Review
Allergy Asthma Immunol Res. 2010 January;2(1):1-13.
doi: 10.4168/aair.2010.2.1.1
pISSN 2092-7355 • eISSN 2092-7363

AAIR
Allergy, Asthma & Immunology Research

Current guidelines for the management of asthma in young children

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The diagnosis and management of asthma in young children is difficult, since there are many different wheezy phenotypes with varying underlying aetiologies and outcomes. This review discusses the different approaches to managing young children with wheezy illnesses presented in recently published global guidelines. Four major guidelines published since 2007 are considered. Helpful approaches are presented to assist the clinician to decide whether a clinical diagnosis of asthma can, or should be made in a young child with a recurrent wheezy illness and which treatments would be appropriate, dependent on risk factors, age of presentation, response to initial treatment and safety considerations. Each of the guidelines provide useful information for clinicians assessing young children with recurrent wheezy illnesses. There are differences in classification of the disease and treatment protocols. Although a firm diagnosis of asthma may only be made retrospectively in some cases and there are several effective guidelines to initiating treatment. Consistent review of the need for ongoing treatment with a particular pharmacological modality is essential, since many children with recurrent wheezing in infancy go into spontaneous remission. It is probable that newer biomarkers of airway inflammation will assist the clinician as to when to initiate and when to continue pharmacological treatment in the future.

Key Words: Asthma; preschool child; guideline

INTRODUCTION

Asthma is a leading cause of chronic disease in children globally. Since the international study of asthma and allergies in childhood (ISAAC) epidemiological research programme was established in 1991, a phase three study in 2002-2003 in 193,404 children aged 6-7 years from 66 centres in 37 countries, conducted 7 years after the phase 1 study showed a marked change in disease prevalence, with increases being twice as common as decreases in the 6-7 year old age group than in the 13-14 year old comparator group of children.[1] There are no global epidemiological studies of asthma or wheezy illnesses in children under 5 years of age. Reasons for this include difficulty in making a confident diagnosis, a lack of objective diagnostic criteria, logistical and ethical problems and the variability of the expression of wheezy illnesses in children 5 years and under.

Asthma guidelines have been developed during the past 17 years to increase the awareness of asthma among health professionals, to improve asthma management, to evaluate published reports on asthma and to promote international collaboration in asthma research. The first international guidelines were formulated by the National Heart Lung and Blood Institute (NHLBI) in the USA in 1991[2] and this expert panel report was updated in 1997[3] and reviewed by Jahad[4] in a meta analysis and updated in 2003[5] and finally published in 2008 as an Expert Panel Report 3 (EPR-3).[6]

Currently there are 4 major guidelines which address the management of asthma in young children. The EPR3 of the National Asthma Education Programme (NAEPP),[6] the PRACTALL Consensus Report published by the European Academy of Asthma and Allergy in 2008,[7] an Evidence Based Approach compiled by the European Respiratory Society task force, published in the European Respiratory Journal in 2008[8] and most recently the Global Initiative (GINA) published new evidence based guidelines for the diagnosis and management of asthma in children 5 years and younger in 2009 (www.ginasthma.org).[9]

The reason for having at least 4 new "global" guidelines published in the past 2 years to address the management of asthma in young children stems from lack of agreement on the diagno-

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Received: September 23, 2009; Accepted: October 28, 2009.
• There are no financial or other issues that might lead to conflict of interest.

sis of asthma in young children, paucity of published studies on different treatments for asthma and wheezy illnesses in the under 5's, a lack of published biopsy studies on the pathology of wheezy illnesses in young children. There are also differences in different regions of the world in resources for treatment, modes of communication and availability of different treatments.

Some have considered that with a lack of hard evidence, as would be obtained by large double blind placebo controlled studies, a consensus approach based on evidence in older children and clinical experience is more appropriate.[7] Even when stricter criteria for recommendations are upheld according to published evidence only,[8] the dilemma of whether asthma can be diagnosed with confidence in the under five aged group arises.[9] It is more difficult to formulate guidelines for asthma in the younger children firstly because the diagnosis for asthma may not be sure and children express different patterns of wheezy illnesses, but also because asthma itself is a "syndrome" composed of heterogeneous diseases.[10]

It is thus believed that asthma is unlikely to be a single disease, but rather a series of complex overlapping individual diseases or phenotypes, each defined by its unique interaction between genetic and environmental factors. These conditions include syndromes exacerbated by exposure to allergens, and aspirin exacerbated, or non-allergic factors, along with syndromes best distinguished by their pathological findings (neutrophilic, eosinophilic, pauci granulocytic), their response to therapy (corticosteroid resistant, or leukotriene receptor antagonist sensitive) and natural history (intermittent or persistent or remittent) depending on the development of airway remodelling and other factors such as exposure and genotype.

It is against this background of a clear heterogeneity in the asthma phenotypes encountered in older children and adults, that the literature is deplete on information on the natural history of the disease, which starts in infancy. It is not known which childhood phenotypes develop into any of the defined adult type asthma phenotypes.

Thus in developing guidelines it would appear that the current objectives and goals have been to recommend treatments, which are effective for "current control" of the disease, rather than treatments which modify the natural history of the disease. Other than "allergen specific immunotherapy" for asthma, caused by and precipitated by a single allergen, which in itself is rare, even in children, there are no other treatments known to modify the natural history of the disease.

An important consideration in the development of guidelines is that the ISAAC data[1] clearly show that the increases noted in childhood asthma have not been confined to the developed countries, but that asthma also poses a huge burden to the underdeveloped world, where resources are scarce and there is competition for resources to treat other diseases such as TB, AIDS, malnutrition, malaria and other infectious diseases.

