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Duration of amoxicillin-clavulanate for protracted bacterial bronchitis in children (DACS): a multi-centre, double blind, randomised controlled trial

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All authors contributed to interpretation of the data, participated in the writing of the manuscript and have approved the final version for submission.

Data sharing statement

Will data collected for the study, including individual participant data and a data dictionary defining each field in the set be made available to others?

No

What data will be made available (deidentified participant data, participant data with identifiers, data dictionary, or other specified data set)?

N/A

Will additional, related documents be made available (eg, study protocol, statistical analysis plan, informed consent form)?

No

When these data will be available (beginning and end date, or “with publication”, as applicable)?

N/A

Where the data will be made available (including URLs or email addresses if relevant)?

N/A

By what access criteria data will be shared (including with whom, for what types of analyses, by what mechanism – eg, with or without investigator support, after approval of a proposal, with a signed data access agreement - or any additional restrictions).

N/A

Summary

Background Protracted bacterial bronchitis (PBB) is a leading cause of chronic wet cough in children. The current standard treatment in European and American guidelines is two-weeks of antibiotics, but the optimal duration of therapy is unknown. We describe the first randomised controlled trial (RCT) assessing the duration of antibiotic treatment in children with chronic wet cough and suspected PBB. We hypothesize that four weeks (4W) of amoxicillin-clavulanate is superior to two weeks (2W) for improving clinical outcomes.

Methods Our parallel double-blind, placebo-controlled, RCT was completed in four Australian hospitals between March 2017 and September 2019 (Australian/New Zealand Registry, ACTRN12616001725459). Children (aged two months to 19 years) with suspected PBB were randomised (1:1) to 4W of amoxicillin-clavulanate (25-35mg/kg twice-daily) or 2W of amoxicillin-clavulanate followed by 2W of placebo using permuted block randomisation (stratified by age and site). Primary outcome was clinical cure (cough resolution) by 28 days. Secondary outcomes were recurrence of PBB at six-months, time to next exacerbation, mean exacerbations during follow-up, change in Parent-proxy Cough-Specific Quality-of-Life (PC-QoL) scores at day 28 and seven month follow-up, adverse events, nasal swab bacteriology and antimicrobial resistance (AMR). Analyses followed the intention to treat principle.

Findings 106 children were randomised. By day 28, clinical cure in the 4W group (32/52, 61.5%) was not significantly different to the 2W group (38/54, (70.4%); adjusted relative risk=0.87, 95%CI 0.60-1.28; p=0.49). Time to next wet cough exacerbation was significantly longer with the 4W group compared to the 2W group (median 150 days (inter-quartile range 37.5-181) vs 35.5 (15-181); adjusted hazard ratio=0.47, 95%CI 0.25-0.90; p=0.02). The 4W group had a non-significantly decreased rate of recurrence of PBB at six months (4W=53.1%;

2W=73.7%); (adjusted odds ratio, $OR_{adj}=0.39$, 95%CI 0.14-1.04; $p=0.07$). There was no difference in mean exacerbations during follow-up between the groups ($OR_{adj}=0.24$, 95%CI 0.58-1.14; $p=0.66$). PC-QoL significantly improved from baseline to day 28 in both groups with no significant inter-group difference (-0.3, 95%CI -1.2-0.7). Data on respiratory pathogens and AMR (n=48 pairs) were similar between groups. Adverse events occurred in 13 (25%) children in the 2W and 10 (19.2%) in the 4W group ($p=0.48$).

Interpretation A 4W course of amoxicillin-clavulanate for treating children with chronic wet cough and suspected PBB confers little advantage compared to a 2W course in achieving clinical cure by 28 days. However, as a 4W duration led to a longer cough-free period, identifying children who would benefit from a longer antibiotic course is a priority.

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Research in context

Evidence before this study

Before the study's commencement we searched PubMed and Cochrane databases for randomised controlled trials (RCT's) to guide antibiotic treatment duration for children with chronic wet cough and/or suspected protracted bacterial bronchitis (PBB). We repeated these searches on February 1, 2021. The search terms used were “protracted bacterial bronchitis”, “wet cough”, “controlled trials”, “antibiotic” and “amoxicillin-clavulanate”.

There is evidence to support the use of antibiotics for the treatment of PBB with a Cochrane review of three RCT's (n=190) finding that antibiotics compared to placebo improved cough resolution at follow-up with the number needed to treat (NNT) for benefit of three. There is a single small prospective RCT (n=50) that found that a two week course of amoxicillin-clavulanate was superior to placebo for achieving cough resolution (48% vs 16%) by two week follow-up.

