Advances in pediatric asthma in 2009: Gaining control of childhood asthma

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This year's summary will focus on recent advances in pediatric asthma as reported in *Journal of Allergy and Clinical Immunology* publications in 2009. New National Asthma Education and Prevention Program asthma guidelines were released in 2007, with a particular emphasis on asthma control. Now that we have worked with the principals of the guidelines for 2 years, new insights are reported on how to implement the guidelines into clinical practice. This year's report will focus on gaps in management that need to be addressed, including health disparities, methods to improve asthma management through opportunities available in school-based asthma programs, and more information on the development of asthma in childhood. This information brings us closer to the point of managing children with controllable asthma and understanding reasons why asthma is not controlled in the remaining children. If we can close these gaps through better communication, improvements in the health care system, and new insights into treatment, we will move closer to better methods to intervene early in the course of the disease and induce clinical remission as quickly as possible in most children. (J Allergy Clin Immunol 2010;125:69-78.)

Key words: *Asthma, asthma control, asthma impairment, asthma risk, asthma severity, early intervention in asthma, biomarkers, genetics, inhaled corticosteroids, leukotriene receptor antagonists, long-acting β-adrenergic agonists, omalizumab, therapeutics*

Abbreviations used

AAAAI:	American Academy of Allergy, Asthma & Immunology
AHR:	Airway hyperresponsiveness
BMI:	Body mass index
FeNO:	Fraction of exhaled nitric oxide
FLG:	Filaggrin
FSC:	Fluticasone propionate–salmeterol combination
FSE:	Future severe exacerbation
HLX1:	Homeobox transcription factor H.20-like homeobox 1 gene
ICS:	Inhaled corticosteroid
LABA:	Long acting β-adrenergic agonists
LTRA:	Leukotriene receptor antagonist
NAEPP:	National Asthma Education and Prevention Program
OR:	Odds ratio
PLAUR:	Plasma urokinase plasminogen activator receptor
RI:	Rhode Island
RSE:	Recent severe asthma exacerbation
RSV:	Respiratory syncytial virus
TBX21:	T-cell specific T-box transcription factor
TSLP:	Thymic stromal lymphopoietin

Last year's summary in this "Advances in pediatric asthma" series included a discussion of elements that would be necessary to implement the asthma guidelines, such as focusing on asthma control in adjusting therapy, applying techniques from managed asthma care to understand populations at risk for poor control, identifying early indicators of developing asthma, anticipating asthma exacerbations, and monitoring progression.[1] That summary ended with some thoughts regarding the introduction of personalized medicine to asthma care for children.

This review will highlight 2009 *Journal of Allergy and Clinical Immunology* publications that provide new information pointing to breakdowns in asthma care that require solutions, the opportunities available to implement school-based asthma programs, and new information that will help us understand the development of asthma in children.

CORE PRINCIPLES OF THE ASTHMA GUIDELINES

The 2007 version of the National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3 emphasized the importance of asthma control, a stepwise approach to asthma management, and the importance of early diagnosis and intervention.[2,3] The new NAEPP asthma guidelines introduced several new terms to apply to asthma management, specifically *assessment of severity*, *control*, *responsiveness*, *impairment*, and *risk*.[2,3] Severity is defined as the intrinsic intensity of the disease process. 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

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limitations that the patient is experiencing now or in the past because of his or her 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 caused by medication or even death. The assessment of severity and control provide guidance on the direction to take in conducting additional diagnostic evaluation, assessing environmental factors and adherence to the management plan, and consequently stepping up or stepping down medications.

