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Issues and answers: Current trends in GINA recommendations for asthma management in children

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Introduction

The Global Initiative for Asthma (GINA) seeks to frame evidence-based strategy recommendations on the management of asthma in clinical practice. GINA recommendations are made with a view to preventing asthma deaths and exacerbations and improving symptom control; human behaviour of health professionals, carers and patients; and global variation in populations, health systems and access to medicines.

In 2019, new evidence on the pharmacological treatment of asthma prompted GINA to update its recommendations, with an emphasis on how to personalise asthma management.[1] For the first time, a separate treatment figure for children aged 6-11 years is included in the GINA recommendations. At the 2020 Here-be-Lungs conference, Professor Petr Pohunek shared his experience of paediatric asthma in the context of the GINA recommendations. He believes that preventative treatment is a key priority in the management of pre-schoolers with asthma.

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LEARNING OBJECTIVES

You will learn:

- New evidence on the pharmacological treatment of paediatric asthma
- The changes in the GINA recommendations, updated in 2019, with regard to the management of asthma in pre-schoolers and children aged 6-11 years
- The principles of personalising paediatric asthma management
- The role of biologicals in the treatment of severe asthma refractory to conventional treatment.

Principles of personalising paediatric asthma management

The goals of asthma management in young children are to achieve good control of symptoms, maintain normal activity levels, minimise future risk of exacerbations, maintain lung function and lung development as close to normal as possible, and minimise medication side effects. These goals are most effectively achieved through a partnership between the patient/caregiver and the health professional team, with a cycle of assessment, adjusting treatment and reviewing the response. In this manner, a personalised asthma plan can be instituted with a greater likelihood of achieving good control.

ISSUE What are the considerations for personalised asthma management in children?

For the first time, a separate treatment figure for children aged 6-11 years is included in the GINA recommendations

It is important to consider how *this* child differs from the 'average' child in terms of asthma - variable factors include response to previous treatment, parent (and child's) preferences in respect of goals, beliefs and concerns about medications, and practical issues such as cost, inhaler technique and adherence.

Assess

- Alternative diagnoses and exclude; if necessary, confirm diagnosis in 6-11-year-old patients
- Symptom control and modifiable risk factors, including lung function in 6-11-year-old patients
- Comorbidities
- Inhaler technique and adherence
- Parent goals and the goals of the 6-11-year-old child.

Adjust

- Treat modifiable risk factors and comorbidities
- Non-pharmacological strategies
- Education and skills training
- Asthma medications.

Review response

- Symptoms
- Exacerbations
- Side effects
- Lung function in 6-11-year-olds
- Parent (and child) satisfaction.

ISSUE At what age can different asthma medications be used?

It is quite common for asthma medications to be used off-label, with the prescriber not being aware of the age limits for different agents (Table 1).

Table 1. Age limits for anti-asthma treatment

6 months	Montelukast Budesonide NEB
1 year	Fluticasone
2 years	Beclomethasone
4 years	Salbutamol (*but even younger*) Fluticasone/salmeterol MDI Fluticasone/salmeterol DPI
5 years	Budesonide DPI Budesonide/formoterol MDI
6 years	Budesonide MDI Budesonide/formoterol DPI Ciclesonide
12 years	Beclomethasone/formoterol MDI

DPI: dry-powder inhaler; MDI: metered dose inhaler; NEB: nebuliser

ISSUE Which inhaler device is best for *this* patient?

It is important to consider how* this *child differs from the 'average' child in terms of asthma

Choice of inhaler device should be based on the child's age and capability. For children younger than three years, a pressurised metered dose inhaler and spacer with face mask are preferred over the alternative of nebuliser with face mask, whereas a mouthpiece is suitable for most 3-5-year-olds. Children should be switched from a face mask to a mouthpiece as soon as they are able to demonstrate good technique.

Medications for symptom control and minimising future risk in children

In very young children, there are so many phenotypes in respect of frequency of wheezing and risk factors that it can be difficult to decide on which therapy regimen is best. By the age of five or six years, phenotypes determining longer-term prognosis are more easily distinguishable. Irrespective of age, Professor Pohunek emphasises that the goal of treatment is to aim for complete symptom control: i.e. no (few) asthma symptoms, no sleep disturbance and no exercise limitation; and risk reduction by maintaining normal lung function, preventing exacerbations, asthma deaths and medication side effects.

A stepwise treatment approach is recommended by GINA based on symptom patterns, risk of exacerbations and side effects, and response to initial treatment. Generally, treatment includes the daily, long-term use of controller medications to keep asthma well-controlled, and reliever medications for as-needed symptom relief.

