# A Randomized Controlled Trial of Nebulized Gentamicin in Non–Cystic Fibrosis Bronchiectasis

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*Rationale*: **Bronchiectasis is a chronic debilitating disease with few evidence-based long-term treatments.**
*Objectives*: **A randomized controlled trial assessing the efficacy of nebulized gentamicin therapy over 1 year in patients with non–cystic fibrosis bronchiectasis.**
*Methods*: **Sixty-five patients were randomized to either twice-daily nebulized gentamicin, 80 mg, or nebulized 0.9% saline, for 12 months. All were reviewed at three-monthly intervals during treatment and at 3 months' follow-up.**
*Measurements and Main Results*: **At each review the following were assessed: quantitative and qualitative sputum bacteriology; sputum purulence and 24-hour volume; $FEV_1$, FVC, and forced expiratory flow, midexpiratory phase; exercise capacity; Leicester Cough Questionnaire and St. George's Respiratory Questionnaire; and exacerbation frequency. Fifty-seven patients completed the study. At the end of 12 months' treatment, compared with the saline group, in the gentamicin group there was reduced sputum bacterial density with 30.8% eradication in those infected with *Pseudomonas aeruginosa* and 92.8% eradication in those infected with other pathogens; less sputum purulence (8.7% vs. 38.5%; $P < 0.0001$); greater exercise capacity (510 [350–690] m vs. 415 [267.5–530] m; $P = 0.03$); and fewer exacerbations (0 [0–1] vs. 1.5 [1–2]; $P < 0.0001$) with increased time to first exacerbation (120 [87–161.5] d vs. 61.5 [20.7–122.7] d; $P = 0.02$). The gentamicin group had greater improvements in Leicester Cough Questionnaire (81.4% vs. 20%; $P < 0.01$) and St. George's Respiratory Questionnaire (87.5% vs. 19.2%; $P < 0.004$) score. No differences were seen in 24-hour sputum volume, $FEV_1$, FVC, or forced expiratory flow, midexpiratory phase. No *P. aeruginosa* isolates developed resistance to gentamicin. At follow-up, all outcome measures were similar to baseline.**
*Conclusions*: **Regular, long-term nebulized gentamicin is of significant benefit in non–cystic fibrosis bronchiectasis but treatment needs to be continuous for its ongoing efficacy.**
**Clinical trial registered with www.clinicaltrials.gov (NCT 00749866).**

**Keywords:** bronchiectasis; nebulized anibiotics; gentamicin

**AT A GLANCE COMMENTARY**

**Scientific Knowledge on the Subject**

Bronchiectasis is a chronic debilitating disease with few evidence-based long-term treatments.

**What This Study Adds to the Field**

This study was a randomized controlled trial demonstrating the efficacy of continuous nebulized gentamicin therapy over 1 year in patients with non–cystic fibrosis bronchiectasis.

Originally described by Laennec in 1819, bronchiectasis is a chronic debilitating condition with patients typically suffering a persistent cough, chronic daily sputum expectoration, recurrent chest infections, and a poor health-related quality of life (1–3).

The airways are abnormally, permanently damaged and dilated and the usual mucociliary clearance mechanism is impaired (4, 5). In most patients, the airways become chronically infected with a variety of bacterial pathogens, which drives neutrophilic inflammation. Previous studies have shown that the bacterial load in the airways correlates with the degree of neutrophilic airways inflammation (6, 7). A vicious cycle of infection and inflammation develops; symptoms persist with frequent exacerbations and further airways damage (8).

Long-term antibiotics offer a real therapeutic option in bronchiectasis: reducing the bacterial burden in the airways may reduce inflammation and promote healing of the bronchial tree, limiting symptoms and potentially improving health-related quality of life. Targeted delivery of aerosolized antibiotics directly to the airways may have significant benefit with minimal adverse systemic effects. Studies are limited, however, with only four randomized controlled trials of nebulized antibiotics to date (9–12). Additionally, little is known about the potential of long-term inhaled antibiotics to contribute to antimicrobial resistance patterns in non–cystic fibrosis bronchiectasis. In 1997, Lin and coworkers (9) found that 3 days' treatment with inhaled gentamicin reduced bacterial load and sputum volume with improved breathlessness and exercise capacity. Randomized controlled trials since then have evaluated the role of nebulized antibiotics in patients colonized with *Pseudomonas aeruginosa*: short-term nebulized tobramycin treatment (over 4 wk) can eradicate *P. aeruginosa* in 35%; hospital admissions with exacerbations were reduced both with 6 months' nebulized tobramycin treatment and also with 12 months' treatment with nebulized tobramycin and ceftazidime (10–12). These studies are promising but have been conducted in a limited subpopulation of patients with bronchiectasis (only those colonized with *P. aeruginosa*), with treatment regimes of variable length and only one study that included a brief follow-up period (11).

The aim of this randomized controlled trial was to assess the efficacy of continuous nebulized gentamicin therapy over 1 year in patients with non–cystic fibrosis bronchiectasis chronically infected with a variety of pathogens and to assess whether treatment effects are sustained over a 3-month treatment-free follow-up period. The primary end point was a greater than or equal to one log unit reduction in sputum bacterial load, regarded as the minimum important reduction necessary to have

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a significant impact on airways inflammation (6, 7). Some of the results of this study have previously been reported in the form of an abstract (13).

## METHODS

This was a randomized controlled trial of 12-month twice-daily nebulized gentamicin compared with twice-daily nebulized 0.9% saline, followed by a 3-month treatment-free follow-up period in adults with non–cystic fibrosis bronchiectasis (September 2007–July 2009; Clinical Trial Registration Number NCT00749866). Randomization was by the study pharmacist and the study was approved by the NHS Scotland Multi-Centre Research Ethics Committee. The primary outcome was greater than or equal to 1 log unit reduction in sputum bacterial density. Secondary outcomes included qualitative sputum bacteriology; emergence of gentamicin-resistant *Pseudomonas* strains; sputum myeloperoxidase and free neutrophil elastase; 24-hour sputum volume; sputum purulence; $FEV_1$, FVC, and forced expiratory flow, midexpiratory phase ($FEF_{25–75\%}$); exercise capacity; the Leicester Cough Questionnaire (LCQ) and St. George's Respiratory Questionnaire (SGRQ) (14, 15); exacerbations; and side effects.

### Patients

All patients had clinically significant and radiologically proved bronchiectasis and were recruited from the regional bronchiectasis service in Lothian (16).

Radiologically, bronchiectasis was diagnosed on high-resolution computed tomography if there was evidence of bronchial dilatation (defined as the diameter of the bronchial lumen being greater than the luminal diameter of the adjacent pulmonary artery) with a lack of tapering on sequential slices. Assessment of bronchiectasis was by evaluation of the bronchi on a lobar basis (for the purposes of this study the lingula was counted as a separate lobe) and severity was graded 1 to 3 according to the Reiff criteria (grade 1 = less than ×2 diameter of adjacent pulmonary artery; grade 2 = ×2–3 diameter of adjacent pulmonary artery; grade 3 = greater than ×3 diameter of the adjacent pulmonary artery), giving a maximum possible total score for six lobes of 18 (17).

Inclusion criteria were chronically infected sputum (defined as pathogenic organisms cultured in at least three sputum samples when clinically stable in the preceding 12 mo); at least two exacerbations in the past year; ability to tolerate nebulized gentamicin (defined as no bronchospasm or fall in $FEV_1$ >15% and >200 ml after nebulization of 80 mg gentamicin with or without prebronchodilation using nebulized 2.5 mg salbutamol); $FEV_1$ greater than 30% predicted; ex-smokers greater than 1 year and less than 20 pack-year history; clinically stable at time of study entry (defined as no requirement for antibiotics or change in respiratory medication in the preceding 4 wk); and not currently receiving long-term antibiotics.

