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Efficacy of oral amoxicillin–clavulanate or azithromycin for non-severe respiratory exacerbations in children with bronchiectasis (BEST-1): a multicentre, three-arm, double-blind, randomised placebo-controlled trial

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Summary

Background Bronchiectasis guidelines recommend antibiotics for the treatment of acute respiratory exacerbations, but randomised placebo-controlled trials in children are lacking. We hypothesised that oral amoxicillin–clavulanate and azithromycin would each be superior to placebo in achieving symptom resolution of non-severe exacerbations in children by day 14 of treatment.

Methods In this multicentre, three-arm, parallel, double-dummy, double-blind, randomised placebo-controlled trial at four paediatric centres in Australia and New Zealand, we enrolled children aged 1–18 years with CT-confirmed bronchiectasis unrelated to cystic fibrosis, who were under the care of a respiratory physician and who had had at least two respiratory exacerbations in the 18 months before study entry. Participants were allocated (1:1:1) at exacerbation onset to receive oral suspensions of amoxicillin–clavulanate (45 mg/kg per day) plus placebo azithromycin, azithromycin (5 mg/kg per day) plus placebo amoxicillin–clavulanate, or both placebos for 14 days. An independent statistician prepared a computer-generated, permuted-block (size 2–8) randomisation sequence, stratified by centre, age, and cause. Participants, caregivers, study coordinators, and investigators were masked to treatment assignment until data analysis was completed. The primary outcome was the proportion of children with exacerbation resolution by day 14 in the intention-to-treat population. Treatment groups were compared using generalised linear models. Statistical significance was set at $p < 0.0245$ to account for multiple comparisons. This trial is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12612000011886) and is completed.

Findings Between April 17, 2012, and March 1, 2017, 604 children were screened and 252 were enrolled. Between July 31, 2012, and June 26, 2017, 197 children were allocated at the start of an exacerbation (63 to the amoxicillin–clavulanate group, 67 to the azithromycin group, and 67 to the placebo group). Respiratory viruses were identified in 82 (53%) of 154 children with available nasal swabs on day 1 of treatment. Primary outcome data were available for 196 (99%) children (one child with missing data [placebo group] was recorded as non-resolved according to criteria defined a priori). By day 14, exacerbations had resolved in 41 (65%) children in the amoxicillin–clavulanate group, 41 (61%) in the azithromycin group, and 29 (43%) in the placebo group. Compared with placebo, relative risk for resolution by day 14 was 1.50 (95% CI 1.08–2.09, $p = 0.015$; number-needed-to-treat [NNT] 5 [95% CI 3–20]) in the amoxicillin–clavulanate group and 1.41 (1.01–1.97, $p = 0.042$; NNT 6 [3–79]) in the azithromycin group. Adverse events were recorded in 19 (30%) children in the amoxicillin–clavulanate group, 20 (30%) in the azithromycin group, and 14 (21%) in the placebo group, but no events were severe or life-threatening.

Interpretation Amoxicillin–clavulanate treatment is beneficial in terms of resolution of non-severe exacerbations of bronchiectasis in children, and should remain the first-line oral antibiotic in this setting.

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Introduction

Although bronchiectasis is a major contributor to chronic respiratory morbidity and mortality globally, few randomised controlled trials (RCTs) have been done to guide management.^{1–3} Bronchiectasis is characterised by acute respiratory exacerbations, which in children are associated with increased parental stress, impaired

quality of life, and lung function decline in severe exacerbations requiring hospitalisation.⁴

Bronchiectasis guidelines advise treating exacerbations with antibiotics for 10–14 days.^{5–7} The predominant pathogens detected in the lower airways of children with bronchiectasis are *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella*

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Research in context

Evidence before this study

Before the start of this study, we searched PubMed and Cochrane databases for randomised controlled trials (RCTs) involving bronchiectasis published between inception and Jan 15, 2011, using the search terms "bronchiectasis", "placebo", and "controlled trials". We then searched using keywords "antibiotics", "bronchiectasis", "randomised", and "exacerbation" in the same databases. Our searches were restricted to reports in English. We identified six RCTs investigating antibiotic treatment of exacerbations in adults, of which only one (using inhaled gentamicin) was placebo-controlled. All had small sample sizes (18–43), three were open-label, and five compared either different antibiotics or different doses of the same agent. None involved macrolide antibiotics or children. During the study period, we published the results of our parallel study, which showed that, within a 20% margin, azithromycin was non-inferior to amoxicillin–clavulanate for achieving symptom resolution at 21 days when treating acute exacerbations of bronchiectasis, but that the episodes took significantly longer to resolve with azithromycin than with amoxicillin–clavulanate. Randomised placebo-controlled trials assessing treatments for exacerbations of bronchiectasis in children are still lacking.

Added value of this study

To our knowledge, this is the first RCT comparing use of any oral antibiotics with placebo for treating exacerbations in patients with bronchiectasis unrelated to cystic fibrosis. In this three-arm RCT, amoxicillin–clavulanate showed benefit compared with placebo in achieving symptom resolution within 14 days in non-severe (non-hospitalised) acute exacerbations of bronchiectasis in children. Exacerbation resolution was slightly but non-significantly more frequent in the azithromycin group than in the placebo group. Compared with placebo, azithromycin treatment was associated with an increased proportion of azithromycin-resistant bacteria isolated from the nasopharynx.

Implications of all the available evidence

Evidence from this study supports the recommendations for use of amoxicillin–clavulanate in the treatment of exacerbations of bronchiectasis in children. Taken together with our previously published non-inferiority RCT comparing amoxicillin–clavulanate and azithromycin, amoxicillin–clavulanate should remain the first-line antibiotic treatment for non-severe exacerbations of bronchiectasis in children. Azithromycin could be reserved for use in selected settings, such as in patients with genuine penicillin hypersensitivity or in situations in which less frequent, supervised dosing might overcome difficulties with adherence.

catarrhalis, whereas (unlike in cystic fibrosis) *Pseudomonas aeruginosa* is uncommon.^{2,8} Accordingly, the combined Australian and New Zealand guidelines for bronchiectasis in children and adults recommend amoxicillin–clavulanate as the empirical first-line oral antibiotic for non-severe exacerbations.⁵ The 2019 British Thoracic Society guidelines for bronchiectasis in adults also recommend using oral amoxicillin or amoxicillin–clavulanate for exacerbations in adults, while highlighting the absence of randomised placebo-controlled trials.⁷ Likewise, the latest European adult guidelines⁶ refer to an earlier publication in which amoxicillin–clavulanate was recommended as the first option for acute exacerbations in patients without *P aeruginosa* infection.⁹

Because young children are often unable to expectorate to provide reliable lower airway specimens, amoxicillin–clavulanate is usually continued for the whole treatment course. Nevertheless, azithromycin, with its broad antimicrobial spectrum and convenient once-daily dosing, has become a popular alternative to amoxicillin–clavulanate. Indeed, in some regions of Australia, more than 50% of children undergoing bronchoscopy for chronic cough had received azithromycin in the preceding 2-week period.¹⁰ Our previous RCT showed that, after 21 days of treatment, oral azithromycin was non-inferior (within a 20% margin) to amoxicillin–clavulanate for managing non-severe (non-hospitalised) exacerbations in children with bronchiectasis.¹¹ However,

those receiving azithromycin took significantly longer (median difference 4 days) to achieve symptom resolution. Although azithromycin is non-inferior to amoxicillin–clavulanate, no superiority RCTs comparing either of these antibiotics to placebo have been done to address the important clinical question of whether oral antibiotics are necessary to treat all non-severe acute exacerbations of bronchiectasis.

