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Publication date
09-06-2023

Published in
Respirology

Link to external publisher version
https://doi.org/10.1111/resp.13950

Editorial Office Notes:

RES-20-694.R2

ORIGINAL ARTICLE

Received 9 June 2020

Invited to revise 19 July and 10 August 2020

Revised 2 and 11 August 2020

Accepted 31 August 2020

Associate Editor: Marcos Restrepo

Senior Editor: Paul King

Publication fee waiver: No

Volume: 26

Outcomes of protracted bacterial bronchitis in children: A five-year prospective cohort study

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Summary at a glance

In this cohort study of 166 children with protracted bacterial bronchitis (PBB), the frequency of wet cough exacerbation decreased with age. At 5-year follow-up a significant proportion had a diagnosis of bronchiectasis, asthma or had persistent wet cough symptoms. Children with PBB require careful follow-up, appropriate investigation and treatment.

Abstract

Background and objective: Long-term data on children with protracted bacterial bronchitis (PBB) has been identified as a research priority. We describe 5-year outcomes for children with PBB to ascertain the presence of chronic respiratory disease (bronchiectasis, recurrent PBB and asthma) and identify the risk factors for these.

Methods: Prospective cohort study undertaken at the Queensland Children's Hospital, Brisbane, Australia of 166 children with PBB and 28 controls (undergoing bronchoscopy for symptoms other than chronic wet cough). Monitoring was by monthly contact via research staff. Clinical review, spirometry and CT chest were performed as clinically indicated.

Results: A total of 194 children were included in the analysis. Median duration of follow-up was 59-months (IQR 50-71 months) post-index PBB episode, 67.5% had on-going symptoms and 9.6% had bronchiectasis. Significant predictors of bronchiectasis were recurrent PBB in year-one of follow-up (Odds Ratio $(OR)_{adjusted}$=7.9, 95%CI 1.5-40.2) and the presence of *Haemophilus influenzae* in the bronchoalveolar lavage ($OR_{adjusted}$=5.0, 95%CI 1.3-8.6). Clinician diagnosed asthma at final follow-up was present in 27.1% of children with PBB. A significant bronchodilator response (FEV_1 improvement >12%) was obtained in 63.5% of these children who underwent reversibility testing. Positive allergen-specific IgE ($OR_{adjusted}$=14.8, 95%CI 2.2-100.8) at baseline and bronchomalacia ($OR_{adjusted}$=5.9, 1.2-29.7) were significant predictors of asthma diagnosis. Spirometry parameters were in the normal range.

Conclusion: As a significant proportion of children with PBB have on-going symptoms at 5-years, and outcomes include bronchiectasis and asthma, they should be carefully followed-up clinically. Defining biomarkers, endotypes and mechanistic studies elucidating the different outcomes are now required.

Key words

Asthma

Bronchiectasis

Cough

Paediatric lung disease

Respiratory Infections (non-tuberculous)

Short title

Protracted bacterial bronchitis outcomes

Introduction

Protracted bacterial bronchitis (PBB) is the commonest cause of chronic wet cough in childhood.[1] PBB, first described in 2006,[2] is defined clinically as a chronic wet cough (>4-weeks duration) without signs or symptoms of another cause that responds to a 2-4 weeks course of an appropriate antibiotic (usually amoxicillin-clavulanate).[3] Although PBB is still underappreciated,[4] there is a growing recognition of the importance of PBB in paediatric pulmonology as highlighted by the recent American Thoracic Society (ATS) patient education series.[5] PBB is now incorporated into major international paediatric chronic cough guidelines[6-8] with its associated pathobiological studies[9-11] and is also included in major reviews linking PBB with bronchiectasis.[12,13]

To date, there has only been one prospective 24-month study on the outcomes of children with PBB.[14] The lack of prospective studies was identified as a research gap in American CHEST[3,8] and European Respiratory Society.[15] Availability of longer-term data will assist clinicians to counsel parents, and to help determine which children are at increased risk of developing chronic lung disease, i.e. bronchiectasis or asthma.

The sole published prospective outcome study,[14] limited to 2-year follow-up, reported data from 106 children with PBB and concentrated on bronchiectasis that was diagnosed in 8.1%. That study also reported that 43.5% of children had recurrent PBB episodes (>3/year).[14] Multivariable regression identified significant risk factors for bronchiectasis as the presence of *Haemophilus influenzae* in bronchoalveolar lavage and recurrent PBB (adjusted odds ratio (OR_{adj}) 11.5 (95%CI 2.3-56.5) and 7.6 (95%CI 1.5-37.8) respectively).[14] As longer-term prospective data is required,[3,7] our current study characterises children from the same cohort

but includes additional children (n=166) followed for at least 4.5-years and with further outcomes explored.

