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A randomised clinical trial of nebulised tobramycin or colistin in cystic fibrosis

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A randomised clinical trial of nebulised tobramycin or colistin in cystic fibrosis. M.E. Hodson, C.G. Gallagher, J.R.W. Govan. ©ERS Journals Ltd 2002.

ABSTRACT: Chronic infection with *Pseudomonas aeruginosa* is associated with progressive deterioration in lung function in cystic fibrosis (CF) patients. The purpose of this trial was to assess the efficacy and safety of tobramycin nebuliser solution (TNS) and nebulised colistin in CF patients chronically infected with *P. aeruginosa*.

One-hundred and fifteen patients, aged ⩾6 yrs, were randomised to receive either TNS or colistin, twice daily for 4 weeks. The primary end point was an evaluation of the relative change in lung function from baseline, as measured by forced expiratory volume in one second % predicted. Secondary end points included changes in sputum *P. aeruginosa* density, tobramycin/colistin minimum inhibitory concentrations and safety assessments.

TNS produced a mean 6.7% improvement in lung function (p=0.006), whilst there was no significant improvement in the colistin-treated patients (mean change 0.37%). Both nebulised antibiotic regimens produced a significant decrease in the sputum *P. aeruginosa* density, and there was no development of highly resistant strains over the course of the study. The safety profile for both nebulised antibiotics was good.

Tobramycin nebuliser solution significantly improved lung function of patients with cystic fibrosis chronically infected with *Pseudomonas aeruginosa*, but colistin did not, in this study of 1-month's duration. Both treatments reduced the bacterial load.
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Endobronchial infection with *Pseudomonas aeruginosa* is a characteristic of cystic fibrosis (CF) [1–4] and is closely associated with progressive deterioration in lung function and mortality in adolescents and adults, with patients losing an average of 2% of their lung function per year [5, 6].

The aim of antibiotic therapy in the chronically infected CF patient is to stabilise lung function and, if possible, to restore some of the lost lung function [7–11]. The regular use of nebulised antibiotic therapy in Europe is common for the treatment of lung infections [12, 13]. This route ensures high antibiotic concentrations at the site of infection while reducing systemic exposure [11, 12, 14]. Nebulised colistin has been shown to reduce the decline in lung function in CF patients compared with placebo, and as a single therapeutic agent it is an established treatment for CF patients with *P. aeruginosa* infection [15].

The clinicians involved in this study have, in general, a policy of treating first isolation of Pseudomonas with ciprofloxacin and inhaled colomycin. All patients are treated for acute exacerbations of infection, and patients with chronic pseudomonal infection are offered maintenance inhaled antibiotics. Colomycin is the drug of first choice, but aminoglycosides are used by some centres to a small degree. There is not a general policy of regular, 3-monthly intravenous antibiotics, although a few patients are receiving this treatment.

Tobramycin nebuliser solution (TNS), a preservative-free formulation for nebulisation, has recently been licensed as a clinically validated drug and delivery system. In the USA, placebo-controlled studies have demonstrated significant improvements in lung function within 14 days for TNS-treated patients [16, 17] and that lung function remained above baseline during long-term intermittent treatment cycles (4 weeks on/4 weeks off) for 18–24 months [18, 19].

In the present study, CF patients infected with *P. aeruginosa* received a 4-week, twice-daily aerosol administration of either TNS or nebulised colistin. The primary objective of the study was to evaluate the change in lung function, as measured by forced expiratory volume in one second (FEV_1) % predicted, with secondary objectives including an evaluation of the change in sputum *P. aeruginosa* density and changes in minimum inhibitory concentrations (MICs) of tobramycin and MICs of colistin against *P. aeruginosa* in the two treatment groups.

