Pro-Con Debate: Protracted Bacterial Bronchitis as a Cause of Chronic Cough in Children

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Abstract

**Pro:** Children with chronic cough present a diagnostic challenge. Protracted bacterial bronchitis (PBB) is a chronic, persistent bacterial infection of conducting airways defined by the presence of cough for longer than 4 weeks that resolves with antimicrobial therapy and without an alternative diagnosis. The diagnosis is made by the findings of increased bronchial secretions and edema of the lower airways on flexible bronchoscopy and positive cultures on bronchoalveolar lavage. It is speculated that an initial respiratory insult such as viral infection disrupts normal surface morphology and ciliary function, which leads to chronic self-perpetuating inflammation with the formation of bacterial biofilms, leading to PBB. PBB is often misdiagnosed as asthma, leading to inappropriate and excessive use of steroids. The importance of timely diagnosis should be emphasized due to the potential that PBB may be a precursor to chronic suppurative lung disease or bronchiectasis if left untreated; however, every patient should be adequately assessed to exclude other causes of chronic cough.

**Con:** Clinical criteria for the diagnosis of PBB are nonspecific and may not distinguish it from other known causes of chronic cough, including viral infections. Benefits from antibiotic therapy (particularly prolonged therapy) have not been demonstrated. Respiratory conditions are the most common reason for antibiotic prescriptions during ambulatory visits in the United States, and many of these prescriptions are inappropriate and/or unnecessary. The proposed diagnostic criteria and recommendations for the treatment of PBB will lead to unnecessary overuse of antibiotics. [Pediatr Ann. 2015;44(8):329-331,334-336]
This feature article focuses on chronic cough in children, which is one of the most common presenting symptoms in the pediatrician’s office. This article provides opposing viewpoints regarding the idea that protracted bacterial bronchitis (PBB) is responsible for a significant proportion of cases of chronic cough in children.

**PROTRACTED BACTERIAL BRONCHITIS: PRO**

Infants and children with chronic cough present a diagnostic challenge to pediatricians. Pediatric chronic cough in children younger than age 15 years is defined as a daily cough lasting longer than 4 weeks. Chronic cough is subdivided into “specific cough” associated with symptoms and signs suggestive of an underlying problem, and “non-specific cough,” which is a cough in the absence of an identifiable etiology. Chronic cough is a common presenting symptom that leads to frequent medical consultations. According to a study by Marchant et al., more than 80% of parents sought medical intervention more than 5 times, and more than 50% of children had more than 10 visits to medical doctors for chronic cough over the course of 12 months.

Chronic cough has negative impacts on schooling and sleep, and substantially reduces the health-related quality of life of children and their parents. The burden of cough is also reflected in the billions of dollars spent annually on over-the-counter cough medications.

An increasing number of algorithms and guidelines have been developed for the evaluation and diagnosis of chronic cough in children.

**Definition of Protracted Bacterial Bronchitis**

PBB is a chronic, persistent bacterial infection of conducting airways that has been increasingly recognized as an important pediatric condition worldwide. It recently has been incorporated in major pediatric cough guidelines in America, Britain, and Australia.

PBB differs from acute bronchitis by cough duration (<2 weeks in acute bronchitis). Historically, PBB has been known as chronic bronchitis of childhood, persistent endobronchial infection, or chronic suppurrative lung disease (CSLD).

The original description of PBB required three criteria: (1) a history of chronic wet cough, (2) positive bronchial alveolar lavage (BAL) culture (≥10^5 colony-forming units/mL), and (3) response to antimicrobial treatment with cough resolution within 2 weeks. The criterion of demonstration of endobronchial airway infection by culturing respiratory pathogens from BAL is not feasible in the routine clinical setting, and recent antibiotic usage (within 1 month) before BAL can result in negative culture. Therefore, protracted bronchitis is clinically defined as (1) the presence of isolated chronic (>4 weeks) wet/moist cough, (2) resolution of cough with antimicrobial treatment, and (3) absence of pointers suggestive of an alternative specific cause of cough.

**Studies of Chronic Cough in Children**

Several studies have evaluated cohorts of children with chronic cough referred to specialists. Asiloy et al. used the American College of Chest Physicians 2006 guidelines for evaluation of chronic cough and concluded that common causes of chronic cough in children were asthma/asthma-like symptoms in 25%, PBB in 23.4%, and upper airway cough syndrome (UACS) in 20.3% of cases. Gastroesophageal reflux disease (GERD) was found only in 4.6% of patients.

