

Review Article

Current Trends in Pediatric Asthma Management

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Pediatric asthma has a significant increase in its prevalence in the past decades with considerable morbidity and mortality. Current asthma care not only focuses on life-saving treatments in acute attack, but also emphasizes the important role of chronic inflammation and the necessity of chronic managements. It has been strongly addressed that poorly adherent patients are more likely to have poor outcomes and quality of lives. In recent two decades, the pharmaceutical terms “relievers” and “controllers”, for rescue at acute stage and maintenance at chronic stage, respectively, have been extensively used for simplification and quick recognition about treatment policy of asthma. It has become a global consensus to educate patients to enhance their understanding and participation in decision-making for attaining better adherence and disease control. Besides, individualized treatment according to patient’s interests is the gold standard in modern medical care even in pediatric patients. Nevertheless, asthma management in young children is still difficult because of the difficulty in balancing between treatment safety and efficacy. Currently, guidelines on asthma treatment have been developed in most countries not only to guide clinical practice for general practitioners, but also to emphasize the importance of education. In addition to adopting a standardized stepwise treatment approach according to disease severity, individualized modifications of strategy based on the level of symptom control as well as the presence of risk factors and co-morbidities are recommended to cater for the patient's needs.

Key words: asthma, education, guideline, chronic inflammation

Introduction

Asthma had become a significant national and global medical issue with increasing

economic and social burdens for both management and prevention.^{1,2,3,4} It is not only the most common non-communicable chronic disease in children but also associated with more missed school days, more emergency depart-

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ment visits, worse health outcomes, and other chronic conditions, such as obesity.^{5,6,7}

Consequences of life-threatening acute attack and worsening pulmonary function markedly impair both safety and quality of life. Managements of asthma in children are always complicated because of the difficulty in accurate diagnosis, objective pulmonary function monitoring, and proper medications administration, especially the necessity of whole family involvement.

Improvements of pathophysiologic knowledge have led to accurate use of bronchodilators and corticosteroids in asthma treatments, resulting in timely relief of acute symptoms in most cases. On the other hand, since asthma is basically a perpetual inflammatory illness of the airway that demands chronic care, comprehensive understanding of chronic inflammation has important implications in current asthma treatments.^{8,9}

Pathophysiology

A history of recurrent respiratory symptoms such as shortness of breath, chest tightness, wheezing and cough, together with variable expiratory airflow limitation constitute a recognizable pattern of asthma. Childhood asthma is essentially a heterogeneous, genetic-predisposing allergic illness that involves the airway.^{3,10} It was noted that most asthmatic children experienced recurrent lower respiratory tract illnesses associated with airway obstruction and elevated levels of immunoglobulin E (IgE) during the first year of life.¹¹

Chronic airway inflammation associated with airway hyperresponsiveness, which usually persists even in the presence of normal pulmonary function tests and absence of symptoms, plays an important role in the pathogenesis of asthma that guides its treatment.^{3,9,12} It has been demonstrated that a variety of immunologic or non-immunologic stimuli can activate several kinds of cells as well as the autonomic nervous system, result-

ing in airway smooth muscle contraction.^{9,13,14} Helper T lymphocytes and other immune cells producing proallergic, proinflammatory cytokines (e.g., interleukin (IL)-4, IL-5, IL-13) and chemokines are key participants in the immune responses^{12,15} that lead to airway edema, cellular infiltration, mucus secretion, and increased mucosal and vascular permeability. Chronic structural changes including epithelial injury, subepithelial fibrosis, goblet cell metaplasia, basement membrane thickening, and airway smooth muscle hypertrophy (i.e., airway remodeling) contribute to the deterioration of pulmonary functions and airflow obstruction.^{13,14,15}

The Relievers

Acute asthma attack is described as acute exacerbation if it is an aggravation of the patient's usual status or an abrupt onset of respiratory distress.^{3,16,17} This concept is important for its differentiation from the chronic status of severe persistent asthma. Although treatment modalities of acute asthma exacerbation continue to evolve,¹⁸ the policy and goals of acute treatment remain almost unchanged and could be summarized as: (1) Maintenance of adequate arterial oxygen saturation, (2) Relief of airflow obstruction, and (3) Early administration of systemic corticosteroids for reduction of airway inflammation.¹⁹