Methods

Patients

Eligible patients were enrolled from 16 CF centres in the UK and Ireland. Inclusion criteria were as follows: age of ⩾6 yrs; documented diagnosis of

cystic fibrosis (sweat chloride $\geqslant 60$ mEq·L^{-1} by quantitative pilocarpine iontophoresis test, sweat sodium $\geqslant 70$ mEq·L^{-1}, homozygosity for ΔF_{508} genetic mutation, or heterozygosity for two well-characterised mutations); FEV1 $\geqslant$ 25% pred (using equations from KNUDSON *et al.* [20]); *P. aeruginosa* present in a sputum or throat culture within the previous 12 months and in the sputum at the screening visit; ability to perform lung function tests and to expectorate sputum. Patients were allowed to continue their routine nonantipseudomonal medications and physiotherapy regimens. Therapy with recombinant human deoxyribonuclease (rhDNase), provided it had been started at least 4 weeks prior to screening, could also be continued.

Patients were excluded if they had received antipseudomonal antibiotics by any route within the previous 14 days or any investigational drug within 4 weeks prior to initial study drug administration. Also excluded were patients with the following: known local or systemic hypersensitivity to aminoglycosides or polymyxins, significant haemoptysis or new changes on chest radiograph, pregnancy, impaired renal function, or a sputum or throat culture yielding *Burkholderia cepacia* within the previous 2 yrs.

The study protocol was approved by the North Thames Multicentre Research Ethics Committee and local ethics committees at each of the participating centres. Written informed consent was obtained from all patients or, in the case of patients aged <18 yrs, from their legal guardian.

Study design and treatment regimen

Following completion of a 2-week screening period, during which eligibility was determined and no antipseudomonal drugs administered, suitable patients were randomised into the two parallel treatment groups. Randomisation was stratified by age (6–12 yrs, 13–17 yrs, $\geqslant$18 yrs) and centre.

Patients received either TNS 300 mg·5 mL^{-1} (tobramycin solution for inhalation (TOBI)®, PathoGenesis Ltd, Hownslow, UK) or colistin sulphomethate sodium (Colomycin® injection, Pharmax Ltd, Kent, UK) 80 mg dissolved in 3 mL of preservative-free normal saline, by inhalation twice daily for 4 weeks. TNS was administered using the PARI LC PLUS™ nebuliser (Pari Medical Ltd, West Byfleet, UK) and CR50 compressor (Medic-Aid, Bognor Regis, UK). Colistin was administered using the Ventstream™ nebuliser (Medic-Aid) and the CR50 compressor (Medic-Aid).

Clinical evaluations and spirometry were performed, and sputum samples obtained for microbiology at screening (week -2), baseline (week 0) and week 4. Clinical evaluation by the investigators and patients was appraised by assessing global improvement using the Global Rating of Change [21]. Lung function was measured by spirometry [22].

The primary efficacy end point of the study was the mean change from baseline to week 4 in FEV1 % pred. The mean relative % change in FEV1 % pred was calculated using the following formula:

$$\frac{\text{FEV1 \% pred}_{\text{week 4}} - \text{FEV1 \% pred}_{\text{week 0}}}{\text{FEV1 \% pred}_{\text{week 0}}} \times 100 = \text{\% change in FEV1 \% pred} \quad (1)$$

Sputum samples were shipped on wet ice to the central laboratory (Dept of Medical Microbiology University of Edinburgh Medical School, Edinburgh, UK) and processed at the laboratory within 48 h of collection. Samples were cultured at baseline and week 4 to assess the following microbiological parameters: sputum *P. aeruginosa* density ($\log_{10}$ colony forming units (cfu)), antimicrobial susceptibility, and incidence of recovery of other microbial pathogens [23].

Patients were asked to report any adverse events occurring during the study period. Any new adverse events occurring during the treatment period were followed up until resolution or until week 8. Airway reactivity (bronchospasm) was assessed by measuring FEV1 before and 30 min after the first and last dose of study drug administration. Serum creatinine, urea by blood urea nitrogen (BUN) and a urine protein dipstick test were performed at screening and end of treatment, but repeated at the other visits if previous findings were abnormal.

