WHEEZE AND ASTHMA IN THE VERY YOUNG

Insights on diagnosis and current care

Introduction
Defining asthma has proved to be a challenge over the decades and not very much progress has been made. Definitions have historically been based on the number of episodes of wheezing to make the diagnosis, driven by the belief that asthma was underdiagnosed. The pendulum has swung; asthma is now overdiagnosed.

Wheeze is common in the preschool age group. Data from the 1990s show that at age six years, 49% of children have had an episode of wheezing. Before the age of three years, 20% had one or more episodes of wheezing; 15% had one or more episodes after the age of three years; and 14% had wheezing episodes both before and after the age of three years (with persistent wheezing most likely to lead to asthma).1

At the Cipla Respiratory Symposium (Stellenbosch, 18 March 2018), Professor Felix Ratjen shared insights on the prediction of asthma from wheeze; and diagnosis and management of asthma in children of preschool age.

Key Messages
- Defining asthma has been, and remains, a challenge
- Wheezing is common in the preschool age group
- Different forms of wheezing during childhood may be associated with different risk factors and prognosis
- It is very difficult to predict the course of asthma symptoms in an individual over time
- Many different options are available for defining the asthma phenotype
- Many tools are available to predict and diagnose asthma
- Short-acting β-antagonists (SABAs), inhaled corticosteroids (ICSs) and montelukast are commonly used for treatment of wheeze and asthma in the very young
- Meta-analysis shows significant reductions in risk of moderate-to-severe exacerbations with daily ICS therapy in preschool children with symptoms of persistent asthma.
Wheeze and asthma phenotypes

Wheezing during childhood may be a heterogeneous condition and different forms may be associated with different risk factors and prognosis. Transient early wheezers have episodes of wheezing in their first years of life, with a high probability of remission before six years of age. Non-atopic wheezers are difficult to differentiate from persistent IgE-associated wheezers; the latter type of wheeze is a risk factor for asthma and persistence of symptoms beyond the age of six.2,3

The effects of early-life wheezing on lung function in infants and subsequently at school-going age have previously been studied. Transient early wheezers start off with the lowest lung function and then catch up and stop wheezing, raising the question of whether some infants are born with smaller airways, resulting in wheeze which may not be related to underlying asthma. Persistent wheezers have reduced lung function at most time points, are most likely to have episodes of wheezing and more often. At age 16 years, late-onset wheezers have the same lung function as never-wheezers. Over time, never-wheezers are less likely to wheeze, but 10% will experience an episode of wheeze.4

The constancy of phenotypes over time is demonstrated by symptoms. Never-wheezers are most likely to be asymptomatic over time; persistent wheezers are those most likely to maintain the phenotype over time. In older children and younger adults, persistent wheezers and never-wheezers can be differentiated most easily, but no clear differentiation between other phenotypes (persistent wheezing from onset, remission, relapse, intermittent wheezing, transient wheezing) is evident, making it very hard to predict the course of asthma symptoms in an individual over time.5

How to define the asthma phenotype

Different opportunities and different options for defining the asthma phenotype include clinical presentation, immunological markers, measures of airway inflammation, lung function and tissue samples. All have been extensively studied in older children as well as in younger children, but not to the same degree.

Airway biopsy of children with difficult asthma shows reticular basement membrane thickening to a similar extent as that seen in asthmatic adults. This is considered by some to be remodelling but has never been demonstrated to be reversible. In comparison to controls, there is considerable overlap between the groups in terms of basement membrane thickening.6

Increased airway smooth muscle mass has been linked to severity and duration of airway disease. This is not unique to paediatric asthma because it is also evident in other conditions such as cystic fibrosis and bronchiectasis.7

Phenotypic data are important to help define the course of symptoms in children and infants with wheezing, over and above parent- or physician-reporting. Epidemiological studies have been helpful in defining association with environmental factors, as well as prognostic indicators. Asthma genetics is highly complex due to gene environment interactions and potential epigenetic modifications, with no simple identifiable gene predictive of asthma. Better phenotypic definition is essential to interpret both genetic and epidemiological data.

