

ORIGINAL ARTICLE

Randomised controlled trial of nebulised gentamicin in children with bronchiectasis

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Aim: Following trials of inhaled antibiotics in adults, this study investigates the efficacy of nebulised gentamicin to improve respiratory function in children with bronchiectasis.

Methods: This is a randomised, double-blind, placebo-controlled, crossover trial of 12-week nebulised placebo/gentamicin, 6-week washout, 12-week gentamicin/placebo. Participants were children (5–15 years) with bronchiectasis, chronic infection (any pathogen), and able to perform spirometry from a hospital bronchiectasis clinic. Primary outcomes were change in forced expiratory volume in 1 s (FEV₁) and hospitalisation days. Secondary outcomes included sputum bacterial density, sputum inflammatory markers, additional antibiotics and symptom severity. Analyses were on an intention-to-treat basis.

Results: Fifteen children (mean 11.7-years-old) completed the study. There was no significant change in mean FEV₁ (56%/55%, $P = 0.38$) or annual rate of hospital admissions (1.1/0, $P = 0.12$) between gentamicin and placebo, respectively. However, *Haemophilus influenzae* sputum growth (27% vs. 80%, $P = 0.002$) and bacterial density (2.4 log₁₀ cfu/mL lower $P < 0.001$) improved with gentamicin. Sputum inflammatory markers interleukin-1 β ($P < 0.001$), interleukin-8 ($P < 0.001$) and tumour necrosis factor- α ($P = 0.003$) were lower with gentamicin. Poor recruitment limited study power and treatment adherence was challenging for this cohort.

Conclusions: In this crossover study of nebulised gentamicin in children with bronchiectasis, there was a reduction in sputum bacterial density and inflammation. However, there were no major improvements in clinical outcomes and adherence was a challenge.

Key words: bronchiectasis; child; gentamicin; inflammation; nebulised antibiotic.

What is already known on this topic

- 1 Non-cystic fibrosis bronchiectasis results from complex interactions between host immunity, pathogens and environment, which also drive disease progression.
- 2 Inhaled antibiotics have some effectiveness in adults with bronchiectasis and children and adults with cystic fibrosis.
- 3 The effectiveness of inhaled antibiotics in children with bronchiectasis is unknown.

What this paper adds

- 1 Treatment of children with non-cystic fibrosis bronchiectasis with inhaled gentamicin leads to significant reductions in sputum bacterial density and inflammation.
- 2 There were no significant improvements in clinical outcomes.
- 3 Like other inhaled antibiotic studies in children, adherence to the treatment regimen was challenging for this cohort.

Bronchiectasis unrelated to cystic fibrosis (CF) is an obstructive respiratory disease characterised by chronic cough and sputum overproduction, recurrent bacterial infection, airway inflammation and progressive lung damage.¹ In New Zealand (NZ), there is an

increasing incidence of bronchiectasis in children <15 years, with 13.2 new cases per 100 000 in 2017,² compared to 3.7/100 000 in 2001/2002.³ Incidence is higher in Māori (17.7/100 000) and Pasifika (28.0/100 000) compared to NZ European/Other children.² Bronchiectasis is often associated with poverty, with incidence 2.4-times higher in the most-deprived compared to least-deprived households.²

Complex interactions between host immunity, pathogens and environment drive disease progression.¹ Predominant pathogens in children are *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis*,¹ with *Pseudomonas aeruginosa* uncommon until adulthood. Sputum indicates neutrophilic inflammation, neutrophil elastase, interleukin-8 (IL-8) and tumour necrosis factor α (TNF α).¹

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Current bronchiectasis management guidelines recommend that patients with three-or-more exacerbations per year and/or chronically infected with *P. aeruginosa* be considered for long-term inhaled antibiotics,^{4,5} based on randomised controlled trials in adults. A recent systematic review and meta-analysis reported significantly reduced sputum bacterial density, exacerbation frequency and increased bacterial eradication in adults treated with inhaled antibiotics.^{6–8} However, there was no consistent improvement in quality of life or lung function (forced expiratory volume in 1 s [FEV₁]).⁶ In children and adults with CF,⁹ there is evidence that long-term inhaled antibiotics improved lung function, quality of life, and reduced exacerbations in some but not all studies. In most of these trials, CF and bronchiectasis participants had chronic *P. aeruginosa* infection.^{6,9}

The efficacy of inhaled antibiotics in children with bronchiectasis is unknown, yet this age group is more closely aligned to those in CF trials. *H. influenzae* is the most common infecting organism in this group and there are several oral antibiotic treatments available. However, inhaled therapy remains an attractive option for delivery of high concentrations of airway-localised antibiotics with few systemic effects over a prolonged period. Aminoglycosides are widely available, funded for this population in NZ and show good efficacy against *H. influenzae* with low resistance. We have shown that nebulised gentamicin is well tolerated by children and achieves *H. influenzae* bactericidal concentrations in sputum.¹⁰ In this randomised controlled trial, we examine the effectiveness of nebulised gentamicin in children with bronchiectasis and chronic respiratory infection.

