Preschool wheeze and asthma – novel approaches to management and understanding of subtypes

Introduction

The Divisions of Pulmonology and Neonatology of Tygerberg Children’s Hospital hosted the eighth annual Here be Lungs Congress, 6-8 March 2019. ‘Here be lungs’, as in ‘Here be dragons’, is a reference to the situation sailors of old found themselves in when they sailed off into unknown, uncharted waters. In Chinese, ‘lung’ means ‘dragon’ and the lung in Chinese medicine is the boundary between the inner and outer world - the lung is the whole respiratory system and has to do with boundary, breath and renewal; across this boundary vital materials are taken in and waste materials excreted.

One of the aims of this conference was to navigate newly described and insufficiently explored neonatal, infant and childhood lung conditions. This best practice report highlights the advice of Professor Soren Pedersen (Denmark) on the management of asthma and wheeze in preschool children, and why it is so important. Professor Adnan Custovic (UK) explains how careful synergy of data-driven methods and clinical interpretation may help us to better understand the heterogeneity of asthma and enable the discovery of true asthma endotypes.
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**KEY MESSAGES**

- When preschool children are classified into a wheeze phenotype, this classification is likely to change significantly within a one-year period.
- Often, a two-month trial of inhaled corticosteroids (ICSs) is required to assist with the asthma diagnosis.
- ICSs remain first-line treatment for multiple-trigger wheeze but may also be considered in patients with episodic viral wheeze with frequent or severe episodes, or if there is suspicion that interval symptoms are being under-reported.
- Response to ICSs is inconsistent, perhaps due to differences in symptom presentation and/or persistence, or other underlying inflammatory features.
- Children with moderate-to-severe asthma are present in each of several different asthma endotypes.
- Clinical evidence of the heterogeneity of severe asthma is indicated by the differential response to each asthma step-up therapy.
- Allergic sensitisation, high allergen exposure and respiratory virus infection act synergistically to increase the risk of exacerbations.
- Add-on omalizumab therapy nearly eliminates seasonal peaks in exacerbations and reduces the need for use of other medications to control asthma.
- Different patterns of immune responses to viruses are associated with fundamentally different longitudinal patterns of asthma.
- Up to 75% of adult chronic obstructive pulmonary disease (COPD) begins with poor lung function trajectories in childhood.
- Social functioning, cognitive functioning and physical wellbeing are compromised in children with uncontrolled asthma, compared to healthy children.
- Poor asthma control is associated with more severe exacerbations and a more rapid loss of lung function.

Management of asthma and wheeze in preschool children

A clinical presentation may have many symptoms that are not specific for asthma - wheeze/cough/breathlessness, tiredness and reduced physical activity, nocturnal wake-ups, recurrent bronchitis or pneumonia (with several courses of antibiotics being ineffective), and cold air or activity-induced symptoms. This makes it very complicated to decide what is asthma and what is not asthma; and who should be treated and who should not. Among children under five years of age, 45% will show symptoms of wheeze and asthma, with 35% continuing to be symptomatic after the age of five years. Viral triggers are common to both groups.

Classification and management of preschool wheezing disorders

Professor Pedersen is of the opinion that phenotyping may be very important in the future, but it has been shown that when children with preschool wheeze are classified into episodic (viral) wheeze or multiple-trigger wheeze, the classification is likely to change significantly within a one-year period, with no mutually exclusive subgroups that remain consistent over time. Furthermore, wheeze patterns in young children vary over time and with treatment, rendering the distinction between episodic viral wheeze and multiple-trigger wheeze unclear in many patients; so it is not easy to make treatment recommendations. ICSs remain first-line treatment for multiple-trigger wheeze but may also be considered in patients with episodic viral wheeze with frequent or severe episodes, or if there is suspicion...
that interval symptoms are being under-reported. Often, a two-month trial of ICSs is required to assist with the asthma diagnosis. Close follow-up to monitor treatment effect is recommended, with treatment being discontinued if there is no benefit. Professor Pedersen recommends TRACK as a valid, easy-to-administer, caregiver-completed questionnaire of respiratory control in preschool aged children with symptoms consistent with asthma (Table 1).

### Table 1. TRACK questionnaire for respiratory control in preschool aged children

<table>
<thead>
<tr>
<th></th>
<th>Question</th>
<th>Score (0-20)</th>
<th>Cut-off score (80)</th>
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<tbody>
<tr>
<td>1</td>
<td>During the past four weeks, how often was your child bothered by breathing problems such as wheezing, coughing or shortness of breath?</td>
<td>0-20</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>During the past four weeks, how often did your child’s breathing problems wake him or her up at night?</td>
<td>0-20</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>During the past four weeks, to what extent did your child’s breathing problems interfere with his or her ability to play, go to school, or engage in the usual activities appropriate for a child of his or her age?</td>
<td>0-20</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>During the past three months, how often did you need to treat your child’s breathing problems with quick-relief medications?</td>
<td>0-20</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>During the past 12 months, how often did your child need to take oral corticosteroids for breathing problems not controlled by other medications?</td>
<td>0-20</td>
<td>80</td>
</tr>
</tbody>
</table>

Each response is scored from 0 to 20 points on the basis of a five-point Likert-type scale for a total score of 0 to 100. A cut-off point score of 80 is thought to accurately identify children whose symptoms are controlled relative to those whose symptoms are not.

