An Approach to the Child with a Wet Cough

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Educational aims:

- To discuss the common causes of acute and chronic wet cough in children.
- To help the reader appreciate the complex interaction between protracted bacterial bronchitis and bronchiectasis.
- To promote a pragmatic approach to the investigation and treatment of children with wet cough.

Abstract

When children have a wet cough, it suggests the presence of secretions in their airways. This often has an infectious aetiology which is usually a self-limiting viral infection requiring no investigation or treatment. In those with acute wet cough it is, however, important to identify features suggestive of community acquired pneumonia or an inhaled foreign body as these causes require specific management. When there is chronic wet cough, the most common diagnoses are protracted bacterial bronchitis (PBB) and bronchiectasis. The relationship between these two conditions is complex as the development of bronchiectasis manifests as a clinical continuum in which the early features of which are indistinguishable from PBB. It is therefore important to identify PBB and chronic cough endotypes which are associated with an increased risk of bronchiectasis. This article offers a pragmatic approach to the investigation and treatment of children with wet cough. It is hoped this will limit unnecessary investigations whist aiding the prompt diagnosis of conditions needing treatment to reduce symptom burden and prevent further lung damage.

Introduction

Coughing is a protective reflex which clears secretions or inhaled material from the airways.[1] It is therefore normal to cough and the mean number of coughing episodes in healthy children has been measured as 11 (range 1-34) per 24 hours.[2] In the developed world, increased frequency of cough is the commonest reason for a child to be taken to their primary care physician (PCP) and for referral into secondary care.[3,4] Cough duration is a primary differentiating factor but frustratingly the definitions of acute and chronic cough vary between guidelines. The UK Paediatric Cough guideline defines a cough as acute if its duration is <3 weeks, prolonged acute if 3-8 weeks and chronic if >8 weeks.[5] Other international guidelines define chronic cough as cough with a duration of >4 weeks.[6,7] The inclusion of 'prolonged acute' limits the number of children with post-viral cough meeting the criteria for chronic cough who may undergo unnecessary investigations. A proportion of children with uncomplicated pertussis may also find their symtpoms resolve during this time. Surveys using parental questionnaires have estimate the prevalence of chronic cough (in the absence of wheeze) as 5-10%.[8] Chronic cough affects childrens sleep, their ability to play and their school performance as well as causing disruption and anxiety for parents and other household members.[9] Recurrent cough refers to repeated episodes, not associated with viral illnesses each lasting >7–14 days. If the cough-free periods between the episodes are short, it can be difficult to distinguish this from chronic cough.[5,10]

The list of differential diagnoses for chronic cough in children is long[11] and is different to that for adults.[12] A helpful way to focus this list is to characterise the cough as wet or dry.[13] Wet, chesty and productive are terms used to describe coughs associated with the presence of secretions in the airways causing a loose, self-propagating sound. Such coughs often have an infectious aetiology. To be grammatically correct, the term 'productive' should be reserved for coughs associated with sputum expectoration and 'wet' for those not associated with this.[14] As most children, however, do not expectorate sputum, 'wet cough' is commonly used to describe all wet or productive coughs. This interpretation of 'wet cough' will be used throughout the remainder of this article.

Acute Wet Cough

Viral Upper Respiratory Tract Infections

Two thirds of children aged 0 to 4 years, visit their PCP at least once a year with acute respiratory infections, and up to three-quarters of them will have a cough which sounds wet.[15] In the majority of cases these episodes are caused by self-limiting, viral, upper respiratory tract infections which do not warrant specific treatment.[16,17] The history and examination findings may alert the clinician

to consider an alternative diagnosis such as community acquired pneumonia (CAP) or an inhaled foreign body.