The role of antibiotics in the management of exacerbations of any severity has also been questioned by some experts, who have suggested that exacerbations triggered by viruses might be self-limiting.¹² In children, almost half of acute exacerbations are associated with viruses.^{11,13} As antimicrobial resistance is of increasing global concern, it is important to determine the efficacy of antibiotics for treating exacerbations.¹⁴ Thus, in the absence of any published randomised placebo-controlled trials of oral antibiotics in either children or adults with an acute exacerbation of bronchiectasis, we aimed to test whether two commonly used but different classes of oral antibiotics, namely amoxicillin–clavulanate and azithromycin, were superior to placebo in achieving resolution of non-severe exacerbations by day 14 of treatment. As secondary aims, we assessed the effects of the antibiotics on exacerbation duration, time to next respiratory exacerbation, parent cough-specific quality-of-life (PC-QOL) score,^{15,16} systemic inflammatory markers, spirometry, upper airway microbiology, and treatment-related adverse effects, as well as describing

the point prevalence of respiratory viruses and atypical bacterial pathogens during exacerbations.

Methods

Study design and participants

A three-arm, parallel-group, double-dummy, double-blind, placebo-controlled interventional RCT was done in four paediatric centres in Australia (Brisbane, Darwin, and Perth) and New Zealand (Auckland).

Children aged 1–18 years who attended one of the four paediatric centres were eligible for enrolment if they had CT-confirmed bronchiectasis; had been diagnosed by a respiratory physician in the 5 years immediately before to study entry or, if diagnosed earlier, had been followed regularly by a respiratory physician for treatment of bronchiectasis; and had had at least two respiratory exacerbations in the 18 months before study entry. Exclusion criteria included cystic fibrosis, liver dysfunction, hypersensitivity to β -lactam or macrolide antibiotics, or having been enrolled previously in this RCT. Patients were also excluded if, at the time of randomisation, they had had a severe exacerbation of bronchiectasis (dyspnoea, hypoxia [oxygen saturation <90% in air], or hospitalisation) within the preceding 8 weeks, had *P aeruginosa* detected within the previous 16 weeks, had ever had non-tuberculous mycobacterial infection, had received β -lactam or macrolide antibiotics within the previous 3 weeks, or were receiving treatment for cancer. Those taking oral non-macrolide antibiotics on a long-term basis (for >4 weeks) for bronchiectasis were not excluded, but these antibiotics were ceased temporarily while the patient received the study medications.

Written informed consent was obtained from parents or caregivers and written assent obtained from children older than 12 years. The human research ethics committee at each participating site approved the trial, which was monitored by an independent data-monitoring committee. The study protocol has been published previously.¹⁷

Randomisation and masking

Randomisation was stratified by centre, age (≤ 5 years or > 5 years), and aetiology of bronchiectasis (patients with post-infectious or idiopathic disease, or those with disease related to immunodeficiency, aspiration, primary ciliary dyskinesia, or other causes). A computer-generated, permuted-block (block size 2–8) randomisation allocation sequence was prepared centrally by an independent statistician and used to allocate children (1:1:1) to one of three groups: an amoxicillin–clavulanate group, an azithromycin group, and a placebo group. Respiratory physicians and research assistants at each site were responsible for enrolment. At the time of an exacerbation, the child was allocated to the next number on the stratified randomisation list maintained by the local hospital pharmacist, who was external to the study. The statistician and the trial pharmacists were not

involved in data collection or conduct of the study after sequence preparation and allocation. Allocation was concealed to all investigators and participants, and was done centrally in each country. The participants, caregivers, study coordinators at various sites, and investigators were masked to treatment assignment until data analysis was completed.

As this was a double-dummy trial, the participants received either one active study medication and equivalent volume of placebo for the other study medication, or placebo for both study medications. The placebo medications (Institute of Drug Technology, Melbourne, Australia) had indistinguishable appearance and taste to those of the respective active antibiotics.¹¹

Procedures

The parents or caregivers of enrolled children were instructed to contact research staff when their child was having an exacerbation. Once an acute exacerbation was confirmed, children were randomly allocated to a study group.

All study medications were supplied as dry powders to be reconstituted at home, with identical instructions to prepare the active medication or its matched placebo by adding equal volumes of water to each of the study medications. Children in the amoxicillin–clavulanate group received oral suspensions of amoxicillin–clavulanate (45 mg/kg per day [maximum 880 mg], divided into twice-daily doses) and placebo azithromycin (once daily); those in the azithromycin group received azithromycin (5 mg/kg per day [maximum 200 mg] as a once-daily dose) and placebo amoxicillin–clavulanate (twice daily); and those in the placebo group received both placebo medications. All treatment courses lasted for 14 days, in alignment with local and international guidelines.^{5–7} Following consultation with respiratory physician colleagues and feedback from parents, 14 days was the longest period deemed acceptable for treating an exacerbation with a placebo with a safety exit after 7 days (appendix p 3). Adherence was assessed by return of study medication bottles and review of cough score and adverse event diaries.¹⁸

Exacerbations, including their resolution or failure to respond to the study medication, were predefined as per our previous study¹⁹ and RCT.¹¹ The baseline state for each child was ascertained at enrolment with use of a validated cough diary card¹⁸ and clinical examination. A non-severe exacerbation was defined as an increase in cough frequency, a change in character of the cough (ie, from dry to wet, or an increase in sputum volume or purulence) for at least 3 consecutive days and without any accompanying dyspnoea, hypoxia (oxygen saturation <90% in air), or need for hospitalisation, according to the treating clinician.¹¹ An exacerbation was considered resolved when a cough score had returned to baseline for at least 2 consecutive days after randomisation and commencement of study medications, and when any other new symptoms associated with the episode (such as fever,

See Online for appendix

lethargy, or general malaise) had resolved. An exacerbation was considered resolved even if the child exited the study protocol for any reason after resolution.¹¹ Treatment was considered to have failed if a cough score had not returned to baseline for at least 2 consecutive days by day 14 after randomisation and commencement of study medications, and also if any associated new symptoms had not resolved. These children were then treated with open-label amoxicillin–clavulanate unless judged by their respiratory physician to require intravenous antibiotics. Treatment failures were also recorded in children whose resolution status was unknown.

