Protracted Bacterial Bronchitis in Young Children: Association with Airway Malacia

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Objective To examine associated findings and clinical outcome in young children with prolonged cough, wheeze, and/or noisy breathing in whom high colony counts of potentially pathogenic bacteria were cultured from bronchoalveolar lavage (BAL) during diagnostic flexible fiberoptic bronchoscopy.

Study design This was a retrospective review of all medical records of children from infancy to 60 months of age seen in our specialty clinic from 1999 to 2009 with protracted cough, wheeze, and/or noisy breathing in whom BAL found $\geq 10^4$ colony forming units per milliliter of potentially pathogenic bacteria. Children with other major diagnoses were excluded.

Results With quantitative culture from BAL, $\geq 10^4$ colony forming units per milliliter of *Streptococcus pneumoniae*, *Haemophilus influenza*, or *Moraxella catarrhalis*, separately or in combination, were found in 70 children. Neutrophilia was present in 87% of BALs. Tracheomalacia, bronchomalacia, or both was present in 52 children (74%). Symptoms were eliminated with antibiotics in all 61 children with follow-up data. Relapse and subsequent successful re-treatment occurred in 43 children.

Conclusions High colony counts of potentially pathogenic bacteria associated with neutrophilia in the BAL identifies protracted bacterial bronchitis. The predominance of airway malacia in these patients suggests an etiologic role for those airway anomalies. The potential for chronic airway damage from protracted bacterial bronchitis warrants further investigation. *(J Pediatr 2012;160:88-92)*.

Infants and children with refractory lower respiratory tract symptoms present a diagnostic challenge to pediatricians.[1] Asthma, cystic fibrosis, foreign body aspiration, anatomical abnormalities of the airways, and other disorders, some controversial,[2,3] enter in the differential diagnosis. As early as the year 2000, Fitch et al[4] performed bronchoalveolar lavage (BAL) on 23 children without asthma who had a chronic cough for at least a month. They reported increased neutrophilia in the BAL of these children, which the authors suggested could relate to an underlying persistent airway infection. Subsequently, Marchant et al[5] evaluated chronic cough in young children and found a high frequency of neutrophilia associated with typical respiratory bacteria, including *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*. Further studies have provided evidence for protracted bacterial bronchitis (PBB) as a cause of chronic cough.[6,7] To see whether these various reports from Australia and Europe reported in the pulmonary literature were present in our own population, we performed a retrospective study of children with unexplained chronic respiratory symptoms in whom we had performed flexible bronchoscopy and BAL. This report describes the anatomy, cell count and differential, and outcome of treatment when we found high colony counts of bacteria on BAL.

Methods

The diagnostic term chronic purulent bronchitis had customarily been given at our center for children in whom BAL had identified $\geq 10^4$ colony forming units per milliliter (cfu/mL) of specific bacteria judged to be potentially pathogenic as the etiology of symptoms. We therefore first performed a computer search for that diagnostic term during the period from 1999 to 2009 for all patients seen by the Pediatric Allergy & Pulmonary Clinic at the University of Iowa Children's Hospital. Approximately 800 to 900 new patients had been seen annually by the clinic during that period, and approximately 100 bronchoscopies had been performed by the pulmonologists in the division each year for various indications. We identified patients <60 months of age with cough, wheeze, and/or noisy breathing present for at least 1 month without other diagnoses for whom BAL cultures grew at least 10^4 cfu/mL of a specific organism. Patients with asthma, cystic fibrosis, and other known chronic diseases were excluded.

