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Smyth AR, Bhatt J, Nevitt SJ

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Cochrane Database of Systematic Reviews 2017, Issue 3. Art. No.: CD002009.

DOI: 10.1002/14651858.CD002009.pub6.

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[Intervention Review]

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

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Editorial group: Cochrane Cystic Fibrosis and Genetic Disorders Group.

Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 3, 2017.

Citation: Smyth AR, Bhatt J, Nevitt SJ. Once-daily versus multiple-daily dosing with intravenous aminoglycosides for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2017, Issue 3. Art. No.: CD002009. DOI: 10.1002/14651858.CD002009.pub6.

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ABSTRACT

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. This is an update of a previously published review.

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: 24 June 2016.

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All randomised controlled trials, whether published or unpublished, in which once-daily dosing of aminoglycosides has been compared with multiple-daily dosing in terms of efficacy or toxicity or both, in people with cystic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; authors also assessed the quality of the evidence using the GRADE criteria. 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 (aged 5 to 50 years) 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 in one second, mean difference 0.33 (95% confidence interval -2.81 to 3.48, moderate quality evidence); forced vital capacity, mean difference 0.29 (95% confidence interval -6.58 to 7.16, low quality evidence); % weight for height, mean difference -0.82 (95% confidence interval -3.77 to 2.13, low quality evidence); body mass index, mean difference 0.00 (95% confidence interval -0.42 to 0.42, low quality evidence); or in the incidence of ototoxicity, relative risk 0.56 (95% confidence interval 0.04 to 7.96, moderate quality evidence). The percentage change in creatinine significantly favoured once-daily treatment in children, mean difference -8.20 (95% confidence interval -15.32 to -1.08, moderate quality evidence), but showed no difference in adults, mean difference 3.25 (95% confidence interval -1.82 to 8.33, moderate quality evidence). The included trials did not report antibiotic resistance patterns or quality of life.

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.

PLAIN LANGUAGE SUMMARY

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

Review question

We looked for evidence to show the differences between giving intravenous antibiotics once daily compared to giving them several times a day when treating flare ups of disease (pulmonary exacerbations) in people with cystic fibrosis. This is an update of an earlier review.

Background

Most people with cystic fibrosis develop persistent lung infections and they may receive frequent courses of intravenous antibiotics to treat pulmonary exacerbations. Giving the antibiotics just once per day rather than several doses per day reduces the cost of treatment and the time involved.

Search date

The evidence is current to 24 June 2016.

Study characteristics

This review includes four studies with a total of 328 children and adults. All the trials compared once-a-day dosing with three times-a-day dosing.

Key results

The review found that when treating people with cystic fibrosis for pulmonary exacerbations, giving the antibiotics once per day was just as good as giving them more frequently in terms of lung function and body mass index. 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 treatment schedules for other outcomes that the studies measured.

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.

Quality of the evidence

We judged that just one of the four studies carried a low risk that any design factors might affect the outcome results. In the remaining three studies, we thought that the fact that it was obvious whether the antibiotics were given once or three times a day could affect

some outcome measures (e.g. lung function). Other risk factors were unclear or at low risk of bias. We assessed the evidence for lung function, body mass index and the evidence for side effects (e.g. toxicity) to be moderate to low quality.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Once-daily compared with multiple-daily dosing with intravenous aminoglycosides for cystic fibrosis						
Patient or population: adults and children with cystic fibrosis						
Settings: outpatients						
Intervention: once-daily dosing of intravenous aminoglycosides						
Comparison: multiple-daily dosing of intravenous aminoglycosides						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Multiple-daily dosing of intravenous aminoglycosides ¹	Once-daily dosing of intravenous aminoglycosides				
Lung function Mean percentage change in FEV ₁ , Follow up: 12 - 14 days	The mean percentage change in FEV ₁ (% predicted) ranged between 9.66 and 14.9 in the multiple-daily dosing groups	The mean percentage change in FEV ₁ (% predicted) was 0.33 higher (2.81 lower to 3.48 higher) in the once-daily dosing groups	NA	289 (3 studies)	⊕⊕⊕○ moderate ²	
Lung function Mean percentage change in FVC (% predicted) Follow up: 12 - 14 days	The mean percentage change in FVC (% predicted) ranged between 12.2 and 13.8 in the multiple-daily dosing groups	The mean percentage change in FVC (% predicted) was 0.29 higher (6.58 lower to 7.16 higher) in the once-daily dosing groups	NA	70 (2 studies)	⊕⊕○○ low ^{2,3}	
Nutritional status BMI Follow up: 12 - 14 days	The mean change in BMI was 0.54 in the multiple-daily dosing group	The mean change in BMI was the same (0.42 higher to 0.42 lower) in the once-daily dosing group	NA	41 (1 studies)	⊕⊕○○ low ^{2,3}	There were also no statistically significant differences in mean change in weight/height percentage, MD

						-0.82 (95% CI -3.77 to 2.13), 22 participants, 1 study
Time to first exacerbation requiring intravenous antibiotics Follow up: 12 months	The median time to next course of intravenous antibiotics was 168 days (95% CI 34 days to 302 days) in the multiple-daily dosing group	The median time to next course of intravenous antibiotics was 131 days (95% CI 76 days to 186 days) in the once-daily dosing group	NA	113 (1 study)	⊕⊕⊕○ moderate ⁴	There was no statistically significant difference between treatment groups (P = 0.48)
Antibiotic resistance patterns following treatment Follow up: NA	Outcome not reported				NA	
Ototoxicity An increase in auditory threshold of 20 dB or more over any frequency range Follow up: 12 - 14 days	8 per 1000	4 per 1000 (0 to 61 per 1000)	RR: 0.56 (0.04, 7.96)	266 (3 studies)	⊕⊕○○ low ^{2,5}	An additional study was not included in analysis due to the cross-over design; there was no evidence of ototoxicity in any individual in this study
Nephrotoxicity The percentage change in creatinine over baseline Follow up: 12 - 14 days	The mean percentage change in creatine over baseline ranged from -1.1% lower to 3.7% higher in the multiple-daily dosing group	The mean percentage change in creatine over baseline was 0.61% lower (4.74% lower to 3.52% higher) in the once-daily dosing group	NA	245 (3 studies)	⊕⊕⊕○ moderate ²	There was a statistically significant difference in subgroup analysis of studies recruiting adults and children; adults MD 3.25 (95% CI -1.82 to 8.33) and children MD -8.20 (95% CI -15.32 to -1.08) An additional study was not included in analysis

