Persistent Bacterial Bronchitis

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What is it?
Persistent bacterial infection of the conducting airways is a well recognized feature of the progressive bronchiectasis noted in patients with cystic fibrosis and is generally recognized to be an important component of the morbidity associated with other forms of bronchiectasis. However the ‘pre-bronchiectasis’ phase of the disease has received very little attention over recent decades in part due to its relatively low prevalence in affluent countries and in part due to with an excessive focus on asthma as the cause of chronic respiratory symptoms. However, anecdotally, the prevalence of persistent bacterial infection of the conducting airways appears to be increasing, probably due to the significant fall in the use of antibiotics to treat young children with acute respiratory tract symptoms[1-3]. Recent reports have identified persistent bacterial bronchitis [PBB] as the commonest cause of a persistent wet cough in childhood and as a major cause of ‘difficult asthma’[4-6].

A variety of pathogens, most notably *H Influenzae*, *Strep Pneumonia* and *Moraxella catarhallis* appear ideally suited to colonise the respiratory tract when presented with impaired mucociliary clearance be it in the middle ear, sinuses or the lower airway. Once established it is likely that these organism can, through quorum sensing[7], organize themselves into colonies establishing their own biofilms within the mucus lining the airways. While in many subjects such colonies are probably transient with innate host responses eliminating the bacteria, in many others the organisms thrive within their biofilms using physical barriers and other strategies to resist clearance. As a result a chronic endobronchial infection develops. Inflammatory cells, most notably neutrophils, vainly strive to eradicate the organisms from the airways. Produces such as human neutrophil elastase and myeloperoxidases stimulate mucus production and causing collateral damage which further impairs mucociliary clearance. Over a period of time the organisms are likely to extend their areas of influence through release of buds containing organisms that seed new colonies.

While such a scenario is widely accepted as occurring in patients with cystic fibrosis and ‘non-CF bronchiectasis’, many clinicians find the concept of the airways of otherwise apparently health children being chronically infected as difficult to accept. However reflecting on the currently accepted ‘vicious circle’ hypothesis[8,9], that is widely accepted as the most likely mechanism for the development of airways damage in most patients with bronchiectasis, it seems clear that chronic colonization of the airways has probably been present for years or even decades before changes are apparent on a CT scan. This hypothesis suggests that impaired mucociliary clearance leads to infection resulting in inflammation leading to mucosal damage, particularly affecting ciliated epithelium leading to further impairment of mucociliary clearance[Fig 1]. Historical data from the 1950’s would support this suggestion as does the clinical histories of most adults with ‘bronchiectasis’ In the earliest days of antibiotic therapy a large cohort of children having clinical features of bronchiectasis [including regular production of purulent sputum] but no changes of bronchiectasis on bronchograms were reassessed 3 years later[10]. Of these, 40% had developed clear evidence of bronchiectasis on repeat bronchography. The author suggested these children with ‘chronic bronchitis’ had ‘pre-bronchiectasis’. Further weight to the suggestion that persistent bacterial endobronchial
infection lasting many years precedes bronchiectasis evident on a CT scan comes from studies involving children and adults with ‘idiopathic’ bronchiectasis. The majority of patients give a history of an ongoing wet cough that has been present from early childhood[11,12]. It is also clear that many children[6,13,14] and adults[11,12] are misdiagnosed as having conditions such as ‘difficult asthma’ for some time before a diagnosis of bronchiectasis is made. Other mechanisms causing leading to bronchiectasis such as the inflammation associated with inflammatory bowel disease and the very occasional severe overwhelming pulmonary infection are very rare. The co-existence of asthma and bronchiectasis is probably no coincidence with atopic asthma being capable of predisposing to infection due to mucus plugging and it is possible that bacterial infection can promote airways hyperresponsiveness resulting in some cases of non-atopic asthma.

