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Protracted bacterial bronchitis in children

CLINICAL REVIEW

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Protracted bacterial bronchitis is a common cause of persistent, wet cough in pre-school children. The condition has been described relatively recently, and knowledge of the diagnosis may be an aid to making the correct assessment of children with chronic cough, helping to ensure that the symptoms are not misinterpreted and treated as asthma.

Persistent cough with lower airway secretions and wet or productive cough are among the most frequent reasons for pre-school children (aged 0 – 6 years) presenting to primary care, particularly in the first two-three years of life (1, 2). For many children, the cause is persistent cough following a viral infection, or repeated viral respiratory tract infections with periods of illness merging into one another (2–4). The cough lasts for weeks or months for some children, and a wet cough with secretions in the lower respiratory tract is considerably more common than dry cough.

Studies indicate that protracted bacterial bronchitis may be the most common cause of chronic wet cough in pre-school children (1), (5–7), but awareness of the condition is limited. This may lead to children receiving other diagnoses and treatment (1, 5). In our experience, many of these children are diagnosed as having asthma, or receive treatment for asthma, but wet cough without variable airway obstruction is seldom asthma (8, 9).

There are no Norwegian guidelines for protracted bacterial bronchitis, but internationally there are recommendations for assessment and management of children with this condition (1, 6, 9)(9–11). We have used these papers and other literature to create the following overview of protracted bacterial bronchitis, with proposals for assessment and treatment, designed especially for Norwegian general practitioners and paediatricians.

Definitions

Chronic cough is defined in reviews and recommendations from the USA and Australia as continual daily coughing for more than four weeks (1, 3, 6, 11). In most children, cough associated with viral respiratory tract infections will abate gradually and cease within 3 – 4 weeks (4, 10), but in a British study, 10 % of children with viral respiratory tract infection still had a cough after 25 days (4).

British authors are of the opinion that a duration of eight weeks better distinguishes chronic cough from expected persistent cough after viral infections (2, 3, 10).

Protracted bacterial bronchitis can be defined in various ways, depending on whether supplementary tests are included in the diagnostic evaluation. Nonetheless, the practical definition of Australian authors is based purely on clinical criteria described in Box 1. Most children will show a response after two weeks of antibiotic treatment, but several authors note that in some cases a response is only seen after four weeks (1, 9, 11).

Box 1 Definitions of protracted bacterial bronchitis, after Chang et al. (1)

Clinical definition of protracted bacterial bronchitis

- Chronic wet cough for more than four weeks
- Absence of symptoms or signs of other chronic pulmonary disease
- Perceptible effect of 14 days of antibiotics treatment

Microbiology-based definition of protracted bacterial bronchitis. As above, but in addition

- Lower respiratory tract infection revealed by bronchial lavage fluid or in secretion with > 10^4 colony-forming units/ml of a bacteria species

Recurrent protracted bacterial bronchitis

- More than three episodes annually

Epidemiology

We could find no reliable figures for the incidence of chronic cough in pre-school children. Several studies show that protracted bacterial bronchitis is by far the most frequent cause of chronic wet cough in children who are referred to a specialist. This is also true when the referral diagnosis was asthma (5, 7, 9). In an Australian multi-centre study, 41 % of 346 children referred with chronic wet cough were diagnosed after a thorough examination as having protracted bacterial bronchitis (7). A large proportion of the children who were given the diagnosis have presented to primary care repeatedly and received various types of treatment, including treatment for possible asthma (7, 8, 12).

Few studies have systematically evaluated the age of symptom onset. Several studies found that children developed chronic wet cough during their first two years of life, and were given the diagnosis protracted bacterial bronchitis around the age of two years (5, 8, 13), but the condition also occurs in older children (1, 7). There was a preponderance of boys in one study (13).

Microbiology and pathophysiology

The bacteria most commonly found in protracted bacterial bronchitis are *Hemophilus influenzae*, followed by *Moraxella catarrhalis* and *Streptococcus pneumoniae* (1). Various types of virus have also been detected in bronchial lavage fluid from children with the condition, but the clinical significance of this is unclear (1).

