PRIMARY CARE RESPIRATORY JOURNAL

http://www.thepcrj.org

REVIEW

Diagnosis of asthma in children under five

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Received 13 November 2006; accepted 15 November 2006

KEYWORDS
Asthma;
Preschool children;
Differential diagnosis;
Viral associated wheeze;
History;
Examination;
Investigation;
Therapeutic trial;
Wheeze;
Cystic fibrosis;
Leukotriene receptor antagonist;
Inhaled corticosteroid

Summary: Cough and wheeze are common symptoms in childhood, but mostly do not signify a serious illness. On the basis of history and examination, such children should be allocated into one of five diagnostic categories. Very few need additional tests, although there are specific pointers in the initial evaluation which should actively be sought, and result in referral for investigation. In a community setting, isolated cough with no wheeze or breathlessness is most unlikely to be due to asthma. In pre-school children who cannot perform lung function tests, a therapeutic trial of asthma treatment may be indicated, but a three step protocol is mandatory, stopping therapy if there appears to be a response, and only restarting if symptoms recur. In older children, documentation of variable airflow obstruction before giving a diagnosis of asthma is important, to avoid over-diagnosis. Prophylactic therapy on a long term basis with inhaled steroids in pre-school children does not reduce the likelihood of progression to asthma in mid-childhood, and the results of treatment in terms of symptoms are disappointing.

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1471-4418
doi:10.3132/pcrj.2007.00001

Introduction

All children cough, probably around 50% wheeze in some way or other before they reach school age, but most children are normal. The general practitioner (GP) faced with a child with chronic and relatively non-specific symptoms such as cough, "wheeze" and breathlessness, needs first to decide into which of five categories to place the child:

1. A normal child (the diagnosis which requires the most skill and experience)

2. A child with a serious illness such as cystic fibrosis, tuberculosis etc (rare, but essential to get right)

3. A child with an 'asthma syndrome'

4. The child with minor health issues which may cause asthma-like symptoms, or co-exist with, and potentially worsen, an asthma syndrome

5. (Usually parental) over-anxiety, and over-interpretation of normal symptoms

If the child is thought to have an 'asthma syndrome', the next question becomes "what sort of asthma syndrome?" Is it the result of T-cell driven, eosinophil-mediated, airway inflammation, or is it the result of a non-inflammatory problem, such as intra-uterine disturbance of airway growth? Resolving this question is fundamental to planning appropriate treatment. This paper assumes that the child is not capable of performing even simple lung function tests, and thus the only tools available are clinical history and examination, possibly simple tests (although these are not likely to be employed often, and even less likely to be helpful in a community setting), and the response to a therapeutic trial of treatment. This is a difficult subject which has been reviewed previously in this Journal,[1,2] and this review aims to update these and other papers. However, if a child *is* capable of performing lung function tests, it is inexcusable to make a diagnosis of asthma without having first documented the presence of airflow obstruction which is variable with time and treatment — using, for example, the presence of an acute response to beta-2 agonist, a short period of home peak flow monitoring, or an exercise challenge.

This review paper will cover only briefly the details of the specific conditions and their diagnosis which are likely to require specialist assistance. The main aim is to highlight pointers which should prompt such a referral.

History taking

The first point to determine is what the family actually mean by the word "wheeze". Wheezing due to airway narrowing sounds like a high-pitched, musical whistle, akin to organ music or the wind whistling in chimneys. However, many parents use the same word to describe many other different noises; for example, a palpable crackling in the chest, a noise as if the child needs to clear his throat, or even nasal snuffling.[3-5] Studies using a video-questionnaire,[6] or objective recording of lung sounds,[7] have demonstrated the unreliability of parental recognition of wheeze. Differentiating stridor from wheeze in the tachypnoeic child may be difficult for parents. The significance of these sounds is very different, and time must be spent when taking a history to determine exactly what is meant.

