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Bronchoscopic Findings in Children With Chronic Wet Cough

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Bronchoscopic Findings in Children With Chronic Wet Cough

WHAT'S KNOWN ON THIS SUBJECT: Chronic wet cough is a common symptom well recognized by pediatricians. Protracted bacterial bronchitis is defined as more than 4 weeks of wet cough that responds to antibiotic treatment. Diagnosis of protracted bacterial bronchitis is not readily accepted by pediatricians

WHAT THIS STUDY ADDS: Children with chronic wet cough often have bronchitis, which is evident during bronchoscopy. Purulent bronchial secretions suggest the presence of bacterial infection. Children with chronic wet cough frequently have a bacterial infection of the lower airway.

abstract

OBJECTIVES: Protracted bacterial bronchitis is defined as the presence of more than 4 weeks of chronic wet cough that resolves with appropriate antibiotic therapy, in the absence of alternative diagnoses. The diagnosis of protracted bacterial bronchitis is not readily accepted within the pediatric community, however, and data on the incidence of bacterial bronchitis in children are deficient. The objective of this study was to determine the frequency of bacterial bronchitis in children with chronic wet cough and to analyze their bronchoscopic findings.

METHODS: We performed a retrospective review of charts of children who presented with chronic wet cough, unresponsive to therapy, before referral to the pediatric pulmonary clinic.

RESULTS: A total of 197 charts and bronchoscopy reports were analyzed. Of 109 children who were 0 to 3 years of age, 33 (30.3%) had laryngomalacia and/or tracheomalacia. The bronchoscopy showed purulent bronchitis in 56% (110) cases and nonpurulent bronchitis in 44% (87). The bronchoalveolar lavage bacterial cultures were positive in 46% (91) of the children and showed nontypable *Haemophilus influenzae* (49%), *Streptococcus pneumoniae* (20%), *Moraxella catarrhalis* (17%), *Staphylococcus aureus* (12%), and *Klebsiella pneumoniae* in 1 patient. The χ^2 analysis demonstrated that positive bacterial cultures occurred more frequently in children with purulent bronchitis (74, 69.8%) than in children with nonpurulent bronchitis (19, 19.8%) ($P < .001$).

CONCLUSIONS: Children who present with chronic wet cough are often found to have evidence of purulent bronchitis on bronchoscopy. This finding is often indicative of a bacterial lower airway infection in these children. *Pediatrics* 2012;129:e364–e369

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KEY WORDS
cough, infection

ABBREVIATIONS
BAL—bronchoalveolar lavage
CFU—colony-forming unit
PBB—protracted bacterial bronchitis

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Chronic wet cough, a common pediatric complaint,[1,2] is defined as a wet cough that lasts for more than 4 weeks.[3,4] Although children rarely expectorate sputum,[5] the wet nature of this cough, often accompanied by a rattle in the chest, is easily recognized by parents and pediatricians.[6,7]

Chronic wet cough is a major clinical finding in children with debilitating pulmonary disorders, including cystic fibrosis,[8] primary ciliary diskinesia,[9] and various immunodeficiency syndromes.[10] Most children with chronic wet cough do not suffer from any of these disorders, however. Rather, chronic wet cough is usually associated with bacterial infections of the lower respiratory tract.[11–13] The diagnosis of "chronic bacterial bronchitis" is not readily accepted in the pediatric population, however, as many physicians assume that this is an "adult" respiratory illness associated with tobacco smoking.[14] Perhaps this is the reason that Marchant and colleagues[2] introduced the diagnosis of protracted bacterial bronchitis (PBB), defining it as chronic wet cough that lasts for more than 4 weeks and responds to antibiotic treatment, in the absence of underlying respiratory disorders.

The goals of our study were to determine the frequency of lower respiratory tract bacterial infections in children with chronic wet cough and to analyze the bronchoscopic findings in these children.

METHODS

The study was approved after full review by the Maimonides Medical Center Institutional Review Board.

We retrospectively reviewed the charts and bronchoscopy reports of 260 children, with a primary complaint of chronic wet cough, who were referred by their primary care pediatricians to the Pediatric Pulmonary Clinic at Maimonides Infants and Children's Hospital from 2004 to 2008. All children had a wet cough of more than 4 weeks' duration. The primary indication for bronchoscopy was presence of an intractable cough that did not respond to conventional therapy with antibiotics and corticosteroids. Secondary indications included suspected foreign body aspiration and the presence of wheezing, unresponsive to bronchodilator therapy.