### Which treatment should be considered?

Response to ICS therapy is inconsistent, perhaps due to differences in symptom presentation and/or persistence, or other underlying inflammatory features. The Individualized Therapy for Asthma in Toddlers (INFANT) study found that phenotyping with aeroallergen sensitisation and blood eosinophils is useful for guiding treatment selection and identifies children with a high exacerbation probability, for whom treatment with a daily ICS is beneficial. Infants and preschoolers with recurrent wheezing or asthma have fewer exacerbations and improve their symptoms and lung function during treatment with an ICS.

With regard to variability of symptoms in asthma, there has long been debate about whether it is preferable to treat intermittently with an ICS when symptoms worsen or if continuous treatment is more beneficial. The reality is that for those preschoolers on chronic, regular treatment, there is only 40-50% adherence. With intermittent treatment, parents will act on multiple antecedent signs and symptoms (respiratory symptoms, allergy/cold, behavioural triggers); however only 55% administer treatment for symptoms such as shortness of breath and gasping.

Regular treatment with an ICS is best documented and numerous studies show better outcomes than intermittent use of an ICS in several indicators of lung function, airway inflammation, asthma control, reliever use and symptom-free days, with lower use of oral steroids. Meta-analysis shows regular ICS treatment is the most effective treatment for frequent wheezing in preschool children. The safety of both regular and intermittent use has been established, but a modest growth suppression was associated with daily, compared to intermittent, inhaled budesonide and beclomethasone, with a reduction in growth rate of approximately 0.4cm. Other studies show temporary reduction in growth velocity in prepubertal children (1.0cm) with intermittent use of an ICS for persistent asthma. Inhibition of growth is most likely to be seen in the 5-9-year age group, but not after 9-10 years of age. The decrease in attained height 1-4 years after the initiation of ICS therapy is thought not to decrease attained adult height. Females are more at risk of growth inhibition.

Professor Pedersen cautioned that with intermittent ICS treatment in preschool, there is a risk of undertreating as parents underestimate symptoms. With continuous ICS treatment there is the risk of overtreatment when patients are not closely followed up - treatment should not continue indefinitely and should be stopped if there are no symptoms.
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Severe and uncontrolled paediatric asthma – additional treatment challenges

Increasing evidence indicates that asthma is an umbrella diagnosis for a collection of distinct diseases (endotypes), with varying phenotypic expression of characteristic symptoms and accompanying variable airflow obstruction. There is little consensus in the medical community on how best to define these endotypes. Careful synergy of data-driven methods and clinical interpretation may help us to better understand the heterogeneity of asthma and enable the discovery of true asthma endotypes. This is essential to achieving better mechanism-based treatment targeting.10

Is severe asthma a separate endotype?

Unbiased, data-driven methodologies have been used to identify asthma subtypes, with inconsistent results. Four features have been identified (age of onset, allergic sensitisation, severity and recent exacerbations) that have given rise to a potentially meaningful five-cluster model of asthma – ‘early-onset mild atopic’ (35.5%), ‘early-onset mild non-atopic’ (25%), ‘late-onset’ (17%), ‘difficult’ (21.5%) and ‘exacerbation-prone’ (2%). Children with moderate-to-severe asthma were present in each cluster, suggesting that severe asthma is not a single entity, but an extreme end of the spectrum of several different asthma endotypes. Lung function was significantly diminished among children with ‘difficult’ asthma and blood eosinophilia was a significant feature of ‘difficult’, ‘early-onset mild atopic’ and ‘late-onset’ asthma. This implies that the same intervention used across all children with severe asthma will not result in a consistently positive outcome.10

Other studies indicate that severe asthma in children is heterogeneous, although in most patients it is characterised by eosinophilic airway inflammation.11 Clinical evidence of heterogeneity in treatment responses comes from the Best Add-on Therapy Giving Effective Responses (BADGER) trial, showing a differential response to each step-up therapy. Long-acting β-agonist (LABA) step-up was significantly more likely to provide the best response at group level, compared to either doubling the dose of ICS or adding leukotriene receptor antagonists (LTRAs). However, many children had a best response to ICS step-up (25%) or LTRA step-up (25%), highlighting the need to regularly monitor and appropriately adjust each child’s asthma therapy and to find biomarkers to help the physician to make an informed decision as to which treatment to prescribe.12

Why do exacerbations occur?

Viewing viral infections as the sole cause of exacerbations is an oversimplification. Large studies examining potential factors associated with exacerbations in adults and children have indicated that allergic sensitisation, high allergen exposure and virus infection (mostly rhinovirus) may act synergistically to exacerbate asthma.