Tools to predict asthma

Asthma predictive index

Asthma predictive index is determined by: One major decisive factor of (i) parent with asthma, (ii) physician diagnosis of eczema (atopic dermatitis) and (iii) sensitivity to allergens in the air (physician-determined through positive skin or blood tests to allergens such as trees, grasses, weeds, moulds or dust mites).
OR

Two minor decisive factors of (i) food allergies, (ii) blood eosinophils >4% or (iii) wheezing apart from colds.

Professor Ratjen believes that on an individual patient level, this asthma predictive index has not been very helpful. If negative, the individual is unlikely to develop asthma; but if positive, it is not very clinically predictive.

Paediatric Respiratory Assessment Measure (PRAM)

For acute asthma, severity scores are helpful. The PRAM scoring table (Table 1) has been used to determine severity in many studies assessing acute asthma treatment in children of all ages. This score is useful but also not predictive of long-term outcomes.

<table>
<thead>
<tr>
<th>Table 1. PRAM scoring table</th>
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<tr>
<td>Oxygen saturation</td>
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<tr>
<td></td>
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<tr>
<td>Suprasternal retraction</td>
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<tr>
<td></td>
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<tr>
<td>Scalen muscle contraction</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Air entry</td>
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<td></td>
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<td></td>
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<tr>
<td>Wheezing</td>
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PRAM score (maximum 12)

<table>
<thead>
<tr>
<th>Score</th>
<th>0-3</th>
<th>4-7</th>
<th>8-12</th>
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<tbody>
<tr>
<td>Severity</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
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Diagnosis of paediatric asthma

The Canadian operational diagnostic criteria for asthma in children aged 1-5 years (Table 2) are useful.9 Documentation of airflow obstruction does not rely on an objective measure, such as lung function testing, which is unavailable in many countries. The challenge of these criteria is that using a response to an inhaled medication as an indicator of asthma is dependent on the fact that the inhalation is performed adequately and that the patient is getting the medication, which is problematic in very young children.
Table 2. Canadian operational diagnostic criteria for asthma in children 1-5 years of age

<table>
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<tr>
<th>Criteria</th>
<th>Preferred</th>
<th>Alternative</th>
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<tr>
<td>1. Documentation of airflow obstruction</td>
<td>Documented wheezing and other signs of airflow obstruction by physician or trained health care practitioner</td>
<td>Convincing parental report of wheezing or other symptoms of airflow obstruction</td>
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<tr>
<td>2. Documentation of reversibility of airflow obstruction</td>
<td>Documented improvement in signs of airflow obstruction to SABA ± oral corticosteroids by physician or trained health care practitioner</td>
<td>Convincing parental report of symptomatic response to a three-month trial of a medium dose of ICS (with as-needed SABA)</td>
</tr>
<tr>
<td>Alternative</td>
<td>Convincing parental report of symptomatic response to SABA</td>
<td></td>
</tr>
<tr>
<td>3. No clinical evidence of an alternative diagnosis (diagnosis by exclusion)</td>
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SABA: short acting β-agonist; ICS: inhaled corticosteroid

If there is no clear reversibility of airflow obstruction, the 2015 Global Initiative for Asthma (GINA) guidelines recommend:
- Check inhalation technique and adherence
- Check asthma diagnosis
- Optimise treatment of risk factors and co-morbidities
- Therapy step-up and refer to asthma specialist
- Diagnosis of severe asthma.

The 2015 GINA diagnostic guidelines for children 1-5 years of age (Figure 1) are complicated and not very practical. Professor Ratjen prefers the Canadian recommendations of when to refer pre-school children with a diagnosis of asthma:
- In the case of mild intermittent symptoms worsening despite treatment with as-needed SABA and asthma education, treatment should be amended to daily low-dose ICS with as-needed SABA and asthma education.
- Patients with persistent symptoms or moderate or severe exacerbations that respond inadequately to daily low-dose ICS with as-needed SABA can be stepped-up to medium-dose ICS; and if this is still inadequate, referral to an asthma specialist is recommended.

Treatment of wheeze and asthma in the very young

Inhaled corticosteroids

Dosing categories in children aged 1-5 years are summarised in Table 3. Most guidelines recommend referral to an asthma specialist prior to use of a high-dose ICS.

