Associated risk factors and diagnostic value of fiberoptic bronchoscopy for protracted bacterial bronchitis in children

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Abstract

Objective: Untreated protracted bacterial bronchitis (PBB), a chronic wet cough prevalent in children, may lead to chronic suppurative lung disease or bronchiectasis. However, clinical diagnostic criteria for PBB are nonspecific; thus, PBB may be misdiagnosed. Thus, we assessed the diagnostic value of fiberoptic bronchoscopy (FOB) and risk factors associated with PBB.

Methods: Children with chronic cough at First Affiliated Hospital of Anhui Medical University from January 2015 to May 2020 were enrolled and allocated to a suspected PBB (n=141) or a non-PBB (n=206) group. All children underwent extensive laboratory, chest imaging, and allergen tests. Children with suspected PBB underwent FOB with bronchoalveolar lavage; lavage and sputum samples were cultured.

Results: All 347 children had chronic wet cough for approximately 2 months. Of 141 children with suspected PBB, 140 received FOB with bronchoalveolar lavage. Visible tracheal changes included pale mucosa, mucosal congestion, edema, swelling, and increased secretions attached to the wall. Sputum was visible primarily in the left main bronchus (78.7%), left lower lobe (59.6%), right upper lobe (62.4%), and right lower lobe (64.5%). Sputum properties and amounts significantly differed between children with vs. without PBB (P < 0.05). Dermatophagoides (odds ratio [OR], 2.642; 95% CI, 1.283–5.369) and milk protein (OR, 2.452; 95% CI, 1.243–4.836) allergies and eczema (OR, 1.763; 95% CI, 1.011–3.075) were risk factors significantly associated with PBB. Conclusion: Dermatophagoides, milk protein, and eczema were associated with increased risk of PBB. Sputum distribution and tracheal wall changes observed through FOB may distinguish PBB and assist in its diagnosis.

1 Introduction

Cough is one of the most common ailments in children.¹ The commonly used definition of chronic cough in children is 4 weeks, although cough in children lasting 3 to 8 weeks has been termed prolonged acute cough.²³ For chronic cough, prevalence is typically >10% across most surveys, ranging from 7%-33%.⁴ Yu et al. reported that healthy children cough on average 10 times a day, and cough occurs most often in the daytime.⁵ Approximately 10%-22% of children 5–11 years of age have a chronic cough in the absence of a cold.⁵ Faniran et al. demonstrated that the prevalence of chronic cough in children 6–12 years of age is between 5% and 10%, with a higher incidence in younger children.⁶⁷ Etiologies of chronic cough include several and heterogeneous diseases, such as asthma, upper airway cough syndrome, and protracted bacterial bronchitis (PBB).⁸ There is evidence that allergens may be cough-related factors.⁹ PBB is the most easily missed diagnosis of chronic cough in children owing to insufficient understanding of this condition.¹⁰ Thus, in clinical practice, it is important to be aware of this lung condition so that appropriate therapy may be started before associated complications arise. The importance of a timely diagnosis and treatment should be emphasized because of the potential for PBB to be a precursor to chronic suppurative lung disease or bronchiectasis when left untreated.

PBB, a clinical condition first described by Marchant et al., is a chronic endobronchial infection caused by
bacteria. The clinical features of PBB are wet cough, especially nighttime coughing, shortness of breath during physical exercise, wheezing, and exacerbations with upper respiratory tract infection. However, these are nonspecific symptoms that may also be asthma manifestations. PBB has been known as suppurative bronchitis, persistent bronchitis, and bronchiectasis prophase. The pathogenic bacteria causing PBB are mainly common respiratory pathogens, including undifferentiated *Haemophilus influenzae* and *Streptococcus pneumoniae*. The diagnostic accuracies of PBB and other chronic cough ailments need to be improved. Many clinicians are unfamiliar with PBB and may fail to recognize milder forms of the syndrome. Clinical criteria for the diagnosis of PBB are nonspecific and may not distinguish it from other known causes of chronic cough, including viral infections.

