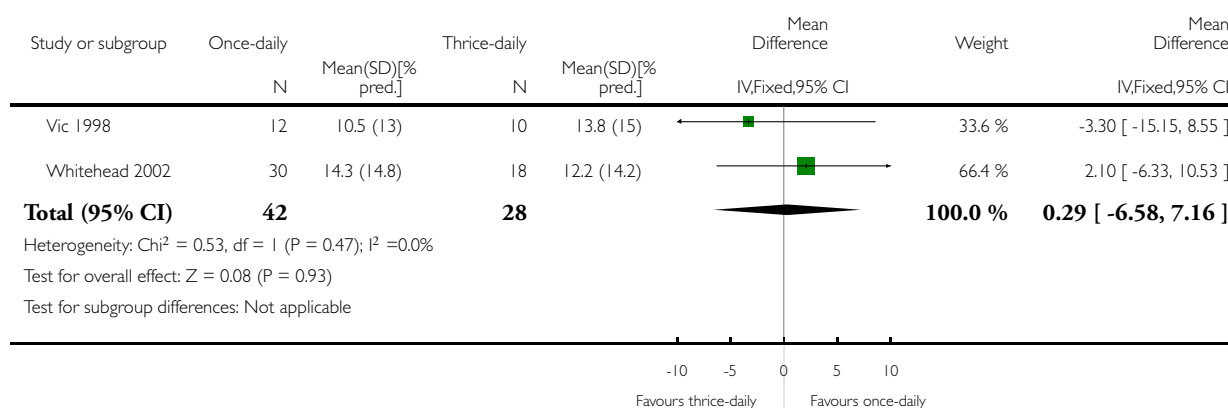-4   -2   0   2   4

Favours thrice-daily        Favours once-daily

## Analysis 1.5. Comparison 1 Once-daily dosing of intravenous aminoglycoside antibiotics versus multiple-daily dosing, Outcome 5 Mean change in body mass index.

Review: Once-daily versus multiple-daily dosing with intravenous aminoglycosides for cystic fibrosis

Comparison: 1 Once-daily dosing of intravenous aminoglycoside antibiotics versus multiple-daily dosing

Outcome: 5 Mean change in body mass index
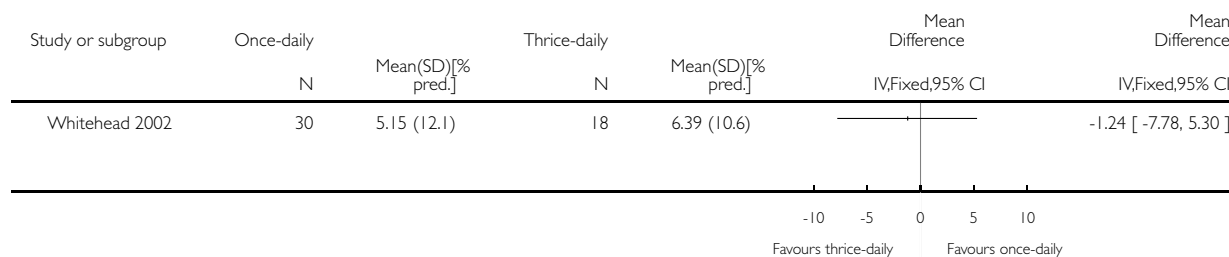
| Study or subgroup | Once-daily | | Thrice-daily | | Mean Difference | Mean Difference |
| --- | --- | --- | --- | --- | --- | --- |
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | IV,Fixed,95% CI |
| Whitehead 2002 | 24 | 0.54 (0.57) | 17 | 0.54 (0.74) | | 0.0 [ -0.42, 0.42 ] |

-0.5   -0.25   0   0.25   0.5

Favours thrice-daily        Favours once-daily

## Analysis 1.6. Comparison 1 Once-daily dosing of intravenous aminoglycoside antibiotics versus multiple-daily dosing, Outcome 6 Development of ototoxicity (after treatment).

Review: Once-daily versus multiple-daily dosing with intravenous aminoglycosides for cystic fibrosis

Comparison: 1 Once-daily dosing of intravenous aminoglycoside antibiotics versus multiple-daily dosing

Outcome: 6 Development of ototoxicity (after treatment)

| Study or subgroup | Once-daily | Thrice-daily | Risk Ratio | Weight | Risk Ratio |
| --- | --- | --- | --- | --- | --- |
| | n/N | n/N | M-H,Fixed,95% CI | | M-H,Fixed,95% CI |
| Vic 1998 | 0/10 | 0/9 | | | Not estimable |
| Whitehead 2002 | 1/18 | 1/10 | | 100.0 % | 0.56 [ 0.04, 7.96 ] |
| Smyth 2005 | 0/107 | 0/112 | | | Not estimable |
| **Total (95% CI)** | **135** | **131** | | **100.0 %** | **0.56 [ 0.04, 7.96 ]** |