The applicability of any guideline for asthma rests on access to medications recommended in such guidelines. Khalied et al.[11] have stressed that access to inhaled corticosteroids is they key to improving quality care for asthma in developing countries. In developed countries a high cost of essential medications can be a major obstacle for patients who need such treatment and in many developing countries many essential drugs are unavailable for asthma treatment and literacy and language barriers are significant obstacles to implementation of guidelines.[12]

It is difficult to apply current new guidelines for the management of children under 5 years, if the only asthma medications on the World Health Organization essential drug list includes Beclomethazone, Epinephrine, Ipratropium bromide and Salbutamol (WHO Essential Drug List, March 2007). Even when optimal treatment available, only 30-40% of patients are totally controlled.[13]

Management goals for childhood asthma are fairly consistent between the different guidelines. The aims are for a "normal life" free of any symptoms (e.g., cough, wheeze and breathlessness), the ability to have a restful sleep, to grow and develop normally, to attend school or preschool regularly and participate in all school activities including sports, to minimise the number of attacks of acute asthma, to avoid hospitalisation and to avoid medication related side effects.

The impact of the disease needs to be weighed against the possible impact of the therapy. In the case of asthma treatment for children there are issues which are also extremely important to the parents, such as normal appetite, good academic performance at school, social development and lack of irritability or disruption of family life. Quality of life is difficult to assess in young children and symptom scores may not correlate well with quality of life ratings. Quality of life may be also influenced by differences in society and cultural needs.

Treatment of the young child also differs from that of the older child because in addition to lung functions being difficult under the age of 5, there are challenges to adequate delivery of inhaled drugs, safety issues and ethical issues. Furthermore, there are dosing issues. For many drugs used in young children careful dose ranging studies have not been conducted and dosing is extrapolated from adult doses.[14] This dilemma results from the difficulties experienced in conducting necessary double bind placebo controlled studies of asthma medications at different ages in young children bearing in mind the rights of the child, the fact that children are not "mini adults", primary and secondary end points of paediatric and infant studies are not always fully objective due to "second party" reporting of outcomes by parents and caregivers and the assessment of ongoing inflammation is difficult. To address the deficiency in paediatric studies the FDA modernization and best pharmaceuticals for children's act has been promulgated, the European Medicines Evaluation Agency has published a "note for guidance on clinical investigation for medical products in the

population" and the Therapeutics Goods Administration (TGA) of Australia has given priority to paediatric submissions to encourage industry to study all new products in children.

In practice this will involve studies in which the dosages are weight related, patients are clearly phenotyped according to the onset and type of wheezy illness, differences in the pharmacokinetics of the drug are studied and measurable effects on inflammation are also considered (e.g., PD20, eNo, urinary leukotrienes, sputum eosinophilic cationic protein and other immunological markers), in addition to variables such as airway hyperresponsiveness, growth, height, quality of life and disease modification.

Bearing in mind the variability of the triggers of wheeze in young children (viruses, allergens, irritants, emotional factors exercise), it is thus difficult to standardise all these variables to study the effects of a particular drug on a particular outcome, in a sufficiently large number of children, including a placebo arm. Furthermore longer studies may be necessary to study whether a particular drug has a disease modifying capability, bearing in mind the tendency of wheezing illnesses to spontaneously remit in a significant number of young children.

It is important to stress that a number of young children presenting with wheeze may not have asthma. The younger the child, the greater the possibility of an alternative diagnosis, e.g., gastroesophageal reflux, cystic fibrosis, aspiration syndrome, immune deficiency, congenital heart disease and bronchopulmonary dysplasia.

Furthermore there are a number of risk factors which increase the likelihood of the development of asthma in young children in addition to genetic factors. Risk factors for asthma attacks include exercise, exposure to specific allergens, viral infections, tobacco smoke, certain foods and food additives such as sulphur dioxide and emotional factors. In addition the choice of treatment will be influenced by the history which should consider the frequency of previous attacks, the severity of previous attacks, previous hospitalisation, repeated use of oral steroids such as prednisolone, the level of treatment previously necessary to obtain "control", attendance at a crèche, concurrent rhinitis and rate of response to treatment.

THE NAEPP EP3 GUIDELINES

The first of the "recently published" guideline for the management of asthma in young children is the EP3 NAEPP report published in 2007.[6] These guidelines point out that 50-80 percent of children who have asthma, develop symptoms before their fifth birthdays, but because the disease is frequently under diagnosed many young children do not receive adequate therapy. On the other hand, since not all wheeze is caused by asthma, one should exert caution to avoid infants and younger children receiving inappropriate prolonged asthma therapy.

The diagnosis of asthma is difficult. If one considers the presence of airway inflammation to be central to the diagnosis of asthma, confirmation of this is not usually possible in younger children, using available clinical tools in practice. However, elevations in both inflammatory cells and mediators have been demonstrated in broncho alveolar large specimens obtained from preschool children who have recurrent wheezing.[15] Thus in children 0-4 years of age, in some cases a therapeutic trial with medications may also aid in confirming a diagnosis, whereas in children 5-11 years one has the advantage of a preceding history and also simple lung function tests for reversibility, to aid the diagnosis.

In the under fives the most common cause of asthma symptoms is viral respiratory infection. Some remit in the preschool years and others persist throughout childhood. It appears that children under 3 years of age who have more than four episodes of wheezing in the past year, affecting sleep are significantly more likely to develop persistent asthma after the age of 5 years, particularly if they have a parental history of asthma, a physician diagnosis of atopic dermatitis, sensitization to aeroallergens, evidence of food sensitisation, a greater than 4 percent peripheral blood eosinophilia or wheezing apart from colds.