		due to the cross-over design; there no statistically significant difference between treatment groups in this study
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*The basis for the **assumed risk** is the mean control group risk across studies or the event rate in the control group (as appropriate). The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
BMI: body mass index; **CI**: confidence interval; **FEV₁** : forced expiratory volume in one second; **FVC**: forced vital capacity; **MD**: mean difference; **NA**: not applicable; **RR**: risk ratio.

GRADE Working Group grades of evidence

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

1. Multiple-daily dosing was thrice daily dosing in all three studies contributing to analysis ([Smyth 2005](#); [Vic 1998](#); [Whitehead 2002](#)).
2. Downgraded once due to risk of bias: two studies were unblinded ([Vic 1998](#); [Whitehead 2002](#)) and one study had incomplete outcome data ([Whitehead 2002](#)).
3. Downgraded once due to applicability: evidence only contributed by studies recruiting adults; results not applicable to children
4. Downgraded once due to applicability: evidence only contributed by one study recruiting children; results not applicable to adults
5. Downgraded once due to imprecision: wide confidence interval due to small number of events in both treatment groups.

BACKGROUND

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); however, in a recent retrospective study nearly one third of individuals who were treated with more than 14 days of antibiotics showed improvements in lung function beyond the antibiotic treatment period, particularly in those who had greater decreases in forced expiratory volume in one second (FEV₁) at the time of exacerbations, and in those who were slower to initially respond to treatment. Whether the improvements in lung function beyond the 14-day period are associated with the antibiotic treatment or concurrent treatments, requires prospective study (Waters 2015).

Description of the intervention

People with CF receive frequent and repeated courses of intravenous antibiotics throughout their lifetime. The quality of evidence comparing intravenous antibiotics with placebo is poor. A recent Cochrane review concluded that no specific antibiotic combination can be considered to be superior to any other, and neither is there evidence showing that the intravenous route is superior to the inhaled or oral routes (Hurley 2015). 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 received 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 2014b).

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; Smyth 2014a).

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 cross-over 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.

Types of outcome measures

Primary outcomes

1. Lung function measurements
 - i) forced expiratory volume in one second (FEV₁)
 - 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))

*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 38° 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 study report.

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 *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*), weekly searches of MEDLINE, a search of Embase to 1995 and the prospective handsearching of two journals - *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis*. Unpublished work is identified by searching 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: 24 June 2016.

Data collection and analysis

Selection of studies

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

Data extraction and management

Two authors independently extracted data and resolved any disagreements by negotiation. We 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). We 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, we 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, we judged there to be a low risk of bias for this domain.

Measures of treatment effect

For dichotomous variables (such as adverse events) we used risk ratios and 95% confidence intervals (CIs) and calculated a pooled estimate of treatment effect across all studies. For continuous variables, such as lung function, we pooled the treatment effect across all studies, using the mean difference and 95% CIs.

Unit of analysis issues

When conducting a meta-analysis combining results from cross-over studies we planned to use the methods recommended by Elbourne (Elbourne 2002). One of the included studies was of cross-over 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, we will use first-arm data, where possible, but only consider the efficacy outcomes.

Dealing with missing data

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

Assessment of heterogeneity

When sufficient studies are included in the review, we 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. We 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

We planned to compare original study protocols to final published papers to identify any selective reporting. If the original study protocols were not available, we 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, we will use a random-effects model.

Subgroup analysis and investigation of heterogeneity

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

Sensitivity analysis

We will undertake a sensitivity analysis if there is risk of small study effects and if they have included sufficient studies in the review.

Summary of findings and quality of the evidence (GRADE)

In a post hoc change from protocol, we have presented a summary of findings table for the comparison of once-daily versus multiple-daily dosing with intravenous aminoglycosides in people with CF (Summary of findings for the main comparison)

We reported the following outcomes in the tables (chosen based on relevance to clinicians and consumers) - lung function (change in

percent (%) predicted FEV₁ and FVC), nutritional status (BMI), time to first exacerbation requiring intravenous antibiotics, antibiotic resistance, ototoxicity and nephrotoxicity.

We determined the quality of the evidence using the GRADE approach; and downgraded evidence in the presence of a high risk of bias in at least one study, indirectness of the evidence, unexplained heterogeneity or inconsistency, imprecision of results, high probability of publication bias. We downgraded evidence by one level if they considered the limitation to be serious and by two levels if very serious.

