Outcomes in Children Treated for Persistent Bacterial Bronchitis

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Background

Persistent bacterial bronchitis [PBB] appears to be under recognized and frequently mis-diagnosed as asthma. In the absence of published data relating to the management and outcomes in this patient group a review of the outcomes of patients with PBB attending a paediatric respiratory clinic was undertaken.

Methods

A retrospective chart review was undertaken of 81 patients in whom a diagnosis of PBB had been made. Diagnosis was made on the standard criteria of a persistent, wet cough present for greater than 1 month that resolves with appropriate antibiotic therapy.

Results

The commonest reason for referral was a persistent cough or 'difficult asthma'. In the majority of subjects symptoms commenced before the age of 2 years and had been present for more than one year in 59% of subjects. At referral 59% were on asthma treatment and 11% on antibiotics. *H influenzae* and *Strep pneumoniae* were the most commonly isolated organisms. Over half of patients were completely symptom free after two courses of antibiotics. Only 13% required 6 or more courses of antibiotics.

Conclusion

PBB is frequently misdiagnosed as asthma, though the two conditions may co-exist. In addition to eliminating a persistent cough, treatment may also prevent progression to bronchiectasis. Further research relating to both diagnosis and treatment is urgently required.

Background

Coughing in childhood is common with around a third of children reporting cough during any particular month and of these a significant proportion will report the presence of a chronic cough[1][2]. For such a common symptom there is remarkably little in the literature regarding aetiology, investigation and management of chronic cough in childhood. Recent reports from Brisbane have emphasized the importance of making a specific diagnosis in children with a chronic cough [>3 weeks][3]. In particular they have highlighted the important prognostic implications of an on-going wet cough and the importance of persistent bacterial bronchitis [PBB] as the commonest cause of a chronic cough [3][4]. A variety of diagnostic labels have been used to describe this condition. Terms such as chronic suppurative lung disease, [CSLD][5][6][7], persistent endobronchial infection, [PEI][8] and persistent bacterial bronchitis[4] describe the pathological process and site of infection. Some use terms, such as 'chronic bronchitis' [9][10][11] or 'protracted bronchitis',[12][13] to describe the clinical phenotype. Others have suggested using the term 'pre-bronchiectasis' [14][15] to highlight the condition's probable role in leading to damaged airways, as evident on HRCT or at bronchography. All these terms describe a condition that has received little attention during the past two decades. Indeed this important cause of chronic morbidity in otherwise healthy children is not mentioned in British paediatric respiratory text books [16][17] though its clinical features are clearly described in an authoritative Australian text book[5]. This is probably due to the intense focus on asthma that has dominated recent decades and the

lack of clarity in defining 'chronic bronchitis'. The lack of agreement regarding terminology has been one of the major factors that has prevented further understanding of the natural history of this condition and has contributed to the lack of research into optimal approaches to treatment.

Consistent with the recently published data from Brisbane[3][4], persistent bacterial bronchitis is the commonest diagnosis made in our clinic amongst those referred with 'difficult asthma' or with a 'chronic cough,' and our impression is that the numbers presenting with PBB are increasing each year. This may be an unforeseen consequence of the substantial reduction in antibiotic prescribing over the past decade [18][19][20].

Since the condition has received so little attention it is not surprising that there is little information in the literature regarding treatment and outcomes. A review of the literature failed to identify any studies that would guide a clinician when treating this condition. Phelan et al suggest that antibiotic therapy 'should be continued until the chest is clear and there are no symptoms'[5]. Our clinical experience and that of others, including the group from Brisbane[4], suggests that appropriate and aggressive medical treatment leads to a dramatic reduction in morbidity and complete resolution of symptoms in the vast majority of patients. This report contains the results of a retrospective review of outcomes in 81 randomly selected patients diagnosed with persistent bacterial bronchitis.