Exclusion criteria were current smokers; cystic fibrosis (cystic fibrosis transmembrane regulator sequences present on genotyping); active pulmonary mycobacterial infection; active sarcoidosis; active allergic bronchopulmonary aspergillosis; chronic obstructive pulmonary disease (18); poorly controlled asthma (≥20% diurnal variation in peak expiratory flows despite treatment); creatinine clearance less than 30 ml per minute; vestibular instability; and previous documented intolerance to aminoglycosides (ototoxicity or nephrotoxicity).

### Interventions

***Study treatment.*** Randomization was to either twice-daily nebulized gentamicin (80 mg, supplied as gentamicin injectable solution and reconstituted for nebulization using 0.9% saline) or twice-daily nebulized 0.9% saline, 5 ml. Porta-Neb Ventstream (Profile Respiratory Systems Ltd, Bognor Regis, West Sussex, UK) nebulizers were used for both groups.

***Nebulized gentamicin treatment.*** A regime of nebulized gentamicin, 80 mg, twice daily was prescribed.

***Nebulized saline.*** Twice-daily 0.9% saline, 5 ml, was administered. This treatment was selected to control for the potential physiotherapy effect of the 0.9% saline used to reconstitute the gentamicin for nebulization in the gentamicin group.

***Study treatment allocation.*** This was a single-masked study. Because of funding limitations, patients could not be masked. The study pharmacist blindly randomized all patients to treatment and all study investigators were masked to treatment allocation throughout the study, until completion of analysis of the results. Patients were instructed in preparation of their medication and its nebulization by the bronchiectasis specialist nurses at the Royal Infirmary of Edinburgh. The same specialist nurses served as the point of contact for any technical problems and were also responsible for reviewing all patients' serum gentamicin levels throughout the study. Any patient with a level greater than 1 mg/ml had their study treatment reduced to once daily. Any patient reporting symptomatic bronchospasm (defined as increased wheeze or breathlessness) had adjunctive treatment with a nebulized $\beta_2$ agonist (salbutamol, 2.5 mg) before their study treatment. The specialist nurses also assessed study compliance.

***Study compliance.*** The twice-daily treatment was self-administered at home. At each 3-monthly review, all patients were supplied with their study treatment and the appropriate number of needles, syringes, and filters necessary for nebulization for the following 3 months. They were asked to return any unused equipment or medication. This was counted, and in addition all were questioned directly regarding their compliance at each visit.

***Exacerbations requiring antibiotic therapy.*** An exacerbation was defined as a clinical deterioration with all of the following: increasing cough, increasing sputum volume, and worsening sputum purulence (19). All patients who experienced an exacerbation during the study were reviewed by the study doctor and received 14 days of antibiotics (prescribed according to sputum bacteriology culture and sensitivities). Regular study treatment continued during the exacerbation. All were reviewed after completion of antibiotics to ensure recovery.

***Routine therapy.*** Any changes made to the patients' usual respiratory medication during the study period were noted.

### Assessments

All patients were reviewed at baseline entry to the study (Month 0) and at Months 3, 6, 9, and 12 of treatment and then after a 3-month treatment-free, follow-up period (Month 15). The assessments conducted at each review are discussed next.

***Sputum analysis.*** The color (purulent, mucopurulent, or mucoid) of a fresh, spontaneously expectorated sample was recorded using a standardized sputum color chart (20).

All sputum expectorated in the 24 hours preceding the review was collected in a sterile, transparent, calibrated container and the volume (in milliliters) was recorded.

***Pulmonary function tests.*** $FEV_1$, FVC, and $FEF_{25–75\%}$ were measured according to standardized guidelines, with the highest of three technically satisfactory measurements recorded (21). Oxygen saturations on room air were recorded.

***Exercise capacity.*** An externally paced, 10-m incremental field walking test was conducted with assessment of dyspnea before and after completion using the BORG scale recorded (22).

***Health-related quality of life.*** The LCQ and the SGRQ were completed. The LCQ is a 19-item self-completed quality of life measure of chronic cough validated for use in bronchiectasis (23). The total severity score ranges from 3–21, a lower score indicating a more severe cough. The minimum clinically important difference for change is 1.3 units (24).

The SGRQ is a 50-item self-administered quality of life measure of the impact of respiratory symptoms validated for use in bronchiectasis (25). The total score ranges from 0–100; a higher score indicates a poorer health-related quality of life. The minimum clinically important difference is 4 units (25).

***Sputum.*** Assessments were performed on spontaneous, early morning sputum. One milliliter of sputum was set aside for bacteriology and the remainder of the sample was processed for assessment of airways inflammation assessment as described below.

***Sputum bacteriology.*** Qualitative and quantitative bacteriology was performed on all sputum samples. Samples were processed within 4 hours from expectoration (26). Sputum was homogenized and liquefied using an equal volume of 0.1% dithiothreitol and serially diluted using sterile 0.9% saline to achieve dilutional factors of $10^{-1}$ to $10^{-4}$. *Pseudomonas* isolation agar (Difco), chocolate with bacitracin agar, and horse blood agar plates were inoculated with 100 μl of sample. Colony-forming units for each predominant pathogen were then identified by standard procedures and counted after 48 hours aerobic incubation (5% $CO_2$ for

**TABLE 1. PATIENT CHARACTERISTICS AT START OF STUDY**

| Characteristic | Gentamicin Group (*n = 27*) n (%) median (*interquartile range*) | Saline Group (*n = 30*) n (%) median (*interquartile range*) | *P* Value |
|---|---|---|---|
| Male sex | 9 (33.3) | 15 (50) | 0.2 |
| Age, yr | 58 (53–67) | 64 (55.7–69) | 0.2 |
| Ex-smokers | 8 (29.6) | 8 (26.7) | 0.8 |
| Pack-year history | 10 (1.2–16) | 7 (4.2–16) | 0.8 |
| Inhaled steroid therapy | 17 (62.9) | 19 (63.3) | 0.6 |
| Oral corticosteroids | 3 (11.1) | 3 (10) | 0.9 |
| Inhaled $\beta_2$ agonists | | | |
| Short acting | 19 (70.4) | 22 (73.3) | 0.8 |
| Long acting | 17 (62.9) | 19 (63.3) | 1.0 |
| Inhaled anticholinergics | | | |
| Short acting | 3 (11.1) | 0 (0) | 0.3 |
| Long acting | 1 (3.7) | 1 (3.3) | 0.2 |
| Etiology | | | |
| Idiopathic | 8 (29.6) | 9 (30) | 1.0 |
| Postinfective | 11 (40.7) | 11 (36.7) | 0.7 |
| Inactive active allergic bronchopulmonary aspergillosis | 6 (22.2) | 6 (20) | 0.8 |
| Inactive sarcoid | 1 (3.7) | 1 (3.3) | 0.9 |
| Immunodeficiency ($IgG_2$ deficiency) | 1 (3.7) | 1 (3.3) | 0.9 |
| Inflammatory bowel disease | 0 | 2 (6.6) | 0.2 |
| CT characteristics | | | |
| Cystic or varicose dilatation | 25 (92.6) | 22 (73.3) | 0.06 |
| Lobes involved | 5 (3–6) | 5 (3–6) | 0.8 |
| Reiff Severity Score | 9 (5–12) | 7.5 (4–14) | 0.6 |

growth on chocolate with bacitracin agar) at 37°C to determine the sputum bacterial density, expressed as $\log_{10}$ cfu/ml$^{-1}$.