BAL	Bronchoalveolar lavage
cfu/mL	Colony forming units per milliliter
GER	Gastroesophageal reflux
PBB	Protracted bacterial bronchitis

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Bronchoscopy

Bronchoscopies had been performed with a 3.5- or 3.8-mm flexible scope with a 1-mm channel by using topical lidocaine and intravenous procedural sedation. Sedation was directed by the bronchoscopist with nursing assistance with individually determined graded doses of midazolam in 0.1 mg/kg aliquots to a maximum of 0.3 mg/kg and fentanyl, 1 μg/kg aliquots to a maximum of 3 μg/kg. After examining for septal deviation, the nare with the apparent greatest potential for easy access was selected. After nasal instillation of 1% lidocaine and 1% phenylephrine in that nare, the bronchoscope was introduced. As the bronchoscope progressed through the airway, additional lidocaine was provided through the bronchoscope channel. Examination was performed for dynamic collapse of trachea or bronchi during spontaneous respiration. Tracheomalacia or bronchomalacia was diagnosed when there was a segmental collapse such that the airway narrowed to a slit during expiration in the absence of suction through the bronchoscope's channel.

Bronchoalveolar Lavage

BAL was performed preferentially distal to the observed site of bronchomalacia. When there was no bronchomalacia, the site lavaged was at the discretion of the bronchoscopist. The right lower lobe and lingula were known to be common choices, but the specific site was not consistently mentioned in the record when localized bronchomalacia was not present. At least two aliquots of preservative-free normal saline, ranging from 5 to 20 mL per aliquot on the basis of the patient's weight, were used for the lavage. The fluid was immediately placed on ice and promptly carried to the laboratory on completion of the procedure. A minimum of a 5-mL sample was sent for cell count and differential, quantitative culture and sensitivities, and a lipid-laden macrophage index.[8] Cell counts and differentials were manually determined with standard techniques. Percentage of neutrophils was determined from the number of neutrophils divided by the sum of neutrophils and macrophages. Lavage fluid was examined quantitatively for bacteria. Viral cultures were not performed.

Quantitative Microbiological Examination

The procedure for bacteriological examination included diluting 0.1 mL of the lavage fluid with 9.9 mL sterile normal saline without preservative. Then 0.1 mL of that 10^{-2} dilution was placed on each of a blood agar plate, eosin methylene blue agar plate, and a chocolate agar plate. The inoculums were then spread with a sterile hockey stick-shaped glass rod, flaming the rod between use on each plate This results in a 10^{-3} dilution on each of those plates. A 10^{-4} dilution was then prepared by transferring 100 μL (0.1 mL) of the 10^{-2} solution to a second 9.9-mL saline solution. When 0.1 mL of that 10^{-4} dilution is then transferred to additional agar plates of the same type, the final dilution of 10^{-5} is then attained. Individual colonies could then be counted, identified, and calculated as cfu/mL of the lavage fluid.

Assessment of Treatment

Treatment was with antibiotics appropriate for the bacteriological findings. Clinical results of the treatment were determined from parental responses at telephone or clinic follow-up. Recurrences of symptoms were similarly treated.

The study was approved by the institutional review board.

Results

Seventy patients (20 female, 50 male) met inclusion criteria. All children except 5 had onset of symptoms before the age of 1 year (median, 3 months of age). None of the patients had fever or toxic appearance associated with their respiratory symptoms. The duration of symptoms before being examined by the pediatric allergy and pulmonary physicians at the University of Iowa was at least 1 month, with a range as long as 60 months (median, 5 months). Cough, alone or with other symptoms, was present at initial examination in 51 cases. Other symptoms included wheeze and noisy breathing (Figure 1). Bronchoscopy was performed from 1 month to as long as 12 months (median, 4 months) after the initial examination in the specialty clinic.