Methods

Study population

Participants were enrolled from the hospital bronchiectasis clinic between June 2003 and December 2005. Inclusion criteria were: (i) 5–15 years of age; (ii) chest CT scan confirmed bronchiectasis; (iii) two positive sputum cultures (any organism) within the last 12 months; and (iv) ability to perform lung function testing and provide sputum samples. Exclusion criteria were CF, co-morbidities, aminoglycoside hypersensitivity or previous use of aminoglycoside antibiotics, or any antibiotic therapy in the preceding 2 weeks.

Study design

This was a randomised, double-blind, placebo-controlled, cross-over trial. Participants received 12 weeks treatment with nebulised saline (placebo), followed by 6 weeks washout and 12 weeks treatment with nebulised gentamicin or the reverse, gentamicin-washout-placebo (Fig. 1). The hospital pharmacy randomised participants to the two study arms in blocks of three. Telephone contact was made during the second week of each period and home community visits occurred monthly.

Medication

After removing the gentamicin and water for injection labels to provide ampoules of identical appearance, the pharmacy dispensed gentamicin 80 mg (2 mL in 2 mL 0.9% saline) or placebo

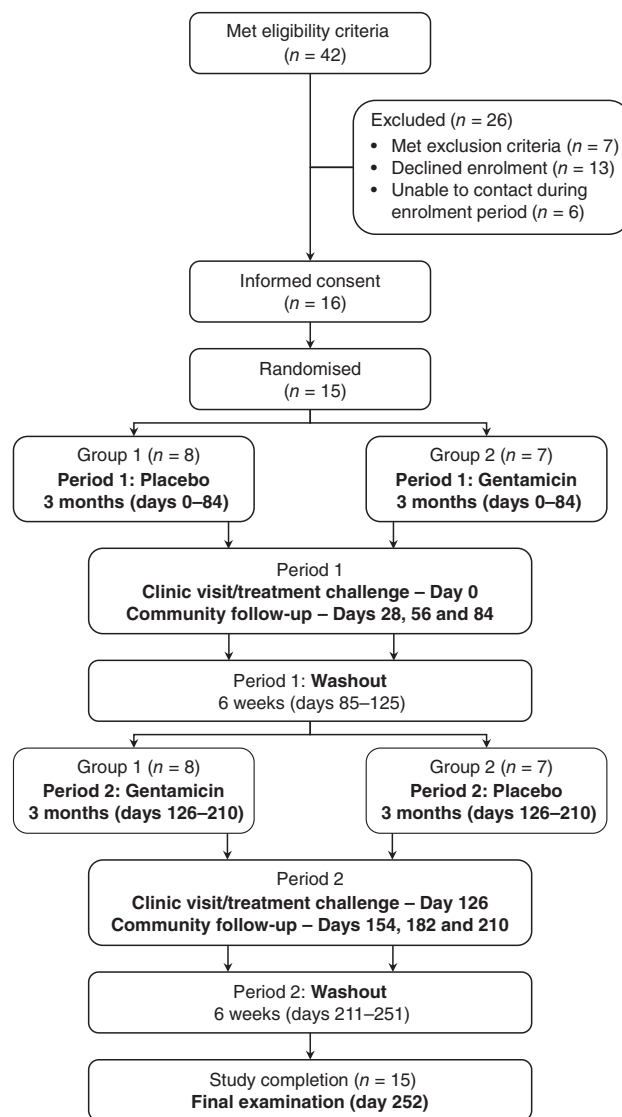


Fig. 1 Flowchart describing randomised controlled trial of nebulised gentamicin for paediatric bronchiectasis.

(2 mL water for injection with 2 mL 0.9% saline).¹⁰ Participants used an LC PLUS nebuliser driven by a PARI TurboBOY N compressor (PARI GmbH, Starnberg, Germany) modified to incorporate a usage meter to record compressor use time.¹⁰ Treatment was 10 min nebulised inhalation twice daily. All participants, caregivers and researchers were blind to group allocation. Pharmacia and Upjohn NZ Ltd (Christchurch, NZ) donated the medication but had no input into the study.

