

CME article

Chronic cough in children

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EDUCATIONAL AIMS

- To provide a framework for the approach to children with chronic coughing who don't already have a specific disorder.
- To review the causes and management of children with chronic non-specific dry coughing.
- To review the causes and management of children with chronic wet cough.
- To define and review 'protracted bacterial bronchitis'.

ARTICLE INFO

Keywords:

Chronic cough
Protracted bacterial bronchitis
Pertussis
Cough variant asthma
Upper airways cough syndrome

SUMMARY

Chronic cough has been variably defined as a cough lasting longer than 3, 4 or 8 weeks. Many post viral or pertussis like illnesses are associated with prolonged coughing that resolves over time. Management involves first trying to make a diagnosis and identify the presence of any underlying condition. Targeted treatments can then be employed. Trials of treatments are often used to make a diagnosis. Because natural resolution of cough is so common any trial of treatment to confirm a diagnosis should be time limited and the treatment only restarted if the coughing returns. Only a small proportion of children with an isolated non-specific dry cough have asthma and care is needed not to over diagnose asthma. Children with chronic wet cough may have protracted bacterial bronchitis (PBB) that responds to a full course of antibiotics. Children with PBB failing to respond to treatment or with specific pointers should be investigated for specific causes of suppurative lung disease.

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INTRODUCTION

Chronic cough is one of the most common symptoms that parents will present with their children to the physician. Coughing is often distressing and impacts on the child's ability to sleep well, play and attend school. There is often a discrepancy between what parents and paediatricians consider to be normal. In addition, the reporting of cough is not always accurate and may depend on how parents or school teachers are affected by the child's coughing. The underlying diagnosis in chronic cough can remain elusive and for many there are no specific or effective treatments available. It is therefore often a frustrating consultation for both paediatricians and parents. Most respiratory disorders can present with coughing and the list of causes of chronic cough is large. Several national and

international guidelines on the management of cough in children have been published.^{1,2}

Cough is one of the most important airway protective reflexes which is under both voluntary and involuntary control. Cough receptors which sense and respond to changes in temperature, chemicals and mechanical stresses are located in the pharynx, larynx and tracheobronchial tree. When stimulated these receptors send signals back to the cough centre in the medulla oblongata which then triggers the easily recognizable sequence of events that constitute a cough. A deep inspiration precedes closure of the glottis with a subsequent forceful contraction of the respiratory muscles, the glottis then opens, and there is a forceful expulsion of air, mucous and potentially any other foreign body. During the initial deep inspiration children can inhale any foodstuff that is in the pharynx or larynx exacerbating any choking or coughing. The mechanism of the cough obviously depends on intact receptors, nerves, a functioning cough centre and sufficiently strong expiratory and laryngeal muscles. The cough reflex is lost when consciousness is significantly impaired. Centrally acting cough

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suppressants are therefore ineffectual because of the degree of sedation required to produce cough suppression.

Normal children cough on average 11 times per day when they are well with the coughing increasing in frequency and severity during the frequent winter URTIs.³

In general there are a few overlapping reasons underlying why children appear to have problem chronic cough:

- they are repetitively trying to prevent pulmonary aspiration
- they have chronic airways irritation and inflammation
- they have chronic airways mucus hypersecretion
- they have some extra respiratory cause of the cough

Given that coughing is an important protective reflex it isn't logical to try to suppress coughing without first identifying and treating the underlying reason.

Definition of chronic cough

One in ten otherwise normal children with acute cough due to an upper respiratory tract infection (URTI) are still coughing 3 weeks later.⁴ Many of these children have what has been labeled a 'post infectious cough' (prolonged acute coughing after an obvious URTI) perhaps due to a pertussis, mycoplasma or other viral infection.^{5,6} Some children have a tendency to develop cough receptor hypersensitivity (CRH) following each viral URTI (recurrent prolonged acute coughing) and this state of CRH can last many weeks to months (Figure 1).^{7,8}

Defining chronic cough as lasting longer than 8 weeks is therefore preferable to using a shorter duration e.g. 3–4 weeks. Eight weeks was used in the British Thoracic Society Guideline Recommendations for the assessment and management of cough in children (1). Providing that the child is otherwise well, waiting for and checking that natural resolution has occurred is reasonable. However this duration of a chronic cough is defined largely on the basis of epidemiology rather than pathology. A cough of shorter duration can be highly significant in neonates or in older children with other 'red flag' symptoms. A wait and see policy should not be undertaken if 'red flag' alerts are present (Box 1).