Marchant et al. found that PBB was the most common cause of chronic cough (39.8%), followed by natural resolution of cough in 22.2% of cases in a group of Australian children. Asthma, GERD, and UACS collectively accounted for only 10% of the cases.

In another multicenter cohort study on chronic cough in children, PBB, asthma, and bronchiectasis were the most common diagnoses.

**Pathogenesis of PBB**

Pathogenesis of PBB involves persistence of bacterial infection in conducting airways. The pathogenic organisms most commonly identified in the airways of children with PBB are nontypeable Haemophilus influenzae (NTHi), Moraxella catarrhalis, and Streptococcus pneumoniae, which are also seen in the early stages of bronchiectasis. It is speculated that an initial respiratory insult such as viral infection disrupts normal surface morphology and ciliary function for many weeks and eventually leads to chronic self-perpetuating inflammation with the formation of bacterial biofilms, leading to PBB.

Persistent airway colonization and neutrophil inflammation may evolve to chronic mucus hypersecretion and further airway inflammation. In some cases, cumulative airway injury from recurrent or persistent bacterial infection can lead to bronchiectasis. Colonization may also be secondary to conditions that impair cough, such as neuromuscular disease, mucus plug-
ging in patients with asthma, airway lesions that impede efficient airway clearance such as tracheobronchomalacia, or mucosal damage secondary to chronic aspiration. Tracheobronchomalacia is a common finding in children with PBB.\textsuperscript{11,20} Immunity also plays a role in pathogenesis; the conducting airways of children with PBB have neutrophilic predominant airway inflammation.\textsuperscript{21,22} The highest incidence of PBB occurs in the first few years of life, at a time when the prevalence of viral lower respiratory tract infections is at its highest.

**Diagnosis and Treatment of PBB**

The definitive diagnosis of PBB is made by flexible fiberoptic bronchoscopy and BAL. The most noticeable finding on bronchoscopy is increased bronchial secretions and edema of the lower airways. In an evaluation of children with chronic cough, Zgherea and Pagala\textsuperscript{18} detected positive bacterial cultures in 46% of patients with a predominance of NTHi (49%) followed by *Streptococcus pneumoniae* (20%), *Moraxella catarrhalis* (17%), and *Staphylococcus aureus* (12%). In the same study, 30% of patients had airway malacia.\textsuperscript{18} Antibiotic use within 1 month prior to BAL often results in a negative culture, even in a child with significant symptoms. Chest radiograph in PBB may be reported as normal but usually reveals peribronchiolar changes such as bronchial wall thickening.\textsuperscript{11,23} Spirometry to evaluate airflow obstruction in older children is usually normal.

If PBB fails to respond or becomes recurrent, further investigations such as complete blood count, assessment of immunoglobulins, functional antibody response to vaccination, sweat test, and high-resolution computed tomography are required to rule out other etiologies such as cystic fibrosis, primary ciliary dyskinesia, immunodeficiencies, or dysfunctional swallowing and aspiration issues.

Treatment is aimed at eradicating the bacteria, improving cough, and keeping the airways clear of infection to allow healing and repair. The duration of treatment of PBB varies from 2 to 4 weeks. Shorter courses of antibiotics tend to result in recurrence or only partial resolution of the cough.

In a retrospective chart review of 81 patients diagnosed with PBB, Donnelly et al.\textsuperscript{23} reported 51% of patients were completely symptom free after two courses of antibiotics, but 13% required six or more courses of antibiotics, or had continuous prophylactic antibiotic for at least one winter to control symptoms.

A more recent randomized double-blind study involving children with wet cough lasting for longer than 3 weeks demonstrated that 2 weeks of amoxicillin and clavulanate led to resolution of cough in 48% of children compared with 16% of those receiving placebo (*P* = .015).\textsuperscript{24}

In children diagnosed with PBB, we suggest 2 weeks of antibiotics (such as amoxicillin and clavulanate) at high doses and then reevaluation of the cough symptoms. Typically, the cough takes 10 to 14 days to resolve. If there has been a clear response to this intervention, the treatment should be continued for an additional 2 to 4 weeks to keep the airways free of colonization and allow repair of the affected airways.\textsuperscript{23}

**Conclusion: Pro**

The diagnostic entity of PBB has been recently recognized as a distinct clinical syndrome. The diagnosis of PBB should be considered in a child with prominent symptoms of chronic, persistent wet cough. PBB is often misdiagnosed as asthma, leading to inappropriate and excessive use of steroids. The diagnosis of PBB should be based on clinical assessment and response to treatment, or definitive diagnosis can be made by performing a bronchoscopy and obtaining BAL cultures. Appropriate diagnosis and treatment can lead to complete resolution of symptoms with dramatic improvement in quality of life. The importance of timely diagnosis and treatment should be emphasized due to the potential that PBB may be a precursor to CSLD or bronchiectasis if left untreated. However, the patient should be adequately assessed to exclude other potential diagnosis causes of chronic cough.