However, there is disagreement among the several national paediatric chronic cough guidelines that include the management of chronic wet cough in children with suspected PBB. Most guidelines/documents (including the American CHEST and European Respiratory Society) suggest two weeks of antibiotics and extending to four weeks if the wet cough does not resolve. However, the British Thoracic Society guideline recommends a much longer course of four to six weeks of antibiotics.

Added value of this study

To our knowledge, this is the first prospective RCT addressing the duration of antibiotic treatment for children with chronic wet cough suspected of having PBB. It shows that while a four week course of amoxicillin-clavulanate did not improve clinical cure (i.e. cough resolution) by 28 day follow-up compared to a two week course, it was associated with improved symptom control during six month follow-up with a significant fourfold increase in time to next wet cough exacerbation.

Implications of all the available evidence

There is insufficient evidence to support an alteration from current guidance which suggests an initial two week course of antibiotics for PBB that can be extended up to a total of four weeks if cough resolution has not occurred. However, some children will likely benefit from a four week course as a longer duration of antibiotics led to a longer cough-free period. Identifying children who would benefit from a longer antibiotic course is a priority.

Introduction

Protracted bacterial bronchitis (PBB) is one of the leading causes of chronic wet cough in young children¹ and is characterised by airway neutrophilia and chronic endobronchial infection.² PBB is defined clinically as a chronic wet cough (>4 weeks duration) that responds to two to four weeks of an appropriate antibiotic (usually amoxicillin-clavulanate) without signs or symptoms of another cause.³

Awareness of PBB has increased in recent years with its integration into international paediatric chronic cough guidelines,⁴⁻⁶ improved understanding of pathobiological mechanisms² and appreciation that untreated wet cough (PBB) is associated with future bronchiectasis.⁷⁻⁸ However, there is a paucity of trial data to guide treatment in children with wet cough and likely PBB. A Cochrane Review of three randomised controlled trials (RCTs) comprising 190 children found that antibiotics reduced the proportion of children with persistent wet cough who were not cured at follow-up (odds ratio (OR)=0.15, 95% CI 0.07-0.31) with the number needed to treat (NNT) for benefit of three (95% CI 2-4).⁹ This review included a small single-centre RCT (n=50 children) that found that a two week course of amoxicillin-clavulanate was superior to placebo for achieving cough resolution (48% vs 16%; p=0.015) by 14 days of treatment for children with chronic (over four weeks duration) wet cough suspected of having PBB.¹⁰ The earlier two RCTs were related to persistent cough and undertaken prior to the description of PBB as a diagnostic entity in 2006.¹¹

Whilst response to antibiotics is part of the definition of PBB, there is little consensus on the optimal duration of antibiotic treatment. The American CHEST Cough Guidelines⁵ recommends an initial two week course of antibiotic treatment (with a further two weeks if the cough does not resolve). Likewise, the suggested approach in the European Respiratory Society

taskforce document on PBB suggests two to four weeks of antibiotics.¹² However, the British Thoracic Society (BTS) Guideline recommends using amoxicillin-clavulanate for four to six weeks.⁴ The different recommendations has created confusion for treating doctors where a recent survey of Australasian respiratory paediatricians found 31% prescribed >4W of antibiotics for PBB.¹³ Unsurprisingly, RCTs to help delineate the optimal duration of antibiotic treatment have been identified as a research priority by American CHEST³ and European Respiratory Society¹² cough related publications.

A longer duration of antibiotic treatment may be rational as bacterial pathogens commonly found in PBB can form biofilms within the airway, potentially requiring longer duration treatment.¹⁴ Also, high rates of PBB recurrence (76-83%) in the following 12 months post-initial antibiotic treatment has been reported.^{8,15} A recent retrospective study described that six weeks of antibiotic therapy (vs two weeks) was associated with reduced rates of recurrent PBB¹⁶ (>three episodes/year), a known risk factor for the development of bronchiectasis.⁸

We thus undertook a multi-centre placebo-controlled RCT to test our primary hypothesis that a four week course of oral amoxicillin-clavulanate is superior to a two week course in achieving clinical cure (cough resolution) in children with suspected PBB within 28 days. Our secondary hypotheses were that children who receive longer duration antibiotics would have: (i) reduced rates of PBB recurrence; (ii) longer time to next exacerbation following clinical cure; (iii) reduced mean exacerbations during follow-up and; (iv) greater improvement in Parent-proxy Cough-Specific Quality-of-Life (PC-QoL)¹⁷ between baseline, day 28 and seven month follow-up. We also evaluated adverse events, nasal swab bacteriology and antimicrobial resistance (AMR).