Data collection

The baseline clinic visit recorded participant demographics, bronchiectasis history, high-resolution computed tomography (HRCT) score by modified Bhalla,¹¹ microbiology and domicile code for NZ deprivation score.¹² Follow-up visits recorded interval

respiratory history, examination findings and current therapies (Appendices S1–S3, Supporting Information). A ‘Symptom Severity Score’ was recorded as a 7-item 5-point visual analogue scale adapted from Leidy *et al.*,¹³ (Appendix S4, Supporting Information). Adverse events were recorded at each visit (Appendix S5, Supporting Information). Height and weight were measured using a portable stadiometer (Seca, Hamburg, Germany) and scales (Model 916, Salter, Kent, UK). Lung function testing was conducted according to American Thoracic Society Guidelines¹⁴ using a portable electronic spirometer (Vitalograph Compact II, Vitalograph Limited, Buckingham, UK). The Auckland Ethics Committee (AKX/03/045), the Māori Research Review Committee, Auckland District Health Board (2003/045) and the New Zealand Medicines and Medical Devices Safety Authority gave approvals. Caregiver/s gave informed consent prior to enrolment. Children assented if older than ten years.

When possible, participants provided a sputum sample (transported on ice to the laboratory within 90 min) for standard microbiology culture. Sputum was examined microscopically for neutrophil and organism (gram stain) counts. Sputum pathogens were identified using standard microbiological techniques and grown on enriched and selective media: (i) blood agar (Oxoid CM271, Oxoid, Basingstoke, UK), with 5% defibrinated horse blood; (ii) chocolate agar supplemented with 18.9 units/mL bacitracin (Sigma, St. Louis, MO, USA); (iii) mannitol salt agar (Oxoid CM85); or (iv) cetrimide-nalidixic acid agar (Oxoid CM559 and SR102). For inflammatory marker measurement, sputum was stored at -70°C until ultracentrifugation at 100000g for 30 min at 4°C .^{15,16} Inflammatory markers (interleukin-1 β (IL-1 β), IL-8, and TNF α) were measured in the soluble phase, using the Luminex xMap immunoassay system (Luminex Corporation, Austin, TX).

Adherence

Adherence was reported three ways: (i) participant report, (ii) monthly used/unused ampoules count and (iii) monthly compressor usage meter reading (min). At study completion, minutes used, per individual, per period was calculated as a percentage of full adherence (3360 min). We defined >50% adherence as acceptable.

Outcome measures

Primary outcomes were (i) change in FEV₁; and (ii) number of days in hospital for respiratory exacerbations. Secondary outcomes were forced vital capacity (FVC), forced expiratory flow (FEF_{25–75%}), total oral and intravenous antibiotics required, schooldays missed and primary health visits for respiratory symptoms, severity symptom scale, sputum microscopy and *H. influenzae* bacterial density and inflammatory marker levels in sputum.

Analyses

Analyses were on an intention-to-treat basis using SAS version 9.1 (SAS Institute Inc., Cary, NC 2713-2414 USA). We converted event outcomes to annual rates. Lung function was recorded as percent predicted (Polgar reference equation).¹⁷ Bacterial density

and inflammatory cytokines were analysed as log₁₀ transformations with bacterial density data presented as cfu/mL and inflammatory cytokines presented as pg/mL.¹⁶ Treatment effect estimates were given relative to placebo utilising parametric or non-parametric statistics with linear mixed model, non-linear mixed model, Wilson signed rank or Prescott exact test. We calculated a sample size of 35 for a power of 90% to detect a significance of $P < 0.05$ using a 10% change in FEV₁ and allowing for a 30% attrition rate.

Results

Participant enrolment and characteristics

We identified 42 children who met the inclusion criteria (Fig. 1). Of these, 15 (36%) commenced treatment, representing 62% of the sample calculated for sufficient power ($n = 24$) and only 46% of the intended sample size ($n = 35$) (Fig. 1). Inability to manage the nebulisation schedule was the most common reason given for declining enrolment.

Participants had a median age of 11.7 (range 5.4–15.9) years and seven were male. Participants were Pasifika (nine), Māori (five) and European (one) ethnicities (Table 1). Two-thirds lived in high deprivation households. Mean household size was 5.3 people with 54% under 15 years of age. Participants had extensive bronchiectasis, with a mean of 4.3 lobes involved and a mean modified Bhalla score of 34 (range 22–56). Thirteen had clubbing and a chest wall deformity. Mean FEV₁ was 63% predicted (range 33–85%) and mean FVC was 77% predicted (range 43–95%). All had chronic *H. influenzae* infection. Aetiology was attributed to immunodeficiency in three participants (common variable immunodeficiency or X-linked agammaglobulinemia; all receiving regular intravenous immunoglobulin), and post-infectious in 12. Eight participants received placebo-washout-gentamicin and seven received gentamicin-washout-placebo treatment regimens (Fig. 1). We conducted 84% of planned visits and collected 81% of sputum samples.

