

THE WHEEZY INFANT AND TODDLER ASTHMATIC – A PRIMARY CARE APPROACH

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ABSTRACT

Wheeze is common in infants and young children. Asthma is but one cause and it is obviously important to exclude or include as it is amenable to specific therapy. It is also obvious that the pre-school or young child is not just a smaller variety of the older child or adult and this is especially true of asthma, where special situations exist with regard to diagnosis and treatment. Although there is a differential diagnosis for the major symptoms that constitute asthma in this age group, no child should be left to wheeze or cough without the possibility of asthma being considered and excluded. New guidelines and reports suggest that differentiation of virally induced wheeze from multi-trigger wheeze (or toddler asthma) is less important than making an attempt to manage the child. If an infant, or young child, has a chronic wheeze and is atopic or responds to a bronchodilator, asthma is more likely and therapy should be tried. If, however, there is no response to the therapy, investigate for other causes. Remember that in South Africa wheeze may also be produced by chronic infections, gastro-oesophageal reflux, cardiac failure, cystic fibrosis and a host of other sinister conditions. Therapeutically, for mild and intermittent wheeze the choice of inhaled corticosteroid (ICS) or a leukotriene antagonist may be valuable options. Therapy is intermittent and should be started pre-emptively. However, for more severe and frequent symptoms regular use of ICS (moderate dose) is clearly the best therapeutic option.

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INTRODUCTION

One-third of all children have had a wheezy illness by their third birthday. Most are caused by viral triggers.¹ However, in patients diagnosed with asthma, symptoms start in the pre-school years in 80% of cases.¹ And this is the basis for both the under-treatment of pre-school/toddler asthma and the over-treatment of pre-school wheeze.

WHAT IS A WHEEZE?

A wheeze is a high-pitched musical sound usually on expiration and it is associated with increased work of breathing.² Wheeze is produced by a narrowing of intra-thoracic airways and usually small airways.

However, the term 'wheeze' is often mis-classified and mis-identified by parents. Control of asthma symptoms is correlated best with composite scores of symptoms rather than wheeze only. Audible wheeze occurs late in airway obstruction and there is no data on the sensitivity or specificity of the term 'wheeze'. Cough correlates with lung function and atopy in pre-schoolers similar to and independent of wheeze.³ Therefore it may be more important in children to use the term 'recurrent troublesome lung symptoms' to describe important chest events.

EPIDEMIOLOGICAL DESCRIPTIONS OF RECURRENT WHEEZE

Wheeze, as a symptom, is common in children of all ages and is often the reason for presentation of a child to a doctor. In the mid-1990s Martinez et al published an epidemiological audit of the outcome of wheezing in childhood.⁴ They classified wheezing into three distinct categories based on outcome:

- transient early wheezing was wheezing in the first three years of life which resolved;
- late-onset wheezing was no wheezing during the first three years of life, but onset during the fourth year;
- persistent wheezing was wheezing continuing from early onset beyond five years of life.

This epidemiological study has documented that, the main wheeze in young children is often not due to asthma, whereas a wheezy older child may well have asthma. Transient (limited to a few months or years) wheezing in infancy is more likely to be a function of small airways,⁴ and wheezing in the first year of life does not persist as asthma in two-thirds of those afflicted.⁴ Recent experimental evidence has shown that it may be possible to predict asthma from lung-function testing of wheezers at three years of age but clearly this is not a

tool routinely available in clinical practice.² Unfortunately, this classification is not helpful in managing wheeze in the clinical setting and in the individual child.

Another publication by a European Respiratory Society (ERS) Task Force in 2008 suggested that the differential diagnosis of recurrent wheeze in pre-schoolers should include two phenotypes:¹

- viral-induced wheeze, and
- multi-trigger wheeze (MTW).

The differences between these two groups are illustrated in Tables I and II.

TABLE I: VIRAL-INDUCED WHEEZE¹

- Wheezing during discrete episodes;
- Usually associated with a viral trigger;
- No symptoms in between;
- Outcome:
 - declines by the age of six;
 - continues into childhood;
 - becomes MTW.

TABLE II: MULTI-TRIGGER WHEEZE¹

- Wheeze during discrete episodes;
- Also symptoms in between episodes;
- URTI usually the trigger;
- But wheeze in response to other triggers:
 - exercise;
 - inhaled allergens;
 - environmental tobacco smoke;
- Possible evolution to asthma but poor evidence to support this.

The major problems with that report were twofold. Firstly, the broad classifications failed to classify correctly many children who wheezed (as wheezing in pre-schoolers may exist on a spectrum of disease as opposed to two distinct clinical entities). Secondly, the majority of the Task Force agreed not to use the term 'asthma' to describe pre-school wheezing illness since there is insufficient evidence showing that the pathophysiology of pre-school wheezing illness is similar to that of asthma in older children and adults. This created much confusion in deciding on treatment principles for individual children.