The Expert Panel 3 concluded that early intervention with inhaled corticosteroids continuously[16] or intermittently[17] did not alter the underlying severity or progression of the disease and that inhaled corticosteroids should be used to control asthma symptoms and improve the child's quality of life, but not for the purpose of changing the natural history of the disease (Evidence A).

It appears that while the disease may in fact progress during the first 5 years of life, the recent childhood management programme study (CAMP) indicated that children aged 5-12 years who have mild or moderate persistent asthma, do not on average have a progressive decline in lung function. In the subset of these who experienced progressive reductions in lung growth compared to predicted measures, this was not prevented by inhaled steroids.[18]

Observational prospective data from Martinez et al. suggests that most loss of lung function occurs during the first 3-5 years of life.[19] Although this is the case, the studies by Guilbert et al.[16] in 2006 showed that ICS clearly reduced the symptom burden and frequency of exacerbations when administered daily for 2 years, but did not prevent the reappearance of symptoms in the year of follow up after discontinuing therapy.

The EP3 guidelines recommend a regular follow up of those children who have moderate a persistent asthma to assess impairment and risk domains for the development of progressive disease. These include requirements for intermittent short acting β_2 stimulants, exacerbations requiring systemic steroids, urgent care visits and if possible pulmonary function measures.

The concept of "reducing impairment" refers to the maintenance of current well-being of the child as evidenced by reduction of symptoms, maintaining near normal pulmonary func-

tion meeting family needs and expectations and maintaining current normal activity levels, exercise and school attendance.

The concept of "reducing risk" outlined by the EP-3 attempts to prevent recurrent exacerbations of asthma and the need for emergency care visits or hospitalisations, prevention of progressive loss of lung function and minimization of adverse events. It is recommended that both domains are considered as both affect quality of life, but that these domains respond differently to treatment. Thus, low dose steroids may reduce impairment (symptoms, SABA use and lung function), but does not reduce exacerbations requiring corticosteroids.

While most of the new guidelines emphasise the role of the clinician in assessing and maintaining "control" of asthma in an established treatment regime, when young patients are seen for their first episode of wheezing and factors like severity, age of onset, family history and the presence of other risk factors will influence the clinician's decision regarding appropriate therapy.

The EPR-3 recommends that "impairment" and exacerbations may be reduced by regular controller treatment in children who have four or more episodes of wheezing in the past year persisting for more than a day, plus a parental history of asthma, atopic dermatitis, sensitization to aeroallergens, a >4% peripheral eosinophilia and wheezing apart from colds. The guideline recommends a stepwise approach to treatment starting with low dose inhaled corticosteroids, or Montelukast.

Doses for most inhaled steroids in the 0-4 year's old group are not published. The daily dose for Budesonide inhalation suspension is recommended at 0.25-0.5 mg and of Fluticasone at 176 μg/day, with no specific doses recommended for Budesonide, Beclomethazone, Fluinisolide, Mometasone or Triamcinolone for the under five year old asthmatics. Daily doses for the 5-11 year old asthmatics are 80-160 μg Beclomethazone, 180-400 μg Budesonide, 500-750 μg Fluinisolide, 160 μg Fluinisolide HFA, 80-176 mg Fluticazone HFA MDI, 100-200 μg Fluticasone DPI and 300-600 μg Triamcinolone.

The above doses are regarded as low daily doses and can be stepped up (usually doubled) to a medium dose in children 5-11 years and quadrupled as a high daily dose in severe childhood asthmatics. In the absence of published studies the EP3 guidelines are extremely cautious in recommending specific doses of inhaled steroid for the 0-4 year old asthmatics. Montelukast 4 mg is recommended for under 5 year olds and 5 mg from 6-11 year olds (Evidence A).

In addition, long term controller therapy with inhaled corticosteroid should be considered to reduce impairment in infants and young children who consistently require treatment more than 2 days per week for more than 4 weeks (Evidence D), for reducing exacerbations requiring systemic corticosteroids within a 6 month period (Evidence D) or during a period of a previously documented risk for a child (e.g., Winter, Spring, specific exposure) (Evidence D), but that discontinuation must be considered when the period of risk has passed.

Once the child is on long term treatment with daily preventers adjustments may be made by assessing both the impairment and risk domains. These must be complemented by adequate education of the child and care giver, with particular attention to the level of adherence, to assess whether treatment should be stepped up or down.

Consideration of referral to a specialist is essential if there are difficulties in controlling the asthma, children who require step 3 or higher or if an exacerbation requires hospitalisation. A specialist would also assess a possible role for immunotherapy and consider the role of allergy.

Furthermore the EP3 panel is of the opinion that ICS may be reduced by 25-50% every 3 months to the lowest possible dose to maintain control (Evidence D). Reduction should be gradual and since guidelines for stepping down treatment have not been validated, and clinical judgement of the individuals' response to therapy is very important. ICS at low doses for extended periods are safe. The potential for adverse events on medium to high dose ICS is usually limited to a small reduction in growth velocity of approximately 1 cm in the first year of treatment which is not progressive over time and can be measured by a stadiometer.[20, 21]

In children who are required to receive high dose corticosteroids, age appropriate dietary intake of calcium and vitamin D should be reviewed with the child's care givers (Evidence D) and slit lamp eye examination and bone densitometry should be considered (Evidence D).

In the USA only the following are approved by the FDA for young children under 4 years: ICS Budesonide nebuliser solution (1-8 years of age), ICS Fluticasone DPI (4 years and older), Salmeterol used in combination with Fluticasone for children 4 years and older, Montelukast 4 mg as a chewable tablet 2-6 years of age and as granules down to 1 year of age. Cromolyn nebuliser is approved for children ≥2 years of age. Appropriate delivery devices are essential. Children under 4 should use a MDI with a valved holding chamber or nebuliser with a face mask. The stepwise approach to treatment recommended by the EP3 is given in Fig. 1.[6]

In this guideline both LABA or Montelukast is given as add on in the 0-4 years of age which differs from some of the other guidelines.