The pathophysiological mechanisms are only partially understood. One hypothesis is that a respiratory insult, for example in the form of an airway infection, damages the normal surface morphology of the respiratory tract, resulting in impaired function of airway epithelial cilia and less effective removal of secretions, thus leading to chronic bacterial infection (14). The bacteria then form a biofilm that enhances their ability to attach to the respiratory tract, providing them with improved nutrition and reducing antibiotic penetration. The result is that bacteria are able to survive on the airway mucosa and cause chronic bronchitis (14, 15) that is accompanied by intense neutrophilic inflammation (14–16).

Children with protracted bacterial bronchitis do not have significant immune system defects – their levels of immunoglobulins, vaccine antibodies and lymphocyte subsets are normal. The levels of several components of the innate immune system may nonetheless differ from healthy individuals, but whether this is a contributory cause of the symptoms or consequences of infection is uncertain (1). Frequent recurrence of protracted bacterial bronchitis is associated with increased interleukin-1 signalling (16).

Several studies have shown that tracheobronchomalacia (defined as a more than 50 % reduction in the diameter of trachea or bronchi on expiration) occurs more frequently in children with protracted bacterial bronchitis. In one study, it was found in 74 % of children with this diagnosis (1, 13, 17). Tracheobronchomalacia predisposes to secretion accumulation, respiratory tract infections and cough, and may contribute to the development of bacterial bronchitis (1, 17). However, it is possible that tracheobronchomalacia develops secondarily to a severe chronic inflammation as a result of protracted bacterial bronchitis of long duration (1).

Symptoms, signs and clinical examination

Many parents report that the symptoms of the disease started in connection with a cold or other airway infection with wet cough, often in connection with starting at daycare. In protracted bacterial bronchitis, the cough continues for four to eight weeks, and often for several months if not treated (1, 3, 9).

In addition to cough, many patients have airway secretions that are audible to the ear (rattles), and vibrations caused by the secretions can be felt by holding the hands over the thorax. The symptoms may last for a long time, be very distressing, disrupt the sleep of both children and parents, and result in absence from school and daycare. If there are no clear clinical signs when the child is examined, it may be useful for parents to record videos or sound. Children seldom have a fever, are often in good general condition, are thriving, growing normally and have no signs of disease in other organs (1).

On auscultation with a stethoscope, various degrees of loose secretions can be heard from the trachea and bronchial tree. Finer crepitations are not usually heard, and the children do not have significant obstruction with visibly or audibly prolonged exhalation or inhalation. Slightly extended exhalation may nonetheless be observed if the child has copious secretions (1).

Supplementary tests

In the event of chronic wet cough, a chest X-ray is recommended. In the case of bacterial bronchitis, this will be normal or reveal minor peri-bronchial changes in the hilus (1). Tidal volume curves and other tests of lung function are usually normal (1). Blood tests are of little value in an initial assessment, and ordinary markers for bacterial infection, such as C-reactive protein (CRP) and white blood cells will be normal.

The incidence of atopic eczema or allergic sensitisation, measured by means of prick tests or in serum, is the same as for children without protracted bacterial bronchitis. Other supplementary tests are considered if other causes of the symptoms are suspected (see differential diagnoses).

Prior to treatment start, a laryngeal aspirate or should be taken and sent for bacterial culture. A positive bacterial culture result may strengthen the probability of the diagnosis, but sensitivity of this test in detecting bacterial infection is low (1, 9).

Treatment

The treatment for protracted bacterial bronchitis is first and foremost antibiotics. Without treatment, many children will have persistent symptoms for a long time. Based on the likely bacterial flora present, the most usual international recommendation for antibiotic treatment is amoxicillin-clavulanic acid (on exemption from registration), whose efficacy has been established in a randomised, placebo-controlled trial (18). Oral cephalosporins, trimethoprim-sulfamethoxazole and macrolides may also be considered, but these are less favourable if the development of antibiotic resistance is to be avoided (1, 6, 11). Antibiotic choice can also be guided by the resistance pattern if bacterial culture is positive.

Treatment duration is open to discussion. Many patients are not well after treatment lasting less than two weeks, or quickly relapse (1, 18). Therefore, treatment for 4 – 6 weeks used to be recommended (10, 19). Our experience tallies with the literature – antibiotic treatment is highly efficacious for some children who become symptom-free after a few days, while others get better gradually over a period of 2 – 4 weeks (8).

One study revealed that those who took longest to become free of symptoms tended to have underlying causes, such as tracheobronchomalacia or bronchiectasis (18). The most recent American guidelines nonetheless

recommend treatment for two weeks initially, partly with a view to minimising side effects and the development of antibiotic resistance (5, 11). If there is not a distinct improvement after two weeks of treatment, it is recommended that treatment be extended to four weeks (11).

