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

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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 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.1 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.2

Protracted bacterial bronchitis (PBB) was first described in detail as a cause for chronic wet cough in children in 2006 by the Brisbane group.3 It has since then been recognized in various guidelines as a cause of chronic wet cough in children.4 Many children with PBB are misdiagnosed as asthma, resulting in the use inappropriate and high doses of inhaled corticosteroids (ICS) in them.5 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.3 A child is diagnosed with PBB when 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 criteria3 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.
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. 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 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. 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.

Children with PBB are frequently misdiagnosed as asthma 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. Features that can help in differentiating PBB from asthma are depicted in Table 2.

**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. All these symptoms may be similar to asthma and hence the common misdiagnosis of asthma in children with PBB.

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**Diagnosis**

In today’s era, the diagnosis of PBB is essentially clinical and does not mandate any investigation. The original definition of PBB, now referred to as PBB Micro however, had a mandatory criteria for positive BAL culture. 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.
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. 2

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. 20

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. 4 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. 4

**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. 7 In earlier days, the term “prebronchiectasis” was used to probably represent this continuum.

Persistent neutrophilic inflammation, caused by the presence of capsulated 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. 21

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 cough and the possibility of bronchiectasis having set in. 22 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. 23 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. 24 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*. 4 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. 11

In a randomized control trial by Marchant et al., 10 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. 23 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. 24

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. 25

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

| Original diagnostic criteria (PBB Micro) | Modified diagnostic criteria (PBB clinical) |
|----------------------------------------|------------------------------------------|
| Chronic wet cough >4 weeks             | Chronic wet cough >4 weeks               |
| Documented lower airway infection      | No symptoms or signs of other causes     |
| (single bacterial species > 10⁴) in sputum or in BAL | of wet or productive cough               |
| Resolution of cough after a 2-weeks    | Resolution of cough after a 2-weeks      |
| course of appropriate antibiotic      | course of appropriate antibiotic         |
|                                       |                                         |
| PBB extended                          | PBB recurrent                           |
| All the criteria of PBB clinical      | Resolution of cough after a 4-weeks      |
|                                        | course of appropriate antibiotic         |

- >3 episodes of PBB in 1 year
The role of once-weekly azithromycin which is proven to halve the rate of pulmonary exacerbations in children with bronchiectasis 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.