Theophylline is not recommended for children under 5 years. Montelukast is recommended as a trial in children 2 years or older, in situations where inhaled medication delivery is suboptimal due to poor technique. There is no data on the use of long acting β_2 agonist under the age of 4 years. Montelukast may also be considered as add on therapy. Recommendations for treatment according to components of severity, impairment and risk according to the NAEPP EP3 guidelines are summarised in Fig. 2 and a figure for assessment of control and adjusting therapy for children 0-4 years of age is given in Fig. 3. The EP3 guidelines

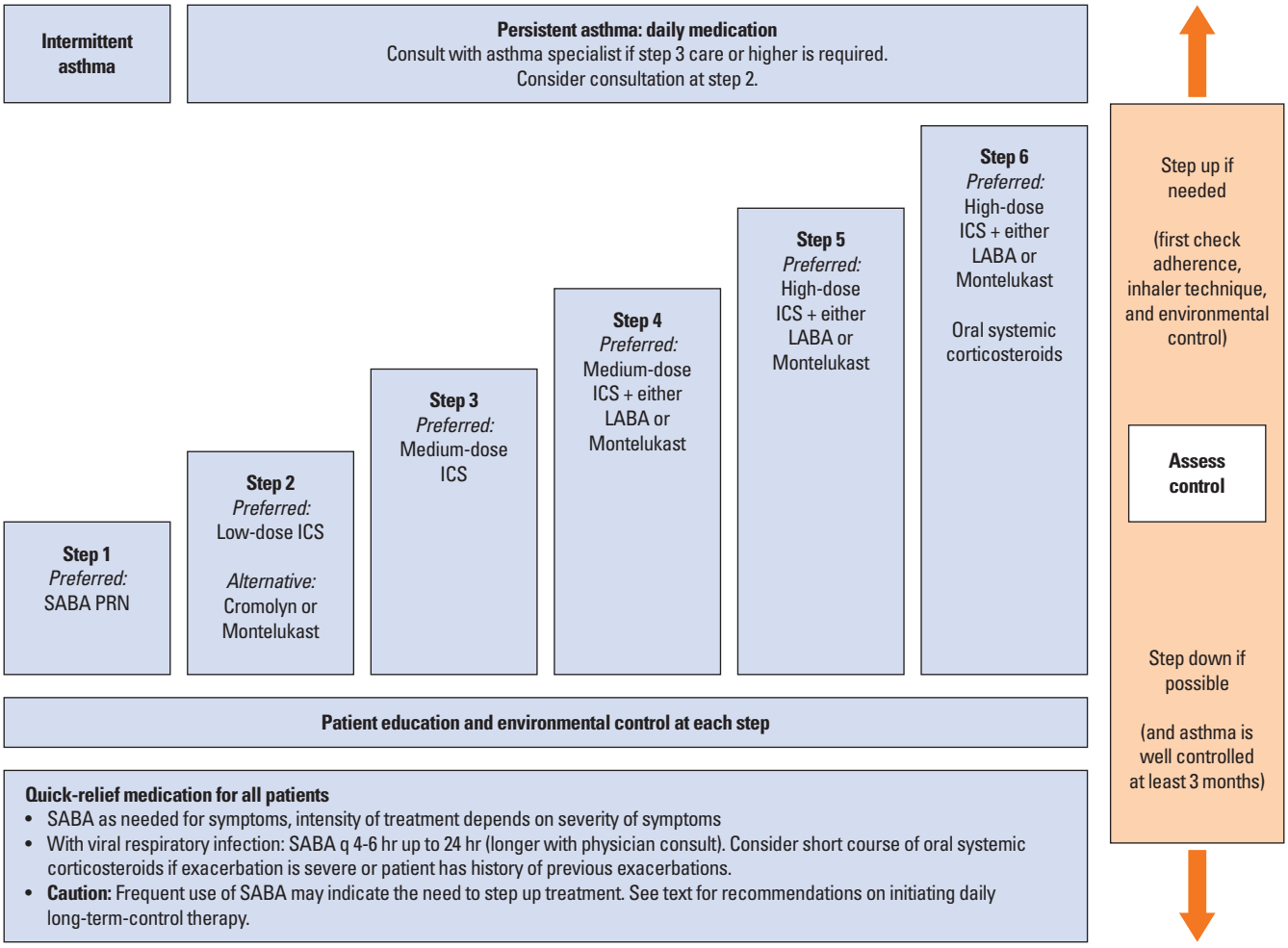

Fig. 1. Stepwise approach for managing asthma in children 0-4 yr of age.
Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy.
ICS, inhaled corticosteroid; LABA, inhaled long-acting β_2-agonist; SABA, inhaled short-acting β_2-agonist.
- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- If clear benefit is not observed within 4-6 wk and patient/family medication technique and adherence are satisfactory, consider adjusting therapy or alternative diagnosis.
- Studies on children 0-4 yr of age are limited. Step 2 preferred therapy is based on Evidence A. All other recommendations are based on expert opinion and extrapolation from studies in older children.

are the most detailed for children under 5 years, but not all of the recommended steps for treatment are evidence based or validated.

THE PRACTALL GUIDELINES

The PRACTALL guidelines[7] for the management of childhood asthma were developed recognising that the evidence base on specific aspects of paediatric asthma management, including therapeutic strategies is severely limited, particularly for children under 5 years. The European Academy of Allergy and Clinical Immunology and the American Academy of Allergy therefore nominated expert teams to find a consensus to serve as a guideline for practice in Europe as well as in North America. Thus these guidelines were not intended for global usage (e.g., in underdeveloped countries).

