

Once versus three-times daily regimens of tobramycin treatment for pulmonary exacerbations of cystic fibrosis—the TOPIC study: a randomised controlled trial

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Summary

Background Intravenous tobramycin (three-times daily) is widely used for pulmonary exacerbations in patients with cystic fibrosis who have chronic *Pseudomonas aeruginosa* infection. We undertook a double-blind, randomised controlled trial to assess the safety and efficacy of once versus three-times daily tobramycin in these patients.

Methods 244 patients from 21 cystic-fibrosis centres in the UK were randomly assigned to once or three-times daily tobramycin (with ceftazidime) for 14 days. Treatment was given as 30-min infusions of tobramycin in 0.9% saline. Primary outcome measure was change in forced expiratory volume in 1 s (FEV₁), over the 14 days of treatment, expressed as a percentage of the predicted normal value for age, sex, and height. We also measured the change in FEV₁ expressed as a percentage of baseline. Secondary outcomes included change in serum creatinine. The study was powered for equivalence, and primary analysis was per protocol.

Findings 219 patients (107 once daily, 112 three-times daily) completed the study per protocol. None was lost to follow-up, although 20 discontinued intervention. Of 122 patients assigned to once daily treatment, three did not receive the study regimen. The mean change in FEV₁ (% predicted) over 14 days was similar on the two regimens (10.4% [once daily] vs 10.0% [three-times daily]; adjusted mean difference 0.4% [95% CI –3.3 to 4.1]). Mean % change in FEV₁ from baseline was also similar in both treatments (21.9% vs 22.1%; –0.1% [–8.0 to 7.9]). There was no significant difference in % change in creatinine from baseline (–1.5% [once daily] vs 1.7% [three-times daily]). However, in children, once daily treatment was significantly less nephrotoxic than was thrice daily (mean % change in creatinine –4.5% [once daily] vs 3.7% [thrice daily]; adjusted mean difference –8.0%, 95% CI –15.7 to –0.4). No patients developed hearing loss during the study, although two reported acute dizziness and were withdrawn from the study.

Interpretation Intravenous tobramycin has equal efficacy if given once or three-times daily (with ceftazidime) for pulmonary exacerbations of cystic fibrosis. The once daily regimen might be less nephrotoxic in children.

Introduction

Aminoglycoside antibiotics are widely used for the management of pulmonary exacerbations in patients with cystic fibrosis who have chronic pulmonary infection with *Pseudomonas aeruginosa*.¹ Patients with the disease might receive repeated and extended courses of treatment with aminoglycosides, often from a young age, which makes them especially vulnerable to the adverse effects of these drugs, mainly nephrotoxicity and ototoxicity. In the kidney, standard doses of aminoglycosides can cause proximal tubular damage, whereas toxic concentrations cause acute tubular necrosis.² In the inner ear, these drugs can damage cochlear hair cells, leading to sensorineural deafness.³

Aminoglycosides are generally given three-times daily. However, a regimen of one dose per day might be more effective because it makes use of concentration-dependent killing (bacterial killing dependent on the highest concentration of tobramycin achieved) and the post-antibiotic effect (bacterial killing continuing even when tobramycin concentrations are no longer measurable).² Once daily treatment also minimises adaptive resistance.⁴ Once daily dosing might also be less nephrotoxic than the three-times daily regimen because a high serum concentration could saturate uptake of aminoglycosides in

the proximal tubule.² This treatment would also substantially reduce the burden of care for families.

The pharmacokinetics of aminoglycosides in patients with cystic fibrosis are different from that in non-cystic-fibrosis individuals (increased volume of distribution and rapid elimination).⁵ In other groups of individuals, investigators have not considered specific outcome measures (improvement in symptoms and lung function) that are relevant to cystic fibrosis, and so the data cannot be extrapolated to these patients. A systematic review⁶ of studies of single versus multiple daily dosing of aminoglycosides in cystic fibrosis identified only three studies relating to 175 affected patients. These studies had insufficient power to detect a difference between regimens.