Our primary aim of this prospective cohort study was to characterise the 5-year outcomes for 166 children with PBB, specifically to: (1) determine chronic respiratory morbidity (i.e. bronchiectasis, recurrent PBB and asthma) and; (2) identify their risk factors. We also report on exacerbation rates and PBB recurrence over time as well as lung function in PBB patients in comparison with disease controls (undergoing bronchoscopy for symptoms other than chronic wet cough).

Methods

Study participants

Participants were enrolled as part of a large prospective cohort cough study to characterise long-term outcomes of children with chronic cough referred to tertiary respiratory care in Brisbane. Children were enrolled at the time of bronchoscopy and written informed consent was obtained from their parent or guardian. Ethics approval was provided by the Queensland Children's Health Services Human Research Ethics Committee (HREC/03/QRCH/17). A total of 194 children were included in the analysis, fulfilling the criteria of PBB (n=166) or controls (n=28) with ≥42-months follow-up post-bronchoscopy.

Follow-up

Respiratory exacerbation frequency was obtained by monthly contact (by research team) with questionnaires completed via telephone, e-mail, web-based methods (SurveyMonkey) or mail. Parents completed cough diaries during symptomatic periods. Antibiotic treatment was prescribed by the child's respiratory physician or general practitioner when persistent wet

cough episodes occurred. Frequency of outpatient review by the child's respiratory physician was determined by the individual patient's clinical progress.

Chest multi-detector with high resolution chest tomography (CT) was performed when there were clinical features suggestive of bronchiectasis in accordance to Australian and New Zealand guidelines[16] such as, (1) chronic wet cough that was non-responsive to 4-weeks of oral antibiotic therapy, (2) persistent chest radiographic changes despite appropriate oral antibiotic therapy, or (3) recurrent hospitalisations for acute respiratory events. Screening for Cystic Fibrosis was undertaken in most children as indicated by the individual child's clinical presentation.

Definitions

PBB was defined as (1) presence of continuous, chronic (>4-weeks duration) wet or productive cough; (2) absence of symptoms or signs (i.e. specific cough pointers) suggestive of other causes of wet or productive cough; and (3) cough resolved following a 2-week course of an appropriate oral antibiotic.[2] Recurrent PBB was defined as >3 PBB episodes within 12-months. Bronchiectasis was defined on CT criteria (based on defined paediatric radiological criteria)[17] and the CT was taken at least 4-weeks post-bronchoscopy. Two respiratory physicians blinded to each other's assessment reviewed the CT with universal agreement required to diagnose bronchiectasis.

Airway provocation tests were not routinely used in our PBB cohort. Further, although controversial, the Australian handbook states "Clinical assessment is more sensitive for confirming the diagnosis of asthma than tests for airway hyper-responsiveness" (http://www.asthmahandbook.org.au).[18] Thus, we used clinician diagnosis of asthma at the

child's most recent clinical assessment, which was based on persistent response to asthma medications and supported, when present by the presence of significant bronchodilator response (BDR) (>12% increase in forced expiratory volume in the first second FEV_1) from baseline on spirometry. Response to asthma medications was defined as persistent improvement of wheeze and/or exertional dyspnoea to short acting $beta_2$-agonist or inhaled corticosteroids. Airway neutrophilia was defined as bronchoalveolar neutrophil $\geq$20% and eosinophilia as BAL eosinophil $\geq$1.5%.[19]

Statistical analysis

When data was not normally distributed (examined using Kolmogorov-Smirnov test), median and inter-quartile range (IQR) were used for descriptive statistics. For categorical variables Fisher's exact or Pearson's X^2 test was used and Mann-Whitney U test used for continuous variables. Risk factors associated with the development of chronic disease were examined using univariable and multivariable logistical regression. Factors with p-value <0.2 were included in the multivariable logistical regression. A p-value <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS statistics v23.0 (SPSS, Inc).