Although the current definition of PBB has revolutionized our understanding and treatment of chronic wet cough in children, many questions remain unresolved. Fiberoptic bronchoscopy (FOB) may help to better define PBB. FOB is currently an integral part of the management of various lung and airway diseases in children and can be performed for diagnostic or therapeutic purposes. It enables an assessment of the anatomical features of the airway and the collection of samples from the distal airways via bronchoalveolar lavage (BAL) for pathological and microbiological examination. If a clinical diagnosis of PBB is made based on an assessment of the anatomical features, some children with post-infection cough or non-PBB would be misdiagnosed as having PBB and would likely be treated with antibiotics, leading to the abuse of antibiotics. However, if the diagnostic criteria for PBB are strictly followed, a diagnosis of PBB may be missed or treatment delayed, affecting prognosis due to the length of time needed for laboratory testing and specimen transport. Some clinicians argue that the diagnostic criteria for PBB are poorly defined and others call for further research. Thus, this study aimed to provide extensive laboratory data, including the results of bacterial cultures of bronchoalveolar lavage fluid (BALF), and other FOB findings to offer a detailed description of the clinical manifestations, laboratory characteristics, and typical microscopic manifestations of PBB in a large cohort of children to aid in the clinical diagnosis of PBB.

## 2. Materials and Methods

### 2.1 Participants

A total of 347 children (228 males and 119 females; median age of 3.9 years) with chronic cough were recruited from the First Affiliated Hospital of Anhui Medical University between January 2015 and May 2020. Most of the children had received various courses of antibiotics prior to hospital admission, but none had a congenital pulmonary abnormality. Written informed consent was obtained from all parents or guardians of the included children. This study was approved by the Ethics Committee at Anhui Medical University and conformed to the guiding principles of the World Medical Association Declaration of Helsinki.

### 2.2 Inclusion criteria

The original diagnostic criteria for PBB included the following: a) wet cough for >4 weeks, (b) BALF culture results of identifiable lower airway bacterial infection, (c) response to antibiotics (amoxicillin/clavulanate) with resolution of cough within 2 weeks, and (d) absence of an alternative specific etiology (Table 1). All children with suspected PBB included in this study underwent collection of a complete medical history and a physical examination after admission. No evidence of chronic lung disease was detected. PBB diagnostic criteria that include pathogenic microorganisms are (1) wet (sputum) cough lasting >4 weeks, (2) evidence of lower respiratory tract infection, (3) positive bacterial culture of sputum or BALF, with a colony count $>10^4$ CFU/mL, and (4) response to antibiotic treatment with resolution of cough within 2 weeks. The following additional definitions are used in clinical practice: PBB-extended is PBB-micro or PBB-clinical (Table 1) requiring 4 weeks of antibiotic treatment for cough resolution, and recurrent PBB is defined as >3 episodes of PBB per year. In the present study, children with chronic cough due to other causes confirmed pursuant to standard clinical practice definitions and children who did not fulfill the criteria for PBB were allocated to the non-PBB group (n = 206), which included children with cough-variant asthma (n = 39) and children with upper airway cough syndrome (n = 78).
Routine examination before FOB treatment included the following: (1) complete blood count, liver, renal, and coagulation function tests, myocardial enzyme test, immune function assessment, C-reactive protein levels, procalcitonin levels, blood and sputum cultures, blood immunoglobulin M (IgM) tests for nine respiratory pathogens, and reverse transcription polymerase chain reaction (RT-PCR) for *Mycoplasma pneumoniae* in the sputum; (2) chest radiography, computed tomography (CT), ultrasonography, electrocardiography, echocardiography, and lung function test; (3) detection of Epstein-Barr virus, hepatitis B and C virus, tuberculosis, and human immunodeficiency virus infection; (4) tests for reactions to common environmental allergens, including dust mites, pollen, milk protein, and seafood; and (5) eczema history, supplementary food, and parity.

2. Pre-hospital treatments

Despite therapy with antibiotics, steroids, and nebulized budesonide suspension plus albuterol at local primary healthcare facilities or the outpatient department of our hospital, the patients’ respiratory symptoms progressively deteriorated. Thus, they were referred to the First Affiliated Hospital of Anhui Medical University.