The evaluation of chronic cough is also notoriously difficult. Coughing is universal in childhood at least at the time of viral upper respiratory infections. There is only poor correlation between objective measures of cough such as diary cards or tape recorders and perception of severity by observers.[8,9] Ambulatory cough monitoring has been used predominantly in older children[10-12] to document how much coughing is normal, but this is not routinely available in clinical practice. Finally, it is important to determine who has the problem; if the *child* makes respiratory noises, but does not have any breathlessness or impairment of quality of life, does the *child* have a problem? I am reluctant to diagnose any form of asthma syndrome in the absence of any breathlessness or respiratory distress.

Having established whether the child truly wheezes, and as far as possible whether there is excessive cough, the next step is to identify the pattern and severity of symptoms. The key distinction in the pattern of symptoms is to determine whether the child has symptoms solely at the time of a viral upper respiratory infection or 'cold' (virus associated wheeze, or VAW), or whether there are additional symptoms in between infections. If it is the latter, symptom frequency and triggers should be determined. Specific triggers may include exercise, excited emotional behaviour including laughing or crying, the presence of dust, exposure to furry pets (the English disease), weather or environmental temperature change, and exposure to strong perfumes or aerosol sprays as well as smoke from cigarettes or open fires. The therapeutic approach to VAW is completely different to that for the child with chronic symptoms in between viral colds.

The severity of symptoms should next be determined, both in terms of the disruption to the child and also to the family, in order to ensure that treatment is appropriately focused. The family of a child who coughs intermittently but is not particularly breathless may merely be seeking reassurance that there is no serious underlying disease, rather than seeking a prescription for regular inhaled medication. Conversely, the family of a child who is a so-called "fat, happy wheezer" may be well aware that their child is not in danger of death, but are very eager for some treatment to try to ensure a good night's sleep. Other factors which may influence treatment decisions are a history of atopy in the child or first degree relatives, which would probably make one more likely to give prophylactic treatment.

Particularly in the child with symptoms between colds, specific questions which should be asked are summarized in Table 1. The upper airway can be the forgotten area of paediatric respirology.[13] Much the commonest cause of chronic cough is the catarrhal child with postnasal drip. Symptoms suggestive of obstructive sleep apnoea should be sought, including snoring, apnoeic pauses, restlessness, daytime somnolence and poor concentration. Adenotonsillectomy may be completely curative of the chronic cough, and can prevent the (rare) dangers of night-time respiratory failure. In general, the earlier the onset of symptoms, the more likely that an important diagnosis will be found. Symptoms from the first day of life should always be investigated; they must be distinguished from symptoms starting at a few weeks of age, which may be due to asthma. The mother should be asked whether the problem started literally from day one of life. If this is the case, structural abnormalities of the airway should be excluded. If there is prominent and persistent rhinitis from birth (almost inevitably and fatuously diagnosed as 'the baby being born with a viral cold'), then primary ciliary dyskinesia (PCD, Kartagener's syndrome) should be considered.[14] A very sudden onset of symptoms is strongly suggestive of endobronchial foreign body. Parents may not volunteer the history, and should be asked specifically whether choking on a foreign body is a possibility.[15] Note that even babies too young to bring their own hands to their mouth may have older siblings who may have pressed small objects onto their face. A diagnosis of possible endobronchial foreign body requires urgent referral by telephone for immediate investigation.

Chronic sputum production or a moist cough when the child does not have a viral cold should always be a cause for concern. It is helpful to distinguish between recurrent bouts of cough, usually with viral colds and with cough-free periods between bouts, and a chronic continuous wet cough with no periods of remission. There is good agreement between parental reports of a wet cough and the presence of lower airway secretions at fibreoptic bronchoscopy.[16] *A child who has had more than 6-8 consecutive weeks of a productive cough merits further investigation*. Two series[17,18] have shown that a proportion of such children have chronic bacterial airway infection, with a neutrophilic bronchoalveolar lavage and a positive bacterial culture, usually with *Haemophilus influenza*. The (as yet unproven) assumption is that such children will go on to develop bronchiectasis if not aggressively treated. Although it may be due to postnasal drip or asthma, causes of chronic pulmonary sepsis (see below) such as cystic fibrosis (CF), PCD and agammaglobulinaemia may need to be excluded.

Gastro-oesophageal reflux is suspected in an infant who is worse after feeds, is an irritable

Table 1 Points to seek in the history suggesting an underlying serious diagnosis.