Therefore, we designed a large, double-blind, randomised controlled trial to compare the safety and efficacy of once versus thrice daily aminoglycosides for pulmonary exacerbations of cystic fibrosis.

Methods

Patients

All participants had a diagnosis of cystic fibrosis (ie, sweat chloride >60 mmol/L or a genotype known to

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Panel: Secondary outcome measures—change in listed factors over 14 days of treatment

- Serum creatinine amounts
- Pure-tone audiogram
Abnormal result was defined as hearing loss developing during treatment of >20 dB, in either ear, at two or more frequencies at 2–8 kHz.⁸
- Clinical score
We used the score suggested by Jensen and colleagues,¹¹ which measures symptoms (cough, sputum, dyspnoea, appetite, and subjective effect of treatment) and clinical findings (crepitations, wheeze, air entry, and general condition)
- Amounts of inflammatory marker C-reactive protein

cause the disease). Patients were eligible if aged over 5 years and able to participate in pulmonary-function tests reliably. *P aeruginosa* had to have been isolated from

respiratory secretions on at least one occasion, with the most recently isolated organism showing sensitivity to tobramycin, ceftazidime, or both. Bacterial culture of respiratory samples was done at patients' local laboratories. All participants enrolled had pulmonary exacerbation as defined by Fuchs and colleagues.⁷

Patients were excluded if they had pre-existing hearing impairment (>20 dB hearing level at any two frequencies between 2 kHz and 8 kHz on the standard audiogram)⁸ or renal impairment (serum creatinine concentrations outside the reference range for the enrolling centre). Patients were not enrolled if they had a history of adverse reactions to either tobramycin or ceftazidime or a previous chronic infection with *Burkholderia cepacia*. Nebulised antibiotics were discontinued on study entry. Female patients of childbearing age were offered a pregnancy test before enrolment and excluded if test results were positive. Patients were enrolled from 21 cystic-fibrosis centres in the UK (15 paediatric and six adult centres).

The study was approved by Trent multicentre research ethics committee and by local ethics committees in all centres. Written informed consent was obtained from adult patients and from parents of children under 18 years (with the child or young person giving assent).

Procedures

Patients were randomly assigned to once or three-times daily tobramycin, given as a 30-min infusion in 0.9% saline (31 mL for children, 65 mL for adults). Patients allocated to the once daily regimen also received two infusions of 0.9% saline per day, which were the same volume as the active infusions to preserve the double-blind study protocol. We used total daily doses equivalent to those previously received by patients during routine treatment. If a patient had not previously had tobramycin, a dose of 10 mg/kg per day was prescribed. Tobramycin concentrations were measured (by fluorescent polarisation immunoassays⁹) immediately before the fourth infusion and 30 min after the end of the fourth infusion. For patients on the once daily regimen, the fourth infusion (on day 2) contained the second active dose; for those having three-times daily treatment, this infusion contained the fourth active dose.

Target concentrations of tobramycin for the once daily regimen were 1 mg/L or less (trough) and 20–30 mg/L (peak); for the three-times daily regimen, these values were 2 mg/L or less and 5–12 mg/L, respectively. If the trough concentration was higher than the target range, the patient was withdrawn from the study. If the peak concentration was outside the target range, an appropriate 10% increase or 10% reduction in dose was made as appropriate. In every case, patients received ceftazidime as the only additional intravenous antibiotic. Treatment was for 14 days (a minimum of 10 days needed for per-protocol analysis) and was given both in hospital and at home. For home treatment, study drugs

