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POSITION PAPER

International consensus on (ICON) pediatric asthma

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Abstract

Asthma is the most common chronic lower respiratory disease in childhood throughout the world. Several guidelines and/or consensus documents are available to support medical decisions on pediatric asthma. Although there is no doubt that the use of common systematic approaches for management can considerably improve outcomes, dissemination and implementation of these are still major challenges. Consequently, the International Collaboration in Asthma, Allergy and Immunology (iCAALL), recently formed by the EAACI, AAAAI, ACAAI, and WAO, has decided to propose an International Consensus on (ICON) Pediatric Asthma. The purpose of this document is to highlight the key messages that are common to many of the existing guidelines, while critically reviewing and commenting on any differences, thus providing a concise reference. The principles of pediatric asthma management are generally accepted. Overall, the treatment goal is disease control. To achieve this, patients and their parents should be educated to optimally manage the disease, in collaboration with healthcare professionals. Identification and avoidance of triggers is also of significant importance. Assessment and monitoring should be performed regularly to re-evaluate and fine-tune treatment. Pharmacotherapy is the cornerstone of treatment. The optimal use of medication can, in most cases, help patients control symptoms and reduce the risk for future morbidity. The management of exacerbations is a major consideration, independent of chronic treatment. There is a trend toward considering phenotype-specific treatment choices; however, this goal has not yet been achieved.

Asthma is the most common chronic lower respiratory disease in childhood throughout the world. Asthma most often starts early in life and has variable courses and unstable phenotypes which may progress or remit over time. Wheeze in preschool children may result from a number of different conditions; around half of preschool wheezers become asymptomatic by school age irrespective of treatment. However, asthma symptoms may persist, often for life, especially in atopic and more severe cases. The impact of asthma on the quality of life of patients, as well as its cost, is very high. Therefore, appropriate asthma management may have a major impact on the quality of life of patients and their families, as well as on public health outcomes (1). Asthma in childhood is strongly associated with allergy, especially in developed countries. Common exposures such as tobacco smoke, air pollution, and respiratory infections may trigger symptoms and contribute to the morbidity and occasional mortality. Currently, primary prevention is not possible. However, in established disease, control can be achieved and maintained with appropriate treatment, education, and monitoring in most children.

In children, asthma often presents with additional challenges not all of which are seen in adults, because of the maturing of the respiratory and immune systems, natural history, scarcity of good evidence, difficulty in establishing the diagnosis and delivering medications, and a diverse and frequently unpredictable response to treatment.

It is therefore not surprising that several guidelines and/or consensus documents are available to support medical decisions on pediatric asthma. These vary in scope and methodology, local, regional, or international focus, or their exclusivity to pediatric asthma. Although there is no doubt that the use of common systematic approaches for management, such as guidelines or national programs, can considerably improve outcomes, dissemination and implementation of these recommendations are still major challenges.

For these reasons, the International Collaboration in Asthma, Allergy and Immunology (iCAALL) (2), formed in 2012 by the EAACI, AAAAI, ACAAI, and WAO, helped organize an international writing group to address this unmet need with an International Consensus on (ICON) Pediatric Asthma. The purpose of this document is to highlight the

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key messages that are common to many of the existing guidelines, while critically reviewing and commenting on any differences, thus providing a concise reference.

Methodology

A working committee was formed and approved by the Steering Committee of iCAALL and the participating organizations (authors 1–11). The criteria used for the formation of the committee were international representation, relevance to the field, and previous participation in pediatric asthma guidelines. The members of the committee proposed relevant documents to be appraised. These were the Australian Asthma Management Handbook, 2006 (AAMH) (3), the Global Strategy for Asthma Management and Prevention, published by GINA and updated in 2011 (GINA) (4), Global Strategy for the Diagnosis and Management of Asthma in Children 5 Years and Younger, 2009 (GINA < 5) (5), the Japanese Guideline for Childhood Asthma, 2008 (JGCA) (6), the National Heart and Blood Institute, National Asthma Education and Prevention Program, Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, 2007 (NAEPP) (7), the Diagnosis and treatment of Asthma in Childhood: a PRACTALL Consensus Report, 2008 (PRACTALL) (8), and the British Guideline on the Management of Asthma, Revised 2011 (SIGN) (9). Each member undertook responsibility for preparing tables and relevant commentaries comparing the included documents in a specific domain. These were subsequently compiled into a first draft which was circulated among the authors for comments and corrections. The revised document was then circulated among an independent reviewing group (authors 12–68), the comments of which were taken into account in the final draft, which was approved by the governing bodies of the participating organizations and submitted for publication. Recommendations were extrapolated from the reference documents and presented using Evidence levels (A–D) (10).

Definition and classifications of pediatric asthma

Definition

The complexity and diversity of asthma in both children and adults are indisputable and what is 'true' asthma is frequently argued, especially in childhood. Nevertheless, no guideline proposes a differentiation between pediatric and adult asthma in regard to the definition.

All current definitions are descriptive, including symptoms and their patterns, as well as underlying mechanisms, at different levels of detail. With only minor deviations in term usage, asthma is understood as a chronic disorder, presenting with recurrent episodes of wheeze, cough, difficulty in breathing, and chest tightness, usually associated with variable airflow obstruction and bronchial (airway) hyperresponsiveness (BHR or AHR).

Chronic inflammation is recognized as the central pathology. In contrast, airway remodeling is only mentioned in the definition of the JGCA. The causal link(s) between chronic inflammation, BHR, and symptoms are poorly defined; some definitions suggest that inflammation causes symptoms and BHR, others that BHR causes the symptoms, and yet others that this relationship is unclear.

Definitions often include more details, such as specific cell types (e.g. mast cells, eosinophils, etc.), timing of symptoms (particularly at night or early morning), reversibility (often), or triggers (viral infection, exercise, and allergen exposure). The relative importance of each of these additional elements can be argued; nevertheless, they are neither necessary for nor exclusive to asthma and therefore do not add appreciably to the sensitivity or specificity of the previously mentioned, generally accepted elements.

Taking the above into account, a working definition, representing a synopsis from all guidelines, is shown in Box 1.

Box 1

Asthma definition

Asthma is a chronic inflammatory disorder associated with variable airflow obstruction and bronchial hyperresponsiveness. It presents with recurrent episodes of wheeze, cough, shortness of breath, and chest tightness.

Classifications

To address diversity and guide management, several factors have been used to classify pediatric asthma (Fig. 1).

Age is an important classification factor, relevant to diagnosis and treatment. There is general consensus that milestone ages are around 5 and 12 years, and important clinical and epidemiological characteristics appear to change around those ages. In some documents, 'infantile' asthma (<2 or 3 years) is further distinguished. Special characteristics of adolescence are emphasized in most documents (Fig. 1A).

There is slightly less consistency when it comes to severity and persistence, which have been extensively used in the past to classify asthma. With respect to persistence, asthma is usually classified as intermittent or persistent; in addition, infrequent and frequent intermittent classes are proposed by the AAMH. With respect to severity, persistent asthma is usually classified as mild, moderate, and severe. However, in PRACTALL and SIGN, only severe asthma is mentioned, while in the JGCA, a 'most severe' class is proposed. Classifications of severity/persistence are challenging as they require differentiation between the inherent severity of the disease, resistance to treatment, and other factors, such as adherence to treatment. Hence, these classifications are currently recommended only for initial assessment of the disease severity and are being replaced by the concept of 'control', which is more clinically useful.

Control is generally accepted as a dynamic classification factor, critical to guiding treatment. Control categories are quite relevant in clinical practice. Slightly different terms are used for the levels of asthma control, which are generally three (controlled, partly controlled, and uncontrolled). In some cases, 'complete' control is described, as a state with no disease activity (Table 1).