Results

Demographics

Of the 536 children enrolled (March 2008 to December 2014), 194 children were included in the analysis; 166 children with PBB had the minimum required follow-up duration (Figure-1). Nine children who withdrew from the study or were lost to follow-up prior to completing the minimum 42-month duration were assumed to be disease-free, thus we used a denominator of 166 for analysis. Twenty-eight children were control participants, undergoing bronchoscopy for symptoms other than chronic wet cough, most commonly stridor or recurrent croup (Supplementary Table S1), were followed-up for at least 42-months. The median age, duration of follow-up and male predominance were similar in both groups (Table-1).

PBB exacerbation frequency and recurrence

Mean PBB episodes decreased progressively with >3-fold decrease across the 5-year follow-up (Figure-2a). Likewise, the proportion of children with recurrent PBB (>3/year) also progressively decreased over time (Figure-2b).

Bronchiectasis, risk factors and outcomes

CT was performed on 45 children with PBB (27.1%) at a median duration of 9-months (IQR 3-22) after enrolment. Bronchiectasis (all cylindrical) was present in 16 children (9.6% of PBB cohort); n=6 (37.5%) were identified in year-1 of follow-up with n=9 (56.3%) in year-2 and only one (6.3%) after year-2. There was no significant difference in time to CT between the children in the PBB group with bronchiectasis (median=13-months, IQR 4-20) and those without (median=5-months, IQR 1-40), (p=0.46). None of the children in the control group demonstrated clinical features suggestive of bronchiectasis.

Univariate analysis identified recurrent PBB, having ≥2 siblings and *H. influenzae* infection (≥10^4 colony-forming units (CFU)/ml BAL) as statistically significant risk factors for future bronchiectasis (Table-2). On multivariable logistical regression, only recurrent PBB in year-1 and BAL infection with *H. influenzae* were significantly associated with future bronchiectasis. All of the 68 children with PBB that cultured *H. influenzae* on their BAL were confirmed as non-typeable (NTHi) but one child had both NTHi and typeable *H. influenzae* (non-type b).

We did not identify any statistically significant predictors for recurrent PBB (Supplementary Table S2). Clinician diagnosed asthma at final follow-up was increased in children with bronchiectasis (n=7/16, 43.8%) compared to those without (n=36/150, 25.3%) although this did not reach statistical significance (p=0.12).

Asthma

At the final clinical review, 45 children (27.1% of PBB cohort) had a clinician diagnosis of asthma compared to 3 (10.7%) in the control group (p=0.09). Of these 45 in PBB cohort with asthma, 16 (35.6%) children had either concurrent bronchiectasis (n=7, 15.6%) or recurrent PBB (n=9, 20%) whilst 29 (64.4%) had non-recurrent or no PBB episodes (n=17, 37.8% and n=12, 26.7% respectively). Post-bronchodilator spirometry was undertaken in 22/45 of which 14 (63.6%) had significant BDR (FEV_1 improvement of >12%) and 2 (9.1%) had borderline BDR (11% improvement).

Univariate analysis identified blood eosinophilia (≥0.3x10^9/L) and a positive allergen-specific immunoglobulin E (IgE) to common inhalant allergens as statistically significant risk factors for asthma. In the multivariable regression, a positive allergen-specific IgE and presence of bronchomalacia were significantly associated with future asthma (Table-3).

Lung function

Children with PBB had spirometry parameters in the normal range at final follow-up (mean FEV_1 %predicted=94.9%, SD 14.5, forced vital capacity (FVC) %predicted=101%, SD 13.4). There was no statistical difference between the PBB patients and controls for FEV_1 %predicted (p=0.59) and FVC %predicted (p=0.36).

Discussion

In this first prospective longer-term outcome study for children with PBB, we followed 166 children with PBB and 28 controls for median duration of 59 and 54 months respectively. At 5 years, an overall >3-fold reduction in PBB exacerbations during follow-up was noted. However, the majority of the cohort (67.5%) had some on-going/intermittent respiratory symptoms (wet cough exacerbation in the final 12-months of follow-up or asthma). Overall, 9.6% of the PBB cohort was diagnosed with bronchiectasis by final follow-up with identified significant risk factors of recurrent PBB in the first follow-up year and *H. influenzae* infection in the BAL at index-PBB diagnosis. Also, by the end of follow-up, 27% of children with PBB had clinician-diagnosed asthma with identified significant risk factors of atopy (positive allergen-specific IgE) and bronchomalacia.