All children with underlying diagnoses of cystic fibrosis, primary ciliary dyskinesia, immunodeficiency syndromes, genetic syndromes, major airway abnormalities, muscle weakness, neurologic disorders, aspiration, and asthma were excluded from the study.

All patients underwent flexible bronchoscopy with bronchoalveolar lavage (BAL) collection. All procedures were videotaped and the bronchoscopic findings were carefully documented.

Laryngomalacia was clinically suspected in the presence of inspiratory stridor and defined as an inward collapse of supraglottic structures in the glottis on inspiration, resulting in airway obstruction.

Tracheomalacia was defined as collapse of at least 50% of the tracheal lumen during expiration. The assessment of airway malacia was routinely made under lighter sedation to minimize the impact of anesthesia on airway dynamics. Patients with severe airway malacia requiring surgical treatment were classified as "major airway abnormalities" and excluded from the study.

The BAL collection and processing were performed in accordance with standard protocol at Maimonides Medical Center. The BAL was collected from either the most affected lung segment, identified visually by the amount of secretions arising from the orifice of a segmental bronchus, or from the right middle lobe if the most affected lung segment could not be identified. The bronchoscope was wedged into a bronchus and 2 to 4, 10-mL, aliquots of normal saline solution were instilled and immediately aspirated through the bronchoscope. In smaller infants, 5-mL aliquots were used. The total volume of instilled lavage fluid was 1 to 3 mL/kg body weight. As per routine procedure at Maimonides Medical Center, the BAL fluid samples were transported at room temperature and plated within 2 hours of collection.

Purulent bronchitis was diagnosed in children with visual evidence of purulent (thick, green) bronchial secretions of grades 5 and 6 on Chang and colleagues' bronchoscopic scoring system.[15] Nonpurulent bronchitis was diagnosed in children who had visual evidence of nonpurulent bronchial secretions, and bronchoscopic score of grade 3 or higher. The BAL fluid was processed with a Papanicolaou staining technique to evaluate the differential and cell count. Two hundred consecutive cells were counted under $\times 400$ magnification, and the relative percentage of macrophages, neutrophils, and eosinophils was determined. The BAL fluid was also sent for Gram stain and quantitative bacterial culture. Bacterial counts $\geq 10^4$ colony-forming units (CFU)/mL were considered suggestive of active lower airway infection. Oropharyngeal flora were excluded from the total bacterial count.

Statistical analysis of the data was performed using SigmaStat (Systat Software Corporation, San Jose, California) and SPSS (IBM Corporation, Armonk, New York). Categorical variables of age range, bronchoscopic findings, BAL cultures, cytology, and associated findings were expressed as a number and percentage of patients. Bacterial species were expressed as percent values. Significance of difference in each categorical variable between 2 groups was assessed using χ^2 analysis. A critical P value of $<.05$ was used to determine statistical significance.

RESULTS

A total of 197 patients were included in the study. Among the study patients, 108 (55%) were 0 to 3 years of age, 71 (36%) were 3 to 7 years, and 18 (9%) were older than 7 years of age. One hundred twenty-six patients (64%) were boys.

Diagnostic bronchoscopy revealed evidence of purulent bronchitis in 56% (110) of children, and nonpurulent bronchitis in 44% (87) of children. Of 109 children who were 0 to 3 years of age, 33 (30.3%) had laryngomalacia and/or tracheomalacia. Laryngomalacia was seen in 13 (20.3%) of 64 children 0 to 3 years of age with purulent bronchitis, and in 5 (11.1%) of 45 children with nonpurulent bronchitis. Tracheomalacia was seen in 9 (14.1%) of 64 children 0 to 3 years of age with purulent bronchitis, and in 6 (13.3%) of 45 children with nonpurulent bronchitis. There was no significant difference in the prevalence of laryngomalacia ($P = .329$) and tracheomalacia ($P = .862$) between purulent and nonpurulent bronchitis groups. Positive bacterial cultures were detected in 46% (91) of children. The distribution of pathogens revealed a predominance of nontypable *Haemophilus influenzae* (49%) followed by *Streptococcus pneumoniae* (20%), *Moraxella catarrhalis* (17%), and *Staphylococcus aureus* (12%). Only 1 patient cultured *Klebsiella pneumoniae*. Positive bacterial cultures were found more frequently in children with purulent bronchitis (84%) than in children with nonpurulent bronchitis (16%) ($P < .001$) (Fig 1).

Severe BAL neutrophilia, defined as more than 25% of neutrophils, occurred more frequently in children with purulent bronchitis (91%) than in children with nonpurulent bronchitis (45%) ($P < .001$) (Fig 1). There was no difference in the presence of BAL eosinophilia, defined as more than 2% of eosinophils, between the 2 groups (Fig 1).