ASTHMA CONTROL: BREAKDOWNS AND POTENTIAL SOLUTIONS

Asthma exacerbations

Several publications emerging from the Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens Study highlight some important features of poorly controlled asthma. The recent publications focused on information derived from the pediatric component of this study. One area of analysis evaluated whether the level of impairment, as defined by the 2007 asthma guidelines, predicts the risk for future asthma exacerbations.[4] Children aged 6 to 11 years and adolescent/adult patients aged 12 years or older were examined on entry into the study and at months 12 and 24. This study reported that children with consistently very poorly controlled asthma over the 2-year period demonstrated a 6-fold increased risk of hospitalization, emergency department visit, or corticosteroid burst (odds ratio [OR], 6.4) compared with the group that improved over the same time period. Adolescent/adult patients with consistently very poorly controlled asthma were more likely to have a corticosteroid burst (OR, 2.8) or have a hospitalization, emergency department visit, or corticosteroid burst (OR, 3.2). They concluded that consistently very poorly controlled asthma is strongly predictive of future asthma exacerbations.

Another study from this group investigated the risk of future severe exacerbations (FSEs) in children with severe/difficult-to-treat asthma and recent severe asthma exacerbations (RSEs).[5] In a multivariate model FSEs at 6 months after enrollment were most strongly associated with RSEs (OR, 3.08) and having 3 to 4 allergic triggers (OR, 2.05). Race (OR, 1.77) and very poorly controlled symptoms (OR, 1.59) also significantly predicted FSEs. Therefore RSEs are an important independent predictor of FSEs in children with severe/difficult-to-treat asthma and should be considered when setting up management plans.

Health disparities

The June *Journal of Allergy and Clinical Immunology* theme issue was focused on asthma disparities, and several reviews provided important observations to consider for improving asthma care. Bryant-Stephens[6] points out that asthma continues to disproportionately affect minority and low-income groups, with African American and Latino children who live in low-socioeconomic-status urban environments experiencing higher asthma morbidity and mortality than white children. She points out that because asthma is a complex disease that affects millions of persons, multifaceted comprehensive interventions that combine all evidence-based successful strategies are essential to finally closing the gap in asthma morbidity. Canino et al[7] also make the point that a multilevel framework for integrating research in health disparities is needed to advance both future research and clinical practice. They propose that several strategies that could be applied in clinical settings to reduce asthma disparities include the need for routine assessment of the patient's beliefs, reduction of financial barriers to disease management, and health literacy and the provision of cultural competence training and communication skills to health care provider groups.

Valet et al[8] indicate that 21% of the US population lives in rural areas. Rural populations have lower income, a higher rate of government versus private insurance, and decreased access to health care compared with persons living in urban areas. Unfortunately, there has been little research on asthma prevalence and severity in rural US populations compared with that on other international populations. Future work is needed to more clearly define asthma prevalence and morbidity among residents of the rural United States, as well as to identify interventions effective in this population.

In an editorial to this theme issue, Apter and Casillas[9] point out that the American Academy of Allergy, Asthma & Immunology (AAAAI) has made a number of efforts to reduce health disparities through Academy CAN! by pairing an allergist/asthma specialist with a community clinic in an underserved area. The AAAAI has also been a member of the Commission to End Health Disparities since its origin in 2004. The AAAAI has several programs in place to try to remedy the problem of a shortage of minority providers underrepresented in medicine, including the Chrysalis Project, the Odyssey Program, and the Fellowship of Excellence Award, as well as developing a partnership with the National Medical Association. However, they also point out that there is much more to do not only to reduce health disparities nationally but also to take a more global approach to address inequities around insurance coverage as part of health care reform.

Community factors

Another important way to look at asthma control is to look at individual populations and to examine ways that might be inherent in the environment or culture that could contribute to poor asthma control or enhance asthma control. Gruchalla et al[10] evaluated the role of various indicators to predict future asthma control in an inner-city population aged 12 through 20 years enrolled in a National Institute of Allergy and Infectious Diseases Inner City Asthma Consortium study that applied a guidelines-based approach to asthma care. Surprisingly, they found that the usual predictors of future disease activity have little predictive power when applied to a highly adherent population with persistent asthma that is receiving guidelines-based care. Therefore they believed that new predictors need to be identified that will be able to measure the continued fluctuation of disease, such as asthma exacerbations and periodic episodes of loss of control, that persists in highly adherent, well–treated populations, such as the one studied.