Community Acquired Pneumonia

CAP should be considered if the wet cough is associated with pyrexia (>38.5^{o}C), increased work of breathing, tachypnoea or focal chest signs. CAP is a clinical diagnosis and imaging or other additional investigations are not routinely required.[18] Viruses are responsible for around half of the cases of CAP in chidren and are more common in infants and young children. The most frequently identified viruses are RSV, parainfluenza, influenza, human metapneumovirus and human bocavirus.[19,20] Bacterial pathogens are responsible for the remaining cases of CAP although some may be a mixed viral / bacterial infection.[21] *Streptococcus pneumoniae* is the commonest bacterial cause of CAP being present in up to one third of children >2 years.[22] Other common pathogens are *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*.[23] When a diagnosis of CAP is made the child should receive a course of antibiotics as bacterial and viral pneumonia cannot reliably be distinguished from each other.[24] Oral amoxicillin is the first line antibiotic.[18] Intravenous antibiotics are only necessary in uncomplicated CAP if the child is unable to take or absorb oral antibiotics (eg vomiting). A macrolide should be considered if there is no response to amoxicillin or mycoplasma or *Chlamydia pneumoniae* are suspected.[18] CAP can be complicated by pleural effusion / empyema. This should be suspected when there is evidence of effusion on examination (decreased air entry and stony dullness to percussion) or persistence of high fever despite adequate antibiotic treatment. Ultrasound is more sensitive than CXR at detecting pleural effusions, and avoids the radiation associated with computerised tomography (CT) scans.[25] A clinically significant effusion / empyema should be drained using chest drain or VATS.[26]

Inhaled Foreign Body

Inhalation of a foreign body (FB) is most common in children aged 0-3 years as they tend to explore the world around them via their mouths.[27] Food stuffs are implicated in around 80% cases with peanuts the number one culprit.[28] At the time of aspiration, common symptoms include coughing, choking, and wheezing but these may be self-limiting. If the problem is not diagnosed at the time of inhalation it may cause an ensuing infection and the child may ultimately present with wet cough. The presence of unilateral chests signs or the history of sudden onset of choking or coughing should raise suspicion of inhaled FB. If suspected, a rigid bronchoscopy should be undertaken to find and remove the FB.

Chronic Wet Cough

Protracted Bacterial Bronchitis

Diagnosis

Protracted bacterial bronchitis (PBB) is the leading cause of chronic wet cough in young children living in developed countries. It these areas it is responsible for up to 40% of those referred to secondary care with a persistent cough.[29,30] The original definition (now called PBB-micro) was (i) history of chronic wet cough, (ii) positive culture of a respiratory pathogen from a bronchoalveolar lavage obtained during flexible bronchoscopy (FB-BAL), (iii) response to two weeks oral amoxicillin-clavulanate acid.[30] When the lower airway is sampled in children with PBB, the most commonly identified organisms are *Haemophilus influenzae* (HiB), *Streptococcus pneumoniae*, *Moraxella catarrhalis* and *Staphylococcus aureus*.[31] An alternative definition was developed (PBB-clinical) as flexible FB-BAL is unnecessary in children with uncomplicated PBB.[32] Both diagnostic criteria are broad, meaning some view PBB as an umbrella term covering a number of different endotypes.[33] 'PBB-extended' and 'recurrent PBB' are additional endotypes used to further define PBB.[32] See Table 1. These endotypes are clinically relevant as those with PBB-extended are more likely to have tracheo-bronchomalacia[34] and those with recurrent PBB are more likely to have subsequent diagnosis of bronchiectasis.[35]

Table 1: Diagnostic criteria for PBB

	Diagnostic Criteria
PBB-micro	I. Chronic wet cough (>4 weeks) II. Lower airway infection (>10^4 colony forming units per ml on BAL) III. Cough resolution following 2 weeks antibiotics
PBB-clinical	I. Chronic wet cough (>4 weeks) II. Absence of symptoms or signs of other causes of wet cough III. Cough resolution following 2 weeks antibiotics
PBB-extended	PBB-micro or PBB-clinical but cough only resolves after 4 weeks antibiotics
Recurrent PBB	Recurrent episodes (>3 per year) of PBB