Pre-school: children five years old and younger

Wheezing episodes should initially be treated with as-needed inhaled short-acting β_2-agonists (SABAs), regardless of whether the diagnosis of asthma has been made. A trial of controller therapy should be considered if the symptom pattern suggests asthma, alternative diagnoses have been excluded, and respiratory symptoms are uncontrolled and/or wheezing episodes are frequent or severe (Table 2). If, upon review, response to treatment is absent or incomplete, consider alternative diagnoses. It is very important to review the need for asthma treatment frequently, as asthma-like symptoms remit in many young children.

Table 2. GINA recommendations for personalised management of asthma in children five years and younger

Asthma medication options *Adjust treatment up and down for each individual child's needs*	**Preferred controller choice**	**Other controller options**	**Reliever**
Step 1 For children with infrequent viral wheezing and no, or few, interval symptoms	–	–	As-needed SABA
Step 2 For symptom pattern consistent with asthma, and asthma symptoms not well controlled or ≥3 exacerbations per year For symptom pattern not consistent with asthma but wheezing episodes requiring SABA ≥3/year	Daily low-dose ICS	LTRA, or Intermittent ICS	As-needed SABA
Step 3* For asthma diagnosis, and asthma not well-controlled on low dose ICS	Double 'low-dose' ICS	Low-dose ICS + LTRA Consider specialist referral	As-needed SABA
Step 4* For asthma not well-controlled on double ICS	Continue controller, refer for specialist assessment	Add LTRA, or increase ICS frequency, or add intermittent ICS	As-needed SABA

*Before stepping up, check for alternative diagnoses, check inhaler skills, review adherence and exposures
SABA: short-acting β_2-agonist, ICS: inhaled corticosteroid, LTRA: leukotriene receptor antagonist

It is quite common for asthma medications to be used off-label, with the prescriber not being aware of the age limits for different agents

ISSUE Which children should be prescribed regular controller treatment?

In general, the following principles apply to the GINA recommendations:

- If the history and symptom pattern suggest a diagnosis of asthma and respiratory symptoms are uncontrolled and/or wheezing episodes are frequent (≥3 episodes per season). Consider in a child with less frequent, but more severe, episodes of viral-induced wheeze.
- If the diagnosis of asthma is in doubt and inhaled SABA therapy (>2 per week over one month) or courses of antibiotics need to be repeated frequently (>6-8 weekly). Referral for specialist opinion should also be considered at this stage.

Although effects of ICSs on growth velocity are seen in pre-pubertal children in the first 1-2 years of treatment, this is not progressive or cumulative. Poorly controlled asthma itself adversely affects adult height.

ISSUE When should step-up of controller treatment be considered?

If, despite three months of adequate controller therapy, symptom control is poor and/or exacerbations persist:

- Confirm symptoms are due to asthma rather than a concomitant or alternative condition
- Check for correct inhaler technique
- Confirm good adherence with the prescribed dose
- Consider a trial of a different treatment option in that step
- Enquire about risk factors (allergens, tobacco smoke).

Children 6-11 years

Professor Pohunek emphasises that the goal of treatment is to aim for complete symptom control

The GINA 2018 recommendations for treatment with SABA alone in step 1 adults and adolescents have been updated and mark an important change in the 2019 GINA recommendations. This change was based on studies that suggest there may be serious risk of exacerbations with SABA-only treatment.

GINA now recommends that all patients receive as-needed or daily low-dose ICS-containing controller (Table 3). The recommendation to take an ICS whenever SABA is taken is based on indirect evidence from a single step 2 study with separate inhalers that showed substantially fewer exacerbations compared with SABA-only treatment.[2] Regular ICS treatment with as-needed SABA is an option, although the likelihood of poor adherence in children with infrequent symptoms should be taken into account. Professor Pohunek points out that the evidence is limited and the recommendations weak, and that yet more changes in future recommendations for children aged 6-11 years will be imminent.

Table 3. GINA recommendations for personalised management of children 6-11 years to control symptoms and minimise future risk

Asthma medication options *Adjust treatment up and down for each individual child's needs*	**Preferred controller choice**	**Other controller options**	**Reliever**
Step 1	–	Low-dose ICS taken whenever SABA taken*, or daily low-dose ICS	As-needed SABA
Step 2	Daily low-dose ICS	LTRA, or low-dose ICS taken whenever SABA taken*	As-needed SABA
Step 3	Low-dose ICS-LABA, or medium-dose ICS	Low-dose ICS + LTRA	As-needed SABA
Step 4	Medium-dose ICS-LABA Refer for expert advice	High-dose ICS-LABA, or add-on tiotropium, or add-on LTRA	As-needed SABA
Step 5	Refer for phenotypic assessment ± add-on therapy e.g. anti-IgE	Add-on anti-IL-5, or add-on low-dose OCS but consider side effects	As-needed SABA

*Off-label, separate ICS and SABA inhalers, only one study in children
SABA: short-acting β2-agonist, ICS: inhaled corticosteroid, LTRA: leukotriene receptor antagonist; LABA: long-acting β2-agonist; OCS: oral corticosteroid

ISSUE

What is the evidence for recommending combination low-dose ICS-LABA as a preferred controller option for step-up?