Exacerbations were confirmed after medical review in the clinic or outreach clinic, or at a home visit. On day 3 of treatment, families were telephoned by research staff to monitor progress and the children were reviewed clinically on days 7 and 14 and at the resolution of the exacerbation. The day of resolution was ascertained by examining cough and symptom diaries, and was then recorded prospectively. Those in remote and rural areas where a home visit was not always feasible had the study medication and PC-QOL questionnaire^{15,16} sent via express post. Parents or caregivers completed daily cough and symptom diaries while receiving the study medication. Children were then followed up with monthly phone calls from research staff for 6 months after the exacerbation or until the next exacerbation after finishing the study medication, whichever was earlier.

In addition to recording a cough diary card¹⁸ at enrolment, a baseline PC-QOL questionnaire was completed, oxygen saturation was measured, and blood was drawn to assess white blood cell count and C-reactive protein concentrations. Children aged 6 years or older underwent spirometry and FEV₁% predicted was recorded, according to current guidelines.²⁰ Where possible, as determined by the clinical setting, these tests were repeated on days 1 and 14 of treatment for an exacerbation.

Nasal swabs were collected on days 1 and 14 of treatment for an exacerbation. They were cultured for respiratory bacterial pathogens, which then underwent antibiotic susceptibility testing as described previously.¹⁷ Day-1 nasal swabs also underwent real-time PCR assays, using established methods,¹⁷ to detect atypical bacteria (*Mycoplasma pneumoniae* and *Chlamydia pneumoniae*) and 18 different viruses: respiratory syncytial viruses (subtypes A and B), adenoviruses, influenza A and B viruses, human parainfluenza virus types 1–3, human metapneumovirus, human coronaviruses (types OC43, HK1, 229E, and NL63), picornaviruses (rhinovirus and enterovirus), human bocavirus 1, and human polyomaviruses (KI and WU).

Outcomes

Children allocated to receive amoxicillin–clavulanate or azithromycin were compared with those in the placebo group. The primary outcome was the proportion of

children whose exacerbations resolved by day 14 in the intention-to-treat population. Prespecified secondary outcomes were exacerbation duration and time to next respiratory exacerbation (in days, from the date of resolution while receiving study medications until the beginning of the next exacerbation), both calculated in children whose exacerbations resolved by day 14; changes in PC-QOL score; biomarkers of systemic inflammation (white blood cell count and C-reactive protein concentration); FEV₁% predicted; nasal carriage of respiratory bacterial pathogens (including antibiotic resistance) between treatment days 1 and 14, and respiratory viruses or atypical bacteria on treatment day 1; and treatment-related adverse effects. The time to next respiratory exacerbation (in days) for each patient was calculated from the day their exacerbation resolved while receiving the study medications. All secondary analyses were done in the intention-to-treat population, and per-protocol analyses were also done. We did a post-hoc analysis based on age group (≤ 5 years or > 5 years) and virus identified on day 1 of treatment for the exacerbation (present or absent) for both the primary and secondary outcomes.

Statistical analysis

The sample size was based on a pilot study comparing oral amoxicillin–clavulanate or azithromycin with placebo in terms of resolution at 14 days.¹⁷ We assumed that exacerbations would resolve by day 14 in 60% of those receiving any antibiotic versus 30% in the placebo group. α was set at 0.0245 to account for the two two-sided primary comparisons and an interim analysis. A sample size of 189 (63 per group) was estimated to provide 84% power to detect a difference in the primary outcome.

The statistical analysis plan was approved by the study investigators and the independent data-monitoring committee before the data were analysed. Data were also analysed before group allocations were revealed. An interim analysis was done by an independent researcher when 50% of the anticipated sample size was achieved. The independent data-monitoring committee deemed that the interim results did not meet the predetermined stopping criteria.¹⁷

We used intention-to-treat and prespecified per-protocol analyses (appendix pp 6–8, 10–12). Site, age, and cause of bronchiectasis were not included in the analyses: these factors were not part of the protocol or the statistical analysis plan and, as in our previous study,¹¹ were only used for stratification during randomisation to allow for balance between the three groups.

We present summary statistics as median (IQR) for continuous data and as frequency (%) for categorical data. The association between treatment group and resolution of exacerbation was investigated with use of a generalised linear regression model with binomial family and log link, and reported as relative risk (RR) and 95% CI. Number-needed-to-treat to benefit (NNT)