Airway malacia, tracheal or bronchial, was observed in 74% of the patients (52 of 70 patients; Table). Bronchomalacia alone was seen most commonly. Quantitative culture results from BAL showed levels of bacteria $\geq 10^4$ cfu/mL (most $\geq 10^5$ cfu/mL) of *S pneumoniae*, *H influenzae*, and *M catarrhalis* (Figure 2). Two or 3 organisms were seen in nearly half the

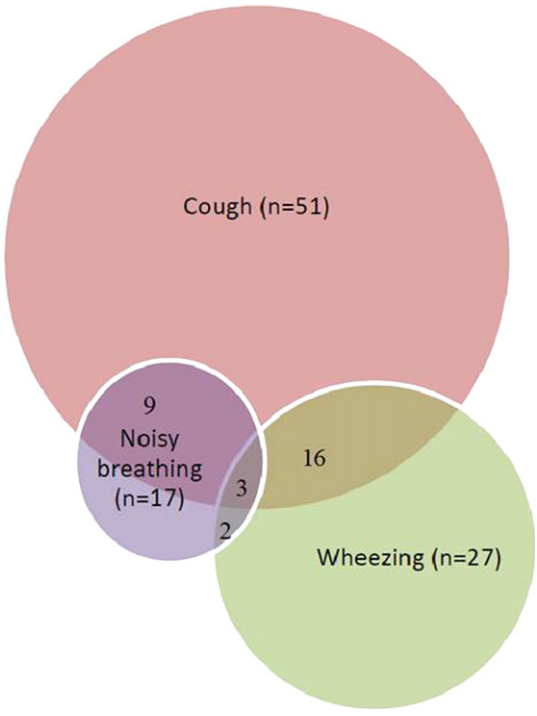

Figure 1. Symptoms at initial examination. The *numbers in the overlapping portions* of this Venn diagram illustrate the number of patients with two or 3 of the indicated symptoms.

Table. Number and percentage of the 70 patients with an airway abnormality seen on bronchoscopy

Airway abnormality	Number of patients (%)
Bronchomalacia alone	30 (43)
Tracheomalacia alone	14 (20)
Both bronchomalacia and tracheomalacia present	8 (11)
Total	52 (74)

cases, 4 with *S pneumoniae* and *H inlfuenzae*, 7 with *S pneumoniae* and *M catarrhalis*, 13 with *H influenzae* and *M cattarhalis*, and 9 showing high colony counts for all 3 organisms. Penicillinase production was common in both *H influenzae* and *M catarrhalis*. Resistance to penicillin was not seen for *S pneumoniae*. Substantial neutrophilia was present in all patients except 9 (median, 44% of cells were neutrophils; range, 9%-99%). Sixty-three patients had the lipid-laden macrophage index reported; none were in a range associated with aspiration.

Outcome data for patients treated were available in the medical record for 61 of the children (87%). Treatment was ≥2 weeks with amoxicillin/clavulanate in 33 patients, trimethoprim/sulfamethoxazole in 16 patients, and other common antibiotics singly or in combination in 12 patients. The symptoms for which the bronchoscopy was performed resolved in all these patients except one. Forty-three children had recurrence of symptoms and required repeated courses of treatment, again with resolution of symptoms. One patient with both bronchomalacia and very severe tracheomalacia eventually had an aortopexy performed to correct the tracheomalacia (but not the bronchomalacia). That patient continued to require antibiotics because of recurrences of protracted cough. Only two of the children went on to demonstrate a clinical pattern of symptoms and response to treatment with oral corticosteroids consistent with asthma.

Discussion

Our findings were consistent with earlier reports that PBB can be a cause of chronic cough in young children. We additionally observed that wheezing and noisy breathing were also associated with PBB. On the basis of our observation of airway malacia in 74% of our patients, we hypothesize that tracheal malacia, bronchial malacia, or both is a predisposing anomaly for PBB. Airway collapse decreases effectiveness of cough and can interfere with normal cephalad mucous flow, an important mechanism for clearing bacteria from the airway.[9]

The bacterial infections we documented are the same bacteria associated with otitis media.[10] It appears that these organisms, commonly present in the oro- and nasopharynx, can cause symptoms when they gain access to an area with a defect in normal host defense. Just as decreased function of the Eustachian tubes results in bacteria being trapped in the middle ear, airway malacia might result in defective clearance of mucus from the affected airway. The child is thus less able to clear aspirated oral secretions, which results in a protracted low-grade infection. Consistent with our results, the symptoms of PBB have been described as typically resolving after a prolonged course of antibiotics.[11] However, our data indicate that recurrences appear to be common.