Methods

Trial Design

This two-arm, parallel-group, double-blind, placebo-controlled RCT was undertaken across four hospitals in three Australian cities (Brisbane, Darwin and Perth) between March 2017 and September 2019. The study was approved by each site's human research ethics committee and monitored by an independent data monitoring committee (iDMC). Written informed consent was obtained from parents/caregivers. The RCT was registered with the Australian/New Zealand Clinical Trials Registry ACTRN12616001725459.

Participants

Eligible children were those aged two months to 19 years with: (i) chronic (daily cough of >four weeks duration) wet/productive cough; (ii) deemed by their treating doctor to require oral antibiotics and; (iii) suspected of having PBB. Children were enrolled from the outpatients or the emergency departments. Exclusions were: (i) hypersensitivity to beta-lactam; (ii) recent antibiotic treatment for their current cough (within preceding three weeks); (iii) presence of chronic respiratory illness (other than asthma); (iv) immunodeficiency; (v) hospitalisation; (vi) chest x-ray abnormality (other than peri-bronchial thickening) or; (vii) previous enrolment in this RCT.

Randomisation and masking

The computer-generated randomisation was stratified by site (Brisbane, Darwin, Perth) and age (<six or $\geq$ six years) using permuted blocks (two-eight block sizes). The 1:1 allocation sequence was prepared centrally by an independent statistician. The child was allocated to the next number on the randomisation stratified list maintained by the local hospital pharmacist (or

representative) who was external to the study. The study statistician and trial pharmacist had no other involvement in the trial after sequence preparation and allocation respectively. Allocation was concealed to all investigators and children. The children, caregivers, all study coordinators, and investigators were blinded to treatment assignment until data analysis was completed.

As per previous studies,^{10,18} study medications were supplied as identical sealed bottles of dry powder with instructions for reconstitution at home with equal volumes of water for placebo and antibiotic. The placebo (manufactured by the Institute of Drug Technology, Melbourne, Australia) had indistinguishable appearance and taste to the active amoxicillin-clavulanate.

Procedures

Following parental/caregiver consent and confirmation of eligibility, baseline assessments were undertaken, and children were randomised to receive either four weeks (4W group) of amoxicillin-clavulanate or two weeks (2W group) of amoxicillin-clavulanate followed by two weeks of placebo. Amoxicillin-clavulanate was reconstituted to 400mg/57mg/5ml and dosed at 25-35mg/kg/dose and administered twice daily with a maximum dose of 880mg/dose. Trial medications were administered by the child's parents/caregiver. Adherence was evaluated by return of study medication bottles and cough diaries.

Parent-proxy Cough-Specific Quality-of-Life (PC-QoL),¹⁷ deep nasal swabs (when possible) were collected at baseline, following completion of treatment (day 28) and completion of follow-up (month seven). Swabs were placed into skimmed milk tryptone glucose glycerol medium and stored at -80°C. Swabs were cultured for common respiratory bacteria and AMR testing using previously established methods.¹⁸ Spirometry was performed at baseline and end

of intervention in children able to perform this test (aged $\geq$ six years) and the FEV₁% predicted was recorded.

Parents/caregivers kept daily cough¹⁹ and adverse event diaries whilst the child was taking the trial medication. Research nurses contacted the parents/carers on days three, seven, 14, 21 and 28 to record medication completion, cough status and adverse events. After the intervention period, the research nurses undertook monthly follow-up by telephone call, e-mail or face to face review to ascertain recurrence of PBB, illness duration and treatment.

Definitions

‘Clinical cure’ defined *a-priori* as absence of cough for at least three days or >75% improvement (over three days) in cough scores (compared to cough at start of RCT), as described previously.^{10,20} The day of resolution was recorded by the study team defined by the first day when ‘clinical cure’ was achieved.

‘Failure’ occurred if the child was still coughing or cough scores failed to demonstrate a 75% improvement from baseline scores (over three days) by week four post-randomisation. These children were then treated with ‘open-label’ amoxicillin-clavulanate unless assessed by their respiratory physician as needing intravenous antibiotics. Children whose resolution status was unknown were also recorded as failures.

Withdrawal criteria from the trial were defined *a-priori* and included withdrawal of consent or a serious adverse event for which continued exposure to the study medication could harm the child.