RESULTS

Description of studies

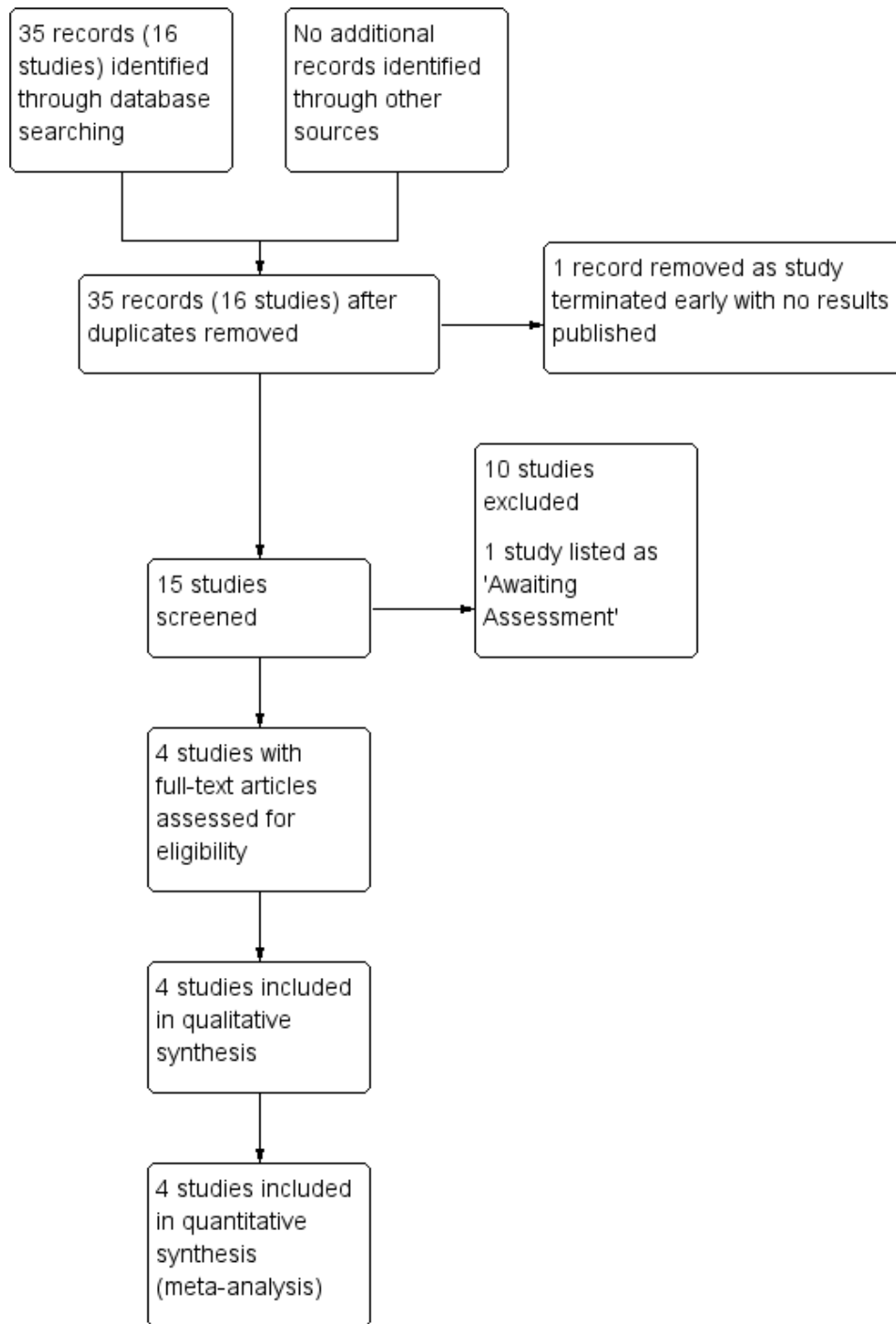
Results of the search

The searches identified 15 studies with publications. 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, pre-

viously listed as ongoing in this review, which was a multicentre RCT based in the USA and funded by the CF Foundation. In this RCT participants were treated either once daily or thrice daily with tobramycin (12 mg/kg/day) plus the usual beta-lactam, but the study failed to recruit a sufficient number of participants and was terminated without any data being made available (Tureen 2001).

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).

Methods

One study was cross-over in design with a three-month washout period (Riethmueller 2009), the remaining three studies were of parallel design (Smyth 2005; Vic 1998; Whitehead 2002). Three studies were unblinded (Riethmueller 2009; Vic 1998; Whitehead 2002) and one was double-blind (Smyth 2005). Data were recorded at the end of the treatment course which was 14 days in three studies (Riethmueller 2009; Smyth 2005; Vic 1998) and 12 days in one study (Whitehead 2002), with no measures of longer-term outcomes. As the Smyth study was an equivalence study, the analysis was per protocol (Smyth 2005).

Participants

The number of participants in each study ranged from 22 (Vic 1998) to 244 (219 of whom completed the study per protocol) (Smyth 2005). One study recruited only adults with an age range of 15 years to 47 years (Whitehead 2002) and one study recruited paediatric participants with a mean age of 11.2 years and a range from 1.7 years to 18.1 years (Riethmueller 2009). The remaining two studies recruited a mixture of children and adults, age range 5.6 years to 19.3 years (Vic 1998) and 5.1 years to 50.4 years (Smyth 2005). There were slightly more males than females in two studies (131 out of 219 (Smyth 2005) and 14 out of 22 (Vic 1998)) and more females than males in two studies (20 out of 30 (Riethmueller 2009) and 33 out of 60 (Whitehead 2002)).

Riethmueller reported that three out of the eight participants lost to follow-up were found to be colonized with resistant *P. aeruginosa* strains and were therefore switched from ceftazidime to meropenem (Riethmueller 2009).

Interventions

All four studies evaluated the efficacy and toxicity of once versus thrice-daily dosing of intravenous tobramycin for a pulmonary exacerbation. No studies were found, which compared once-daily aminoglycoside dosing with any other frequency of dosing. One study additionally evaluated the use of continuous ceftazidime infusions, which is beyond the remit of this review (Riethmueller 2009).

The total daily dose of tobramycin in each group was 15 mg/kg/day in one study (Vic 1998) and 10 mg/kg/day in the remaining three studies (Riethmueller 2009; Smyth 2005; Whitehead 2002). In two studies, tobramycin was given in combination with ceftazidime 200 mg/kg/day (Riethmueller 2009; Vic 1998) and in a third study tobramycin was combined with ceftazidime 150 mg/kg/day in three divided doses (Smyth 2005). Whitehead administered tobramycin in combination with a beta-lactam antibiotic,

chosen by the clinician (either piperacillin, piperacillin/tazobactam, aztreonam, azlocillin, imipenem, meropenem or ceftazidime) (Whitehead 2002).