Our study's findings are consistent with our previous 2-year follow-up[14] study in which 8.1% had later diagnosis of bronchiectasis (median duration 9-months), with predictors of recurrent PBB (OR_{adj}=11.5, 95%CI 2.3-56.5) and *H. influenzae* infection in their BAL (OR_{adj}=7.6, 95%CI 1.5-37.8). In this longer-term (≥4.5-years) follow-up of 166 children with PBB, we describe additional important and novel clinical findings that is globally relevant in the context of the increasing recognition of PBB worldwide.[5,20,21]

Firstly, a higher proportion (9.6%) of this larger PBB cohort had subsequent radiologically-confirmed bronchiectasis at median time of 13-months. The higher proportion is expected considering the longer follow-up duration but highlights that while bronchiectasis was identified in most (93.8%) by 2-year follow-up, a minority can have bronchiectasis later.

Secondly, this study with a larger cohort has consolidated the knowledge that recurrent PBB and *H. influenzae* infection are significant risk factors for future bronchiectasis although the OR_{adj} of these factors (7.9 (95%CI 1.5-40.2) and 5.0 (95%CI 1.3-18.6) respectively) were slightly lower than previously found.[14] These findings further support the paradigm linking PBB with bronchiectasis as a clinical spectrum, as previously described.[13,22]

Thirdly, a major novel finding from this study is approximately one quarter (27.1%) of children had clinician-diagnosed asthma at 5-year follow-up. Of those children who were able to perform spirometry the majority (72.7%) demonstrated significant or borderline (i.e. FEV_1 improvement of ≥11%) BDR supporting the diagnosis. Further support for the clinician-diagnosed asthma was the significant association with baseline blood eosinophil and allergen-specific IgE levels. The high rates of asthma diagnoses amongst the PBB cohort is interesting and exceeds asthma rates in controls (10.7%) and background asthma prevalence (11%) in Australia.[23] This figure is similar to a retrospective UK study on PBB that described 31% of children also having asthma as defined by bronchodilator response (≥15% FEV_1) or a clear response to oral steroids.[24] Our finding of atopy (reflected by positive allergen-specific IgE) being associated with clinician-diagnosed asthma is not surprising as this is a well described.[25,26] The relationship between bronchomalacia and asthma was unanticipated however, emphasising the diagnostic challenge and likely clinical overlap between PBB and allergic asthma.[27]

The overlap between asthma, PBB and bronchiectasis outcomes at 5-years supports the concept of PBB clinical pheno-and/or endo-types[9] although further in-depth studies are clearly needed. The co-occurrence of asthma with bronchiectasis highlights the heterogeneity of this disease and the importance of identifying treatable traits to ensure personalised and precision

management.[13] Indeed, innate immune system activation (elevated toll-like receptor-2/-4, interleukin-1β/-8) and increased bacterial colonisation has been demonstrated in PBB,[28,29] neutrophilic asthma[30-32] and bronchiectasis[31] highlighting a possible similar underlying pathological process. For the subset of children who eventually develop bronchiectasis, several pathobiological mechanisms may be important, including aberrant host responses with elevated levels of airway interleukin-1β,[31] dysfunctional capacity to synthesize interferon-gamma in vitro in response to NTHi,[33] and/or impaired efferocytosis.[34]

Whilst this is the largest prospective, longitudinal follow-up of children with PBB, our study has several important limitations. For ethical reasons (association between radiation and future cancer risk), we did not subject each child to a CT scan at baseline or at the end of follow-up, i.e. only 27% of our cohort had a CT chest during follow-up. Nevertheless, children in this cohort were seen by expert respiratory physicians who are well attuned to diagnosing bronchiectasis. In our setting about 1/3 of children undergoing elective bronchoscopy have a subsequent CT and 16/45 (35.6%) of our PBB cohort who had a CT scan had bronchiectasis, a rate lower than that reported in another study where 43.8% of children with chronic productive cough had bronchiectasis on CT.[35] Thus, whilst case-ascertainment may be accurate, under-estimation is likely considering 70 children with our identified risk factors did not have a CT during follow-up. Further, we assumed children lost to follow-up were well. While this is likely true as we are the only children's hospital in the state and children with on-going problems would be re-referred, it is possible that the proportion with bronchiectasis may indeed be higher.