A retrospective examination was made of all the case notes to discover how many patients had received intravenous or inhaled TNS or colomycin in the 6 months prior to the study.

Statistical analysis

A target sample size of 60 per group was chosen to yield 80% coverage probability of the 95% confidence intervals, with length 6.5% on either side of the observed mean relative change in FEV1 % pred for the tobramycin group.

Efficacy analyses were completed for intent-to-treat (ITT) patients, defined as patients who had received at least one dose of study medication and had FEV1 measurements at baseline and at week 4.

The analysis of change in sputum *P. aeruginosa* density (cfu·mL^{-1}) was also performed for a microbiologically evaluable population consisting of patients who had received at least one dose of study medication and had microbiologically evaluable sputum samples at baseline and at week 4.

Demographics and baseline characteristics were compared using the paired t-test or Chi-squared test. The analyses of relative change in FEV1 % pred were performed as Wilcoxon signed-rank tests. The initial statistical analysis plan only included within-group comparisons for the efficacy parameters. However, subsequent between-group comparisons for the lung function end points were conducted using the Wilcoxon rank-sum test.

Changes in sputum *P. aeruginosa* density were analysed using the paired t-test. The treatment groups' MICs were compared using the Cochran-Mantel-Haenszel test, controlled by centre. Airway

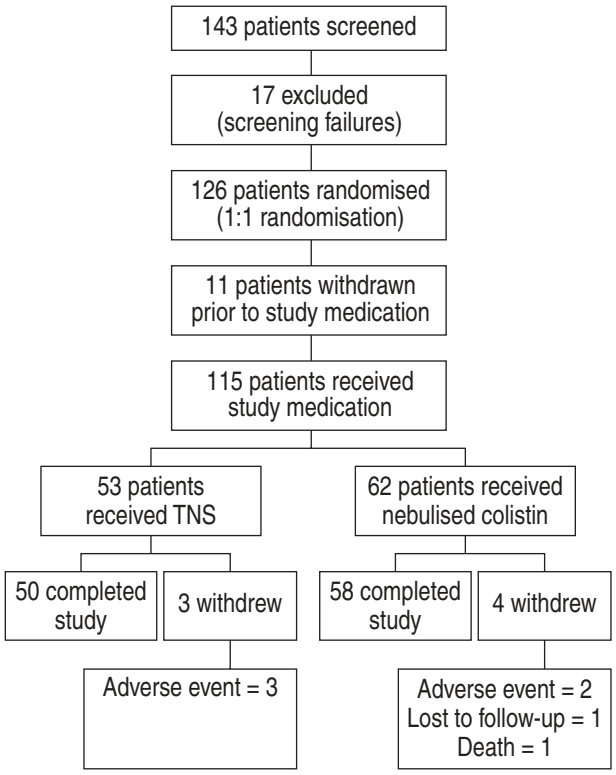

Fig. 1.–Trial profile. TNS: tobramycin nebuliser solution.

reactivity was analysed within each group using a paired t-test.

Results

The study was completed through to follow-up at week 8 in 50 of 53 patients in the TNS-treatment group (94.3%) and 58 of 62 patients in the colistin-treatment group (93.5%) (fig. 1). Treatment compliance, defined as use of $\geqslant$75% of the dispensed ampoules, was 98.1% in the TNS-treatment group and 87.1% in the colistin-treatment group.

The patient groups were similar at baseline with respect to age, sex, rhDnase usage, lung function and sputum *P. aeruginosa* density (table 1).

Lung function

Within the TNS-treatment group, there was a highly significant 6.70% increase (p=0.006) in FEV1 % pred from baseline to week 4 in the ITT patient population; whereas, within the colistin-treatment group, the 0.37% change in FEV1 % pred was not significantly different from baseline (table 2). Furthermore, the increase in FEV1 % pred was significantly larger in the TNS-treatment group when compared to the colistin-treatment group (p=0.008). When the % change in FEV1 % pred was analysed according to patient age, TNS treatment was found to be especially beneficial for younger patients (table 2).