Gentamicin susceptibility testing was performed for all isolates of *P. aeruginosa* and gram-negative enteric bacteria at Months 0, 12, and 15 in our routine laboratory, according to the Clinical and Laboratory Standards Institute Guidelines (27). The following zone diameters were used with 10-μg gentamicin disk to report susceptibility with *Pseudomonas* strains: resistance less than or equal to 12 mm; indeterminate 13–14 mm; and sensitive greater than or equal to 15 mm (27).

***Airways inflammation.*** Sputum was ultracentrifuged at 50,000 × *g* for 90 minutes at 4°C. The sol phase was removed and immediately frozen at −70°C. Analysis for neutrophil myeloperoxidase (MPO) and free elastase was performed per patient after their completion of the study, as previously described (28, 29).

***Systemic inflammation.*** Venous blood was collected for total leukocyte count, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR).

***Toxicity.*** Serum gentamicin levels and urea and electrolytes were measured at 2 weeks after initiation of treatment and then at each 3 monthly assessment until completion of the study and 3 months after completion of treatment. At the same time points, all patients were directly asked whether they had any dizziness or change to their hearing.

### Statistics

All statistics were performed using SPSS for Windows, Version 17 (SPSS, Chicago, IL) and GraphPad Prism Version 5.0 (Graphpad Software, La Jolla, CA). The primary aim was to detect a one log unit reduction in bacterial density (cfu per milliliter). Using a two-sided, two-sample test with 80% power and 1% level of significance, 24 patients per group were necessary and to allow for a 20% dropout rate we selected 30 patients per group.

Only patients who completed the study were included in the final analysis. Analysis of the results comprised a Mann-Whitney *U* test for unpaired numerical data and Wilcoxon for paired numerical data were used. A Fisher exact test was used to compare categorical variables. Data are presented as median (interquartile range). A two-tailed *P* value of less than 0.05 was considered statistically significant.

## RESULTS

### Patients

Sixty-five patients were recruited to the study, with 32 randomized to nebulized gentamicin and 33 to nebulized saline. In the gentamicin group, there were two unexpected sudden deaths (previously undiagnosed metastatic colorectal cancer at Month 3 and myocardial infarction at Month 5). There were no deaths in the saline group. In the gentamicin group, there were three withdrawals: two felt unable to tolerate the nebulized therapy (Months 3 and 6, respectively) and one felt unable to commit to the study reviews (Month 6). In the saline group, there were three withdrawals, two of whom felt unable to tolerate the nebulized therapy (Month 3 for both) and the third was unable to commit to the study reviews (Month 3). In total, 57 patients completed the study, with 27 in the gentamicin group and 30 in the saline group. The baseline characteristics for each group in the analysis are shown in Table 1.

### Sputum Bacteriology

***Quantitative bacteriology.*** There was no significant difference in bacterial density between the groups at baseline with a median of 8.02 (7.63–8.3) $\log_{10}$ cfu/ml in the gentamicin group and 7.88 (7.34–8.17) $\log_{10}$ cfu/ml in the saline group ($P = 0.29$). At the end of 12 months' treatment, the bacterial density had significantly reduced in the gentamicin group (2.96 [1.0–5.9] $\log_{10}$ cfu/ml) compared with the saline group (7.67 [7.34–8.17] $\log_{10}$ cfu/ml; $P < 0.0001$). At follow-up, however, bacterial density was similar in both groups (gentamicin group, 7.29 [5.88–7.76] $\log_{10}$ cfu/ml; saline group, 7.49 [6.46–8.19] $\log_{10}$ cfu/ml; $P = 0.12$). Figure 1 shows the changes in bacterial density at each of the study time points for both groups.

***Qualitative bacteriology.*** There was no significant difference in the infecting pathogen between the groups at baseline (Table 2). Table 3 shows the change in sputum infection for both groups throughout the study.

By 1 year, within the gentamicin group, 30.8% (4 of 13 patients) infected with *P. aeruginosa* achieved eradication and 3.7% (1 of 13 patients) cultured a different pathogen, *Staphylococcus aureus*. A total of 92.8% (13 of 14 patients) originally infected with pathogens other than *P. aeruginosa* achieved eradication. In those not achieving eradication, there was still a significant reduction in bacterial density from a median 8.06

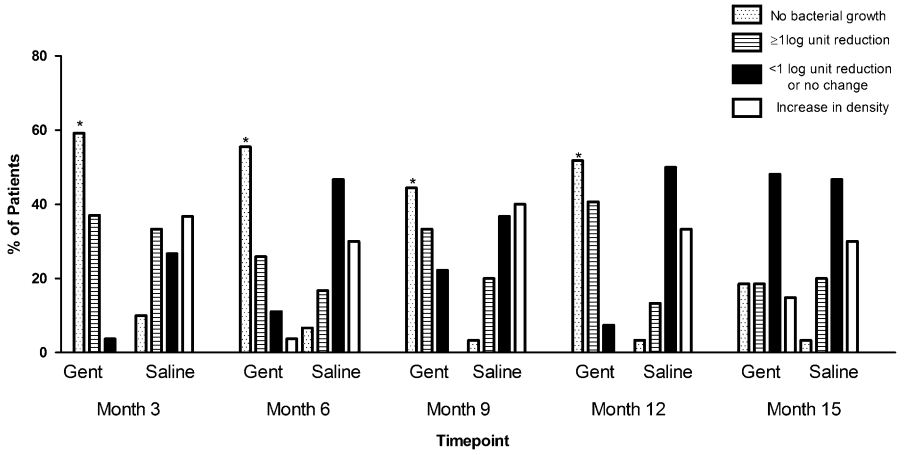


*Figure 1.* Treatment effect on sputum bacterial density. All changes in bacterial growth are in comparison with sputum bacterial density at the baseline visit, Month 0. Between group (gentamicin vs. saline) comparisons were made at each time point using the Fisher exact test for bacterial clearance and greater than or equal to 1 log unit reduction in density versus less than 1 log unit reduction or no change or increase in bacterial density. *$P < 0.0001$. Gent = gentamicin group; saline = saline group.

(7.5–8.4) $\log_{10}$ cfu/ml at baseline to 6.17 (5.81–7.15) $\log_{10}$ cfu/ml at the end of treatment.

At entry to the study, all patients with *P. aeruginosa* and gram-negative enteric pathogens had strains fully susceptible to gentamicin. Of these, no patients in either group at the end of treatment or at follow-up had developed gentamicin indeterminately resistant or resistant strains.

### Sputum Neutrophil Myeloperoxidase and Free Elastase

There was no significant difference in sputum myeloperoxidase or free elastase activity at baseline. At the end of treatment, concentrations of myeloperoxidase and free elastase activity were significantly lower in the gentamicin group compared with the saline group. At follow-up, however, concentrations of both myeloperoxidase and free elastase activity was similar in both groups (Table 4).

### Sputum Purulence and Volume

There was no significant difference in sputum purulence between the groups at baseline or after 3 months' treatment. At treatment Months 6, 9, and 12 significantly fewer patients in the gentamicin group had purulent sputum compared with the saline group. At follow-up, there was no difference in sputum purulence between the groups (Table 4).

There was no significant difference between the groups in 24-hour sputum volume at any time point (Table 4).

### Lung Function and Exercise Capacity

There was no significant difference between the groups in $FEV_1$, FVC, or $FEF_{25–75\%}$ at any time point (Table 5 and Figure 2).

There was no significant difference in exercise capacity between the groups at baseline or throughout the study until Month 12 when exercise capacity had improved significantly more in the gentamicin group compared with the saline group. At follow-up, however, there was no significant difference between the groups (Table 5 and Figure 2).