Total events: 1 (Once-daily), 1 (Thrice-daily)

Heterogeneity: not applicable

Test for overall effect: Z = 0.43 (P = 0.67)

Test for subgroup differences: Not applicable

0.05   0.2   1   5   20

Favours once-daily        Favours thrice-daily

**Analysis 1.7. Comparison 1 Once-daily dosing of intravenous aminoglycoside antibiotics versus multiple-daily dosing, Outcome 7 Percentage change in creatinine with treatment.**

Review: Once-daily versus multiple-daily dosing with intravenous aminoglycosides for cystic fibrosis

Comparison: 1 Once-daily dosing of intravenous aminoglycoside antibiotics versus multiple-daily dosing
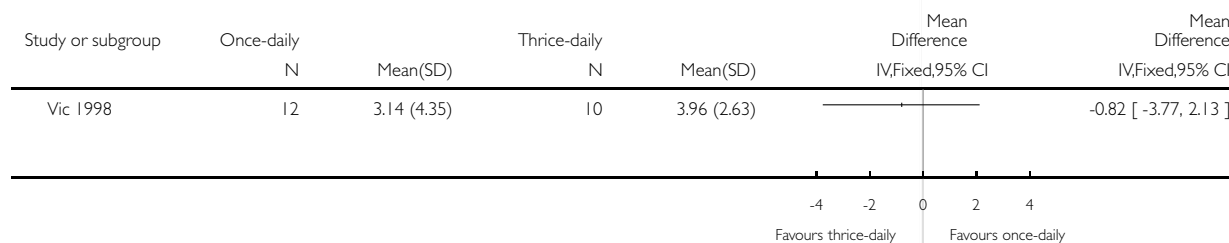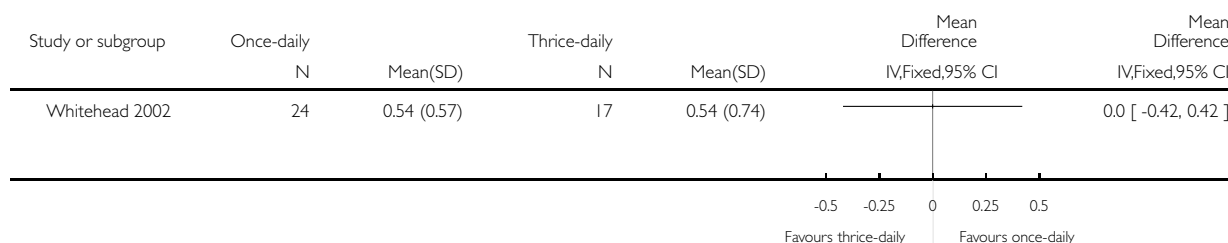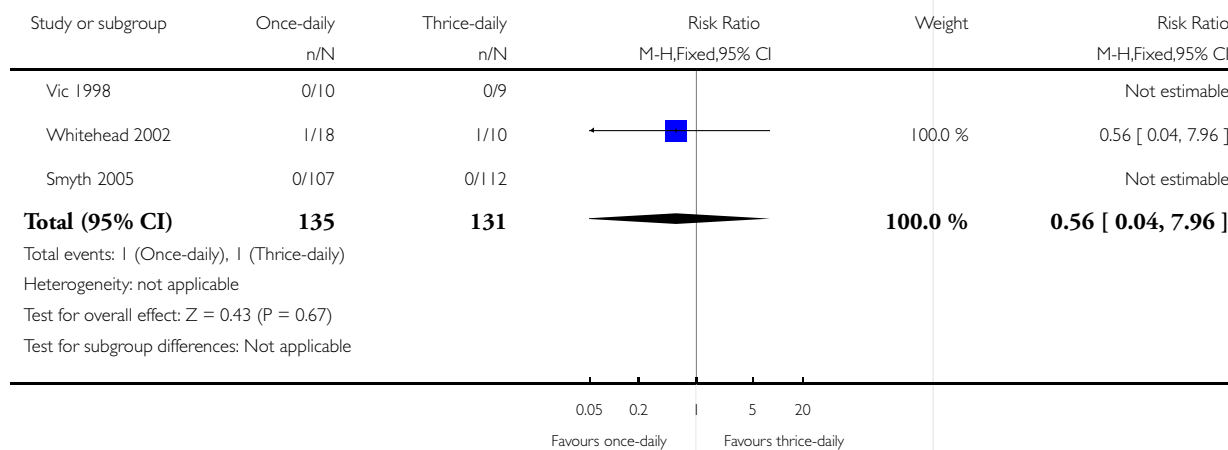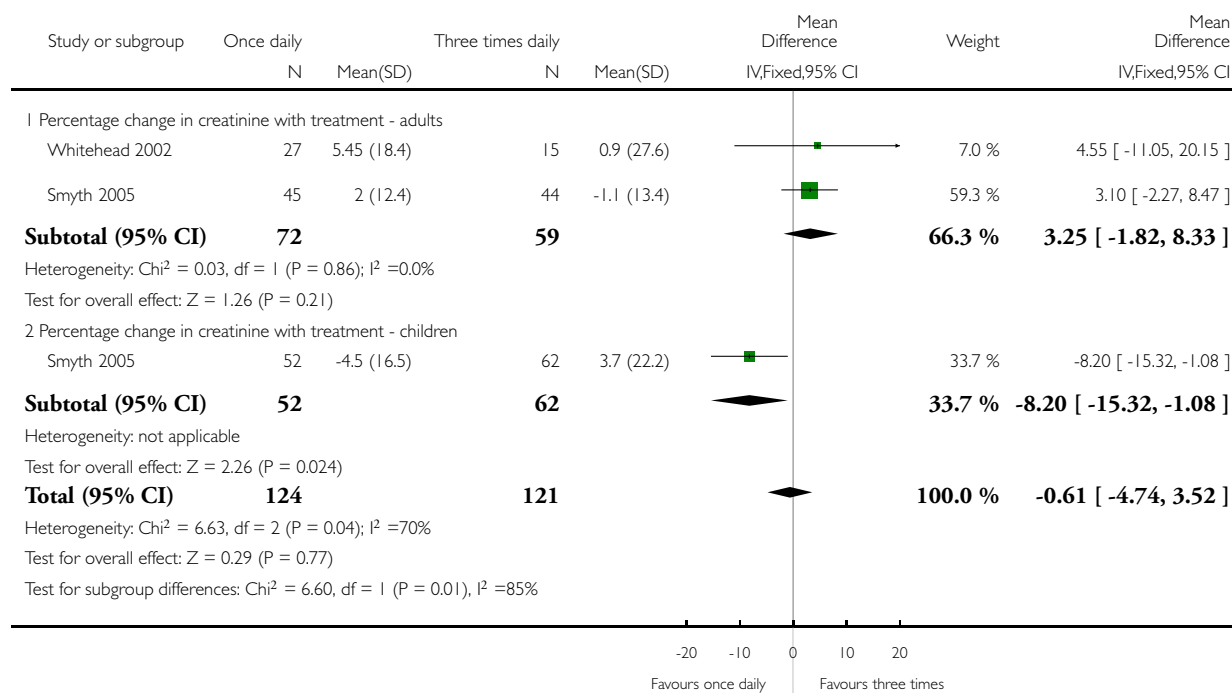
Outcome: 7 Percentage change in creatinine with treatment