Challenges for the future include establishing a universally accepted definition of PBB that would allow further understanding of this condition, including its epidemiology, clinical features, natural history, and effective approaches to treatment to help prevent inappropriate use of antibiotics.

**PROTRACTED BACTERIAL BRONCHITIS: CON**

**Proposed Definitions of Protracted Bacterial Bronchitis Will Lead to Unnecessary Antibiotic Use**

Cough may have multiple etiologies and is a common cause for children’s ambulatory care visits.\textsuperscript{25} The authors of the “pro” viewpoint in this article (Bidiwala et al.) posit that PBB is an important cause of chronic cough in children, and relatively long courses of antibiotics have been recommended for treatment. However, proposed definitions and management for PBB are problematic for multiple reasons. First, diagnosis of PBB relies on clinical and microbiologic criteria that insufficiently distinguish it from other known causes of chronic cough. Second, there is insufficient evidence demonstrating benefit from antibiotic therapy. Finally, the adverse, unintended impact of increased antibiotic use and subsequent antibiotic resistance with implementation of PBB treatment recommendations have not been fully considered or estimated.

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Other infectious causes of chronic cough, such as viral infections or pertussis, may be difficult to distinguish from PBB. In a study of young children (median age 2.6 years) with chronic cough in Australia, PBB was the most common reported diagnosis. However, viral upper respiratory tract infections (URIs) are also extremely common in this age group. Many cases of PBB may be “prolonged acute cough” lasting 4 to 8 weeks, which most commonly follows viral URIs and typically resolves without intervention. Sequential viral URIs may resemble one prolonged illness. In a prospective study of acute respiratory tract infections in healthy children, 8% of children were still coughing 28 days after onset. Determination of a specific infectious etiology of prolonged cough is challenging in the outpatient setting. Few children receive microbiologic confirmation of an etiology, and thus treatment decisions are made based on symptoms and signs.

Bidiwala et al. acknowledge the impracticality of a microbiological diagnosis for PBB and maintain that clinical criteria should be used. However, the proposed clinical definitions of PBB lack specificity and will lead to considerable unnecessary antibiotic use. Chang et al. define PBB as the presence of chronic (>4 weeks) wet cough, resolution of cough with antimicrobial treatment, and absence of alternative etiologies. Asiloy et al. define protracted bronchitis as a history of chronic moist cough and a response to antibiotic therapy with resolution of cough within 2 to 4 weeks. Marchant et al. define probable PBB as a history of chronic moist cough and either positive BAL culture or immediate response to antibiotic therapy with resolution of the cough within 2 weeks. All three of these definitions establish diagnoses after antibiotic therapy is administered. Thus, clinicians will be reliant only on duration of wet cough to determine whether antibiotics should be given. Although a trial of albuterol or an antihistamine is a diagnostic strategy used for other causes of cough, empiric therapy with antibiotics can select for antibiotic-resistant organisms, with potential adverse effects for the patient and community. Interestingly, the position statement by the Thoracic Society of Australia and New Zealand cited by Bidiwala et al. specifically makes the point that wet cough actually may be dry cough with minimal secretions and caution that the “positive” response in medication trials should not be assumed to be due to the medication. It also should be noted that the definition by Marchant et al. includes patients with symptoms as short as 3 weeks, further lowering specificity.

The benefit of antibiotic therapy for PBB has not been demonstrated. Although a review of antibiotic therapy for prolonged wet cough in children concluded that antibiotics are likely to be beneficial, it was based on only two publications, both of which were of limited quality. Both studies relied on nasopharyngeal culture for determination of bacterial infection, and predominantly isolated *M. catarrhalis, S. pneumoniae*, and *H. influenzae*, all of which are known to colonize the normal upper airway. The studies included children with duration of cough as short as 10 days. Both studies used physician-assessed “clinical cure” as the outcome measure, but these outcome measures were not fully defined. Limited data have been published since this review. Marchant et al. found that children with prolonged cough treated with a combination of amoxicillin and clavulanate had higher rates of cough resolution (48%) than those who received placebo (16%). However, their study only included 25 patients in each treatment arm and defined prolonged cough as 3 rather than 4 weeks. The score used to calculate self-rated improvement in cough may not be appropriate for the young children in the study population. Furthermore, prior diagnostic evaluations and therapies for the children were not described. Lastly, differences in referral patterns to pediatric pulmonologists may result in selection bias for enrolled patients, particularly in a small study.