At week 4, investigators assessed the change in the patients′ general medical condition through the completion of a Global Rating of Change questionnaire. More TNS-treated patients (21 of 53, 39.6%) than colistin-treated patients (10 of 62, 16.1%) were assessed as having an improved medical condition (p=0.006 Fisher′s exact test). Similarly, more patients in the TNS-treatment group (13 of 53, 24.5%) rated themselves as improved at the end of the treatment period, as compared to those treated with colistin (8 of 62, 12.9%).

Microbiology

In the ITT population at week 4, a mean decrease of 0.86 $\log_{10}$ cfu·mL^{-1} was observed in TNS-treated patients (p<0.001), and a mean decrease of 0.60 $\log_{10}$ cfu·mL^{-1} was observed in colistin-treated patients (p=0.007) (table 3).

To take account of the heterogeneity of MIC values commonly observed with *P. aeruginosa* infections in CF airways, the authors determined the percentage of patients whose highest MIC of tobramycin against *P. aeruginosa* (based on analysis of different colonial morphotypes) was $\geqslant$4 mg·L^{-1} at baseline and/or week 4. After 4 weeks of TNS treatment, there was a

Table 1.–Baseline characteristics of patients

Characteristic	TNS	Colistin	p-value
Patients n	53	62	
Sex			
Male	20 (37.7)	32 (51.6)	0.136[#]
Female	33 (62.3)	30 (48.4)	
Age yrs			
Mean±SD	21.3±9.6	20.1±9.4	0.505[¶]
Median (range)	20.0 (7–42)	18.0 (8–50)	
DNase use	36 (67.9)	34 (45.2)	ND
Nebulised antibiotic in previous 6 months[#]	48 (90.6)	50 (80.6)	ND
FEV1 % pred	55.4±22.9	59.4±22.6	0.349[¶]
FVC % pred	72.5±21.7	76.40±19.2	0.327[¶]
$\log_{10}$ cfu·mL^{-1}[+]	6.30±1.52	6.77±1.34	0.077[¶]

Data are presented as mean±SD and n (%) unless otherwise stated. DNase: deoxyribonuclease; TNS: tobramycin nebuliser solution; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; ND: not done; cfu: colony forming unit. [#]: Chi-squared test; [¶]: paired t-test; [+]: sputum *Pseudomonas aeruginosa* density.

Table 2. – Change in lung function following 4 weeks of nebulised antibiotic therapy

Assessment	FEV1 % pred % change from baseline		p-value¶
	TNS	Colistin	
ITT population			
Patients at week 4 n	50	59	
Mean±SD	6.70±15.12	0.37±18.78	0.008
p-value (within)#	0.006	0.473	
Age group 6–12			
Patients at week 4 n	11	11	
Mean±SD	11.51±24.33	-8.11±18.38	
p-value (within)#	0.148	0.17	
Age group 13–17			
Patients at week 4 n	11	14	
Mean±SD	14.43±7.32	6.01±25.78	
p-value (within)#	<0.001	0.399	
Age group >18			
Patients at week 4 n	28	34	
Mean±SD	1.77±10.80	0.79±14.75	
p-value (within)#	0.393	0.757	

TNS: tobramycin nebuliser solution; ITT: intent-to-treat; FEV1: forced expiratory volume in one second. #: within-group paired t-testing; ¶: between-group testing using Wilcoxon rank-sum test.

nonsignificant increase in the percentage of patients with at least one *P. aeruginosa* isolate, with a tobramycin MIC value $\geqslant$4 mg·L^{-1} from 38% to 49%; whereas, in the colistin-treatment group, it remained unchanged at 55%. After 4 weeks of TNS treatment, there was a nonsignificant decrease in the percentage of patients whose *P. aeruginosa* had colistin MIC values $\geqslant$4 mg·L^{-1} from 27% to 16%; whereas, in the colistin treatment group, it remained unchanged at 34%. There was no evidence of the development of highly tobramycin-resistant *P. aeruginosa* (MIC $\geqslant$128 mg·L^{-1}) in either treatment group over the duration of the study.