**TABLE 2. SPUTUM BACTERIAL INFECTION AT ENTRY TO THE STUDY (MONTH 0) FOR THE GENTAMICIN AND SALINE GROUPS**

| Timepoint | Gentamicin Group n (%) | Saline Group n (%) | *P* Value |
|---|---|---|---|
| Baseline chronically infected | 27 (100) | 30 (100) | |
| *Pseudomonas aeruginosa* | 13 (48.1) | 11 (36.7) | 0.5 |
| *Haemophilus influenzae* | 11 (40.7) | 15 (50) | 0.3 |
| *Staphylococcus aureus* | 2 (7.4) | 1 (3.3) | 0.5 |
| *Streptococcus pneumoniae* | 1 (3.7) | 0 (0) | 0.3 |
| *Moraxella catarrhalis* | 0 (0) | 2 (6.7) | 0.5 |
| Other (coliforms) | 0 (0) | 1 (3.3) | 0.3 |

### Health-related Quality of Life

At each 3-monthly interval during treatment, significantly more patients in the gentamicin group achieved a clinically significant improvement in both LCQ score and SGRQ score compared with patients in the saline group (Table 6). This effect was only sustained at follow-up with the SGRQ score.

### Systemic Inflammation

There was no significant difference in CRP, ESR, or total leukocyte count between the groups at baseline. At Months 3 and 9, CRP was significantly lower in the gentamicin group and at Month 3 total leukocyte count was also lower in the gentamicin group. No other significant differences were seen in CRP and total leukocyte count at any time point during the study (Table 7). There was no significant difference between the groups in ESR at any time point.

### Exacerbations

There were fewer exacerbations during the 12 months' treatment in the nebulized gentamicin group compared with the saline group (0 [0–1] exacerbations and 1.5 [1–2] exacerbations, respectively; $P < 0.0001$).

A total of 33.3% of patients in the gentamicin group had an exacerbation during the 12 months' treatment compared with 80% in the saline group ($P = 0.0005$). The median time to first exacerbation during the 12 months' treatment was 120 (87–161.5) days in the gentamicin group compared with 61.5 (20.7–122.7) days in the saline group ($P = 0.02$).

There was no significant difference in the number of exacerbations that occurred during the 3-month treatment-free follow-up period with 0 (0–1) exacerbations occurring in the gentamicin group and 0 (0–1) exacerbations occurring in the saline group.

### Gentamicin Toxicity

Serum gentamicin levels at the end of treatment were 0.13 (0–0.37) mg/ml. Only one patient developed a serum gentamicin level greater than 1 mg/ml during the study. This occurred at treatment Month 9 (level 1.25 mg/ml) and after reduction of study treatment to once daily all subsequent levels (at weekly intervals for 3 wk) were less than 1 mg/ml for the subject concerned.

### Adverse Effects

In the total cohort originally allocated to nebulized gentamicin, 21.9% (7 of 32 patients) reported bronchospasm and received

**TABLE 3. QUALITATIVE SPUTUM BACTERIOLOGY THROUGHOUT THE STUDY**

| | Month 0 n (%) | Month 3 n (%) | Month 6 n (%) | Month 9 n (%) | Month 12 n (%) | Month 15 n (%) |
|---|---|---|---|---|---|---|
| Gentamicin group | | | | | | |
| *Pseudomonas aeruginosa* and enteric gram-negative species | 13 (48.1) | 8 (29.6) | 7 (25.9) | 8 (29.6) | 7 (25.9) | 10 (37) |
| Other PPMs | 14 (51.8) | 4 (14.8) | 3 (11.1) | 3 (11.1) | 2 (7.4)* | 8 (29.7) |
| MNF or no bacterial growth | 0 | 15 (55.6) | 17 (62.1) | 16 (59.2) | 18 (66.7) | 9 (33.3) |
| Saline group | | | | | | |
| *Pseudomonas aeruginosa* and enteric gram-negative species | 12 (40) | 11 (36.7) | 10 (33.3) | 9 (30) | 9 (30) | 7 (23.3) |
| Other PPMs | 18 (60) | 17 (56.7) | 19 (63.3) | 20 (66.7) | 20 (66.7) | 22 (73.3) |
| MNF or no bacterial growth | 0 | 2 (6.7) | 1 (3.3) | 1 (3.3) | 1 (3.3) | 1 (3.3) |

*Definition of abbreviations*: MNF = mixed normal flora; PPMs = potentially pathogenic microorganisms (*H. influenzae, S. pneumoniae, M. catarrhalis, S. aureus*).
* 3.7% (one) patient was originally infected with *P. aeruginosa* at the start of the study.

adjunctive nebulized $\beta_2$ agonist treatment. Despite this, two patients required withdrawal from the study (one at Month 3 and one at Month 6) because they remained unable to tolerate the treatment. The remaining five patients successfully completed the study and were included in the final analysis.

In the total cohort originally allocated to nebulized saline, 6% (2 of 33 patients) reported bronchospasm and received adjunctive nebulized $\beta_2$ agonist treatment. Despite this, both required withdrawal from the study (both at Month 3) because they remained unable to tolerate the treatment. A total of 16.7% (five patients) in the saline group who completed the study reported a salty taste with nebulization.

No nephrotoxicity was detected and no ototoxicity was reported. A total of 11.1% of patients in the gentamicin group (three patients) reported an unpleasant taste after nebulization.

### Compliance

One patient in the gentamicin group had compliance issues. On counting of total drug doses returned, by the end of the 12 months' treatment this study patient had taken only 67.9% of the total doses prescribed throughout the study. This patient was included in the final analysis. There were no issues with compliance in the saline group.

### Changes to Routine Respiratory Medication

No changes were made to any patient's routine respiratory therapy during the study.

## DISCUSSION

This randomized controlled trial has proved efficacy for nebulized gentamicin in non–cystic fibrosis bronchiectasis. Regular, long-term nebulized gentamicin significantly reduces sputum bacterial density and airways inflammation, with less sputum purulence. Patients had greater exercise capacity, fewer exacerbations, and an improved health-related quality of life.

The pathophysiologic basis of bacterial infection and airways inflammation in bronchiectasis was originally proposed by Cole (8) approximately two decades ago and offers a clear target for therapeutic intervention. Nebulizing antibiotic therapy allows direct treatment to the damaged airways and with localized treatment, systemic side effects are limited (30). Gentamicin was selected because it is broad spectrum for the pathogens seen in non–cystic fibrosis bronchiectasis; inexpensive (current cost for a 12-mo 80-mg twice-daily course totals £1124.20 or US $1,683); and has previously been shown to achieve good sputum concentrations (31, 32).

There have been no previous long-term studies of nebulized gentamicin in bronchiectasis and the optimum dose and regime is unknown. There has been one study to date exploring the dosage of nebulized gentamicin in non–cystic fibrosis bronchiectasis in adults (31). Crowther Labiris and coworkers (31) found that a single dose of 160 mg of nebulized gentamicin achieved good sputum concentrations (97.2 [0.3–194.2] μg/g sputum) 2 hours after nebulization (31). There were, however, reports of an unpleasant taste and mouth irritation after nebulization. Although there have been no previous long-term studies, anecdotal opinions of nebulized gentamicin in bronchiectasis have preferred 80-mg twice-daily dosing (33). In the 2 years before the commencement of our study, we conducted a small pilot study (n = 5) within our bronchiectasis clinic at the Royal Infirmary of Edinburgh, using 80 mg of nebulized gentamicin twice daily and found it to be well tolerated with no reported bronchoconstriction and no detectable serum concentrations. For our study, we selected a regime of 80 mg twice daily as a dose likely to achieve adequate sputum concentrations with minimal adverse effects and systemic toxicity, particularly for long-term administration.