Methods

The notes of 81 patients, in whom a firm diagnosis of PBB had been made, were reviewed by a single member of the respiratory team [DD]. The diagnosis was established using the standard criteria of a persistent, wet cough present for greater than 1 month that resolves with appropriate antibiotic therapy[4][5][12][13]. This approach is directly analogous to the diagnosis of asthma, in which a diagnosis is made on the basis of history and clear response to appropriate treatment which can include reversibility with β agonists or unequivocal dramatic improvement in symptoms when inhaled corticosteroids are commenced. Patients were randomly identified by reviewing clinic letters from the past 5 years. A database containing all clinic letters from this period was searched for the term 'persistent endobronchial infection' [the term used in our clinic]. This identified all patients in whom the diagnosis was considered to be part of the differential diagnosis. Patients' notes were then examined to determine whether the diagnosis had been confirmed and, if so, they were included in the notes review until the selected target of 80 sets on notes were examined. The patients were identified by a new member of the respiratory team [DD] to avoid recall bias that might be introduced if patients had been identified from memory by physicians and nurses, which would probably have led to those with the most persistent symptoms being over represented. Patients with significant neurological conditions, such as severe cerebral palsy, in whom such problems are relatively common and those following chemotherapy were excluded.

The approach to treatment was based on high dose antibiotic therapy capable of treating *H influenzae* and *Strep pneumoniae* [most commonly amoxicillin with clavulanic acid 40 mgs amoxicillin content/day] for two weeks and reviewing response to therapy. If the cough cleared the antibiotic was continued for a further 4 – 6 weeks in the first instance.

Patients were discharged from the clinic when they had been through one autumn/winter without reoccurrence of the chronic cough.

A proforma was used to record all required information such as: age of onset, symptoms at presentation, previous treatment(s), investigation results, response to prescribed treatment and current respiratory status. All data was then entered into an SPSS spreadsheet. Descriptive statistics were then carried out.

Results

The majority of patients were referred from primary care, with a significant minority being referred from secondary care. The cohort included 41 girls and 40 boys aged 5 months to 14 years,9 months [median 3 yrs 9 mths], when first seen in the clinic. Symptoms commenced before the age of two years in 59% of children, [fig 1]. The commonest initiating event was an acute lower respiratory tract infection [LRTI],42%, with 'pneumonia' accounting for a further 30%. In the majority this was a clinical diagnosis without documented x-ray changes. The commonest reason for referral was a persistent cough or 'difficult asthma', accounting for approximately 47% and 45% of the group respectively. At presentation 95% of patients had a persistent cough, usually described as 'wet' or a 'smoker's cough'. 'Wheeze' [48%] and shortness of breath [43%] were also common. 'Wheeze' was the primary symptom in 5% of children, though on closer questioning almost all these children had a ruttle[21] [a form of rale observed in young children characterised by course discontinuous noises probably originating in the large airways] rather than classical wheeze. In many of those reporting shortness of breath it was apparent that this was attributable to bouts of coughing. At least one parent smoked in 31% of families for whom a smoking history was available.

Symptoms had been present for more than one year in 59% of subjects, [Fig 2]. The majority of patients were on medication at referral, including 59% on asthma treatment, (of whom 39 out of 48 were on inhaled corticosteroids, ICS), and 11% on antibiotics. A further 7.5% had been on ICS in the past. Only a small minority had abnormalities on auscultation with coarse inspiratory and expiratory noises being the only abnormal findings. However when requested to cough >95% had a wet cough.

Chest x-rays were carried out in 98% of patients. Of these, 30% were reported as normal. The commonest abnormality reported was bronchial wall thickening. Patchy consolidation was reported on at least one CXR in 25% of children. A further 19% had recurrent consolidation, with the same area being affected in 9 children and different areas being affected in 6. Bronchiectasis was confirmed in 4 out of the 14 patients who had a HRCT scan. Of these three had HRCT scans prior to, or immediately after, referral from local district general hospitals, the fourth having been referred with a foreign body that had been inhaled at least 6 month prior to referral. Two have since had repeat scans having been asymptomatic for some time and both show resolution of the original changes.

A cough swab was obtained in 63% of patients, and over half grew pathogens. Of the infected samples, 81% grew *H influenzae* and 37% grew *Strep pneumoniae*, (30% grew both). Other organisms occasionally detected were moxarella and other streptococci.

Over half of patients, [51%], were completely symptom free after two courses of antibiotics. Only 13% required 6 or more courses of antibiotics, or had continuous prophylactic antibiotics for at least one winter. At the time of the notes review all patients were well, although 5% [4 patients] were still under active follow up and receiving intermittent antibiotics. A firm diagnosis of concomitant asthma based on a bronchodilator response of >15% FEV_1 or a clear response to oral steroids had been made in 31% of patients.