It is unclear whether children with frequently recurrent cough in the absence of URTI should be assessed and managed any differently from children with true chronic coughing. Brooke et al.⁹ investigated the long term outcome of 125 pre-school children with recurrent cough. Over time more than 50% had outgrown the coughing, but only 10% had started to wheeze. The remainder of children who continued to have recurrent cough showed an increased prevalence of nocturnal coughing and decreased threshold to inhaled methacholine. Interestingly, nearly 17% of the control children were nocturnal coughers.⁹

CLINICAL APPROACH

In the history the characteristics of the cough should be carefully elicited (Box 2). There are certain characteristic cough types which are readily recognized including:

Pertussis or whooping cough which is characterized by severe paroxysms of coughing. In this, a spasm or paroxysm of coughing is followed by a gasping inspiration producing the characteristic whoop. The characteristic whoop of pertussis may not be heard in very young infants or older aged children and adolescents.^{10,11}

A loud or brassy cough may be characteristic of tracheomalacia, and particularly when associated with tracheoesophageal fistula (a 'ToF cough').

Psychogenic coughs may appear like 1] dry repetitive habit 'tic-like' coughs or 2] bizarre and honking with the child not being very disturbed by the cough. Both coughs usually disappear when the child is engrossed in an activity or asleep.

Most doctors and parents will also differentiate between a wet and dry cough. Often parents will use terminology which is less clear such as 'a chesty cough' or a 'smoker's cough'. Children under 5 years rarely spit out phlegm but rather swallow it. A chronic productive or wet cough suggests some underlying cause for mucous hypersecretion that needs investigated whereas a dry cough suggests airway irritation, inflammation or a non-airways cause of the cough. It is important to note that some children with dry coughing will have periods with a wet cough e.g. with respiratory infections.

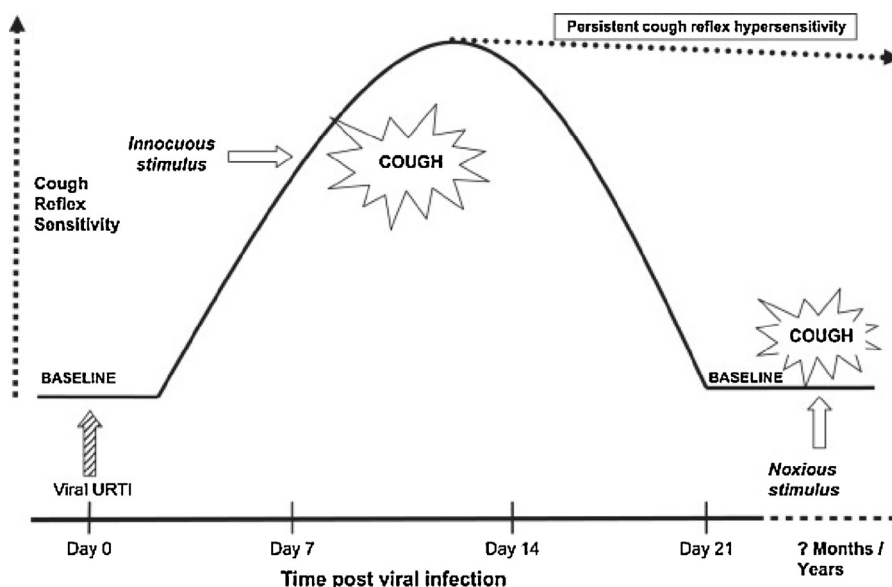


Figure 1. Schematic of proposed changes in cough reflex sensitivity following viral upper respiratory tract infection. (reprinted with permission from L. McGarvey et al., *Pulmonary Pharmacology & Therapeutics* 2009; 22: 59–64).

Box 1. List of some red flag symptoms and signs in chronic cough.