In a large study of children aged 4-11 years with a history of an exacerbation in the previous year, combination ICS-LABA was non-inferior to the same dose of ICS alone for severe exacerbations, with no difference in symptom control or reliever use.[3] A study of maintenance and reliever therapy with low-dose budesonide-formoterol in children showed a large reduction in exacerbations compared with the same dose of budesonide-formoterol with SABA reliever, or compared with higher-dose ICS.[4] This regimen is not approved for children <12 years.

Biologicals – treatment of severe asthma

Severe asthma can be defined as asthma that is uncontrolled despite maximal optimal therapy and treatment of contributory factors, or that worsens when high-dose treatment is decreased.[5] Current treatment options for severe therapy-resistant asthma include inhaled steroids with high lung deposition and less systemic effect, tiotropium (licensed for use from six years of age) and oral steroids in sparing regimens. Biologicals for treatment of severe asthma target Th2-mediated inflammation and include anti-IgE (omalizumab), anti-IL-5 (mepolizumab, reslizumab, benralizumab), and the newer anti-IL-4/IL-23 (lebrikizumab, dupilumab, tralokinumab, pitrakinra), which are not yet widely available or licensed for use in children.

Effectiveness and safety of use of biologicals for therapy in children has been documented only in some substances; however, effectiveness similar to that seen in adults can be expected as the inflammatory mechanisms are the same or similar. Available for use from the age of six years, biologicals are a logical step forward in the treatment of asthma and allergy, and substantial effects may be seen on the development and natural history of asthma. It is Professor Pohunek's opinion that biologicals should replace corticosteroids in all confirmed severe asthma that is refractory to conventional treatment and where all other factors have been excluded.

It is very important to review the need for asthma treatment frequently, as asthma-like symptoms remit in many young children

Omalizumab

Omalizumab, a humanised mouse recombinant DNA-derived monoclonal antibody with good effect against human high-affinity IgE receptor, has been approved by the European Medicines Evaluation Agency (EMEA) since 2009 for use in patients aged 6-12 years for severe persisting asthma that cannot be controlled, even with high-dose inhaled steroids. A further benefit of omalizumab is an observed improvement of other allergic symptoms.[6]

The dosage scheme of omalizumab is quite complicated, dependent on body weight and IgE level. Professor Pohunek's experience is that omalizumab therapy only every four weeks represents too long a period between treatment and that patients start to feel some symptoms earlier, which resolve upon modifying the treatment schedule to every three weeks. There is sufficient evidence that omalizumab therapy is effective in childhood asthma.

Due to high cost and the unknown long-term impact on the health of omalizumab-treated individuals, use remains restricted. Currently, it is not known for how long treatment should be administered and if, under specific conditions, this treatment should be stopped after asthma control is achieved.

Mepolizumab

A humanised monoclonal antibody against IL-5, mepolizumab is approved for use from six years of age. It targets eosinophils and may induce partial maturational arrest of the eosinophil lineage in the bone marrow and eosinophilopoiesis in tissue. Mepolizumab may also reduce remodelling in the bronchial mucosa. Long-term safety data in children are similar to those seen in adults.[7]

ISSUE

How to choose an add-on biological for severe asthma?

Depending on assessment of severe asthma phenotype and other factors, patient eligibility and response to biologicals will vary (Table 4). Review of the response to the biological at 4-6-month follow-up should include assessment of symptom control, exacerbations and lung function; comorbidities such as nasal polyposis and atopic dermatitis; treatment intensity, side effects and affordability of the medications; and patient satisfaction.

Table 4. Selecting the appropriate add-on biological

Patient eligibility	Factors which may predict good response
Anti-IgE for severe allergic asthma	
• Sensitisation on skin-prick testing or specific IgE • Total serum IgE and weight within dosage range • Exacerbations in the last year	• Blood eosinophils ≥260/µl • FeNO ≥20ppb • Allergen-driven symptoms • Childhood-onset asthma
Anti-IL-5/anti-IL-5R for severe eosinophilic asthma	
• Exacerbations in the last year • Blood eosinophils ≥300/µl	• Higher blood eosinophils • More exacerbations in the previous year • Adult onset of asthma • Nasal polyposis

KEY LEARNINGS

- Early diagnosis and timely initiation of appropriate preventative pharmacotherapy are key issues in paediatric asthma
- In young children at higher risk of asthma, there is an increased emphasis on preventative treatment with ICSs in the case of recurrent symptoms
- In children older than five years with persistent asthma in whom low-dose monotherapy is not sufficient, a single-inhaler combination of ICS + LABA is an important part of the pharmacotherapeutic regimen
- The choice of asthma medication should respect the allowed age range
- Patient eligibility and response to add-on biologicals for the treatment of severe asthma is affected by phenotype, levels of blood eosinophils and other factors.

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Click on references to access full articles for additional reading

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