Outcomes

All four studies reported on lung function using FEV₁ and FVC (Riethmueller 2009; Smyth 2005; Vic 1998; Whitehead 2002); one study additionally reported FEF_{25-75%} (Whitehead 2002). Ototoxicity and nephrotoxicity were also reported by all included studies (Riethmueller 2009; Smyth 2005; Vic 1998; Whitehead 2002). Furthermore, all four studies also reported some measure of nutritional status, although the unit of measurement varied - two studies reported weight in kg (Riethmueller 2009; Smyth 2005), one study reported BMI (Whitehead 2002) and the fourth study reported weight/height % (Vic 1998). Three studies reported on changes in inflammatory markers (Smyth 2005; Vic 1998; Whitehead 2002). One study additionally reported participant preference of treatment regimens, clinical score and white cell count (% neutrophils) (Whitehead 2002). A further study also reported the time to next intravenous antibiotics and attempted to interpret changes in the antibiotic resistance patterns of *P. aeruginosa*, but there were insufficient data to do this (Smyth 2005).

Excluded studies

As detailed in the tables, 10 studies were excluded (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 (Adeboyeke 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 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 for these studies (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

See: [Summary of findings for the main comparison](#)

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

The evidence grades stated for the outcomes reported in the Summary of Findings table are based on GRADE ([Data collection and analysis](#)) and further details are provided in the Summary of Findings table ([Summary of findings for the main comparison](#)).

Primary outcomes

I. Lung function

a. Mean percentage change in FEV₁

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 FEV₁ (% predicted) was 0.33 (95% CI -2.81 to 3.48) (moderate quality evidence) ([Analysis 1.1](#)). There was no significant difference between antibiotic regimens in the increment in FEV₁ 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) (low quality evidence) ([Analysis 1.2](#)).

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) ([Analysis 1.3](#)).

Secondary outcomes

I. 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 (Analysis 1.4). The mean change in 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) (low quality evidence), this suggests that the mean increase in BMI was similar in both the once-daily and thrice-daily groups (Analysis 1.5).

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

Data were available from one study for the time to next course of intravenous antibiotics for 113 participants (56 on once daily, 57 on thrice daily) (Smyth 2005). The median time was 131 days (95% CI 76 days to 186 days) for once daily and 168 days (95% CI 34 days to 302 days) for three-times daily treatment ($P = 0.48$) (moderate quality evidence).

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 participants after treatment and found no evidence of ototoxicity in any individual (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 168 out of 219 participants who completed treatment per protocol had audiograms performed at the start and finish of their intravenous antibiotic course; 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 in the four studies considered, risk ratio 0.56 (95% CI 0.04 to 7.96) (low quality evidence) (Analysis 1.6).

Furthermore, in the TOPIC trial 69 participants had a follow-up audiogram between six and eight weeks after the end of treatment; there were no significant differences between the audiograms and no difference between regimens (Mulheran 2006).

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) (Analysis 1.7). In contrast, data from one study showed that 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) (moderate quality evidence) (Analysis 1.7). Two studies measured N-acetyl- β -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 α -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

Summary of main results

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 328 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 (moderate

to low quality evidence), 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 forced

expiratory volume in one second (FEV₁)) 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 (low quality evidence). However, the results of studies of nephrotoxicity suggested that the rise in creatinine was significantly less in children with once-daily treatment (moderate quality evidence). 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.

Finally, in a chronic disorder such as cystic fibrosis (CF), long-term measures of health status are important. There was no difference found 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.

Overall completeness and applicability of evidence

In each of the four studies included in this review the chosen aminoglycoside was tobramycin. There are several antibiotics in this class which are used in clinical practice. However gentamicin, which is widely used for the management of other infections in children and adults, is associated with increased toxicity in CF (Smyth 2008). Treatment guidelines from the UK CF Trust recommend that gentamicin should not be used (CF Trust 2009). Once- versus multiple-daily dosing has not been evaluated for other aminoglycosides such as amikacin, which is indicated for the management of pulmonary infection with non-tuberculous mycobacteria in CF (Floto 2016) - a problem which is increasingly prevalent in people with CF. There are limited data on the long-term effects of different aminoglycoside dosing regimens on toxicity to hearing or renal function and on other outcomes such as antibiotic resistance.

Quality of the evidence

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), as did the study by Whitehead (Whitehead 2002). The largest study included in this review was judged to have signed a low risk for all forms of bias (Smyth 2005). The remaining three studies did not describe allocation concealment, were not blinded and did not perform an intention-to-treat analysis (Riethmueller 2009; Vic 1998; Whitehead 2002).

With regards to the assessment of the quality of evidence presented in the summary of findings table, we graded the evidence as moderate quality for most outcomes (there was a risk of bias in two of the included studies) and low quality where the results are not applicable to a particular section of the population (either adults or children).

Potential biases in the review process

The lead author of this review (AS) was chief investigator for the TOPIC study, which is the largest study included in this review (Smyth 2005). The risk of bias judgements were made jointly by all three authors.

Agreements and disagreements with other studies or reviews

This is the only systematic review to compare once with multiple-daily dosing of aminoglycosides in people with CF. However, our findings are in agreement with a meta-analysis which looked at the same comparison in people treated with aminoglycosides for a variety of infections (Barza 1996).

AUTHORS' CONCLUSIONS

Implications for practice

Moderate to low quality evidence found in 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 (which can be open label and non-randomised) comparing the two regimens are desirable. Acute renal failure has been reported in association with the use of aminoglycosides 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). 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*.

ACKNOWLEDGEMENTS

We are grateful for the contribution made to this review previously by Dr Hazel Evans and Dr Kelvin Tan.

We are very grateful for the provision of data from the authors of the Rietmueller and Whitehead studies (Riethmueller 2009; Whitehead 2002).