- Coughing started suddenly with a choking episode or an inhaled foreign body is suspected
- Coughing is relentlessly progressive
- There are already specific pointers for an underlying diagnosis including
 - Weight loss, night sweats suggestive of TB
 - Haemoptysis
 - Signs of chronic lung disease or ill-health already present (poor growth, finger clubbing, chest wall abnormality and abnormal lung sounds)
- Coughing with a background history of recurrent pneumonia
- Cough starting in neonatal period
- Swallowing difficulties
 - With craniofacial abnormality
 - With neuromuscular disorder
- Dyspnoea – chronic or exertional
- Wet cough lasting more than 3-4 weeks

Box 2. A list of some key questions to ask in the history.

1. How and when the cough started?
2. Is the cough an isolated symptom?
3. What triggers the cough?
4. Does the cough disappear when the child goes to sleep?
5. What is the nature and quality of the cough?
6. What treatments has the child been tried on and how beneficial were they?
7. What other medication is used? e.g. ACE inhibitors
8. Is there a family history of respiratory, allergic or infectious disease?
9. Does the child smoke? Do the parents smoke? Is there evidence of any environmental pollutant at home?
10. How disruptive is the cough?
11. Is there evidence of Obstructive Sleep Apnoea? How large are the tonsils?

Physical Examination

It is important to do a full clinical examination. General inspection including assessment of growth may reveal evidence of failure to thrive, or clues to atopic status (eczema, allergic salute of Allergic Rhinitis). Low muscle tone particularly in infants may be associated with feeding difficulties and specific neuromuscular conditions with respiratory sequelae. Similarly, craniofacial and palatal abnormalities can be associated with swallowing dysfunction. Examination of the nose and throat may reveal evidence of rhinitis or post-nasal drip or very rarely problems with dentition associated with acid GOR. Check the auditory meatus as wax in the external auditory meatus can be associated with chronic cough via stimulation of the Arnold's nerve reflex. Some respiratory signs should prompt full investigations including finger clubbing, chest deformity, abnormal breath sounds or reduced or asymmetrical air entry. Abnormalities in other systems particularly the cardiovascular system may point to a particular diagnosis. Enlargement of lymph glands, liver or spleen should lead to investigations of possible chest masses or TB.

It is worth trying to observe the child's cough. In children who are old enough to cough on request, both the sound of the cough and the presence of palpable airway secretion should be assessed. This can easily be done in younger children by placing one hand on the anterior and the other hand on the posterior chest.

INVESTIGATION

Most children with problem chronic coughing will require investigations or a diagnostic trial of specific therapy.

- Infants and especially those who cough or become chesty during or after a feed, should have their feeding observed by a trained nurse or speech and language therapist.
- With the help of a physiotherapist obtain a sample of sputum. The sample can be studied for bacteria, atypical organisms and viruses. Some centres are able to perform a differential cell count on an induced sputum sample. An elevated percentage

eosinophils (>3%) is supportive evidence for asthma and the presence of bacteria associated with neutrophilia is in keeping with a bacterial infection such as protracted bacterial bronchitis.

- A chest radiograph will give a good overview of the state of the lungs and may give indications for further investigations. A chest radiograph may not be indicated if a mild specific disorder is definitively diagnosed (e.g. asthma / allergic rhinitis or if a pertussis-like illness is clearly resolving). However, a normal chest radiograph does not always exclude significant pathology such as bronchiectasis and further imaging may be needed.
- Spirometry and bronchodilator responsiveness. In children over 5 years this gives a good overview of the current state of the airway calibre and whether they widen with bronchodilator.
- Allergy testing – skin prick testing or IgE specific tests when positive put the cough into a background of atopy and make cough variant asthma a possible diagnosis.