**References**

1. Chang AB, Robertson CF, Van Asperen PP, et al. A multi centre study on chronic cough in children: burden and etiologies based on a standardized management pathway. Chest 2012;142(4):943–950. DOI: 10.1378/chest.11-2725.
2. Chang AB, Redding GJ, Everard ML. State of the art—chronic wet cough: Protracted bronchitis, chronic suppurative lung disease and bronchiectasis. Pediatr Pulmonol 2008;43(6):519–531. DOI: 10.1002/ppul.20821.
3. Marchant JM, Masters IB, Taylor SM, et al. Evaluation and outcome of young children with chronic cough. Chest 2006;129(5):1132–1141. DOI: 10.1378/chest.129.5.1132.
4. Kantar A, Chang AB, Shields MD, et al. ERS statement on protracted bacterial bronchitis in children. Eur Respir J 2017;50(2):1602139. DOI: 10.1183/13993003.02139-2016.
5. Chang AB, Upham JW, Masters IB, et al. Protracted bronchitis: the last decade and the road ahead. Pediatr Pulmonol 2016;51(3):225–242. DOI: 10.1002/ppul.23351.
6. Craven V, Everard ML. Protracted bacterial bronchitis: reinventing an old disease. Arch Dis Child 2013;98(1):72–76. DOI: 10.1136/archdischild-2012-302760.
7. Marchant JM, Gibson PG, Grissell TV, et al. Prospective assessment of protracted bacterial bronchitis: airway inflammation and innate immune activation. Pediatr Pulmonol 2008;43(1):1092–1099. DOI: 10.1002/ppul.20906.
8. Kompare M, Weinberger M. Protracted bacterial bronchitis in young children: association with airway malacia. J Pediatr 2012;160(1):88–92. DOI: 10.1016/j.peds.2011.06.049.
9. Pritifis KN, Litt D, Manglani S, et al. Bacterial bronchitis caused by *Streptococcus pneumoniae* and nontypable *Haemophilus influenzae* in children: the impact of vaccination. Chest 2013;143(1):152–157. DOI: 10.1378/chest.12-0623.
10. Marchant J, Masters IB, Champion A, et al. Randomised controlled trial of amoxicillin clavulanate in children with chronic wet cough. Thorax 2012;67(8):689–693. DOI: 10.1136/thoraxjnl-2011-201506.
11. Narang R, Bakevell K, Peach J, et al. Bacterial distribution in the lungs of children with protracted bacterial bronchitis. PLoS ONE 2014;9(9):e108523. DOI: 10.1371/journal.pone.0108523.
12. Wurzel DF, Marchant JM, Yerkovich ST, et al. Prospective characterisation of protracted bacterial bronchitis in children. Chest 2014;145(6):1271–1278. DOI: 10.1378/chest.13-2442.
13. Stewart PS. Mechanisms of antibiotic resistance in bacterial biofilms. Int J Med Microbiol 2002;292(2):107–113. DOI: 10.1078/1438-4221-00196.
14. Chang AB, Boyce NC, Masters IB, et al. Bronchoscopic findings in children with non-cystic fibrosis chronic suppurative lung disease. Thorax 2002;57(11):935–938. DOI: 10.1136/thorax.57.11.935.
15. Baines KJ, Upham JW, Yerkovich ST, et al. Mediators of neutrophil function in children with protracted bacterial bronchitis. Chest 2014;146(4):1013–1020. DOI: 10.1378/chest.14-0131.
16. Hodge S, Upham JW, Pizzuto S, et al. Is alveolar macrophage phagocytic dysfunction in children with protracted bacterial bronchitis a forerunner to bronchiectasis? Chest 2016;149(2):508–515. DOI: 10.1016/j.chest.2015.10.066.
17. Chatteraj SS, Ganesan S, Jones AM, et al. Rhinovirus infection liberates planktonic bacteria from biofilm and increases chemokine responses in cystic fibrosis airway epithelial cells. Thorax 2010;66(4):333–339. DOI: 10.1136/thx.2010.151431.
18. Bush A. Persistent bacterial bronchitis: time to venture beyond the umbrella. Front Pediatr 2015;7:264. DOI: 10.3389/fped.2017.00264.
19. Chang AB, Landau LI, Van Asperen PP, et al. Cough in children: definitions and clinical evaluation. Med J Aust 2006;184(8):398–403. DOI: 10.5694/j.1326-5377.2006.tb0290.x.
20. Chang AB, Van Asperen PP, Glasgow N, et al. Children with chronic cough: when is watchful waiting appropriate? Development of likelihood ratios for assessing children with chronic cough. Chest 2015;147(3):745–753. DOI: 10.1378/chest.14-2155.
21. Al Subie H, Fitzgerald DA. Non-cystic fibrosis bronchiectasis. J Paediatr Child Health 2012;48(5):382–388. DOI: 10.1111/j.1440-1754.2010.01871.x.
22. Goyal V, Grimwood K, Marchant J, et al. Does failed chronic wet cough response to antibiotics predict bronchiectasis? Arch Dis Child 2014;99(6):522–525. DOI: 10.1136/archdischild-2013-304793.
23. Donnelly DE, Critchlow A, Everard ML. Outcomes in children treated for persistent bacterial bronchitis. Thorax 2007;62(1):80–84. DOI: 10.1136/thx.2006.058933.
24. Pichichero ME, Zagursky R. Penicillin and cephalosporin allergy. Ann Allergy Asthma Immunol 2014;112(5):404–412. DOI: 10.1016/j.anai.2014.02.005.
25. Gross-Hodge E, Carroll WD, Rainford N, et al. Duration of initial antibiotic course is associated with recurrent relapse in protracted bacterial bronchitis. Arch Dis Child 2019. 317917. DOI: 10.1136/archdischild-2019-317917.
26. Valery PC, Morris PS, Byrnes CA, et al. Long-term azithromycin for indigenous children with non-cystic fibrosis bronchiectasis or chronic suppurative lung disease (bronchiectasis intervention study): a multicentre, double-blind, randomised controlled trial. Lancet Respir Med 2013;1(8):610–620. DOI: 10.1016/S2213-2600(13)70185-1.