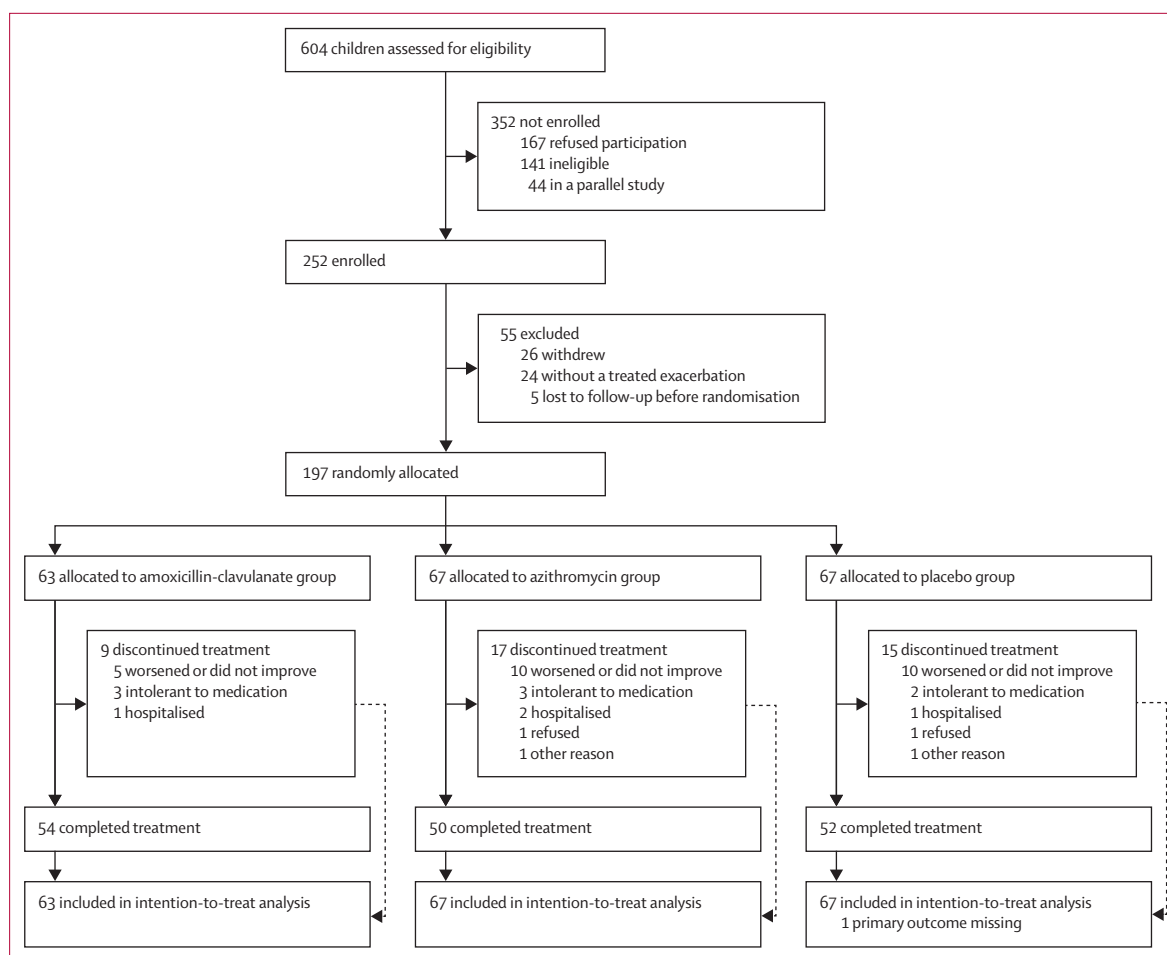


Figure: Trial profile

was calculated with a generalised linear model with binomial family and identity link. For both models, treatment group was included as the main effect and no covariables were included. The associations between treatment group and exacerbation duration and between treatment group and time to next exacerbation were both investigated with use of median regression. Those children whose exacerbations had not resolved by day 14 received open-label amoxicillin-clavulanate and were not included in these analyses. Children who did not have a further exacerbation were censored at day 180 (6 months), which was the total duration of follow-up.

The associations between treatment group and changes in secondary outcomes between treatment days 1 and 14 were also investigated with use of median regression. The association between treatment group and microbiological results was assessed with the χ^2 test. For bacteriological results, we also used a generalised linear model for the binomial family and identity link (estimating the risk difference) to control for baseline bacterial prevalence (appendix pp 13–14). Post-hoc

analyses based on age group and presence of viruses or atypical bacteria were also done and are reported in the appendix (pp 6–8).

All data were analysed with Stata version 15.1. Additional details of the study methods are described in the appendix (pp 3–4).

This study is registered as an international standard RCT with the Australian New Zealand Clinical Trials Registry (ACTRN12612000011886).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. VG, ABC, MJB, and RSW had access to the raw data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between April 17, 2012, and March 1, 2017, 604 children were screened and 252 were enrolled. 197 children were

| | Amoxicillin-clavulanate (n=63) | Azithromycin (n=67) | Placebo (n=67) |
|---|-----------------------------------|---------------------------|----------------------------|
| Sociodemographic | | | |
| Age, years | 6·0 (3·6–9·5) | 5·9 (3·4–8·7) | 6·0 (3·7–8·6) |
| Sex | | | |
| Male | 33 (52%) | 33 (49%) | 38 (57%) |
| Female | 30 (48%) | 34 (51%) | 29 (43%) |
| Indigenous ethnicity | 28 (44%) | 30 (45%) | 30 (45%) |
| Medical history | | | |
| Preterm birth (<37 weeks' gestation) | 21/60 (35%) | 10/62 (16%) | 15/64 (23%) |
| Breastfeeding (ever in infancy) | 45 (71%) | 53 (79%) | 47 (70%) |
| Tobacco smoke exposure | 14 (22%) | 18 (27%) | 23 (34%) |
| Age at diagnosis of bronchiectasis, years | 3·3 (1·9–5·8) | 3·3 (1·9–5·5) | 3·2 (1·8–5·8) |
| Number of lobes affected | 3 (2–3·5) | 2 (2–3) | 3 (2–4) |
| Number of non-hospitalised exacerbations in past 12 months | 3 (2–5·5) | 3·5 (2–5) | 3 (1–5) |
| Number of hospitalisations in past 2 years for bronchiectasis exacerbations | 1 (0–2) | 1 (0–2) | 1 (0–1) |
| Long-term (>4 weeks) use of non-macrolide antibiotics | 6 (10%) | 5 (7%) | 3 (4%) |
| Trimethoprim-sulfamethoxazole | 6 (10%) | 4 (6%) | 3 (4%) |
| Doxycycline | 0 | 1 (1%) | 0 |
| Underlying cause of bronchiectasis | n=62 | n=65 | n=67 |
| Post-infectious | 44 (71%) | 45 (69%) | 40 (60%) |
| Idiopathic | 10 (16%) | 12 (18%) | 15 (22%) |
| Immunodeficiency | 0 | 0 | 2 (3%) |
| Aspiration | 4 (6%) | 3 (5%) | 7 (10%) |
| Primary ciliary dyskinesia | 1 (2%) | 2 (3%) | 2 (3%) |
| Other | 3 (5%) | 3 (5%) | 1 (1%) |
| Comorbidities | | | |
| Tracheomalacia | 5 (8%) | 11 (16%) | 7 (10%) |
| Syndromic (eg, trisomy 21) | 3 (5%) | 2 (3%) | 3 (4%) |
| Asthma | 14 (22%) | 15 (22%) | 15 (22%) |
| Examination findings | | | |
| Weight at enrolment, kg | 21·7 (15·5–32·3) | 21·55 (16·6–40·9) | 21·2 (15·6–36·4) |
| Oxygen saturation, % | 99 (98–100), n=52 | 99 (98–99·5), n=60 | 99 (98–100), n=62 |
| Cough score ¹⁸ | 1 (0–1) | 1 (0–2) | 1 (0–2) |
| Digital clubbing | 9 (14%) | 12 (18%) | 13 (19%) |
| Chest wall deformity | 14 (22%) | 18 (27%) | 15 (22%) |
| Wheeze at baseline | 1 (2%) | 1 (1%) | 3 (4%) |
| Crackles at baseline | 2 (3%) | 2 (3%) | 4 (6%) |
| FEV ₁ , % predicted | 91·0 (82·0–100·0), n=33 | 91·0 (81·0–97·0), n=27 | 90·5 (79·0–103·0), n=34 |
| PC-QOL score ¹⁵ | 6·1 (4·3–6·8) | 6·3 (5·2–6·9) | 6·5 (4·3–7·0) |
| Serum biomarkers | | | |
| White blood cell count, × 10 ⁹ /L | 8·2 (7·4–9·3), n=29 | 8·1 (6·7–9·4), n=25 | 8·3 (6·3–9·6), n=30 |
| C-reactive protein concentration, mg/L | 2 (2–2), n=30 | 2 (2–2), n=25 | 2 (2–2), n=30 |

Data are median (IQR), n (%), or n/N (%). PC-QOL=parent cough-specific quality-of-life.