2.5 Fiberoptic bronchoscopy

All patients were treated with budesonide suspension and albuterol aerosol inhalation before the procedure. A definitive diagnosis of PBB can be made by flexible FOB and BAL. FOB and BAL were performed and reviewed within 30 minutes under local anesthesia, which included lidocaine sprayed into the nasal cavity, throat, main bronchus and left and right bronchi, and sedation with an intravenous infusion of midazolam (0.1–0.3 mg/kg). Before and after FOB, clinical findings and chest images were evaluated. For children >5 years of age, a FB-15V bronchoscope (inside diameter 2.0 mm; outside diameter 4.8 mm) was used for all procedures, whereas for children <5 years of age a FB-10V bronchoscope (inside diameter 1.2 mm; outside diameter 3.6 mm) was used for. Repeated BAL was performed by wedging the FOB in a subsegmental bronchus, instilling saline (0.5 mL/kg for a total <5 mL at a time), and collecting the lavage sample (BALF) in a sterile tube. The bronchial segment selected for lavage was the area with the most visible secretions.

BALF samples were transferred to the laboratory at the hospital for cell counting, cytologic analysis, and *M. pneumoniae*, bacterial, fungal, and acid-fast bacilli cultures. BAL virology testing for respiratory pathogens was conducted using next-generation sequencing to test for the presence of adenovirus, cytomegalovirus, *Haemophilus influenzae*, human parainfluenza, and respiratory syncytial virus.

2.6 Follow-up visits

Telephone follow-up visits were conducted 1, 6, and 12 months after hospital discharge to request information on medication adherence and cough resolution time of children to determine the effectiveness of antibiotic therapy.

2.7 Statistical Analysis

SPSS 23.0 statistical software was used for data analysis. Measured data conforming to a normal distribution are expressed as mean ± standard deviation (SD), comparisons between two groups were performed using independent samples t-tests, data with a non-normal distribution are represented by medians and interquartile ranges (Mann-Whitney test), and counted data are denoted as percentages. Potential PBB risk factors were analyzed by chi square tests and logistic regression (variables selected had values of *P* < 0.05). *P* < 0.05 was considered statistically significant.

3. Results

3.1 Clinical characteristics

The mean (SD) age of the included children with PBB was 3.90 (1.75, 6.03) years, and the male to female ratio was approximately 3:2. No statistical differences were observed between the age or gender groups (*P* > 0.05). Although parents typically reported wheezing, auscultatory feedback was rare, and more frequently
“rattling chest” and crackles were reported. It was also commonly reported that the increase in sputum led to faster and “thicker” breathing when the child was lying down.

The length of time that the cough had been present prior to this study did not differ substantially between children with PBB (n =141) vs. without PBB (n = 206). There was no difference in feeding method (i.e., breast, formula, or mixed) between children with vs. without PBB. Although the probability of bronchomalacia may be markedly increased among children who are not firstborn due to insufficient raw materials and lack of calcium supplements, there was no significant difference between children with PBB vs. without PBB, whether or not they were firstborn (Table 2).

3.2 Associated risk factors

Children with a history of allergies received 23 allergen tests. Dermatophagoides allergy was substantially higher in children with PBB than in children without PBB (P < 0.05). The proportion of children with PBB having milk protein allergy (19.1%) was markedly higher than that for children without PBB (7.8%). Eczema was also significantly different between the two groups: 24.8% of children with PBB vs. 15% of children without PBB. Logistic regression analyses indicated that milk protein allergy (P =0.01), eczema (P =0.046), and dermatophagoides allergy (P =0.008) were statistically significantly different in children with PBB vs. children without PBB (Table 3).

3.3 FOB and BAL

All children with PBB were subject to FOB, except for one child who did not undergo FOB and BAL. The FOB results indicated that for the airway mucosa of children with PBB, there was an extensive increase in secretions of the tracheobronchial wall or lumen, with white viscous secretions or suppurative secretions attached to the wall or blocking the lumen (Figure 1A). A few may show cellulose-like changes, resulting in lumen clogging that is difficult to remove. The symptoms of the children can be divided into two categories: acute and chronic suppurative changes. The acute changes included the main manifestations: mucosal congestion, edema (Figure 1B, D), swelling, and increased secretions that may be attached to the wall in a membrane form and may be accompanied by a mucous plug that blocked the lumen (Figure 1E). The chronic suppurative changes included pale mucosa and edema (Figure 1C). After FOB lavage, most of the sputum was removed (Figure1F). Chest radiography results for children with PBB appeared normal, but CT results indicated that patchy inflammatory shadows were present in some of these children.