It is well recognized that managing asthma in adolescence is a challenge, particularly for children in the inner-city environment. Naimi et al[11] sought to describe adherence to preventative asthma medications and explore relevant beliefs and attitudes, as well as to seek out ideas for improving adherence from inner-city youth. As expected, they found that adherence was poor and concluded that examining and acknowledging health beliefs of older teens in the context of their life structure could facilitate discussions about self-management. Some of the beliefs from subjects included the feeling that taking the medications was not necessary, and some of them even doubted their benefit.

Another observation is that self-reported asthma among Puerto Ricans is very high, with increased asthma morbidity, including hospitalizations. Therefore Esteban et al[12] sought to characterize differences in asthma severity and control among 4 groups: island Puerto Ricans, Rhode Island (RI) Puerto Ricans, RI Dominicans, and RI Whites. The study included 805 children aged 7 to 15 years. They found that island Puerto Ricans had significantly milder disease than the other 3 groups. They also found that island Puerto Ricans had more emergency department visits over a 1-year period than the 3 RI groups. They proposed several explanations for this phenomenon, including the threshold for seeking urgent care and the self-assessment of severity. They proposed that perhaps objective indicators, such as biomarkers, might be useful in assessing the asthma severity/control variability among patient populations.

Recognizing that the asthma burden in the United States is not evenly distributed, Gupta et al[13] determined the effect of positive socioenvironmental community factors on childhood asthma prevalence in Chicago. A survey was conducted, and the neighborhoods were geocoded and divided based on asthma prevalence. Among the many important observations, they noted that childhood asthma increased as the black population increased in a community. When considered alongside sociodemographic/individual characteristics, overall community vitality, as well as social capital, continued to contribute significantly to asthma variation. This type of information might be useful for the allocation of public health resources to better address asthma management.

School-based asthma programs

A good place to identify children with asthma whose symptoms are uncontrolled is the school system. Children with asthma experience school absence, and when the disease is uncontrolled, they cannot perform to their best capacity. The August 2009 theme issue was focused on managing asthma and allergies in schools.[14] Kruzick et al[15] evaluated asthma control in schoolchildren from the Denver Public School System. They reported that despite having access to care, children still had poor asthma control, illustrating the need for additional programs to help identify and monitor those children at high risk for asthma morbidity.

On the bright side of this concerning picture, the school system can serve as a great place to provide health education that is focused on assisting students in managing asthma, food allergy, and other chronic diseases. In fact, asthma, because it is so prevalent, can serve as a model to organize school-based disease management programs. Insights into this area are provided by Bruzzese et al[16] and Cicutto[17] in 2 complementary reviews. They summarize their experience with school-based asthma programs and offer clinicians, including specialists, some insights on using such programs to improve access to care, for teaching self-management skills in schools, and for improving school personnel management skills. Practical, targeted, and cost-effective strategies can be developed to significantly improve outcomes.

The school is not only important as an education setting for asthma care, but it is also a source for allergen exposure. Consequently, Salo et al[18] reviewed the many sources and clinical significance of allergen exposure in the school setting. They conclude that there are limited data available to evaluate to what extent exposure to allergens contributes to allergic sensitization and exacerbation of allergic symptoms. Information on cost-effective strategies to reduce allergen exposure is also limited. Furthermore, in published studies the effectiveness of interventions varied substantially.

Asthma therapy

The revised asthma guidelines contained a significant revision of the section describing the management of acute asthma exacerbations.[2,3] A supplement to the August 2009 issue was focused on reviewing current knowledge related to asthma exacerbations.[19] Camargo et al[20] highlight the key points of the Expert Panel Report 3, especially those areas that have been significantly changed from the previous report. They emphasize that early treatment of asthma exacerbations is the best strategy for management. Important elements of early treatment at the patient's home include a written asthma action plan; recognition of early signs and symptoms of worsening; appropriate intensification of therapy by increasing short-acting β-agonists and, in some cases, adding a short course of oral corticosteroids; removal or withdrawal from an environmental factor contributing to the exacerbation; and prompt communication between the patient and clinician, seeking emergency care for severe manifestations, or both.