Primary outcomes

Lung function (FEV₁% predicted) was not significantly different between placebo (mean = 55% (range = 24–74%)) and gentamicin (56% (25–80%); $P = 0.38$) (Table 2) with no significant treatment effect on FEV₁ (% predicted) between gentamicin and placebo (+1.01 (−1.3 to +3.3), $P = 0.38$), or gentamicin and baseline (+1.52 (−4.6 to +7.6), $P = 0.62$) (Table 3).

Three participants were admitted to hospital with respiratory exacerbations during the gentamicin treatment period (one admitted twice, with the longest admission for severe viral influenza) with no admissions during the placebo period. However, this did not reach statistical difference between the gentamicin (1.1 (0.0–8.7) admissions/annum) and placebo (0.0 (0.0–0.0)) periods ($P = 0.123$; Table 2).

Secondary outcomes

There was no significant change in FVC with gentamicin (−0.27 (−2.6 to +2.1)) compared to placebo ($P = 0.82$). Airway resistance (FEF_{25–75%}) improved with gentamicin, with a treatment

Table 1 Baseline demographics and clinical characteristics of study participants

Variable	Both groups (n = 15)
Participant demographics	
Age in years, median (range)	11.7 (5.4–14.9)
New Zealand born, n (%)	13 (87)
Ethnicity, n (%)	
Pacific	9 (60)
Māori	5 (33)
NZ European	1 (7)
Gender, n (%)	
Male	7 (47)
Female	8 (53)
Body Mass Index (BMI), mean (range)	65th (1st–99th) percentile
Household characteristics	
Caregiver, n (%)	
Solo	7 (47)
Dual	8 (53)
Household size, mean (range)	5.5 (3.0–8.0)
Household Deprivation†, mean (range)	8 (2–10)
Smoke exposure, n (%)	8 (53)
Clinical characteristics	
Clubbing, n (%)	13 (87)
Age of diagnosis in years, mean (range)	8.2 (1.6–12.2)
Years since diagnosis, mean (range)	3.7 (0.8–9.8)
CT score (modified Bhalla), mean (range)	34 (17–56)
Chest deformity, n (%)	11 (73)
Bilateral bronchiectasis, n (%)	15 (100)
Lobes affected, mean (range)	4.3 (3.0–5.0)
Aetiology, n (%)	
Immunodeficiency	2 (13)
Definitive or likely post-infectious	33 (87)
Lung Function (% predicted)‡, mean (range)	
FVC	77 (43–95)
FEV ₁	63 (33–85)
FEF _{25–75}	53 (16–124)
Infection-chronic <i>Hflu</i> infection, n (%)	15 (100)
Admissions per annum for respiratory exacerbations§, mean (range)	1.0 (0.0–3.5)
Days in hospital per annum, mean (range)	12.3 (0.0–51.5)
Treatment	
Inhaled bronchodilator use, n (%)	5 (33)
Regular inhaled corticosteroids use, n (%)	4 (27)
Twice daily airway clearance (physiotherapy), n (%)	15 (100)
Long-term antibiotic use, n (%)	2 (13)

† Area-level socio-economic deprivation was measured using the NZ Index of Deprivation.¹² The index is constructed from nine Census 2006 variables and provides a summary deprivation score from 1 to 10 for small areas. A score of 1 is allocated to the least deprived 10% of areas, and 10 is allocated to the most deprived 10% of areas. ‡ Polgar reference equation.¹⁷ § Mean of previous 2 years. CT, computed tomography; FEF_{25–75%}, forced expiratory flow; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

effect of +4.35 (+1.1 to +7.6) compared to placebo ($P = 0.011$; Table 3). Eight participants received additional oral antibiotics for respiratory exacerbations during the placebo period (113 days/agent) and three during the gentamicin treatment period (20 days/agent) (Table 2; $P = 0.01$). Compared to placebo, children were less likely to receive additional antibiotics for respiratory exacerbations when they were receiving nebulised gentamicin (odds ratio (OR) = 0.19 (95% confidence interval (CI) 0.10–0.33) ($P < 0.001$; Table 3). Symptom severity (−2.02 (−3.6 to −0.5)) improved with gentamicin, compared to placebo ($P = 0.012$; Table 3).