Outcomes

The proportion of children with clinical cure at any time by 28 days follow-up in the 4W group were compared to that in the 2W group (primary outcome). Secondary outcomes were time to next wet cough exacerbation after clinical cure, recurrence of PBB at six months, mean exacerbations during follow-up, PC-QoL¹⁷ score change between baseline and day 28 and between day 28 and seven months, nasal swab bacteriology and AMR patterns, and treatment-related adverse events. Time to next exacerbation (in days) was calculated from the date of clinical cure with data censored at 180 days. For children who did not have an exacerbation during follow-up this was recorded as 181 days. Children who failed to achieve clinical cure by 28 days were excluded from recurrence of PBB, mean exacerbations during follow-up and time to next wet cough exacerbation follow-up analyses, as they received additional treatment (e.g. intravenous antibiotics) which would invariably influence these outcomes. Recurrence was defined *a-priori* as a new wet cough lasting for more than four weeks (PBB) or an episode of wet cough of at least two weeks duration which was treated with antibiotics by the child's general practitioner or treating physician.¹⁹ Mean exacerbations during follow-up was determined by the number of defined wet cough recurrence events for each child during the six month follow-up period.

Adverse events resulting in discontinuation, were recorded from the enrolment to the end of the follow-up period. If a serious adverse event occurred within the 28 day treatment period and was determined to be associated with the trial medication, the trial medication was ceased.

Sample size and statistical analysis

Our sample size calculations were based on our previous double-blind RCT performed on the efficacy of two weeks of amoxicillin-clavulanate for treatment of children with suspected PBB.¹⁰ We estimated that 63% of the 2W group and 90% of the 4W group would be cough-free at 28 days (i.e. relative 30% improvement). A sample size of 100 provided 91% power at 0.05 significance level. Further details and the power of the sample size relevant for secondary outcomes varied from 93% (PC-QoL) and 89% (PBB recurrence), see appendix page one. Our original target was 100 children, but we continued to recruit until a given time point and achieved a sample size of 106.

The statistical analysis plan was approved by the study investigators, statistician and iDMC before the data was analysed. The data was analysed prior to unblinding of group allocation. Stratification factors were not included in the analysis as they were used only for randomisation purposes allowing for balance between groups (as per our previous study¹⁰) and were not part of the protocol or the statistical analysis plan.

Summary statistics are presented as either mean (SD) or median (25th-75th) for continuous data, depending on their distribution and as frequency (%) for categorical data. Two-tailed statistical significance was defined at $p < 0.05$. Intention to treat analysis was used to assess the primary outcome with the association between treatment group and clinical cure investigated using a generalised linear regression model with binomial family and log link and was reported as adjusted relative risk (RR_{adj}) and 95% confidence intervals (CI).

Secondary outcomes were assessed using modified intention to treat analysis, excluding children with missing data. For categorical data, Pearson's Chi squared test or Fisher's exact

test was used to assess inter-group differences and Mann-Whitney U test was used for continuous variables. Median regression was used to account for the possibility of skewed data and the relative small sample size, to calculate the effect of treatment group on time to next exacerbation as well as difference in change in PC-QoL between baseline and day 28 and between day 28 and seven months to account for baseline differences. We used Cox proportional hazard modelling and Kaplan-Meier analysis to compare the two groups for time to next exacerbation. Nasal swab bacteriology and AMR data was only included on those children who provided swabs at baseline and day 28. All children who were lost to follow-up after starting the study medication were treated as not resolved.

Post-hoc analyses

We undertook several post-hoc analyses. Firstly, we calculated the mean total antibiotic days received for each group during the study, as it is helpful for clinicians when balancing the potential benefits of an initial four week treatment course with the pressure to limit antibiotic duration as part of antibiotic stewardship. Secondly, as duration of cough at baseline could be an important determinant of response to antibiotic treatment, we assessed whether those with brief duration of cough at baseline (<eight weeks) responded better to longer duration (4W vs 2W) antibiotic therapy as well as assessing the effect of prolonged cough at baseline (>21.4 weeks) on achieving clinical cure within 28 days in children in the 4W group. Lastly, as there is debate on including stratification factors in the statistical analysis,²¹ we repeated the primary and key secondary outcome analyses incorporating the stratification factors.

We used Stata (version 16.0) to analyse the data. The study conforms to CONSORT 2010 guidelines on reporting of randomised trials.

Results

Between 8 March 2017 and 30 September 2019, 731 children were screened and 106 randomised (see figure 1). Of these participants 611 did not meet inclusion criteria, 12 declined and two were lost to follow-up. Most baseline demographics and clinical characteristics were similar between the two groups (table 1). However, the 4W group were older, had lower previous use of antibiotics for their chronic cough and a longer duration of cough at enrolment (median 21.4 vs 15.1 weeks). The primary and secondary outcomes were thus adjusted for age, previous use of antibiotics for current cough and duration of cough at enrolment during analysis (see appendix page one for effect of incorporating stratification factors on analysis). Of the 66 children who completed 28 days treatment and returned medication bottles, medication adherence was 33/35 (94%) in the 4W group and 29/31 (94%) in the 2W group ($p=0.48$).

