

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

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 step-wise 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

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

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 Chapman⁴ 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 al⁸ 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) FEV₁ and forced vital capacity, and (5) bronchodilator response and FEV₁/forced vital capacity—that appear to provide independent information in the assessment of asthma. Bender and Zhang⁹ 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 al¹⁰ 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-Khan¹¹ 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 al¹² 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 al¹³ 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 Claudio¹⁴ 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 al¹⁵ 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

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.

control measures and improved parents' confidence in managing their child's asthma.

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 al¹⁷ 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 al¹⁸ 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 al²⁰ 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 al²¹ 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.

Interesting observations in select populations can also help our understanding of pathways to asthma. Foster et al²² noted an increased incidence of asthma in HIV⁺ children treated with highly active antiretroviral therapy (HAART) than HIV⁺ children not receiving HAART and hypothesized that this might be driven by immunoreconstitution of CD4⁺ T cells. Burgess et al²³ examined the association between childhood eczema and asthma and concluded that childhood eczema increased the likelihood of childhood asthma, of new-onset asthma in later life, and of asthma persisting into middle age; however, this finding was no longer evident when adjusted for allergic rhinitis. Shaaban et al²⁴ using the European Community Respiratory Health Survey investigated the onset of asthma in patients with allergic and nonallergic rhinitis in an adult population. They noted a relationship of allergic rhinitis, especially with sensitization to mite, was associated with increased risk of asthma independently of other allergens. These observations prompt studies of early intervention for allergic rhinitis or eczema either directly for these allergic disorders or as indicators for initiating treatment of asthma to determine their effect on altering the course of asthma. Lowe et al²⁵ also studied the relationship of eczema to asthma and reported that eczema in the first 2 years of life is associated with an increased risk of childhood asthma in boys, but there was no evidence of this relationship in girls. Beasley et al²⁶ based on observations in the International Study of Asthma and Allergies in Childhood program, reported that use of paracetamol (acetaminophen) in the first year of life and in later childhood is associated with risk of asthma at age 6 to 7 years and might be a risk factor or signal for the development of asthma in childhood.

Tepper et al²⁷ reported that atopic characteristics of the infant could be important determinants of airway physiology based on observations that infants sensitized to egg or milk compared with infants sensitized to neither egg or milk had lower flows and greater airway reactivity but no difference in exhaled nitric oxide. However, infants with total serum IgE levels >20 IU/mL had higher exhaled nitric oxide levels compared with infants with IgE levels ≤20 IU/mL but no difference in forced flows or airway reactivity.

Elliott et al²⁸ examined the relationship between breast-feeding and later asthma and allergy outcomes using a large birth cohort in the United Kingdom and did not find a relationship. This is consistent with other reports that suggest breast-feeding may be helpful in reducing the likelihood of wheezing in young children but does not affect the course of later outcomes.²⁹ Finally, Stern et al³⁰ examined the contribution of sex and early life factors to asthma diagnosed in young adults. They concluded that asthma with onset in early adulthood has its origins in childhood. Factors associated with chronic asthma at 22 years of age included onset at 6 years of age and persistent wheezing in early life, sensitization to *Alternaria alternata*, low airway function at age 6 years, and bronchial hyperresponsiveness at 6 years. In a comprehensive review of the literature, Sly et al³¹ concluded that objective assessment of atopy by quantitating allergen-specific IgE in serum against common food allergens and local aeroallergens by 2 years of age in conjunction with the presence of other atopic manifestations can help identify the wheezing children at high risk of developing persistent asthma. Nicolaou et al³² noted that day care attendance was associated with a reduced risk of current wheezing in 5-year-old children. The protective effect appeared strongest for children who entered day care between the ages of 6 and 12 months.

This information helps set the stage for early identification of children at risk for developing asthma and for designing trials to develop methods to modify the course of asthma. Indeed, some of these risk factors have already been used to design trials for intervention in young children at high risk for developing asthma.³³

Asthma and obesity

National attention has been directed to the growing epidemic of obesity. The May 2008 theme issue was devoted to asthma and obesity. Litonjua and Gold³⁴ comment that the prevalence of both asthma and obesity has increased, and both have their beginnings in early childhood. Therefore, common exposures that predispose individuals to both conditions may explain the association. They discuss some common factors, such as common genetic predictors, prenatal exposure to specific nutrients and overall maternal nutrition, patterns of colonization of the neonatal and infant gut, birth weight and infant weight gain, sedentary behaviors, and levels of adipokines in early life, as features to explore.