Treatment

As 'cough resolution following antibiotic treatment is part of the PBB diagnostic criteria, diagnosis cannot be made until the treatment has been completed and the response assessed. Amoxicillin-clavulanate is the most commonly used first line antibiotic but there is a lack of evidence to guide the duration of this course.[36,37] The 2008 UK National Paediatric Cough Guideline suggested 4-6 weeks.[38] This recommendation was based on expert opinion as there were no prospective studies

available at that time. In 2012, a randomised controlled trial (RCT) showed that two weeks of oral amoxicillin-clavulanate was associated with higher rates of cough resolution compared to placebo.[34] The rate of cough resolution in the treatment group, however, was only 48% which led many clinicians to continue using a longer antibiotic course. A survey of UK clinical practice showed 42% of clinicians prescribed two weeks, 32% four weeks and 26% six weeks of antibiotics. International guidelines recommend starting with a two week treatment course and extending it to four weeks if cough resolution is not achieved.[14,39]

Relapse of PBB

Retrospective reviews report the incidence of chronic cough relapse in PBB as high as 76%.[37] It is not known if relapses of PBB reflect incomplete treatment of the original infection or acquisition of a new infection. Recurrent PBB (>3 episodes / year) is associated with a future diagnosis of bronchiectasis.[35,40] Children with frequent relapses should therefore be considered for investigations to exclude bronchiectasis. In this group, the role of antibiotic prophylaxis in preventing further relapses and the possible development of bronchiectasis needs further study. The relationship between PBB and bronchiectasis is discussed in more detail below.

Bronchiectasis

Presentation

The predominant symptom of bronchiectasis is persistent wet cough which may become intermittent if treated with antibiotics. Other features that should alert the clinician to this diagnosis include: recurrent lower respiratory tract infections, haemoptysis, chest pain, failure to thrive, persistent crackles or wheeze on auscultation, shortness of breath, finger clubbing, unusual organisms (i.e. *Pseudomonas aeruginosa*) isolated from lower airway microbiology samples, persistent CXR changes or abnormal spirometry. This array of signs and symptoms highlights the potential high burden of bronchiectasis for the child and their family.

Diagnosis

Bronchiectasis is conventionally defined as irreversible dilation of the bronchial tree diagnosed using CT scan. Other features of bronchiectasis seen on CT scan are listed in Table 2.[41] There is evidence, however, that mild bronchiectasis can be reversible if it is appropriately treated or the causative factor removed.[42] Clinically this can halt the expected decline in lung function.[43,44] For irreversible dilation of the bronchial tree to be confirmed, the child would need to have at least two chest CT scans which would be associated with significant radiation exposure.[45] It has therefore

been suggested that bronchiectasis should not solely be a radiological diagnosis but instead defined as a clinical syndrome which is confirmed radiologically. The suggested syndrome is persistent or recurrent (>3) episodes of chronic (>4 weeks) wet cough, sometimes with coarse crackles and finger clubbing.[41] Increased broncho-arterial ratio (BAR) measured from chest CT images (obtained with a standardised inspiratory volume) should be used as the radiological confirmation. BAR is the inner diameter of airway as a ratio to outer diameter of accompanying vessel (within 5mm in a non-tangential plane). In children an abnormal BAR is defined as >0.80.[41] This is lower than the ratio used in adults reflecting different normal values.[46]

Table 2 – Features of bronchiectasis seen on chest CT.

	Radiological Feature
1	Increased broncho-arterial ratio (BAR)[#] - *signet ring sign*
2	Bronchial wall thickening
3	Lack of bronchial wall tapering - *tramlines*
4	Presence of bronchial structures in the lung periphery
5	Mucus plugging
6	Air trapping - *mosaic perfusion*

[#]Defined as the inner diameter of airway as a ratio to outer diameter of accompanying vessel (within 5mm in a non-tangential plane).