Clinical cure (by day 28) occurred in 32/52 (61.5%) children in the 4W group compared to 38/54 (70.4%) children in the 2W group. There was no difference in clinical cure between the groups ($RR_{adj}=0.87$, 95%CI 0.60-1.28; $p=0.49$; table 2).

Children in the 4W group had a fourfold increase in the time to next wet cough exacerbation (median 150 days, IQR 37.5-181) compared to children in the 2W group (median 35.5 days, IQR 15-181); (hazard ratio_{adjusted}=0.47, 95%CI 0.25-0.90; $p=0.02$; figure 2; table 2). The 4W group had a non-significantly reduced rate of recurrence of PBB within six month follow-up with an occurrence of 17/32 (53.1%) compared to 28/38 (73.7%) in the 2W group (adjusted odds ratio, $OR_{adj}=0.39$, 95%CI 0.14-1.04; $p=0.07$; table 2). There was no significant difference in mean exacerbations during follow-up between both groups ($OR_{adj}=0.24$, 95%CI 0.58-1.14; $p=0.66$; table 2).

The median PC-QoL from baseline to day 28 significantly improved in both groups (4W=1.9, IQR 1.1-3.1; 2W=2.1, IQR 1.3-3.1), however there was no difference between the groups (-0.3, 95%CI -1.2-0.7; table 2). There was no median change in PC-QoL recorded between day 28 and month seven follow-up in either group (difference between change in groups 0.1, 95%CI -1.0-1.2; table 2).

Paired baseline and day 28 swabs were available for 48 children (see appendix table 1, page two). At baseline, 11 (22.9%) children's swab cultured bacteria with *M. catarrhalis* (n=seven), *S. pneumoniae* (n=four), *S. aureus* (n=two), Methicillin resistant *Staphylococcus aureus* (MRSA; n=one) and non-typeable *H. influenzae* (NTHi; n=one) as identified pathogens. Day 28 swabs had bacterial growth in ten children with *S. aureus* (n=six), MRSA (n=two), *M. catarrhalis* (n=four) and *S. pneumoniae* (n=one) identified pathogens. There was no significant difference between groups on prevalence of any pathogens or AMR identified (data not shown).

Overall, 23 children (22.1%) had one or more symptoms attributable to use of amoxicillin-clavulanate (nausea, vomiting, diarrhoea or rash; table 2) but there was no difference between groups for adverse event frequency (p=0.48). A total of 16 (15.1%) children did not complete the trial medications with eight (7.5%) attributable to adverse events and four (3.8%) attributable to poor response to antibiotic (failure) requiring treatment with open-label or alternative antibiotic. Whilst the proportion of children who failed to complete the four weeks of trial medication was higher in the 2W group (n=12) compared to the 4W group (n=4), there was no difference between groups (p=0.06). No children died during the trial or follow-up period.

In the post-hoc analyses, the mean number of antibiotic days the children received during the intervention and six month follow-up period was 36.5 in the 2W group compared to 33.3 in the 4W group ($OR_{adj}=0.99$, 95%CI 0.96-1.01; $p=0.33$). Prolonged duration (4W vs 2W) antibiotic treatment had no significant effect on clinical cure in children with brief duration of cough (<eight weeks) ($n=22$) at baseline ($RR_{adj}=0.32$, 95%CI 0.33-1.73), $p=0.51$). In children who received 4W antibiotics, clinical cure was achieved in 16/26 (61.5%) in both those with short (≤ 21.4 weeks) and prolonged (>21.4 weeks) duration of cough at baseline ($p=1.0$), suggesting that duration of cough does not appear to be associated with response to four weeks of antibiotics. An additional post-hoc analysis that included stratification factors for the primary and key secondary outcome analyses, demonstrated very little change in the respective values (see appendix, page one) compared to the analyses without adjusting for stratification.

Discussion

In this multicentre placebo-controlled RCT involving 106 children with chronic wet cough (suspected PBB), four weeks of antibiotic therapy showed no benefit in achieving clinical cure by 28 days of follow-up, compared to two weeks. However, children prescribed four weeks of antibiotics had a greater than fourfold increase in time to the next wet cough exacerbation. There was a trend to reduced rate of PBB recurrence with the longer duration antibiotic course but there was no difference between the groups for the other secondary outcomes of mean exacerbations during follow-up, change in PC-QoL, adverse events, nasal swab bacteriology or AMR.