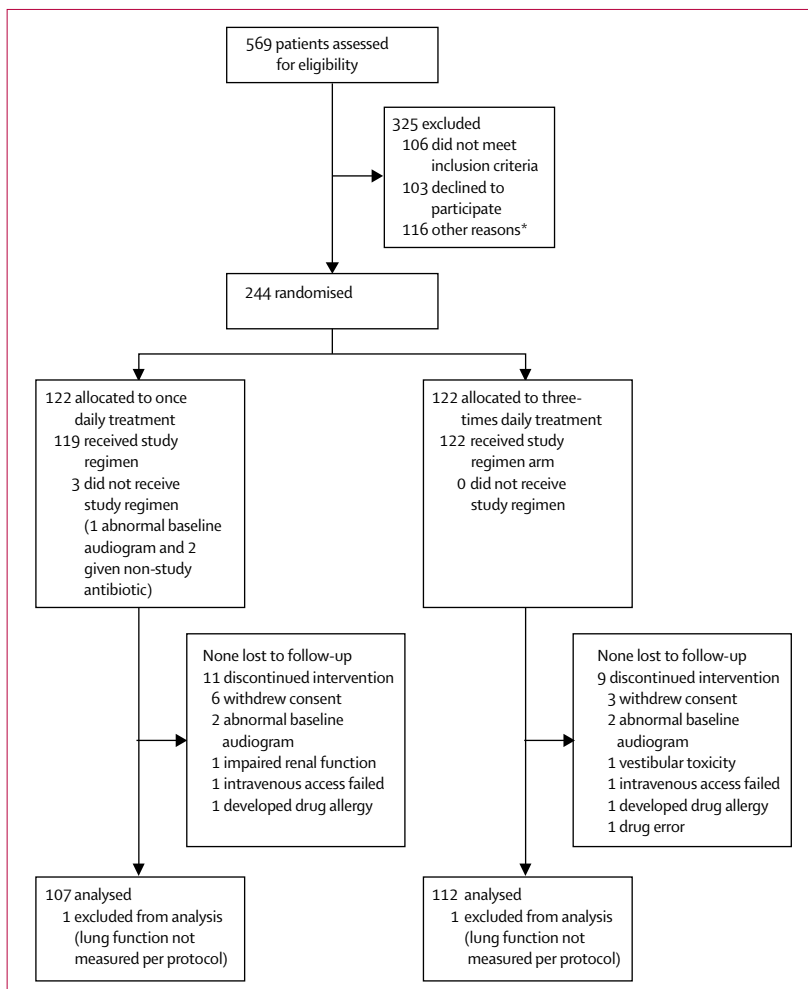


Figure 1: Trial profile

*Other reasons included: not possible intravenous access, cancelled intravenous antibiotic course, previous allergic reaction to ceftazidime, and the clinician wanted to use a non-study antibiotic.

	Once daily treatment (n=107)	Three-times daily treatment (n=112)
Age (years; median [range])	14.8 (5.1–50.4)	14.9 (5.5–43.4)
Male patients (%)	63 (59%)	68 (61%)
FEV ₁ (L; mean [SD])	1.59 (0.78)	1.58 (0.75)
FEV ₁ (% predicted; mean [SD])	60.0% (20.6)	60.8% (24.2)
Creatinine (mmol/L; mean [SD])	66.0 (17.6)	67.0 (21.3)
Patients with respiratory cultures at enrolment	96 (90%)	104 (93%)
Cultures showing <i>P aeruginosa</i> at enrolment	75 (78%)	86 (83%)
Samples in which all strains of <i>P aeruginosa</i> are sensitive to tobramycin	66 (88%)	74 (86%)

Data are mean (SD) or number (%) unless otherwise indicated.

Table 1: Baseline characteristics of patients completing study per protocol

were supplied in an infusion device (Eclipse, I-Flow, Lake Forest, CA, USA) by a homecare company (Clinovia, Harlow, UK).

Patients were recruited by a local investigator in every centre, and were randomly assigned to once or three-times daily treatment in permuted blocks of six, stratified by centre and type of clinic (adult vs paediatric). The allocation sequence was generated by the pharmacy at the coordinating centre at Nottingham City Hospital, Nottingham, UK, and a study number was assigned by telephone. Both the local investigator, who also undertook assessment of clinical outcome measures, and the patient, remained masked to treatment allocation. A separately designated clinician in every centre was aware of patients' treatment allocations to interpret tobramycin concentrations and change doses if necessary.