Shore³⁵ extends this discussion by presenting several mechanisms associated with obesity that contribute to asthma, including reduced lung volume and tidal volume in obesity that promote airway narrowing; low-grade inflammation that may act on the lungs to exacerbate asthma; obesity-related changes in adipose-derived hormones including leptin and adiponectin; and comorbidities of obesity, such as dyslipidemia, gastroesophageal reflux, sleep-disordered breathing, type 2 diabetes, or hypertension that may provoke or worsen asthma. Therefore, novel therapeutic strategies for treatment of the obese patient with asthma may result from a better understanding of the mechanisms that contribute to both disorders.

Mehra and Redline³⁶ identified a coaggregated relationship between obesity and sleep apnea that may affect asthma control through augmented inflammation and oxidative stress affecting cardiopulmonary disease. Mosen et al³⁷ demonstrate that obesity is associated with worse asthma outcomes, especially an increased risk of asthma-related hospitalization. Although this relationship between asthma and worse outcomes has not been clearly demonstrated in children, the pattern is set because infants with higher weight-for-length scores at 6 months of age have a greater risk of recurrent wheezing by age 3 years.³⁸ Therefore, early interventions to prevent excess infant adiposity might help reduce children's risk of asthma-related symptoms.

Asthma exacerbations

The revised asthma guidelines also redirect attention to assessing and preventing asthma exacerbations. The October 2008 theme issue was focused on asthma exacerbations.³⁹ Sears⁴⁰ provides an excellent review on the epidemiology of asthma exacerbations, indicating that exacerbations are often, but not always, associated with viral infection, especially rhinovirus, with significant interaction with allergen sensitization and exposure. Seasonal patterns of exacerbations are seen especially in children, and may be aggravated by lack of adequate maintenance anti-inflammatory treatment during the high-risk viral season, especially that reflected in the Northern Hemisphere in the month of September after returning to school. Therefore, recognizing these risk factors can be used to design prevention measures to reduce morbidity and mortality associated with asthma exacerbations.

Sykes and Johnston⁴¹ and Kelly and Busse⁴² provide detailed discussions on the mechanisms of asthma exacerbations, especially related to rhinovirus infection. Most important for therapeutic advances will be the evaluation of the possibility of defective epithelial antiviral response to rhinovirus in asthma.⁴²

Covar et al from the National Heart, Lung, and Blood Institute Childhood Asthma Research and Education Network,⁴³ based on evaluation of the previously reported Pediatric Asthma Controller Trial study,⁴⁴ noted that children with mild-to-moderate persistent asthma with previous exacerbations are more likely to have a repeat exacerbation despite controller treatment. They also noted that ICSs are superior to montelukast at modifying the exacerbation risk. Of interest, they also noted that available physiologic measures, biomarkers, and diary cards are not reliable predictors of asthma exacerbations. Sorkness et al⁴⁵ reported on the asthma index, a continuous variable to characterize exacerbations of asthma, and proposed it as a tool for quantitative comparisons among groups and for exploring time-linked associations between asthma control and other viral and biologic variables of interest.