Investigations were generally only carried out in those requiring more than two courses of antibiotics and these were generally unhelpful. IgG subclass abnormalities were detected in 28 out of 36 patients, with raised and low levels being equally common. Only 3 patients had a low IgA level. Subclasses were normal in these subjects and all three are currently symptom free. IgE was found to be raised in 10 out of 35 patients. Antibody levels for Hib, tetanus and pneumococcus were checked in a third of the children. Only 41% of Hib levels were within the normal range, but almost all levels returned to normal after re-vaccination. With tetanus and pneumococcus, 69% and 70% had protective or 'normal' levels respectively. Other investigations, such as sweat tests and ciliary biopsies, were all negative.

Bronchoscopy was undertaken in 19 subjects. Culture results were similar to cough swab results with *H influenzae*, followed by *Strep pneumoniae* being the most commonly identified organisms. The cytology in lavage samples was dominated by neutrophils which accounted for the majority of cells. Other than secretions and oedematous mucosa, the only abnormality seen was malacic airways in two subjects. Oedematous mucosa and closure of airways on suction during bronchoalvolar lavage was very common but appeared to be secondary to the endobronchial inflammation.

Discussion

The data presented in this report helps to highlight the importance of making an accurate diagnosis in children with persistent cough and, in particular, a persistent wet cough. 95% of the children included in this study who presented with persistent bacterial bronchitis were effectively cured with appropriate antibiotic therapy at the time of the notes review. However a small number had a more protracted course even though they did not have an identifiable underlying cause such as cystic fibrosis, PCD or significant immunodeficiency.

Though this is a retrospective, observational study involving children with an established diagnosis of PBB, the data generated from this study is very similar to that in the prospective study from Marchant et al[3][4] in which 102 children with chronic persistent cough were put through a formal protocol. By far the most common diagnosis in their study was PBB, which accounted for 40% of cases, of whom 62% had an onset of

symptoms in the first year of life. 54% had been labelled as having asthma, the others having been referred with persistent cough or 'bronchitis'. The second commonest diagnosis was bronchiectasis, which is likely to be part of the PPB spectrum. As in our series, no significant underlying predisposing factor such as cystic fibrosis or PCD was identified, while bronchiectaisis on HRCT was uncommon. The range of organisms identified was similar, with *H influenzae* and *Strep pneumoniae* accounting for 47% and 35% of isolates respectively, and more than one organism being isolated from many patients. They report that most patients in this study became symptom free, though the report includes few details regarding treatment, other than to note that repeated courses of treatment were required in a significant number. Their patients appeared to have been symptomatic for a shorter period than ours, with a median duration of 6 months [IQR 3 – 12].

Two other recent studies involving preschool children have further highlighted the prevalence of PBB inpatients with troublesome respiratory symptoms. One identified 'bacterial bronchitis' in 43% of children with persistent *wheeze*, despite 'adequate' treatment for asthma [24% were on oral steroids] [22]. In the same study a significant number of children had co-existing reflux and positive bacterial cultures. Aspiration is likely to be an important pre-disposing condition in early childhood leading to disruption of the normal epithelium and colonisation by organisms such as *H influenzae*. In a second study, a positive bacterial culture was obtained at bronchoscopy in 61% of 23 children with recurrent cough and/or wheeze who had failed to respond to empirical treatment for asthma and gastroeosophogeal reflux[23].

PBB has received little attention in recent decades which is unfortunate as our experience, and that of the Brisbane group, is that, if recognised, it is a curable condition. In many centres there remains a reluctance to accept this diagnosis as an important cause of cough in children[24]. As noted in the introduction, this may, in part, be attributable to confusion surrounding nomenclature, with many terms being used for the same condition. The benefits for the child of making an accurate diagnosis are likely to go well beyond eliminating the cough. It seems probable that, in a significant proportion of patients, the lower airways inflammation accompanying PBB would progress inexorably over varying periods of time to 'idiopathic bronchiectasis', as has been suggested by many authors over the years [5][14][15]. Clearly it is difficult to prove this suggestion as it would be unethical to randomise children to effective treatment and placebo to observe the natural history. The suggestion that bronchiectasis represents a late stage in the progression of 'chronic bronchitis'or PBB, was first made in the 1940's as a result of undertaking bronchograms in children with chronic productive cough suggestive of bronchiectasis[14]. Of those with a prolonged wet cough but without evidence of bronchiectaisis at presentation, 40% had developed clear evidence of bronchiectasis on repeat bronchography within three years. The author suggested these children with 'chronic bronchitis' had 'pre-bronchiectasis'. Consistent with this suggestion is the observation that the clinical features of patients included in this report, and that of the Brisbane group, are remarkably similar to those outlined in recent studies involving children and adults with 'idiopathic' bronchiectasis. It is reported that the majority of adult patients give a history of an on going wet cough from early childhood[25][26]. It is