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

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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
- Smyth 2014a**
Smyth AR, Bhatt J. Once-daily versus multiple-daily dosing with intravenous aminoglycosides for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2014, Issue 2. DOI: 10.1002/14651858.CD002009.pub5
- * Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Riethmueller 2009

Methods	<p>Randomised controlled study.</p> <p>Cross-over design (3 arm); mean (SD) washout period 37 (21.6) weeks.</p> <p>Location: multi-centre study (5 centres in total, 3 centres randomised with 3 protocols and 3 centres with 2 protocols) in Germany.</p> <p>Duration: regular 2-week treatment cycles with follow up 3 weeks after termination of each cycle for up to 1.5 years</p>
Participants	<p>80 participants with CF colonised with <i>P aeruginosa</i>. 38 participants from 3 centres treated with either once-daily or thrice daily tobramycin both in combination with thrice-daily ceftazidime. 8 participants lost to follow up (3 of whom colonised with resistant <i>P aeruginosa</i>) so 30 analysed (14 received thrice daily first and once-daily for next IV course)</p> <p>Age mean (range): 11.2 (1.7 to 18.1) years.</p> <p>Gender split: 10 male, 20 female.</p>
Interventions	<p>Consecutive elective courses of IV antibiotics. Mean (SD) interval between 2 treatments was 37 (21.6) weeks</p> <p>Group 1: once-daily dosing (10 mg/kg/day) of tobramycin over 30 minutes</p> <p>Group 2: thrice-daily dosing (10 mg/kg/day) of tobramycin over 30 minutes.</p> <p>2-week cycle either in hospital or at home. 60 courses given (16 at home - 8 of each regimen)</p> <p>Combination therapy with ceftazidime (200 mg/kg/day thrice-daily)</p>
Outcomes	<p>Lung function: FEV₁ and FVC.</p> <p>Weight (kg).</p> <p>Ototoxicity.</p> <p>Nephrotoxicity: NAG and α-1-microglobulin.</p>
Notes	<p>Elective antibiotic courses, antibiotics for pulmonary exacerbations excluded from study</p> <p>Treatment arm not presented here was continuous ceftazidime over 23 hours and tobramycin (10 mg/kg/day) once daily</p> <p>Paper reports no carry-over or centre effect.</p>

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.

Riethmueller 2009 (Continued)

Blinding (performance bias and detection bias) All outcomes	High risk	Unblinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No intention-to-treat analysis. 80 participants in total, papers report 30 out of 38 participants randomised to once-daily and thrice-daily tobramycin completed study and 56 out of 67 participants randomised to once-daily tobramycin with either thrice daily or continuous ceftazidime completed study. Further breakdown not available. Only reasons given were resistant strains of <i>P aeruginosa</i> (3 out of 8 in first comparison and 4 out of 11 in second comparison)
Selective reporting (reporting bias)	Low risk	Published protocol compared to final paper; no missing outcomes identified
Other bias	Low risk	Publication bias not identified.

Smyth 2005

Methods	Randomised placebo-controlled study. Central randomisation, stratified by centre and adult versus paediatric (5 to 16 years). Parallel design. Location: multicentre (21 centres) in the UK. Duration: 14 days of IV antibiotic treatment; follow up from when participants entered study to study closure in 2003 (enrolment took place between Feb 1999 and April 2003) , follow up for time to next exacerbation was 12 months
Participants	244 participants aged over 5 years with diagnosed CF (sweat test or genotyping) randomised, pulmonary exacerbation defined. 122 in each treatment arm, but 3 participants in once-daily arm did not receive study regimen (reasons given); 11 in once daily group and 9 in 3x daily group discontinued (reasons given). One from each group excluded from analysis as lung function not measured per protocol. Per protocol analysis (n = 219) . Once-daily group (n = 107): 63 males; age median (range) 14.8 (5.1 to 50.4) years. Thrice-daily group (n = 112): 68 males; age median (range) 14.9 (5.5 to 43.3) years
Interventions	Group 1: once-daily dosing (10 mg/kg/day) of tobramycin and two doses of 0.9% saline at the same volume as the active infusion over 30 minutes Group 2: thrice-daily dosing (10 mg/kg/day) of tobramycin or dose last shown to give therapeutic levels over 30 minutes. 14 days of treatment both in hospital or at home. Combination therapy with ceftazidime.

Smyth 2005 (Continued)

Outcomes	Lung function: FEV ₁ and FVC. Weight (kg). Ototoxicity. Nephrotoxicity: serum creatinine and urine NAG. Changes in inflammatory markers (C reactive protein). Clinical score. Time to next intravenous antibiotics.	
Notes	Sample size calculation undertaken.	
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 (5 to 16 years)
Allocation concealment (selection bias)	Low risk	Adequate, allocation performed centrally at the pharmacy at the co-ordinating centre and study number assigned by telephone
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo (0.9% saline) masked; all participants received 3 infusions per day - either 3 active or 1 active and 2 placebo Clinical assessor and participant blinded, but a separately designated clinician in each centre aware of allocation to interpret tobramycin concentrations and change doses if necessary
Incomplete outcome data (attrition bias) 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, reasons given)
Selective reporting (reporting bias)	Low risk	Published protocol compared to final paper, no outcomes missing
Other bias	Low risk	No reporting or publication bias.