Lack of clarity regarding recognition, diagnosis and treatment of this condition is reflected in the extremely limited literature that refers to this condition. The widespread use of antibiotics from the 1950’s is believed to have been a major factor in the enormous decline in the number of cases of bronchiectasis in subsequent decades and with this would be a significant fall in the number of children with a PBB – most cases would have probably been aborted by the use of antibiotics very early in the course of the illness while organisms were still trying to gain a foothold. As a result it received little attention since it did not appear to be a common or important condition. This was compounded by the lack of agreement regarding nomenclature and the intense focus on asthma that dominated the literature for the past 20 to 30 years. A variety of diagnostic labels have been used to describe this condition. Terms such as chronic suppurative lung disease, [CSLD][15-17], persistent endobronchial infection, [PEI][13] and persistent bacterial bronchitis[2] describe the pathological process and site of infection. Some use terms, such as ‘chronic bronchitis’ [18-20] or ‘protracted bronchitis’, to describe the clinical phenotype. Others have suggested using the term ‘pre-bronchiectasis’ [10,13] to highlight the condition’s role in the causation of sufficient damage to the airways to be evident on HRCT or a bronchogram. While we have generally used the term persistent endobronchial infection it would seem reasonable, in order to standardize nomenclature, to use the term persistent bacterial bronchitis as advocated by Anne Chang and colleagues. Though she and her groups use the terms PBB, CSLD and bronchiectasis on the basis that it is not proven beyond doubt that they are part of the spectrum I would argue that until proved otherwise they should indeed be viewed as part of a continuum with common aetiologies and treatment. This argument is re-enforced by the observations made over many decades that in many children CT ‘bronchiectasis’ can resolve[13,15,21]. To consider ‘bronchiectasis’ as a distinct entity is akin to cardiologists treating patients with myocardial infarcts and ignoring the fact that this defined event is the consequence of a disease that has taken many decades to progress to that event.

Clinical Features
Recent reports from Brisbane and Sheffield have emphasized the importance of making a specific diagnosis in children with a chronic cough [4-6]. 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. As with any such progressive condition the clinical features at presentation range widely from a persistent but not particularly troublesome wet cough in the morning which may appear to disappear in the summer to a very troublesome cough both day and night with expectoration of obviously purulent sputum. Systemic symptoms range from minimal to severe and is not obviously correlated in many with the severity of the pulmonary symptoms. Typical systemic symptoms, if present may include general malaise, general ‘mardyiness’, decreased appetite and in the most extreme examples almost encephalopathic sleepiness which reverse rapidly with antibiotic symptoms.

If a careful cough history is not taken it is easy to mistake the condition for asthma with parents often reporting a night time cough, shortness of breath on exercise, wheeze and exacerbations with viral infections. On closer questioning the cough generally sounds productive [a wet cough] and is generally most prominent first thing in the morning as opposed to the dry cough typically in the early hours that characterizes the symptoms characterized by many untreated asthmatics. The shortness of breath on exercise often turns out to be a consequence of the coughing rather than an independent symptom and the wheeze is typically a rattle – a course non-musical noise often mistakenly referred to as upper airways noises and representing excessive secretions in the chest [in contrast to the true musical nature of a genuine wheeze][22,23]. Expectoration of sputum is rare in young children who general swallow any excessive sputum but information can be gleaned sometimes if the coughing leads to vomiting.

The severity of reported symptoms is likely to be influenced by the extent of the endobronchial infection, the duration of symptoms and host factors and will probably change over time. While symptoms can be very troublesome from the start in many patients in others there is slowly progressive increase in symptoms over time. There is a tendency for symptoms to be come somewhat less troublesome in adolescence and early childhood but whether this is genuine improvement or whether the patient simply accepts that is how they are and are getting on with life is unclear.

Because of the lungs limited repertoire of responses to potential harmful stimuli the clinical picture when faced by a viral lower respiratory tract infection, asthma, recurrent aspiration, PBB and a variety of other stimuli can look very similar. In trying to disentangle the patients with PBB from those with frequent viral respiratory tract infections it is often helpful to ask when the child last did not cough, most children with frequent viral infections causing coughs having at least a few days to weeks between episodes. While a wet cough implies the presence of secretions in the conducting airways this may be due to a variety of causes including untreated asthma and asthmatics during acute exacerbation.