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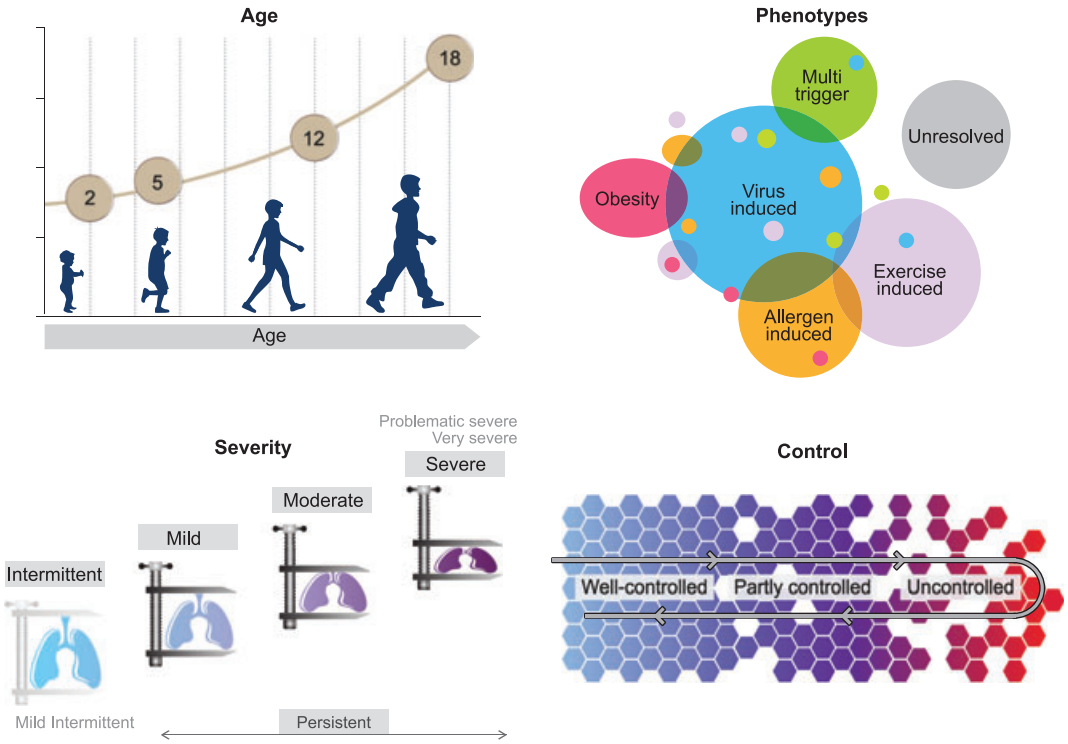

Figure 1 Pediatric asthma is a diverse condition and several factors can be used for its classification. Important changes in clinical presentation take place in relation to age (upper left). Although limits are arbitrary and may differ between individuals, infancy, preschool age, school age and adolescence are generally considered as milestones. Phenotypes (upper right) may result from different underlying pathophysiologies (endotypes), however, there is considerable overlap and possible changes over time. Severity (lower left) can range from very mild to life-threatening; although not necessarily discrete, a stepwise approach has been used to characterize severity and inform treatment initiation. More recently, the level of control (lower right) of both current symptoms and risk of future morbidity is preferred as a measure, towards which asthma management is evaluated.

In assessing severity and control, a distinction between current impairment and future risk is proposed by NAEPP and GINA. Although not stated in the other documents, these two elements are clearly distinguishable and may differentially respond to treatment; therefore, they should be considered independently.

Subgrouping into phenotypes is frequently mentioned: GINA and GINA <5 refer to different phenotypic classification systems, commenting that their clinical usefulness remains a subject of investigation. NAEPP suggests that evidence is emerging for phenotypic differences that may influence treatment choices, but does not propose a specific classification system. PRACTALL proposes a phenotypic classification according to apparent trigger (virus-induced, exercise-induced, allergen-induced, and unresolved), suggesting that these should be taken into account for treatment selection. The above variation may reflect the rapidly developing evidence with respect to different subgroups of pediatric asthma. For many patients, several apparent triggers may be identified, also varying over time, highlighting the difficulty in providing a simple phenotype classification system. Future phenotypic classifications should demonstrate important advantages in management. Notably, most documents give special consideration to 'exercise-induced asthma' and 'severe asthma'.

Research Recommendations

- Asthma phenotypes in childhood should be further characterized in detail and defined, using epidemiological, statistical, and biological criteria
- Geopolitical particularities (e.g. low-income countries, climate zones) to be taken into account
- The existence of distinct pathophysiological mechanisms underlying a clinical presentation (endotypes) should be evaluated in children
- The clinical value of phenotype/endotype classifications, including differential response to treatment and/or natural history, needs to be demonstrated
- Phenotype-specific biomarkers will be useful in practice
- The time points when wheeze/asthma changes character may be identified with more precision

Guideline Update Recommendations

- Remodeling can be considered in future definitions of asthma
- Current impairment and future risk should be considered in future guidelines

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Table 1 Asthma control

Domain	Component	Level of control			
		Complete	Good	Partial	None
Impairment	Symptoms – daytime	None	≤ 2/week	>2/week	Continuous
	Symptoms – nighttime/awakenings	None	≤ 1/month	>1/month	Weekly
	Need for rescue medication	None	≤ 2/week	>2/week	Daily
	Limitation of activities	None	None	Some	Extreme
	Lung function – FEV1, PEF (predicted or personal best)	>80%	≥ 80%	60–80%	<60%
Risk	Exacerbations (per year)	0	1	2	>2
	Medication side effects	None		Variable	

Components of asthma control include current impairment (symptoms, need for rescue medication, limitation of activities, lung function in children >5 years) and future risk (exacerbations, medication side effects). Levels of control are indicative; the most severe impairment or risk defines the level.

- Phenotype/endotype differences in diagnosis and management should be addressed in more detail

Pathogenesis and pathophysiology

There is general agreement that asthma is a disease of chronic inflammation, airway hyperresponsiveness, and chronic structural changes known as airway remodeling (Fig. 2). Some of the guidelines provide extensive discussion of these topics, while others focus mostly on diagnosis and treatment and mention these concepts in introductory remarks or as part of an asthma definition.

Asthma can begin at any age but most often has its roots in early childhood (11). The prevalence of asthma has increased in many countries (12), although in some cases it may have leveled off (12, 13). As asthma inception depends on both genetics (14, 15) and the environment (16), modifiable environmental factors have been sought in an effort to identify targets for prevention. Many guidelines mention infections, exposure to microbes, stress, pollutants, allergens, and tobacco smoke as possible contributing factors. The development of allergen-specific IgE, especially if it occurs in early life, is an important risk factor for asthma, especially in developed countries (17).

Unfortunately, to date this knowledge has not translated into successful programs for primary prevention. Although increased exposure to mainly indoor allergens has been implicated in the development of asthma through induction of allergic sensitization (17, 18), current guidelines avoid giving specific recommendations, as the few existing intervention studies have produced conflicting results (19–21). Avoidance of exposure to tobacco smoke during pregnancy and infancy is the only properly documented modifiable environmental factor that can be safely recommended for the primary prevention of asthma (Evidence B). Other, potentially useful, interventions, such as maternal diet (22) or vitamin D supplementation (23), require confirmation, whereas agents that would mobilize regulatory immune mechanisms for the primary prevention of asthma (e.g. oral bacterial products, immunomodulators) are being actively pursued (24).

Persistent asthma is universally regarded as a disease of chronic airway inflammation. Increased populations of mast cells, eosinophils, lymphocytes, macrophages, dendritic cells, and others contribute to inflammation (25, 26). Structural cells such as epithelial cells and smooth muscle cells may also contribute to the inflammatory milieu (27, 28). The inflammatory and structural cells collectively produce mediators such as cytokines, chemokines, and cysteinyl leukotrienes that intensify the inflammatory response and promote airway narrowing and hyperresponsiveness (29). AHR is associated with excessive smooth muscle contraction in response to nonspecific irritants and viral infections, and for allergic individuals, exposure to specific allergens (30, 31). Neural mechanisms, likely initiated by inflammation, contribute to AHR (32).

Acute episodes of airway narrowing are initiated by a combination of edema, infiltration by inflammatory cells, mucus hypersecretion, smooth muscle contraction, and epithelial desquamation. These changes are largely reversible; however, with disease progression, airway narrowing may become progressive and constant (33). Structural changes associated with airway remodeling include increased smooth muscle, hyperemia with increased vascularity of subepithelial tissue, thickening of basement membrane and subepithelial deposition of various structural proteins, and loss of normal distensibility of the airway (34, 35). Remodeling, initially described in detail in adult asthma, appears to be also present in at least the more severe part of the spectrum in pediatric asthma (36, 37).