Table 1: Characteristics of randomly allocated participants at enrolment

randomly allocated at the beginning of an exacerbation between July 31, 2012, and June 26, 2017: 63 (32%) to the amoxicillin-clavulanate group, 67 (34%) to the azithromycin group, and 67 (34%) to the placebo group (figure). The final follow-up visit was on Dec 27, 2017. All children who discontinued study medication and were not hospitalised were treated with oral amoxicillin-clavulanate as per study protocol, except one child in the amoxicillin-clavulanate group (who was given sulfamethoxazole-trimethoprim by their respiratory physician) and one child in azithromycin group (who was prescribed roxithromycin by their respiratory physician).

Characteristics at baseline (table 1) and at commencement of treatment for an exacerbation (table 2) were similar among the three groups. Adherence data were available for 158 (80%) children. Adherence was greatest in the amoxicillin-clavulanate group (52 [98%] of 53), followed by the placebo group (48 [94%] of 51), and the azithromycin group (45 [83%] of 54). Compared with placebo, there was no between-group difference in adherence in the amoxicillin-clavulanate group ($p=0\cdot289$) or the azithromycin group ($p=0\cdot083$). Primary outcome data were available for 196 (99%) children. One child in the placebo group was uncontactable for 1 month after starting the study medication and (in accordance with our intention-to-treat analysis plan) was thus deemed non-resolved before unmasking.

29 (43%) children in the placebo group had exacerbation resolution by day 14, compared with 41 (65%) children in the amoxicillin-clavulanate group (RR for resolution 1·50 [95% CI 1·08–2·09] vs placebo, $p=0\cdot015$; NNT 5 [95% CI 3–20]). This higher rate of resolution in the amoxicillin-clavulanate group was formally statistically significant (as per our a-priori definition)¹⁷ after accounting for use of the same placebo group in comparisons with the amoxicillin-clavulanate group and the azithromycin group, as well as for the interim analysis. In the azithromycin group, exacerbations had resolved by day 14 in 41 (61%) children (RR for resolution 1·41 [1·01–1·97] vs placebo, $p=0\cdot042$; NNT 6 [3–79]), although this difference did not meet our predefined significance threshold.¹⁷

The median duration of exacerbation in the placebo group (10 days [IQR 6–12]) was longer than that in the amoxicillin-clavulanate group (7 days [6–10], $p=0\cdot018$), but did not differ significantly from that in the azithromycin group (8 days [5–12], $p=0\cdot24$). The median time to next exacerbation after resolution was similar in all three groups: 89 days (40–180) in the placebo group, 89 days (31–180, $p=1\cdot00$ vs placebo) in the amoxicillin-clavulanate group, and 83 days (51–180, $p=0\cdot86$ vs placebo) in the azithromycin group (appendix p 15).

Changes in PC-QOL scores, white blood cell counts, and C-reactive protein concentrations did not differ significantly between the placebo group and either the

amoxicillin–clavulanate or the azithromycin group (table 3). Spirometry at the beginning of treatment was done in 44 (22%) participants in the study, as 93 (47%) participants were aged less than 6 years, 22 (11%) participants lived at a remote site, and in 38 (19%) children the research staff did not carry spirometry equipment when a home visit was required. Paired spirometry results (at days 1 and 14 of treatment) were available for only 28 (14%) children. FEV₁% predicted values showed significantly greater improvement from day 1 to day 14 in the amoxicillin–clavulanate group than in the placebo group, although participant numbers providing these data were small (table 3). Day 1–14 changes in FEV₁% predicted values did not differ significantly between the azithromycin and placebo groups (table 3).

Of the 128 paired nasal swabs available for analysis, no significant between-group differences were observed in the bacteria isolated at treatment day 1. However, by day 14, potentially pathogenic bacteria were isolated from the nasopharynx in significantly fewer patients in the amoxicillin–clavulanate ($p < 0.0001$) and azithromycin ($p < 0.0001$) groups than in the placebo group (table 4). In the azithromycin group, the proportion of azithromycin-resistant bacterial isolates increased from day 1 (two [9%] of 22 patients with pathogenic bacterial isolates) to day 14 (five [63%] of eight), whereas these proportions of antibiotic-resistant bacteria did not change substantially between days 1 and 14 in the amoxicillin–clavulanate or placebo groups. 11 (92%) of the 12 children with azithromycin-resistant bacterial pathogens on day 1 had been prescribed azithromycin previously by their respective respiratory physicians.

99 respiratory viruses were detected by PCR in 82 (53%) of 154 children with available nasal swabs on day 1 of treatment (table 2, appendix p 9). One (1%) child had three viruses identified, another 15 (10%) children had two viruses detected, and 66 (43%) had a single virus identified from their nasal swab specimens. *C pneumoniae* bacteria were detected by PCR in nasal swabs from five (3%) children (two of whom had viruses co-detected), and *M pneumoniae* bacteria were detected in three (2%) children (one of whom also had a virus co-detected). Rhinovirus was the most common virus, detected in 53 (65%) of 82 children with viruses identified (34% of children with available nasal swabs). Respiratory viruses were detected in a significantly higher proportion of participants on day 1 in both antibiotic treatment groups than in the placebo group: 31 (63%) of 49 nasal swabs in the amoxicillin–clavulanate group ($p = 0.0078$ vs placebo), 31 (61%) of 51 in the azithromycin group ($p = 0.0149$ vs placebo), and 20 (37%) of 54 in the placebo group. However, the relative distributions of virus types were similar across the three groups, although (with the exception of rhinoviruses) the numbers of individual virus types detected were small (appendix p 9).