Airway malacia might result in impairment of normal pulmonary defense mechanisms postulated by Donnelly et al as a cause of PBB.[11] Masters et al observed that children with airway malacia have increased frequency of respiratory illness, severity of illness, and tendency for delayed recovery.[12] Boogaard et al also reported chronic bacterial bronchitis in children with tracheomalacia and bronchomalacia who presented with cough, noisy breathing, and recurrent wheeze.[13] Although cough was the most prominent presenting symptom in our patients, wheeze can occur from the malacia itself, and the noisy breathing described in some patients was likely from the

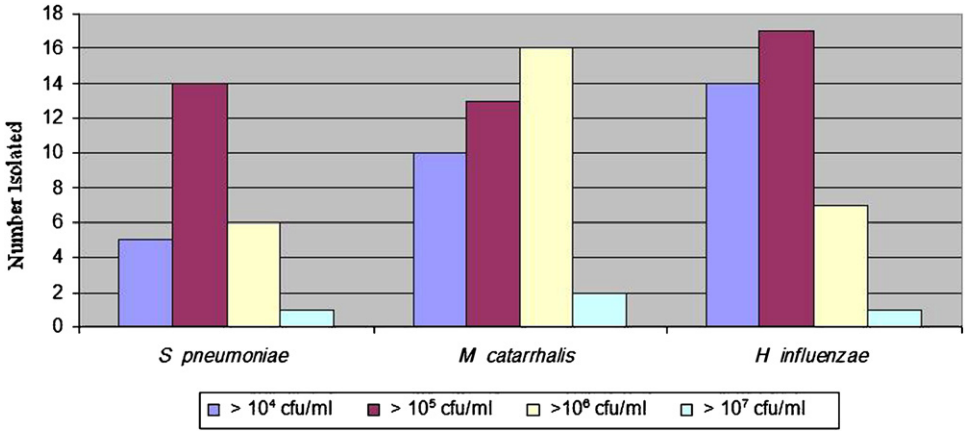

Figure 2. Quantification of bacteria cultured from BAL fluid (cfu/mL). More than one organism was present in many cases (see text for details).

rattling sound of restricted airway mucus. Although bacterial infection might in some cases be a primary event that causes tracheal or bronchial damage resulting in malacia,[14] it is more likely that the malacia is generally the primary factor that results in PBB. Supportive of malacia as the primary risk factor is the spontaneous remission with treatment and time that generally occurs as the airways increase in diameter and clearance of mucus consequently improves.

In addition to PBB, there are a variety of other terms that have been used to describe this condition, including chronic suppurative lung disease, protracted endobronchial infection, pre-bronchiectasis, and various other combinations of these terms. At our own institution, our pulmonology faculty had previously been encouraged to identify this disorder as chronic purulent bronchitis. However, that terminology may not have been consistently used by all during the period examined. Consequently, the 70 patients we identified are almost certainly not the only patients with PBB encountered during that period. Moreover, some children with PBB may have never undergone bronchoscopy. Therefore, we cannot estimate the prevalence of this disorder. However, by whatever terminology, PBB most likely has been under-recognized and often misdiagnosed. Because of the similarity of symptoms in these children to others with infantile and preschool-age asthma, children with malacia may be misdiagnosed as severe-protracted or therapy-resistant asthma.

Prolonged cough, wheezing, and noisy breathing have also been frequently attributed to gastroesophageal reflux (GER). Although we examined for lipid-laden macrophages with a published index, we recognize that this is not a reliable marker of aspiration by itself. However, data have not been supportive of GER as an etiology of respiratory symptoms.[15] Also, when children with GER and cough have been examined for inflammation in the lower airway, it was PBB and not reflux that was associated with the cough.[16,17] When studied, GER has not been associated with increased airway inflammation.