Examination is frequently unremarkable until the child is asked to cough or ‘huff’. Auscultation is generally normal but in the presence of a lot of secretion coarse expiratory and, in particular, inspiratory noises may be heard. Again similar findings can be heard in the recovery phase of an severe exacerbation of asthma. These noises are often referred to as a ‘wheeze’ or ‘conducted noises’ – doctors often being as imprecise about the term wheeze as parents. As with patients who have cystic fibrosis a ‘clear
chest’ means very little and asking the child to cough is generally far more informative. Initial investigations include culture of sputum or a cough swab and a chest x-ray which may be normal, scruffy with peribronchial wall thickening or, in a very small minority, fairly extensive changes bilaterally. The CXRs are never diagnostic.

A definitive diagnosis can be made by assessing response to treatment or by bronchoscopy. In a patient with a history strongly suggestive of the condition in whom other cases such as asthma have been considered and been excluded or felt to be unlikely. The key diagnostic response is to eliminate a persistent cough with a high dose oral antibiotic such as co-amoxiclav [amoxicillin with clavulanic acid] which treats the common suspects. Typically any systemic symptoms will improve in the first week but the cough frequently takes 10 -14 days to go. [there is frequently a history of short courses of 5 or 7 days antibiotics helping but as soon as the antibiotic was stopped the cough returned]. In a small minority even this is insufficient and intravenous antibiotics may be indicated. At this point the infection is probably cleared but the abnormal airway permits recolonisation. If there is a clear and unequivocal response our policy is to continue for a further 4 - 6 weeks to permit the airways to recover. Since some two thirds of such patients are cured with 1 – 3 such course it is reasonable in the majority to treat first and only investigate further if there are further reoccurrences but other centres will investigate at an earlier stage. Investigations are those for bronchiectasis and generally include immunology, sweat test and genetics, IgE RASTS and as appropriate, a video fluoroscopy of swallowing, occasionally a pH probe and a CT scan. Many of these are combined with a bronchoscopy[25] which can confirm the diagnosis and identify other risk factors such as tracheobronchial malacia. In studies of difficult asthma and wheeze authors have been surprised to find high levels of bacterial colonization [26,27] It should be noted that a bronchoscopy with a month or two of a course of antibiotics may give false negative culture results. The results of the CT scans do not significantly alter therapy and in many cases are not predictive of the difficult involved in cure the subject. In most with relatively minor changes of bronchiectasis the changes are reversible while the danger of a ‘normal’ CT is that the child is not given aggressive treatment. The commonest risk factors we identify are previous viral LRTI, poor asthma control leading to mucus plugging leading to a persistent cough which is largely refractory to changes in treatment, tracheomalacia and aspiration in those with cerebral palsy.

For a condition that has received so little attention there is no firm evidence bas for treatment. Many text books do not even recognize the condition and the only guidance in the one that describes the condition most effectively recommends treating with antibiotics until the cough has gone[15]. Ideally the condition will be picked up early when it is at its most straightforward to eradicate but this is the time when diagnosis is most difficult, overlapping with viral LRTIs, post viral cough which will resolve and early asthma. Until we have definitive test the falling use of antibiotics is likely to result in many missing treatment at the earliest stages. Our approach is that if the child is not coughing then it is likely that there is little or no inflammation and the airway will be healing. Eradicating the infection involves antibiotics [usually oral but on occasion intravenous antibiotics are required]. Keeping the airways free of recolonisation may require long
term oral and/or nebulised antibiotics with physiotherapy with the aim of curing the condition.

Research is required to improve diagnosis, particularly in the earliest stages, and to try and improve our understanding of how to optimize treatment while minimizing the use of antibiotics. It may be the key intervention is to couple reduced antibiotic prescribing for viral infections in primary care with an awareness that a persistent cough lasting longer than say 3 weeks might require oral antibiotics [not forgetting the possibility of asthma].

References


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‘Bronchiectasis’

Vicious Circle Hypothesis

Inflammation

Airways damage

Impaired mucociliary clearance

Physiotherapy

Antibiotics

PEI Bronchiectasis vs IHD MI