| | Amoxicillin–clavulanate (n=63) | Azithromycin (n=67) | Placebo (n=67) |
|--|-----------------------------------|---------------------------|---------------------------|
| Age, years | 6.7 (3.7–10.0) | 6.1 (3.8–9.4) | 6.3 (4.6–9.5) |
| Weight, kg | 21.3 (15.4–33.6) | 22.3 (16.9–50.1) | 22.5 (17.1–47.8) |
| Cough score ¹⁸ | 3 (3–4) | 3 (3–4) | 3 (2–4) |
| Days between start of exacerbation and commencing study drug | 3 (2–5) | 3 (3–5) | 4 (3–5) |
| Fever present | 7/63 (11%) | 13/67 (19%) | 10/67 (15%) |
| Oxygen saturation, %* | 98 (97–99), n=45 | 98 (98–99), n=46 | 98 (97–100), n=59 |
| Respiratory rate, breaths per min* | 24 (20–27), n=45 | 24 (22–28), n=46 | 24 (22–26), n=59 |
| Wheeze present* | 8/48 (17%) | 11/47 (23%) | 10/61 (16%) |
| Auscultatory crackles* | 18/48 (38%) | 21/47 (45%) | 23/61 (38%) |
| Abnormal ear, nose, and throat examination* | 36/48 (75%) | 38/47 (81%) | 50/61 (82%) |
| PC-QOL score ¹⁵ | 4.6 (2.9–5.7), n=58 | 4.1 (3.2–5.2), n=60 | 4.6 (3.7–5.7), n=61 |
| White blood cell count, × 10 ⁹ /L* | 9.3 (6.8–11.2), n=18 | 9.2 (6.7–9.8), n=13 | 9.0 (7.6–10.3), n=25 |
| C-reactive protein concentration, mg/L* | 2.3 (2.0–7.1), n=15 | 2.0 (2.0–2.2), n=18 | 5.7 (2.0–15), n=27 |
| FEV ₁ % predicted* | 81.0 (73.0–89.0), n=15 | 92.0 (76.0–98.0), n=11 | 86.0 (79.0–96.0), n=23 |
| Respiratory virus detected* | 31/49 (63%) | 31/51 (61%) | 20/54 (37%) |
| Atypical bacterial pathogens* | 1/49 (2%) | 5/51 (10%) | 2/54 (4%) |
| <i>Chlamydia pneumoniae</i> | 0 | 4/51 (8%) | 1/54 (2%) |
| <i>Mycoplasma pneumoniae</i> | 1/49 (2%) | 1/51 (2%) | 1/54 (2%) |

Data are median (IQR) or n/N (%). PC-QOL=parent cough-specific quality-of-life. *Some children were not seen by a study doctor on day 1 of treatment for their exacerbation, had incomplete information (including blood samples), or were unable to undergo spirometry.

Table 2: Characteristics of patients and exacerbations on day 1 of treatment

One (1%) child in the azithromycin group exited the study at day 2 of treatment and one (1%) in the placebo group exited at day 6 because of medication refusal. Eight (4%) children stopped the study medication and received open-label antibiotics because of gastrointestinal adverse events (three [5%] in the amoxicillin–clavulanate group, three [4%] in the azithromycin group, and two [3%] in the placebo group). All eight, as well as the two who refused medication, received open-label amoxicillin–clavulanate as per the study protocol. One child in each of the three groups was hospitalised for worsening symptoms, and one other who was receiving azithromycin was hospitalised with seizures (figure, table 5).

We did a per-protocol analysis for primary and secondary outcomes (appendix pp 6–12, 5), as well as a post-hoc analysis on the basis of age group (≤ 5 years or > 5 years) and virus identified on day 1 of treatment for the exacerbation (present or absent) for the primary and secondary outcomes. Adjusted data for the minor imbalance between groups for nasal swab bacteria at baseline are also presented in the appendix (pp 13–14). The results of per-protocol analyses were similar to those of the intention-to-treat analyses for both primary and secondary outcomes.

| | Amoxicillin-clavulanate | | | | Azithromycin | | | | Placebo | | | | | |
|--|-------------------------|------------------------|------------------------|-----------------------------|-------------------------------------|----|------------------------|------------------------|-----------------------------|-------------------------------------|----|------------------------|-------------------------|-----------------------------|
| | N* | Day 1 | Day 14 | Change from day 1 to day 14 | Difference in change versus placebo | N* | Day 1 | Day 14 | Change from day 1 to day 14 | Difference in change versus placebo | N* | Day 1 | Day 14 | Change from day 1 to day 14 |
| PC-QOL score | 53 | 4.6 (2.9 to 5.7) | 6.5 (5.2 to 7.0) | 0.8 (0.2 to 2.1) | 0.1 (-0.6 to 0.7) | 53 | 4.1 (3.2 to 5.2) | 6.5 (5.0 to 6.9) | 1.3 (0.4 to 2.3) | 0.6 (0.0 to 1.3) | 54 | 4.6 (3.7 to 5.7) | 5.6 (4.4 to 6.8) | 0.7 (0.1 to 1.5) |
| White blood cell count, × 10 ⁹ /L | 15 | 9.3 (6.8 to 11.2) | 8.3 (6.4 to 11.2) | 0.1 (-2.4 to 2.5) | -0.8 (-3.6 to 2.0) | 18 | 9.2 (6.7 to 9.8) | 7.8 (7.0 to 12.8) | 0.0 (-0.2 to 0.7) | -0.9 (-4.5 to 2.7) | 7 | 9.0 (7.6 to 10.3) | 8.9 (7.1 to 10.5) | 1.0 (-1.4 to 2.6) |
| C-reactive protein concentration, mg/L | 16 | 2.3 (2.0 to 7.1) | 2.0 (2.0 to 2.0) | -0.4 (-5.6 to 0.2) | 3.7 (-4.6 to 12.0) | 19 | 2.0 (2.0 to 2.2) | 2.0 (2.0 to 2.0) | 0.0 (0.0 to 0.0) | 3.7 (-2.4 to 9.8) | 7 | 5.7 (2.0 to 15.0) | 2.0 (2.0 to 2.0) | -4.2 (-13.0 to 0.0) |
| FEV ₁ % predicted | 9 | 81.0 (73.0 to 89.0) | 90.5 (81.0 to 98.5) | 10.0 (5.0 to 11.0) | 10.0 (3.9 to 16.1) | 13 | 92.0 (76.0 to 98.0) | 94.0 (87.0 to 96.0) | 2.0 (-1.6 to 3.0) | 2.0 (-5.0 to 9.0) | 6 | 86.0 (79.0 to 96.0) | 91.0 (84.0 to 102.0) | 0.0 (-1.0 to 4.0) |

Data are median (IQR), except difference in change versus placebo (reported as median change [95% CI] from regression analyses). PC-QOL=parent cough-specific quality-of-life. *Number of participants with paired values available (days 1 and 14).

Table 3: PC-QOL scores and laboratory and FEV₁% predicted results on days 1 and 14

Discussion

The results of this study show that use of oral amoxicillin-clavulanate for 14 days for non-severe exacerbations of bronchiectasis in children was superior to placebo in achieving exacerbation resolution by the end of treatment and in decreasing the duration of exacerbations. For both of these outcomes, azithromycin was associated with some improvements but did not meet our prespecified margin of statistical significance for superiority over placebo. Between-group differences were not observed for time to next exacerbation, PC-QOL scores, or inflammatory markers (C-reactive protein concentration or white blood cell count). Adherence was highest in the amoxicillin-clavulanate group, and both antibiotics were well tolerated. Although both antibiotics reduced the overall presence of bacterial pathogens in the nasopharynx at day 14 compared with placebo, the proportion of bacterial isolates with antibiotic resistance was significantly increased in the azithromycin group, but not in the amoxicillin-clavulanate group, compared with placebo at the end of treatment. Overall, 53% of participants with available nasal swabs had respiratory viruses detected at the beginning of an exacerbation.

