

## REVIEW ARTICLE

# Protracted Bacterial Bronchitis: An Underdiagnosed Cause for Chronic Wet Cough in Children

KR Bharath Kumar Reddy<sup>1</sup>, Karambir S Gill<sup>2</sup>, Susha Nair<sup>3</sup>, Barnali G Bhattacharya<sup>4</sup>

## ABSTRACT

Protracted bacterial bronchitis (PBB) is a common cause for chronic wet cough in children. Protracted bacterial bronchitis is defined by persistent productive cough in a child lasting for more than 4 weeks duration in the absence of symptoms or signs of other causes of chronic wet cough and which resolves following a 2–4-week course of an appropriate oral antibiotic. The microbiological criteria in certain situations include a positive bronchoalveolar lavage (BAL) culture. The most common organisms responsible for PBB are non-typable *Hemophilus influenzae* (NTHi) (47–81%), *Streptococcus pneumoniae*, and *Moraxella catarrhalis*. Human adenovirus (HAdV) is a known viral pathogen. The pathophysiology is an initial viral insult to the respiratory tract that disrupts the normal morphology and mucociliary function that leads to chronic inflammation and formation of biofilms that reduce the antibiotic penetration. Persistent neutrophilic inflammation, caused by the presence of capsulated organisms in the respiratory tract results in a loss of ciliary function, increased mucus production and bacterial stasis, resulting in a vicious cycle of chronic inflammation and infection and eventually bronchiectasis. Protracted bacterial bronchitis can be associated with other chronic conditions with impaired mucociliary clearance and large airway malacias. It is most common in the preschoolers aged between 10 months and 4.8 years. These children appear generally healthy with normal growth and development and lack signs of chronic suppurative lung disease such as clubbing, chest deformities, or crepitations. A child with PBB typically presents with history of prolonged wet cough that is more at night and with postural changes. They can also present with shortness of breath and noisy breathing. The symptoms can also be aggravated with viral infections, resulting in exacerbations during these acute episodes. All these symptoms may be similar to asthma, and hence PBB is commonly misdiagnosed and treated as asthma. Chest radiography in PBB shows occasional perihilar changes due to peribronchial wall thickening. A computed tomography (CT) scan is indicated only if there is a recurrence, treatment failure, or suspicion of bronchiectasis. Flexible bronchoscopy with BAL is reserved in recurrent PBB and in those with treatment failure, as it is not easily available in most settings. Protracted bacterial bronchitis, which is not treated adequately, can predispose to bronchiectasis and chronic suppurative lung disease. Protracted bacterial bronchitis typically responds to a 2–4-week course of appropriate antibiotics. The antibiotic of choice is amoxicillin-clavulanate followed by macrolides, trimethoprim-sulfamethoxazole, or cephalosporins in select patients.

**Keywords:** Asthma, Bronchitis, Bronchoscopy, Chronic cough, *Hemophilus influenzae*, Protracted bacterial bronchitis.

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## INTRODUCTION

Chronic cough is one of the most difficult problems faced by pediatricians in clinic practice and a common reason for parents to seek specialty care for their children.<sup>1</sup> Of this, chronic “wet cough” is a distinct entity that needs to be recognized and treated early to ensure prevention of long-term complications. This terminology is used to replace “productive cough” in children as they do not expectorate.<sup>2</sup>

Protracted bacterial bronchitis (PBB) was first described in detail as a cause for chronic wet cough in children in 2006 by the Brisbane group.<sup>3</sup> It has since then been recognized in various guidelines as a cause of chronic wet cough in children.<sup>4</sup> Many children with PBB are misdiagnosed as asthma, resulting in the use inappropriate and high doses of inhaled corticosteroids (ICS) in them.<sup>1</sup> This review hence outlines the definition, etiopathogenesis, diagnosis, and management of PBB to enable pediatricians identify and treat it appropriately.

## DEFINITION

Protracted bacterial bronchitis is defined by either the clinical criteria or the microbiological criteria. The clinical criteria include: (a) a persistent daily productive cough in a child lasting for more than 4-week duration, (b) absence of symptoms or signs (Table 1) suggestive of other causes of chronic wet cough (specific cough pointers), and (c) resolution of cough following a 2–4-week course of an appropriate oral antibiotic.<sup>5</sup> A child is diagnosed with PBB when

<sup>1</sup>Department of Pediatric Pulmonology and Sleep, Shishuka Children's Specialty Hospital, Bengaluru, Karnataka, India

<sup>2</sup>Department of Pediatrics, Dayanand Medical College and Hospital, Ludhiana, Punjab, India

<sup>3</sup>Department of Pediatrics, Shishuka Children's Specialty Hospital, Bengaluru, Karnataka, India

<sup>4</sup>Department of Pediatrics, Children's Clinic, Pune, Maharashtra, India

**Corresponding Author:** KR Bharath Kumar Reddy, Department of Pediatric Pulmonology and Sleep, Shishuka Children's Specialty Hospital, Bengaluru, Karnataka, India, Phone: +91 9845138419, e-mail: drbharathreddykr@gmail.com

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all three criteria are present, and the clinical criteria are more widely used for its applicability in day-to-day clinical practice.