An additional limitation, due to the young age of the cohort, was that we were unable to perform spirometry on all children, impairing the accuracy of asthma diagnosis.[36] We thus defined asthma as clinician-diagnosed asthma at final clinical review, whilst supported by BDR in a subgroup. Ideally, a study that includes additional tests in the entire cohort (e.g. exhaled nitric oxide and airway provocation test) may more definitively have confirmed a diagnosis of asthma. Whilst these tests are useful in adults for diagnosing asthma, they are more controversial in children with the Australian guidelines on use of broncho-provocation issued a consensus statement (i.e. no high quality evidence) and measurement of exhaled nitric oxide is "not recommended as a diagnostic test for asthma in routine clinical practice" (http://www.asthmahandbook.org.au).[18] Further, bronchomalacia had a statistically significant association with clinician-diagnosed asthma, which compounds these findings and possibly contributes to the higher rates of wheeze and asthma medication use.

In conclusion, this 5-year follow-up study supports the hypothesis that PBB is antecedent to bronchiectasis in a subset of children and those with recurrent PBB at 12-months of follow-up or *H. influenza* on BAL should be closely monitored and considered for CT evaluation to identify and treat bronchiectasis early. Children with PBB should be carefully followed-up as a substantial proportion of children have on-going symptoms at long-term follow-up and parents should be counselled about recurrent PBB and the possibility of future bronchiectasis and asthma. The major novel findings however are the association between PBB and asthma suggesting the co-existence of these two conditions and highlighting the importance of identifying potentially treatable traits in children with chronic respiratory diseases. Studies to further elucidate the pathobiology underlying the overlapping entities of PBB, bronchiectasis and asthma are needed to further understand the different clinical phenotypes.

Acknowledgements

We are grateful to all the parents and children who participated in this study. We also thank Sandy Goodwin for maintaining the database, Sophie Anderson-James, Helen Petsky and Samantha Prime for collecting the specimens and clinical data. The study was funded by an Australian National Health and Medical Research Council (NHMRC) Project Grant (APP1042601) and NHMRC Centre of Research Excellence in preventing and managing bronchiectasis (APP1170958). JM is supported by a Queensland Children's Hospital Foundation (CHF) fellowship (RPC0772019). AC is supported by a NHMRC practitioner fellowship (APP1154302) and CHF top-up fellowship (#50286). None of the authors received an honorarium or other form of payment to produce the manuscript.

Disclosure statement:

Some results have been previously reported in the form of an abstract.

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Ruffles T, Marchant J, Masters IB, Buntain H, Busch G, Upham J, Wurzel D, Yerkovich S, Gibson P, Baines K, Simpson J, Pizzutto S, Hodge S, Hodge G, Chang AB. Eur Respir J. Sep 2018, 52 (suppl 62) OA3608; DOI: 10.1183/13993003.congress-2018.OA3608

Author contributions:

T.J.C.R. co-conceptualized the study, is responsible for the content of the manuscript including data analysis and manuscript preparation, and was involved in data collection.
J.M.M. co-conceptualized the study, contributed to data acquisition and contributed to data analysis and manuscript preparation.
I.B.M. contributed to data acquisition and provided critical review of the manuscript.
S.T.Y. co-conceptualized the study and contributed to data analysis and provided critical review of the manuscript.
D.W. co-conceptualized the study, contributed to data acquisition and contributed to data analysis and manuscript preparation.
P.G.G. provided critical review of the manuscript.
G.B. contributed to data acquisition and study co-ordination and provided critical review of the manuscript.
K.B. provided critical review of the manuscript.
J.L.S. provided critical review of the manuscript.
H.C.S-V was responsible for characterization of *Haemophilus influenza* isolates and provided critical review of the manuscript.
S.J.P. provided critical review of the manuscript.
H.M.B. contributed to data acquisition and provided critical review of the manuscript.
G.H. provided critical review of the manuscript.
S.H. provided critical review of the manuscript.
J.W.U. provided critical review of the manuscript.
A.B.C. co-conceptualized the study and contributed to all aspects, including hypothesis delineation, study design, data acquisition, interpretation of results and manuscript preparation.