Research Recommendations

- Increased efforts for understanding the mechanisms of pediatric asthma are clearly needed
- The basic mechanisms underlying pediatric asthma phenotypes/endotypes should be better characterized
- The presence and progression of airway remodeling in different pediatric asthma phenotypes/endotypes requires considerable effort
- Primary prevention should be the focus of intensive research. Early life and/or pregnancy are evident targets
- Secondary prevention, especially in children with atopic dermatitis, may also result in improved outcomes

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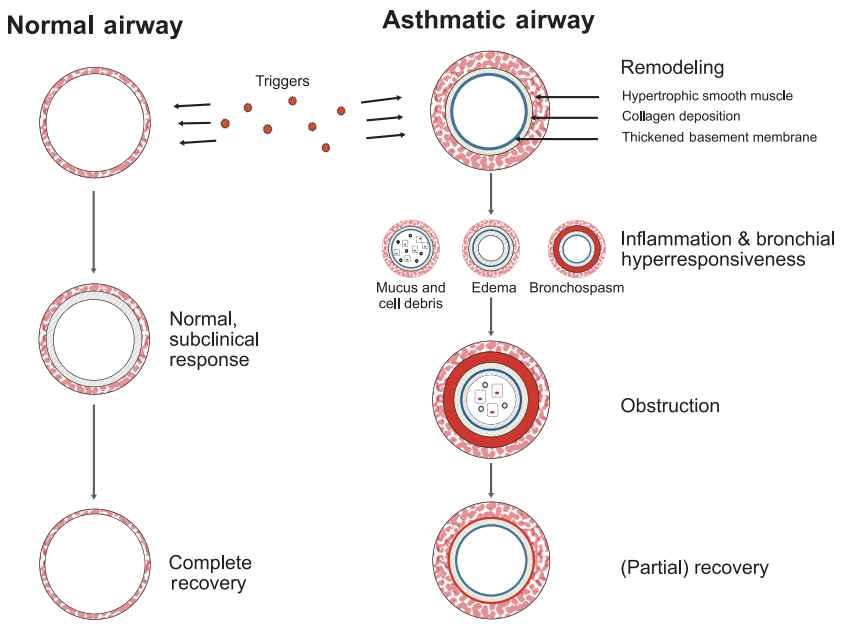

Figure 2 In children, as in adults, pathological changes of the bronchi ('airway remodeling'), are present in the airways. Inflammation is triggered by a variety of factors, including allergens, viruses, exercise etc. These factors also induce hyperreactive responses in the asthmatic airways. Inflammation and hyperreactivity lead to airway obstruction. Although pathophysiological changes related to asthma are generally reversible, partial recovery is possible.

Guideline Update Recommendations

- Pathophysiological mechanisms have a background role in guidelines. Nevertheless, current knowledge on bronchial inflammation and remodeling in children can be detailed

Natural history

Asthma may persist or remit and relapse (38). Natural history and prognosis are particularly important in children, because a considerable proportion of children who wheeze outgrow their symptoms at some age (39). The likelihood of long-term remission, on the one hand, or progression and persistence of disease, on the other, has received considerable attention in the medical literature over the last decade (40–42). However, the natural history of asthma, with the exception of the common understanding that asthma starts early in life and may run a chronic course, is not prominent in many current guidelines.

The most detailed reference to natural history is made in the NAEPP. Among children who wheeze before the age of 3 years, the majority will not experience significant symptoms after the age of 6 years. Nevertheless, it appears that decrements in lung function occur by the age of 6 years, predominantly in those children whose asthma symptoms started before 3 years of age. The Asthma Predictive Index (API) uses parental history of asthma and physician diagnosis of atopic dermatitis as major criteria, along with peripheral blood eosinophilia, wheezing apart from colds, and physician diagnosis of allergic rhinitis as minor criteria, to predict disease persistence at the age of 6 years, in children younger than 3 years with a history of intermittent wheezing (43). As shown in at least three independent populations (43–45), the API holds a modest ability to predict disease persistence into early school age and is also recommended by GINA <5 (Evidence C). However, extrapolation of findings from epidemiological studies to the assessment of future risk in individual patients in the clinical setting, or in different populations, may not be as straightforward (46).

PRACTALL also stresses the variable natural history patterns of recurrent wheezing in early childhood. Infants with recurrent wheezing have a higher risk of developing persistent asthma by the time they reach adolescence, and atopic children in particular are more likely to continue wheezing. In addition, the severity of asthma symptoms during the first years of life is strongly related to later prognosis. However, both the incidence and period prevalence of wheezing decrease significantly with increasing age.

Research Recommendations

- Predictive (bio)markers of persistence are needed
- It will be beneficial to further characterize the stability/natural history of pediatric asthma phenotypes
- The relationships between inception, exacerbations, and remodeling should be explored in childhood asthma
- Further research into asthma predictive indices may improve their performance and/or generalize their applicability

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- The effect of guideline-proposed treatment on the natural history of asthma warrants further study

Guideline Update Recommendations

- Natural history is an important element of pediatric asthma requiring more attention
- The evaluation of risk for persistence should be emphasized

Diagnosis

History of recurrent episodes of wheezing is universally accepted as the starting point for asthma diagnosis in children. The required number/rate of such episodes is generally not specified, although an arbitrary number of three or more has been proposed. Typical symptom patterns are important for the establishment of the diagnosis. These include recurrent episodes of cough, wheeze, difficulty in breathing, or chest tightness, triggered by exposure to various stimuli such as irritants (cold, tobacco smoke), allergens (pets, pollens, etc.), respiratory infections, exercise, crying, or laughter, appearing especially during the night or early morning (Evidence A–B). Personal history of atopy (e.g. eczema, allergic rhinitis, or food/aeroallergen sensitization) and family history of asthma strengthen the diagnosis (Table 2).

Taking into account that asthma symptoms are not pathognomonic and may occur as a result of several different conditions, differential diagnosis is very important and includes common childhood problems as well as a long list of mostly infrequent but rather severe diseases, which are listed with minor differences in all guidelines (Table 3).

Evaluation of lung function

Evaluation of lung function is important for both diagnosis and monitoring. Nevertheless, normal lung function tests do not exclude a diagnosis of asthma, especially for intermittent or mild cases (47). Therefore, these tests are considered supportive. Performing the tests when the child is symptomatic may increase sensitivity.

Spirometry is recommended for children old enough to perform it properly; the proposed range of minimum age is between 5 and 7 years. At this time, given the sparse evidence available, decision points do not differ from those used in adults (FEV1: 80% of predicted, reversible after bronchodilation by $\geq 12\%$, 200 ml, or $\geq 10\%$ of predicted); however, these should be re-evaluated. Spirometry may not be readily available in some settings, particularly low-income countries.

Peak expiratory flow (PEF) measurements, including reversibility or variability, may also help support a suspected diagnosis, in children capable of performing them properly. However, NAEPP points out that a normal range for PEF is wide and so it is more useful for monitoring rather than diagnosis.

In children younger than 5 years, newer lung function tests that require less cooperation have been used (such as oscillometry

Table 2 Diagnosis of pediatric asthma

History
Recurrent respiratory symptoms (wheeze, cough, dyspnea, chest tightness)
typically worse at night/early morning
exacerbated by exercise, viral infection, smoke, dust, pets, mold, dampness, weather changes, laughing, crying, allergens
Personal history of atopy (eczema, food allergy, allergic rhinitis)
Family history of asthma or atopic diseases
Physical examination
Chest auscultation for wheezing
Symptoms/signs of other atopic diseases such as rhinitis or eczema
Evaluation of lung function (spirometry with reversibility testing, preferred to PEFR, which can nevertheless be used if resources are limited)
Evaluation of atopy (skin prick tests or serum-specific IgE)
Studies for exclusion of alternative diagnoses (e.g. chest X-ray)
Therapeutic trial
Evaluation of airway inflammation (FeNO, sputum eosinophils)
Evaluation of bronchial hyperresponsiveness (nonspecific bronchial challenges, e.g. methacholine, exercise)

To diagnose asthma, confirm the presence of episodic symptoms of reversible airflow obstruction, and exclude other conditions (Table 3). Diagnosis components are listed above in (relative) sequence of importance.