AETIOLOGY OF CHRONIC COUGH

Several attempts have been made to extensively investigate cohorts of children with chronic cough who have been referred to specialist centres and are summarised in [Table 1](#).^{10–12}

Marchant et al reported that the common causes of chronic cough in children in an Australian setting differed from those commonly reported in adults (asthma, GORD, upper airways syndrome). They found that protracted bacterial bronchitis (defined later) was the commonest cause (40%). Natural resolution occurred during the period while investigations were being undertaken in 22%. Asthma, gastro-oesophageal reflux disease (GORD) and upper airways cough syndrome (UACS) collectively accounted for only 10%. However, two other studies, one from the USA and the second from Turkey, reported higher percentages of children with asthma, GORD and UACS ([Table 1](#)).^{13–15}

The differences in the common causes found may be related to 1] different durations for the definition of chronic cough, 2] different local disease prevalence, 3] different referral practices from primary care, 4] different ages of children studied and 5] different uses of 'trials of treatment' and some aspects of selective investigations. Given that natural resolution of chronic cough in children is common the use, timing and order of 'trials of treatment' could have a profound effect on the final diagnosis arrived upon. It is likely that very young children, as in the Australian study, differ most from adults.

Table 1

Summary findings from three studies comprehensively investigating children with chronic cough.

Study	Marchant JM et al Chest 2006; 129(5): 1132-1141 Australia	Khoshoo V et al Chest 2009; 136: 811-815 USA	Asilsoy S et al Chest 2008; 134: 1122-1128 Turkey
Country	Australia	USA	Turkey
Number	108 children referred to tertiary respiratory centre	40 children referred to pulmonary clinic	108 children referred to Children's Hospital & Research Centre
Average age of child when studied (years)	Median 2.6 years	Mean 7.8 years	Mean 8.4 years
Definition of chronic cough (greater than)	3 weeks	8 weeks	4 weeks
Average length of coughing at referral	Median 6 months	18 weeks	4.16 months
Evaluations undertaken	CXR, FEV1, ENT assessment, bronchoscopy/BAL Sweat test, IgGs, allergy tests, HRCT, pH studies, mycoplasma/pertussis tests	CXR, FEV1, ENT assessment, bronchoscopy/BAL Sweat test, IgGs, allergy tests, HRCT, pH studies, mycoplasma/pertussis tests	CXR, FEV1, ENT assessment, bronchoscopy/BAL, IgGs, allergy tests, HRCT, gastroesophageal scintigraphy, mycoplasma/pertussis tests
Final diagnosis	PBB – 40% Natural Resolution – 22% Bronchiectasis – 6% Asthma – 4% UACS – 3% GORD – 3% Habit – 1%	GORD – 27% UACS – 23% Asthma – 13% Infection – 5% Aspiration – 2% Multiple aetiologies – 20% All tests normal – 10% (? habitual cough)	Asthma – 25% PBB – 23% UACS – 20% PBB + asthma – 12% UACS + asthma – 7% GORD – 5% Bronchiectasis – 3% Natural resolution 2% Others – TB, mycoplasma

It is difficult to know how representative these studies are for chronic cough in the community given the relative low prevalence of post viral syndromes and pertussis detected. These contrast with the community based study of a large number of children coughing greater than 2 weeks more than one third of whom tested positive for a recent pertussis illness. Natural resolution of the cough occurred in almost all the children. The median duration of cough was 118 days in the pertussis positive group, 39 days in mycoplasma positive group and 70 days if neither positive (likely postviral cough).^{5,6}

This suggests that and pertussis, postviral and mycoplasma illnesses are common causes of prolonged coughing in the community especially in older children. Recent reports from the USA and Australia have confirmed an increase in older children and adolescents with pertussis.^{8,13,16}

It clearly is not ethically correct (other than in a research setting) to subject all children to a full battery of potentially invasive tests for conditions that experience shows is likely low probability.

There is currently a clinical trial testing the added value of a chronic cough management pathway compared with usually practice underway in several centres in Australia.¹⁷ In the meantime, the presence or absence of pointers suggesting specific and serious lung disease will determine the requirements for more detailed investigations.

SPECIFIC CAUSES AND MANAGEMENT OF CHRONIC COUGH

Otherwise healthy child with chronic dry or recurrent cough

The term 'non-specific isolated chronic dry cough' is used for an otherwise well child for whom no specific diagnosis can be arrived at. They truly have increased coughing and this collective term likely includes children with a range of conditions such as:

1. *Post-infectious cough or pertussis.* About one third of children older than 5 years with prolonged acute coughing have pertussis with the median duration of cough approaching 4 months.² The paroxysmal spasms of cough followed by an inspiratory whoop typically seen in young children may not be seen in very young infants or older children. Others have Mycoplasma or a

respiratory viral infection eg rhinovirus or RSV.^{5,6,18} In the vast majority the cough resolves naturally with time. It is important to confirm cough resolution. It is likely that these children are experiencing a slow recovery of their airway mucosal epithelial cells and during this time they have cough receptor hypersensitivity (Figure 1). Anti-asthma therapy does not seem to be beneficial.