The symptom of wheeze causes a significant diagnostic dilemma in the very young child because as a recurrent or persistent problem there are a number of important causes, not all of which are amenable to specific therapy (see Table III).

TABLE III: CAUSES OF CHRONIC WHEEZING IN INFANCY

- Small airways;
- Asthma;
- Post-bronchiolitis;
- Cystic fibrosis;
- Chronic infections;
- Gastro-oesophageal reflux;
- Immune deficiency;
- Foreign body;
- Cardiac pathology;
- Lymphadenopathy due to TB, HIV.

CAUSES OF WHEEZING IN INFANCY

The first episode of wheezing in the first year of life is likely to be labelled 'bronchiolitis', a specific acute inflammatory disease of the bronchi caused by the respiratory syncytial virus (RSV), rhinovirus (RV) and, less commonly, other viruses.⁵ This condition is short-lived, associated with a mild upper respiratory tract infection, low-grade fever and hyperinflation of the chest and may be quite profound. Many studies have investigated the treatment of acute viral bronchiolitis and the only therapy that is recommended is oxygen for hypoxic infants.⁶ No medical therapies are of any value.⁶

The close relationship between atopy and viruses is such that atopy probably predisposes to a sensitivity of the airway to viruses, which are the most important triggers of acute exacerbations of asthma in younger children and infants.⁷ RSV infection can predispose to asthma, but this may be due to a pre-existing immune disorder predisposing to allergy and infection.⁸ Alternatively, it may be possible that RSV bronchiolitis damages the airway epithelium to the degree that other aero-allergens gain easier access to inflammatory cells, thereby setting in motion the immune model for asthma (through the TH₂ pathway).⁸ Certainly, it has been shown that RSV bronchiolitis severe enough to cause hospitalisation is a risk factor for allergic asthma in early adolescence.⁹

In South Africa the concept of 'wheezy phenotypes' is not applicable to a large percentage of the population who wheeze in response to other significant diseases (see Table III). Here a clue to many is the failure to thrive or poor weight gain. Other history and examination clues are found in the markers of specific diseases, such as stigmata of AIDS, tuberculosis, congenital cardiac disease, cystic fibrosis and gastro-oesophageal reflux. A careful examination is mandatory on an infant who is wheezing. Most of these significant diseases are marked by associated signs. They should not be missed. A chronic cough (CC) in a young child will create the same diagnostic dilemma, and again a differential diagnosis is important, especially in the child who is failing to thrive, has a cardiac murmur or vomits regularly, when HIV-associated infections, a congenital cardiac abnormality or gastro-oesophageal reflux are likely.

WHEN IS PRE-SCHOOL WHEEZE ASTHMA?

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation causes an associated increase in airway hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment.¹⁰ More simply, 'Asthma should be diagnosed in a child with a CC or wheeze who responds to a bronchodilator (asthma therapy)'.¹¹

TABLE IV: FEATURES SUGGESTIVE OF ASTHMA IN CHILDREN <5 YEARS**EVIDENCE A**

Exercise-induced cough or wheeze;
Cough at night;
Symptoms persisting after the age of 3 years.

EVIDENCE B

Absence of seasonal variation;
Symptoms worsening with certain exposures;
Colds repeatedly going to the chest;
Response to a bronchodilator;
Response to a course of steroids;
Concomitant rhinitis, eczema or food allergies;
Family history of allergy or asthma.

EVIDENCE C

Wheezing more than 1 month.

EVIDENCE D

Modified bronchodilator response test.

Despite the epidemiological classification of wheezy youngsters, the diagnostic approach to these children is poorly described. In view of the uncertainty of diagnosis and heterogeneity of wheezing phenotypes in young children, when deciding about appropriate management of recurrent wheezing in children under the age of five years it is useful to check the following clinical points (see Table IV). These clinical points indicate a diagnosis of 'asthma' rather than other causes of wheezing.¹²

Publication of the 'Asthma Prediction Index',¹³ which makes use of features of atopy to diagnose asthma, has helped and suggests that asthmatic versus viral wheezers are more likely to be atopic. Another useful diagnostic tool for diagnosing asthma is the 'Modified Bronchodilator Response Test' (MBRT). In this test a patient suspected of having asthma (often a young child with persistent or recurrent wheezing) is given a bronchodilator by nebuliser or MDI with spacer and the symptoms/signs are evaluated 10–15 minutes later. Only asthmatics have sufficient bronchial hyper-responsiveness to respond to a bronchodilator. Most other causes of wheezing in young children will not respond. In these children further testing (such as a chest X-ray) may be useful.

In an older child the diagnosis of asthma must be made based on a typical history and examination, followed by a demonstration of reversibility:

- FEV₁ increase > 12% with bronchodilator;
- FEV₁ decline > 15% during an exercise challenge;
- positive metacholine challenge test;
- role of exhaled nitric oxide (FeNO) is controversial.