Table 3 Pediatric asthma differential diagnosis

Infectious & Immunological disorders
Allergic bronchopulmonary aspergillosis
Anaphylaxis
Bronchiolitis
Immune deficiency
Recurrent respiratory tract infections
Rhinitis
Sinusitis
Sarcoidosis
Tuberculosis
Bronchial pathologies
Bronchiectasis
Bronchopulmonary dysplasia
Cystic fibrosis
Primary ciliary dyskinesia
Mechanical obstruction
Congenital malformations
Enlarged lymph nodes or tumor
Foreign body aspiration
Laryngomalacia/tracheomalacia
Vascular rings or laryngeal webs
Vocal cord dysfunction
Other systems
Congenital heart disease
Gastroesophageal reflux disease
Neuromuscular disorder (leading to aspiration)
Psychogenic cough

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(48) or specific airway resistance (49)); however, these are not generally available outside specialized centers.

Evaluation of AHR and airway inflammation

Airway hyperresponsiveness, assessed by provocation with inhaled methacholine, histamine, mannitol, hypertonic saline, or cold air, has been used in adults to either support or rule out the diagnosis of asthma. The use of these methods in children is supported with reservation by most asthma guidelines. However, accuracy in children is lacking, as the inhaled dose is not adjusted for the size of the patient. Exercise can also be used to assess AHR, but standardization of testing is difficult for children of differing ages (50). These methodological issues have contributed to the tests being mainly limited to use in research rather than clinical practice (51, 52).

Although the guidelines do not stress the utility of obtaining fractional exhaled nitric oxide (FENO) measurements, recent data support that it may be useful as a diagnostic tool. An evidence-based guideline for the use and interpretation of FENO has been recently published (53). It supports the use of FENO to detect eosinophilic airway inflammation, determining the likelihood of corticosteroid responsiveness, monitoring of airway inflammation to determine the potential need for corticosteroid, and unmasking of nonadherence to corticosteroid therapy. However, in many countries, the capacity to measure FENO is unlikely to be available outside specialized centers.

Sputum eosinophils, although promising, have not been supported by data robust enough to make this parameter clinically useful and therefore are not currently recommended for diagnosis or monitoring of childhood asthma.

Evaluation of atopy

There is general consensus that atopy should be evaluated in children when there is a suspicion or diagnosis of asthma. Identification of specific allergic sensitizations can support asthma diagnosis, can indicate avoidable disease triggers, and has prognostic value for disease persistence (52, 54). Both in vivo (skin prick tests) and in vitro (specific IgE antibodies) methods can be used, considering the ease of performance, cost, accuracy, and other parameters.

Special considerations

There are important differences in the approach to diagnosis according to age. Most guidelines recognize the difficulty in diagnosing asthma in children younger than 2–3 years. In addition to the lack of objective measures at that age, the suboptimal response to medications and variability of natural history make diagnosis in this age-group, at best, provisional (55, 56).

In cases of uncertainty in the diagnosis, particularly in children below the age of 5 years, a short therapeutic trial period (e.g. 3 months) with inhaled corticosteroids is suggested. Considerable improvement during the trial and deterioration when it is stopped supports a diagnosis of asthma, although a negative response still does not completely exclude the diagnosis (Evidence D).

Although the diversity of childhood asthma is generally recognized and various phenotypes or subgroups are mentioned in different documents, there is little detail or agreement on diagnostic requirements for particular phenotypes, with the exception of exercise-induced asthma.

Research Recommendations

- Identify biomarkers for airway inflammation that are both informative for initial and ongoing treatment decisions and also practical for clinical use
- Diagnostic and prognostic markers for asthma and/or specific phenotypes are clearly needed
- Indirect, noninvasive measures of airway pathology will help the diagnostic investigation in young children
- Development of easy to use lung function tests for young children will improve diagnosis
- Study of lung function cutoff points (FEV1, bronchodilator response) in children is needed

Guideline Update Recommendations

- Newer lung function tests (e.g. oscillometry) may be included as aid to asthma diagnosis in young children
- Pediatric lung function cutoff points should be considered as data become available
- Peripheral airway parameters may be helpful in the diagnostic evaluation
- The role of FENO in diagnosis and monitoring can be reevaluated
- The role of AHR assessment in clinical practice should be clearly defined

Principles of pediatric asthma management

Although there is considerable variation in the way that different guidelines structure and present the principles and components of asthma management, the key messages are consistent, including a number of components that are a consequence of its chronic and variable course (Fig. 3).

Patients and their parents or caregivers should be educated to optimally manage the disease, in collaboration with healthcare professionals. Education and the formation of a partnership between them are crucial for the implementation and success of the treatment plan (Evidence A–B).

Identification (Evidence A) and avoidance (Evidence B–C) of specific (i.e. allergens) and nonspecific triggers (e.g. tobacco smoke, but not exercise) and risk factors are also of significant importance, because these may drive or augment inflammation.

Assessment and monitoring should be performed regularly because of the variable course of asthma and importantly to reevaluate and fine-tune treatment (Evidence A–B).

Pharmacotherapy is the cornerstone of treatment. The optimal use of medication can, in most cases, help patients control their symptoms and reduce the risk for future morbidity.

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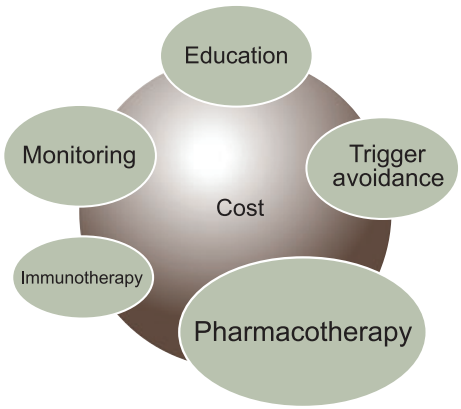

Figure 3 Asthma management should be 'holistic', including all the elements necessary to achieve disease control: patient and parent education, identification and avoidance of triggers, use of appropriate medication with a well-formed plan, and regular monitoring, are all crucial for success. Management should be adapted to the available resources.

Allergen-specific immunotherapy should be considered for children whose symptoms are clearly linked to a relevant allergen (Evidence B).

The management of asthma exacerbations is a major consideration, independent of chronic treatment.

There is a trend toward considering phenotype-specific treatment choices; however, there is as yet no consistent approach to this. Exercise-induced asthma is recognized in all guidelines, and specific instructions are suggested for its management. In addition, the specific challenges of treating severe and difficult asthma are highlighted throughout the documents. Age-specific instructions are usually proposed in 2 or 3 strata. It is generally accepted that recommendations in the youngest age-group are based on very weak evidence.

Overall, the treatment goal is disease control, including reduction in future risk of morbidity such as exacerbations. In the past, there were suggestions that early treatment may be able to alter the natural course of the disease; however, a number of recent studies (57–59) have shown that even prolonged treatment with inhaled corticosteroids, despite its many benefits (60), is unable to do so (Evidence A). Allergen-specific immunotherapy is currently the only treatment with long-term disease-modifying potential (61–63); however, the evaluation of the evidence base for this effect is controversial among experts and therefore needs further studies.

Research Recommendations

- Whether phenotype-specific management strategies can be more effective than currently used ones should be investigated
- Diagnosis, management, and treatment for severe asthma require additional effort

Guideline Update Recommendations

- Phenotype-specific management principles can be useful
- Probabilistic models, taking into account future risk, may be helpful in guideline design

Education

Asthma education should not be regarded as a single event but rather as a continuous process, repeated and supplemented at every subsequent consultation. There is general consensus on the basic elements of asthma education: it should include essential information about the (chronic/relapsing) nature of disease, the need for long-term therapy, and the different types of medication ('controllers' and 'relievers'). Importantly, education should highlight the importance of adherence to prescribed medication even in the absence of symptoms and should involve literal explanation and physical demonstration of the optimal use of inhaler devices and peak flow meters. Education should be tailored according to the sociocultural background of the family (64).

Education for self-management is an integral part of the process (Evidence A); it does not intend to replace expert medical care, but to enable the patient and/or the caregiver to help reach and maintain control of asthma, forming a functional partnership with the healthcare professional in dealing with daily aspects of the disease. This involves the ability to avoid or manage identifiable triggers, such as infections, allergens, and other environmental factors (e.g. tobacco smoke).