No patients in either treatment group became colonised with either *B. cepacia* or *Stenotrophomonas maltophilia* during the 4 weeks of the study. The organisms that were isolated more frequently in the TNS group than in the colistin group following treatment were *Candida albicans* (11.3% *versus* 4.8%) and *Aspergillus fumigatis* (5.7% *versus* 3.2%). Colistin treatment more frequently resulted in colonisation with *Haemophilus influenzae* (8.1% *versus* 1.9%) and *Staphylococcus aureus* (6.5% *versus* 0%).

Table 3. – Change in sputum *Pseudomonas aeruginosa* density following 4 weeks of nebulised antibiotic therapy

Log_{10} cfu·mL^{-1}	Change from baseline	
	TNS	Colistin
ITT population		
Patients assessed at week 4 n	50	50
Mean±SD	-0.86±1.43	-0.60±1.61
p-value (within)#	<0.001	0.007
Microbiologically-evaluable patients		
Assessed at week 4 n	42	37
Mean±SD	-0.79±1.35	-0.47±1.53
p-value (within)#	<0.001	0.049

TNS: tobramycin nebuliser solution; cfu: colony forming unit; ITT: intent-to-treat. #: between-group testing using the Wilcoxon rank-sum test.

Adverse events

The incidence of adverse events was comparable in the TNS and colistin groups (table 4). Thirty-four of 53 patients (64%) in the TNS-treatment group and 31 of 62 patients (50%) in the colistin-treatment group reported at least one treatment-emergent adverse event. For both treatment groups, the highest incidence of adverse events related to the respiratory system and to the "body as a whole". Twenty-six of 53 (49%) TNS patients and 22 of 62 (36%) colistin patients reported at least one respiratory system adverse event; pharyngitis was the most common treatment-emergent event in the TNS-treatment

Table 4. – Incidence of adverse events (AE)

	TOBI	Colistin
Patients n	53	62
Patients with $\geqslant$1 treatment-emergent AE#	34 (64.2)	31 (50.0)
Respiratory system AE		
Total#	26 (49.1)	22 (35.5)
Cough-increased#	5 (9.4)	11 (17.7)
Sputum-increased#	6 (11.3)	8 (12.9)
Dyspnoea#	5 (9.4)	7 (11.3)
Pharyngitis#	7 (13.2)	3 (4.8)
Patients with $\geqslant$1 serious AE#	8 (15.1)	7 (11.3)

Data are presented as n (%). TOBI: tobramycin solution for inhalation. #: no significant difference was detected between groups.

Table 5. – Acute change in forced expiratory volume in one second (FEV_1) from pre- to 30 min post-administration of the study drug at baseline and week 4

% Change in FEV_1	TNS	Colistin
Week 0		
Patients n	51	62
Mean±SD	-4.49±8.11	-3.87±9.36
p-value#	<0.001	<0.001
Week 4		
Patients n	48	58
Mean±SD	-2.57±5.39	-2.59±9.02
p-value#	0.002	0.030

TNS: tobramycin nebuliser solution. #: within-group testing using the paired t-test.

group and increased cough in the colistin-treatment group.

There were no clinically significant changes in renal function over the 4-week treatment period in either group.

Airway reactivity

Airway reactivity is an expected response to the administration of nebulised antibiotics in some CF patients. In this study, 85% of patients were receiving β_2-adrenoreceptor agonists. The acute change in FEV_1 (from pre- to 30 min post-administration of study drug) at baseline and week 4 showed significant falls in both treatment groups, with a degree of tolerance developing over the treatment period (table 5). Airway reactivity, as defined by a $\geqslant$10% loss in FEV_1 30 min after nebulisation of the study drug, was recorded in 6 of 53 (11.3%) patients in the TNS-treatment group and 11 of 62 (17.7%) patients in the colistin-treatment group.