Based on the rescue purpose, short-acting inhalational β_2 -agonists (SABA) are the reliever of choice.^{12,19} SABA acts by binding to the β_2 -adrenergic receptors which generates intracellular signals and ultimately leads to muscle relaxation.²⁰ It has become part of the treatment policy that every patient should have a SABA inhaler, and young children need to be given a supplementary aerochamber or spacer.^{3,8}

Other frequently used relievers are inhalational anti-cholinergics which are much less potent than β_2 -agonists, but can be used in combination with SABA to improve lung func-

tion and reduce the rate of hospitalization in children presenting to the emergency department with acute asthma.¹⁵ The use of inhalational corticosteroids (ICS) in the acute setting has been evaluated currently without evidence to support an increased dose of ICS as part of a self-initiated treatment strategy.²¹

The Controllers

Controllers (or maintenance drugs) are used for regular maintenance treatment and should have anti-inflammatory effects.⁸ ICS is the drug of choice as a controller for the long-term management of asthma in both adults and children. In addition, low-dose ICS is the cornerstone of care for asthma patients of all severities.³ ICS can alleviate clinical asthma symptoms and suppress the expressions of biomarkers of airway inflammation. Early intervention with ICS may preserve pulmonary function and prevent irreversible airway obstruction and remodeling.²²

The leukotriene receptor antagonists (LTRA) and anti-IgE monoclonal antibody are targeting drugs used as optional controllers or add-on therapy. LTRA have been frequently used in young children who cannot adequately use ICS and served as an alternative first-line treatment for persistent asthma in young children.¹² There is less evidence on the role of anti-IgE therapy in pediatric asthma, although efficacy and safety of omalizumab have been recognized in children and adolescents with uncontrolled and persistent allergic asthma.²³

Long-acting β_2 agonist (LABA) also has an add-on effect on that of ICS but its use in pediatric asthma has encountered ongoing safety concerns and is not suggested in preschool children. However, evidence has clarified their restricted use as an add-on therapy to ICS when indicated.^{12,24}

Standardized Stepwise Chronic Care

In the late 1980s, Australia and New Zealand investigators published their national guideline of recommendations for the diagnosis and treatment of asthma. A stepwise manner of treatment according to disease severity was proposed.^{25,26} Thereafter, the international guideline of Global Initiative for Asthma (GINA) was developed in the early 1990s under the auspices of the National Institutes of Health in the United States and the World Health Organization.^{3,26} GINA also designed a standardized stepwise approach suitable for both adults and children.^{3,27} The strategy has been modified according to evidence-based studies and the methodology has been changed to fit into the stepwise framework (Table 1). Special considerations in patients less than 5 years old were also updated. Medical care entities in European and Asian regions also nominated expert teams to endeavor to reach a consensus in treatment policy that can serve as a specific guideline for pediatric asthma.^{8,12}

Severity-Based Management

The severity of chronic asthma could be divided into (mild) intermittent, mild persistent, moderate persistent, and severe persistent. Based on this classification, there are corresponding recommended medications.⁸ After initial managements, patients should be re-evaluated for treatment responsiveness to guide the necessary adjustments according to a step-up or step-down model.²⁸

If symptoms do not improve satisfactorily, then a step-up approach would be adopted through doubling dosage or adding medicines as needed. If good control is achieved, treatment would be stepped down and maintained for a period of usually three months.²⁹

Control Level-Based Management

The step-by-step approach to asthma treatment comprises: (1) assessment of asthma control, (2) adjustment of treatment, and (3)

Table 1. Comparison between severity-based and control level-based stepwise approaches in asthma management.

