

CMEARTICLE

Recurrent wheeze and cough in young children: is it asthma?

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Three-year-old Sam came with his father to see you for a troublesome cough that had not “gone away” for the past four weeks. Sam had been given cough syrups and repeated courses of antibiotics, which did not cure him. This was not the first episode, as Sam had been having frequent ‘colds’ since he was two-and-a-half years old, notably after attending a childcare centre. On examination, he had chronic eczema involving the flexures, but no wheezing on lung auscultation. There were no signs of respiratory distress, added heart sounds or clubbing.

WHAT IS RECURRENT WHEEZE AND COUGH?

Although recurrent wheeze and cough are commonly presented to the family physician, there is currently no standard definition for it. Some authors have defined recurrent wheeze as more than one episode of wheeze within the last 12 months⁽¹⁾ and recurrent cough as two or more episodes of cough without a cold in the past year.^(2,3) Guidelines by the American College of Chest Physicians (ACCP)⁽⁴⁾ and Thoracic Society of Australia and New Zealand (TSANZ)⁽⁵⁾ have categorised cough according to duration (e.g. acute, chronic) rather than frequency. Recurrent cough that is frequent with short intervals of resolution is difficult to distinguish from persistent chronic cough.⁽³⁾

HOW RELEVANT IS THIS TO MY PRACTICE?

Many preschool children present to the primary care practitioner with recurrent wheeze and cough.^(6,7) These symptoms cause considerable morbidities and can lead to treatment with inhalers, antibiotics or cough mixtures, hospitalisations and considerable healthcare costs.⁽⁸⁾

A clinical diagnosis of asthma is often considered in a child with prolonged cough, particularly if there is associated wheezing and chest tightness.⁽⁹⁾ Although asthma is a common cause of cough and wheeze in children⁽¹⁰⁾ and the leading cause of childhood morbidity,⁽¹¹⁾ episodic cough and wheezing is also common in nonasthmatic children.⁽¹⁰⁻¹⁵⁾ Although approximately 40% of all young children worldwide have at least one episode of asthmatic symptoms such as wheezing, coughing or dyspnoea,^(14,16) only 30% of preschoolers with recurrent wheezing are eventually diagnosed with asthma at the age of six years.⁽¹⁷⁾

Other conditions that cause cough and wheeze have been misdiagnosed as asthma.⁽¹⁰⁾ Misdiagnosis has led to the commencement of inhaled corticosteroids (ICS), resulting in

some children developing significant steroidal side effects.⁽¹⁸⁾ Therefore, caution is needed in order to avoid inappropriate diagnosis and prolonged ICS therapy. On the other hand, asthma in early childhood is frequently underdiagnosed, resulting in children not receiving timely or adequate therapy.⁽¹⁹⁾ Furthermore, diagnosis is complicated by the difficulty in obtaining objective measurements of lung function in this age group.⁽²⁰⁾ Major global guidelines⁽²¹⁻²⁴⁾ that address the diagnosis and management of asthma in young children have acknowledged this difficulty in establishing a firm diagnosis of asthma in children under the age of five years. This article focuses on the key points that a primary care practitioner should consider in making a diagnosis of asthma in a young child.

DIAGNOSING ASTHMA IN YOUNG CHILDREN

A careful history-taking of symptomatology, triggers, family history-taking and physical findings is pertinent to the evaluation of a child suspected to have asthma.⁽⁹⁾

Symptomatology and triggers

Wheeze

Wheeze is the most common symptom associated with asthma in children aged five years and younger.⁽¹⁰⁾ Wheezing in early childhood is predominately linked to viral infection.⁽²⁵⁻²⁷⁾ While some infants with recurrent wheeze eventually develop asthma, a large proportion stop wheezing by school age and outgrow the symptoms.⁽¹⁷⁾ Since many children wheeze due to viral infections, ascertaining whether asthma is the cause of the recurrent wheezing is a challenge. Early childhood wheezing has been phenotypically categorised as episodic (viral) wheeze and multiple-trigger wheeze.⁽²²⁾

Episodic (viral) wheeze refers to wheezing during discrete episodes in association with a viral respiratory illness, with

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absence of wheeze during the interval in-between episodes. Multiple-trigger wheeze refers to wheezing that occurs during discrete exacerbations and intervals between viral infections, possibly due to other triggers such as crying, laughter and exercise. The likelihood of asthma was noted to be much lower in children with episodic (viral) wheeze compared to children with multiple-trigger wheeze who wheezed during and in between episodes of viral infections (interval symptoms).