Of the 108 sputum samples cultured, 82 (76%) grew *H. influenzae*. Overall, 12 (80%) of 15 participants grew *H. influenzae* while on placebo and 4 (27%) 15 with gentamicin ($P = 0.001$). *H. influenzae* clearance occurred in 60% of participants receiving gentamicin and 13% on placebo (13%; $P = 0.008$). *H. influenzae* bacterial density was 2.44 log₁₀ cfu/mL lower with gentamicin compared to placebo ($P < 0.001$; Table 2) with a gentamicin-related treatment effect of −2.74 (−4.0 to −1.5) log₁₀ cfu/mL on *H. influenzae* bacterial density ($P < 0.001$; Table 3). Other bacterial species identified were *Streptococcus pneumoniae* (9%), *Moraxella catarrhalis* (3%) and *Staphylococcus aureus* (2%). *P. aeruginosa* was not found and 15% of samples had no or mixed bacterial growth.

Sputum inflammatory markers were significantly reduced following gentamicin treatment compared to placebo, IL-1β (76%; $P < 0.001$), IL-8 (74%; $P < 0.001$) and TNFα (59%; $P = 0.003$) (Table 2). This corresponded to a gentamicin treatment effect of −0.62 (−1.0 to −0.3) for IL-1β ($P < 0.001$), −0.43 (−0.7 to −0.2) for IL-8 ($P < 0.001$) and −0.39 (−0.6 to −0.1) for TNFα ($P = 0.003$) (Table 3).

Safety outcomes and treatment adherence

Mean adherence was 52% (range 21–84%) by participant report, 41% (9–72%) by ampoule count and 34% (0–72%) by usage meter recording (Table 2). Adherence by report decreased over time, while the other two methods remained constant through the study. The Pearson correlation between report and count was 0.516, between report and usage meter was 0.452, and between count and usage meter was 0.743. Mean compressor usage was lower for gentamicin (28%) compared to placebo (41%). No serious adverse events were recorded and there was no difference between adverse events in the two arms ($P > 0.10$; Table 2).

Discussion

This is the first double-blind, randomised, placebo-controlled trial of nebulised antibiotics in children with bronchiectasis. Using a crossover design, children with bronchiectasis were treated with inhaled gentamicin or placebo. There was no improvement in the primary outcomes of FEV₁ and hospital admission for respiratory exacerbations with gentamicin. Sputum inflammatory markers (IL-1β, IL-8 and TNFα) and *H. influenzae* density decreased with gentamicin, as did oral antibiotic use and symptom severity. Airway resistance also improved. However, treatment adherence was poor, with more hospitalisations in the gentamicin group, and there was no significant clinical improvement in children with bronchiectasis.

Table 2 Primary and secondary outcomes

Outcome/measure	Baseline	Placebo	Gentamicin	P-value
Primary outcomes				
FEV ₁ (% predicted), mean (range)	56 (25–86)	55 (24–74)	56 (25–80)	0.384
Respiratory exacerbations, mean (range)				
Admissions/annum†	1.0 (0.0–3.5)	0.0 (0.0–0.0)	1.1 (0.0–8.7)	0.123
Length of stay (days/annum)†	12.3 (0.0–51.5)	0.0 (0.0–0.0)	19.3 (0.0–183.0)	0.120
Secondary outcomes				
FVC (%predicted), mean (range)	77 (43–95)	74 (40–88)	73 (33–88)	0.820
Additional antibiotics				
Oral antibiotic (days/agent)	N/A	113	20	0.010
Oral or intravenous antibiotic (days/agent)	N/A	113	66	0.360
Primary care visits (ever), mean/person	N/A	0.3	0.1	0.450
School missed (days), mean/person	N/A	6.0	9.1	0.359
Symptom severity score, mean (range)	9.4 (3–17)	+1.0 (–4.6 to +9.3)	–1.5 (–7.6 to +3.5)	0.012
Sputum microbiology				
Hflv bacterial density (log ₁₀ cfu/mL)	5.60	4.82	2.38	<0.001
Sputum inflammatory markers (log₁₀ pg/mL), mean (95% CI)				
IL-1β	2.98 (2.26–3.70)	3.48 (3.15–3.81)	2.85 (2.51–3.19)	<0.001
IL-8	4.73 (4.46–5.00)	5.08 (4.93–5.24)	4.50 (4.50–4.82)	<0.001
TNFα	2.93 (2.53–3.32)	3.31 (3.09–3.52)	2.91 (2.69–3.13)	0.003
Safety outcomes				
Treatment emergent adverse effects and bronchospasm (pre/post inhalation)				
		<ul style="list-style-type: none"> • No serious adverse or treatment emergent effects identified • No ototoxicity or nephrotoxicity identified • No participant withdrawal due to adverse effects • No significant difference in reported symptoms between placebo and gentamicin treatment (rhinitis, increased cough, sore throat, headache, fever, chest pain, increased sputum, abdominal pain, dizziness, nausea, vomiting, diarrhoea, fatigue, rash, increased dyspnoea or reduced appetite) – all <i>P</i> > 0.10 		
Adherence measures‡				
	Total	Placebo	Gentamicin	
Participant report, mean (range)	52% (21–84%)	58%	47%	N/A
Ampoule count, mean (range)	41% (9–72%)	41%	36%	N/A
Compressor usage meter, mean (range)	34% (0–72%)	41%	28%	N/A