The primary outcome measure was change in forced expiratory volume in 1 s (FEV₁), expressed as a percentage of the predicted normal value for age, sex, and height (% predicted FEV₁),¹⁰ during 14 days of treatment. We also measured the percentage change in FEV₁ from baseline. Secondary outcomes were the change in other clinical measures during treatment (panel).

We also planned to assess other outcome measures in a subgroup of patients. These measures were changes in

concentrations of urinary N-acetyl-β-D glucosaminidase (NAG), a proximal tubular enzyme, and the time to a next course of intravenous antibiotics. Individuals were from six centres at which the local investigators had agreed to provide additional data: Nottingham City Hospital, Nottingham, UK (adult and paediatric); Birmingham Heartlands Hospital, Birmingham, UK (adult and paediatric); the Royal Liverpool Children's Hospital, Liverpool, UK; and Arrows Park Hospital, the Wirral, UK (paediatric). The baseline characteristics of these patients were similar to that of the larger study group.

The computer package MW/Pharm¹² (University Centre for Pharmacy, Groningen, Netherlands) was used to calculate the minimum and maximum steady-state values of tobramycin (C_{min,SS} and C_{max,SS}) in a subgroup of patients, together with the concentration corrected to precisely 30 min after the infusion was completed.

Statistical analysis

The trial was designed as an equivalence study.¹³ We estimated an SD for change in FEV₁ over 14 days of 9% predicted (from routinely measured data at the coordinating centre). Regimens were regarded as equivalent if the difference between treatments in change in FEV₁ (using 95% CI) was less than 4% of predicted FEV₁. We estimated that with 110 patients randomly assigned to each regimen, the study would have 80% power that the regimens would be deemed equivalent if they were truly identical.

An independent data monitoring committee was appointed to review the data. Since we were undertaking an equivalence study, the primary analysis was per protocol but an intention-to-treat analysis was also undertaken. The mean difference between treatments and 95% CI for the true difference was obtained from analysis of variance, with adjustment for centre and type of clinic, to show the restriction implied by the randomisation.

For both treatment regimens, survival analysis (log-rank test) was used to compare the time to next course of intravenous antibiotics. For this outcome measure,

	Once daily treatment		Three-times daily treatment		Adjusted mean difference (95% CI)
	Mean (SD) change	n	Mean (SD) change	n	
Per protocol					
% predicted FEV ₁ from start of treatment					
All	10.4% (13.8)	107	10.0% (14.0)	112	0.4% (-3.3 to 4.1)
Children	9.9% (15.7)	61	9.9% (14.8)	64	-0.1% (-5.6 to 5.5)
Adults	11.1% (10.8)	46	10.2% (13.1)	48	0.8% (-4.1 to 5.8)
FEV ₁ % of baseline					
All	21.9% (30.5)	107	22.1% (30.1)	112	-0.1% (-8.0 to 7.9)
Intention to treat					
% predicted FEV ₁ from start of treatment					
All	9.8% (13.4)	119	9.8% (14.4)	120	0.2% (-3.3 to 3.8)

Mean differences adjusted for centre and type of clinic (ie, adult vs paediatric).

Table 2: Comparison of change in FEV₁ between treatment groups according to type of analysis

	Mean change in creatinine (SD) % baseline		Adjusted mean difference (95% CI)	P
	Once daily treatment	Three-times daily treatment		
Per protocol				
All	-1.5% (15.0) (n=97)	1.7% (19.1) (n=106)	-3.1% (-8.0 to 1.7)	0.21
Children	-4.5% (16.5) (n=52)	3.7% (22.2) (n=62)	-8.0% (-15.7 to -0.4)	0.04
Adults	2.0% (12.4) (n=45)	-1.1% (13.4) (n=44)	4.1% (-1.3 to 9.5)	0.14
Intention to treat				
All	-0.8% (15.4) (n=107)	1.5% (18.9) (n=111)	-2.1% (-6.8 to 2.6)	0.4
Children	-3.7% (16.2) (n=57)	3.1% (22.0) (n=65)	-6.5% (-13.7 to 0.8)	0.08
Adults	2.5% (13.8) (n=50)	-0.8% (13.3) (n=46)	4.2% (-1.3 to 9.7)	0.13

Data missing for 16 of 219 patients in per-protocol analysis and for 26 of 244 in intention-to-treat analysis.