The use of a written, personalized management plan is generally recommended (Evidence B); the term 'asthma action plan' is most commonly used. This should optimally include the daily medication regimen, as well as specific instructions for early identification and appropriate management of asthma exacerbations or loss of asthma control. Educated interpretation of symptoms is of primary importance, as well as the use of PEF monitoring values as a surrogate measure of current asthmatic status (Evidence A), although this may be challenging in younger children. Supplemental material and/or links to information resources for structured templates and further guidance are available in several documents (AAMH, GINA, NAEPP, and SIGN). Unfortunately, the uptake of written action plans is poor, both by patients and by practitioners.

It is generally recognized that different approaches should be sought for different age-groups; in particular, JGCA and PRACTALL recommend an age-specific stratification of educational targets, with incremental participation of older children in self-management programs.

Most educational interventions have been shown to be of added value (and thus should be intensely pursued) mainly in patients with moderate or severe asthma; milder cases may benefit as well, but clinical effect is more difficult to formally demonstrate.

Primary asthma education in the office/clinic may be complemented by educational interventions at other sites. School-

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based programs (65), often peer-led in the case of adolescents, may have increased penetration and acceptance in large numbers of asthmatic children (Evidence B). Patients and their families may also be provided brief, focused educational courses when being admitted to hospital emergency departments for asthma exacerbations, while use of computer- and Internet-based educational methods represent other proposed alternatives, especially for older children and adolescents (Evidence B).

Focused training in pharmacies and education of the general public receive relatively less priority by current guidelines. Finally, education of health authorities and politicians is only mentioned by PRACTALL. Education of healthcare professionals is self-evident.

Research Recommendations

- Educational programs largely depend upon local culture; therefore, local versions, based on these principles, should be developed
- Improving uptake of asthma management plans, both by families and by practitioners, is needed

Guideline Update Recommendations

- Implementation strategies on a local and national level should be explored
- Tailoring education according to the sociocultural level of the patient's parents may have important practical consequences

Trigger avoidance

Asthma symptoms and exacerbations are triggered by a variety of specific and nonspecific stimuli. It is reasonable that avoidance of these factors may have beneficial effects on the activity of the disease. The airway pathophysiology mediated through IgE to inhalant allergens is widely acknowledged; however, not every allergen is equally significant for all patients. Thus, there is general consensus that sound allergological workup (including careful history for the assessment of clinical relevance, skin prick testing, and/or specific IgE measurement) should precede any effort to reduce exposure to the corresponding allergen (Evidence B).

There is some ambiguity with respect to the role of allergen avoidance. Some documents (JGCA, NAEPP3, and PRACTALL) provide specific recommendations for the reduction in allergen exposure for sensitized patients with asthma. Indoor allergens (dust mite, pet, cockroach, and mold allergens) are considered the main culprits and are targeted by specific interventions (Evidence B–D, depending on allergen and intervention). Other guidelines (AAMH, GINA, and SIGN) are more cautious in the interpretation of the evidence and underline the unproven effectiveness of current avoidance strategies on asthma control. Complete allergen avoidance is usually impractical, or impossible, and often limiting to the patient, and some measures involve significant expense and inconvenience. Moreover, the prevailing view is that single interventions for indoor allergens have limited effectiveness; if measures are to be taken, a multifaceted, comprehensive approach is prerequisite for clinical benefit (Evidence A), while tailoring environmental interventions to specific sensitization profiles has been shown to be of added value (66). Outdoor allergens are generally less manageable, because their levels cannot be modified by human intervention and staying indoors for appropriate periods may be the only recommendable approach.

Indoor and outdoor pollution can be major triggers particularly in developing countries (67). It is clear that smoking cessation in adolescents and reduction in exposure to environmental tobacco smoke, as well as to various indoor and outdoor pollutants and irritants, should be attempted in children with asthma (Evidence C). Vigorous measures are needed to achieve avoidance. Likewise, in the relatively uncommon case of drug-sensitive (e.g. NSAIDs) or food-sensitive (e.g. sulfites) children with asthma, complete avoidance should be advised, but only after thoroughly assessing the causality.

Research Recommendations

- Additional trials of multifaceted interventions may help clarify the role of allergen avoidance
- Assessment of personal exposure is crucial to quantitate any effect

Guideline Update Recommendations

- Local environmental differences in relation to exposures should be emphasized

Pharmacotherapy

The goal of asthma treatment is control using the least possible medications. Asthma pharmacotherapy is regarded as chronic treatment and should be distinguished from treatment for acute exacerbations that is discussed separately.

In the initial assessment, and especially if the patient has not received asthma medication before, there is a unique opportunity to evaluate disease severity. Most guidelines propose the use of severity as the criterion for selecting the level of treatment at the first assessment. GINA omits this step in this edition, while PRACTALL suggests that both severity and control can be used.

After the initial assessment, pharmacological therapy is selected through a stepwise approach according to the level of disease control. In evaluating control, the differentiation between current impairment and future risk is considered in NAEPP and GINA. This additional consideration is important in appreciating the independence of these elements.

If control is not achieved after 1–3 months, stepping up should be considered, after reviewing device use, compliance, environmental control, treatment for comorbid rhinitis, and, possibly, the diagnosis. When control has been achieved for

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at least 3 months, stepping down can be considered (Evidence A–B).

Drug classes and their characteristics

Despite the progress in asthma research, current asthma medications belong to a small range of pharmacological families. Corticosteroids, beta-2 adrenergic agonists, and leukotriene modifiers are the predominant classes. Chromones and xanthines have been extensively used in the past but are now less popular, the former because of limited efficacy and the latter because of frequent side effects. Omalizumab, a monoclonal antibody against IgE, is the newest addition to asthma medications, the first from the family of immunomodulatory biological agents, of which several other molecules are currently under evaluation in clinical trials. Medications are classified, according to their use, as those used for acute relief and those used for long-term control.

Medications used for acute relief of symptoms

'Relievers' are used for the acute, within minutes, relief of asthma symptoms, through bronchodilation. Use of inhaled short-acting beta-2 adrenergic agonists (SABA), most commonly salbutamol, as first-line reliever therapy is unanimously promoted for children of all ages (Evidence A). They are typically given on an 'as needed' basis, although frequent or prolonged use may indicate the need to initiate or increase anti-inflammatory medication. Compared to other relievers, SABA have a quicker and greater effect on airway smooth muscle, while their safety profile is favorable; a dose-dependent, self-limiting tremor and tachycardia are the most common side effects.

Oral SABA are generally discouraged. Anticholinergic agents, mainly ipratropium, are second-line relievers, but are less effective than SABA.

Medications used for long-term asthma control

Inhaled corticosteroids (ICS). The use of ICS as daily controller medications in persistent asthma is ubiquitously supported, as there is robust evidence that therapeutic doses of ICS improve symptoms and lung function, decrease need for additional medication, and reduce rate of asthma exacerbations and asthma-induced hospital admissions in children of all ages (68). Because of their pleiotropic anti-inflammatory activity, initiation of ICS therapy generally constitutes the first step of regular treatment (Evidence A).

Most children with mild asthma can be well controlled with low-dose ICS (Table 4). Although dose–response curves have not been established for every ICS formulation and for all age-groups, efficacy appears to reach a plateau for most patients and outcomes around or below medium dose range (69, 70). It should be noted, however, that the evidence on the role of low-dose ICS as maintenance treatment for the prevention of intermittent, virus-induced wheezing in young children is limited and controversial (71).

Table 4 Inhaled steroid (ICS) dose equivalence

Drug	Low daily dose (μg)
Beclomethasone dipropionate HFA	100
Budesonide	100
Budesonide (nebulized)	250
Ciclesonide	80
Flunisolide	500
Flunisolide HFA	160
Fluticasone propionate HFA	100
Mometasone furoate	100
Triamcinolone acetonide	400

Inhaled steroids and their entry (low) doses. Medium doses are always double (2×), while high doses are quadruple (4×), with the exception of flunisolide and triamcinolone which are 3×.

After control has been achieved, patients should be gradually titrated down to the lowest effective dose. The clinical response may vary among patients; therefore, the optimal maintenance dose is sought on an individual basis.

The clinical benefit of ICS must be balanced against potential risks, with linear growth remaining the dominant concern. Several studies in older children have consistently demonstrated a modest but significant effect (~1 cm in the first year) (59, 72, 73), while studies in preschool-age children are less consistent. The effect appears to improve with time; however, there are concerns about subgroups who may be more susceptible or permanently affected (59, 74). Recent data from the CAMP study suggest that an effect on adult final height cannot be excluded (75).

