Advances in pediatric asthma in 2008: Where do we go now?

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This year's summary focuses on recent advances in pediatric asthma as reported in Journal publications in 2008. New National Asthma Education and Prevention Program asthma guidelines were released in 2007 with a special emphasis on asthma control. Attention was redirected to methods that could reduce impairment, specifically symptom control, and minimize risk, including exacerbations. Journal theme issues in 2008 focused on several relevant asthma topics including asthma exacerbations, exercise-induced bronchospasm, asthma and obesity, and occupational asthma. This review highlights Journal articles and related articles that reinforce principles of the guidelines and also direct us to new information that will advance asthma care for children. A major step forward will be finding ways to implement the asthma guidelines. (J Allergy Clin Immunol 2009;123:28-34.)

Key words: *Asthma, asthma control, asthma impairment, asthma risk, asthma severity, early intervention in asthma, biomarkers, genetics, therapeutics*

Abbreviations used
AHR: Airway hyperresponsiveness
EIB: Exercise-induced bronchoconstriction
FeNO: Fraction of exhaled nitric oxide (ppb)
ICS: Inhaled corticosteroid
LABA: Long-acting β-adrenergic agonist

Last year, this Advances in Pediatric Asthma review included a summary of key features in the updated asthma guidelines and discussed new findings related to pediatric asthma.[1] The asthma guidelines emphasized the importance of asthma control, a stepwise approach to asthma management, and the importance of early diagnosis and intervention.[2,3] This review highlights 2008 Journal publications that reinforce principles in the current guidelines and add new information to consider for future guidelines and observations that advance our ability to adapt personalized medicine to the management of childhood asthma (Table I).

IMPLEMENTING THE ASTHMA GUIDELINES

Several key terms were introduced with the new National Asthma Education and Prevention Program asthma guidelines, including *severity*, *control*, *responsiveness*, *impairment*, and *risk*.[2,3] *Severity* is defined as the intrinsic intensity of the disease process and can be measured most readily and directly in patients who are not receiving long-term controller therapy. *Control* is the degree to which the manifestations of asthma (symptoms, functional impairment, and risks of untoward events) are minimized and the goals of therapy are achieved. *Responsiveness* is the ease with which control is achieved by therapy.

Asthma severity and asthma control are both divided into 2 domains: impairment and risk. *Impairment* is the assessment of the frequency and intensity of symptoms, as well as the functional limitations that the patient is experiencing now or in the past because of asthma. *Risk* is the estimate of the likelihood of an asthma exacerbation, progressive loss of pulmonary function over time caused by asthma, or an adverse event from medication or even death. The assessment of severity and control provides guidance for the direction to take in stepping up or stepping down medications. In a recent theme issue on asthma in *The Lancet*, McIvor and Chapman[4] provide an overview of the past 20 years of asthma guidelines by pointing out some of the challenges in addressing the appropriate target audience and assuring application of these principles to improve outcomes. They point to the many ways that clinicians have ignored key messages in these reports and support the new direction in making guidelines practical and implementable. There are ways to do this, but it will require cooperation from all stakeholders including patients, health care providers, and clinicians, to name a few.

Asthma control

Now that attention is redirected to achieving well controlled asthma, we must carefully monitor asthma control to evaluate the benefits and risks of interventions. Asthma is a complex disease, and key to understanding individual patients is the careful assessment of control to guide treatment and help anticipate and thus prevent exacerbations and progression of the disease.[5,6] Careful identification of asthma phenotypes will lead to new insights into the mechanisms of this complex, heterogeneous disease.[7]

Holt et al[8] applied factor analysis to explore the relationships between measures of asthma morbidity and to identify heterogeneous components of asthma health status in children age 5 to 12 years. They identified 5 factors—(1) inflammatory markers, (2) symptom/medication use, (3) asthma exacerbations, measures

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of lung function based on (4) FEV_1 and forced vital capacity, and (5) bronchodilator response and FEV_1/forced vital capacity—that appear to provide independent information in the assessment of asthma. Bender and Zhang[9] examined adherence and asthma control and concluded that although negative affect and adherence were predictive of asthma control, the relationship of each to asthma control was distinctly different. They observed that the accuracy of symptom perception may be influenced by patient and parent affect characteristics.

Management

Asthma management in children carries with it concern for adverse effects of commonly used medications. A brief report by Pelkonen et al[10] provided reassuring information that short courses of high-dose inhaled corticosteroid (ICS) and long-term use of low-dose to medium-dose ICS, specifically budesonide, was not associated with the development of lens opacities or clinically important increases in intraocular pressure.