Table 3: Change in creatinine from baseline according to type of analysis

patients were followed up from when they entered the study until study closure in April, 2003. Subgroup analysis was undertaken for paediatric (5–16 years old) and adult (>16 years old) groups. Analysis was undertaken using SPSS version 10.0.5.

The protocol for this study was peer-reviewed and accepted by *The Lancet*; a summary of the protocol was published on the journal's website, and the journal then made a commitment to peer-review the primary clinical manuscript.

Role of the funding source

The study protocol was drawn up independently by the TOPIC steering committee and approved by the clinical trials advisory committee of the UK CF Trust. The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

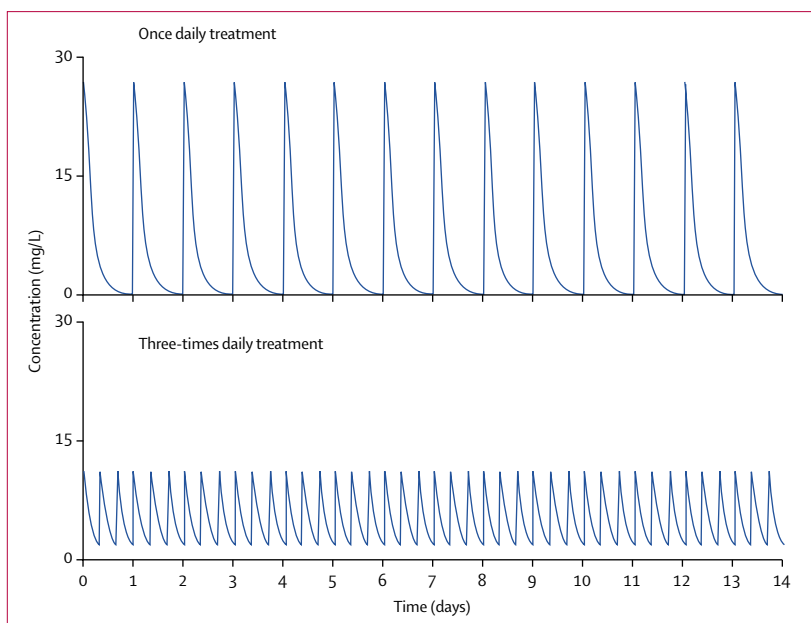


Figure 2: Concentration-time curves for once daily and three-times daily tobramycin

Results

Figure 1 shows the trial profile. Enrolment took place between February, 1999, and April, 2003. Of 219 patients completing the study, 125 were assigned a paediatric randomisation code and 94 an adult code. However, six patients seen in paediatric clinics were assigned an adult code because bodyweight was greater than 40 kg, and five seen in adult clinics were assigned a paediatric code (bodyweight <40 kg). Results of analysis are presented by initial classification to preserve stratification, but reanalysis by chronological age did not affect the results. Table 1 shows the baseline characteristics of patients completing the study per protocol.

Table 2 shows the mean change in % predicted FEV₁ from the start of treatment and the mean change in FEV₁ as a percentage of baseline, which were equivalent for the two regimens. Although the 95% CI were wide because of smaller sample sizes than the group as a whole, no apparent difference was recorded between regimens in adult or paediatric subgroups. The two regimens were also equivalent in terms of change in % predicted FEV₁ in the intention-to-treat analysis (data were available for 239 of 244 patients in the trial).

Table 3 shows the mean percentage change in creatinine amounts from baseline in the once and three-times daily groups. Creatinine concentrations fell for once daily treatment and rose for three-times daily treatment. In the paediatric subgroup, creatinine amounts fell by about 5% with once daily treatment and rose by about 4% with three-times daily treatment, and this difference was significant in the per-protocol analysis. The difference was of similar magnitude, but not significant in the intention-to-treat analysis.