**TABLE 4. SPUTUM INFLAMMATORY INDICES, VOLUME, AND PURULENCE BETWEEN THE GROUPS THROUGHOUT THE STUDY**

| Sputum Characteristic | Month 0 | Month 3 | Month 6 | Month 9 | Month 12 | Month 15 |
|---|---|---|---|---|---|---|
| Sputum myeloperoxidase, units/ml | | | | | | |
| Gentamicin group | 51.6 (29.8–132.6) | 21 (3.4–50.3) | 18.2 (7.7–41.2)* | 29.7 (9.9–41.1) | 13.8 (3–34.4)* | 47.7 (9.2–254.7) |
| Saline group | 40.5 (17.1–104.4) | 44.6 (13.6–114.5) | 52.1 (22.1–110.8) | 49.8 (22.6–94.2) | 58.2 (27–101.8) | 67.5 (24.1–94.9) |
| Sputum free elastase activity, units/mg | | | | | | |
| Gentamicin group | 3.6 (0–17.6) | 0 (0–0)† | 0 (0–2.9) | 0 (0–7.6) | 0 (0–1.8)* | 7.1 (0–56) |
| Saline group | 4.1 (0–19) | 0 (0–20.4) | 0 (0–29.1) | 0.9 (0–19.4) | 1.8 (0.17–16) | 2.8 (0.9–18.2) |
| % purulent sputum | | | | | | |
| Gentamicin group | 66.7 | 42.8 | 8.7* | 9.1* | 8.7* | 65.2 |
| Saline group | 40.7 | 40 | 50 | 40 | 38.5 | 44 |
| 24-h sputum volume, ml | | | | | | |
| Gentamicin group | 13.5 (10–24.5) | 15 (9–17.5) | 10 (2.5–15) | 10 (2.5–15) | 6 (1.2–13.7) | 15 (8–15) |
| Saline group | 8 (4.5–20) | 4.5 (2.8–16.2) | 3 (3–10) | 4.5 (0.5–10) | 6.5 (1–15) | 5 (1.6–14) |

* $P \leqslant 0.02$
† $P < 0.05$.

**TABLE 5. LUNG FUNCTION AND EXERCISE CAPACITY BETWEEN THE GROUPS THROUGHOUT THE STUDY**

| | Month 0 | Month 3 | Month 6 | Month 9 | Month 12 | Month 15 |
|---|---|---|---|---|---|---|
| $FEV_1$, L %predicted | | | | | | |
| Gentamicin group | | | | | | |
| Actual | 1.8 (1.34–2.31) | 1.74 (1.39–2.28) | 1.66 (1.32–2.03) | 1.63 (1.28–2.07) | 1.60 (1.34–2.08) | 1.69 (1.30–2) |
| % predicted | 72.9 (60–81.2) | 70.5 (56.7–88.2) | 65.5 (53.4–88.2) | 69.1 (53.3–76.6) | 70 (55–82) | 68.1 (55.7–77.4) |
| Saline group | | | | | | |
| Actual | 1.61 (1.22–2.35) | 1.68 (1.28–2.23) | 1.66 (1.22–2.10) | 1.61 (1.24–2.15) | 1.62 (1.24–2.10) | 1.67 (1.29–2.16) |
| % predicted | 63.4 (45.5–80.4) | 64.9 (52–80.3) | 66.2 (45.9–81.4) | 67.3 (46.4–76.8) | 61.5 (52.6–80.5) | 64.3 (48.4–78.1) |
| FVC, L %predicted | | | | | | |
| Gentamicin group | | | | | | |
| Actual | 2.89 (2.21–3.41) | 2.86 (2.16–3.29) | 2.79 (2.2–3.28) | 2.74 (2.11–3.33) | 2.65 (2.18–3.11) | 2.69 (2.19–3.17) |
| % predicted | 88.9 (82.7–94.1) | 89.3 (78.9–95.1) | 87.1 (77.5–92.1) | 87.8 (75.6–93.9) | 87 (75.1–92.7) | 85.9 (80.7–94.1) |
| Saline group | | | | | | |
| Actual | 2.93 (2.12–3.35) | 2.83 (2.14–3.35) | 2.87 (2.25–3.30) | 2.68 (2.11–3.33) | 2.68 (2.20–3.22) | 2.67 (2.21–3.20) |
| % predicted | 85 (71.1–99.4) | 89.4 (67.7–96.9) | 87.2 (69.8–99.5) | 86.9 (71–94.2) | 85.7 (58–103.4) | 83.8 (66.3–96.3) |
| $FEF_{25-75}$ ($L.s^{-1}$) | | | | | | |
| Gentamicin group | 1.06 (0.66–1.62) | 1.04 (0.65–1.52) | 0.77 (0.59–1.44) | 0.73 (0.59–1.31) | 0.9 (0.6–1.4) | 0.93 (0.53–1.48) |
| Saline group | 0.98 (0.49–1.55) | 0.85 (0.55–1.52) | 0.91 (0.52–1.53) | 0.74 (0.55–1.49) | 0.9 (0.58–1.6) | 1 (0.52–1.71) |
| $FEV_1$/FVC % predicted | | | | | | |
| Gentamicin group | | | | | | |
| Actual, L | 0.67 (0.61–0.78) | 0.7 (0.55–0.77) | 0.63 (0.54–0.68) | 0.63 (0.54–0.68) | 0.65 (0.57–0.75) | 0.62 (0.55–0.75) |
| % predicted | 84.5 (73.3–91) | 83.1 (68.3–89.7) | 79.7 (68.7–95.3) | 76.3 (63.2–80.7) | 78.3 (73.2–88.3) | 75.7 (69.3–89.2) |
| Saline group | | | | | | |
| Actual, L | 0.65 (0.5–0.74) | 0.62 (0.51–0.73) | 0.62 (0.5–0.7) | 0.62 (0.5–0.72) | 0.63 (0.51–0.74) | 0.64 (0.46–0.73) |
| % predicted | 75.7 (58.6–90.6) | 76.9 (63.4–86.2) | 74.4 (63.4–85.5) | 73.5 (58.3–88.6) | 75.3 (62.7–93.2) | 78 (57.8–88.4) |
| Incremental field walking test distance, m | | | | | | |
| Gentamicin group | 350 (270–530) | 390 (287.5–562.5) | 445 (272.5–590) | 450 (372.5–642.5) | 510* (350–690) | 420 (340–580) |
| Saline group | 345 (257.5–450) | 340 (250–440) | 340 (260–530) | 360 (260–525) | 415 (267.5–530) | 385 (232.5–490) |

* $P = 0.03$.

Most patients with bronchiectasis are chronically infected with pathogenic bacteria in their airways even when apparently clinically stable. Angrill and coworkers (34), in their study of 77 patients, found 64% to be colonized, most frequently with *Haemophilus influenzae* (55%) followed by *P. aeruginosa* (26%). King and coworkers (35) conducted a prospective 5-year follow-up study of 89 patients with bronchiectasis, of whom 79% had pathogens in their sputum when clinically stable (*H. influenzae* in 47%; *P. aeruginosa* in 26%; with *Moraxella catarrhalis*, *Streptococcus pneumoniae*, and *S. aureus* responsible for infection in the remaining 27%) and found that the infecting pathogen varied little over the 5-year follow-up period. Previous randomized controlled trials of aerosolized antibiotics have included only patients colonized with *P. aeruginosa*. Our study was unique to include patients infected with a variety of pathogens and our baseline demographics support the previous studies in terms of incidence of infecting pathogen (34, 35).