Thus, it is important to ask parents whether the child wheezes only during a cold (viral infection), during sleep, or when there are other triggers such as cigarette smoke, allergens, exercise, laughing or crying. In infants and toddlers, crying and laughing are an exercise equivalent.⁽²³⁾

Cough

While diagnosis of asthma is easier in a child who presents with wheezing, cough and breathlessness, it is more challenging when recurrent cough presents in the absence of wheeze. Results of questionnaire-based surveys of parents suggest that the prevalence of recurrent cough in the absence of wheeze in children is high and ranges from 5% to 10% at any one time.⁽²⁸⁾ Children presenting with recurrent cough have been labelled as having 'cough-variant asthma', which had led to some being inappropriately treated for asthma.⁽²⁹⁾ Evidence supports the view that in the absence of wheeze or dyspnoea, very few children with nonspecific isolated cough have asthma.^(2,29,30)

According to the GINA (Global Initiative for Asthma) guidelines,⁽²³⁾ cough that (a) occurs in the absence of a viral respiratory infection; (b) is triggered by exercise, laughing or crying; or (c) occurs when the child is asleep (nocturnal cough) strongly supports a diagnosis of asthma. However some studies have shown that in the absence of wheeze and dyspnoea, neither the presence of nocturnal cough^(2,30,31) nor cough triggered by vigorous exercise⁽²⁹⁾ was useful for ascertaining whether a child has asthma. In addition, exercise-induced cough has been shown to be a poor predictor of bronchoconstriction.⁽³²⁾

Nonetheless, considering asthma as a diagnosis in the absence of wheeze is not unjustified. If the child is not wheezing during consultation, accurate identification of wheeze from history-taking alone can be difficult.^(22,33,34) This is because parental understanding of wheeze may differ from that of the doctor and wheeze can be underrecognised by parents.⁽³⁴⁻³⁹⁾

If ICS are used as a therapeutic trial in children who present solely with recurrent cough in the absence of wheeze, it is preferable to cease rather than escalate treatment if there is no response. Also, for children with an established diagnosis of asthma, cough should not be used as the predominant symptom to direct asthma therapy.⁽²⁹⁾

Personal and family history of atopy

Numerous studies have linked family history of atopy (particular maternal asthma) and atopic manifestations in the

child as risk factors for the development of asthma in preschool children who wheeze.

Maternal asthma was shown to be an independent risk factor for persistent wheezing in the Tucson study.^(14,17) A large population-based Finnish study⁽⁴⁰⁾ found maternal asthma to be the strongest predictor of childhood asthma, while a school-based study of Southern Californian children⁽⁴¹⁾ reported that parental and sibling history of asthma and allergy was most strongly associated with the risk of early-onset persistent asthma. Data from a longitudinal study of Australian children⁽⁴²⁾ also identified maternal asthma, among other factors, as an independent risk factor for the development of asthma during infancy. Other independent risk factors included male gender, young maternal age and maternal smoking during infancy.

The Alspac study⁽⁴³⁾ found that in children who started wheezing before the age of six months, atopic eczema and parental history of asthma were important risk factors, both for development of wheeze and its persistence beyond six months. Kurukulaaratchy et al reported that the presence of eczema, allergic rhinitis and parental or sibling history of asthma in childhood wheezers conferred significant risk of wheeze persisting until schoolgoing age.⁽⁴⁴⁾

Key clinical signs⁽²⁴⁾ that suggest an atopic phenotype include the following:

- Atopic eczema or dermatitis
- Dry skin
- Dark rings under the eyes (allergic shiners)
- Irritated conjunctivae
- Persistent oedema of the nasal mucosa, nasal discharge, 'allergic salute' and 'allergic crease' on the bridge of the nose.

The presence of atopic dermatitis, allergic rhinitis and parental asthma, and wheezing apart from colds are used as major and minor criteria in the Asthma Predictive Index (API).^(45,46) According to the GINA guidelines,⁽²³⁾ API is a simple clinical criterion-based tool developed using data from the Tucson (USA) Children's Respiratory Study,⁽¹⁷⁾ which has been shown to predict the presence of asthma in later childhood. Castro-Rodríguez et al's study has shown that a child with a positive API has a 4- to 10-fold greater chance of developing asthma between the ages of 6 and 13 years, while 95% of children with a negative API remained asthma-free.⁽⁴⁵⁾ A modified version of the index, the modified API (mAPI), applies the criteria in children with four or more wheezing episodes per year to predict the risk of developing asthma at schoolgoing age. The mAPI criteria are listed in Table I. Chang et al's study⁽⁴⁷⁾ concluded that mAPI can aid clinical decision-making in assessing future asthma risk in preschool-age children.

mAPI was used as entry criteria for the PEAK (Prevention of Early Asthma in Kids) trial,⁽⁴⁸⁾ which showed improved outcomes in terms of exacerbations, controller medication usage and episode-free days in the cohort treated with ICS as compared to those treated with a placebo. Although the application of the

Table I. Modified Asthma Predictive Index.