In these guidelines 4 patterns of asthma are proposed:
1. Transient wheezing: in the first 2-3 years
2. Non-atopic wheezing: triggered by viral infections and remitting later in childhood
3. Persistent asthma: with atopy, eosinophilia, food allergy, positive parental history and high indoor allergen exposure
4. Severe intermittent wheezing: infrequent episodes with minimal morbidity between episodes but with atopic characteristics present.

<table>
<tr><td colspan="2" rowspan="2">Components of severity</td><td colspan="4">Classification of asthma severity (0-4 yr of age)</td></tr>
<tr><td>Intermittent</td><td colspan="3">Persistent</td></tr>
<tr><td colspan="2" rowspan="5"></td><td></td><td>Mild</td><td>Moderate</td><td>Severe</td></tr>
<tr><td rowspan="4">Impairment</td><td>Symptoms</td><td>≤2 days/wk</td><td>>2 days/wk but not daily</td><td>Daily</td><td>Throughout the day</td></tr>
<tr><td>Night-time awakenings</td><td>0</td><td>1-2x/mo</td><td>3-4x/mo</td><td>>1x/wk</td></tr>
<tr><td>Short-acting β_2-agonist use for symptom control (not prevention of EIB)</td><td>≤2 days/wk</td><td>>2 days/wk but not daily</td><td>Daily</td><td>Several times per day</td></tr>
<tr><td>Interference with normal activity</td><td>None</td><td>Minor limitation</td><td>Some limitation</td><td>Extremely limited</td></tr>
<tr><td rowspan="2">Risk</td><td rowspan="2">Exacerbations requiring oral systemic corticosteroids</td><td>0-1/yr</td><td colspan="3">≥2 exacerbations in 6 mo requiring oral systemic corticosteroids,
or ≥4 wheezing episodes/1 yr lasting >1 day AND risk factors for persistent asthma</td></tr>
<tr><td colspan="4">Consider severity and interval since last exacerbation.
Frequency and severity may fluctuate over time.
Exacerbations of any severity may occur in patients in any severity category.</td></tr>
<tr><td colspan="2" rowspan="2">Recommended step for initiating therapy</td><td>Step 1</td><td>Step 2</td><td colspan="2">Step 3 and consider short course
of oral systemic corticosteroids</td></tr>
<tr><td colspan="4">In 2-6 wk, depending on severity, evaluate level of asthma control that is achieved.
If no clear benefit is observed in 4-6 wk, consider adjusting therapy or alternative diagnoses.</td></tr>
</table>

Fig. 2. Classifying asthma severity and initiating treatment in children 0-4 yr of age. Assessing severity and initiating therapy in children who are not currently taking long-term control medication.
EIB, exercise-induced bronchospasm.
- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- Level of severity is determined by both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2-4 wk. Symptom assessment for longer periods should reflect a global assessment such as inquiring whether the patient's asthma is better or worse since the last visit. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past 6 months, or ≥4 wheezing episodes in the past year, and who have risk factors for persistent asthma may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

The PRACTALL guidelines are fairly easy for the clinician to follow. A key point to making a firm diagnosis of asthma in infants 0-2 years is the persistence of symptoms. In children 3-5 years persistence versus intermittent wheezing is more suggestive of asthma, whereas in children 6-12 years, allergen induced symptoms and seasonality suggest a diagnosis of asthma.

These guidelines stress the importance of the history (family history, previous or current eczema, exacerbation rate, identifiable triggers [e.g., exercise]) examination (evidence of atopy such as drug, skin, dermatitis, conjunctivitis and rhinitis). Tests such as skin prick tests and Immunocap RASTs are considered important when assessing all children with recurrent wheeze and lung function and peak flow reversibility should be conducted in those old enough to perform such tests.

The guidelines encourage the clinician to decide whether episodes are precipitated mainly by colds: "virus induced asthma", exercise: "exercise induced asthma", allergens "allergen induced asthma" or different aetiologies (including irritant exposure). Using such an approach, "asthma phenotypes" are identified.

In order to obtain a confident diagnosis of atopy, the history should focus on frequency of symptoms (including wheeze, nocturnal cough, exercise induced wheeze and persistence of cough with colds) as well as more indirect assessments such as fatigue, poor school performance, avoidance of normal play and specific triggers (e.g., exercise). The clinical examination should look for evidence of eczema, dry skin, allergic shiners, irritated conjunctive and persistent oedema of the nasal mucosa, allergic salute and allergic crease on the bridge of the nose.

Recommendations include avoidance of exposure to tobacco-smoke, a balanced diet, avoidance of obesity and encouragement of exercise. Allergen avoidance is recommended when there is sensitisation and a clear association between allergen exposure and symptoms. The PRACTALL guidelines also provide a treatment algorithm for the treatment of asthma in

Components of control		Classification of asthma control (0-4 yr of age)		
		Well controlled	Not well controlled	Very poorly controlled
Impairment	Symptoms	>2 days/wk	≥2 days/wk	Throughout the day
	Night-time awakenings	≤1x/mo	>1x/mo	>1x/wk
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting β_2-agonist use for symptom control (not prevention of EIB)	≤2 days/wk	>2 days/wk	Several times per day
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/yr	2-3/yr	>3/yr
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Recommended action for treatment		• Maintain current treatment • Regular follow up every 1-6 mo • Consider step down if well controlled for at least 3 mo	• Step up (1 step) and • Re-evaluate in 2-6 wk • If no clear benefit in 4-6 wk, consider alternative diagnoses or adjusting therapy • For side effects, consider alternative treatment options	• Consider short course of oral systemic corticosteroids • Step up (1-2 steps), and • Re-evaluate in 2 wk • If no clear benefit in 4-6 wk, consider alternative diagnoses or adjusting therapy • For side effects, consider alternative treatment options