Problems in identifying PBB include confounding results that can occur because of contamination of the bronchoscope during passage through the upper airway. Although high colony counts provide evidence for the likelihood of the infection being from the lower airway, the presence of neutrophilia in the BAL provides important supporting evidence for the clinical relevance of the high bacterial count.

Identification of airway malacia can be confounded by excessive sedation.[18] Relatively light procedural sedation may be needed for malacias to be visualized. Tracheal or bronchial malacia may not be visualized during quiet or assisted ventilation as during general anesthesia.[19] An example of that problem was illustrated in one more recent instance in which malacia was initially not seen by one of the authors (M.W.) during sedation with intravenous propofol by using a newly introduced anesthesiologist-directed sedation team service. A BAL had initially been performed electively in the right lower lobe. But then as sedation was lightened before removal of the bronchoscope, malacia was apparent in the left lower lobe. A repeat BAL from the left lower lobe demonstrated impressive neutrophilic inflammation, and the BAL from the right lower lobe demonstrated no inflammation. The high number of malacias seen in our patients with PBB therefore may have been an underestimation because malacia easily can be missed.

Inflammation, manifested by high levels of neutrophils, was present in most of our patients with high bacterial counts. However, 9 patients had levels that were not elevated despite bacteriology consistent with PBB. An apparent response of symptoms to antibiotics was still observed in those patients. We can only speculate whether this was a sampling phenomenon, much as aforementioned when bacteria seeded many airways but resulted in inflammation in an airway not sampled during the BAL.

Some of the patients were reported to have received earlier courses of antibiotics without apparent clinical response, but dose and duration were generally not available. Although response to our antibiotic treatment was consistently observed, it was our clinical impression that maximum doses and longer courses were needed, and subsequent relapses were common.

The natural history of untreated PBB is not known. Chang et al hypothesized that PBB, when recurrent and left untreated, could progress to bronchiectasis.[15] We did not evaluate for bronchiectasis, nor did we routinely examine for a defect in immunity in these children. However, other symptoms of immune deficiency were not apparent. Specifically, none of the children had sepsis, bacterial pneumonia, meningitis, or evidence of other serious bacterial infections. In a few of our first experiences identifying patients with PBB, we had examined for abnormalities of antibody function without finding any.

Coughing, wheezing, and noisy breathing in young children is very common. PBB should not be the first consideration for such children. A systematic approach generally permits identification of those clinical presentations. Moreover, there is concern about excessive use of antibiotics in young children that may occur from considering PBB before more common causes.[20] Preschool-age children who are subsequently recognized to have asthma, the most common cause of chronic or recurrent cough and wheeze, appear to be at particular risk for receiving antibiotics when they are most likely just experiencing viral respiratory infection-induced lower airway disease.[21,22] The high frequency of viral respiratory infections and the confusion about the diagnosis of asthma in the preschool-age child[23] probably contribute to this excessive frequency of prescribing antibiotics.

A limitation of our study is absence of a control group. Consequently, we do not know how many children had airway malacia in the absence of clinically apparent symptoms. We also do not know how many children had airway neutrophilia or bacteria but recovered spontaneously without ever being examined or treated. Such a control group is unlikely to ever be studied because an invasive procedure, bronchoscopy, can only be justified when troublesome symptoms are present.

A trial of a course of antibiotics effective for *S pneumoniae*, *H influenzae*, and *M catarrhalis* becomes justified when symptoms are protracted and more common problems are

not identified. However, a definitive diagnosis requires flexible bronchoscopy, which is probably most indicated with equivocal responses to antibiotics and for patients experiencing recurrences despite treatment. Longer follow-up of patients with PBB is needed to identify the risk of permanent airway damage. ■

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