† Three participants were hospitalised during the study, two had one admission and one had two admissions. ‡ Expressed as percentage of perfect usage (report: no missed nebulisations; ampoule count: Two ampoules/day; compressor use: 56 h). FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; N/A, not applicable; Hflv, *Haemophilus influenzae*; IL-1β, interleukin-1β; IL-8, interleukin-8; TNFα, tumour necrosis factor-α. Bold indicates statistically significant results.

H. influenzae is an important pathogen associated with bronchiectasis in children.¹ Unlike *P. aeruginosa*, where there are few effective oral antibiotics, there are several oral antibiotics available to treat *H. influenzae*. Nevertheless, inhaled antibiotic therapy remains an attractive option due to localised, high concentration delivery, few systemic side effects and suitability for long term treatment. Gentamicin was a pragmatic choice due to its low cost, wide availability, funding, demonstrated sputum concentrations 25 times the minimum inhibitory concentration for *H. influenzae*, low resistance and topical use for other infections, such as eye disease.¹⁰ In this study, inhaled gentamicin treatment was associated with reduced *H. influenzae* sputum density and improved bacterial clearance. Findings were similar in adults, where bacterial density and eradication were significantly improved with inhaled antibiotics.⁶ However, these effects were transitory as *H. influenzae* density returned to baseline levels following washout.^{7,19}

Airway inflammation is implicated in bronchiectasis aetiology and progression.¹ Sputum inflammatory marker concentrations

were reduced with gentamicin compared to placebo in some but not all previous studies.⁶ Similar to findings in adults,⁶ we found no change in lung function with inhaled gentamicin in children with bronchiectasis. Lung function improvements were found in some studies of children and adults with *CF* receiving inhaled antibiotics for *P. aeruginosa*.⁹ Significant improvements in exacerbation frequency are associated with inhaled antibiotics in adults,⁶ and in some studies (3/11) of children with *CF*.⁹ However, we found no change in exacerbation frequency with inhaled gentamicin. We observed a statistically significant improvement in the symptom severity score of 2.5 points with gentamicin compared to placebo. With no other improvements; however, the clinical significance of this is uncertain. While more adverse events are reported in bronchiectasis compared to *CF* trials, notably bronchoconstriction and wheeze necessitating discontinuation,⁶ no treatment-associated adverse events occurred in this trial.

In paediatric populations, adherence to inhaled antibiotic treatments is poor and has implications for treatment burden, clinical

Table 3 Treatment effect outcomes

Outcome/measure	Treatment effect (gentamicin vs. placebo)		
	Estimate†	Plot	P-value
Primary outcomes			
FEV ₁ (% predicted)			
Gentamicin versus placebo	+1.01 (−1.3 to +3.3)		0.38‡
Gentamicin versus baseline	+1.52 (−4.6 to +7.6)		0.62‡
Hospital admissions (gentamicin: placebo)	3:0		0.13§
Secondary outcomes			
FVC (% predicted)	−0.27 (−2.6 to +2.1)		0.82‡
FEF _{25–75%} (% predicted)	+4.35 (+1.1 to +7.6)		0.011‡
Additional Antibiotics, odds ratio (95% CI)			
Oral antibiotic (days)	0.19 (0.10 to 0.33)		<0.001¶
Oral or intravenous antibiotic (days)	0.86 (0.61 to 1.21)		0.36¶
Primary care visits (ever), odds ratio (95% CI)	0.40††		0.45§
School missed (days), median	0 (−69 to +143)		0.36‡‡
Symptom severity score	−2.02 (−3.6 to −0.5)		0.012‡
Sputum microbiology			
Hfla bacterial density (log ₁₀ cfu/mL)	−2.74 (−4.0 to −1.5)		<0.001‡
Sputum inflammatory markers (log ₁₀ pg/mL), mean (95% CI)			
IL-1β	−0.62 (−1.0 to −0.3)		<0.001‡
IL-8	−0.43 (−0.7 to −0.2)		<0.001‡
TNFα	−0.39 (−0.6 to −0.1)		0.003‡