TABLE V: CRITERIA FOR DIAGNOSING ASTHMA IN THE PRE-SCHOOL CHILD

- Wheeze on exercise or illness in between viral illness;
- History of other allergic disorders – allergic rhinitis or eczema;
- Family history of asthma;
- Response to controller therapy and worsening on cessation.

The GINA Guideline of 2015¹⁴ made the point that there is agreement that asthma in the pre-school child is a difficult diagnosis to make and that differentiation into phenotype should not be the aim – as the clinical significance of this is uncertain. Asthma is more likely if the criteria in Table V are met.

TREATMENT OF PRE-SCHOOL WHEEZE AND ASTHMA

The literature is full of algorithms for the management of both chronic and acute asthma in children,^{12,14,15} but treatment of the pre-school or young child remains a problem. However, the principles of treatment remain the same, and it is as important to treat inflammation in the persistent chronic young asthmatic as it is in the older child and adult.

The key to treatment decisions in the local context depends on the therapeutic tools that are available for treating asthma and non-asthmatic wheeze in very young children. Unfortunately, until recently, our therapeutic armamentarium was severely limited. Most available anti-asthma therapies have been disappointing in their effect on pre-school wheeze. This is true for both bronchodilators and anti-inflammatory drugs.

Four recent meta-analyses have informed opinion that use of inhaled corticosteroids is better than montelukast in pre-school children.^{16–19} There are, however, clear guidelines here (see Table VI).

If the infant has a clear MTW and the criteria in Table VI are met, then first-line therapy should be regular ICS use: daily medium-dose ICS use is best.¹⁹ In the case of clear virally induced wheeze, either ICS (high-dose)¹⁹ or montelukast should be tried and titrated to clinical response. In this latter scenario, intermittent use (less than ten days) would be the first option. In addition, pre-emptive use (at the first sign of a 'cold') would be the best time to start.

The value of long-acting B₂ agonists in older children is controversial because they have not shown the same efficacy as in adults, and yet this is the group of patients where an alternative to ICS is particularly appealing. In the case of young children there is little information about these agents and their use is extrapolated from data for school-aged children and even adults. Recently, a retrospective study of young asthmatics demonstrated that the outcomes for young children with asthma are markedly

TABLE VI: WHEN TO TREAT PRE-SCHOOL CHILDREN WITH REGULAR INHALED CORTICOSTEROIDS²⁰

- Attacks are severe – requiring hospital admission;
- Attacks are frequent;
- Interval symptoms are being under-reported;
- Any controller therapy should be viewed as a trial of treatment and discontinued if there is no response;
- Taper down to lowest possible dose.

improved with a combination of fluticasone and salmeterol, but prospective studies are still required.²¹ Anecdotal clinical experience suggests that there is a place for their use but only once the dose of inhaled steroid is significant, the diagnosis of asthma is established and symptoms persist.

THE IMPORTANCE OF MANAGING INFANT WHEEZE CORRECTLY

Although quality of life and socio-economic factors are difficult to quantify in young children, this is an age group when recurrent illness and decreased activity will have a profound impact on the development and socialisation of the child. In a study conducted in Scandinavia, children less than two years of age accounted for 44% of annual inpatient asthma costs and children two to five years old for 31% of such costs, even though the former group made up only 1% of the asthma population and the latter group 27%.²²

Patients are often told that asthma in childhood is usually outgrown. This is not, however, the case and on average only about one-third of patients have some symptom relief, and then usually only at the time of puberty.²³ Many of these children, however, develop symptoms again in later life.^{24,25} For this reason it may be possible and even essential to reduce or stop therapy in adolescence but the patient and their parents should be alerted to the possibility of recurring symptoms.

Whatever therapy is ultimately chosen for managing asthma in the young child, it is important to meet the 'Goals of treatment' as set out in guidelines and ensure that quality of life is restored.

Professor Cas Motala was a scientist who kept the latest publications in mind when treating patients. However, more importantly, Cas was interested in people. He would always make sure children were treated as individuals and that therapy for infants and pre-school children who wheeze should be individualised and used only where it worked.

CONCLUSION

Wheeze is common in infants, young children and even older children. Asthma is but one cause and obviously important to exclude or include as it is amenable to specific therapy. It is also obvious that the pre-school or young child is not just a smaller variety of the older child or adult and this is especially true of asthma therapy, where special situations exist with regard to diagnosis and treatment. Although there is a differential diagnosis for the major symptoms that constitute asthma in this age group, no child should be left to wheeze or cough without the possibility of asthma being considered and excluded. This age group reveals many issues with regard to standard inhaled therapy, and for mild and intermittent wheeze the choice of ICS or a leukotriene antagonist may be valuable options. Consider intermittent use. However, for more severe and frequent symptoms regular use of ICS is clearly the best therapeutic option. The message seems simple: if an infant or a young child has a chronic wheeze and responds to a bronchodilator, asthma therapy should be tried. If there is no response to the MBRT, investigate for other causes.

DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interests.

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