Angrill and coworkers (6) in a separate study evaluated the relationship between bacterial infection and airways inflammation using bronchoalveolar lavage in both infected and noninfected patients with bronchiectasis and control subjects. Infected patients had an exaggerated inflammatory response (greater number of neutrophils; higher concentrations of elastase, MPO, and other inflammatory markers) compared with noninfected patients. The diagnostic cut-off value used to define bacterial infection in bronchial washings in the study was $10^3$ cfu/ml, and with a one log unit increase, at $10^4$ cfu/ml, there was a significant increase in airway inflammatory markers. Hill and coworkers (7) found similar results using sputum in patients with chronic bronchitis and bronchiectasis, specifically demonstrating a significant increase in markers of airways inflammation with sputum bacterial loads of greater than or equal to $10^6$ cfu/ml. Before entering our study, all patients had significant bacterial density in their sputum with a median of 8.02 $\log_{10}$ cfu/ml in the gentamicin group and 7.88 $\log_{10}$ cfu/ml in the saline group with high levels of MPO and free elastase activity when clinically stable. Our primary end point was a greater than or equal to one log unit reduction in sputum bacterial load, regarded as the

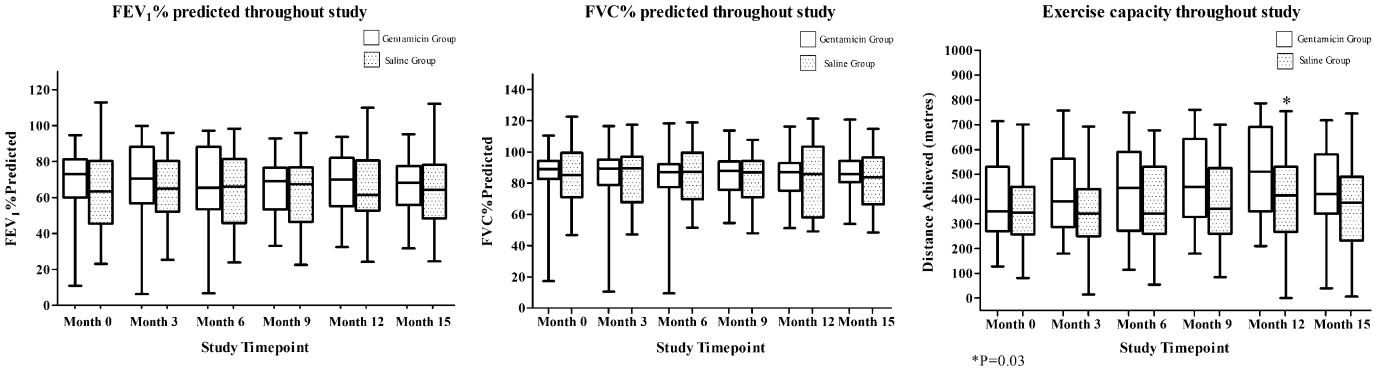


***Figure 2.*** Effect on $FEV_1$ % predicted, FVC % predicted, and exercise capacity throughout the study period in each group. The *horizontal lines* represent the median and interquartile ranges and the *whiskers* represent the 5th−95th percentile. **P* = 0.03.

**TABLE 6. PERCENT OF PATIENTS WITH A CLINICALLY SIGNIFICANT IMPROVEMENT IN LCQ AND SGRQ SCORE COMPARED WITH THEIR BASELINE SCORE AT ENTRY TO THE STUDY FOR EACH TREATMENT TIMEPOINT AND AT FOLLOW-UP BETWEEN THE GROUPS**

| | Month 3 | Month 6 | Month 9 | Month 12 | Month 15 |
|---|---|---|---|---|---|
| % LCQ ⩾ 1.3 unit improvement | | | | | |
| Gentamicin group | 54.5* | 68.1* | 65* | 81.4* | 48 |
| Saline group | 20 | 23.8 | 20 | 20 | 20 |
| % SGRQ ⩾ 4 unit improvement | | | | | |
| Gentamicin group | 78.2† | 81.8† | 71.4† | 87.5† | 60.8† |
| Saline group | 31.8 | 34.7 | 23.8 | 19.2 | 19 |

*Definition of abbreviations*: LCQ = Leicester Cough Questionnaire; SGRO = St. George's Respiratory Questionnaire.
* $P < 0.01$
† $P < 0.004$.

minimum important reduction necessary to have a significant impact on airways inflammation. A significant reduction in bacterial density was seen after 3 months of nebulized gentamicin, an effect sustained throughout the 12 months' of treatment. Similar to the study by Barker and coworkers (11), in the gentamicin group pathogen eradication was achieved in 30.8% of patients colonized with *P. aeruginosa* and in those infected by other pathogens, eradication was achieved in 92.8%. In those not achieving complete eradication of pathogens, there was still a significant reduction in bacterial density seen. Furthermore, parallel reductions in sputum MPO was seen, although not significantly so until treatment Month 6. Free elastase activity also significantly reduced after 3 months' treatment. These treatment effects further corroborate Cole's hypothesis of infection and inflammation in bronchiectasis (8). In the saline group, there was no change in bacterial density or infecting pathogen and airways inflammation seen throughout the study.

Emerging strains of antibiotic-resistant bacteria is an increasing problem in lung infection. In bronchiectasis, the potential virulence of the pathogens typically responsible for chronic bronchial infection combined with the repeated courses of antibiotics required for exacerbations makes the potential development of antimicrobial resistance an almost expected phenomenon, but one that poses a real threat to a chronically unwell population with significant disease burden. To date, there are little data available regarding the impact of long-term inhaled antibiotics on susceptibility patterns in non–cystic fibrosis bronchiectasis. Three studies of nebulized tobramycin in patients chronically infected with *P. aeruginosa* have included observation of emergence of tobramycin-resistant *Pseudomonas* strains (12, 36, 37). Couch (36) found resistance in 11% of patients after 4 weeks' treatment, although 3% of those treated with placebo also developed resistance. Scheinberg and Shore (37) noted that after 12 weeks' nebulized tobramycin, 7% developed a resistant *P. aeruginosa*. Drobnic and coworkers (12) in their inhaled tobramycin study found resistance developed during treatment in 10% of patients, but they also observed resistance developing during the placebo period in 10%; reassuringly 2 months after completion of the study, all patients had tobramycin-susceptible strains of *P. aeruginosa*. In our study, all patients chronically infected with *P. aeruginosa* or gram-negative enteric organisms were fully susceptible to gentamicin before entry to the study and we had no emergence of resistant strains. No patient had a gentamicin-resistant *Pseudomonas* strain or gram-negative enteric bacterial isolate at the end of the 12 months or indeed at follow-up, 3 months after completion of treatment. However, a recent study by Gillham and coworkers (38) found variation in morphotype and antibiotic susceptibility in colonies of *P. aeruginosa* isolated from non–cystic fibrosis bronchiectasis sputum indicating that further studies are needed to explore the relevance and clinical implications of *in vitro* susceptibilities in these complex, chronically infected patients with recurrent exacerbations. A limitation of our study is that we did not did do susceptibility testing more frequently throughout the 12 months' treatment, because it is possible that changes in zone diameter not reaching defined resistance diameters may have occurred. Furthermore, only *Pseudomonas* strains and gram-negative bacterial isolates were tested for gentamicin susceptibility; we did not routinely test for gentamicin susceptibility in all other potentially pathogenic microorganisms isolated.

Purulent sputum in stable bronchiectasis is associated with bacterial infection, varicose or cystic airway dilatation, and an $FEV_1$ less than 80% predicted (20). Increased sputum purulence is also associated with increased neutrophilic airways inflammation in patients with chronic bronchitis and bronchiectasis (39). In our study, two thirds of patients in the gentamicin group had purulent sputum at baseline but this had significantly reduced to 8.7% after 6 months' treatment and was sustained for the remainder of the gentamicin treatment. No such similar effect was seen in the saline group where 40% of patients had purulent sputum at baseline and 38.5% after 12 months' treatment. We did not, however, observe any significant change in the volume of sputum expectorated over 24 hours between the groups throughout the study. It is questionable how reliable this end point is, however, because such factors as patient compliance, swallowed secretions, and collection of saliva may affect it.