There is global evidence for the efficacy of antibiotic treatment for chronic wet cough in children with NNT for benefit of three (95% CI 2-4)⁹ with a systematic review finding supporting data from cohort studies.²² We used amoxicillin-clavulanate in our RCT as it is the most commonly used antibiotic in studies for the treatment of PBB²² being effective against the β -lactamase producing strains of the most frequently encountered organisms, *H. influenzae*, *S. pneumoniae* and *M. catarrhalis*.

The optimal duration of antibiotic treatment for PBB, however, remains unknown.⁶ To our knowledge this study is the first RCT assessing the duration of antibiotic treatment for children with chronic cough suspected of having PBB. Our study is important as it addresses an identified research need^{3,12} and somewhat resolves the controversy concerning which guideline recommendations should be used for achieving cough resolution (i.e. clinical cure). The BTS guidelines recommend up to four or six weeks⁴ of antibiotics whilst most other guidelines recommend two weeks^{5,12} (followed by a further two weeks if the cough does not resolve) be given to children who presents with chronic wet cough and suspected to have PBB. To date,

there is only a single RCT (n=50) examining the efficacy of antibiotics in children suspected of having PBB.¹⁰ The RCT used a two week course of amoxicillin-clavulanate and found that at two week follow-up clinical cure was superior to placebo (48% vs 16%), NNT (benefit at two weeks)=4, 95%CI 2-27.¹⁰ In our current RCT, the 2W group's clinical cure rate (by week four) was higher (38/54, 70·4%) and similar to the 4W group (32/52, 61·5%). Non-inferiority between the groups cannot be claimed but our cure rate figures are similar to a retrospective study that described cough resolution in 33/43 (77%) when children with chronic wet cough were given a six to eight week course of antibiotics.¹⁵

An important finding from our study was the significant increase in the time to next wet cough exacerbation in the 4W compared to the 2W group (150 vs 35·5 days) and also the reduced levels of recurrence (53% vs 73%), although the latter did not reach significance (p=0·07). This suggests the use of four weeks of antibiotics may provide greater wet cough symptom control across six months follow-up. These findings are supported by a recent retrospective chart review study that found that six weeks of antibiotics reduced rates of recurrent PBB over 12 month follow-up compared to a two week course.¹⁶ Taken together, these findings may have important implications for the management of children with PBB as recurrent PBB (>three episodes/year) within 12 months of index PBB diagnosis is associated with future diagnosis of bronchiectasis.⁸ Our study is unable to resolve the controversy about which guideline recommendations should be used to reduce future PBB episodes. A placebo-controlled RCT with longer follow-up is required before a change to clinical practice can be advocated. Antimicrobial stewardship is an important consideration when deciding on antibiotic treatment duration. The improved wet cough symptom control during follow-up provided by an initial four week course of antibiotics resulted in a similar mean total antibiotic duration between the groups during the trial and six month follow-up, taken in context with the finding of no

difference between the groups for AMR of nasal respiratory pathogens, this provides reassurance of responsible prescribing when a four week course of antibiotics is being considered for treatment of suspected PBB.

Possible mechanisms to explain the improved symptom control during follow-up with longer duration antibiotic treatment are speculative. One explanation is that a longer duration of antibiotics is required to overcome biofilms, known to occur with common PBB organisms.¹⁴ Biofilms enhance bacterial attachment and decrease antibiotic penetration which may make it difficult to eradicate bacteria with standard length courses of antibiotics.²³ A second possible explanation relates to the epithelial damage and subsequent impaired mucociliary clearance anticipated by the chronic neutrophilia associated with PBB, providing an environment that facilitates bacterial adherence and subsequent biofilm formation. With the finding that cilia recovery can take 13-17 weeks following bronchiolitis,²⁴ it is logical that the recovery following prolonged neutrophilic bronchitis may equally take several months. Given that common PBB pathogens such as non-typeable *H.influenzae* are unable to adhere to healthy differentiated epithelia²⁵ it is suggested that continued antibiotic treatment beyond the initial two week course may keep the airways free from colonisation and allow adequate recovery of the epithelial integrity.²⁶ This mechanism may also contribute toward the association of longer duration of wet cough symptoms with greater time to cough resolution with antibiotic treatment.²⁷ Given that a longer duration of wet cough is associated with elevated levels of bronchoalveolar lavage interleukin-1 and neutrophils²⁸ it is logical that a more prolonged exposure to more intense neutrophilic inflammation will result in an increase in the time required for airway epithelial repair to occur.