The original microbiological criteria<sup>3</sup> of PBB includes, in addition to the clinical criteria, a positive bronchoalveolar lavage (BAL) culture of  $10^4$  colony-forming units of a bacterial species. This, however, may not always be practical in a clinical setting, where facilities for BAL are not available and the use of prior antibiotics could result in a negative culture.

**Table 1:** Specific cough pointers<sup>4</sup>

Symptoms: Chest pain, history suggestive of inhaled foreign body, exertional dyspnea, hemoptysis, failure to thrive, feeding difficulties (including choking/vomiting), cardiac or neurodevelopmental abnormalities, recurrent sinopulmonary infections, immunodeficiency, or epidemiological risk factors for exposure to tuberculosis
Signs: Respiratory distress, digital clubbing, chest wall deformity, or auscultatory crackles
Investigations: Chest radiographic changes (other than perihilar changes) or lung function abnormalities

## Etiopathogenesis

As the “protracted” in PBB suggests, the pathogenesis of PBB is due to the “persistence” of bacterial infection in the bronchi. The pathogenic organisms most commonly identified are non-typable *Hemophilus influenzae* (NTHi), *Streptococcus pneumoniae*, and *Moraxella catarrhalis*.<sup>6,7</sup>

*Hemophilus influenzae* (47–81%) is the most common bacteria<sup>8</sup> detected in BAL cultures of children with PBB of which the non-typable strains were most prevalent (NTHi).<sup>9</sup> The second most common organism detected in BAL cultures varied between *S. pneumoniae* (24–39%) in some studies,<sup>3,10</sup> and *M. catarrhalis* (19–43%) in few others.<sup>11</sup> There can however be more than one organism identified in the BAL cultures of children with PBB, but the relevance of this finding to clinical outcome or presentation is not yet clear.

Of the viral pathogens identified in children with PBB, human adenovirus (HAdV) was found to be the most common, followed by respiratory syncytial virus, parainfluenza virus, and metapneumovirus.<sup>12</sup>

The pathophysiology of PBB is postulated to begin with an initial insult to the respiratory tract with a viral infection that disrupts the normal morphology and mucociliary function for many weeks. This further leads to chronic inflammation and formation of biofilms, which can progress to develop PBB. A biofilm is a matrix created by certain specific bacteria which reduces the antibiotic penetration and protects these bacteria against antibiotics. This further makes it difficult to eradicate these bacteria with the regular course and short duration of antibiotics.<sup>13</sup>

Protracted bacterial bronchitis can be associated other chronic respiratory conditions such as an impaired mucociliary clearance, anomalies of the airways, and systemic immune defects. There is documented evidence of the strong association of PBB with large airway malacia on bronchoscopic examination. It was seen to be to the tune of 74% in one retrospective study<sup>8</sup> and almost 68% in a prospective study.<sup>12</sup> It however remains unclear whether the reduced airway clearance, accumulation of secretions, cough, and frequent respiratory infections lead to PBB in children with tracheobronchomalacia, or if the chronic infection and inflammation of PBB lead to secondary airway malacia.<sup>14</sup>

Although it is noted that there is a preserved systemic adaptive immunity with normal immunoglobulin levels, B-cell function, and T-cell function, the presence of neutrophilia in the lower airways of children with PBB probably suggests the role of pulmonary innate immunity and neutrophil pathways in its pathogenesis.<sup>15</sup> Furthermore, an increased expression of interleukin-1 (IL-1) pathway members leads to a persistence of activated M1 macrophages in the airways, which has shown to have a proinflammatory effect resulting in chronic inflammation. This could especially be associated with recurrent episodes of PBB.<sup>16</sup>

**Table 2:** Differences between asthma and protracted bacterial bronchitis (PBB)

Clinical features	Asthma	PBB
Character of cough	Dry cough	Persistent wet cough
Nocturnal cough	Present	Present
Postural variation	No change	Worsens on changing posture
Shortness of breath	Not associated with cough episodes	Associated with cough episodes
Chest sounds	Wheeze	“Rattle” sounds
Response to medication	Responds to inhaled corticosteroids	Responds to appropriate antibiotics

Despite ongoing research, the etiopathogenesis of PBB still remains a scientific mystery. There is insufficient evidence to explain who develops PBB, which PBB children will develop recurrence, and which cases may progress to bronchiectasis.