Variable	Severity-based management	Control level-based management
Items for initial assessment	Clinical features / symptoms and pulmonary function	Symptom control level and future risk of adverse outcome
Parameters guiding initial treatment	Level of severity (each level has a corresponding step for adequate medications)	Symptom control level and future risk of exacerbation to guide appropriate step taken (i.e., more advanced step if unstable)
Assessment of treatment response	Re-assessment of severity level under current medications	Re-assessment of control level and asthma severity
Adjustment of treatment	Step-up or step-down according to asthma severity level	Step-up or step-down according to asthma control level
Goals of asthma management	Symptoms control and maintenance of normal respiratory function	Symptom control and risk reduction

review of response. Re-assessment of asthma control in this cycling model for patient care should be continued. The assessment of asthma control includes two major domains, including the degree of symptom control and future risk of adverse outcomes, as well as other issues such as inhaler technique, adherence, side-effects, and comorbidities.³ Adjustment of treatment and choice of controller depend on the two domains of assessment of asthma control. As long as good control has been maintained for 2 – 3 months, treatments may be stepped down in order to identify the patient's minimum effective treatment dosage. On the contrary, if a patient needs rescue medications more than twice per week and/or experiences obvious airflow obstruction detected objectively, the patient is diagnosed as having uncontrolled asthma for which a step-up treatment should be considered.

The severity of asthma for this approach is retrospectively assessed by the level of treatment needed to control the illness: if the patient responds well to step 1 or step 2 therapy, the severity is classified as mild; if step 3 therapy is necessary for control, the severity is moderate; if step 4 or step 5 therapy is required, it is regarded as severe asthma regardless of treatment responses.

The Justified Issues

Because of the high prevalence of asthma, it is a well-accepted policy in public health to publish asthma guidelines for general practitioners to follow and for patient education accordingly. General practitioners should be aware about basic knowledge and treatment steps of asthma. For example, the Japanese guidelines have provided information on asthma managements from infancy to puberty, and announced that non-specialists should refer to the guidelines for routine medical treatments.⁸ The Japanese guidelines further depicted three fundamental factors of childhood asthma care: (1) a long-term management with anti-inflammatory controller drugs, (2) elimination of airborne antigens from the patient's living environment, and (3) enlightenment and education about bronchial asthma pathophysiology.⁸

Global Initiative for Asthma (GINA) is a leading organization aiming at disseminating information about the care of patients with asthma as well as providing a platform for translating scientific evidence into better asthma care with improved patient adherence and self-management.^{3,27} International and national guidelines raise awareness about the burden of asthma, and focus on effective methods to manage and control asthma. The trend is to simplify the guidelines for promoting easy use and avoiding confusion.⁸ The important issues are summarized briefly in Table 2.

Emphasis on Chronic Care

The concept of chronic care is frequently neglected by patients/caregivers with resultant failure of disease control. Most patients had poor knowledge about asthma, leading to improper use of medications. Therefore, it is necessary to improve education about the nature of disease and medication compliance for patients and their parents/guardians.³⁰ The care team should emphasize that asthma is a chronic inflammatory disease with variable and not always obvious symptoms and it is essential to take daily medication even in the absence of symptoms especially in those with moderate and severe asthma.¹²

Enhancement of Diagnosis Accuracy

Incorrect diagnosis (under- or over-diagnosis) of asthma leads to under- or over-treatments. Under-diagnosis contributes to an increased risk of life-threatening exacerbation, while over-diagnosis increases costs and unnecessary side effects.³¹ Making correct diagnosis is the priority for improving outcome. Consistently, guidelines put an emphasis on making accurate diagnosis prior to treatment as objectively as possible with detailed documentation for further reference, as it is often difficult to confirm the diagnosis afterwards.³ Early diagnosis for childhood asthma is also highly emphasized in the Japanese guidelines.⁸

Adjustment of Management Methodology

The methodology in international guidelines was modified in accordance with evidence-base studies to ensure most effective implementation of clinical guidelines.²⁷ Since 2006, new classification of asthma according to the level of control has been developed to guide treatment instead of using the conventional level of severity as reference. The updated GINA guidelines further adopted a practical assessment approach with recommendations presented in a user-friendly format includ-

Table 2. The justified and emphasized issues in chronic care of childhood asthma.