2. *Cough variant asthma.* Some children with asthma have coughing as the predominant feature and wheezing has not been heard by a health professional. A trial of anti-asthma therapy (inhaled corticosteroids, ICS) may be required especially if there are other atopic diseases (eczema, allergic rhinitis). Trials of asthma therapy should be effectively delivered, given over a limited time frame and have objective end points. At the end of the trial the asthma medication should be stopped. A negative response suggests the coughing is unresponsive to ICS and asthma unlikely. A positive response may indicate natural resolution of the cough or cough variant asthma. If coughing recurs then the medication can be restarted. A second positive response is suggestive of cough variant asthma.
3. *Allergic Rhinitis and/or post nasal drip (upper airways syndrome).* This is not accepted by all as a common cause of true chronic coughing in children. Children with allergic or perennial rhinitis undoubtedly have a clearing the throat type snorting cough. True coughing may be due to associated allergic airways inflammation (asthma). Cough due to allergic rhinitis should respond to allergen exclusion where possible and intranasal steroids with or without antihistamines.
4. *Psychogenic coughs.* There appears to be 2 types of psychogenic cough. Firstly, children may develop a dry repetitive 'tic-like' cough after an episode of bronchitis. This type of cough is usually not very disruptive and parents often can identify that the cough has become a habit. Other children develop bizarre honking coughs which, by being very disruptive to school and family life, bring some secondary gain for the child. Typically these coughs do not upset the children (la belle indifference), the coughing reduces when the child is engrossed in some activity and when asleep. Biofeedback, distraction and suggestion psychotherapies may be required.
5. Other potential causes include;
 - a. Wax in the external ear canal has been associated with chronic coughing.
 - b. Hypertrophied tonsillar tissue impinging on the epiglottis.

- c. Gastro esophageal reflux (GOR) is a major cause of chronic coughing in adults and responds to a long course of proton pump inhibitors. It has been much more difficult to show GOR to be the cause in children and evidence including multichannel intraluminal impedance and pH monitoring associating GORD and cough in children has been reviewed and is conflicting.^{19–21} While empirical treatment helps GOR symptoms it seems to do little for the respiratory symptoms. However, anecdotally most physicians have encountered children who have persistent cough with perhaps other symptoms of gastro-oesophageal reflux whose cough responds magically to antireflux therapy and in selected children a trial of antireflux therapy can be useful.
 - d. Children started on ACE inhibitors may have a problem dry cough which stops once the ACE inhibitor is stopped. However, children with cardiac problems can also cough because of associated airway problems, pulmonary odema, Kartagener's syndrome or immunodeficiency.
 - e. Children's Interstitial Lung disease (child) usually presents with breathlessness but early evolving cases can be associated with a dry repetitive cough
6. Chronic non-specific isolated dry cough is a label used when there are no pointers to a specific diagnosis.

Productive (moist or wet) cough

A chronic cough that sounds wet or productive implies either an increase in airway secretions or abnormalities in clearance. Children with persistent productive (moist or wet) cough should be investigated to determine if they have any of the specific suppurative lung conditions with persistent endobronchial infections that eventually may lead to bronchiectasis such as those listed in **Box 3**.

Persistent bacterial bronchitis (PBB) seems to be a common and increasingly recognised cause of chronic wet cough in young children and often occurs on a background of mild asthma or has been misdiagnosed as asthma.²² Seear et al.²³ reintroduced the term paediatric chronic bronchitis to describe a cohort of children with chronic productive cough that didn't fit any other major diagnostic category. Some of the children reported had previously had invasive medical therapy (prolonged ventilation, cardiac surgery) and many came from poor socioeconomic backgrounds with an over representation of native American Indians.²³ Further reports from Chang AB (Australia) and Everard M (Sheffield, UK) highlighted the existence of this condition which has now largely been accepted.^{22–24,28} These children have chronic wet productive coughing, with bacteria such as Pneumococcus, Haemophilus influenza, and Moraxella persisting in the airways and if a bronchoalveolar lavage or sputum is obtained there is an associated neutrophilia. Spirometry in older children is usually normal (but the child may cough during the procedure) and the CXR typically is