British guidelines also recommend physiotherapy to mobilise secretions (10), but there are no studies that have shown the efficacy of this therapy. We consider treatment to mobilise secretion when there is poor response to antibiotic treatment and in cases of underlying airway malacia.

Recommendations for assessment and treatment of children with chronic wet cough are being drawn up for the Norwegian Association of Paediatricians' guidelines.

Differential diagnoses

The most common differential diagnosis will be prolonged cough following infection. It is important to distinguish possible ongoing protracted bacterial bronchitis from persistent cough following a viral infection or several successive viral infections with wet cough (acute bronchitis) (2, 3, 10, 20).

Other causes that should be considered are foreign bodies in the respiratory tract and cough due to adenotonsillar hypertrophy. Rare, but important differential diagnoses are cystic fibrosis, bronchiectasis, primary ciliary dyskinesia, pulmonary aspiration and immunodeficiency (20).

A tidal volume curve that shows obstruction during exhalation may indicate airway malacia as the cause of the symptoms, and in the event of obstruction that is reversible with salbutamol, asthma should be considered (1, 9). Asthma may be considered in cases of chronic wet cough, but is seldom a cause, and should not be diagnosed in cases of chronic wet cough alone. The cough accompanying asthma will most frequently be dry, and the symptoms dominated by recurrent and reversible episodes of bronchopulmonary obstruction. Protracted bacterial bronchitis may nevertheless be a complication of asthma, or occur concurrently with asthma, when there will usually still be episodes of obstruction in addition to chronic cough (1).

When protracted bacterial bronchitis is suspected and antibiotics are ineffective, the child should be assessed for other possible causes (19), and other severe pulmonary disease must also be considered if *Pseudomonas aeruginos*a develops in the bacterial culture. Further assessment is also recommended in the event of a second recurrence of symptoms (1, 2).

Relevant investigations will then be a sweat test (cystic fibrosis), nasal nitric oxide measurement (primary ciliary dyskinesia), CT thorax (bronchiectasis) and immunological assessment, initially with measurement of immunoglobulins and vaccine antibody levels (2, 21). Bronchoscopy may also be relevant when the above tests have not identified any cause (2).

Prognosis

There have been few studies of the natural history of protracted bacterial bronchitis in children. Some follow-up studies in young children show that recurrence of protracted bacterial bronchitis or episodes of persistent cough occur considerably more frequently among these children than in a healthy control group (1). Protracted bacterial bronchitis has also proved to constitute a risk factor for the development of bronchiectasis, and detection of *H. influenzae* in respiratory tract secretions in children with protracted bacterial bronchitis is the greatest risk factor for bronchiectasis subsequently (1, 22). There is therefore speculation as to whether untreated bacterial bronchitis resulting from protracted chronic inflammation is a precursor to chronic purulent pulmonary disease and bronchiectasis, and whether treatment may influence this development (1).

The fact that most children diagnosed with protracted bacterial bronchitis are of pre-school age, suggests that many cases may resolve spontaneously with time. Our experience has also been that most children are preschoolers, aged 1 – 3 years and in older children with typical symptoms, we often find other underlying causes.

Treatment level and unanswered questions

Persistent cough is very common among pre-school children, most of whom are assessed by their general practitioner. It is crucial that general practitioners determine whether the symptoms represent repeated viral infections with symptom-free periods in between or whether the symptoms have been continuously present over a long period. In many children, protracted cough will also cease without treatment, but protracted bacterial bronchitis should be suspected when there is no further improvement in symptoms after at least four to eight weeks, and there are substantial lower airway secretions (3, 6).

When assessing protracted bacterial bronchitis, efforts should be made to limit the use of antibiotics (23). We are therefore of the opinion that if there is strong suspicion of the condition, the child should be referred to a specialist for assessment, since the symptoms may represent other conditions that require further investigation and appropriate treatment. We do not recommend that treatment for suspected protracted bacterial bronchitis be started in primary health care.

More knowledge is needed about the incidence, underlying causes, risk factors and treatment of protracted bacterial bronchitis (23). Which children should receive treatment, for how long, whether the treatment affects the tendency to relapse, and the long-term prognosis are important questions that probably require large, randomised multi-centre studies to address. Optimal studies should include bronchoscopy of patients.

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