Abbreviations

BAL = bronchoalveolar
BE = bronchiectasis
BDR = bronchodilator response
CFU = colony-forming units
CSLD = chronic suppurative lung disease
CT = chest tomography
FEV_1 = forced expiratory volume in the first second
FVC = forced vital capacity
H. influenzae = Haemophilus influenza
IgE = immunoglobulin E
IQR = inter-quartile range
M. catarrhalis = Moraxella catarrhalis
NTHi = non-typeable *Haemophilus influenza*
OR_{adj} = adjusted odds ratio
PBB = protracted bacterial bronchitis
PCR = polymerase chain reaction
S. aureus = Staphylococcus aureus
S. pneumonia = Streptococcus pneumonia

Table 1 – Demographic data of study participants

	PBB n=166	Control n=28	p-value
Age recruitment median, year	2.1 (0.4-13.6)	2.1 (0.25-13.2)	0.33
Age follow-up median, year	7.8 (4.3-20)	8.1 (3.9-16.9)	0.20
Sex, Male (%)	105 (63.3)	19 (67.9)	0.56
Aboriginal or Torres Strait Islander (%)	6 (3.6)	0	
Household tobacco smoke exposure (%)	50 (30.1)	8 (28.6)	1.00
Length of current cough, median (IQR), weeks	20 (4-52)	0 (0-2)	
>5 doctor visits for cough in last 12 months (%)	144 (87.9)	12 (42.9)	
Immunisation with pneumococcal conjugate vaccine and *H. influenzae* type b (%)	165 (99.4)	27 (96.3)	
Duration of follow-up in months, median (IQR)	59 (50-71)	54 (44-64)	0.23

PBB = protracted bacterial bronchitis. IQR = Interquartile range.

Table 2 – Univariable and multivariable analysis of risk factors for bronchiectasis in PBB

	BE present	BE absent	Univariable analysis		Multivariable analysis*	
	n=16, n (%)	n=150, n (%)	OR (95% CI)	p-value	$OR_{adjusted}$ (95%CI)	p-value
Sex, Male	11 (69)	105 (70)	0.94 (0.31-2.87)	0.92		
Recurrent PBB Yr one	14 (88)	74 (49)	7.19 (1.58-32.73)	**0.011**	7.9 (1.5-40.2)	**0.004**
≥ 2 siblings	9 (56)	46 (31)	2.91 (1.02-8.28)	**0.046**	2.9 (0.9-9.7)	0.82
Childcare attendance	12 (85)[a]	100 (81)[b]	1.27 (0.26-6.10)	0.77		
Smoke exposure	4 (25)	47 (31)	0.73 (0.22-2.38)	0.60		
Asthma	2 (13)	43 (30)	0.36 (0.08-1.63)	0.18	0.9 (0.2-4.8)	0.9
Tracheomalacia	7 (44)	67 (45)	1.0 (0.34-2.72)	0.94		
Bronchomalacia	4 (25)	47 (31)	0.73 (0.22-2.38)	0.60		
BAL neutrophilia (>20%)	9 (56)	74 (52)[c]	1.20 (0.42-3.40)	0.73		
BAL eosinophil (>1.5%)	3 (19)	10 (7)[c]	3.23 (0.79-13.23)	0.10	3.5 (0.6-19.7)	0.18
BAL pathogen						
Adenovirus PCR	2 (13)	22 (17)	0.8 (0.16-3.50)	0.71		
S. aureus	3 (19)	11 (7)	2.92 (0.72-11.80)	0.13	2.8 (0.5-14.1)	0.24
H. influenzae	12 (75)	56 (37)	5.04 (1.55-16.37)	**0.007**	5.0 (1.3-18.6)	**0.011**
M. catarrhalis	9 (56)	36 (24)	2.46 (0.86-7.08)	0.094	2.3 (0.7-7.8)	0.18
S. pneumoniae	3 (19)	34 (23)	0.78 (0.21-2.92)	0.72		

*factors included in the model are listed in this column. PBB = protracted bacterial bronchitis. BE = bronchiectasis. BAL = bronchoalveolar lavage. PCR = polymerase chain reaction. Incomplete data available for highlighted variables [a] n=14, [b] n=131, [c] n=135. Boldface denotes statistical significance p<0.05

Table 3 – Univariable and multivariable analysis of risk factors for clinician-diagnosed asthma