Previous exposure to tobramycin or colistin

Twenty-five of 53 (47%) TNS-treated patients had received nebulised or intravenous tobramycin in the 6 months before the study. Comparable figures for colistin were 51 of 62 (82%) (p=0.0001, Fisher's exact test) (table 6).

Discussion

The results of this study demonstrated that TNS produced a significant improvement in lung function as well as a significant decrease in sputum *P. aeruginosa* density in chronically infected CF patients. Nebulised colistin produced a significant decrease in sputum *P. aeruginosa* density, but did not significantly improve lung function.

A double-blind trial design could not be followed for this study for a number of reasons. Colistin requires reconstitution with saline before administration and has a tendency to foam, whereas TNS is supplied as a liquid in ampoules and has a very distinctive taste. Blinding was further complicated by the use of different breath enhanced nebulisers; TNS was administered *via* the PARI LC PLUS™ (the approved nebuliser; Pari Medical Ltd) and colistin was administered *via* the Ventstream™ nebuliser (Medic-Aid), as a pre-trial survey identified this as the most commonly chosen nebuliser for this purpose in current clinical practice. A majority of patients had received nebulised colistin in the 6 months prior to this study, and hence would likely be aware of which treatment they were receiving. The absence of a double-blind trial means that the self-assessments by the patients and the clinical global assessments by the investigators could have been biased because of awareness of receiving a "new treatment". However, the key primary and secondary end points of this study were objective.

The study utilised the approved dosage regimen and nebuliser for TNS. The choice of colistin treatment regimen (1 megaunit *b.i.d.*) was consistent with current clinical practice [13] and the recommended British National Formulary dosage. It was also the dose received by 80% of patients prescribed colistin therapy in the 6 months prior to study start. However, a few centres in the UK and Denmark do routinely use 2 megaunits *b.i.d.* It could be suggested that the lack of improvement in this study in the colistin treatment arm was due to previous exposure to colistin. However, although only a few of the patients had previously received inhaled aminoglycosides, most of them would have received intravenous gentamicin or tobramycin.

The baseline demographics of both groups were similar (table 1). Although there was no statistically significant difference, more patients in the TNS group received dornase alfa (Pulmozyme®, Genentech, Inc.,

Table 6. – Previous exposure to tobramycin and colistin

Patients randomised to	Time before treatment	Tobramycin			Colistin		
		Inhaled	*i.v.*	Either	Inhaled	*i.v.*	Either
TOBI#							
	1 month	2	8	9	40	1	41
	6 months	3	22	25	43	4	45
Colistin¶							
	1 month	3	6	9	48	2	50
	6 months+	3	26	29	50	3	51

TOBI: tobramycin solution for inhalation. #: n=53; ¶: n=62; +: data on one patient missing due to lost notes.

San Francisco, CA, USA) than in the colistin-treated group. It is possible that dornase alfa enhances the penetration of the antibiotic to the bronchial epithelium.

The lack of improvement in FEV_1 % pred observed for the colistin group is consistent with a previous study of nebulised colistin. A placebo-controlled study of 40 Danish patients given either nebulised colistin (1 megaunit) or placebo twice daily for 30 days showed that while the FEV_1 % pred declined in both treatment groups, the decline in the colistin treatment arm was less than that observed for the placebo arm [15].

The sample size of this trial was based on demonstrating within-group significance for the treatment groups. However, the between-group differences proved to be statistically significant, favouring the TNS-treatment group.