Causes

A list of the common causes of bronchiectasis is shown in Table 3. In all these conditions the underlying pathophysiology is a cycle of lower airway infection and / or inflammation causing lung damage.[47] In the early stages the infection and inflammation is likely to result in chronic wet cough before lung damage is severe enough to cause airway dilatation. This phase may be indistinguishable from PBB. The longitudinal development of bronchiectasis can therefore manifest clinically as an overlapping continuum of PBB, chronic suppurative lung disease (CSLD) and eventually bronchiectasis.[40] In addition to the chronic wet cough, children in the first phase are likely to have audible and palpable secretions, impaired regional muco-ciliary clearance, endobronchial bacterial infection and neutrophilic airway inflammation.[32] As the child moves towards CSLD digital clubbing may develop as well as chest wall deformity and auscultatory chest signs.[48] The radiological confirmation of airway dilation (likely to start as reversible and then becoming fixed) confirms the final phase.

Table 3 - Conditions associated with the development of bronchiectasis in children

	Clinical Features (Specific Cough Markers)	**Diagnostic Test**
Mucociliary abnormalities		
Cystic fibrosis (CF)	Failure to thrive, steatorrhoea	Sweat test, genetics
Primary ciliary dyskinesia (PCD)	Dextrocardia, sinus & ear disease	Nasal nitric oxide, ciliary studies
Infection		
Recurrent PBB	>3 episodes PBB/ year	None
Post-LRTI	Previous LRTI	None
Post-tuberculosis	Previous tuberculosis	None
Post-infective bronchiolitis obliterans	LRTIs, crackles, dyspnoea	CT scan with expiratory images
Immunodeficiency		
Primary / secondary / syndrome associated	Recurrent, severe or atypical infections	Immune, genetic or serology blood tests
Lung damage		
Aspiration	Neurodevelopmental delay, recurrent LRTIs, choking episodes	Video fluoroscopy
GORD	Vomiting, dyspepsia, water brash	pH study / impedance manometry
Airway abnormalities		
Tracheomalacia / bronchomalacia	Brassy cough	Bronchoscopy
Inhaled foreign body	Acute choking episode	Bronchoscopy
Pre-existing lung disease		
Allergic bronchopulmonary aspergillosis	Dypnoea, wheeze	Total IgE, specific IgE, precipitins
Interstitial / connective tissue lung disease	Autoimmune disease, medications	Disease specific serology
Non-post-infectious bronchiolitis obliterans	Post transplantation, medication	CT scan with expiratory images
Prematurity	Premature birth	None

Treatment

The primary aim of bronchiectasis treatment is to address the underlying cause to stop the progression of the disease thus preventing further lung function decline.[43,44] The treatment of radiologically confirmed bronchiectasis in children is covered in detail in other review articles.[41,49] I have therefore only included the following brief overview. Any underlying cause should be addressed. Lower airway infection with pathogenic organisms needs to be identified and treated aggressively. This can be accomplished using oral, nebulised or intravenous antibiotics depending on the severity of the symptoms. Isolation of virulent organisms such as *Pseudomonas aeruginosa* should prompt attempts at eradication. Prophylactic oral antibiotics with agents such as azithromycin can reduce exacerbations but may be associated with antibiotic resistance.[50] As in CF, there may be a role for nebulised antibiotics to supress chronic infection with *Pseudomonas aeruginosa.* Airway clearance is viewed by most clinicians as a vital part of clinical care but there is a lack of supporting evidence. Dornase alfa is commonly used in CF but has been shown to be harmful in non-CF bronchiectasis.[51] Nebulised hypertonic saline is therefore the most widely used mucolytic.

Other Causes of Chronic Wet Cough

All the conditions associated with bronchiectasis may present in the early stages with chronic wet cough without evidence of CSLD or bronchiectasis. In these children, the aim for the Respiratory Paediatrician is to prevent the development of bronchiectasis, or if this is already present, to prevent it from worsening. Some causes of chronic wet cough are not associated with bronchiectasis. These include the small subset of children with asthma who present with a wet rather than the usual dry cough. These children must be carefully evaluated to confirm the diagnosis of asthma and exclude a second lung pathology.