A detailed history, targeted towards other respiratory conditions is an essential first step in evaluating the child with non-specific respiratory symptoms.

• Are the child/family really describing wheeze?
• Upper airway symptoms — snoring, rhinitis, sinusitis
• Symptoms from the first day of life
• Very sudden onset of symptoms
• Chronic moist cough/sputum production
• Worse wheeze or irritable after feed, worse lying down, vomiting, choking on feeds
• Any feature of a systemic immunodeficiency
• Continuous, unremitting or worsening symptoms

feeder (often arching away from the breast or bottle) and vomits or possets easily. A therapeutic trial of thickening of feeds, acid reduction (proton pump inhibitor or H_2 antagonist) and prokinetic therapy (low dose erythromycin, domperidone) is reasonable on clinical suspicion without further investigation. Choking on feeds, particularly in a child with known neurodevelopmental handicap or neuromuscular disease suggests that incoordinate swallowing due to bulbar or pseudo-bulbar palsy may be the cause of symptoms. Laryngeal cleft or H-type tracheo-oesophageal fistula may present with symptoms at the time of feeding.

Another pointer to the need to refer is whether there are any periods of remission. Although symptom-free periods do not exclude the possibility of a serious underlying disease, the child who has no days free of symptoms certainly merits critical consideration of alternative diagnoses. Finally, a history of systemic infections or poor weight gain in the context of chronic respiratory disease should never be dismissed lightly.

Is the child normal?

Having described some of the rarities which may cause diagnostic confusion, it is timely to review some conditions seen in normal children. These include: pertussis and similar syndromes, characterised by paroxysmal coughing, sometimes with a whoop, post-tussive vomiting, or colour change; 'Nursery School Syndrome', usually in firstborn children who are placed early in a child care facility and who get a succession of viral colds which merge into each other; and prolonged post-viral cough. None of these respond to asthma therapy; in my practice, I now spend more time telling parents their children do not have asthma than actually making a new diagnosis.

Physical examination

Most often there will be no physical signs. Digital clubbing is an obvious and important sign, but will not be found if not actively sought. My experience has been that children are not uncommonly referred with obvious chronic clubbing which has never been noticed. The upper airway should be inspected for rhinitis and also for nasal polyps, the latter being virtually pathognomonic of CF in this age group. The nature and severity of any chest deformity should be noted: although a severe Harrison's sulcus and pectus carinatum can be due to uncontrolled asthma, the more severe the deformity, the greater the likelihood of another diagnosis. Palpation of the chest with the palms of the hands during quiet breathing or, in an older child, during blowing or huffing, may be a better way of detecting airway secretions than auscultation. Careful auscultation may however elicit unexpected findings such as crackles, fixed monophonic wheeze, asymmetric signs, or stridor, all of which necessitate a further diagnostic work-up. Finally, signs of cardiac and systemic disease should be sought.

Key features to be sought on physical examination are given in Table 2, and a summary guide to differential diagnosis in Table 3. For interest, the confirmatory diagnostic tests (usually performed after hospital referral) for some of these conditions are listed in Table 4.

What is the role of the chest X-ray (CXR)?

Most hospitals rightly offer open access for CXR, and the radiation dose using modern techniques is trivial (equivalent to one transatlantic trip in Concorde). Even so, I contend that a CXR is

Table 2 Points to seek on examination suggesting underlying serious diagnosis
Most children will have no physical signs; however, none will be found unless they are actively sought.

- Digital clubbing, signs of weight loss, failure to thrive
- Upper airway disease - enlarged tonsils and adenoids, prominent rhinitis, nasal polyps
- Unusually severe chest deformity (Harrison's sulcus, barrel chest)
- Fixed monophonic wheeze
- Stridor (monophasic or biphasic)
- Asymmetric wheeze
- Signs of cardiac or systemic disease

Table 3 Diseases which present as recurrent cough and wheeze

These conditions need to be considered and excluded prior to escalating therapy. Most will require referral if suspected in general practice.