FOB results indicated that sputum was frequently observed in the left main bronchus (78.7%), right lower lobe (64.5%), right upper lobe (62.4%), left lower lobe (59.6%), dorsal segment (46.8%), right middle lobe (39%), right main bronchus (30.5%), left upper lobe (17%), and carina (14.2%). The distribution of sputum in children with PBB was significantly different from that in children without PBB (P <0.05). In addition to sputum, the proliferation of lymphoid follicles in the throat wall of children with PBB was substantially higher than that for children without PBB (P <0.05) (Table 4).

3.4 Post-hospital discharge therapy

All children with PBB were treated with antibiotics and nebulization: budesonide suspension (2 mL) plus salbutamol solution (1.5 mL) plus normal saline (2 mL). For children with large patchy shadows on chest radiographs, back patting was employed for postural drainage after admission.

3.5 Laboratory results

After admission, the results of mycoplasma antibody and nucleic acid tests showed no statistically significant difference between the groups of children with vs. without PBB. The results of venous blood tests before bronchoscopy indicated that there were no marked differences in white blood cell, C-reactive protein, and hemoglobin levels between the two groups, but the proportion of neutrophils in the blood of children with PBB was markedly higher than that of children without PBB (P < 0.05) (Table 5). Which may be attributable to airway inflammation. The results also indicated that in the PBB group, the level of basic humoral
immunity (IgA, IgM) appeared normal, but the proportions of CD19+, CD16+CD56+, and CD23+ cells were significantly higher, whereas the proportions of CD3+ and CD3+CD4+ cells were notably decreased.

Of 141 children with PBB, 85 underwent lung function tests after admission. There were 36 cases with abnormal pulmonary ventilation function, 2 cases with mild hybrid ventilation dysfunction and normal small airway function, 3 cases with increased severe airway resistance and decreased compliance, 2 cases with increased severe airway resistance and normal compliance, 3 cases with increased airway resistance and normal compliance, and 3 cases with moderately increased airway resistance and normal compliance.

3.6 Pathogens

The presence of bacteria or viruses in the BALF samples was analyzed by direct immunofluorescence. Of these samples, 26 cultures were positive for the presence of bacteria or viruses, including 9 cases with Streptococcus pneumoniae, 2 cases with Escherichia coli, 5 cases with Staphylococcus aureus, 2 cases with Klebsiella acidophilus, 2 cases with Pseudomonas aeruginosa, 5 cases with Morella, and 1 case with oral streptococcus. There were eight respiratory pathogens detected in the BALF, and 7 cases (5.0%) were nucleic acid–positive for mycoplasma.

4 Discussion

Cough is one of the most common concerns among patients seeking medical attention. Chronic cough frequently occurs in Chinese children. In chronic cough, PBB is the most easily overlooked diagnosis. Although PBB has been shown to be an essential cause of chronic cough in young children, there are few studies assessing PBB characteristics, and little is known about the etiology of PBB among children in China. Thus, PBB is often misdiagnosed as bronchial asthma or bronchial pneumonia because pediatricians lack an awareness of this disease. Our study describes the typical sputum distribution and tracheal wall changes observed by FOB in children with PBB and highlights the importance of a definitive diagnosis of PBB.

PBB is caused by a persistent bacterial infection of the bronchial lining cells. The bacteria form a biofilm in the respiratory tract that contributes to respiratory tract mucociliary clearance dysfunction, defects in systemic immune function, and respiratory tract malformation (such as the softening of the cartilage in the wall of the trachea). Clinically, PBB is often misdiagnosed as recurrent pneumonia, asthmatic bronchitis, bronchial asthma, or post-infection cough, and the results of chest radiography may be reported as normal but typically reveal peribronchiolar changes, such as bronchial wall thickening. Granted that diagnostic criteria vary by country, there are still deficiencies and room for improvement in the clinical diagnosis of PBB. Therefore, if evidence of PBB infection is found via FOB on the basis of the typical manifestations, such as the specific locations of sputum, PBB can be clinically diagnosed with higher accuracy. Concurring with published reports, our results indicated that FOB appeared to be safe in children. In our study, the average age of children was 3.9 years, and we observed no adverse effects after FOB. After timely treatment, the cough and sputum sounds on auscultation of the lungs disappeared rapidly.