FOUR OR MORE wheezing episodes per year AND	
At least ONE major criteria	OR At least TWO minor criteria
1. Physician diagnosis of atopic dermatitis at age 2 or 3 yrs	1. Physician diagnosis of allergic rhinitis
2. History of physician diagnosis of asthma in a parent	2. Wheezing apart from colds
	3. Eosinophilia (4%)

Table II. Red flags requiring further evaluation.

<ul style="list-style-type: none"> • Symptom onset from birth or neonatal period. • Respiratory symptoms associated with feeds or vomiting. • Recurrent productive cough suggestive of chronic suppurative lung disease. • Failure to thrive. • Failed therapeutic trial with conventional therapy. • Clinical findings suggesting alternative diagnoses, e.g. finger clubbing, heart murmurs or focal lung signs. • Underlying neurodevelopmental disease. • Parental anxiety or need for reassurance.

mAPI in our primary care setting may be limited, knowing the criteria used in the index reinforces the importance of history-taking for frequent wheezers. The clinical challenge comes when there are less frequent episodes of wheeze, less obvious family history and difficulty in characterising the child's symptomatology.

Therapeutic trial

In children with troublesome symptoms, particularly those with four or more wheezing episodes a year, a therapeutic trial in the form of low-dose ICS may aid in the diagnosis of asthma.⁽²¹⁻²³⁾ The child should be closely monitored for improvement of symptoms. Treatment should be stopped if a clear beneficial effect is not obvious within four to six weeks despite correct device technique and adherence to inhaled medication, and the diagnosis re-evaluated. If there is a clear and positive response for at least three months, a stepdown in therapy should be undertaken to the lowest possible dose of medication required to maintain asthma control.⁽²²⁾ Diagnosis of asthma is supported by clear improvement in symptoms with treatment and worsening upon cessation. The therapeutic trial may need to be repeated more than once in order to ascertain the diagnosis, due to the variable disease nature in young children.⁽²³⁾

Features that prompt alternative diagnosis

The primary care practitioner should be alert to the presence of unusual or atypical features that would suggest another underlying condition. Neonatal or very early onset of symptoms suggests congenital causes of airway obstruction, such as

tracheomalacia or bronchomalacia.⁽⁴⁹⁾ Children with underlying neurodevelopmental disease that is associated with impaired swallowing and recurrent aspirations may also wheeze.^(49,50) Wheezing that occurs after feeds or is associated with vomiting may be related to gastro-oesophageal reflux disease.⁽⁴⁹⁾

Failure to thrive in a child with persistent respiratory symptoms may be associated with recurrent pneumonia as a result of a significant underlying disease such as cystic fibrosis, immunodeficiency, primary cilia dyskinesia, cardiac disease, gastro-oesophageal reflux disease or congenital malformation.⁽⁵¹⁾ Recurrent productive cough may be indicative of underlying suppurative lung disease. It is noteworthy that asthma misdiagnosis was noted to be common in children with persistent bacterial bronchitis or bronchiectasis.⁽⁵²⁾

Children whose wheezing symptoms are refractory to conventional asthma therapies should be referred for further evaluation.⁽⁵³⁾ Children with finger clubbing, focal lung or cardiovascular signs, which suggest an alternative diagnosis, should be referred for further investigations.⁽¹²⁾ Table II summarises some 'red flags' requiring further evaluation.

Additional diagnostic tests

Asthma can be clinically diagnosed, but where indicated, further investigations may include chest radiography, tests for atopy and lung function tests. Chest radiography may help rule out structural abnormalities, chronic infection (e.g. bronchiectasis, tuberculosis) or other diagnoses.⁽⁵⁰⁾ Objective assessment of atopy (e.g. by serum quantitation of allergen-specific immunoglobulin E) may aid diagnosis of asthma.^(54,55) Lung function tests do not play a major role in the diagnosis of asthma in younger children due to their inability to perform reproducible manoeuvre. Unlike routine measurement of peak flow in a clinic by the attending physician, most tests in preschool children may require trained technicians and specialised laboratory equipment.⁽²⁰⁾

You confirmed that Sam has a positive family history of asthma and that he had previously experienced relief of his breathlessness after using his sibling's salbutamol inhaler. You discussed with Sam's father on how you arrived at Sam's diagnosis of asthma, his possible trigger factors, and your plan for a therapeutic trial of inhaled beclomethasone 200 mcg twice daily, given via a pressurised metered dose inhaler and a spacer (with a face mask). You also advised the father on how to make use of the written asthma action plan (WAAP) to help him better manage his son. At Sam's scheduled review four weeks later, his cough had disappeared, and he was able to sleep through the night and run without coughing. His self-reported Asthma Control Test (for children) indicated good control, and the agreed plan was to step down the dose of inhaled beclomethasone to 100 mcg twice daily.