A Pragmatic Approach to the Child with Wet Cough

Acute Wet Cough

Most children with acute wet cough require no investigations or treatment as it is caused by a self-limiting viral infection. A good history and examination should identify children meeting the criteria for CAP and those whose symptoms are secondary to an inhaled foreign body.

Chronic Cough

A possible approach to the investigation and treatment of children with chronic wet cough is shown in Figure 1. The figure demonstrates the paucity of evidence on which most of these decisions are made and highlights the need for good quality studies. The first step is a detailed history and examination to identify of specific cough markers suggesting an underlying cause. Examples are shown in Table 3. If specific cough markers are present, the investigation(s) can be focused and if the diagnosis confirmed, appropriate treatment started.

In children with chronic wet cough but no specific cough markers, assessing the response to antibiotics is the next step. In our department, a two week trial of oral amoxicillin-clavulanate is first-line, extended to four weeks if the cough persists. Cough resolution after two weeks suggests a diagnosis of PBB and after four weeks PBB-extended. Children with PBB need to be followed-up to assess for relapse. Further episodes of chronic cough can be treated with courses of amoxicillin-clavulanate. Children with chronic wet cough unresponsive to four weeks antibiotics[52] and those with recurrent PBB[35] have increased risk of bronchiectasis so should be investigations appropriately. As recurrent PBB has increased risk of bronchiectasis and by definition respond to oral antibiotics, there is logic in trying to prevent further episodes and reduce the risk of bronchiectasis by prescribing a prophylactic antibiotics. The potential advantages of this need to be balanced against the risk of antibiotic resistance which is greatest in those who are non-adherent.[53]

Investigations

The presence of cough specific features shown in Table 3 will guide the clinician regarding the investigations needed to confirm the suspected diagnosis. The plan of investigations will need to be re-evaluated if the suspected diagnosis is excluded. See Table 4 for a summary of investigations.

Microbiology

Although the invasive nature of FB-BAL means it is unwarranted in children with uncomplicated PBB, knowledge of the causative organism is helpful to ensure appropriate antibiotic stewardship.[31] Obtaining non-invasive lower airway samples using cough swabs, spontaneously expectorated sputum or induced sputum should therefore be considered in any child with a wet cough prior to starting antibiotics. FB-BAL should be considered in children with recurrent PBB, radiologically confirmed bronchiectasis or chronic wet cough unresponsive to four weeks of antibiotics as it may aid diagnosis and guide future treatment. As well as standard culture and sensitivities, TB polymerase chain reaction (PCR) / cultures should be considered depending on the risk.[54] A per-nasal swab for pertussis culture / PCR should be considered in all children with a wet cough lasting long than two weeks and in any child whose cough is associated with a whoop.[55]

Radiology

In children with acute wet cough, a CXR is not routinely required for the diagnosis of CAP and should only be performed if there is doubt about the diagnosis or concerns about complications such as pleural effusion.[18] In children with chronic wet cough, a CXR can be useful to exclude significant pathology but a normal CXR does not exclude bronchiectasis. High resolution chest CT is the gold standard radiological investigation for bronchiectasis. Due to the associated radiation dose,[45] this should only be performed if clinically indicated and timed to maximise diagnostic benefit as well as limit the need for a repeat scan. If the underlying cause is untreated, the continuum of bronchiectasis development means a previously normal chest CT does not exclude future bronchiectasis. Chest CT should be considered in children with signs or symptoms of CSLD or those at increased risk of developing bronchiectasis, in particular recurrent PBB or chronic wet cough unresponsive to four weeks antibiotics. If obliterative bronchiolitis is suspected then expiratory images should be obtained to look for air trapping.

Spirometry

Spirometry should be performed in all children with chronic wet cough dependent on age and ability to co-operate. Children with PBB or mild bronchiectasis are likely to have normal lung function.