Fig. 3. Assessing asthma control and adjusting therapy in children 0-4 yr of age.
EIB, exercise-induced bronchospasm.
- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- The level of control is based on the most severe impairment or risk category. Assess impairment domain by caregiver's recall of previous 2-4 wk. Symptom assessment for longer periods should reflect a global assessment such as inquiring whether the patient's asthma is better or worse since the last visit.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate poorer disease control. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have not-well-controlled asthma, even in the absence of impairment levels consistent with not-well-controlled asthma.
- Before step up in therapy: Review adherence to medications, inhaler technique, and environmental control. If alternative treatment option was used in a step, discontinue it and use preferred treatment for that step.

children over 2 years of age.[7]

The treatment algorithm is a step-up and step-down approach, but is not graded by level of impairment or risk as is suggested in the EP3 guidelines. For acute attacks, Ipratropium bromide combined with β_2 agonists may result in favourable outcomes in children.[22] Inhaled corticosteroids are recommended as a first line treatment for persistent asthma with leukotriene receptor antagonists as an alternative.[23]

Evidence for the anti-inflammatory effects of Montelukast on nitric oxide exhalation is cited[24] and its usefulness as add on treatment to inhaled corticosteroids[25] justifies its place in step up treatment. Because efficacy of LABA in the management of young children is still unclear[26] and suggestions that children using LABA's regularly[27] may have an increased risk of exacerbations and hospitalisations, the PRACTALL guidelines only recommend their use in severe asthmatics unresponsive to inhaled corticosteroids at high doses, or in those in whom the addition of LTRA's have not improved the patient's symptoms. LABA's should never be used without concomitant inhaled corticosteroids.

The PRACTALL guidelines also address asthma treatment in children 0-2 years. Intermittent β_2 agonists are the first choice and LTRA's are recommended for long or short term treatment of viral wheezing. Nebulised or MDI plus spacer delivered in-

haled corticosteroids are recommended for persistent asthma, especially when severe episodes requiring frequent oral corticosteroids have occurred. Evidence of atopy should lower the threshold for inhaled corticosteroid therapy, which should be first line in such cases. There are very few studies of the efficacy and safety of allergen immunotherapy for asthmatics under the age of 5 years.

Sublingual immunotherapy (SLIT) may be a safe and effective alternative to subcutaneous injections in children with asthma[28] and the effects may be long lasting,[29] but immunotherapy is not recommended when asthma is unstable. Patients should have few, if any, symptoms and a FEV1 of at least 80% of predicted value. Age is not an absolute contraindication and therapy can be given from 3 years of age, with caution by well trained staff in specialist centres.

Children under 5 years should be given practical instructions on inhaler use while their parents require training in inhaler devices and strategies for managing episodes. They should be provided with theoretical and practical education including a written action plan. Asthma education is an integral part of asthma management and must be offered to all parties involved. The asthma quiz for kids[30] and the paediatric asthma control tests[31] are patient based tools for identifying children with uncontrolled asthma.

THE ERS TASK FORCE GUIDELINES

These guidelines were developed as evidence based guidelines while recognising that there is limited evidence available for the treatment of wheezing disorders in preschool children. The cumulative prevalence of wheeze is almost 50% by the time children are 6 years old.[32] It is proposed that given the multifactorial nature of all wheezing disorders in childhood, the clinical phenotypes described in the literature are extremes of a broad spectrum of wheezing disorders.[33] These guidelines utilised the Cochrane Library, Pubmed and EMBASE to search for evidence based treatments and graded the evidence into high, moderate or low grade evidence based on study design and quality and also applied the GRADE methodology.[34]

They concluded that almost all of the evidence available was of low quality. In quoting the GINA definition that asthma is a syndrome with a highly variable clinical spectrum characterised by airway inflammation,[35] they point out that inflammation has been poorly studied in preschool children and may be absent in very young children who wheeze. Thus, the majority of the task force agreed not to use the term "asthma" to describe preschool wheezing since there is "insufficient evidence showing that the pathophysiology of preschool wheezing is similar to that of asthma in older children or adults".

It is believed that specific combinations of genetic and environmental factors determine the patient's phenotype, but that in clinical practice most of these factors are as yet unknown. Furthermore the guidelines stress that the descriptions of wheeze used in epidemiological studies (transient versus persistent wheeze) can only be applied retrospectively.[19] It was thus suggested that definitions of temporal patterns of a wheeze would be more useful to clinicians, than retrospective definitions of wheeze which would be more useful for epidemiological studies.

A temporal pattern of wheeze is thus suggested. Wheeze may be an "episodic viral wheeze", with the child being well between episodes. These episodes are caused by rhinovirus, respiratory syncytial virus, human meta pneumo virus, para influenza virus and adenovirus.

Whether or not the initial episode is classified as "bronchiolitis" is irrelevant. Episodic viral wheeze disappears by the age of six years, but may continue into school age or change into "multiple-trigger wheeze". "Multiple-trigger wheeze" describes children who also respond with wheezing to other triggers. These include tobacco, crying, laughter or exercise.[36] Many believe that "multiple-trigger wheeze" reflects chronic allergic airway disease and could be classified as asthma. This classification differs from the retrospective epidemiological classification of wheezing reported from the Tucson birth cohort[19] of "transient" and "persistent wheezing". Children with transient wheezing, wheezed during the first 3 years of life and do not have a personal history of eczema or a family history of asthma. The group of "late onset wheezers" who started wheezing after 3 years often had associated maternal asthma, male sex and a history of rhinitis.

The diagnosis of wheezing is made by history taking alone and investigations are justified when symptoms are present from birth, airway obstruction is abnormally severe and recovery is slow, or incomplete, or associated with repeated admissions.