† Treatment effect estimates were given relative to placebo utilising parametric or non-parametric statistics with linear mixed model, non-linear mixed model, Wilson signed rank or Prescott exact test. ‡ Linear mixed model. § Prescott's exact test. ¶ Non-linear mixed model. †† 95% CI not included due to insufficient data. ‡‡ Wilcoxon signed-rank test. Positive values indicate an increase with gentamicin treatment, negative values indicate a decrease with gentamicin treatment. CI, confidence interval; FEF_{25–75%}, forced expiratory flow; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; Hfla, *Haemophilus influenzae*; IL-1β, interleukin-1β; IL-8, interleukin-8; TNFα, tumour necrosis factor-α. Bold indicates statistically significant results.

care, health-care costs and accuracy of trial data. Studies in children with CF report 48% adherence by prescription pick-up²⁰ and 36% by nebuliser usage.²¹ We found similarly, with 41% usage by ampoule usage and 34% by nebuliser time. Adherence is better in adults, with 86% adherence by nebuliser usage reported in one study.¹⁹ The reported unpleasant taste of nebulised gentamicin²² or the significant burden of daily nebuliser use could play a role in poor adherence. Indeed, families who declined participating in our study considered the nebuliser regimen unsustainable. High treatment adherence in CF has the potential to reduce hospitalisations and associated health-care costs.^{20,23} Therefore, improving treatment adherence in children with bronchiectasis has the potential to improve clinical outcomes, reduce disease burden and lower health-care costs.

While this is the first study to examine nebulised antibiotics in children with bronchiectasis, a significant limitation was reduced study power due to low enrolment numbers. Study refusal was

high (31%) and only 15 of the 35 required for 90% power commenced the study. Historically, trials of inhaled antibiotics in bronchiectasis have struggled to recruit participants, resulting in timeline extensions and expansion to new sites, yet closing early with insufficient participants.²⁴ The twice-daily nebuliser regimen was onerous and treatment adherence was poor. The requirement for at least two positive sputum cultures (any organism) within the last 12 months was the most difficult inclusion criterion to meet. We believe this reflects the difficulty for children to expectorate sputum rather than that the proportion with chronic infection was low. At the time of this study, lung function and hospitalisation had been used as primary outcome measures in adults with bronchiectasis and were thus deemed appropriate. Indeed, there were more hospitalisations in the gentamicin period, largely driven by one participant with a severe viral influenza infection and while overall this did not reach significance it could reflect a type-2 error. Other studies have opted for bacterial

loads and inflammatory markers, which were secondary outcomes in our study, as primary outcomes.^{6–8,19} More recently, clinically meaningful outcomes such as exacerbation frequency and/or time to next exacerbation have been used in trials of nebulised antibiotics for adults with bronchiectasis.^{6–8,19}

Conclusions

In this crossover study of nebulised gentamicin in children with bronchiectasis, there was a reduction in sputum bacterial density and inflammation. However, there were no major improvements in clinical outcomes and adherence was a challenge. Our findings are in keeping with results from similar trials in adults with bronchiectasis. While guidelines have kept inhaled antibiotics as an option for paediatric bronchiectasis treatment, the outcomes have been poorer in this population than anticipated.