- Upper airway disease — adenotonsillar hypertrophy, rhinosinusitis, postnasal drip
- Congenital structural bronchial disease — complete cartilage rings, cysts, webs
- Bronchial/tracheal compression — vascular rings and sling, enlarges cardiac chamber, lymph nodes enlarged by tuberculosis or lymphoma
- Endobronchial disease — foreign body, tumour
- Oesophageal/swallowing problems — reflux, incoordinate swallow, laryngeal cleft or tracheo oesophageal fistula
- Causes of pulmonary suppuration — cystic fibrosis, primary ciliary dyskinesia, any systemic immunodeficiency including agammaglobulinaemia, severe combined immunodeficiency
- Miscellaneous — bronchopulmonary dysplasia, congenital or acquired tracheomalacia, pulmonary oedema secondary to left-to-right shunting or cardiomyopathy

Table 4 Investigations to be considered in the child with recurrent cough and wheeze

A selective approach is necessary, depending on what clues have been elicited from history, examination and simple investigations. Most of these tests will be carried out only after referral to a specialist

- Suspected upper airway disease — polysomnography, RAST or skin prick tests (radiograph of postnasal space is rarely useful)
- Known or suspected neuromuscular disease with dysfunctional swallow — speech and language therapy assessment, which may be combined with videofluoroscopy
- Suspected oesophageal disease — pH probe, barium swallow, tube oesophagram, oesophagoscopy
- Suspected cystic fibrosis — sweat test, nasal potentials, genotype, stool elastase, three day faecal fat collection
- Suspected primary ciliary dyskinesia — saccharine test, nasal ciliary motility, electron microscopy including orientation studies, nasal and exhaled nitric oxide, culture of ciliary brush biopsy, genetic studies becoming available
- Suspected systemic immunodeficiency — immunoglobulins and subclasses, vaccine antibodies, lymphocyte subsets, lymphocyte and neutrophil function tests, HIV test, referral to Paediatric immunologist
- Suspected structural airway disease — fibreoptic bronchoscopy
- Suspected tuberculosis — Heaf test, fibreoptic bronchoscopy and/or gastric lavage, combined with culture and PCR; ELISPOT
- Suspected cardiovascular disease — echocardiogram, barium swallow to exclude a vascular ring or pulmonary artery sling, angiography (CT or MRI)
- Suspected bronchiectasis — high resolution CT scan, investigations for local or systemic immunodeficiency

unnecessary in the vast majority of infants with chronic cough and/or wheeze seen in the community. Furthermore, many of the conditions listed in Table 3 cannot be excluded by this investigation and require further tests (Table 4). I would suggest that — most often — either the diagnostic situation is clear cut, in which case a CXR is unnecessary, or it is not, in which case the child needs to be referred. There will be exceptions, and it may be deemed proper to request a CXR — for example, to reassure parents.

What type of "asthma"?

Not all that wheezes is asthma and not all that is labelled asthma is due to inflammation. Table 5 summarises the different asthma 'syndromes', but

Table 5 Features of the different 'asthma syndromes'
It should be noted that overlap syndromes are very common.

Preschool Asthma Syndrome	Inflammatory component	Extent of BHR component	Extent of PAL
1. Chronic lung disease of prematurity	? (probably none)	+	+ (antenatal onset)
2. Post-bronchiolitis (usually RSV)	? (probably none)	+	+ (antenatal onset)
3. Virus associated wheeze	—	—	+ (antenatal onset)
4. Atopy associated wheeze	+ (probably often eosinophilic)	+	+ (probably antenatal and postnatal onset)
5. Obliterative bronchiolitis (e.g. post adenoviral infection)	—	—	+ (postnatal onsetl)
6. Non-atopy associated, later onset wheeze	?present, ?type	Probably present	+ (probably at least postnatal onset)

BHR = Bronchial hyper-reactivity; PAL = persistent airflow limitation; RSV = respiratory syncytial virus

it should be noted that overlap syndromes are probably the commonest. Two areas of controversy relate to the pathophysiology of VAW and whether cough variant asthma exists.

What causes VAW?