Sensitisation to hen's egg at the age of 1 year is a reasonable marker for allergic sensitisation to aeroallergens at age 3 years with a specificity of >90% and sensitivity of 30%.[37]

There appear to be no studies supporting the usefulness of pulmonary function tests in children with non-specific symptoms, or in distinguishing between episodic and multiple trigger wheeze, but a bronchodilator response in young children may assist in discriminating common wheezing disorders from other conditions. Reference values for FeNo are only available for children over 4 years.[38]

Biopsy evidence of inflammation of the airways in young children is scarce and the only consistent biopsy finding in wheezy children is thickening of the basement membrane,[39] but not in infants at median age of 12 months, whereas a study done at mean age 29 months in wheezy children[40] reported eosinophilic airway inflammation and reticular basement membrane thickening, implying an age window during when "inflammation" develops.

Treatment guidelines stress the importance of allergen avoidance but it is unclear whether the required reduction in allergen

exposure can be achieved in normal life and there are no studies or allergen avoidance in preschool children with wheeze.[41] Studies on the effectiveness of parental education are disappointing.[42]

Treatment guidelines of the ERS task force recommend inhaled β_2 agonists as the most effective bronchodilators available; suggesting that single isomer R-albuterol is preferable. There are no published randomised placebo controlled trials in preschool children on the addition of long acting β_2 agonists to inhaled corticosteroids. Inhaled corticosteroids are effective for symptom control, reduction of exacerbations, lung function and airway responsiveness in children with multiple-trigger wheeze.[43]

Doses recommended in preschool children up to 400 μg Beclomethazone equivalent may be used with metered dose inhaler plus a spacer, without benefit from higher doses. Those with a positive family history, over 2 years and frequent symptoms show the best response to inhaled steroids. However one study using inhaled Fluticazone to wheezy infants showed no improvement in lung function.[44] It is suggested that after a trial of 3 months of inhaled corticosteroids, treatment should be withdrawn in those who become almost completely free of wheeze to assess the need for ongoing therapy.

For episodic viral wheeze the clinical benefits of inhaled corticosteroids are controversial and maintenance treatment up to 400 μg/day does not reduce the severity or frequency of attacks in these children. Nasal steroids have not been demonstrated to be of benefit in preschool children with recurrent wheeze with allergic rhinitis. Furthermore there is no evidence that parent initiated oral steroids are associated with benefit, in terms of hospital admissions, symptom scores, or bronchodilator use.

A study of Montelukast in 689 young children with multiple-trigger wheeze achieved an improvement in symptom and a 30% reduction in exacerbations.[23] Cromones and Xanthenes are not recommended and neither is allergen immunotherapy outside the setting of a randomised controlled trial.

THE NEW GINA GUIDELINES

A comprehensive strategy for asthma management and prevention in children 5 years and younger has recently been published.[9] It addresses risk factors associated with the development of asthma, the diagnosis of asthma and management and pharmacological treatment (education, control, pharmacotherapy and the management of acute exacerbations). These guidelines are evidence based using Categories A-D in which Category A is derived from a rich body of data of randomised controlled trials, Category B from a limited body of controlled trial data, post hoc analysis or meta analysis of RCT, Category C for non-randomised or observational studies and Category D for panel consensus judgment.

For risk factors of asthma the guidelines recognise that there is mixed evidence for house dust mite avoidance and no evidence that anti-house dust measures prevent the onset of asthma. Unless the child is sensitised to a pet species, there is insufficient data to recommend for or against the presence of a pet in the house. Sensitization to cockroaches is associated with an increased risk of developing asthma[45] and sensitization to Alternaria is a risk factor for more severe asthma.[46] There is no evidence that diet in pregnancy or breast feeding or probiotics influences the development of asthma, but some evidence that a farming environment may be protective.

A diagnosis of asthma should be considered when a young child presents a symptom pattern of wheeze/cough occurring recurrently, during sleep, with activity, laughing or crying in the presence of a positive family history and evidence of allergic sensitisation. Although no tests diagnose asthma with certainty in young children, a therapeutic trial with short acting bronchodilators and inhaled glucocorticosteroids for at least 8-12 weeks may provide some guidance as to the presence of asthma (Evidence D). Lung function, bronchial challenge and other physiological tests do not have a major role in the diagnosis of asthma in children 5 years and younger. To aid early identification of asthma in the clinical setting, a number of risk profiles and predictive assessments have been published. The Asthma Predictive Index (API)[47] based on the Tuscan study showed that a child with a positive API has a 4-10 fold greater chance of developing asthma between ages 6 and 13 while 95% of children with a negative API remained free of asthma (Evidence C).

For children under 5, asthma management plans based on the level of respiratory symptoms are just as effective as plans based on self monitoring of lung function (Evidence B).[48] The relationship between "current control" and "future risk" described in the NAEPP guidelines[6] have not yet been carefully studied in small children. The importance of good daily asthma control is stressed. The guidelines warn against excessive or prolonged unnecessary use of inhaled, or systemic corticosteroids, since many children with wheezing go into remission. No objective measures to assess clinical control have been validated in children younger than 4 years. It appears that "asthma" is rare in the transient wheeze groups, but there are other phenotypes.

Inhaled glucocorticosteroids are effective in the management of asthma in young children (Evidence A), but do not induce a remission. Low doses have not been associated with any clinically serious adverse systemic effects.

Table 1 lists the low doses which have not been associated with clinically adverse effects in trials including measures of safety. Table 2 presents the GINA management approach based on asthma control for children 5 years and younger.