Infants and young children are at particular risk for respiratory exacerbations that might or might not be early indicators of emerging asthma. Several recent publications addressed the role of steroid therapy in managing these acute exacerbations in young children. Ducharme et al[21] examined the efficacy and safety of preemptive treatment with high-dose fluticasone, 750 μg twice daily for up to 10 days for each episode, in reducing the severity of recurrent virus-induced wheezing in children. Compared with placebo, the high-dose inhaled fluticasone reduced the use of oral corticosteroids but was associated with a smaller gain in height and weight. They called for an assessment of long-term adverse effects before this method was applied to clinical practice.

Panickar et al[22] evaluated the effect of a short course of oral prednisolone, 10 mg once a day for children 10 to 24 months of age and 20 mg once a day for older children, on reducing the duration of hospitalization after a wheezing illness in preschool children. They did not find a significant difference in the duration of hospitalization for the 2 study groups and thus did not find evidence to support this practice of managing wheezing illness in young children.

Bush,[23] in an accompanying editorial, concluded that prednisolone should be administered to preschoolers only when they are severely ill in the hospital. Intermittent, high-dose inhaled corticosteroids (ICSs) should not be used. However, the ICS seemed to be more effective than the oral corticosteroid but carried some risk with regard to growth. Nevertheless, the significant morbidity and limitations of both treatment strategies call for better treatment modalities to manage such illness in children. Kelly[24] recently summarized the information available for steroid dosing in children for the management of acute asthma exacerbations that was used in the Expert Panel Report 3 update. An important point is that there is evidence of potential long-term consequences to excessive number of bursts, as well as the dose used for the burst. Therefore using lower doses for shorter periods of time appears to be a worthwhile strategy. Perhaps the most effective method of managing severe exacerbations is prevention of exacerbations, as will be discussed in later sections of this review.

Earlier this year, concern was raised regarding potential behavior-related adverse effects associated with montelukast therapy. The pharmaceutical firm compiled information from its past studies to address these concerns, including risk for suicidality. Philip et al[25,26] reported that behavior-related adverse experiences were infrequent in clinical trials, and those leading to

discontinuation of treatment were rare. Furthermore, there were no reports of completed suicide, and reports of possibly suicidality-related events were rare in patients receiving montelukast and similar to those in control subjects. In an accompanying editorial, Dr Kimberly Kelsay,[27] a child psychiatrist who specializes in managing behavior disorders in children with asthma and allergies, indicated that although these results are reassuring, they were derived from a postmarketing analysis. She suggested that the US Food and Drug Administration might consider mandating standardized methodology to assess these adverse events as new medicines are developed and tested.

NEW INSIGHTS THAT COULD IMPROVE ASTHMA CONTROL IN CHILDREN

Development of childhood asthma

A key to controlling asthma is early recognition and early intervention, perhaps even prevention. Several studies in the past year provided new insights on the development of asthma in children. Recent reports by Suttner et al[28-30] speak to the genetic aspects influencing the development of childhood asthma. First, a study of gene variants in homeobox transcription factor H.20-like homeobox 1 *(HLX1)*, a regulator of T_H1 differentiation and suppressor of T_H2 commitment, in German children suggested that polymorphisms in *HLX1* increase the risk for childhood asthma.[28] Second, a study gene variants in the T-cell specific T-box transcription factor *(TBX21)*, a factor that induces the differentiation of T_H1 and blocks T_H2 commitment together with *HLX1*, indicated that *TBX21* polymorphisms contribute to the development of asthma, potentially by altering *TBX21* promoter activity.[29] Furthermore, a risk score model indicated that *TBX21* and *HLX1* polymorphisms might have synergistic effects on asthma risk. Third, an assessment of genetic variants in the transcription factor *GATA3*, which is necessary for the differentiation of naive T_H2 cells and also the maintenance of T_H2 cytokine expression in differentiated T_H2 cells, showed none of the variants were associated with allergy or asthma phenotypes.[30] Therefore these studies show that better understanding of the functional effect of the associated polymorphisms for *HLX1* and *TBX21* could help identify critical pathways in the development of childhood asthma.