Methods	Randomised controlled study. Parallel design. Location; multi-centre (3 centres) in France. Duration: 14 days treatment (first of these in hospital, then re-admitted for Day 14)
Participants	22 participants with diagnosis of CF and chronic colonisation with <i>P aeruginosa</i> enrolled when requiring IV antibiotics for a pulmonary exacerbation. Once daily: n = 12 (8 male); mean (SD) age 11.4 (4.2) years, age range 5.6 - 19.3 years. Thrice daily: n = 10 (6 male); mean (SD) age 10.7 (2.9) years, age range 7.4 - 17.2 years. Pulmonary exacerbation defined.
Interventions	Group 1: once-daily dosing (15 mg/kg/day) of tobramycin over 30 minutes Group 2: thrice-daily dosing (15 mg/kg/day) of tobramycin each over 30 minutes. 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 Inflammatory markers.
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	Randomised controlled study. Parallel design. Location: single centre in UK. Duration: 12 days treatment in hospital. Audiograms performed at least 2 weeks post-treatment
Participants	60 participants with diagnosis of CF and a pulmonary exacerbation with <i>P aeruginosa</i> (defined). 34 randomised to the once-daily group and 26 to the 3-times daily group. 11 withdrawn (4 from the once-daily group and 7 from the thrice-daily group) - 8 (4 from each group) due to tobramycin resistance, 1 (thrice-daily group) due to concurrent colomycin treatment leading to a reduction in tobramycin dose, 2 (thrice-daily group) refused to continue. Therefore 49 studied: Once-daily group: n = 30 (16 male); mean age 21 years; age range 16 to 32 years. Mean (range) weight 55.3 (40 - 73) kg. Thrice-daily group: n = 19 (11 male); mean age 22 years; age range 15 to 47 years. Mean (range) weight 54.0 (38.5 - 76) kg
Interventions	Group 1: once-daily dosing (n = 34) (10 mg/kg/day) of tobramycin administered over 60 minutes Group 2: thrice-daily dosing (n = 26) (10 mg/kg/day) of tobramycin each administered over 30 minutes. 12 days of treatment. Combination therapy with beta-lactam.
Outcomes	Lung function: FEV ₁ , FVC, FEF _{25-75%} . Body mass index. Ototoxicity. Nephrotoxicity: serum creatinine. Clinical score. White cell count (% neutrophils). C-reactive protein. Participant preference.
Notes	Equivalence study. Sample size calculation undertaken.

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) All outcomes	High risk	Unblinded. Audiologist blinded to treatment regimen.

Whitehead 2002 (Continued)

Incomplete outcome data (attrition bias) All outcomes	High risk	No intention-to-treat analysis. 60 recruited, 49 studied. No ITT analysis. Reasons for withdrawal given, but seem to be related to treatment
Selective reporting (reporting bias)	Unclear risk	Protocol not published in advance.
Other bias	Low risk	No publication bias.

CF: cystic fibrosis

FEV₁: forced expiratory volume at one second

FEF_{25–75%}: forced mid-expiratory flow FVC: forced vital capacity

NAG: N-acetyl-beta-D glucosaminidase

P. aeruginosa: *Pseudomonas aeruginosa*

vs: versus

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Adeboyeke 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	Study 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 study with efficacy measured on a symptom score.
Winnie 1991	Comparison of three times versus four times daily tobramycin dosing
Wood 1996	Comparison of twice daily versus three times daily tobramycin dosing

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

FEV₁: 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

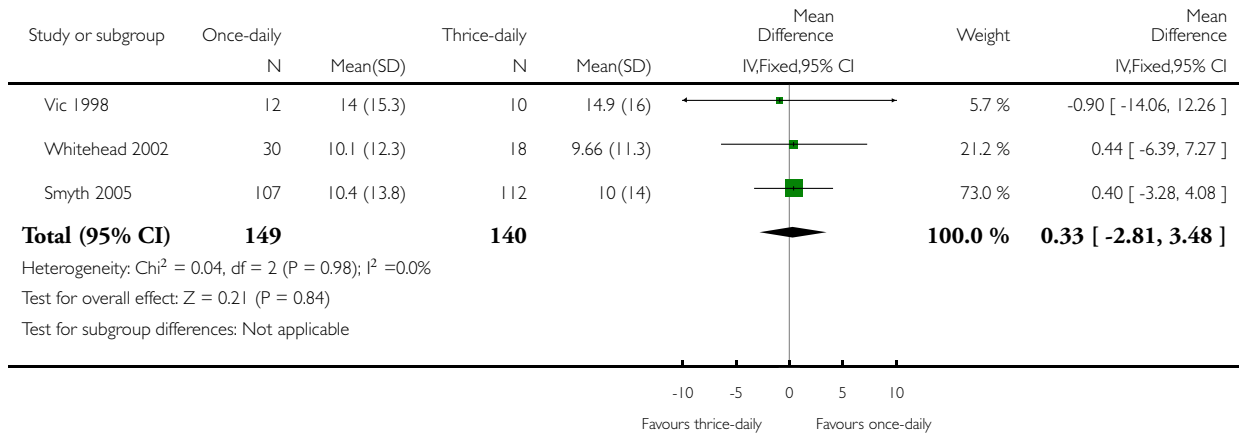
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean percentage change in FEV ₁ (% predicted)	3	289	Mean Difference (IV, Fixed, 95% CI)	0.33 [-2.81, 3.48]
2 Mean percentage change in FVC (% predicted)	2	70	Mean Difference (IV, Fixed, 95% CI)	0.29 [-6.58, 7.16]
3 Mean change in FEF ₂₅₋₇₅ (% predicted)	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 BMI	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 (% predicted).