In adults with bronchiectasis, antibiotic treatments can reduce airway and systemic inflammation, sputum volume, purulence, and bacterial density, and improve symptoms.^{21,22} Antibiotics are considered crucial interventions in the treatment of bronchiectasis.^{3,5-7} In the absence of other RCT-level evidence in either children or adults, our placebo-controlled trial now provides evidence confirming recommendations for the use of oral amoxicillin-clavulanate to treat non-severe exacerbations of bronchiectasis in children.⁵

The superiority of amoxicillin-clavulanate over placebo in achieving cough resolution (NNT 5 [95% CI 3–20]) and decreasing exacerbation duration is consistent with the results of a previous RCT, which also described the efficacy of amoxicillin-clavulanate compared with placebo for treating chronic wet cough in children with suspected protracted bacterial bronchitis. That study showed results at 2 weeks similar to our own with regard to achieving cough resolution (NNT 4 [95% CI 2–27]).²³ To the best of our knowledge, no other comparable paediatric studies have been done to date. An RCT in adults with moderate exacerbations of mild-to-moderate chronic obstructive pulmonary disease (COPD) showed that 8 days of amoxicillin-clavulanate was more effective than placebo, with an absolute difference in proportion cured of 14.2% (95% CI 3.7–24.3; NNT 7).²⁴ However, these NNT values suggest that, although amoxicillin-clavulanate is efficacious, antibiotics are not always needed to achieve resolution of an exacerbation in bronchiectasis—an observation reported previously in adults with COPD.²⁵ Thus, studies to identify those children with bronchiectasis exacerbations who are most likely to benefit from antibiotics are needed.

| | Start of treatment (day 1) | | | | | End of treatment (day 14) | | | | | | |
|---------------------------------|----------------------------|----------|-----------------------------------|----------|------------------------|---------------------------|--------------------------|----------|-----------------------------------|----------|------------------------|----------|
| | Placebo (n=47), n (%) | | Amoxicillin-clavulanate (n=39) | | Azithromycin (n=42) | | Placebo (n=47), n (%) | | Amoxicillin-clavulanate (n=39) | | Azithromycin (n=42) | |
| | n (%) | p value* | n (%) | p value* | n (%) | p value* | n (%) | p value* | n (%) | p value* | n (%) | p value* |
| <i>Streptococcus pneumoniae</i> | 11 (23%) | 0.11 | 4 (10%) | 0.43 | 7 (17%) | 0.38 | 6 (13%) | 0.085 | 1 (3%) | 0.38 | 3 (7%) | 0.38 |
| Azithromycin-resistant | 4 (36%)† | 0.68 | 1 (25%)† | 0.31 | 1 (14%)† | 0.058 | 2 (33%)† | 0.50 | 0 | 0.50 | 3 (100%)† | 0.058 |
| Penicillin-resistant | 2 (18%)† | 0.36 | 0 | 0.23 | 0 | 1.0 | 2 (33%)† | 0.50 | 0 | 0.50 | 1 (33%)† | 1.0 |
| <i>Haemophilus influenzae</i> | 13 (28%) | 0.044 | 4 (10%) | 0.065 | 5 (12%) | 0.19 | 6 (13%) | 0.021 | 0 | 0.19 | 2 (5%) | 0.19 |
| Azithromycin-resistant | 0 | NA | 0 | NA | 0 | NA | 0 | NA | 0 | NA | 0 | NA |
| Ampicillin-resistant | 3 (23%)† | 0.94 | 1 (25%)† | 0.24 | 0 | 0.54 | 1 (17%)† | NA | 0 | NA | 0 | 0.54 |
| <i>Moraxella catarrhalis</i> | 14 (30%) | 0.92 | 12 (31%) | 0.20 | 18 (43%) | <0.0001 | 15 (32%) | 0.076 | 6 (15%) | 0.076 | 1 (2%) | <0.0001 |
| β-lactamase positive | 14 (100%)† | 0.37 | 12 (100%)† | NA | 17 (94%)† | NA | 15 (100%)† | NA | 6 (100%)† | NA | 1 (100%)† | NA |
| <i>Staphylococcus aureus</i> | 8 (17%) | 0.91 | 7 (18%) | 0.50 | 5 (12%) | 0.040 | 15 (32%) | 0.037 | 5 (13%) | 0.037 | 3 (7%) | 0.040 |
| Azithromycin-resistant | 3 (38%)† | 0.71 | 2 (29%)† | 0.51 | 1 (20%)† | 0.10 | 3 (20%)† | 0.37 | 2 (40%)† | 0.37 | 2 (67%)† | 0.10 |
| Meticillin-resistant | 1 (13%)† | 0.19 | 3 (43%)† | 0.25 | 2 (40%)† | 0.50 | 2 (13%)† | 0.20 | 2 (40%)† | 0.20 | 0 | 0.50 |
| Any of the above pathogens | 32 (68%) | 0.11 | 20 (51%) | 0.13 | 22 (52%) | <0.0001 | 32 (68%) | <0.0001 | 11 (28%) | <0.0001 | 8 (19%) | <0.0001 |
| Azithromycin-resistant (any) | 7 (22%)† | 0.54 | 3 (15%)† | 0.22 | 2 (9%)† | 0.0060 | 5 (16%)† | 0.84 | 2 (18%)† | 0.84 | 5 (63%)† | 0.0060 |

Data are n (%) of children with paired nasal swabs (on days 1 and 14 of treatment), unless otherwise specified. NA=not applicable. *Versus placebo group at the same timepoint. †Percentages are the proportion of isolates with the specified resistance out of the total number of isolates of that species.

Table 4: Nasal swab bacteriology on days 1 and 14 of study medication

In contrast to oral amoxicillin-clavulanate, azithromycin is not recommended as a first-line agent for treating non-severe exacerbations of bronchiectasis. Nonetheless, we included this antibiotic in our RCT as it is commonly used in settings in which treatment adherence is problematic.^{10,26} Although both proportion of children with treatment resolution and median length of exacerbation were similar in the amoxicillin-clavulanate (resolution 65%, duration 7 days) and azithromycin (61%, 8 days) groups, the differences between azithromycin and placebo were not formally statistically significant. However, the duration of exacerbation could only be meaningfully calculated in those whose exacerbation had resolved by day 14 because the children who exited the study protocol or did not achieve resolution were given open-label antibiotics per study protocol (and including them in the analysis would thus not reflect the true effect of intervention), and the number of children with resolution in placebo group was significantly lower than those in the antibiotic groups. Our previous RCT showed that, although 3 weeks of oral azithromycin treatment was non-inferior (within a 20% margin) to 3 weeks of oral amoxicillin-clavulanate for achieving symptom resolution by day 21 in children with non-severe exacerbations of bronchiectasis,¹¹ the episode duration was significantly shorter in children allocated to receive amoxicillin-clavulanate (median duration 10 days [IQR 6–15]) compared with azithromycin (14 days [8–16]). This difference in duration is clinically significant because of the stress, anxiety, and loss of work for parents associated with bronchiectasis exacerbations.⁴ Nevertheless, in the current study, when compared with placebo, both antibiotics by day 14 had similar effect sizes with respect to symptom resolution and episode duration. Indeed, the p value comparing azithromycin to placebo

| | Amoxicillin-clavulanate (n=63) | Azithromycin (n=67) | Placebo (n=67) |
|--|-----------------------------------|------------------------|-------------------|
| Nausea | 7 (11%) | 8 (12%) | 9 (13%) |
| Vomiting | 7 (11%) | 10 (15%) | 8 (12%) |
| Diarrhoea | 8 (13%) | 7 (10%) | 3 (4%) |
| Rash | 1 (2%) | 2 (3%) | 1 (1%) |
| Hospitalised while receiving medications | 1 (2%) | 2 (3%) | 1 (1%) |
| Any adverse events | 19 (30%) | 20 (30%) | 14 (21%) |