also clear that many children[15][27] and adults[25] [26] are misdiagnosed as having conditions such as 'difficult asthma' for some time before a diagnosis of bronchiectasis is made. Moreover, the widely accepted 'vicious circle' [28][29] hypothesis would predict that the development of bronchiectasis, as evident on HRCT, is preceded by a period of chronic inflammation driven by persistent bacterial infection of the conduction airways. Unfortunately most publications relating to 'idiopathic' bronchiectasis focus on the diagnosis and management of 'established' bronchiectasis and ignore the antecedent stages of the disease. Focusing on bronchiectasis in this way is analogous to discussing the treatment of myocardial infarction and ignoring antecedent symptoms, such as angina.

The levels of bronchiectasis in our clinic and this series are comparable with those of Marchant et al [4], but are much lower than those reported from other tertiary clinics[15][27][30]. This may reflect our delay in proceeding to HRCT and the relatively short duration of symptoms in Marchant's study. It has been known for decades that the appearance of bronchiectasis, on bronchography[31] or HRCT[5], can resolve with appropriate treatment, and this has been highlighted again in a recent study [15]. This is entirely consistent with the proposition that the spectrum of PBB ranges from early colonisation, with minimal disruption of the airways, through to 'established bronchiectasis', which is simply a stage in the progression that can be identified radiologically on HRCT. PPB, without a significant underlying problem, appears curable, at least in the paediatric population. Since, in our experience, the HRCT appearances do not impact on management or outcomes we generally reserve HRCT for those with most troublesome symptoms. In patients with PBB and a significant underlying condition, such as CF, PCD or immunodeficiency, the progression to HRCT evident bronchiectasis is likely to be more rapid, and account for the high levels of identifiable predisposing factors evident in those investigated for established bronchiectasis in childhood[27]. Even in those with a significant immunodeficiency, resolution of bronchiectatic changes on HRCT is not uncommon with aggressive therapy [Wallis C personal communication].

The 'vicious circle' hypothesis proposes that the initial event involves impairment of the normal pulmonary defense mechanisms, which allows inhaled bacteria such as *H influenzae* to reside in the airways for longer than normal[28][29]. The most common insult in early childhood is likely to be viral lower respiratory tract infections, LRTIs, which are known to disrupt normal surface morphology and cilial function for many weeks[32]. The high incidence of PBB commencing in the first few years of life, at a time when the prevalence of viral LRTIs are at their highest, would support this suggestion. In most studies attempting to identify a cause for bronchiectasis, 'post LRTI' remains the commonest aetiology with 'unknown' being next[33]. Previous 'hospitalised pneumonia' is a major risk factor for bronchiectasis[15][33]. Our experience suggests that many with a chronic cough, which has been attributed to a 'pneumonic illness', have been symptomatic for some time before the pneumonic illness, which probably represented an acute exacerbation of PBB.

Of interest is the significant number of patients with both asthma and PBB in our series. This has been observed in other reports in which the incidence of asthma in those with bronchiectasis is significantly higher then the general population.[34][35][36][37]. It has been suggested that this is due to the inflammation associated with bronchiectasis causing 'reactive airways'. However, it seems more likely that increased mucus secretion and mucus plugging, together with disruption of the epithelium, leads to a predisposition to PBB consistent with the 'vicious circle' hypothesis. The classic example of asthma and PBB co-existing is the so called 'right middle lobe syndrome'[38] but, as with bronchiectasis, this probably represents the most easily defined example of a spectrum of severity. We are very conscious that highlighting this condition carries the risk of over-prescribing of antibiotics for asthmatic patients. It is important to recognise that PBB is characterised by a prolonged moist cough and that antibiotics are not indicated for acute exacerbations of asthma.