**TABLE 7. MARKERS OF SYSTEMIC INFLAMMATION BETWEEN THE GROUPS THROUGHOUT THE STUDY**

| Marker | Month 0 | Month 3 | Month 6 | Month 9 | Month 12 | Month 15 |
|---|---|---|---|---|---|---|
| C-reactive protein, mg/L (normal range <7 mg/L) | | | | | | |
| Gentamicin group | 7 (3–12) | 2.5 (1–6)* | 3.5 (1–10.2) | 3 (1.5–8)* | 4 (1.5–8.5) | 7 (3–13) |
| Saline group | 7 (4–18) | 6.5 (3.2–9.7) | 5 (3–8) | 8 (4–14.5) | 7 (4–12) | 7 (4–9) |
| Erythrocyte sedimentation rate, mm/h | | | | | | |
| Gentamicin group | 17 (11–29) | 10 (7–18.7) | 13 (6–22.2) | 14 (9–22) | 17 (7.5–21) | 17 (10–38) |
| Saline group | 16 (9–25.5) | 10 (6–21.7) | 12 (5.5–23) | 12.5 (6.5–22.5) | 14 (6.5–25.5) | 11 (8–19) |
| Total leukocyte count, x $10^9$/L (normal range 4–11 × $10^9$/L) | | | | | | |
| Gentamicin group | 7.3 (5.9–9.2) | 5.8 (5–7.2)* | 6.6 (5.3–7.7) | 6.5 (4.8–8.5) | 7.1 (4.9–8.2) | 6.4 (4.8–10.1) |
| Saline group | 7.7 (6.9–8.9) | 7.2 (5.9–8.2) | 6.8 (6.1–8.4) | 7.7 (6.2–9.1) | 7.1 (6.1–9.1) | 7.5 (6.5–8.7) |

* $P < 0.03$.

The correlation between airways inflammation and systemic inflammation has previously been shown to be poor (6). In our study, despite good improvement in bacterial clearance, there was no significant change in systemic inflammation between the groups at the end of 12 months' treatment.

Exercise capacity has been used as a marker of treatment response in previous interventional studies with regular chest physiotherapy and treatment of exacerbations having significant improvement on distance achieved in the incremental shuttle walk test (40, 41). Lin and coworkers (9) in their randomized controlled trial of nebulized gentamicin over 3 days found a significant improvement in patients' 6-minute-walk test. In our study, after 12 months' treatment, patients receiving nebulized gentamicin had significantly improved their exercise capacity compared with those receiving nebulized saline. The distance achieved improved by a median of 160 m, compared with baseline. However, despite this improvement in exercise capacity, no similar effects were seen in $FEV_1$, FVC, or mid-expiratory flows. The value of spirometric makers as a measure of treatment effect in non–cystic fibrosis bronchiectasis is questionable. Orriols and coworkers (10) in their randomized controlled trial of nebulized ceftazidime and tobramycin in 15 patients also observed no change in $FEV_1$ or FVC. Previous trials of other long-term interventional studies including inhaled corticosteroid therapy and regular chest physiotherapy have also not observed any changes in $FEV_1$ (40, 42).

Infective exacerbations are a significant cause of morbidity and often necessitate use of both primary and secondary health care resources (43). Recurrent exacerbations are associated with a poor health-related quality of life and add further insult to the persistently damaged, inflamed airways. Reducing exacerbations is a major goal of management in this chronic condition with previous long-term antibiotic studies evaluating the impact of treatment on exacerbations. Orriols and coworkers (10) found a reduced number of hospital admissions and inpatient days with 12-month nebulized ceftazidime and tobramycin. Drobnic and coworkers (12) found a reduced number of exacerbations requiring hospital admission and for those admitted a shorter length of stay in their 6-month randomized controlled trial of nebulized tobramycin. In our study, patients receiving nebulized gentamicin had fewer exacerbations during treatment and took twice as long to their first exacerbation during the treatment phase than patients in the saline group.

With significant reductions in sputum bacterial density and inflammation and improved exercise capacity and fewer exacerbations, significantly more patients in the gentamicin group had a clinically significant improvement in health-related quality of life as assessed by both the LCQ and the SGRQ, arguably the most important goal of management in chronic disease. However, within the saline group a small percentage of patients also had an improvement in health-related quality of life. This suggests a small physiotherapy effect or a potential placebo effect as a consequence of either a new treatment, the impact of the frequent study reviews, or immediate access to tertiary care support if they felt unwell.

We found nebulized gentamicin to be a reasonably well tolerated therapy, with few adverse effects. Despite no significant bronchospasm with the initial gentamicin challenge, 7 of the original 32 patients subsequently developed bronchospasm. These patients received adjunctive nebulized $\beta_2$ agonist and five were able to continue with the nebulized gentamicin and complete the study. However, in the study by Barker and coworkers (11) of 4 weeks' nebulized tobramycin there was an overall increased incidence of reported wheeze, cough, chest pain, and dyspnea with treatment; 70% of patients reported at least one respiratory symptom. No patient suffered other adverse effects commonly related to gentamicin; particularly, there were no cases of nephrotoxicity or ototoxicity. Only one patient developed a significantly detectable serum level of gentamicin at Month 9, requiring a reduction in treatment dose to 80 mg once daily. These findings suggest that with close monitoring, nebulized gentamicin is a safe treatment.

Despite significant benefits with nebulized gentamicin throughout 12 months' treatment, it was disappointing that none of the treatment effects were sustained in the 3-month treatment-free follow-up period, with sputum characteristics returning to values similar to baseline. Only one randomized controlled trial of nebulized antibiotics has previously included a follow-up period during which time eradication of *P. aeruginosa* from the sputum was sustained, but this was only over 2 weeks' follow-up period and it is not known whether this effect would be sustained over a longer follow-up period (11). Although our findings during the follow-up period are disappointing, they provide clear guidance for clinicians that for treatment with nebulized gentamicin to be effective, it must be continuous. Further studies are needed, however, to decide on the optimum regime.

There is a paucity of evidence for effective long-term treatments in non–cystic fibrosis bronchiectasis. This randomized controlled trial has shown that regular nebulized gentamicin can significantly reduce sputum bacterial infection, reduce airways inflammation, improve sputum purulence, improve exercise capacity, reduce exacerbations, and improve health-related quality of life in chronically infected patients with bronchiectasis, irrespective of infecting pathogen.

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## References

1. Laennec R. A treatise in the diseases of the chest and on mediate auscultation (1819), 4th ed. London: Longman; 1834.
2. King PT, Holdsworth SR, Freezer NJ, Villanueva E, Holmes PW. Characterisation of the onset and presenting clinical features of adult bronchiectasis. *Respir Med* 2006;100:2183–2189.
3. Martinez-Garcia MA, Perpina-Tordera M, Roman-Sanchez P, Soler-Cataluna JJ. Quality-of-life determinants in patients with clinically stable bronchiectasis. *Chest* 2005;128:739–745.
4. Barker AF. Bronchiectasis. *N Engl J Med* 2002;346:1383–1393.
5. Currie DC, Pavia D, Agnew JE, Lopez-Vidriero MT, Diamond PD, Cole PJ, Clarke SW. Impaired tracheobronchial clearance in bronchiectasis. *Thorax* 1987;42:126–130.
6. Angrill J, Agusti C, De Celis R, Filella X, Rano A, Elena M, De La Bellacasa JP, Xaubet A, Torres A. Bronchial inflammation and colonization in patients with clinically stable bronchiectasis. *Am J Respir Crit Care Med* 2001;164:1628–1632.
7. Hill AT, Campbell EJ, Hill SL, Bayley DL, Stockley RA. Association between airway bacterial load and markers of airway inflammation in patients with stable chronic bronchitis. *Am J Med* 2000;109:288–295.
8. Cole PJ. Inflammation: a two-edged sword–the model of bronchiectasis. *Eur J Respir Dis Suppl* 1986;147:6–15.
9. Lin HC, Cheng HF, Wang CH, Liu CY, Yu CT, Kuo HP. Inhaled gentamicin reduces airway neutrophil activity and mucus secretion in bronchiectasis. *Am J Respir Crit Care Med* 1997;155:2024–2029.