Understanding prenatal conditions that predispose to childhood asthma will also be useful in identifying children at risk for asthma. As such, Bisgaard et al[31] identified high body mass index (BMI) in newborns and smoking by the mothers as features associated with reduced neonatal lung function. Yemen and Gaston[32] believed that an observation of interest in this report was that infants exposed (by history) to maternal acetaminophen tended to have more airway reactivity. Based on plausible mechanisms of acidic acetaminophen nitration formation and possible placental transfer to the infant, this phenomenon merits future studies.

Cookson et al[33] identified maternal anxiety symptoms (OR, 1.64; highest vs lowest quartile of anxiety scores at 32 weeks' gestation) as an indicator of stress during fetal life that might program the development of asthma during childhood. Keski-Nisula et al[34] evaluated the association between intrauterine microbial growth at the time of delivery and the development of asthma and allergic sensitization among offspring. Intrauterine growth of potential pathogenic anaerobic bacteria and *Streptococcus* species at birth was associated with an increased risk of asthma ever and current asthma at the age of 15 to 17 years compared with the risk seen in subjects with negative microbial cultures.

Another area of interest includes potential postnatal conditions that can contribute to developing asthma. Upham et al[35] found that in children with a family history of atopy, relative deficiency of circulating plasmacytoid dendritic cells during infancy appears to be a risk factor for more frequent and more severe respiratory tract infections, wheezing, and a diagnosis of asthma. Infants with higher numbers of these cells were protected against these outcomes. Gergen et al[36] examined the association between total IgE levels and asthma in the National Health and Nutrition Examination Survey. They noted that total IgE levels are associated with asthma only among persons who have positive results for at least 1 allergen-specific IgE.

As previously mentioned, acetaminophen has been implicated in the development of asthma. Farquhar et al[37] reviewed the available literature on the associations between acetaminophen use and the development of asthma and its severity. They believed that there is evidence to suggest such an association and indicated that randomized controlled trials must be conducted to explore the association with both development and maintenance of asthma. Antibiotics are another medication implicated in the development of asthma. Foliaki et al[38] identified an association between antibiotic use in the first year of life and current symptoms of asthma, rhinoconjunctivitis, and eczema in 6- to 7-year-old children. They suggested that further research is required to determine whether the observed associations are causal or are due to confounding by indication or reverse causation.

It has been recognized that infants hospitalized for bronchiolitis have a high rate of early childhood asthma. To expand on this observation, Carroll et al[39] reported a dose-response relationship, as determined by the level of health care needed, between the severity of infant bronchiolitis and the increased odds of both early childhood asthma and asthma-specific morbidity. Caudri et al[40] recognized the difficulty of diagnosing asthma in preschool children and subsequently developed a clinical prediction score. They found that 8 clinical parameters independently predicted asthma at 7 to 8 years, including male sex, postterm delivery, parental education and inhaled medication, wheezing frequency, wheeze/dyspnea apart from colds, respiratory tract infections, and eczema. They incorporated these indicators into the asthma prediction score and suggested that it could be useful in prognosis and treatment decisions.

Pali-Scholl and colleagues[41] provided an update on allergies in pregnancy, lactation, and early childhood. They believed that recent studies and meta-analyses could not confirm the protective effect of an allergen-poor diet on the part of the mother during pregnancy and lactation. Likewise, the type of bottle feeding or the introduction of solid food into the child's diet might not significantly influence the development of atopy, allergy, or asthma in a child's life. The few preventative measures remaining to reduce the risk of allergic sensitization and atopic diseases in mother and child are the avoidance of smoking and alcohol consumption during pregnancy and lactation and the avoidance of the impairment of gastric function. Therefore more studies are needed for the development of final and evidence-based recommendations to prevent allergy induction.