## Clinical Presentation

A child with PBB typically presents with history of prolonged wet cough that is more at night and increases with postural changes. They can also present with shortness of breath, “wheezing,” as claimed by parents, and noisy breathing or a coarse “rattling” sound which can be felt over the chest.<sup>6</sup> All these symptoms may be similar to asthma and hence the common misdiagnosis of asthma in children with PBB.

The common age of presentation is typically in the preschoolers between 10 months and 4.8 years<sup>5</sup> and those more likely to be attending day care, although PBB can also be diagnosed in older children even up to 12 years of age.<sup>1</sup> These prolonged symptoms can be extremely troubling for parents, disturbing the sleep of both children and caretakers, and resulting in generalized tiredness, lack of energy, and absence from day care or school.

Children with PBB appear generally healthy with normal growth and development and show neither signs of any systemic infection nor signs of chronic suppurative lung disease such as clubbing, chest deformities, or coarse crackles.<sup>12</sup>

Children with PBB are frequently misdiagnosed as asthma<sup>1</sup> due to the complaints of noisy breathing and persistent nocturnal cough. The symptoms of PBB can also be aggravated with viral infections, resulting in exacerbations during these acute episodes.<sup>17</sup> Features that can help in differentiating PBB from asthma are depicted in Table 2.

## Diagnosis

In today's era, the diagnosis of PBB is essentially clinical and does not mandate any investigation.<sup>6</sup> The original definition of PBB, now referred to as PBB Micro however, had a mandatory criteria for positive BAL culture.<sup>18</sup> However, in most clinical settings, it seemed impractical and impossible to perform bronchoscopy on every child with chronic wet cough. Hence, the diagnostic criteria have since been modified as shown in Table 3.

Investigations may sometimes be required to rule out other causes of chronic wet cough or in situations where the diagnosis is uncertain, especially in PBB extended or PBB recurrent.

The role of radiological investigations in PBB is limited. Chest radiography is essentially normal with occasional perihilar changes

**Table 3:** Different diagnostic criteria for protracted bacterial bronchitis (PBB)

Original diagnostic criteria (PBB Micro)
Chronic wet cough >4 weeks
Documented lower airway infection (single bacterial species $>10^4$ ) in sputum or in BAL <sup>3</sup>
Resolution of cough after a 2-weeks course of appropriate antibiotic <sup>3</sup>
Modified diagnostic criteria (PBB clinical)
Chronic wet cough >4 weeks
No symptoms or signs of other causes of wet or productive cough <sup>19</sup>
Resolution of cough after a 2-weeks course of appropriate antibiotic
PBB extended
All the criteria of PBB clinical
Resolution of cough after a 4-weeks course of appropriate antibiotic
PBB recurrent <sup>5</sup>
>3 episodes of PBB in 1 year

due to peribronchial wall thickening. A computed tomography scan is warranted in rare situations, only in cases of recurrent PBB, treatment failure, or a suspicion of bronchiectasis.<sup>2</sup>

Lung function testing is performed in cases where obstructive airway disease is suspected to be a differential diagnosis. In PBB, spirometry or impulse oscillometry is found to be normal, which helps with the judicious use of inhaled corticosteroids, which can be unnecessarily used in children with chronic cough.<sup>20</sup>

Although isolation of a pathogen was required for a microbiological diagnosis, flexible bronchoscopy with BAL is currently reserved in cases of recurrent PBB and in those with treatment failure. Although the procedure is safe and complications are rare, it still remains an invasive procedure that may be warranted only in select cases and where facilities are easily available.<sup>4</sup> BAL should preferably be performed from at least two lobes. The right middle lobe and lingula are preferred, or one can choose any other most affected lobe. The European Respiratory Society recommends using three aliquots of saline to obtain a sample from each of the lobes chosen. The first aliquot of the BAL is sent for microbiological culture, as this is more proximal, while the second and third are sent for cytological and noncellular studies.<sup>4</sup>

## NATURAL COURSE OF PBB

Protracted bacterial bronchitis which is not treated adequately can predispose to bronchiectasis and chronic suppurative lung disease (CSLD), thus exhibiting a single clinical continuum from PBB to CSLD.<sup>2</sup> In earlier days, the term "prebronchiectasis" was used to probably represent this continuum.