The combination of these three factors increased the risk of hospital admission 20-fold among children and eight-fold among adults. There is an association between increased serum IgE levels with concurrent respiratory virus infection and an increased probability of acute, severe asthma exacerbations.13,14

Strategies to reduce risk of exacerbations

Omalizumab – a recombinant humanised monoclonal antibody against human IgE - used as add-on therapy in a cohort of inner-city youths reduced the rate of autumn exacerbations (70%), with a marked reduction in hospitalisation for exacerbation compared to the period before anti-IgE treatment was introduced. Further to improved asthma control, add-on omalizumab nearly eliminated seasonal peaks in exacerbations and reduced the need for other medications to control asthma. A persistent positive effect on the severe exacerbation rate was seen, with a modest effect on asthma control.15,16

It is necessary to consider the expense of biologics such as omalizumab and the question of whether they need to be administered throughout the year. A study of pre-seasonal (four-month) treatment with
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"In asthma ... intermittent unpredictable symptoms and perceived loss of control could significantly impact quality of life.”
Professor Sorensen Pedersen

an anti-IgE shows that this strategy can be used to great effect. The biggest effect of anti-IgE was in the most severe group (STEP 5,) which had an exacerbation during the run-in period; but there was little difference compared to placebo in children in STEP 2-4. Also of interest was the observation that those on anti-IgE treatment had significantly increased IFN-α in response to respiratory virus infection, correlating with those afforded the greatest protection from exacerbations.17

Severe, therapy-resistant asthmatic children show very high levels of atopy (markedly stronger IgE responses and higher skin-test wheals) when compared to difficult and mild-to-moderate asthmatic children. How is allergic asthma defined? Sensitisation is an umbrella term. Machine-learning methodologies have identified four different sensitisation clusters, reflecting multiple different atopic vulnerabilities where timing and type of allergic sensitisation may be predictive of asthma. Only one of these groups, ‘multiple early sensitisation’ representing 25% of sensitised children, is relevant to asthma, with a 30-fold increase in the likelihood of asthma. This ‘multiple early’ subtype is associated with all severe outcomes.18-20

A recent study of innate antiviral immune responses mapped cytokine responses induced by rhinovirus. Machine-learning models suggest that there are six different patterns of immune responses to viruses. These are associated with fundamentally different longitudinal patterns of disease. Children with strong interferon, proinflammatory and regulatory responses do not have asthma. Two patterns are associated with asthma, but with very different types of the disease. Very low interferon responses, high proinflammatory responses and moderate regulatory responses are associated with a high risk of exacerbation, lower respiratory tract infection, troublesome early childhood wheezing and early sensitisation. A high interferon response with moderate proinflammatory and regulatory responses is associated with late-onset mild allergic asthma.21

Impact of severe wheezing on lung function trajectories

Children with persistent wheeze, frequent asthma exacerbations, and multiple early atopy have persistently diminished lung function throughout childhood and are at risk of a progressive loss of lung function from age three to 11 years. Up to 75% of adult COPD begins with poor lung function trajectories in childhood, with maternal smoking, multiple early-life sensitisation and wheezing exacerbations having a major impact. Reducing childhood smoke exposure and minimising the risk of early-life sensitisation and wheezing exacerbations may reduce the risk of diminished lung function in early adulthood.22,23

Why achieve control in paediatric asthma?

What is the impact of asthma control on quality of life?

In asthma, physiological abnormalities may be mild or absent on a chronic basis, but intermittent unpredictable symptoms and perceived loss of control could significantly impact quality of life. Uncontrolled asthma impacts the sleep of children to a significantly greater degree than well-controlled asthma. Social functioning, cognitive functioning and physical well-being are compromised in those with uncontrolled asthma, when compared to healthy children and patients with controlled asthma. Children with uncontrolled asthma are also at higher risk for anxiety and depression.24,25

Those with uncontrolled asthma are at higher risk for limitations in outdoor activity, physical activity and daily activity, which can lead to social isolation. Children with asthma have lower physical functioning, general well-being and emotional functioning domain scores and those with untreated asthma have a higher percentage of body fat and a greater frequency of obesity than their healthy peers. Uncontrolled asthma is associated with reduced fitness levels and less time spent in intensive activity during the day. Improvement in asthma control is associated with a continuous, clinically relevant increase in daily physical activity and cardiovascular fitness from four weeks onwards. To help patients achieve optimal health, asthma management should include routine assessment of activity limitations.25-28
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Decline in lung function does not occur in all asthma patients. Identified risk factors for lung function decline include young age, male gender, longer duration of disease, black ethnicity, more prominent eosinophilic airway inflammation, asthma exacerbations and smoking. Poor asthma control is associated with more severe exacerbations and a more rapid loss in lung function, compared to patients taking the ICS, budesonide.29

References


25. Hasenkorn T, Hov N, Miller DP, et al. Omalizumab in children with severe asthma and a history of severe asthma exacerbations and a more rapid loss in lung function compared to patients taking the ICS, budesonide. 29

26. Hasenkorn T, Chen H, Miller DP, et al. Omalizumab in children with severe asthma and a history of severe asthma exacerbations and a more rapid loss in lung function compared to patients taking the ICS, budesonide. 29