Bronchodilator reversible airway obstruction suggests asthma. Non reversible airway obstruction or a mixed obstructive / restrictive pattern is seen in moderate to severe bronchiectasis.[41]

Excluding CF

The implementation of the UK national CF newborn screening program has reduced the number of children with CF presenting with chronic wet cough.[56] However, this can still occur due to a missed or false negative screen. A sweat test should therefore be undertaken in children with confirmed bronchiectasis of unknown aetiology or those with CF specific cough markers. These include failure to thrive, steatorrhoea, recurrent LRTIs, isolation of suspicious organisms from lower airway cultures (*Pseudomonas aeruginosa*, *Burkholderia cepacia complex*), recurrent rectal prolapse, hyponatraemic dehydration or pseudo-barters syndrome.

Excluding PCD

Children should be considered for PCD testing if they have a persistent wet cough or PCD cough specific markers. These include: situs anomalies, congenital cardiac defects, persistent rhinitis, chronic middle ear disease (with or without hearing loss), neonatal upper / lower respiratory symptoms or neonatal intensive care admittance in a term baby. The diagnostic work-up for PCD should include nasal nitric oxide measurement, high speed video analysis (including ciliary beat frequency and beat pattern analysis) and ciliary ultrastructure analysis by transmission electron microscopy.[57]

Immunology investigations

A first line immunodeficiency screen should include a full blood count, IgA, IgE, IgG, IgM together with functional antibodies to HiB, *pneumococcus* and *Tetanus*.[58] It should be performed in children with the relevant cough specific markers, recurrent PBB or wet cough not responding to four weeks antibiotics. More in-depth immunological investigations should be considered if immunodeficiency is suspected despite first line investigations being normal. Guidance from a Paediatric Immunologist is likely to be helpful.

Gastroenterology Investigations

Gastro-oesophageal reflux disease is best diagnosed by a pH or impedance study. Aspiration into the airway is confirmed using video fluoroscopy. These investigations are only needed if there is clinical suspicion from the history or examination.

Table 4 – Investigations for Children with Chronic Wet Cough

First Line Investigations (Consider in all)	Second Line Investigations (Consider in selected children)
CXR	Chest CT
Non-invasive lower airway microbiology sample	Flexible bronchoscopy with BAL
Spirometry	Immunology bloods
	Sweat test
	Ciliary studies
	pH / impedance study
	Video fluroscopy

CXR: chest radiograph

Summary

The vast majority of children with acute wet cough need no investigation or treatment as the cause is a self-limiting viral infection. The challenge for the clinician is to identify those with CAP or an inhaled foreign body as they require specific treatment. A small percentage of children with a viral illness may develop post-viral cough, continuing to be symptomatic for up to eight weeks. The differential diagnosis for children with wet cough of this duration includes pertussis.

In children from developed countries, PBB is the commonest cause of chronic wet cough. The disease course in PBB can by uncomplicated with two weeks of antibiotics resulting in cough resolution and no relapse but sadly this is the minority. It is important to identify the endotypes associated with relapse or future complications as they may require further investigation and / or treatment to prevent further lung damage. These include PBB-extended, recurrent PBB and those with a wet cough unresponsive to four weeks of antibiotics.

Bronchiectasis is caused by a vicious cycle of infection, inflammation and lung damage. This manifests clinically as a continuum of PBB, CSLD and eventually bronchiectasis. In the early stages when chronic wet cough is the main / only symptom, the aim of treatment should be stopping the development of bronchiectasis. If this is already established, the aim of treatment is to limit symptom burden and prevent progression. Preventing the development of lung disease in childhood is the key in reducing the burden of respiratory disease in adult life.

Directions for future research

- Investigation of the optimal duration of initial antibiotic treatment in children with presumed PBB.
- Detailed assessment of PBB endotypes and their association with a future diagnosis of bronchiectasis.
- Further investigation into the cause of chronic cough relapse in PBB (new infection versus incomplete treatment).

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Figure One – A possible approach to the investigation and management of children with chronic wet cough. Clinical assessments shown in dashed boxes ([1]assessment made at completion of antibiotic course, [2]assessment made during follow-up). Management decisions shown in solid boxes shaded according to available supporting evidence.