A child could have more than one adverse event.

Table 5: Adverse events

was 0.042, suggesting that statistical significance might have been achieved in a two-arm comparison between azithromycin and placebo (ie, without the need to adjust for multiple comparisons). Furthermore, given the higher-than-anticipated proportion of participants who achieved resolution in the placebo group, it is possible that this study was insufficiently powered to show statistical superiority of azithromycin. Taken together, this and our previous RCT¹¹ support the empirical use of amoxicillin-clavulanate treatment as the first-line antibiotic choice for non-severe exacerbations of bronchiectasis in children. Furthermore, data from this study indicate that azithromycin increased the proportion of azithromycin-resistant bacteria in the nasopharynx, which is a recognised reservoir for the transmission of antibiotic-resistant organisms.²⁷

Our RCT has additional limitations. First, the doses of antibiotics might not be the optimum doses for use in clinical practice. We used 45 mg/kg per day of the 7:1 amoxicillin-clavulanate formulation. Although 80 mg/kg per day amoxicillin is recommended for treating childhood pneumonia in settings where

penicillin resistance is common in *S pneumoniae*,²⁸ the combination of *H influenzae* as the predominant lower airway pathogen⁸ and a declining prevalence of antibiotic-resistance in *S pneumoniae*²⁹ suggests that the lower dose of amoxicillin–clavulanate might have been sufficient and, at worst, we might have underestimated the antibiotic effect. Similarly, in the absence of studies comparing different doses of azithromycin to treat lower respiratory tract infections or bronchiectasis exacerbations, the commonly recommended 5 mg/kg per day regimen was used. This dosage corresponded to the total weekly dose of 30–35 mg/kg used successfully in a previous RCT of long-term azithromycin to reduce exacerbation frequency in children with bronchiectasis,³⁰ although higher daily doses of 12 mg/kg for 5 days have been used in preschool-aged children with acute wheezing illnesses.³¹

Second, some data on secondary outcomes were not available for all children. Paired PC-QOL data were available for only 160 (81%) of 197 children (53 in the amoxicillin–clavulanate, 53 in the azithromycin, and 54 in the placebo groups); however, paired PC-QOL data from at least 51 children in each group, based on a between-group difference of 0.9 points (the minimum important difference), provides power of 99%. In addition, paired blood results and spirometry data were available for a small proportion of children in each group. Although the improvement in FEV₁% predicted values differed significantly in the amoxicillin–clavulanate group (N=9) compared with the placebo group (N=6), the small samples mean that these results must be interpreted cautiously.

Third, the higher-than-expected proportion of children with spontaneous resolution in the placebo group might reflect a milder nature of exacerbations in this group versus the two antibiotic groups, or could be directly related to the lower prevalence of respiratory viruses at the beginning of an exacerbation in the placebo group (37%) compared with the other groups (63% and 61%) in this study. Virus-associated exacerbations are known to be more severe and more likely to necessitate intravenous antibiotics and hospitalisation than those in which respiratory viruses are not detected.¹³ In the placebo group, the median duration of exacerbation was 11 days in the virus-positive group and 7 days in the virus-negative group (appendix pp 7–8). Although we cannot explain the increased viral presence in both the antibiotic groups compared with the placebo group, the baseline parameters of the exacerbation were similar among all three groups (table 1). The role of viruses in non-severe bronchiectasis exacerbations should be explored further, and more studies are needed to identify the subset of non-severe exacerbations that might resolve without antibiotics. We plan to evaluate this further by exploring various clinical and microbiological factors associated with the resolution of exacerbations.

Finally, although deep nasal swabs do not directly reflect the lower airway microbiology, we used them to

ascertain the effects of antibiotics on carriage and resistance in bacterial respiratory pathogens at this site, which is the principal reservoir for spreading antibiotic-resistant respiratory bacteria within the community.²⁷ Paired nasal swabs for bacterial culture were available for less than 70% of children. Although numbers of children with macrolide-resistant pathogens were similar in the placebo and azithromycin groups on day 14, the proportional increase in carriage of macrolide-resistant pathogens in the azithromycin group was significant.

In conclusion, this randomised placebo-controlled trial showed that, for non-severe exacerbations of bronchiectasis in children, oral amoxicillin–clavulanate was superior to placebo after 14 days of treatment in terms of achieving symptom resolution and shortening the exacerbation duration. Azithromycin was associated with some improvements in exacerbation resolution and duration compared with placebo, but did not meet the threshold for significance defined in this three-arm trial. Importantly, azithromycin was also associated with an increase in the proportion of bacteria with azithromycin resistance compared with placebo. The results suggest that amoxicillin–clavulanate should remain the first-line oral antibiotic for the treatment of non-severe exacerbations of bronchiectasis in children, with once-daily azithromycin reserved for those with genuine penicillin hypersensitivity or for situations in which directly observed therapy is feasible in settings of poor treatment adherence.

Contributors

ABC conceived the study. ABC, PSM, KG, K-AFO'G, PJT, and MC participated in study design. VG, ABC, PSM, CAB, IBM, HMB, and AS actively recruited participants. VG and GBM participated in coordination and data acquisition. AC randomly allocated patients in the pharmacy and dispensed medications. VG participated in coordination, follow-up, and statistical analysis. HS-V developed the protocol for processing of nasal swabs for bacterial results. VG, ABC, MJB, and RSW had access to the raw data and RSW supervised the statistical analyses. VG drafted the initial manuscript, with substantial revisions undertaken by ABC and KG. All authors contributed to editing the manuscript and approved the final version.

Declaration of interests

We declare no competing interests.

Data sharing

The protocol for this study has been published previously. As per our institutions' policies involving Indigenous children from Australia and New Zealand, and in accordance with national guidelines, we are unable to share individual participant data with others as specific consent for this was not obtained. The statistical analysis plan will be made available upon individual request to the corresponding author.

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