Since this entity has not been well described, there is no consensus regarding treatment. It is likely, in the very early stages following the initial insult, that standard, short courses of antibiotics will be sufficient to clear the organisms from the airway and permit healing. However, by the time patients have been referred to secondary care, symptoms have often been present for many months or years. Our approach is to attempt to eradicate infection and then to keep the airways clear of infection while the repair process takes place. Initially, we use a two week course of an antibiotic such as amoxicillin with clavulanic acid at high dose and review the response at two weeks, an approach also adopted by Marchant et al[4]. Typically the cough takes 10 -14 days to resolve. If there has been a clear response to this intervention the treatment is continued for a further 4 to 6 weeks in order to keep the airways free from colonisation and permit repair of the affected airways. As noted in the results section, most children remain symptom free after one or two such courses. The minority of patients appear to require prolonged courses, particularly through the winter, but even in these we generally observe resolution of symptoms after variable periods of time. For those whose symptoms reoccur after two courses of antibiotics, physiotherapy is included in the treatment regimen. Other centres have reported using 3 or 6 months of antibiotics as their initial approach. While none of the subjects included in this report required intravenous therapy we have found increasing need for this approach in the past 2 years. More recently we have been using nebulised antibiotics [colistin] for those with more troublesome symptoms. Indeed it has been used very successfully in a small number whose cough has failed to resolve even with intravenous antibiotics. The ease with which symptoms are treated is likely to be influenced in part by the duration of symptoms. An adult study of PBB proven by bronchoscopy, without bronchiectasis on HRCT, found that even three weeks of oral antibiotics failed to clear the cough and all their subjects required intravenous antibiotics[39].

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The progressive fall in antibiotic prescribing for viral respiratory tract infections in early childhood over the past decade[18][19.][20] has been appropriate. However, this may have the consequence of inadvertently increasing the incidence of PBB, and possibly 'idiopathic bronchiectasis', in coming decades[37]. Our clinical impression is that PBB is becoming more common and difficult to treat over the past decade. While there has

been much emphasis on the reduction in antibiotic prescribing for upper respiratory tract infections in children, there has been far less attention paid to those who might benefit from 'delayed prescribing'[40]. It has variously been suggested that antibiotic prescribing should be considered in patients with a persistent, wet cough lasting more than 2[40][41], 4[12] or 6[9] weeks. We feel that prescribing antibiotics should be seriously considered if a wet cough persists for more than three to four weeks providing that the possibility of mild asthma is considered. Careful clinical assessment is required if we are to ensure that those with probably bacterial colonisation are treated appropriately, while avoiding a drift back to the treatment of asthma exacerbations and simple viral respiratory tract infections with antibiotics. Early in the course of PBB short courses of antibiotics are probably adequate but, once established for months or years, longer courses are required to permit recovery of the epithelial integrity.

In summary the diagnosis of PBB can be made at bronchoscopy, or can be based on clinical assessment and response to treatment. Patient numbers appear to be increasing which may be attributable to the reduction in inappropriate antibiotic prescribing in the community, which has not been accompanied by the appropriate use of 'delayed prescribing'[40]. Diagnosis and appropriate treatment can lead to complete resolution of symptoms with dramatic improvements in quality of life. Identifying underlying causes other than previous lower respiratory tract infections in non-specialist clinics is uncommon, but causes should be sought in those with recurrent symptoms despite appropriate treatment. PBB is frequently misdiagnosed as asthma leading to inappropriate and excessive use of inhaled steroids. Not uncommonly the two conditions co-exist causing significant challenges in diagnosis and management.

Bronchiectasis has been termed an orphan disease due to the relative lack of research into the diagnosis and management of this condition[37][42]. There has been even less research into the accurate identification and management of children with PBB and 'pre-bronchiectasis'. Challenges for the future include establishing a universally agreed nomenclature; further clarifying diagnostic techniques; devising management algorithms and developing randomised clinical trials aimed at both PBB of relatively recent onset and for those with symptoms that have been present for many months or years.

Images

Fig 1 Age of onset for symptoms
Fig 2 Duration of symptoms at diagnosis

Competing Interests

None

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Ethical Approval

The manuscript describes the outcome of an audit undertaken within the respiratory team in which we wished to get a handle on the outcomes achieved by our service. In the process of the audit it became evident that there has been nothing published on treatment

and outcomes for this condition for more than half a century and therefore we have written up the audit for publication. Because of its origins this was not initially submitted for ethical approval as our initial aim was simply to quantify effectiveness of our approach and treatment outcomes.

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