There is increasing evidence that the main problem is due to *in utero* airway maldevelopment. Summarising this evidence, three separate studies have shown that babies born to mothers who smoke, or who are atopic, or (interestingly but with no explanation) have hypertension in pregnancy, have abnormal lung function shortly after birth, presumably a reflection of an abnormal intra-uterine process.[19-21] Three prospective studies (Tucson, Boston, Perth) showed that in babies with VAW, lung function was abnormal prior to the first episode of wheeze.[22-24] Unlike in older children and adults, two studies showed no evidence of bronchial hyper-reactivity in VAW.[25,26] A double blind trial showed that VAW does not respond to inhaled steroids.[27] In a study using blind bronchoalveolar lavage at the time of routine paediatric surgery, there were no eosinophils in the lavage of children with VAW, quite different from atopic asthmatics.[28,29] One is forced to the conclusion that VAW is nothing to do with eosinophilic inflammation, and should not be treated the same way.

Unfortunately, many infants do not fit neatly into the categories of either non-atopic VAW, or majorly atopic interval and viral-associated symptoms. Even many atopic wheezers will outgrow their symptoms within a few years.[30] It is easy in retrospect to allocate the preschool infant to one of the Tucson categories (transient wheeze, persistent wheeze), but the GP faced with a wheezing infant has to use clinical judgment to decide on best treatment and likely prognosis.

Does cough variant asthma exist?

Cough is undoubtedly a common symptom of asthma; can it be the only symptom, and if so, how commonly? The answer will be different, depending on the setting in which the question is posed. There is no doubt that large epidemiological studies show that *in a community setting*, where by definition the vast majority of children are well, isolated cough is rarely due to asthma and rarely responds to asthma medications.[31,32] There is also no doubt that isolated cough may frequently be over-diagnosed as asthma.[33] Chronic non-specific cough frequently improves with time and without treatment.[34,35] However, in a specialist clinic, where a highly selected group of children are seen, children who cough in response to typical asthma triggers, and improve when treated with asthma medications are not uncommonly seen.[36] My diagnostic criteria are:

1. Abnormally increased cough, and also episodes of breathlessness and respiratory distress, with no evidence of any non-asthma diagnosis
2. Clear-cut response to a therapeutic trial of asthma medications (see below)
3. Relapse on stopping medications with second response to recommencing them

Many children with chronic cough have only a non-specific problem, and have been shown on bronchoscopic and blind lavage studies to have no evidence of eosinophilic airway inflammation.[29,37] Follow up studies show that most will get better over 1-2 years. Others, however, will show evidence of deterioration of BHR over time, wheeze, and develop the picture of classical asthma.[38] If coughing is troublesome and the precautions outlined above are followed, then there is little to be lost attempting a brief therapeutic trial. The only danger is that ineffectual and potentially harmful medication may be continued long term unless a trial off therapy is rigorous. In older children who can perform lung function, there is no justification for a therapeutic trial without making every attempt to document variable airflow obstruction.

Therapeutic trials: in whom, with what?

Ultimately, after a detailed evaluation, diagnostic doubt may remain and the question of a therapeutic trial is raised.[2] If the main problem is cough and wheeze at the time of viral colds, and the GP is satisfied that the symptoms are sufficiently outside the normal range such that treatment is indicated, then intermittent bronchodilator therapy with either an anticholinergic or beta-2 agonist is suggested. Both medications may be tried: despite popular belief that there are no beta receptors in the airway under one year of age, there is definite physiological evidence that at least some children respond to inhaled beta-agonists.[39] The drug delivery device should be a mask and spacer, with appropriate instruction in use (Table 6). If this is ineffective, and the possibility of an 'asthma syndrome' is still being considered, then intermittent, very high dose inhaled steroids may be tried[40] (for example, budesonide 1 mg bd for 5 days with viral colds) or intermittent montelukast,[41] 4 mg for one week at the time of viral colds. These last may be combined if neither alone is sufficient. As with much therapeutic endeavor in this age group, the evidence base is weak.