There are insufficient data to recommend prolonged duration of antibiotic therapy to treat PBB. In their descriptive study, Donnelly et al. used 4 to 6 weeks of antibiotics to treat patients with PBB, of whom 49% required at least one additional antibiotic course. Thirteen percent required six or more antibiotic courses, and one patient received continuous prophylaxis for a winter season. However, nonresponse to initial antibiotic therapy doesn’t indicate that further therapy is required, as there may be a nonbacterial etiology, or the patient may have an anatomic abnormality or immunodeficiency. Even if a bacterial cause is present that necessitates antibiotic therapy, shorter duration of therapy is likely sufficient. Antibiotic duration as short as 3 days has been shown to sterilize lung fields. Antibiotic duration as short of 6 days has been shown to adequately treat ventilator-associated tracheitis and prevent subsequent development of pneumonia. There are very few data to support a specific duration of antibiotic therapy for children with community-acquired pneumonia, let alone PBB. Although
it is possible that some children with PBB may have early bronchiectasis or cystic fibrosis, general recommendations for prolonged duration of therapy should be made with caution until further data are available, including impact on antibiotic resistance.

Ideally, studies to determine the potential benefit of antibiotics for PBB should include a valid reproducible measure of the duration and quality of cough of the enrolled patients and include thorough assessment for alternative causes, including asthma. Although a microbiologic diagnosis may not be feasible, serum biomarkers may be helpful to establish a bacterial etiology, as has been shown with community-acquired pneumonia, and can be an avenue of future investigation. In the adoption of a standardized management pathway, the diagnosis of PBB was shown to vary across clinical settings, likely reflecting differences in local referral patterns to pediatric pulmonologists. Thus, large multicenter studies will be necessary to overcome selection bias. Adverse events attributable to an antibiotic should be measured, including rates of antibiotic resistant organisms, Clostridium difficile colitis, and allergic reactions.

The repercussions of a recommendation for the treatment of PBB should be considered in the context of the high number of pediatric ambulatory visits for respiratory complaints and existing antibiotic use in the United States. From 2006 to 2008, per the National Ambulatory and National Hospital Ambulatory Medical Care Survey, respiratory conditions accounted for more than 70% of visits in which antibiotics were prescribed, accounting for 21.7 million visits per year. Furthermore, 23% of antibiotics were for respiratory conditions for which antibiotics were not clearly indicated. Antibiotics are prescribed during nearly 1 in 6 pediatric ambulatory care visits for asthma, totaling nearly 1 million unnecessary antibiotic prescriptions per year. The Centers for Disease Control and Prevention has identified unnecessary antibiotic use in respiratory illnesses, including bronchitis, as a key focus of their “Get Smart for Healthcare Campaign” for antimicrobial stewardship. Parental expectations can influence physician practices regarding antibiotic prescribing. Lack of alternative therapeutic interventions provided by clinicians may increase demands by parents for antibiotics. Clinicians are more likely to make a bacterial diagnosis when they perceive that parents expect antibiotics. Even considering that a small percentage of children with cough will have symptoms of “wet cough” for longer than 4 weeks, inherent diagnostic uncertainty and misapplication of criteria for PBB will undoubtedly lead to large increases in unnecessary antibiotic consumption.

Conclusion: Con

In summary, although a small cohort of children with PBB may exist, the proposed criteria for PBB are non-specific and may lead to substantial overdiagnosis. Data demonstrating the efficacy of PBB are derived from a limited number of patients with variable investigations for alternative diagnoses and imprecise inclusion criteria and outcomes measured. Adverse events and the impact of prolonged antibiotic therapy on the selection of antibiotic-resistant organisms have not been evaluated. Future research should incorporate additional diagnostic criteria to better target therapy and avoid unnecessary antibiotic use.

REFERENCES

18. Zgherea D, Pagala S. Bronchoscopic findings in children with chronic wet cough. Pe-