| Study or subgroup | Once daily | | Three times daily | | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | | | |
| 1 Percentage change in creatinine with treatment - adults | | | | | | | |
| Whitehead 2002 | 27 | 5.45 (18.4) | 15 | 0.9 (27.6) | | 7.0 % | 4.55 [ -11.05, 20.15 ] |
| Smyth 2005 | 45 | 2 (12.4) | 44 | -1.1 (13.4) | | 59.3 % | 3.10 [ -2.27, 8.47 ] |
| **Subtotal (95% CI)** | **72** | | **59** | | | **66.3 %** | **3.25 [ -1.82, 8.33 ]** |
| Heterogeneity: Chi² = 0.03, df = 1 (P = 0.86); I² =0.0% | | | | | | | |
| Test for overall effect: Z = 1.26 (P = 0.21) | | | | | | | |
| 2 Percentage change in creatinine with treatment - children | | | | | | | |
| Smyth 2005 | 52 | -4.5 (16.5) | 62 | 3.7 (22.2) | | 33.7 % | -8.20 [ -15.32, -1.08 ] |
| **Subtotal (95% CI)** | **52** | | **62** | | | **33.7 %** | **-8.20 [ -15.32, -1.08 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 2.26 (P = 0.024) | | | | | | | |
| **Total (95% CI)** | **124** | | **121** | | | **100.0 %** | **-0.61 [ -4.74, 3.52 ]** |
| Heterogeneity: Chi² = 6.63, df = 2 (P = 0.04); I² =70% | | | | | | | |
| Test for overall effect: Z = 0.29 (P = 0.77) | | | | | | | |
| Test for subgroup differences: Chi² = 6.60, df = 1 (P = 0.01), I² =85% | | | | | | | |

```
        -20   -10    0    10    20
     Favours once daily    Favours three times
```

# WHAT'S NEW

Last assessed as up-to-date: 4 February 2014.

| Date | Event | Description |
|---|---|---|
| 4 February 2014 | New search has been performed | One study by Tureen, previously listed as 'Ongoing', has been removed as it failed to recruit sufficient participants and was terminated<br>A new search of the Cystic Fibrosis & Genetic Disorders Group's Cystic Fibrosis Trials Register identified no new references which were potentially eligible for inclusion in the review |