It is necessary to develop and validate a questionnaire to assess asthma control in preschool-aged children. Murphy et al[42] evaluated a 33-item questionnaire and subsequently identified 5 items incorporated into the Tests for Respiratory and Asthma Control in Kids. The Tests for Respiratory and Asthma Control in Kids is thus an easy-to-administer, caregiver-completed questionnaire

of respiratory control in preschool children with symptoms consistent with asthma.

Assessment of variable treatment response

Over the past 10 years, it has become clear that treatment response can vary among subjects. It is therefore important not only to measure treatment response but also to understand factors that influence and perhaps predict variable treatment response. In addition, better measures of treatment response are needed for children, especially young children who are unable to perform spirometery. Larsen et al[43] examined the utility of impulse oscillomtery in a long-term comparison of 3 controller regimens in children with persistent asthma. They concluded that impulse oscillomtery might offer additional insights into the response of asthmatic subjects. The pattern of improvement seen in reactance area over the course of therapy suggested that this test could detect alterations in airway mechanics not reflected by spirometry. This change in reactance area might reflect ongoing improvement in small airways function.

It is important to determine the repeatability of commonly used outcomes for treatment response to understand the association of genetics to drug response. Wu et al[44] used data from the National Heart, Lung, and Blood Institute Childhood Asthma Management Program to measure intraclass correlation coefficients for each outcome over repeated visits over a period of 4 years. They reported that within-treatment group repeatability of FEV_1 and methacholine PC_{20} is high, and thus these phenotypes are considered heritable.

Several studies have now reported features associated with response to ICSs in older children and adults. Bacharier et al[45] reported that more favorable responses to an ICS than to placebo in high-risk preschool children over a 2-year period were more likely in those with an emergency department visit or hospitalization for asthma within the past year, children with aeroallergen sensitization, boys, and white participants. Knuffman et al[46] noted that in older children those with a parental history of asthma, increased fraction of exhaled nitric oxide (FeNO) levels, low methacholine PC_{20} values, or a history of ICS use can expect the best long-term outcomes with ICS therapy compared with leukotriene receptor antagonists (LTRAs).

Leukotrienes are recognized contributors to the inflammatory process of asthma, and leukotriene modifiers are considered a therapeutic option for the treatment of asthma. Leukotriene E_4 mediates many of the principal features of asthma, including bronchial constriction, hyperresponsiveness, eosinophilia, and increased vascular permeability.[47] Tantisira and Drazen[48] reviewed published association studies implicating the role of leukotriene pathway genes in asthma pathogenesis and treatment response. These preliminary observations will now be followed up with a broader scope of investigation through increased sample sizes and genome-wide association approaches. O'Byrne et al[49] reviewed the available literature on the efficacy of LTRAs and synthesis inhibitors in asthmatic subjects. Based on this review, they concluded that LTRAs have an excellent safety profile and are a viable alternative to low-dose ICS treatment but should be reserved for patients who cannot or will not use ICSs. LTRAs are also alternatives to long-acting β-adrenergic agonists (LABAs) as add-on therapy to ICSs, but their efficacy is less than that of ICSs/LABAs.

Effect of body growth on asthma development

Body habitus is thought to play a role in asthma development and presentation. Coogan et al[50] assessed the relation of BMI to asthma incidence in the Black Women's Study. They found a positive association between BMI and asthma risk that was similar in magnitude to those observed in longitudinal studies of white women. Clerisme-Beaty and Rand,[51] in an associated commentary, indicated that the weight of epidemiologic evidence is now strong and compelling that obesity is an important risk factor for asthma. Therefore it is now time to conduct well-designed mechanistic studies to clarify the causal effects of obesity on asthma incidence and morbidity in different populations. If there is an association, then greater emphasis must be placed on weight control in children and adults.