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References

- Chang AB, Bush A, Grimwood K. Bronchiectasis in children: Diagnosis and treatment. *Lancet* 2018; **392**: 866–79.
- Telfar Barnard L, Zhang J. *The Impact of Respiratory Disease in New Zealand*. Wellington: Asthma and Respiratory Foundation of New Zealand; 2018. <https://www.asthmafoundation.org.nz/research/the-impact-of-respiratory-disease-in-new-zealand-2018-update>.
- Twiss J, Metcalfe R, Edwards E, Byrnes C. New Zealand national incidence of bronchiectasis "too high" for a developed country. *Arch. Dis. Child.* 2005; **90**: 737–40.
- Polverino E, Goeminne PC, McDonnell MJ *et al.* European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur. Respir. J.* 2017; **50**: 1700629.
- Chang AB, Bell SC, Torzillo PJ *et al.* Chronic suppurative lung disease and bronchiectasis in children and adults in Australia and New Zealand Thoracic Society of Australia and New Zealand guidelines. *Med. J. Aust.* 2015; **202**: 130.
- Laska IF, Crichton ML, Shoemark A, Chalmers JD. The efficacy and safety of inhaled antibiotics for the treatment of bronchiectasis in adults: A systematic review and meta-analysis. *Lancet Respir. Med.* 2019; **7**: 855–69.
- De Soya A, Aksamit T, Bandel TJ *et al.* RESPIRE 1: A phase III placebo-controlled randomised trial of ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis. *Eur. Respir. J.* 2018; **51**: 1702052.
- Aksamit T, De Soya A, Bandel TJ *et al.* RESPIRE 2: A phase III placebo-controlled randomised trial of ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis. *Eur. Respir. J.* 2018; **51**: 1702053.
- Smith S, Rowbotham NJ, Regan KH. Inhaled anti-pseudomonal antibiotics for long-term therapy in cystic fibrosis. *Cochrane Database Syst. Rev.* 2018; **3**: CD001021.
- Twiss J, Byrnes C, Johnson R, Holland D. Nebulised gentamicin-suitable for childhood bronchiectasis. *Int. J. Pharm.* 2005; **295**: 113–9.
- Bhalla M, Turcios N, Aponte V *et al.* Cystic fibrosis: Scoring system with thin-section CT. *Radiology* 1991; **179**: 783–8.
- Salmond C, Crampton P, Atkinson J. *NZDep2006 Index of Deprivation*. Wellington: Department of Public Health, University of Otago; 2007. <https://doi.org/10.1111/j.1753-6405.2008.00275.x>.
- Leidy NK, Margolis MK & Merchant S *et al.* Preliminary Results of a U. S.-Based Study to Validate the Acute Bronchitis Symptom Severity Scale. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 7th Annual International Meeting. Value Health, Arlington, Virginia, USA, 2002; 263.
- Miller MR, Hankinson J, Brusasco V *et al.* Standardisation of spirometry. *Eur. Respir. J.* 2005; **26**: 319–38.
- Tsang KW, Ho PI, Chan KN *et al.* A pilot study of low-dose erythromycin in bronchiectasis. *Eur. Respir. J.* 1999; **13**: 361–4.
- Tsang KW, Ho PL, Lam WK *et al.* Inhaled fluticasone reduces sputum inflammatory indices in severe bronchiectasis. *Am. J. Respir. Crit. Care Med.* 1998; **158**: 723–7.
- Polgar G, Promadhat V. *Pulmonary Function Testing in Children: Techniques and Standards*. Philadelphia: WB Saunders; 1971.
- Prescott RJ. The comparison of success rates in cross-over trials in the presence of an order effect. *Appl. Statistics.* 1981; **30**: 9–15. <https://doi.org/10.2307/2346652>.
- Haworth CS, Bilton D, Chalmers JD *et al.* Inhaled liposomal ciprofloxacin in patients with non-cystic fibrosis bronchiectasis and chronic lung infection with *Pseudomonas aeruginosa* (ORBIT-3 and ORBIT-4): Two phase 3, randomised controlled trials. *Lancet Respir. Med.* 2019; **7**: 213–26.
- Quittner AL, Zhang J, Marynchenko M *et al.* Pulmonary medication adherence and health-care use in cystic fibrosis. *Chest* 2014; **146**: 142–51.
- Daniels T, Goodacre L, Sutton C, Pollard K, Conway S, Peckham D. Accurate assessment of adherence: Self-report and clinician report vs electronic monitoring of nebulizers. *Chest* 2011; **140**: 425–32.
- Quon BS, Goss CH, Ramsey BW. Inhaled antibiotics for lower airway infections. *Ann. Am. Thorac. Soc.* 2014; **11**: 425–34.
- Tappenden P, Sadler S, Wildman M. An early health economic analysis of the potential cost effectiveness of an adherence intervention to improve outcomes for patients with cystic fibrosis. *Pharmacoeconomics* 2017; **35**: 647–59.
- Chalmers JD, McDonnell MJ, Rutherford R *et al.* The generalizability of bronchiectasis randomized controlled trials: A multicentre cohort study. *Respir. Med.* 2016; **112**: 51–8.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1. Visit checklist used by researcher to ensure completion of all study visit activities.

Appendix S2. Researcher form for recording participant history.

Appendix S3. Researcher form for recording clinical examination results.

Appendix S4. Participant Severity Symptom Score Questionnaire.

Appendix S5. Researcher form for recording adverse effects.