*(Continued)*

| | | |
|---|---|---|
| 4 February 2014 | New citation required but conclusions have not changed | No new information has been added to this update, hence the conclusions have remained the same |

# H I S T O R Y

Protocol first published: Issue 2, 2000

Review first published: Issue 4, 2000

| Date | Event | Description |
|---|---|---|
| 3 January 2012 | New citation required but conclusions have not changed | Additional information from the Rietmueller study has been included, but did not change the conclusions of the review (Riethmueller 2009). |
| 3 January 2012 | New search has been performed | A search of the Group's Cystic Fibrosis Trials Register identified four references to three studies (Adeboyeku 2011; Al Ansari 2006; Riethmueller 2009). Two of these were additional references (full papers) to an already included study, previously only available in abstract form (Riethmueller 2009). One of the identified references has been excluded (Adeboyeku 2011) and the other one is currently listed as 'Awaiting classification' while we seek further information from the study investigators (Al Ansari 2006). |
| 9 September 2009 | New citation required but conclusions have not changed | This new citation has been generated as the review team who worked on the updates published since Issue 3, 2007 changed from the team on previous updates. Jayesh Bhatt is now co-author on this review |
| 6 April 2009 | New search has been performed | A search of the Group's Cystic Fibrosis Trials Register identified three new references which were potentially eligible for inclusion in the review. Two references (Touw 2007a; Touw 2007b )were additional references to an already included study (Smyth 2005). One reference was excluded (Postnikov 2007). |
| 12 November 2008 | Amended | Converted to new review format. |
| 3 May 2007 | Amended | Kelvin Tan ceased to be actively involved with this review as from January 2006. As of March 2007 Dr Jayesh Bhatt has become an active author on this review |

| 3 May 2007 | New search has been performed | A search of the Group's Cystic Fibrosis Trials Register identified two new references (Burkhardt 2006; Hamner 2006); these are now listed under 'Excluded studies'. |
|---|---|---|
| 3 May 2006 | New search has been performed | A new study has been included (Smyth 2005). A further study , previously listed as "Awaiting assessment", has been added to the list of excluded studies (Heininger 1993). |
| 3 May 2006 | New citation required and conclusions have changed | Substantive amendment |
| 27 November 2003 | New search has been performed | Two new references to the already included Whitehead 2001 study have been added. Following the full publication of the Whitehead 2001 study, there have been minor changes to data originally obtained via personal communication<br>Further unpublished data from the Whitehead study has been made available to the reviewers by Steve Conway (Leeds, UK) |
| 27 November 2003 | Amended | Kelvin Tan has stepped down as lead reviewer and has been replaced by Alan Smyth. Kelvin Tan is remaining as a co-reviewer. Hazel Bunn has stepped down as an active co-reviewer on this review |
| 28 August 2001 | New search has been performed | The Group's specialised register was searched in June 2001. Two studies (Master 2001; Riethmueller 2009) were identified in the search. The Master study (Master 2001) was excluded as detailed in the 'Characteristics of excluded studies' section. The Riethmueller study (Riethmueller 2009) was published in abstract form only. The authors of this study kindly provided further information, which determined that descriptive data on efficacy would be included in the update<br>Two studies are still ongoing and are described in the 'Characteristics of ongoing studies' section |

## CONTRIBUTIONS OF AUTHORS

Kelvin Tan prepared the protocol, selected and assessed trials and interpreted the data. He was the lead author on the review until October 2003; from Issue 1, 2004 he was a co-author actively involved in updating the review. As from February 2006 he has ceased to be actively involved in the review.

Hazel Evans helped to write the protocol, select and assess trials and interpret data. She also contributed to the writing of the initial review. As of October 2003 she is no longer actively involved with the review.

Alan Smyth co-wrote the updated review and from Issue 1, 2004, is the lead author and acts as guarantor of the review.

Jayesh Bhatt joined the review as from March 2007. He has written much of the text for the updated versions of the review.

## DECLARATIONS OF INTEREST

The contact author (AS) is the principal investigator for the TOPIC study: Tobramycin Once-daily Prescribing In Cystic Fibrosis.

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

## INDEX TERMS
### Medical Subject Headings (MeSH)

Aminoglycosides [*administration & dosage]; Anti-Bacterial Agents [*administration & dosage]; Bacterial Infections [*drug therapy]; Cystic Fibrosis [*complications]; Drug Administration Schedule; Drug Therapy, Combination [methods]; Injections, Intravenous; Lung Diseases [drug therapy; microbiology]; Randomized Controlled Trials as Topic

### MeSH check words

Adolescent; Adult; Child; Female; Humans; Male