To assess the effect of the once and three-times daily regimens on the proximal tubule, we measured NAG concentrations before the first dose of tobramycin and after 14 days of treatment. Data were available for 107 patients who completed the study per protocol (59 once daily vs 48 three-times daily). For adults and children, the increase seen in NAG was 33% less for once daily than three-times daily treatment ($p=0.049$). A similar difference in favour of the once daily regimen was seen in children ($p=0.02$). The difference in the adult subgroup was not significant ($p=0.31$). Serum magnesium concentration on day 14 was measured in 145 of 244 patients. Magnesium was below the reference range (0.7–1.0 mmol/L) in seven patients (four [once daily] vs three [thrice daily]); hypomagnesaemia was borderline in all these patients (0.60–0.69 mmol/L).

No patient showed deterioration in hearing in audiograms from days 1 and 14 of treatment. Two patients (one on each regimen) reported acute dizziness and were withdrawn from the study. In both patients, symptoms resolved without treatment.

On days 0 and 14, we measured concentrations of C-reactive protein in 143 patients in the per-protocol analysis (67 once daily; 76 three-times daily). Mean fall

(SD) in concentration on once daily treatment was 12.2 mg/L (38.2) and on three-times daily treatment 5.6 mg/L (16.8); adjusted mean difference -6.3, 95% CI -16.1 to 3.6, $p=0.21$. This fall occurred mainly in adults.

Clinical scores were available for 154 patients (77 on each regimen). Comparison of clinical scores at baseline versus day 14 showed no significant difference between regimens, either overall (median change in score -6, IQR -9 to -5 [once daily]; -6, -8 to -4 [three-times daily], $p=0.46$) or in adult or child subgroups. Data for the time to next course of intravenous antibiotics were available for 113 patients (56 on once daily, 57 on thrice daily). Median time was 131 days (95% CI 76–186) for once daily and 168 days (34–302) for three-times daily treatment ($p=0.48$).

Pharmacokinetic modelling was undertaken in 108 of the 219 patients who completed treatment per protocol (51 [once daily], 57 [three-times daily]). Figure 2 shows typical concentration-time curves for both treatment regimens. Tobramycin concentrations (mg/L) differed between treatments for $C_{min,SS}$ (once daily vs three-times daily; mean 0.1 [SD 0.2] vs 1.0 [0.4]), $C_{max,SS}$ (28.4 [5.07] vs 9.9 [1.4]), and the calculated 30-min peak values (24.8 [4.7] vs 8.4 [1.2]).

Discussion

We have shown that once daily tobramycin (with ceftazidime) has equivalent efficacy to conventional three-times daily treatment for pulmonary exacerbations of cystic fibrosis. In children, we noted a difference in percentage change in serum creatinine concentrations that was in favour of once daily tobramycin and significant in the per-protocol group. This group had a full course of treatment and was therefore at greatest risk of toxic effects. A smaller rise in the proximal tubular enzyme NAG was also seen in this subgroup than the thrice daily group. These results suggest that once daily treatment might be less nephrotoxic than thrice daily treatment in children. We recorded a rise in creatinine in adult patients on once daily treatment, although the difference between regimens was not significant.

However, our study did not have sufficient power to exclude greater nephrotoxicity in adult patients receiving once daily treatment. Because toxic effects are cumulative, further longitudinal studies are needed. We did not identify any patients who developed ototoxic effects while on the study regimen. There is evidence that patients with cystic fibrosis could have a lower probability of hearing loss with aminoglycoside exposure than unaffected individuals, which has led to speculation that the cystic-fibrosis defect could be protective.³

The once daily regimen was designed to increase the maximum tobramycin concentration. The calculated value for once daily treatment (28.4 mg/L) was much higher than that for three-times daily treatment (9.9 mg/L), which should achieve the greatest effect of concentration-dependent killing. The concentration-time curve for once

daily treatment (figure 2) favours the post-antibiotic effect and should keep adaptive resistance to a minimum. However, the favourable pharmacokinetics of once daily tobramycin did not translate into greater clinical efficacy than for thrice daily treatment in this study.