Identifying which group of children with PBB may benefit from a more prolonged course of antibiotic treatment is important. Our study was not designed to answer this question but a recent study found that for each additional month of wet cough an extra 1·0 days of antibiotic treatment was required.²⁷ Our post-hoc analysis finding that duration of cough at baseline (≤ 21.4 weeks vs >21.4 weeks) had no effect on clinical cure in response to 4W antibiotic therapy is limited by a possible type-1 error in this small sample size. Further research is required to understand the significance of duration of cough on antibiotic treatment requirement. Ideally a larger RCT enhanced with use of possible biomarkers should be undertaken to examine this question. Unnecessary use of antibiotics promotes increased antimicrobial resistance whilst inadequate treatment may be associated with poorer clearance of airway pathogens with on-going airway inflammation and recurrent PBB. Children with recurrent PBB within 12 months of index PBB diagnosis are at increased risk (7.9 fold compared to those without recurrent PBB) of having bronchiectasis being diagnosed within five year follow-up.⁸ Also, the duration of wet cough is associated with increased HRCT severity score²⁹ and there is increasing evidence to suggest that left untreated wet cough progresses to chronic suppurative lung disease and then bronchiectasis.⁷

There are important limitations with our study. The lower rate of clinical cure by day 28 achieved by the 4W group was an unexpected finding that may be explained by the apparent differences between the groups, despite randomisation. The 4W group were older, had lower previous use of antibiotics for their chronic cough and notably had a longer duration of cough at enrolment (21·4 vs 15·1 weeks) all of which would contribute to a more severe disease profile.²⁷ However, our analysis adjusted for these baseline differences between the groups. Our study is an assessment of children with chronic wet cough and suspected PBB, given a response to antibiotics is part of the definition and the optimal duration of treatment is yet to

be determined the true number of PBB diagnoses at baseline cannot accurately be determined. Another important limitation is the relatively small sample size which may have exaggerated baseline differences between the groups and made our study underpowered to identify important differences in treatment effects such as rate of recurrence. Further, the duration of follow-up was limited to six months and thus does not allow estimation of the rate of recurrent PBB, an important predictor for the development of bronchiectasis.⁸ Lastly, paired nasal microbiology samples were available in only 45% of the participants. The young children invariably found the swab collection distressing and parents often refused the follow-up swab or even the follow-up face to face appointment in preference to a telephone appointment if their child's wet cough had resolved. The presence of indigenous children within the study cohort and the associated higher prevalence of bronchiectasis in these communities³⁰ could be thought to affect the generalisability of the findings to populations outside of Australia, however the 12 indigenous children (11% of cohort) enrolled in our RCT did not appear to have a specifically severe course with ten (83%) demonstrating clinical cure at four weeks and only one (8%) being subsequently diagnosed with bronchiectasis. However, it is nevertheless important to validate our findings in a larger RCT including additional population groups with potentially differing antimicrobial resistance profiles, age groups and clinical settings, and incorporate longer durations of antibiotic treatment stratified by the duration of chronic wet cough at presentation. At this point, our results are likely not generalisable to clinical settings with a high burden of disease like tuberculosis and HIV.

In conclusion, whilst a four week course of amoxicillin-clavulanate did not improve clinical cure by 28 day follow-up it was associated with improved symptom control during six month follow-up with a significant greater than fourfold increase in time to next wet cough exacerbation when compared to two week treatment. Currently there is insufficient evidence

to support an alteration from the current guidance which suggests an initial two week course of antibiotics for PBB that can be extended up to a total of four weeks if cough resolution has not occurred.⁵ Identifying which group of children with PBB may benefit from extended duration antibiotics is a priority. Further, larger placebo controlled RCT's incorporating differing populations and longer duration of follow-up are required.

Table 1 - Baseline characteristics

	2W group	4W group
	(N=54)	(N=52)
Sociodemographic		
Age (years)	1.7 (1.2-3.8)	2.2 (1.3-4.1)
Sex, male	31 (57.4%)	33 (63.5%)
Indigenous ethnicity	5 (9.3%)	7 (13.5%)
Medical history		
Prematurity (<37 weeks)	9 (16.7%)	10 (19.2%)
Breast fed (ever in infancy)	46 (85.2%)	41 (78.8%)
Tobacco smoke exposure*	12 (22.2%)	15 (28.8%)
Day care / school attendance	39 (72.2%)	38 (73.1%)
Previous diagnosis of pneumonia	10 (18.5%)	10 (19.2%)
Clinical		
Duration of cough at enrolment (weeks)	15.1 (8.6-30.0)	21.4 (9.2-39.8)
>5 doctor visits for cough in 12 months*	41 (77.4%)	41 (78.8%)
Previous antibiotics for current cough	29 (53.7%)	21 (40.4%)
PC-QoL	3 (2-4.5)	3.5 (2-5)
Examination findings		
Weight for age, z-score	0.56 (-0.21-0.92)	0.85 (-0.14-1.73)
Wheeze (n=92)	5 (10.4%)	0 (0.0%)
Crackles (n=92)	5 (10.4%)	1 (2.3%)
Chest wall deformity (n=99)	4 (8.0%)	1 (2.0%)
Clubbing (n=99)	0 (0.0%)	0 (0.0%)

Abnormal ENT examination (n=98)	12 (24·5%)	8 (16·3%)
FEV ₁ % predicted (n=15)	98 (84-110)	98 (93·5-104)
FVC % predicted (n=15)	104 (91-116)	100·5 (92-110)

Data are median (IQR) or n (%) unless otherwise stated.