Of consideration is whether early use of a low-dose ICS in children at high risk for asthma can prevent lung function deficits as seen in older children and adults. A study of high-risk children randomised to receive low-dose ICS vs placebo over 24 months, with 12-month follow-up after termination of treatment, indicated a greater proportion of symptom-free days in treated patients. Upon treatment discontinuation, there was no difference between the two groups, indicating that low-dose ICS therapy conveyed no long-term improvement in risk of developing symptoms or risk of developing asthma.

Intermittent ICS in episodic wheezing is not useful; number of symptom-free days is no different in patients treated with intermittent budesonide vs placebo.

Pre-emptive treatment with ICS in preschool-age children with moderate-to-severe virus-induced wheezing reduced

Table 3. ICS dosing categories in children 1-5 years of age

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>Daily ICS dose (µg)</th>
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<tbody>
<tr>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Beclomethasone</td>
<td>100</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>100</td>
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<tr>
<td>Fluticasone</td>
<td>100-125</td>
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**Wheeze and Asthma in the Very Young**

**Figure 1. GINA diagnosis algorithm for children one to five years of age**

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*Documentation by a physician or trained health care practitioner; †Episodes of wheezing with/without difficulty breathing; ‡Severity of an exacerbation documented by clinical assessment of signs of airflow obstruction, preferably with the addition of objective measures such as oxygen saturation and respiratory rate, and/or validated score such as the Paediatric Respiratory Assessment Measure (PRAM) score; †Based on marked improvement in signs of airflow obstruction before and after therapy or a reduction of ≥3 points on the PRAM score, recognising the expected time response to therapy; **A conclusive therapeutic trial hinges on adequate dose of asthma medication, adequate inhalation technique, diligent documentation of the signs and/or symptoms, and timely medical reassessment; if these conditions are not met, consider repeating the treatment or therapeutic trial; ††The diagnosis of asthma is based on recurrent (≥2) episodes of asthma-like exacerbations (documented signs) and/or symptoms. In case of a first occurrence of exacerbation with no previous asthma-like symptoms, the diagnosis of asthma is suspected and can be confirmed with recurrence of asthma-like symptoms or exacerbations with response to asthma therapy; †‡8 days/month with asthma-like symptoms; †§Episodes requiring rescue oral corticosteroids (OCSs) or a hospital admission; †¶In this age group, the diagnostic accuracy of parental report of a short-term response to as-needed SABA may be unreliable due to misperception and/or spontaneous improvement of another condition. Documentation of airflow obstruction and reversibility when symptomatic, by a physician or trained health care practitioner, is preferred; †***Based on 50% fewer moderate/severe exacerbations, shorter and milder exacerbations, and fewer, milder symptoms between episodes. ICS = Inhaled corticosteroid
the use of rescue oral corticosteroids in a trial comparing high-dose fluticasone (500µg/day) vs placebo. Treatment with fluticasone was also associated with a smaller gain in height and weight, suggesting caution for the use of high-dose ICS in this setting.11

Montelukast
Montelukast is very popular for treatment of wheezy toddlers because it does not require inhalation. Some benefit has been demonstrated in reduction of symptomatic days, but overall the effect is relatively small.12 Montelukast is also used post-respiratory syncytial virus infection. Similarly, some data suggest that while it may be helpful, the overall effect is limited.13

Treatment meta-analysis
Meta-analysis shows significant reductions in risk of moderate-to-severe exacerbations with daily ICS therapy in preschool children with symptoms of persistent asthma. An ICS has generally been shown to be superior to montelukast in this setting. Therapy should be re-evaluated frequently and adjusted based on symptom pattern.14

Conclusions
Many questions remain unanswered with regard to the early origins of childhood asthma, with no clear tools for diagnosis. Phenotypic classifications currently used are not adequate, but should improve with new understanding of immunological pathways and better definition of the inflammatory process in the airways. It is hoped that current and future studies, such as the Canadian Healthy Infant Longitudinal Development (CHILD) study, will provide insight into some of these considerations.

References