Anti leukotrienes improve asthma outcomes in young children (Evidence A), however the role of leukotrienes as add on therapy in children under 5 years whose asthma is uncontrolled on inhaled glucocorticosteroids has not yet been specifically evaluated. Leukotriene receptor antagonists are safe.

Table 1. Low daily doses* of inhaled glucocorticosteroids for children 5 yr and younger

Drug	Low daily dose (μg)
Beclomethasone dipropionate	100
Budesonide MDI + spacer	
Budesonide nebulized	200
500	
†Ciclesonide	NS
Fluticasone propionate	100
†Mometasone furoate	NS
†Triamcinolone acetonide	NS

*A low dose is defined as the dose which has not been associated with clinically adverse effects in trials including measures of safety. This is not a table of clinical equivalence.
†NS = not studied in this age group.

Table 2. Asthma management approach based on control for children 5 yr and younger

Asthma education Environmental control As needed rapid-acting β_2-agonists		
Controlled on as needed rapid-acting β_2-agonists	Partly controlled on as needed rapid-acting β_2-agonists	Uncontrolled or only partly controlled on low-dose inhaled glucocorticosteroid*
⬇	⬇	⬇
Controller options		
Continue as needed rapid-acting β_2-agonists	Low-dose inhaled glucocorticosteroid	Double low-dose inhaled glucocorticosteroid
	Leukotriene modifier	Low-dose inhaled glucocorticosteroid plus leukotriene modifier

*Oral glucocorticosteroids should be used only for treatment of acute severe exacerbations of asthma. Shaded boxes represent the preferred treatment options.

Long acting bronchodilators are not recommended for children under 5 years (Evidence D) and cromolyn cannot be recommended (Evidence A). Suggested levels of control are provided in Table 3 for children 5 years and younger with asthma.

The treatment of intermittent wheezing remains controversial where a diagnosis of asthma seems unlikely. Evidence for efficacy of short term controllers (e.g., inhaled glucocorticosteroids, leukotriene modifiers and oral glucocorticosteroids) is lacking. The initial treatment is a dose of rapidly acting inhaled β_2 agonist every 4-6 hours as needed for a day or more until symptoms disappear (Evidence A). Regular controller treatment may be indicated in a child with less frequent but more severe episodes of viral induced wheeze (Evidence D). The new GINA guidelines also provide detailed management plans for acute exacerbations.

CONCLUSIONS

All the recent guidelines have stressed the difficulties in making a firm diagnosis of asthma in children under 5 and several wheezy phenotypes have been identified. Each of the guidelines provides a unique perspective and important insights into the problems facing clinicians treating young children with asthma and there are a number of recommendations which are clear and are repeated in each of the guidelines.

However, following guidelines depend on factors within the guidelines themselves, social-cultural context of the strategies used to spread them and organizational, economic and political context for the implementation of guideline strategies.[49] Knowledge, attitude, skills, experiences, beliefs and values play a fundamental role both for the physician, the parent and the patient. Lack of consensus among different new guidelines can be a major obstacle to doctors adopting a particular guideline and complex guidelines are not practical for busy doctors to follow.

Lack of familiarity with guidelines is a common problem and it has been estimated that over 10% of doctors ignore the existence of 78% of available guidelines.[49] Guidelines may not be followed if they are considered to be based on "opinion", poor evidence, or do not consider patients values and preferences.

Thus for the under 5's we have a lot of information through extensive reviews of the available literature on studies of asthma aetiology, phenotypes, natural history and pharmacotherapy which is consolidated in the available guidelines.

In the future new guidelines are expected to be published using the GRADE system (Grading of Recommendations, Assessment, Development and Evaluation) whose activity is endorsed by the WHO[34] and an attempt has been made to include aspects of the GRADE recommendation in the ERS guidelines.[8]

This new method will not only assess the quality of the evidence across studies for each important outcome but the balance between benefits, harm and strengths of recommendations, bringing scientific evidence near to real life situations which will make guidelines easier to apply.

The available guidelines do not adequately address the management of asthma or wheezing phenotypes for children under the age of 5 in the underdeveloped world where there is a lack of resources, but also because there is an absence of studies on asthma management in practice in the under 5's in these regions.

It would be prudent for regions and countries to consider all the available guidelines and to adapt then so that they are understandable in regional contexts and that the recommendations are in line with available resources in a particular region

Table 3. Levels of asthma control in children 5 yr and younger*

Characteristic	Controlled (All of the following)	Partly controlled (Any measure present in any week)	Uncontrolled (3 or more of features of partly controlled asthma in any week)
Daytime symptoms: wheezing, cough, difficult breathing	None (less than twice/wk, typically for short periods on the order of minutes and rapidly relieved by use of	More than twice/wk (typically for short periods on the order of minutes and rapidly relieved by use of a rapid-acting bronchodilator)	More than twice/wk (typically last minutes or hours or recur, but partially or fully relieved with rapid-acting bronchodilator)
Limitations of activities	None (child is fully active, plays and runs without limitations or symptoms)	Any (may cough, wheeze, or have difficulty breathing during exercise, vigorous play, or laughing)	Any (may cough, wheeze or have difficulty breathing during exercise, vigorous play, or laughing)
Nocturnal symptoms/awakening	None (including no nocturnal coughing during sleep)	Any (typically coughs during sleep or wakes with cough, wheezing, and/or difficult breathing)	Any (typically coughs during sleep or wakes with cough, wheezing, and/or difficult breathing)
Need for reliever/rescue treatment	≤2 days/wk	>2 days/wk	>2 days/wk

*Any exacerbation should prompt review of maintenance treatment to ensure that it is adequate. Although patients with current clinical control are less likely to experience exacerbations, they are still at risk during viral upper respiratory tract infections and may still have one or more exacerbations per year.

to facilitate their implementation and thus improve the management of asthma in young children around the world.

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