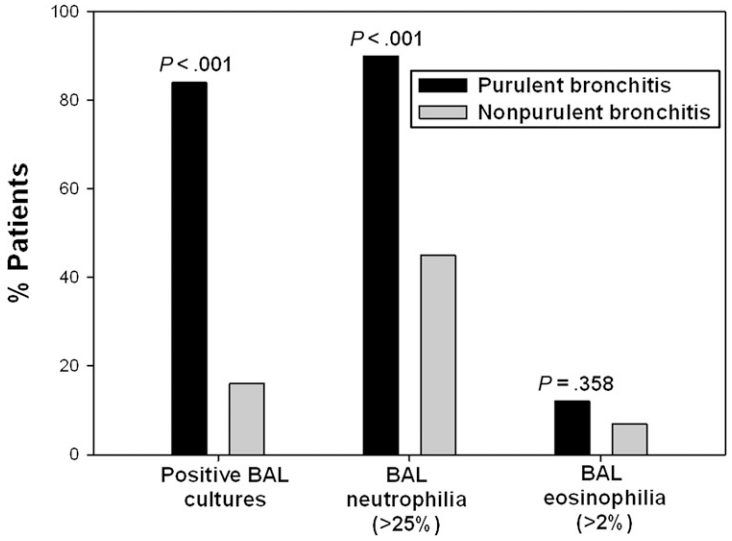

FIGURE 1
BAL cultures and cytology in children with purulent bronchitis and nonpurulent bronchitis.

DISCUSSION

In this study, we found that purulent bronchitis was present in 56% of children with chronic wet cough. There has been increasing evidence to support the association of chronic wet cough with bacterial infections of the lower airway. The first publications on wet cough in the 1930s to 1940s described chronic wet cough as a symptom of bronchiectasis.[16,17] The widespread use of antibiotics in the treatment of chronic productive cough in children, which began in the 1950s, resulted in a major decline in the incidence of suppurative lung disease in children.[18]

Over the past decade, there has been a progressive decline in the prescription of antibiotics for viral respiratory infections.[19] Although certainly appropriate, this may have resulted in an increased incidence of suppurative lung disease in children.[20,21] This has sparked a worldwide interest in childhood lower respiratory tract bacterial infections. Consequently, PBB, the term introduced by our Australian colleagues,[2] is now considered to be one of the leading causes of chronic wet cough in children. Donnelly and coworkers[22] retrospectively reviewed the charts of 81 children with PBB, and found that half of the patients were symptom free after 2 weeks of appropriate antibiotic therapy.

In our study, the most common pathogens cultured from the BAL were nontypable *H influenzae* (49%) and *S pneumoniae* (20%). These findings are in agreement with the data published by Marchant and colleagues,[12] who studied 108 children with chronic cough and obtained *H influenzae* and *S pneumoniae* from BAL in 47% and 35% of isolates, respectively.

We defined "purulent bronchitis" as the visual presence of purulent (thick, green) bronchial secretions, grades 5 and 6, according to Chang and colleagues' bronchoscopic scoring system.[15] It was shown previously that the scale of sputum purulence correlates with the severity and/or activity of bronchial disease[23] and that visual grading of bronchial secretions is significantly related to an infection-positive state.[15] We were able to show that children with purulent bronchitis had positive bacterial cultures and BAL neutrophilia significantly more often than children with nonpurulent bronchitis. This finding is in agreement with a recent report by Kompare and Weinberger,[24] which revealed BAL neutrophilia and positive

bacterial cultures in young children with noisy breathing, cough, and wheezing diagnosed with purulent bronchitis during bronchoscopy.

In general, there is no consensus on a numerical cutoff for quantitative bacterial BAL cultures to distinguish a bacterial lower airway infection from upper airway contamination. The cutoff of 10 CFU/mL was used in patients with ventilator-associated pneumonia[25] and 10^4 CFU/mL in patients with acute bacterial pneumonia,[26,27] whereas 10^5 CFU/mL is the usual cutoff number for patients with cystic fibrosis.[28] Riise et al[29] suggested the cutoff of 10^3 CFU/mL in adult patients with chronic bronchitis. As in the study by Kompare and Weinberger,[24] we chose to base our definition of positive bacterial culture on presence of 10^4 CFU/mL of BAL fluid.