Risks for subcapsular cataracts or bone mineral density reduction in childhood are very low.

Most of the information available refers to low to medium doses, and there is minimal information on high-dose ICS. Furthermore, the total steroid load in cases of concomitant use of local steroids for allergic rhinitis or eczema should be taken into account.

Inhaled steroids differ in potency and bioavailability; however, because of both a relatively flat dose–response relationship in asthma and considerable interpersonal variability, few studies have been able to confirm the clinical relevance of these differences.

Leukotriene receptor antagonists (LTRA). Among leukotriene modifiers, montelukast is available worldwide; zafirlukast is mentioned only in NAEPP and pranlukast only in JGPA. LTRA are effective in improving symptoms and lung function and preventing exacerbations at all ages (76, 77) (Evidence A). They are generally less efficacious than ICS in clinical trials, although in some cases noninferiority has been shown (78, 79). Furthermore, there is evidence suggesting particular effectiveness of montelukast in exercise-induced asthma, possibly superior to other treatments (80). Therefore,

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in most guidelines they are recommended as second choice after low-dose ICS, or occasionally as 'alternative first-line treatment' (AAMH, PRACTALL), for the initial step of chronic treatment. In the context of the next treatment steps, they are also effective as add-on medications, but less so in comparison with LABA (81). PRACTALL also suggests that LTRA may be particularly useful when the patient has concomitant rhinitis.

Montelukast is relatively free of adverse effects. With zafirlukast, signs of hepatic dysfunction should be monitored.

Long-acting beta-2 adrenergic agonists (LABA). LABA, including salmeterol and formoterol, have long-lasting bronchodilator action. In older children and adults, ICS–LABA combinations have been shown to improve asthma outcomes to a better extent than higher doses of ICS (82–84). However, a small, but statistically significant risk for severe exacerbations and death associated with daily use of LABA has been described (85–87). Furthermore, the evidence base of the efficacy of ICS–LABA combinations in young children is not as robust as that of older children and adults (88, 89). These concerns are probably behind the rather controversial position of LABA in pediatric asthma treatment.

All documents agree that LABA should only be prescribed in combination with ICS and are therefore relevant as add-on treatment. In some cases, ICS–LABA combinations are recommended as the preferred add-on treatment in children >5 years (SIGN, GINA), or >12 years (NAEPP), in other they are suggested as an option for children >5 years (AAMH, NAEPP) or at any age (JGPA), while in other as an add-on treatment at a subsequent step (PRACTALL); GINA <5 does not recommend them for children <5 years because of the lack of data.

In the absence of data of safety and efficacy in children younger than 5 years, it is probably better to be cautious, until such data are produced. For older children, it is clear that ICS+LABA are an important treatment option, preferable for at least a subpopulation of patients (90). It is important to appreciate the right balance between risk and benefits of therapy (91, 92).

The use of a single combination inhaler, rather than separate inhalers, is generally recommended to maximize adherence and efficacy and reduce the possibility of overuse of LABA and underuse of ICS with potential for serious side effects.

Taking advantage of the fast action of formoterol, a strategy proposing the use of a single inhaler for both reliever and controller medication (SMART strategy) has been evaluated in several trials, mostly in adults. The efficacy has also being shown in children (87, 93).

Chromones. Cromolyn sodium and nedocromil modulate mast cell mediator release and eosinophil recruitment. Several studies have shown some effectiveness in children >5 years; however, evidence is not robust (94, 95). They are administered 3–4 times a day and are certainly less effective than ICS. On the other hand, they have an excellent safety profile. On the basis of these, chromones are considered having a limited role, but are 'traditionally' included in most guidelines as second-line medications for mild disease/initial treatment steps and prevention of exercise-induced asthma. In any case, they are not available anymore in many countries.

Theophylline. Theophylline, the most used methylxanthine, has bronchodilatory properties and a mild anti-inflammatory action. It may be beneficial as add-on to ICS, however, less so than LABA (Evidence B). However, it has a narrow therapeutic index and can have serious side effects, therefore requiring monitoring of blood levels (96). As a result, its role as controller medication is very limited and is only recommended as second-line treatment, where other options are unavailable (96).

Omalizumab. Omalizumab is indicated for children with allergic asthma poorly controlled by other medications (Evidence B). It reduces symptoms and exacerbations and improves quality of life and to a lesser extent lung function (97–100).

Strategies for asthma pharmacotherapy

Detailed strategies for prescribing asthma medications are proposed in all guidelines. Although there are differences on structure and detail between the documents, several common elements can be identified. Age is always taken into account. In infants, the evidence base for treatment is small, and responses are inconsistent and frequently suboptimal. In adolescents, issues that may affect asthma management are mostly related to lack of compliance.

There is consensus that medication for acute relief of symptoms (typically, a short-acting inhaled beta-2 agonist) should be available to all patients with asthma, irrespective of age, severity, or control. The reliever is used as needed; frequent or increased use may indicate lack of control and the need to initiate/step up controller therapy.

A number of steps of controller therapy can be described:

Step 0: In the lowest step, no controller medication is proposed.

Step 1: The next step entails the use of one controller medication. An ICS at low dose is the preferred option in most cases (Evidence A). LTRA are recommended as second option (GINA, GINA < 5, NAEPP, SIGN < 5 years), only if steroids cannot be used (SIGN 5–12 years), equivalent (PRACTALL, AAMH), or even preferred option (JGCA < 5 years). Possible explanations for these variations are that generally ICS are more effective than LTRA in direct comparisons (101, 102), although there are patients that may respond better to LTRA, especially in the younger and less atopic children (103). LTRA have a favorable safety profile and ease of administration and acceptance by the parents and patients (104). Chromones (NAEPP, AAMH, JGCA, and SIGN) and theophylline (in children > 5 years, NAEPP, JGCA, SIGN) are also included as options at this step. However,

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chromones are not available anymore in many countries, while, for the reasons mentioned above, theophylline should probably be excluded from this step, with the exception of developing countries where first-line medication may be unavailable or unaffordable.

Step 2: ICS can be increased to a medium dose, or a second medication can be added. This is probably the most variable and to some extent controversial step. For children older than 5 years, GINA and SIGN recommend the combination of ICS + LABA, the JGCA and AAMH documents prefer increasing ICS dose, NAEPP has no preference for children 5–12 years, but recommends either doubling ICS or ICS + LABA for children > 12 years, while PRACTALL suggests either doubling ICS or ICS + LTRA. For children younger than 5 years, increasing ICS is the commonest approach (GINA < 5, AAMH, JGCA, and NAEPP); SIGN suggests ICS + LTRA, while PRACTALL suggests either doubling ICS or ICS + LTRA.

Nonetheless, the above variation refers to preferred choices among lists of options that are similar among the documents. With respect to the younger age-group, the small number of studies explains this discrepancy. In older children, choices of safety *vs* efficacy may influence the recommendations. However, there is good evidence suggesting that the response to medication may differ considerably among individuals (90, 103), suggesting the need for some flexibility in choice and an option to try a different strategy if the first is not successful.

Step 3–4: The subsequent step(s) represent the maximization of conventional treatment, with the use of additional medications and/or further increase in the ICS dose. This may include two distinct steps: In the first, LABA or LTRA (or exceptionally theophylline) are added to the medium-dose ICS, and in the second, the ICS dose is increased (NAEPP, AAMH). Omalizumab is also considered at this step by NAEPP.

Step 5: In cases where control cannot be achieved with the maximum dose of inhaled corticosteroids and additional medication, the final resort is the use of oral corticosteroids. This step is not always part of the algorithm (JGCA, AAMH, SIGN < 5 years), possibly because at this stage specialist consultation is warranted. GINA includes omalizumab here.

All guidelines recommend that asthma education, avoidance of triggers, evaluation of compliance, and correct use of inhaler device, and even reconsideration of the diagnosis, should be carried out before stepping up treatment, in children in whom control is difficult to achieve. In addition, concomitant diseases, such as allergic rhinitis, should always be taken into account (105).

On the basis of the above, a simplified algorithm is shown in Fig. 4.

It should be noted that in low-income countries, an important obstacle to asthma management is the cost of medications. Essential asthma drugs (SABA and ICS) are proposed by The Union Asthma Guidelines (106).