TAKE HOME MESSAGES

1. Wheezing in preschool children is predominately linked to viral infections.
2. Episodic cough and wheezing is common in non-asthmatic children, and misdiagnosis can lead to ICS being started, resulting in significant side effects.
3. Early childhood wheezing has been phenotypically categorised as episodic (viral) wheeze and multiple-trigger wheeze.
4. Children with multiple-trigger wheeze are more likely to have asthma compared to those with episodic (viral) wheeze.
5. It is important to look for atopic features, assess family history and ask parents whether wheeze occurs only during colds (viral infections) or also in response to other triggers such as cigarette smoke, allergens and exercise.
6. In the absence of wheeze or dyspnoea, very few children with nonspecific isolated cough have asthma.
7. Asthma should still be considered as a diagnosis in a child with isolated cough because accurate identification of wheeze from history-taking can be difficult.
8. A therapeutic trial with low-dose inhaled corticosteroids can aid in the diagnosis of asthma.
9. The primary care practitioner should be alert to the presence of unusual or atypical features (red flags) that would suggest another underlying condition.
10. Children whose wheezing symptoms are refractory to conventional asthma therapies should be referred for further evaluation.

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ABSTRACT A clinical diagnosis of asthma is often considered when a child presents with recurrent cough, wheeze and breathlessness. However, there are many other causes of wheeze in a young child. These range from recurrent viral infections to chronic suppurative lung disease, gastro-oesophageal reflux disease and rare structural abnormalities. Arriving at a diagnosis includes taking into consideration the symptomatology, triggers, atopic features, family history, absence of red flags and therapeutic trial, where indicated.

Keywords: asthma, childhood wheeze, diagnosis, primary care practitioner

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SINGAPORE MEDICAL COUNCIL CATEGORY 3B CME PROGRAMME

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	True	False
1. A large proportion of early childhood wheezers eventually develop asthma at schoolgoing age.	<input type="checkbox"/>	<input type="checkbox"/>
2. Maternal smoking during infancy is not a risk factor for developing asthma.	<input type="checkbox"/>	<input type="checkbox"/>
3. Trigger factors in children with episodic wheeze include cigarette smoke, allergens and exercise.	<input type="checkbox"/>	<input type="checkbox"/>
4. Risk of asthma is higher in children with multiple-trigger wheeze compared to episodic wheeze.	<input type="checkbox"/>	<input type="checkbox"/>
5. The presence of eczema in childhood wheezers confer significant risk of the wheeze persisting until schoolgoing age.	<input type="checkbox"/>	<input type="checkbox"/>
6. Lung function tests can reliably aid diagnosis of asthma in preschool children.	<input type="checkbox"/>	<input type="checkbox"/>
7. Exercise-induced cough has been shown to be a poor predictor of bronchoconstriction.	<input type="checkbox"/>	<input type="checkbox"/>
8. Asthma is still a possible diagnosis in cases where wheezing is not reported.	<input type="checkbox"/>	<input type="checkbox"/>
9. In children who cough but do not wheeze, treatment should be escalated if there is no response to a trial of inhaled corticosteroids.	<input type="checkbox"/>	<input type="checkbox"/>
10. Diagnosis of asthma is supported by worsening of symptoms upon cessation of inhaled corticosteroids.	<input type="checkbox"/>	<input type="checkbox"/>
11. Cough should not be used as the predominant symptom to direct asthma therapy, even in children with an established diagnosis of asthma.	<input type="checkbox"/>	<input type="checkbox"/>
12. Therapeutic trial with inhaled corticosteroids should be continued for at least six months in order to see whether there is a clear beneficial effect.	<input type="checkbox"/>	<input type="checkbox"/>
13. If there is a clear and positive response for at least three months, a step-down in therapy should be undertaken to the lowest possible dose of medication required to maintain asthma control.	<input type="checkbox"/>	<input type="checkbox"/>
14. A therapeutic trial may need to be repeated more than once in order to confirm the diagnosis.	<input type="checkbox"/>	<input type="checkbox"/>
15. Neonatal onset of wheeze is an indication for referral for further evaluation.	<input type="checkbox"/>	<input type="checkbox"/>
16. Children with underlying neurodevelopmental disease associated with impaired swallowing and recurrent aspirations should be considered for a therapeutic trial of inhaled corticosteroids.	<input type="checkbox"/>	<input type="checkbox"/>
17. Failure to thrive may signify underlying alternative diagnosis.	<input type="checkbox"/>	<input type="checkbox"/>
18. Asthma misdiagnosis was noted to be common in children with persistent bacterial bronchitis or bronchiectasis.	<input type="checkbox"/>	<input type="checkbox"/>
19. Objective assessment of atopy by serum quantitation of allergen-specific immunoglobulin E is not useful for diagnosis of asthma in preschool children.	<input type="checkbox"/>	<input type="checkbox"/>
20. Pulmonary function tests can be routinely done in preschool children.	<input type="checkbox"/>	<input type="checkbox"/>

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