normal or has non-specific bronchial wall thickening. The cough responds to a full or prolonged course of antibiotic (eg co-amoxiclav, for 2–4 weeks). These authors speculated that either an early respiratory insult (e.g. infectious or medically induced) has led to chronic self-perpetuating inflammation with the formation of bacterial biofilms that can be difficult to treat. Douras et al.²⁵ evaluated 93 selected children with wet cough lasting >6 weeks who did not have asthma and reported that the duration of cough and intensity of BAL neutrophil count related to worse HRCT scan scores. In addition, they noted that some children were referred late for evaluation (wet coughing for > 12 months) and, like Chang et al., speculated that the emphasis of 'asthma under diagnosis' in the last 2 decades of asthma literature may have contributed to a misdiagnosis of children with chronic cough.²² Recently, Kompare and Weinberger²⁶ have reported a large series of children with protracted bacterial bronchitis which mostly had started in infancy.²⁶ Almost three quarters of the children had an associated airway malacia (tracheal, bronchial). These children responded well to antibiotics, although a significant number relapsed and needed further courses of antibiotics.

A positive response to a full course of an appropriate antibiotic and the child returning to completely good health confirms the diagnosis of PBB and further investigations will likely be unnecessary.

However, if PBB fails to respond or is PBB becomes recurrent further investigations are required to rule out the other conditions listed above. It is quite possible, although as yet unproven, that each episode of recurrent bacterial bronchitis is triggered by a viral infection and we currently only recommend a second 2 week course of antibiotic should this recurrence of wet productive cough last longer than 3 weeks. It is important to establish the presence of an underlying diagnosis to allow disease specific therapy to be instituted. This includes a sweat test and genotyping (cystic fibrosis), nasal nitric oxide, ciliary ultrastructure and beat frequency (Primary Ciliary Dyskinesia), white cell count, immunoglobulins and functional antibody studies (lung infections associated with immune deficiencies), barium swallow, swallowing videofluoroscopy and 24 pH studies (recurrent pulmonary aspiration).

An HRCT is useful to define the extent of lung disease and to confirm the presence of bronchiectasis. A bronchoscopy may also be required to rule out a retained foreign body and to obtain lung samples for microbiology.

It is still uncertain as to whether PBB is a fore runner to bronchiectasis or adult COPD.

Chronic brassy barking or seal-like cough

This cough suggests a tracheal or glottic cause eg tracheo- and / or bronchomalacia. Many children who have undergone tracheoesophageal fistula (TOF) surgery have tracheomalacia and develop a loud cough ("TOF – cough") which is especially disruptive during an intercurrent infection.

Relentlessly progressive coughing

A cough that is progressively becoming more severe and violent needs investigated early. Causes, apart from pertussis, include an expanding intrathoracic tumour, a retained inhaled foreign body and TB.

Haemoptysis

Chronic cough with haemoptysis requires investigation and may be due to cystic fibrosis or other bronchiectasis, retained inhaled foreign body, tumour, pulmonary haemosiderosis or arteriovenous malformation.

Box 3. List of major conditions associated with chronic wet coughing.

- Persistent bacterial bronchitis
- Cystic Fibrosis
- Immune deficiencies
- Primary ciliary disorders
- Recurrent pulmonary aspiration
- Retained inhaled foreign body

There are many other rare causes for chronic coughing in children including the dry cough associated with the children's Interstitial Lung Diseases (child).

MANAGEMENT

The management of cough relies on firstly making the correct diagnosis and then managing the underlying condition. Treatment of the symptom of cough in isolation is usually unsatisfactory. Many cough suppressants are no more than soothing preparations for the throat. Cough suppressants such as opioids which are effective usually produce significant sedation if used in the dose required for cough suppression. There is little evidence of benefit in chronic cough without a clear underlying diagnosis. It is important to:

- Remove the child from environmental tobacco smoke or other pollutant exposure.
- Try to make a specific diagnosis and use specific treatments (find and use the relevant up to date guideline).