Delivery devices

In addition to the selection of medication, understanding and selection of the optimal device for inhaled drug delivery is an important consideration. Devices fall under three categories: pressurized meter-dose inhalers (pMDI), dry powder inhalers (DPI), and nebulizers. Breath-actuated MDIs have distinct characteristics. There is no robust evidence suggesting major differences in effectiveness between the device types; however, each type has specific merits and limitations (107). There is general consensus that prescription of a device should be individualized, with major criteria being the patient's ability to use, preference, and cost. A detailed review of different devices has been recently published (108). Training is vital (109). pMDI and DPI are preferred to nebulizers, as they are at least equally effective (110, 111), cheaper, and easier to use and maintain. Spacers should always be used with MDIs in 0- to 5-year-olds and in exacerbations; they are also preferable in older children. Care needs to be taken to minimize static charge in plastic spacers (112). A mouthpiece should substitute for the mask when the child is able to use it. In areas where commercially produced spacers are unavailable or unaffordable, a 500-ml plastic bottle spacer may be adapted to serve as an effective spacer for children of all ages (113). The effects of anatomical differences and low inspiratory flows of young children on medication deposition by different drug delivery devices and spacers are not well understood.

Taking the above into account, a simplified selection scheme is shown in Box 2.

Research Recommendations

- Clinical trials should be designed to evaluate individual responses to different medications in asthma
- Measurable predictors of response to different therapies should be developed
- New strategies with existing medications should be studied, especially in the youngest age-group
- More data are needed on medication deposition by different delivery devices and spacers in young children
- The role of immunomodulators on asthma treatment can be expanded

Guideline Update Recommendations

- The individual response to different medications, frequently responsible for treatment failures, should be stressed in future documents
- More detailed recommendations on stepping down/stopping treatment are needed
- The position of chromones and theophylline should be reevaluated
- The possibility of moving between medications of the same step can be considered
- Strategies for the assessment of compliance with inhaler therapy should, when possible, be incorporated in treatment plans

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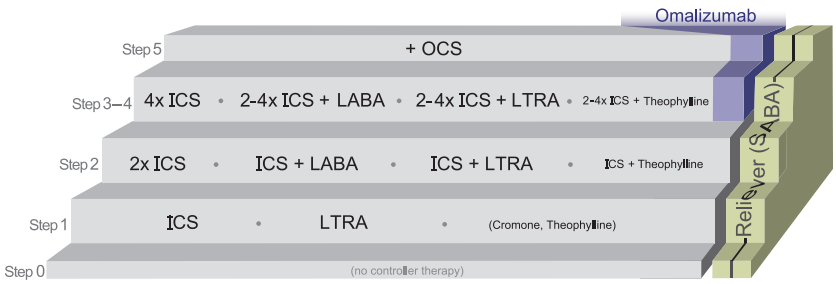

Figure 4 The stepwise approach to asthma treatment in childhood aims at disease control. Reliever medication should be used at any level of severity/control, if symptoms appear/exacerbate. At the mildest spectrum of the disease, no controller medication is needed (step 0). The next step entails the use of one controller medication (step 1). If this is not enough, two medications, or a double dose of inhaled steroid, can be used (step 2). In more difficult cases, increase of inhaled steroid dose, alone or in combination with additional medication is needed (step 3–4). Oral corticosteroids are kept as the last resort, for very severe patients (Step 5). Among biological treatments, omalizumab has specific indications for children at step 3 or higher. Stepping up or down should be evaluated at regular intervals, measured by level of control. Treatment adherence, exposure to triggers and alternative diagnoses should always be considered before stepping up. It should be stressed that medications in each step are not identical, in either efficacy or safety, and preferred choices can be described, especially for different age groups. For more details on this, the reader is referred to the text. Nevertheless, there is also considerable variation in the individual response to each medication, therefore, close monitoring and relevant adjustments are equally or even more important. An easy way to memorize this stepwise approach is that the number of each step suggests the number of medications, or ICS level, to be used.

Box 2

Inhaled medication delivery devices

0 to ~5 years

pMDI with static-treated spacer and mask (or mouthpiece as soon as the child is capable of using)

>~5 years

Choice of: pMDI with static-treated spacer and mouthpiece, DPI (rinse or gargle after inhaling ICS), breath-actuated pMDI (depending on patient ability to use, preference)

Nebulizer: second choice at any age

Immunotherapy

Allergen-specific immunotherapy (SIT) involves the administration of increasing doses of allergen extracts to induce persistent clinical tolerance in patients with allergen-induced symptoms. Subcutaneous immunotherapy (SCIT) has been shown to be clinically effective in allergic asthma, leading to a significant reduction in symptoms, airway hyperresponsiveness, and medication requirements (Evidence A–B). These effects are generally considered to be greatest when standardized, single-allergen extracts of house dust mites, animal dander, grass, or tree pollen are administered, whereas definitive evidence is currently lacking for the use of multi-allergen extracts and for mold and cockroach allergens (114, 115).

In clinical practice, allergen is typically administered for 3–5 years. A specific age limit, above which SIT can be initiated, has not been clearly defined; PRACTALL suggests that it may represent an acceptable intervention above 3 years of age, while GINA <5 years suggests that no recommendation can be made at this age, because of scarce evidence.

SIT has some important advantages over conventional pharmacological treatment (116); first, it is the closest approach to a causal therapy in allergic asthma; second, its clinical effect has been shown to persist after discontinuation of treatment (61, 62); and third, SIT has been linked with a preventive role against the progression of allergic rhinitis to asthma and the development of sensitization to additional allergens (63, 117). However, several experts feel that these aspects of SIT have not been adequately demonstrated.

Nevertheless, convenience and safety of administration have been a matter of concern. Apart from common local side effects at the injection site, systemic reactions (including severe bronchoconstriction) may occasionally occur, and these are more frequent among patients with poor asthma control (118). It is therefore generally agreed that SIT should only be administered by clinicians experienced in its use and appropriately trained to identify and treat potential anaphylactic reactions. Furthermore, SIT is not recommended in severe asthma, because of the concern of possible greater risk for systemic reactions.

Clinical benefits of SIT are differentially weighed against safety issues, so some recommendations vary between guidelines. AAMH, SIGN, and NAEPP acknowledge a clear role for immunotherapy as an adjunctive treatment, provided that clinical significance of the selected allergen has been demonstrated. PRACTALL also endorses immunotherapy and further suggests SIT to be considered as a potential preventive measure for the development of asthma in children with allergic rhinitis. According to GINA, the option of immunotherapy should only be considered when all other interventions, environmental and pharmacologic, have failed. However, in such unresponsive condition, the efficacy of immunotherapy is neither warranted.

In the context of ICON, the discussion on the role of SIT in childhood asthma has also been controversial. It is clear

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that additional studies are needed to be able to provide clear recommendations in the future.

Sublingual immunotherapy (SLIT) is painless and child-friendly in terms of administration route, offering the desirable option of home dosing and a more favorable safety profile compared to SCIT. Most documents require additional evidence of efficacy before recommending SLIT as a valid therapeutic option in asthma management. Nevertheless, a relevant meta-analysis confirmed significant efficacy in children with asthma (119).

Research Recommendations

- The long-term effects of SIT in young children, including its asthma-preventing capacity, should be further investigated
- Large studies of SLIT in pediatric asthma are needed
- Identification of surrogate markers for response to treatment should be sought

Guideline Update Recommendations

- Comparisons of SIT with pharmacotherapy should be taken into account
- A recommendation on SLIT may be considered

Monitoring

When asthma diagnosis has been confirmed and treatment initiated, ongoing monitoring of asthma control is strongly recommended (Evidence B–C). Control can be assessed at regular intervals, based on the components described in Table 1. Generally, only minimal symptoms are acceptable. For patients on daily controller therapy, reviews approximately every 3 months are suggested; after an exacerbation, a shorter interval should be considered (Evidence D). Several validated tools for assessing asthma control in children have been published (120–124).

Spirometry is recommended as a valuable measure for monitoring lung function in children who can perform it (Evidence B). Peak expiratory flow monitoring is recommended as an option for assessing control and home monitoring of more severe patients, or those with poor perception of severity (Evidence B).

Monitoring adherence to asthma therapy and assessment of inhaler technique are important (109, 125, 126). Self-monitoring at home (e.g. symptoms, PEF), as part of a personal management plan, is encouraged.