The recent report of an adolescent suicide attributed to initiation of montelukast has raised concern regarding psychological adverse effects associated with leukotriene modifiers. Holbrook and Harik-Khan[11] examined data from 3 controlled trials conducted within the American Lung Association Asthma Clinical Research Centers and did not find evidence of a negative effect of montelukast on emotional well being, but additional studies will be needed to examine the potential for idiosyncratic reactions.

Questions continue to be raised regarding the benefits of early intervention with ICS. Based on analysis from an early intervention study with budesonide (Inhaled Steroid Treatment As Regular Therapy in Early Asthma study) conducted in 7241 patients age 5 to 66 years with recent-onset, mild persistent asthma, Busse et al[12] concluded that this form of early intervention improved asthma control including significantly lower risk of severe asthma-related events with less additional medication use.

Managed care

Now that revised guidelines are available, it will be important to assess ways to integrate these principles into managed care systems. These systems can be used to examine the efficacy of treatment strategies. For example, Zeiger et al[13] examined the effect of single controller ICS compared with other drug regimens and concluded that total direct costs and asthma-related utilizations were meaningfully less in the year after being dispensed single controller ICS compared with single controller leukotriene modifiers or most combination controllers.

Despite significant advances in care that have seen the reduction in asthma mortality over the last 10 years, certain patient populations still experience greater morbidity, and this disparity must be addressed. Stingone and Claudio[14] examined allergy care in urban children and found that many children do not receive comprehensive asthma treatment that includes management of allergies and education on avoidance of household allergens. This might indicate lower access to medical care among families ineligible for public programs. Alternatively, perhaps unique programs will have to be applied to reduce health disparities. Canino et al[15] evaluated the effectiveness of a culturally adapted family asthma management intervention and found that this home-based program tailored to cultural needs of low-income Puerto Rican families resulted in a number of improved asthma control measures and improved parents' confidence in managing their child's asthma.

TABLE I. Key advances in pediatric asthma in 2008

1. For asthma guidelines to be effective, clinicians must incorporate key messages into practice, specifically application of spirometry and appropriate use of long-term controller therapy.
2. Careful identification of asthma phenotypes combined with biomarkers and genetics will lead to new insights into the mechanisms of this complex, heterogeneous disease.
3. Attention must now be directed to reducing health disparities with better understanding of methods that lead to poor asthma control in susceptible populations.
4. Risk profiles are developing that will lead to early identification of children susceptible to persistent asthma and prompt early intervention strategies.
5. Asthma and obesity represent growing epidemics that often coexist with beginnings in early childhood.

NEW INSIGHTS THAT COULD AFFECT FUTURE ASTHMA MANAGEMENT

Although the asthma guidelines summarize a significant amount of information about asthma, there is much that we do not know about the susceptibility, variability, recovery, and mechanisms of the disease.[16] This section highlights new findings that should receive attention in revising future asthma guidelines.

Early indicators associated with asthma

Our ability to prevent the development of asthma is strongly linked to our ability to identify characteristics that are associated with a high likelihood of developing the disease. Some studies have pointed to prenatal indicators, and others have examined postnatal factors. In regard to prenatal factors, Pistiner et al[17] reported that cesarean delivery was not associated with the development of asthma but was associated with allergic rhinitis and atopy among children with a parental history of asthma or allergies. On the other hand, Kumar et al[18] reported a relationship of prematurity and chorioamnionitis on early childhood wheezing, an effect that was stronger in African Americans. These observations require confirmation to set up risk profiles for features that signal a child at risk for persistent asthma.

Several studies reported on features associated with developing asthma in children. McDonald et al,[19] in a longitudinal study in Manitoba, found a negative association between delay in administration of the first dose of whole-cell diphtheria-tetanus-pertussis immunization in childhood and the development of asthma, with the association greater with delays in all of the first 3 doses.

Kim et al[20] sought to describe patterns of sensitization and allergic disease in an unselected agricultural Chinese population. They noted that although atopic sensitization was common in this rural farming population, particularly to shellfish, peanut, dust mite, and cockroach, the prevalence of allergic disease was quite low. However, Donohue et al[21] observed in an inner-city population that children age 2 to 3 years who develop anticockroach, mouse IgE are at increased risk of wheeze and atopy with a dose-response relationship between higher IgE class and prevalence of wheeze, rhinitis, or atopic dermatitis. Thus, the pattern of specific sensitization could be important in determining the disease course.