Non-specific isolated cough in an otherwise well child

A recent overview of Cochrane Library reviews on the treatment of chronic non-specific cough in children concluded that there was little evidence to recommend anti-histamines, inhaled corticosteroids (ICS), beta 2 agonists, leukotriene receptor antagonists or gastro-oesophageal reflux treatments. Very high dose ICS may have some benefit but the benefits are likely outweighed but the side effects.²⁷ However, because most of these coughs resolve naturally over time a positive response does not confirm the diagnosis. Trials of these therapies need to be time-limited and retried.²⁸

Chronic wet cough

Chronic wet cough is a specific pointer to a potentially more serious lung condition. Protracted bacterial bronchitis seems to be the most common cause and almost by definition responds well to antibiotics. The overview of Cochrane Library reviews on the treatment of chronic wet cough in children concluded that antibiotic therapy was reasonable first step but warned that the children should be reevaluated to ensure cough resolution.²⁷

RESEARCH DIRECTIONS

- The role of recurrent viral bronchitis as a cause of chronic cough
 - What would be the benefits of rapid viral, pertussis and mycoplasma diagnosis in reducing unnecessary investigations and reassuring parents?
 - Do children with recurrent problem coughing have the same factors and diagnoses as those with chronic persistent cough?
 - Are there any predictors for response to trials of ICS (eg Exhaled Nitric Oxide) ?
- The natural history of protracted bacterial bronchitis – how often is it a pre-bronchiectasis condition?
- What is the best treatment of **recurrent** protracted bacterial bronchitis?
- Why does protracted bacterial bronchitis occur? Is there an immune deficiency?
- What are the indications and best method for investigations into GORD as a cause of chronic cough?

CONFLICT OF INTEREST

MD Shields – nil immediately relevant to this review. MD Shields has received honoraria (from Glaxo Smith Kline, AstraZeneca, Novartis, Merck Sharp Dohme) for talks given at educational meetings. He has received sponsorship from the same companies to attend the ERS, EAACI and BTS annual educational meetings.

GM Doherty– nil immediately relevant to this review. GM Doherty has received honoraria (Novartis) for talks given at educational meetings. He has received sponsorship from Glaxo-Smith Kline to attend the ERS annual educational meetings.

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- (C) Should you successfully complete the test, you may download your accreditation certificate (subject to an administrative charge).

CME QUESTIONS

MCQs

1. A two year old boy presents with a twelve week history of wet-sounding cough. His parents report no other symptoms. On physical examination there is an intermittent palpable 'rattle' over the upper chest. Initial investigations should include:
 - a. Spirometry
 - b. Bronchoalveolar lavage
 - c. High-resolution computed tomography of the chest
 - d. Chest radiograph
 - e. All of the above
2. The following is true of gastroesophageal reflux
 - a. It is known to be a frequent cause of cough in children
 - b. It can be associated with severe suppurative lung disease
 - c. Fundoplication should be considered in isolated persistent cough which fails to respond to maximal medical anti-reflux therapy
 - d. An elevated lipid-laden macrophage index is a specific indicator of chronic cough secondary to reflux
 - e. A similar proportion of adults and children with cough have GORD
3. Chronic cough secondary to pertussis
 - a. Is unlikely in the absence of the characteristic inspiratory 'whoop'.
 - b. Responds well to an appropriate course of macrolide antibiotics
 - c. Should be treated with high-dose systemic steroids
 - d. May occur in fully vaccinated young children
 - e. Occurs in around 5% of children over the age of five with a cough of more than two weeks
4. Cough-variant asthma
 - a. Is more common than wheeze-variant asthma
 - b. Requires treatment with inhaled corticosteroids for more than six months before effects can be seen
 - c. Will usually present with a wet-sounding cough
 - d. Frequently responds to inhaled bronchodilators
 - e. Is more common in children with a personal history of atopy
5. Normal children
 - a. Usually cough more than 30 times per day
 - b. Have a 10% chance of cough persisting for more than 3 weeks after an URTI
 - c. Generate increased intrathoracic pressure against an open glottis at the start of a cough
 - d. Cough more frequently during REM sleep
 - e. All of the above