Our study is consistent in many respects with published studies on PBB in children, including the median age of children with PBB and the predominance of boys. We also discovered that the percentage of children with PBB having lymphoid follicular hyperplasia was far greater than the percentage of children without PBB. Anatomically, the right bronchus is oriented more vertically and it is shorter than the left bronchus, and thus sputum is likely to accumulate in the former. However, using FOB, we found that the most common sites of accumulated thick sputum in children diagnosed with PBB were the left main bronchus, right lower lobe, right upper lobe, left lower lobe, dorsal segment, right middle lobe, right main bronchus, left upper lobe, and carina. The specific distribution of sputum in the trachea and lungs of children with PBB is inconsistent with assumptions based on human anatomy, demonstrating that sputum distribution as determined through FOB examination may aid the diagnosis of PBB. Indeed, without the manifestations observed using FOB, the clinical manifestations of children with PBB are not specific to the disorder.

Consistent with the diagnostic criteria of PBB, positive bacterial cultures of BALF obtained by FOB can
be used to diagnosis PBB. However, our results indicated that the positive rate of such cultures for bacteria was extremely low: of 140 children who received FOB combined with BAL, only 26 (19%) of the cultures were positive. The pathogenic bacteria causing PBB are mainly common respiratory pathogens, such as undifferentiated *Haemophilus influenzae* and *Streptococcus pneumoniae*. However, the colonies cultured in this study were mostly *Streptococcus pneumoniae* and *Escherichia coli*. This finding may be attributable to the use of antibiotics by these patients before hospitalization.

Marseglia et al. found that milk protein is a risk factor associated with PBB. We found that in addition to milk protein, dermatophagoides and eczema may also be risk factors associated with PBB. Therefore, when a child with a history of eczema and milk protein and dermatophagoides allergies develops a chronic cough, PBB should be suspected.

Similar to other studies, the clinical symptoms in most of the children were significantly ameliorated after BAL. Our study also showed that children with patchy opacities observed via CT had good absorption of inflammatory lesions after elective follow-up BAL.

Although response to antibiotics is part of the diagnostic criteria for PBB, the optimal duration of initial therapy is still unknown. In our study, children with PBB showed marked improvement after 2 weeks of therapy with amoxicillin and clavulanate potassium. This is consistent with the findings of Marchant et al. Budesonide suspension plus a salbutamol solution has also been shown to suppress the inflammatory response, decrease complications, and shorten the course of lung inflammation. Donnelly et al. found that 13% of patients required longer antibiotics. However, prolonged use of antibiotics can lead to drug resistance, affecting children’s health. The British national pediatric cough guidelines (2008) recommended administering oral antibiotics for 4–6 weeks because some children need longer antibiotic treatment. In the present study, the symptoms of most children were relieved after 2 weeks of antibiotic use, which may be related to the use of antibiotics before hospitalization.

In conclusion, dermatophagoides and milk protein allergies and eczema were associated with increased risk of PBB. Thus, when children with these associated risk factors have chronic cough, PBB should be suspected. The distribution of sputum in the trachea and lungs of children with PBB was specific to PBB. Thus, in addition to assessment of typical clinical features, diagnosis may be improved by the use of FOB. Early FOB and BAL were effective in alleviating the clinical symptoms of PBB in children.

**Abbreviations**

- PBB, protracted bacterial bronchitis
- FOB, fiberoptic bronchoscopy
- BAL, bronchoalveolar lavage
- BALF, bronchoalveolar lavage fluid

**Declarations**

**Conflict of interests**

The authors declare that there are no conflict of interests.

**Consent for publication**

The patients’ guardians consented to the submission of these case reports to the journal, and we have obtained written informed consent.

**Availability of data and material**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Author contributions**

RZ contributed to the conception of the manuscript and drafted the manuscript; WHL, CRB, and JYZ contributed to obtaining and interpreting the clinical information and to manuscript revision; LW, CG, and HG contributed to the conception of the manuscript and made substantial contributions to manuscript revision.
All authors have read and approved the final manuscript for publication and agreed to be accountable for all aspects of the work.

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References


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