The improvement in FEV_1 % pred seen in TNS-treated patients is also consistent with previous studies of nebulised tobramycin. Two double-blind, placebo-controlled clinical trials of TNS (300 mg tobramycin *b.i.d.*) delivered *via* the PARI LC PLUS™ nebuliser (Pari Medical Ltd) to 520 CF patients in the USA showed that TNS resulted in a 11.9% improvement in FEV_1 % pred after 28 days of treatment [17]. In addition, an earlier crossover study of 71 CF patients in the USA given 600 mg tobramycin three times daily *via* ultrasonic nebuliser produced an absolute increase in FEV_1 % pred of 9.7 percentage points higher than for placebo [24]. In the 1993 study, RAMSEY *et al.* [24] required patients to be within 10% of their best forced vital capacity measurement in the previous 6 months at enrolment or 2 weeks after completing intravenous therapy for a pulmonary exacerbation; none of the other studies had this requirement.

Young patients with better preserved function benefited most. This has been seen in other studies of inhaled antibiotics and dornase alfa and may be due to better penetration of inhaled treatment in patients with more preserved lung function.

Both TNS and colistin significantly decreased sputum *P. aeruginosa* density after 4 weeks of treatment (table 3); however, the less than one $\log_{10}$ decrease observed for both treatment groups is less than half the reduction than that observed in the earlier studies of nebulised tobramycin described above [17]. Notably, density of *P. aeruginosa* in sputum at baseline was also higher in these studies than in the current study. In the present study, the small but significant change in cfu may not fully account for the improvement in lung function. As previously suggested [17], in addition to bactericidal activity, inhaled antibiotics may have anti-inflammatory effects and reduce production of bacterial virulence factors.

The differences in the magnitude of the improvement in FEV_1 % pred, the reduction of *P. aeruginosa* and baseline *P. aeruginosa* sputum density in these various studies may be due to national/regional differences in the antibiotic therapies patients received prior to enrolling in the studies. In particular, most CF patients in the UK and Ireland receive nebulised antibiotic as part of their standard care; in the present study, 98 patients (85%) had received aerosol antibiotics in the previous 6 months. In the USA, nebulised antibiotics were used much less frequently prior to TOBI registration [25]. In the present study, the greatest benefit from TNS treatment was seen in children and young adults, a finding that has previously been documented [17].

Baseline resistance was present for both tobramycin and colistin at the parenteral break-point levels ($\geqslant 4\ \mu g \cdot mL^{-1}$). A small increase in tobramycin MIC values was noted for TNS-treated patients, while there was no change in colistin MIC values for colistin-treated patients. However, there was no relationship between baseline MICs and improvement in lung function (FEV_1 % pred) for either tobramycin or colistin (data not shown). Parenteral break-points are of limited clinical relevance for nebulised therapy in CF patients, since nebulisation ensures high antibiotic concentrations at the site of infection [11, 14, 17].

Both nebulised antibiotic regimens were well tolerated in these patients and 94% of randomised patients completed the study treatment. Since 48 of the 62 (77%) colistin-treated patients had recently received prior nebulised colistin therapy, there may have been some under-reporting of events in this group due to familiarity with the product and because patients intolerant of colistin's adverse effects would have been excluded from entry into the study. The results of serum chemistry, urine protein and airway reactivity did not show any clinically significant adverse effects of either study drug.

In conclusion, in this short-term study, tobramycin nebuliser solution significantly improved the lung function of cystic fibrosis patients chronically infected with *Pseudomonas aeruginosa*, but colistin did not. Both treatments significantly reduced the bacterial load, although both groups had had prior exposure to both intravenous and nebulised antibiotics in different amounts. The improvement in lung function with tobramycin nebuliser solution was more apparent in children and young adults. Both nebulised antibiotics had equivalent and acceptable safety profiles. The statistically significant between-group differences will lend support to the choice of tobramycin nebuliser solution when optimising antibiotic regimens in the management of chronic pulmonary infection due to *Pseudomonas aeruginosa* in cystic fibrosis patients who are not showing improvement with conventional therapy including inhaled colistin.

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