2W group=two weeks amoxicillin-clavulanate plus two weeks placebo.

4W group=four weeks amoxicillin-clavulanate.

PC-QoL=Parent-proxy Cough-Specific Quality-of-Life.

*Data missing in one child.

Table 2 - Clinical cure by day 28, recurrence of PBB, Mean exacerbations during follow-up, time to next exacerbation, quality of life and adverse events

	2W group (N=54)	4W group (N=52)	Difference between groups (95% CI) p-value	
Clinical cure by 28 days (n=106)	38 (70.4%)	32 (61.5%)	RR _{adj} 0.87 (0.60, 1.28)	p=0.49
Recurrence of PBB (n=70)*	28 (73.7%)	17 (53.1%)	OR _{adj} 0.39 (0.14, 1.04)	p=0.07
Mean exacerbations (SD) (n=70)*	1.13 (0.96)	1.06 (1.24)	OR _{adj} 0.24 (0.58, 1.41)	p=0.66
Median exacerbations (n=70)*	1 (0-2)	1 (0-2)	OR _{adj} -0.26 (-1.3, 0.78)	p=0.62
Time to next exacerbation (n=70)*	35.5 (15-181)	150 (37.5-181)	HR _{adj} 0.47 (0.25, 0.90)	p=0.02
PC-QoL change (D0 to D28) (n=87)	2.1 (1.3-3.1)	1.9 (1.1-3.1)	-0.2 (-1.0, 0.6)	
PC-QoL change (D28 to 7M) (n=67)	0 (-0.9-1.6)	0 (-1.6-0.7)	0.1 (-1.0, 1.2)	
Adverse events (n=104)				
Nausea or vomiting	4 (7.7%)	0 (0%)		
Diarrhoea	8 (15.4%)	8 (15.4%)		
Rash	2 (3.9%)	2 (3.9%)		
Any	13 (25.0%)	10 (19.2%)	OR _{adj} 0.75 (0.28-2.01)	p=0.57

Data are median (IQR) or n (%) unless otherwise stated.

2W group=two weeks amoxicillin-clavulanate plus two weeks placebo.

4W group=four weeks amoxicillin-clavulanate.

PC-QoL=Parent-proxy Cough-Specific Quality-of-Life.

Time to next exacerbation (in days) was calculated from the date of clinical cure with data censored at 180 days. Children who did not have an exacerbation during follow-up were recorded as 181 days.

Only those children with clinical cure by 28 days included.

All outcomes were adjusted for age, duration of cough at enrolment and previous use of antibiotics for current cough.

To compare difference between groups, median regression with 95% CI is reported.

Figure 1 – Trial profile

A total of 731 children were screened with 611 not meeting inclusion criteria with commonest reason being an absence of wet cough (n=267), duration of cough <28 days (n=112) and recent use of antibiotics for wet cough (n=32).

2W group=two weeks amoxicillin-clavulanate plus two weeks placebo.

4W group=four weeks amoxicillin-clavulanate.

Figure 2 - Proportion of children with recurrence of PBB

Kaplan-Meier plot. Outcomes were adjusted for age, duration of cough at enrolment and previous use of antibiotics for current cough.

2W group=two weeks amoxicillin-clavulanate plus two weeks placebo.

4W group=four weeks amoxicillin-clavulanate.

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Declaration of interests

Dr. Chang reports grants from National Health and Medical Research Council, Australia (NHMRC); Other fees to the institution from work relating to being a IDMC Member of an unlicensed vaccine (GSK) and an advisory member of study design for unlicensed molecule for chronic cough (Merck) outside the submitted work.

Dr. Schultz reports personal fees from Vertex Pharmaceuticals, outside the submitted work.

Dr. Upham reports personal fees from Astra Zeneca, personal fees from GSK, personal fees from Novartis, personal fees from Sanofi, outside the submitted work.

The other authors declared no conflicts of interest.

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Figure 1 - Trial Profile

Figure 2 - KM

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