	Asthma	No asthma	Univariable analysis		Multivariable analysis*	
	n=45, n (%)	n=121, n (%)	OR (95% CI)	p-value	$OR_{adjusted}$ (95%CI)	p-value
Prematurity	7 (25)[a]	10 (12)[f]	2.34 (0.80-6.98)	0.12	5.0 (0.6-43.2)	0.14
≥ 2 siblings	14 (31)	41 (34)	0.88 (0.42-1.83)	0.74		
Childcare attendance	29 (81)[b]	82 (82)[g]	0.91 (0.34-2.40)	0.85		
Smoke exposure	17 (38)	34 (28)	1.55 (0.76-3.20)	0.23		
Recurrent PBB year one	20 (44)	68 (56)	0.62 (0.31-1.24)	0.18	0.2 (0.02-1.5)	0.10
Tracheomalacia	21 (47)	53 (44)	1.12 (0.56-2.23)	0.74		
Bronchomalacia	18 (40)	33 (27)	1.78 (0.87-3.65)	0.071	5.9 (1.2-29.7)	**0.025**
BAL neutrophilia (≥20%)	25 (57)[c]	58 (50)[h]	1.29 (0.64-2.61)	0.47		
BAL eosinophil (≥1.5%)	2 (4)	11 (9)	0.47 (0.09-2.19)	0.33		
Blood eosinophilia	23 (52)[c]	35 (20)[i]	2.57 (1.26-5.34)	**0.009**	0.9 (0.2-4.0)	0.92
Allergen specific IgE	11 (50)[d]	13 (20)[j]	4.08 (1.45-11.45)	**0.008**	14.8 (2.2-100.8)	**0.002**
BAL pathogen						
Adenovirus PCR	10 (23.3)[e]	15 (13)[k]	2.02 (0.85-5.03)	0.12	5.1 (0.7-35.1)	0.099
S. aureus	4 (9)	10 (8)	1.08 (0.32-3.64)	0.90		
H. influenzae	14 (31)	54 (44)	0.56 (0.32-1.16)	0.12	0.9 (0.2-3.4)	0.83
M. catarrhalis	9 (20)	34 (28)	0.64 (0.27-1.16)	0.29		
S. pneumoniae	9 (20)	28 (23)	0.83 (0.36-1.93)	0.67		

*factors included in the model are listed in this column

PBB = protracted bacterial bronchitis. BE = bronchiectasis. BAL = bronchoalveolar lavage. PCR = polymerase chain reaction. Incomplete data available for highlighted variables [a] n=28, [b] n=36, [c] n=44, [d]

n=22, [e] n=116, [f] n=81, [g] n=100, [h] n=115, [i] n=117, [j] n=66, [k] n=43. Boldface denotes statistical significance $p<0.05$.

Figure legends

Figure 1 – CONSORT diagram. PBB = protracted bacterial bronchitis. Controls underwent bronchoscopy for symptoms other than chronic wet cough most commonly stridor or recurrent croup (Supplementary Table S1).

Figure 2

A – Mean PBB episodes per year of follow-up. Bars represent standard deviation. Yr 1 (n=166), Yr 2 (n=159), Yr 3 (n=157), Yr 4 (n=94), Yr 5 (n=85). Mean PBB episodes per year decreased from 3.9 in year one to 1.2 in year five.

B – Percentage of children with recurrent PBB per year of follow-up. Yr 1 (n=166), Yr 2 (n=159), Yr 3 (n=157), Yr 4 (n=94), Yr 5 (n=85). The proportion of children with recurrent PBB decreased from 51.5% to 12.9%.

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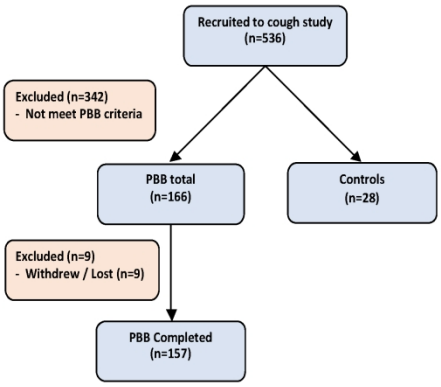

Figure 1 – CONSORT diagram. PBB = protracted bacterial bronchitis. Controls underwent bronchoscopy for symptoms other than chronic wet cough most commonly stridor or recurrent croup (Supplementary Table 1).

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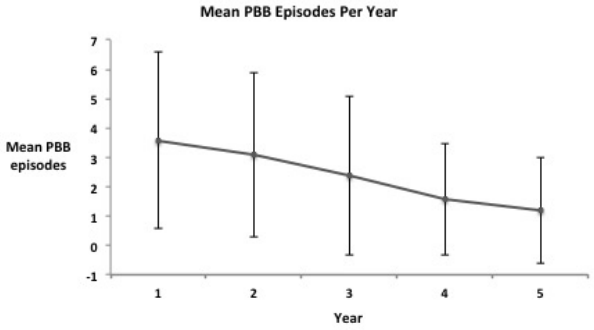

Figure 2a – Mean PBB episodes per year of follow-up. Bars represent standard deviation. Yr 1 (n=166), Yr 2 (n=159), Yr 3 (n=157), Yr 4 (n=94), Yr 5 (n=85). Mean PBB episodes per year decreased from 3.9 in year one to 1.2 in year five.