Exercise-induced asthma exacerbations

In association with the 2008 Summer Olympics, the August 2008 theme issue was devoted to a discussion of exercise and asthma. Fitch et al⁴⁶ provided a workshop summary on asthma and the elite athlete. They indicate that long-term intense endurance training, particularly in unfavorable environmental conditions, appears to be associated with an increased risk of developing asthma and airway hyperresponsiveness (AHR) in elite athletes. They reinforced the policy requiring Olympic athletes to demonstrate the presence of asthma, exercise-induced bronchoconstriction (EIB), or AHR to be approved to use inhaled β_2 -agonists. Anderson and Kippelen⁴⁷ discuss airway injury as a mechanism for EIB in elite athletes. They propose that the pathogenesis of EIB relates to epithelial injury arising from breathing poorly conditioned air at high flow rates for long periods or high volumes of irritant particles or gases. Furthermore, this repeated injury-repair process over time can lead to an alteration in the contractile properties of the smooth muscle, making it more sensitive to mediators of bronchoconstriction. Pedersen et al⁴⁸ suggest that elite swimmers do not have susceptible airways but develop respiratory symptoms, airway inflammation, and AHR during their swimming careers. Rundell and Slee⁴⁹ provide a detailed discussion of the advantages and disadvantages of each diagnostic procedure for EIB. Weinberger⁵⁰ reviewed the use of long-acting β -adrenergic agonists (LABAs) in asthma management. Although the benefits of LABA have been demonstrated to be useful for many patients whose symptoms are not adequately controlled with conventional doses of ICS alone, there appears to be considerable individual variability. He indicates that some patients may show loss of bronchoprotective effect for EIB that will occur with regular use of LABA and may be clinically important. Until a predictive marker is available to recognize these patients, clinicians would be wise to add LABAs selectively rather than using combinations as initial therapy.

Poorly controlled asthma

It is important to understand the phenotype of difficult-to-control asthma to identify mechanisms and potential therapeutic

interventions. Sharma et al,⁵¹ using the database developed in the National Heart, Lung, and Blood Institute Childhood Asthma Management Program, evaluated the subgroup with consistent bronchodilator response over time and noted that this phenotype is associated with poor clinical outcomes. Therefore, the clinician should recognize this pattern, and it should prompt a re-evaluation of the patient's asthma medication regimen. Patients with difficult-to-control asthma are often resistant to steroid therapy; however, the cause is unknown. Goleva et al⁵² noted that the classic macrophage activation and induction of LPS signaling pathways along with high endotoxin levels detected in bronchoalveolar lavage in subjects with corticosteroid-resistant asthma suggest that LPS exposure might contribute to corticosteroid-resistant asthma, prompting an evaluation of conditions that lead to the presence of LPS in the airways.

Monitoring progression

Our March 2008 theme issue was devoted to asthma progression.⁵³ Several key articles in that issue addressed topics such as the natural history of asthma,⁵⁴ immunologic and inflammatory mechanisms that drive asthma progression to remodeling,⁵⁵ interpatient variability in rates of asthma progression,⁵⁶ and methods to assess progression in the clinic setting.⁶ Clearly, this is an area of current interest, and we have much to learn about the integration of clinical symptoms, environmental exposures, pulmonary physiology, biomarkers, and genetics to monitor disease progression, as well as interventions that will successfully alter the course of the disease.

Several new reports helped provide some insight into asthma progression. Leigh et al⁵⁷ studied human rhinovirus infection on airway epithelial cells and reported that rhinovirus upregulates growth factors involved in airway remodeling, specifically amphiregulin, activin A, and vascular endothelial growth factor. Sackesen et al⁵⁸ reported that childhood asthma is associated with significant decreases in various components of both enzymatic and nonenzymatic antioxidant defenses. Also of interest, Fitzpatrick et al⁵⁹ described compromised alveolar macrophage phagocytosis in children with poorly controlled asthma. These are all factors that could contribute to asthma progression.

Epidemiology of asthma and environmental impact

Our knowledge of environmental and occupational factors that contribute to respiratory disease is rapidly expanding.⁶⁰ It is important not only to understand the specific impact of allergens and pollutants but also to conduct careful assessments of regional exposure. Gupta et al⁶¹ characterized the geographic variability of childhood asthma prevalence among neighborhoods of Chicago and reported wide variability by neighborhood. O'Connor et al⁶² noted short-term increases in air pollution were associated with adverse respiratory health effects in inner-city children with asthma.

In relation to allergen exposure, Tovey et al⁶³ examined a birth cohort and reported a nonlinear relationship between mite exposure and clinical outcomes in a generally high mite allergen environment with lowest and highest mite exposure associated with lowest prevalence of asthma. In relation to tobacco smoke exposure, Kumar et al⁶⁴ reported that caregiver smoking was strongly associated with child exposure and lower socioeconomic status, non-Hispanic ethnicity, and caregiver depression symptoms.