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 FEV₁ (% predicted)

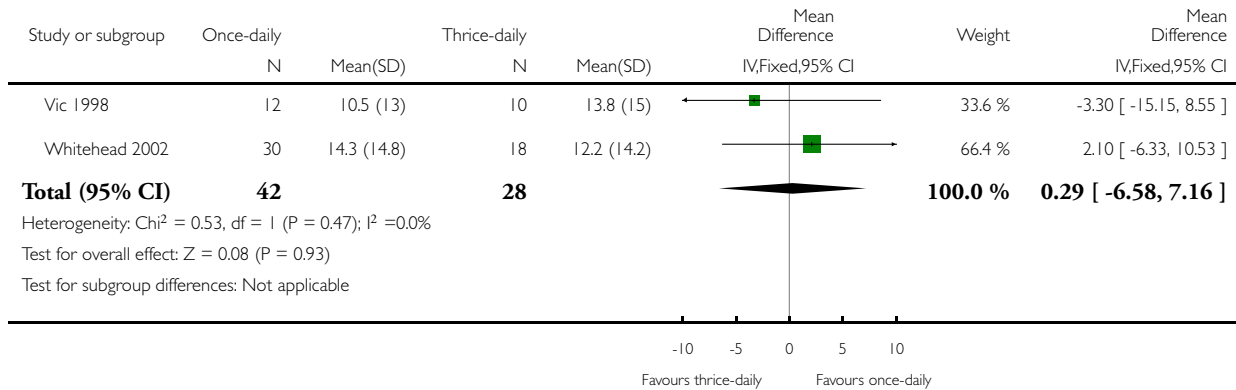


Analysis 1.2. Comparison 1 Once-daily dosing of intravenous aminoglycoside antibiotics versus multiple-daily dosing, Outcome 2 Mean percentage change in FVC (% predicted).

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: 2 Mean percentage change in FVC (% predicted)

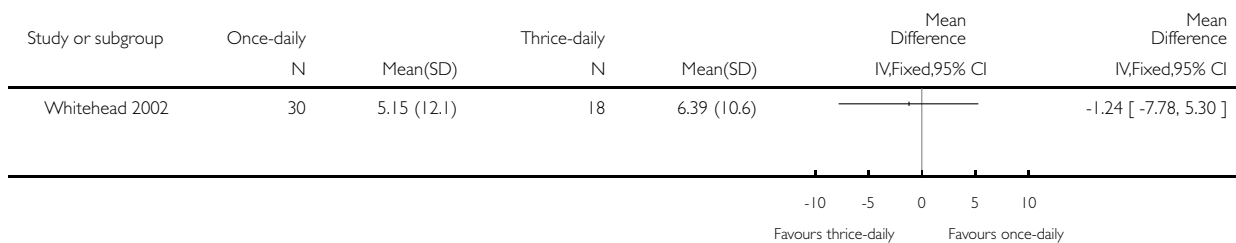


Analysis 1.3. Comparison 1 Once-daily dosing of intravenous aminoglycoside antibiotics versus multiple-daily dosing, Outcome 3 Mean change in FEF₂₅₋₇₅ (% predicted).

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: 3 Mean change in FEF₂₅₋₇₅ (% predicted)

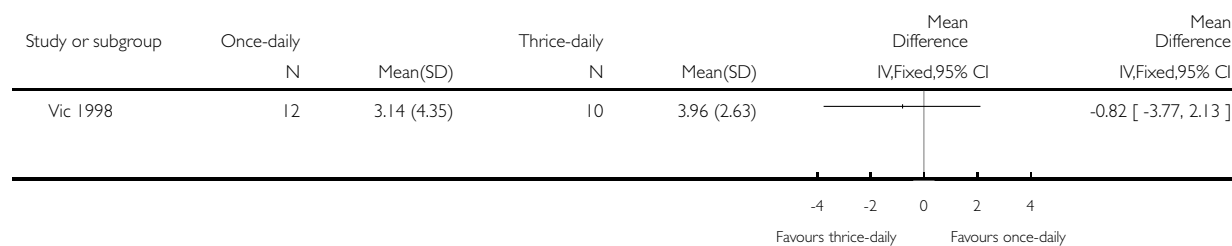


Analysis 1.4. Comparison 1 Once-daily dosing of intravenous aminoglycoside antibiotics versus multiple-daily dosing, Outcome 4 Mean change in weight/height %.

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: 4 Mean change in weight/height %

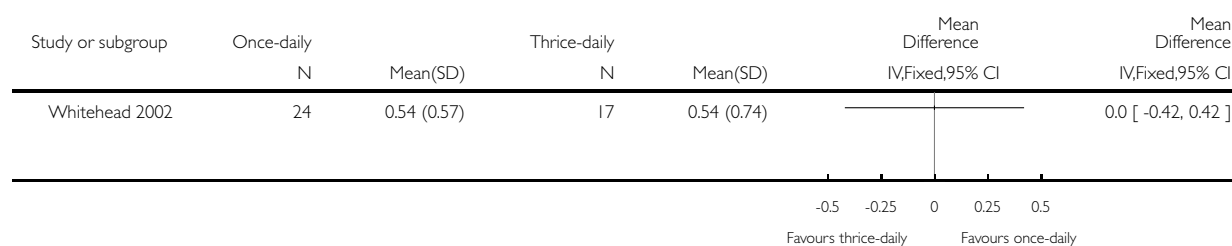


Analysis 1.5. Comparison 1 Once-daily dosing of intravenous aminoglycoside antibiotics versus multiple-daily dosing, Outcome 5 Mean change in BMI.