Emphasis on Chronic Care
- Participants: Physicians and parents
- Key point: To emphasize the chronic inflammatory nature of asthma
Enhancement of Diagnosis Accuracy
- Participants: General practitioners and specialists
- Key point: To avoid over- or under-diagnosis
Adjustment of Management Methodology
- Participants: Expert workshop in health-promoting institutes or organizations
- Key point: To update knowledge on asthma care
Education to Health Care Personnel
- Participants: Physicians, parents, nurse, school teachers, and other caregivers
- Key point: To organize a healthcare team
Patient Education and Health Literacy
- Participants: Parents, school-aged children and adolescents
- Key point: To provide formal instructions and possible internet resources
Individualized Treatment and Action Plan
- Participants: Physicians and patient-centered care team
- Key point: To design optimal treatment plan according to PEFR or ACT
Fitness of Local Practices and the Availability of Health Care Resources
- Participants: Healthcare professionals and public health officials
- Key point: To ensure adequate health resources redistribution with justice
Environment Control and Allergen Avoidance
- Participants: Caregivers at home and school
- Key point: To identify allergens and irritants and avoid them

ing extensive use of summary tables, clinical tools, and flow charts so as to be both clinically relevant and feasible for implementation during busy clinical practice.³

Education of Health Care Personnel

To improve asthma care, the health care leaders should ensure the availability of medical resources as well as develop means to implement and evaluate effective management programs.³ It has been proposed that education of both patients and physicians would be effective in achieving good asthma control and curtailing health care costs.⁴ For example, the

Saudi Initiative for Asthma Group, a subsidiary of the Saudi Thoracic Society, developed an updated guideline to simplify clinical practice for general practitioners.³²

Patient Education and Health Literacy

Education to a patient is necessary for improving adherence. Suboptimal adherence to prescribed medication is an important contributor to severe and poorly-controlled asthma.¹⁸ To attain optimal education, it is necessary to develop a patient-friendly educational program using clear visual aids and simple words to present the written materials.³ Patients should realize that they have been prescribed the right drug at the right dose and right time.³³ The materials used to promote health literacy should be easy to obtain, process, and understand. A pilot study suggested that a multidimensional web-based educational, monitoring, and communication platform may have a positive impact on pediatric patients' asthma-related knowledge and on proper use of asthma medications.³⁴

Individualized Treatment and Action Plan

If possible, treatment should be individualized according to disease phenotype.^{8,18} Allergic asthma is now an easily recognized pediatric asthma phenotype usually responds well to ICS treatment.³ LTRA once-daily controller therapy is suggested for viral wheezers.⁸ Peak expiratory flow rate (PEFR) is used for simplifying objective evaluation of pulmonary function in older children, and also for monitoring illness and guiding the design of individualized action plan. Not only is Asthma Control Test (ACT) questionnaire an appropriate method for monitoring a patient's symptoms,^{8,35} but it is also useful in encouraging patient involvement in his/her own medicine choice and shared decision-making when combined with an effective educational program. By identifying barriers to care, health care providers can establish an action plan to

meet each patient's individualized needs.³⁶

Fitness of Local Practices and the Availability of Health Care Resources

Implementation of asthma guidelines should begin with the establishment of goals and strategies for asthma care through collaboration among diverse professional groups including both primary and secondary health-care professionals, public health officials, patients, asthma advocacy groups, and the general public.³ The issues of asthma care vary among different countries, depending on the local context, culture, and environment, the health care system, economics, and access to health resources. Therefore, goals and implementation strategies vary from country to country.²⁷

Environment Control and Allergen Avoidance

Allergen or irritant exposure, weather change, or viral respiratory infections frequently trigger asthma exacerbations. It has been shown that food-specific IgE appears during infancy and frequently disappears during childhood, whereas inhalant-specific IgE appears later with increasing frequency from two years of age.³⁷ Avoidance of exposure to tobacco smoke is essential for children of all ages as well as pregnant women. An European report suggests allergen testing for patients of all ages to confirm the possible contribution of allergens to asthma exacerbations.¹²