Additional recommendations, not uniformly suggested, include monitoring of quality of life (AAMH, NAEPP, and SIGN) (Evidence C), and of adverse effects of asthma therapy, particularly growth rate (AAMH, NAEPP, PRACTALL, and SIGN). Multiple monitoring methods may be useful in some cases.

Monitoring FENO is not recommended by the referenced pediatric asthma guidelines; however, it has been recently favorably reevaluated (94, 127). In contrast, the role of monitoring bronchial hyperresponsiveness or induced sputum eosinophilia is not currently well established (128–131).

Monitoring should continue/intensify after stepping down or pausing controller therapy.

Research Recommendations

- The kinetics of airway inflammation and BHR should be better understood and their role in monitoring identified
- Identification of additional noninvasive markers of airway inflammation, relevant to clinical management, will be useful

Guideline Update Recommendations

- Newer data on the role of different monitoring tests in improving asthma control can be included
- The role of FENO in monitoring should be reevaluated
- More attention should be given to recommendations about stepping down or stopping controller treatment

Asthma exacerbations (attacks, episodes)

Asthma exacerbations are of critical importance, as they are associated with high morbidity, including emergency visits, hospitalizations, and occasional mortality (132, 133). While detailed criteria for the assessment of severity are proposed (Table 5), there are no objective criteria for the definition of an exacerbation and/or its differentiation from lack of control. The terminology is variable, and the terms 'exacerbation', 'attack', 'episode', or 'seizure' (as translated from Japanese) are used almost interchangeably. The optional use of the adjectives 'acute' and 'severe' suggests that subacute and less severe epi-

Table 5 Assessment of exacerbation severity

	Mild	Moderate	Severe	Very severe
Wheeze	Variable	Moderate to loud	Loud – on both inhalation and exhalation	Often quiet
Breathlessness	Walking	At rest	At rest/sits upright	
Speaks in	Sentences	Phrases	Words	Unable to speak
Accessory muscle use	No	Common	Marked	Paradoxical
Consciousness	Not affected	Not affected	Agitated, confused	
Respiratory rate	Slightly increased	Increased	Highly increased	Undetermined
Pulse	<100	<140 (depending on age)	>140	Bradycardia
PEF (% of predicted or personal best)	>60–70	40–70	<40	<25
SaO_2 (% on air)	>94–95	90–95	<90	
PCO_2 (mmHg)	<42	<42	≥42	

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sodes may also be within the limits of the concept. A formal definition is only suggested by GINA < 5. There are descriptive definitions in GINA, NAEPP, and AAMH. SIGN includes different algorithmic definitions according to severity (near-fatal asthma, life-threatening asthma, acute severe asthma, moderate asthma exacerbation, and brittle asthma). No definitions are proposed in JGPA and PRACTALL. The acute or subacute and progressive nature of symptom intensification is generally highlighted. It is also generally accepted that the measurement of the associated reduction in airflow is preferable to symptoms in objective assessment. The use of oral steroids is a marker of the presence and/or severity of an exacerbation and has been proposed as part of its definition (134). However, medication use is a result of the exacerbation and therefore cannot formally define it without generating a vicious circle. Taking the above into account, a working definition is shown in Box 3.

Exacerbations can be of varying severity, from mild to fatal, usually graded in three or four categories, from mild to life-threatening. Severity is assessed based on clinical presentation and objective measures (Table 5). Such classification may be difficult to apply in infants and preschool children because of the lack of lung function assessment.

Exacerbation management (Box 4) can take place in different settings: at home, the doctor's office, emergency unit, hospital, or intensive care unit, largely in relation to severity, timing, availability, and organization of medical services.

Bronchodilation is the cornerstone of exacerbation treatment (Evidence A); it should already be started at home, as part of the asthma action plan, and should also be the first treatment measure in the emergency department (ED), immediately following severity assessment. Salbutamol inhaled at doses ranging from 2 to 10 puffs (200–1000 μg), every 20 min for the first hour, given via MDI-spacer (nebulized also possible), is recommended. The addition of ipratropium bromide may lead to some additional improvement in clinical symptoms (Evidence A–B). The response should be assessed after the first hour; if not satisfactory, the patient should be referred to a hospital (if at home) and the next level of therapy should be given.

Administration of supplemental oxygen is important to correct hypoxemia (Evidence A), with parallel O_2 saturation monitoring. In severe attacks, PCO_2 levels may also need to be monitored.

Systemic corticosteroids, preferably oral, are most effective when started early in an exacerbation (Evidence A). The recommended dose is prednisolone 1–2 mg/kg/day, up to 20 mg in children <2 years and up to 60 mg in older children, for 3–5 days. It is pointed out, however, that some recent studies showed negative results using the lower dose. Whether oral steroids should be initiated by parents at home is debated; if this happens, it should be closely monitored by the prescribing physician. Very high-dose inhaled steroids may also be effective either during the exacerbation or preemptively after a common cold (135, 136); however, they are not generally recommended to substitute systemic ones, although some experts feel that this may be an option. There is also some evidence for a modest preemptive effect of montelukast (137); however, this is not currently recommended.

Additional measures at the hospital and/or the intensive care unit include continuous inhaled beta-2 agonists, intravenous bronchodilators such as salbutamol, and aminophylline (Evidence B). There is little or no evidence on magnesium sulfate or helium–oxygen mixture in children; however, these could be options in cases not responding to the above treatments.

Research Recommendations

- Improved asthma exacerbation treatment remains an important unmet need. New medications and/or strategies are needed
- More specific information is needed on dose- and age-appropriate use of anticholinergic therapy in the treatment for asthma
- Evaluation of clinical patterns and/or biomarkers may help making the definition of exacerbations more specific

Guideline Update Recommendations

- The role of high-dose ICS in exacerbations (effective or not) should be clarified
- The follow-up after an exacerbation, including systemic steroid treatment, can be defined in more detail

Box 3

Asthma exacerbation definition

An exacerbation of asthma is an acute or subacute episode of progressive increase in asthma symptoms, associated with airflow obstruction

Box 4

Key points in asthma exacerbation treatment

Bronchodilation: inhaled salbutamol, 2–10 puffs; or nebulized, 2.5–5 mg, every 20′ for the first hour, and according to response thereafter

Ipratropium, 2–8 puffs; or nebulized, 0.25–0.5 mg, can be added to salbutamol

If there is no improvement, children should be referred to a hospital

Oxygen supplementation: aim at SaO_2 > 95%

Systemic corticosteroids: oral prednisolone, 1–2 mg/kg/24 h, usually for 3–5 days

At the hospital or ICU, if necessary, consider:

IV beta-2 agonists, IV aminophylline, IV magnesium sulfate, helium–oxygen mixture

Conclusions

Despite significant improvements in our understanding of various aspects of childhood asthma, as well as major efforts in producing high-quality guidelines and/or consensus docu-

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ments to support management, millions of patients worldwide continue to have suboptimal asthma control (138), possibly due to suboptimal treatment (139). Regardless of some variability in specific recommendations, wording and structure, all the major documents providing advice for best clinical practice in pediatric asthma management point toward the same core principles and agree among the majority of their choices. However, implementation of such guidelines and access to standard asthma therapy for children remain challenging in many areas of the world.

It is expected, by increasing the accessibility and promoting dissemination of these core principles, in parallel to continued efforts for evaluating and incorporating evidence into improved guidelines, that we will be able to help improve the quality of life of children with asthma and to reduce the burden of this contemporary epidemic. Further understanding of the underlying pathophysiology and improved classification of subtypes may lead to more effective personalized care. Local adaptation of the above principles will also contribute to the same direction (1).

Conflict of interest

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He is also a member of the advisory board on asthma in children for GSK, MSD, CHIESI, and Stallergenes. W. Burks has consulted for Dannon Co. Probiotics, Exploramed Development LLC, Intelliject, McNeil Nutritionals, Merck & Co., Novartis, Nutricia, Pfizer, Portola Pharmaceuticals and Schering-Plough; has received grants from the Food Allergy and Anaphylaxis Network, the Food Allergy Initiative, the NIH, the National Peanut Board, SHS, and the Wallace Research Foundation; and owns stock or stock options in Allertein and Mast Cell, Inc. T. B. Casale has received payment from consultancy from MedImmune. J. A. Castro-Rodriguez has received payment for development of educational presentation from AZ, GSK, MSD, Novartis. T. Frischer has worked on a national advisory board for MSD. T. W. 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