Scholtens et al[52] studied overweight status and changes in overweight status in children aged 1 to 8 years in relation to asthma symptoms in childhood. They observed that children with a currently high BMI are at increased risk of dyspnea and airway hyperresponsiveness (AHR) at 8 years. Of interest was the observation that a high BMI at an earlier age is not related to an increased risk if the child has become normal weight at 6 to 7 years. Schwartzstein and Gold,[53] in an associated editorial, pointed to questions that still remain, such as whether asthma is leading to a sedentary existence and causing a high BMI rather than whether obesity is causing asthma. Musaad et al[54] found that measures of central obesity are more associated with the presence of asthma and asthma severity in children with allergic rhinitis when compared with standard BMI measures. Therefore measurements of waist circumference should be included with measuring weight and height in children to better assess obesity and asthma risk.

Asthma exacerbations and viral infection

Viral infections are a frequent cause of asthma exacerbations in children and might play a significant role in the development of asthma. Stensballe et al[55] examined the causal direction of the associations of respiratory syncytial virus (RSV)–induced hospitalization and asthma in a population-based cohort. They found a bidirectional association such that severe RSV infection is associated with a short-term increase in the risk of subsequent asthma and asthma is associated with a long-term 3-fold increased susceptibility for severe RSV disease. They hypothesized that severe RSV and asthma might share a common genetic predisposition, environmental exposure, or both. Stensballe et al[56] also examined the influence of maternally derived RSV-neutralizing antibodies in cord blood on RSV hospitalization and recurrent wheeze in infancy. They reported that maternally derived RSV-neutralizing antibodies protect against RSV hospitalization and also when the infant has recurrent wheeze. However, they also observed that high maternally derived RSV-neutralizing antibody levels were associated with an increased risk of recurrent wheeze. Glezen,[57] in an associated editorial, reviewed the fundamentals of RSV infection and the persistent damage it can cause to respiratory epithelium. He suggested several strategies to protect infants in the first months of life through maternal immunization followed by active immunization in the infant. The many complex factors associated with viral resistance pose challenges for designing future interventions.

Several studies provide insight related to RSV-associated respiratory illness and asthma. Juntti et al[58] addressed the

question of whether infants contracting an early RSV infection differ from healthy children in their cytokine production at birth. Their studies suggest that natural differences in innate immunity predispose children to severe RSV infection rather than the infection modifying immune responses in childhood. Dakhama et al[59] sought to define the role of RSV-specific IgE, a component of the host response to RSV infection, in the enhancement of airway responsiveness on reinfection of newborn mice. They reported that RSV-specific IgE enhances the development of T_H2-biased airway responsiveness on reinfection of mice initially infected as newborns. They postulated that RSV-specific IgE might play a role in post-RSV wheezing in children with this antibody response after RSV infection.

Miller et al[60] sought to determine the presentation and burden of disease caused by human rhinovirus C among young hospitalized children. They found that human rhinovirus C was detected in 7% of children hospitalized for fever or respiratory conditions and constituted almost half of all rhinovirus-associated hospitalizations. Therefore this novel group of rhinoviruses causes a substantial burden of pediatric disease. Gern and Busse,[61] in an accompanying editorial, point to the significant advances made in understanding the biology of disease through the application of molecular tools. They make the point that the recognition of "new" pathogens by means of molecular sleuthing brings renewed hope for new therapeutic strategies for virus-induced wheezing and exacerbations of asthma. Furthermore, Subrata et al[62] used a genomics-based approach involving profiling of PBMC subpopulations collected during exacerbations versus convalescence by means of microarray and flow cytometry. They reported that viral respiratory tract infections in atopic children appear to initiate an atopy-dependent cascade that amplifies and sustains airway inflammation initiated by innate antiviral immunity through harnessing underlying atopy-associated mechanisms. They propose that these interactions might account for the unique susceptibility of atopic subjects to severe virally induced asthma exacerbations.