Persistent neutrophilic inflammation, caused by the presence of encapsulated organisms in the respiratory tract, results in subsequent loss of ciliary function, increased mucus production, and bacterial stasis, promoting a further vicious cycle of chronic inflammation and infection, and finally predisposing to bronchiectasis.<sup>21</sup>

Protracted bacterial bronchitis typically responds to a 2–4-week course of appropriate antibiotics. However, in cases of recurrent episodes or a poor response to 4 weeks of antibiotics, the child needs to be investigated for other causes of chronic wet cough and the possibility of bronchiectasis having set in.<sup>22</sup> Surprisingly, in a study by Goyal et al., of the 144 children studied retrospectively after receiving 4 weeks of antibiotics, it was found that nearly 105 (83.8%) children had bronchiectasis diagnosed on a multidetector CT (MDCT) scan when compared to 25% in who cough had resolved after antibiotics.<sup>22</sup> This study concluded that an MDCT should be

performed in a child whose cough does not completely resolve following 4 weeks of appropriate antibiotics. In a prospective longitudinal cohort study by Wurzel et al., it was found that in children with PBB, recurrent episodes (>3/year) and presence of *H. influenzae* in the lower airway were two significant risk factors for bronchiectasis.<sup>12</sup> Hence, one must keep in mind the possibility of bronchiectasis developing in children with PBB who are not treated early and appropriately.

## TREATMENT

The most common causative organisms found in the lower respiratory tract of children with PBB were *H. influenzae*, *S. Pneumoniae*, *M. catarrhalis*, and *Staphylococcus aureus*.<sup>4</sup> The antibiotic used in a majority of studies was amoxicillin-clavulanate (co-amoxiclav) which was found to have significant bactericidal activity against these organisms and hence considered the most appropriate drug for the management of PBB. The minimum duration of oral antibiotics required was found to be 2 weeks.<sup>11</sup>

In a randomized control trial by Marchant et al.,<sup>10</sup> 50 children diagnosed with PBB supported by BAL data were categorized into two groups to receive either placebo or amoxicillin-clavulanate. Outcomes were determined by the resolution of cough observed by study specific descriptive cough scores. It was thus concluded that 2-week treatment with amoxicillin-clavulanate in conventional doses had a significant cough resolution when compared to a placebo. Donnelly et al. found that more than 51% of children were completely symptom free with two courses of antibiotics, with only 13% requiring repeated courses beyond that.<sup>23</sup> Children treated with oral antibiotics demonstrated good response in most studies, with no need for intravenous antibiotics unless the child developed CSLD, which warranted further evaluation and possible intravenous therapy.

In patients where co-amoxiclav cannot be used, macrolides, trimethoprim-sulfamethoxazole, or cephalosporins have been used as alternatives. However, caution is to be exercised while prescribing oral cephalosporins as an alternative to penicillin drugs in view of cross-allergic reactions.<sup>24</sup>

In children with recurrence of symptoms, it is important to first consider nonadherence to therapy or other causes of chronic wet cough. These are children who need to be further investigated for bronchiectasis or CSLD subsequently. Children with recurrent PBB defined as more than 3 episodes in a year would need to be treated with 6 weeks of antibiotics and not the routine 2-week course.<sup>25</sup>

The role of once-weekly azithromycin which is proven to halve the rate of pulmonary exacerbations in children with bronchiectasis<sup>26</sup> has not been studied in children with PBB. There is also no proven evidence or systemic approach to starting prophylactic antibiotics in children with PBB. Although treatment to clinical PBB seems simple, there is definitely a knowledge gap in managing children with recurrent PBB, which requires more robust studies in the future.

## CONCLUSION

Protracted bacterial bronchitis is an underdiagnosed entity, albeit one of the most common causes for chronic wet cough in children. The most common organism being *H. influenzae*, and the treatment of choice is proven to be a 2-week course of co-amoxiclav in conventional doses. Protracted bacterial bronchitis when left untreated can predispose to bronchiectasis or CSLD and hence needs to be diagnosed and treated early. In resource-limited settings, the clinical criteria for the diagnosis of PBB is proven to be sufficient to warrant therapy. Children with recurrent PBB would require a CT scan to evaluate for other causes of chronic wet cough and bronchiectasis and may need up to 6 weeks of antibiotic therapy. Further research is needed on the prevalence of PBB in India, the microbiological patterns, and the need for prophylaxis in children with recurrent PBB.

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