The TOPIC study has had sufficient statistical power to show equivalent efficacy between once and three-times daily tobramycin in cystic fibrosis. The CI for the difference between the two regimens (ie, improvement in % predicted FEV₁) means that a difference of greater than 4.1% is most unlikely. This finding is similar to our predefined clinical consensus that a difference of up to 4%, should be presumed equivalent. We think that our results are generalisable, because the study included both children and adults and was done pragmatically in many cystic-fibrosis centres.

The largest trial previously undertaken was in 60 adults with the disease and showed equivalent efficacy for forced vital capacity, body-mass index, and C-reactive protein. However, the study had insufficient power to show equivalence for FEV₁ or creatinine.¹⁴ Apart from our trial, the only other study to investigate children with cystic fibrosis was not large enough to show equivalent efficacy, but did show evidence of lowered nephrotoxicity with once daily treatment (significantly reduced concentrations of urinary β_2 microglobulin on day 14 of treatment).¹⁵ Our study also showed a smaller rise in proximal tubular enzymes with once daily than three-times treatment. Proximal tubular damage (indicated by enzymuria) in patients with cystic fibrosis receiving tobramycin resolves after treatment is completed.¹⁶ Symptomatic hypomagnesaemia has been reported in patients receiving aminoglycosides.¹⁷ We recorded mild hypomagnesaemia in seven patients at the end of treatment, none of whom was symptomatic.

Acute renal failure complicating intravenous antibiotic therapy has been reported in patients with cystic fibrosis;^{18–20} this failure was not seen in any patient taking part in the TOPIC study. The potential to reduce nephrotoxicity is an important advantage of a once daily regimen, although this reduction might not hold true for patients aged over 16 years. The primary defect of cystic fibrosis is not thought to affect renal function; indeed, affected patients have enhanced renal clearance.⁵ The mechanism for the apparent difference between adults and children seen in this study is not clear.

Our study might be criticised because most but not all patients had an initial respiratory sample positive for *P aeruginosa* on study entry (table 1). However, all patients had previously had the organism isolated and the responsible clinician had decided to prescribe the antipseudomonal antibiotics ceftazidime and tobramycin, independent of any consideration of enrolment into the TOPIC study. In most samples, all isolated strains of *P aeruginosa* were fully sensitive to tobramycin. In a national survey of UK cystic-fibrosis centres done by our group, 86% of centres reported that they would use

tobramycin, if in-vitro resistance was reported.¹ Our study was a pragmatic clinical trial designed to mimic current clinic practice. Infection with *P aeruginosa* was not an outcome measure and the organism-specific characteristics of the two groups at baseline were similar (table 1).

Our results are likely to affect aminoglycoside prescription in cystic fibrosis in clinical practice. Once daily treatment might be preferred by patients receiving intravenous antibiotics because of its convenience. Antipseudomonal antibiotics are usually given as combinations of two or more drugs in cystic fibrosis because of concerns about emerging antibiotic resistance.²¹ Most other antipseudomonal antibiotics need to be given three times, and so further development of other once daily antibiotics would be useful. However, the combination of once daily tobramycin with other approaches, such as a continuous supply of antibiotics (eg, ceftazidime via a portable infusion pump²²), could further simplify treatment for patients with cystic fibrosis in the future.

Contributors

A Smyth conceived and designed the study, enrolled patients, and wrote the manuscript. K Tan designed the study, enrolled patients, and reviewed the manuscript. P Hyman-Taylor coordinated the study, collected data, and reviewed the manuscript. M Mulheran collected and interpreted audiological data, and reviewed the manuscript. S Lewis formulated the analysis plan, liaised with the data monitoring committee, and did the statistical analysis. D Stableforth and A Knox contributed to study design, enrolled patients, and reviewed the manuscript.

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Conflict of interest statement

AS has received support from Profile Pharma and Forest Laboratories; both companies market a nebulised antibiotic used in cystic-fibrosis treatment. He has provided paid expert testimony on the role of aminoglycosides in acute renal failure in cystic fibrosis. DS has received support from Forest Laboratories.

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