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 BMI

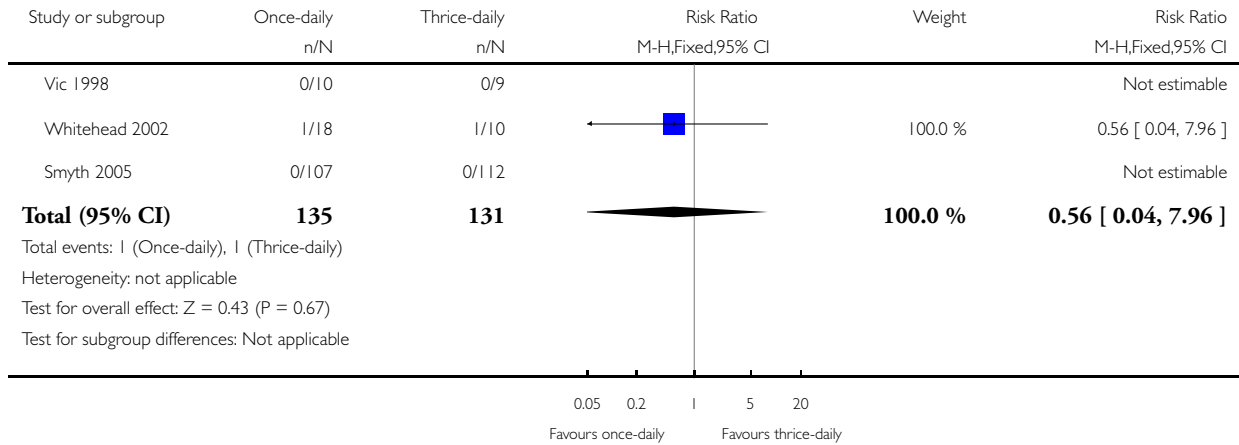


Analysis 1.6. Comparison 1 Once-daily dosing of intravenous aminoglycoside antibiotics versus multiple-daily dosing, Outcome 6 Development of ototoxicity (after treatment).

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)

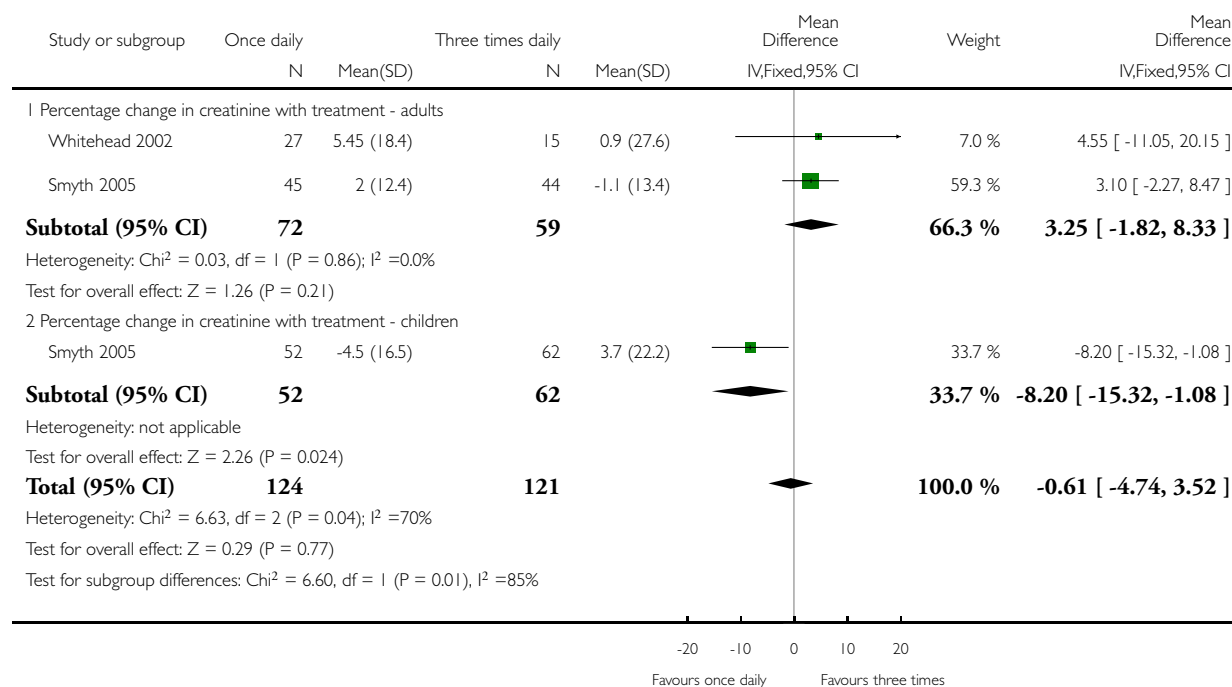


Analysis 1.7. Comparison 1 Once-daily dosing of intravenous aminoglycoside antibiotics versus multiple-daily dosing, Outcome 7 Percentage change in creatinine with treatment.

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



WHAT'S NEW

Last assessed as up-to-date: 20 March 2017.

Date	Event	Description
20 March 2017	New search has been performed	A search of the Cystic Fibrosis and Genetic Disorders Group's Trials Register did not identify any references which were potentially eligible for inclusion in the review. A summary of findings table has been included in this update.
20 March 2017	New citation required but conclusions have not changed	A new co-author, Sarah Nolan, has joined the review team. No new references were added to this update, hence our

(Continued)

conclusions remain the same

HISTORY

Protocol first published: Issue 2, 2000

Review first published: Issue 4, 2000

Date	Event	Description
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
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 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
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 (Adeboyeke 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 (Adeboyeke 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).

(Continued)

		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 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 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.

Sarah Nevitt joined the review team in September 2016 and has prepared the summary of findings table.

DECLARATIONS OF INTEREST

The contact author (ARS) declares relevant activities of membership of a Raptor steering committee, consultancies for Vertex, Gilead and Roche. Prof Smyth has given lectures at symposia sponsored by Gilead and Actavis. He is also the principal investigator for the TOPIC study: Tobramycin Once-daily Prescribing In Cystic Fibrosis.

The co-author (JB) has no potential interest to declare.

The co-author (SJN) has no potential interest to declare.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK.

This systematic review was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

INDEX TERMS

Medical Subject Headings (MeSH)

*Pseudomonas aeruginosa; Aminoglycosides [administration & dosage; adverse effects]; Anti-Bacterial Agents [*administration & dosage; adverse effects]; Body Mass Index; Cystic Fibrosis [*complications]; Drug Administration Schedule; Drug Therapy, Combination [methods]; Forced Expiratory Volume [drug effects]; Injections, Intravenous; Pseudomonas Infections [*drug therapy]; Randomized Controlled Trials as Topic; Tobramycin [*administration & dosage]; Vital Capacity [drug effects]; beta-Lactams [administration & dosage]

MeSH check words

Adolescent; Adult; Child; Child, Preschool; Female; Humans; Male; Middle Aged; Young Adult