10. Orriols R, Roig J, Ferrer J, Sampol G, Rosell A, Ferrer A, Vallano A. Inhaled antibiotic therapy in non-cystic fibrosis patients with bronchiectasis and chronic bronchial infection by *Pseudomonas aeruginosa. Respir Med* 1999;93:476–480.
11. Barker AF, Couch L, Fiel SB, Gotfried MH, Ilowite J, Meyer KC, O'Donnell A, Sahn SA, Smith LJ, Stewart JO, *et al.* Tobramycin solution for inhalation reduces sputum *Pseudomonas aeruginosa* density in bronchiectasis. *Am J Respir Crit Care Med* 2000;162:481–485.
12. Drobnic ME, Sune P, Montoro JB, Ferrer A, Orriols R. Inhaled tobramycin in non-cystic fibrosis patients with bronchiectasis and chronic bronchial infection with *Pseudomonas aeruginosa. Ann Pharmacother* 2005;39:39–44.
13. Murray MP, Doherty CJ, Greening AP, Gray RD, Simpson AJ, Haslett C, Wilkinson TS, Chalmers JD, Hill AT. Long term nebulised gentamicin in non-cystic fibrosis bronchiectasis improves microbial load, exercise tolerance, exacerbation frequency and health related quality of life. British Thoracic Society Winter Meeting December 2009. London, UK. *Thorax* 2009;64:A103.
14. Birring SS, Prudon B, Carr AJ, Singh SJ, Morgan MD, Pavord ID. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). *Thorax* 2003;58:339–343.
15. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992;145: 1321–1327.
16. Naidich DP, McCauley DI, Khouri NF, Stitik FP, Siegelman SS. Computed tomography of bronchiectasis. *J Comput Assist Tomogr* 1982;6:437–444.
17. Reiff DB, Wells AU, Carr DH, Cole PJ, Hansell DM. Ct findings in bronchiectasis: limited value in distinguishing between idiopathic and specific types. *AJR Am J Roentgenol* 1995;165:261–267.
18. Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004;23:932–946.
19. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987;106:196–204.
20. Murray MP, Pentland JL, Turnbull K, MacQuarrie S, Hill AT. Sputum colour: a useful clinical tool in non-cystic fibrosis bronchiectasis. *Eur Respir J* 2009;34:361–364.
21. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, *et al.* Standardisation of spirometry. *Eur Respir J* 2005;26:319–338.
22. Revill SM, Morgan MD, Singh SJ, Williams J, Hardman AE. The endurance shuttle walk: a new field test for the assessment of endurance capacity in chronic obstructive pulmonary disease. *Thorax* 1999;54:213–222.
23. Murray MP, Turnbull K, MacQuarrie S, Pentland JL, Hill AT. Validation of the Leicester Cough Questionnaire in non-cystic fibrosis bronchiectasis. *Eur Respir J* 2009;34:125–131.
24. Raj AA, Pavord DI, Birring SS. Clinical cough. IV: What is the minimal important difference for the Leicester Cough Questionnaire? *Handb Exp Pharmacol* 2009;187:311–320.
25. Wilson CB, Jones PW, O'Leary CJ, Cole PJ, Wilson R. Validation of the St. George's Respiratory Questionnaire in bronchiectasis. *Am J Respir Crit Care Med* 1997;156:536–541.
26. Murray MP, Doherty CJ, Govan JR, Hill AT. Do timing and storage of sputum influence quantitative bacteriology in bronchiectasis? *J Med Microbiol* 2010;59:829–833.
27. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial disk susceptibility tests, ninth edition, and performance standards for antimicrobial susceptibilty testing, sixteenth informational supplement; M02–A9 and M100–S16 package. Wayne, PA: CLSI; 2006.
28. Steinman RM, Cohn ZA. The interaction of soluble horseradish peroxidase with mouse peritoneal macrophages in vitro. *J Cell Biol* 1972;55:186–204.
29. Buttle DJ, Burnett D, Abrahamson M. Levels of neutrophil elastase and cathepsin b activities, and cystatins in human sputum: relationship to inflammation. *Scand J Clin Lab Invest* 1990;50:509–516.
30. Palmer LB, Smaldone GC, Simon SR, O'Riordan TG, Cuccia A. Aerosolized antibiotics in mechanically ventilated patients: delivery and response. *Crit Care Med* 1998;26:31–39.
31. Crowther Labiris NR, Holbrook AM, Chrystyn H, Macleod SM, Newhouse MT. Dry powder versus intravenous and nebulized gentamicin in cystic fibrosis and bronchiectasis. A pilot study. *Am J Respir Crit Care Med* 1999;160:1711–1716.
32. Twiss J, Byrnes C, Johnson R, Holland D. Nebulised gentamicin-suitable for childhood bronchiectasis. *Int J Pharm* 2005;295:113–119.
33. Currie DC. Nebulisers for bronchiectasis. *Thorax* 1997;52:S72–S74.
34. Angrill J, Agusti C, de Celis R, Rano A, Gonzalez J, Sole T, Xaubet A, Rodriguez-Roisin R, Torres A. Bacterial colonisation in patients with bronchiectasis: microbiological pattern and risk factors. *Thorax* 2002; 57:15–19.
35. King PT, Holdsworth SR, Freezer NJ, Villanueva E, Holmes PW. Microbiologic follow-up study in adult bronchiectasis. *Respir Med* 2007;101:1633–1638.
36. Couch LA. Treatment with tobramycin solution for inhalation in bronchiectasis patients with *Pseudomonas aeruginosa. Chest* 2001;120:114S–117S.
37. Scheinberg P, Shore E. A pilot study of the safety and efficacy of tobramycin solution for inhalation in patients with severe bronchiectasis. *Chest* 2005;127:1420–1426.
38. Gillham MI, Sundaram S, Laughton CR, Haworth CS, Bilton D, Foweraker JE. Variable antibiotic susceptibility in populations of *Pseudomonas aeruginosa* infecting patients with bronchiectasis. *J Antimicrob Chemother* 2009;63:728–732.
39. Stockley RA, Bayley D, Hill SL, Hill AT, Crooks S, Campbell EJ. Assessment of airway neutrophils by sputum colour: correlation with airways inflammation. *Thorax* 2001;56:366–372.
40. Murray MP, Pentland JL, Hill AT. A randomised crossover trial of chest physiotherapy in non-cystic fibrosis bronchiectasis. *Eur Respir J* 2009; 34:1086–1092.
41. Murray MP, Turnbull K, Macquarrie S, Hill AT. Assessing response to treatment of exacerbations of bronchiectasis in adults. *Eur Respir J* 2009;33:312–318.
42. Tsang KW, Tan KC, Ho PL, Ooi GC, Ho JC, Mak J, Tipoe GL, Ko C, Yan C, Lam WK, *et al.* Inhaled fluticasone in bronchiectasis: a 12 month study. *Thorax* 2005;60:239–243.
43. Kelly MG, Murphy S, Elborn JS. Bronchiectasis in secondary care: a comprehensive profile of a neglected disease. *Eur J Intern Med* 2003;14:488–492.