Only 16% of children with purulent bronchitis in our study had negative BAL cultures. Recently, Zemanick and coworkers[30] found that negative BAL cultures are not uncommon, even during an acute pulmonary exacerbation of cystic fibrosis, and postulated that the cause may have been inadequate BAL sampling, or antibiotic therapy before the BAL collection. It is possible that antibacterial therapy administered before bronchoscopy increased the frequency of negative BAL cultures in our patients. Stralin et al[31] showed that polymerase chain reaction identified *S pneumoniae* in the BAL of 31% of patients who received antibiotics before bronchoscopy, whereas routine BAL culture was positive in only 2.9% of these patients. This suggests that false-negative BAL cultures may be related to antibacterial therapy before BAL collection. In our institution, the standard handling time between collection and plating of BAL fluid is 2 hours, similar to that suggested previously.[29] It is possible, however, that friable microorganisms may have lost their viability during this time, and that our positive culture yield might have been be higher with a handling time of 1 hour, as suggested by King.[32]

In our study, the congenital tracheomalacia was found in 24% of small children with purulent bronchitis. This exceeds the prevalence of congenital tracheomalacia within the general pediatric population, reported as 1 in 2100 newborns.[33] The tracheomalacia and/or bronchomalacia were found in 52 (74%) of 70 studied children with chronic purulent bronchitis by previous investigators.[24] They suggested that airway malacia may play a role in the development of purulent bronchitis, possibly through its adverse effect on mucous clearance. We concur with the suggestion that presence of tracheomalacia may impair mucus clearance and cause retention of tracheobronchial secretions, which facilitates persistence of lower airway infection. Laryngomalacia was also frequently found in small children with purulent bronchitis in our study (20.3%). It was previously suggested that laryngomalacia is associated with both swallowing dysfunction[34] and gastroesophageal reflux,[35] which results in microaspiration of food and gastric content. It may be suggested that repeated episodes of microaspiration contribute to the development of bacterial bronchitis in small children with laryngomalacia.

Although chronic productive cough has been linked to asthma,[36] conflicting opinions remain with regard to the role of asthma as a cause of chronic wet cough in children.

British and Australian Asthma Guidelines state that the presence of a moist cough lowers the probability of asthma in children.[37,38] Similarly, the "Recommendations for the assessment and management of cough in children," written by Shields and the British Thoracic Society Cough Guideline Group,[39] advised against labeling children with chronic wet cough as "asthmatics." The Thoracic Society of Australia and New Zealand also advised against the use of term "cough variant asthma" in children with chronic cough, when unassociated with wheeze or dyspnea.[40]

The relationship between bacterial infection, chronic wet cough, and symptoms of asthma in children has not yet been well established. It has been suggested that bacterial-induced neutrophil-mediated inflammation may contribute to symptoms of asthma in children.[41–43] The possibility of coexisting diagnoses of asthma and PBB in certain patients has also been addressed by previous investigators.[13,44] The presence of a relatively large group of children with nonpurulent bronchitis and negative bacterial cultures among our study patients may point out the existing connection between chronic wet cough and asthma, which is also suggested by findings of BAL eosinophilia seen in some children in our study.

Our study has a number of limitations. The retrospective design of the study did not allow us to obtain any reliable data regarding prior treatment in our study patients. As a result, we were unable to determine if negative BAL cultures were related to antibacterial therapy that may have been administered before bronchoscopy in some of our patients. Similarly, we were not able to analyze the impact of anti-inflammatory therapy, such as inhaled corticosteroids and montelukast, on bronchoscopy findings. We did not have any reliable data on the prevalence of certain comorbities, such as gastroesophageal reflux and chronic sinusitis, which could contribute to development of chronic cough in our study patients. We did not routinely screen the BAL fluid for the presence of viruses, which could potentially cause a purulent appearance of lower airway secretions and BAL neutrophilia. The protracted nature of the cough, however, which lasted weeks,

months, or even years in some of our patients, suggests a bacterial etiology for their bronchitis. We were unable to analyze further the group of children with wet cough and nonpurulent bronchitis, and can only assume that some of them had asthma. Finally, the absence of reliable follow-up prevented us from making a definitive conclusion regarding the efficacy of antibacterial treatment in our patients with chronic wet cough and purulent bronchitis.

CONCLUSIONS

In conclusion, a substantial number of children with chronic wet cough can be found to have a bacterial infection of the lower airway. Presence of purulent bronchitis during bronchoscopy is strongly associated with bacterial lower airway infection in this population of patients. Laryngomalacia and tracheomalacia are frequently detected in children with chronic wet cough. Further prospective studies will be required to better define the relationships among chronic wet cough, bacterial bronchitis, and asthma.

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