Rabinovitch et al⁶⁵ reported an interesting relationship of increased urinary cysteinyl leukotrienes, albuterol use, and montelukast responsiveness in children exposed to tobacco smoke, especially girls. They suggested that perhaps measurement of leukotriene E₄ to fraction of exhaled nitric oxide (ppb; FeNO) ratios may help predict responsiveness to montelukast. Rayens et al⁶⁶ reported a reduction in asthma emergency department visits among both children and adults associated with implementation of smoke-free legislation in a community setting.

Management

Although much has been accomplished in improving asthma care, there still are higher emergency department visit rates for acute asthma observed among specific demographic groups, including women and children, and widening disparities among black subjects, which calls for further investigation and improved methods of care.⁶⁷ In a study of moderate-to-severe asthma in children, Strunk et al⁶⁸ found that neither azithromycin, a macrolide antibiotic, nor montelukast, a leukotriene receptor antagonist, were effective ICS-sparing alternatives. In a study of young children with moderate to severe intermittent wheezing, Bacharier et al⁶⁹ reported that episodic use of either budesonide or montelukast early in respiratory tract illnesses, when added to albuterol, did not increase the proportion of episode free days or decrease oral corticosteroid use, but did reduce the severity of acute illnesses, especially in those considered at risk for developing asthma.

MOVING TOWARD PERSONALIZED MEDICINE

Application of biomarkers and genetics along with defined therapeutic targets offer the hope of individualizing our approach to asthma care. Exhaled nitric oxide is a biomarker of allergic airway inflammation that has received the most attention to date. Moeller et al⁷⁰ provided evidence that high FeNO levels were associated with young children with recurrent episodes of wheezing and at high risk for developing asthma compared with those with recurrent cough and children less likely to develop asthma. Szeffler et al and the National Institute of Allergy and Infectious Diseases Inner City Asthma Consortium⁷¹ studied the benefits of adding FeNO measurements to a guidelines-based approach to asthma care and concluded that FeNO resulted in higher doses of ICS without clinically important improvements in symptomatic control. Exhaled breath condensates offer the potential to measure biomarkers affected by allergen and air pollution in an easily accessible manner,^{72,73} but the role of mediators measured from this source for clinical management remains to be defined.

Knowledge regarding genetics and the resultant complex disease of asthma continues to develop with information related to the effect of the environment on gene-environment interactions, the contribution of T_H2 immunity gene variants to allergic inflammation, and the role of filaggrin mutations in atopic dermatitis.^{56,74,75} To date, 6 genes have been identified by means of positional cloning as linking with asthma: *ADAM33*, *GRPA*, *PHF11*, *DPP1V*, *HLA-G*, and *CYFIP2*.⁷⁴ However, application of this information to clinical practice awaits confirmation through validation and replication studies. In addition, the following observations were reported: genetic association of acidic mammalian chitinase, CHIA, with atopic asthma and serum total IgE levels in an Indian population⁷⁶; increased susceptibility to asthma

and poor asthma control in children and young adults with genetic variation at a locus controlling ORMDL3 expression⁷⁷; increased serum TGF- β 1 levels and airflow obstruction with C-509T polymorphism⁷⁸; and functional relevant Toll-like receptors 1 and 6 and a potential protective role in childhood asthma.⁷⁹ In addition, Hunninghake et al⁸⁰ observed that dust mite allergen levels modified the effect of IL10 single nucleotide polymorphisms on allergy and asthma exacerbations, and Weidinger et al⁸¹ observed that filaggrin mutations affect the development of eczema and confer significant risks of asthma in the context of eczema. Bouzigon et al⁸² reported an increased risk of asthma associated with 17q21 genetic variants related to early-onset asthma with increased risk through early-life exposure to environmental tobacco smoke.

With the increased understanding of biologic mechanisms and gene-environment interactions, the hope is that this information will help identify therapeutic targets, such as transcription factors, that could lead to new treatment strategies.⁸³⁻⁸⁷

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