If intermittent therapy is unsuccessful, or thought to be inappropriate because the symptoms are chronic, what about a trial of prophylactic medication? There is an important decision to be made first; are the symptoms sufficiently severe as to justify daily therapy? There might be two reasons to prescribe daily inhaled corticosteroids to preschool children: firstly, for present relief of symptoms; and secondly, to prevent progression from intermittent to continuous wheeze. There have been at least four randomised controlled trials[42-45] which have shown quite clearly that early institution of inhaled or nebulised corticosteroids have no impact on disease progression. Therefore, the only reason to prescribe regular inhaled corticosteroids is if the present severity of the condition merits them; there is no evidence that withholding them will compromise future lung function. Indeed, even in adults the pendulum is swinging away from early institution of inhaled corticosteroids for the mildest asthma patients.[46]

If intermittent therapy is unsuccessful, and the symptoms are of sufficient severity, then a trial with a continuous anti-inflammatory medication (inhaled corticosteroid, leukotriene receptor antagonist) should be considered. It may seem illogical to use a prophylactic inhaled steroid in VAW, but occasionally a trial of inhaled steroids may be merited under carefully circumscribed conditions, particularly if the child is suffering multiple, very severe episodes. Occasionally, there is a dramatically beneficial effect, and the family

Table 6 Proper use of spacers in pre-school children

Instruction	Comment
Shake inhaler between each activation	Multiple activations reduce drug delivery
No delay between activating inhaler and applying mask to face	Delay leads to medication being adsorbed onto sides of chamber and not inhaled
Do not give to crying infants	There will be no drug delivered to the airways, even though the infant appears to be inhaling deeply
Wash (non-metal) spacers weekly with washing up liquid, do not rinse or rub dry	Minimizes medication adsorption onto sides of chamber

realizes that in fact the child had interval symptoms that were not appreciated until they were treated. The other circumstance under which I would consider a therapeutic trial is in the child with non-specific chronic symptoms, especially if atopic.

The choices would appear to be either inhaled bronchodilators, oral leukotriene receptor antagonist, inhaled corticosteroids, or oral steroid. Cromoglycate is not useful in preschool children[47] There are no real evidence-based data to guide the clinician in this dilemma; my own practice is to use moderately high dose inhaled steroids (for example, budesonide 800 mcg/day) via a spacer, with a mask if age-appropriate. If the child does not show any response, then asthma is a highly unlikely diagnosis. The alternative choices for a therapeutic trial would be high dose beta-2 agonists, montelukast, or oral prednisolone. It is true that asthmatics should show some response to bronchodilators, but it is likely that if they fail, a trial of a more potent medication is likely to be performed to ensure that asthma can be ruled out, and the beta-2 agonist trial only delays matters. Oral steroids are effective in asthmatics, but also treat allergic rhinitis and temporarily reduce the size of the adenoids, and so are not specific for lower airway inflammation — as well as having a greater potential for side-effects. Montelukast may also treat upper airway symptoms,[48] but in reality there is no evidence base to choose between this medication and inhaled corticosteroids.

If the symptoms disappear after two to three months on inhaled steroids, the treatment must be stopped to ensure that the child has not improved coincidentally, after, for example, prolonged post-mycoplasma or post-viral cough. Only if symptoms recur on stopping inhaled steroids can the diagnosis of a steroid responsive 'asthma syndrome' be said to be established, and long-term treatment instituted provided symptom severity merits it. It should be noted that, even in groups of pre-school children highly selected as being at high risk for asthma, the actual symptom benefit was not impressive.[43]

Finally, if there is no response to an appropriate therapeutic trial, and symptoms continue, then referral to a paediatrician with special expertise in respiratory medicine should be considered.

Conclusions

A careful history and physical examination, with judicious use of therapeutic trials, will enable most children with cough and wheeze under the age of five to be managed successfully. There is still a need for more research to help us identify which children with early onset wheeze have airway inflammation which requires treatment in order to prevent an adverse outcome, and we need more research to help us find a treatment which, unlike inhaled corticosteroids, is disease modifying. Currently there are three indications for referral:

1. If the diagnosis is in doubt
2. If the treatment is not working
3. If any party (GP or family) is not happy

Observance of these rules should allow one to avoid most diagnostic blunders.

Conflict of interest declaration

Andrew Bush has received fees for lecturing and expenses for attending International meetings, from GSK, AZ, Altana and MSD.

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