Anti-mite measure is an essential element of inhalant allergen avoidance including modifying the internal environment to make it more resistant to mite, including the use of mite-impermeable mattress and pillowcases.³⁸ Although allergen exposure in the house environment was well studied, it is less understood in the school environment. School-based (e.g., kindergarten and baby care centers) asthma education and environmental intervention are also necessary to help alleviate pediatric

asthma morbidity.³⁹

Special Considerations

The level of education should be based on the age of patient and the severity of disease. Parents of preschool children should receive practical training in both the use of inhaler devices and strategies for asthma management. School-age children and their parents should be offered both practical and theoretical asthma education, while adolescent patients can be taught directly regarding all aspects of disease managements.¹²

Adolescents

Adolescents may have the cognitive and emotional capacity to participate in health care decisions. The information should be provided completely if possible.⁴⁰ However, the growing adolescent who is facing and learning independence has a well-known poor compliance. Targeting patient-specific barriers to adherence may be more effective in improving adherence than merely emphasizing the importance of inhaler use.⁴¹ To objectively improve the controller medication adherence for adolescents, physician feedback, school nurse directly observed therapy, and group interactive learning should be considered.⁴²

School-Age Children

Physicians are suggested to foster a partnership among children, families, school nurses, and staff for providing continuous care throughout the school years⁴³ and for supporting teamwork intervention to improve medication adherence.⁴⁴ Objective pulmonary function tests have been reported to significantly improve the diagnosis and treatment in this age group. For children 6 – 11 years, although theophylline is usually not recommended,³ it still has therapeutic benefits and corticosteroid-sparing effects in select groups of children refractory to ICS, LTRAs, or LABAs.¹²

Preschool Children

Making a diagnosis of asthma in young preschool children is difficult and is a subject of debate in scientific literature. When combined with frequent coughs and wheezing, repeated respiratory infections in children can mimic chronic or episodic asthma. However, early diagnosis is still a golden rule that demands meticulous efforts.⁸ It is important to be aware of very mild symptoms because, with low level of physical activity in preschool children, the subclinically increased bronchial responsiveness may be inconspicuous to parents and pediatricians despite continual clinical follow-ups since birth.⁴⁵ Nevertheless, a presumptive diagnosis of asthma can still be made based on symptom patterns and a careful clinical assessment of physical findings and family history. Besides, the presence of atopy is a valuable diagnostic clue as early allergic sensitization increases the possibility that a wheezing child is asthmatic.²⁶

The routine and frequent uses of oral steroid and high-dose ICS for wheezing episodes in young children raise the concerns about over-treatment and potential long-term systemic side effects.³ On the other hand, the use of ICS has also been demonstrated to improve lung function, decrease the number of symptom-free days, alleviate symptoms, reduce the need for additional medication, relieve caregiver burden, curtail systemic corticosteroid use, and decrease the incidence of exacerbation episodes in young children.^{46,47} In infant and toddler at risk of asthma, potential therapeutic benefits need to be balanced with the risk of treatments through regular assessments of risk factors and symptoms with corresponding adjustment of medications.⁴⁸ There are insufficient data about the efficacy and safety of inhalational regimen of combined ICS and LABA in this age group.³

Conclusions

The aggressiveness of asthma treatment has to be tailored to balance between disease progression and treatment-associated side effects. Taking into account the immunogenic and chronic inflammatory nature of the disease, a sustained and aggressive approach according to disease severity and existence of risk factors is currently recommended.

In addition to aggressive and sustainable treatment, implementation of educational programs for medical personnel, caregivers, and patients is important for improving both the understanding of disease nature and the compliance with treatments in the shared decision-making process. Because of the difficulty in achieving a precise balance between safety and efficacy, design of an optimal treatment plan remains a formidable challenge to pediatricians when caring for children less than five years of age for whom frequent reassessment of symptoms and monitoring of side-effects are recommended according to all of the current guidelines.

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