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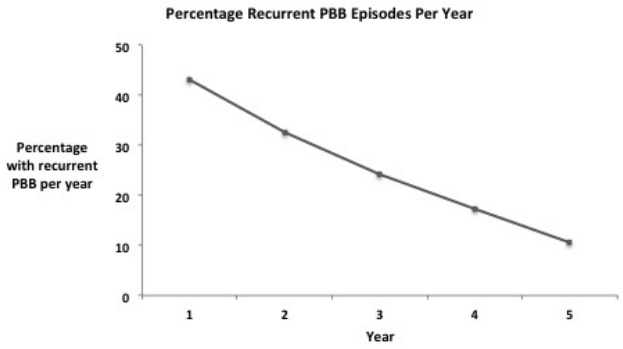

Figure 2b – Percentage of children with recurrent PBB per year of follow-up. Yr 1 (n=166), Yr 2 (n=159), Yr 3 (n=157), Yr 4 (n=94), Yr 5 (n=85). The proportion of children with recurrent PBB decreased from 51.5% to 12.9%.

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Supplementary Information template:

SUPPLEMENTARY INFORMATION

Outcomes of protracted bacterial bronchitis in children: A five-year prospective cohort study

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(*List available Supplementary Information items in the following order*)

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Supplement Table S1 – Indication for bronchoscopy in control subjects

Bronchoscopy Indication	Frequency (%) n=28
Stridor	11 (39)
Recurrent croup	5 (18)
Recurrent wheeze	3 (11)
Dry cough	3 (11)
Suspected foreign body	2 (7)
Apnoeic episodes	2 (7)
Exertional dyspnoea	2 (7)

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Supplement Table S2 – Univariable and multivariable analysis of risk factors for recurrent PBB

	Recurrent PBB n=111, n (%)	Non-recurrent PBB n=55, n (%)	Univariable analysis OR (95% CI)	Univariable analysis p-value	Multivariable analysis* OR (95% CI)	Multivariable analysis* p-value
Sex, Male	81 (73)	35 (64)	1.54 (0.58-2.54)	0.22		
≥ 2 siblings	73 (66)	38 (69)	1.16 (0.58-2.33)	0.67		
Childcare attendance	76 (84)[a]	35 (76)[c]	1.71 (0.70-4.12)	0.24		
Smoke exposure	36 (32)	15 (27)	1.28 (0.63-2.61)	0.50		
Asthma	26 (23)	19 (35)	0.58 (0.29-1.18)	0.13	1.5 (0.7-3.1)	0.30
Tracheomalacia	46 (41)	28 (51)	0.68 (0.36-1.31)	0.25		
Bronchomalacia	30 (27)	21 (38)	0.60 (0.30-1.19)	0.14	0.6 (0.3-1.3)	0.19
BAL neutrophilia (>20%)	57 (54)[b]	26 (48)[d]	1.28 (0.66-2.52)	0.46		
BAL eosinophil (>1.5%)	11 (10)	2 (4.0)	2.91 (0.62-13.63)	0.17	5.9 (0.7-48.9)	0.1
BAL pathogen						
Adenovirus PCR	17 (16)[b]	8 (15)[d]	1.91 (0.45-2.82)	0.82		
S. aureus	10 (9)	4 (7)	1.26 (0.38-4.22)	0.71		
H. influenzae	47 (42)	21 (38)	1.19 (0.61-2.30)	0.61		
M. catarrhalis	29 (26)	14 (25)	1.19 (0.61-2.30)	0.93		
S. pneumoniae	25 (22)	12 (21)	1.04 (0.48-2.27)	0.92		

*factors included in the model are listed in this column

PBB = protracted bacterial bronchitis. BAL = bronchoalveolar lavage. PCR = polymerase chain reaction. Incomplete data available for highlighted variables [a] n=90, [b] n=105, [c] n=46, [d] n=54.

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Please make sure that all Supplementary Information items are referenced by in-text citations in the main manuscript