Preventing asthma exacerbations

Khan et al[63] developed the Pediatric Dyspnea Score and compared it with traditional markers of asthma control in predicting outcomes after discharge from an asthma hospitalization. They concluded that the easy-to-use Pediatric Dyspnea Score could be applied in children as young as 6 years of age to predict adverse outcomes after hospitalization and could thus be used as a tool to help guide inpatient discharge.

Another method of controlling exacerbations is attention to the maintenance regimen of long-term controller therapy. Several interesting reports occurred in the past year that prompt a careful evaluation of our current practice. Spahn et al[64] compared the rates of asthma-related emergency department visits and hospitalizations in the fall between users and nonusers of a fluticasone propionate–salmeterol combination (FSC) in the preceding summer. They found a decreased risk of serious asthma-related outcomes in the subsequent fall for children dispensed summertime FSC. They proposed that continuous use of FSC before seasonal viral exposure might decrease seasonally related exacerbations.

Lanier et al[65] evaluated the efficacy and safety of omalizumab in children aged 6 to 12 years with moderate-to-severe persistent allergic asthma that was inadequately controlled despite treatment with medium- or high-dose ICSs with or without other controller medications. Omalizumab significantly reduced asthma exacerbations by 43% versus placebo while providing an acceptable safety profile. Currently, approval for use of omalizumab in this age group awaits US Food and Drug Administration review.

Another topic that has been resurrected is the association of β-adrenergic polymorphisms and increased risk for asthma events. Basu et al[66] explored the role of the Arg16 allele on asthma exacerbations in the context of the use of on-demand albuterol and regular salmeterol. They concluded that the Arg16 genotype of the adrenergic β_2-receptor agonist gene is associated with exacerbations in asthmatic children and young adults exposed daily to β_2-agonists, regardless of whether the exposure is to albuterol or a LABA, such as salmeterol. It should be pointed out that one criticism of this conclusion is that it is derived from a cross-sectional study and does not evaluate this phenomenon in a randomized controlled fashion. Studies that have been conducted in this manner have not always found this association. Therefore one can question whether the Arg16 polymorphism is a gene variant associated with more severe asthma. Perhaps β-adrenergic polymorphisms should be measured in all patients with asthma to determine their risk for asthma exacerbations. Studies need to be performed to determine whether alternative treatment strategies to increased β-adrenergic agonist therapy are more beneficial in these patients.

INSIGHTS THAT COULD INFLUENCE FUTURE ASTHMA CARE

Severe asthma

Several recent studies provided insight into severe asthma in children. Zeiger et al[67] evaluated data in the Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens Study and noted a significantly higher rate of asthma exacerbations in children versus adults despite specialist-prescribed optimal controllers and acute intervention with oral corticosteroids. Therefore they concluded that better use of present interventions with improved objective adherence or new therapeutic modalities to reduce asthma-related health care use are needed. Su et al[68] reported relationships between the intensity of an endogenous epigenetic control (ie, the balance of histone deacetylase and acetyltransferase activities) in healthy and atopic asthmatic children with the physiologic intensity of AHR. This prompted their recommendation to better understand the interplay in individuals of different clinical phenotypes between distinct patterns of epigenetic regulation, altered immune capacity, and resulting physiologic alterations. In addition, Fitzpatrick et al[69] reported that children with severe asthma have increased biomarkers of oxidant stress in the epithelial lining fluid that are associated with increased formation of glutathione disulfide and a shift in the glutathione redox potential toward the more oxidized state. Therefore additional therapies to decrease oxidant stress might be a therapeutic consideration.

Progression

Dolhnikoff et al[70] examined extracellular matrix remodeling of the distal lung using immunohistochemistry and image analysis and reported that the outer area of the small airways is a major site of remodeling in patients with fatal asthma, potentially

contributing to functional changes and the loss of airway-parenchyma interdependence observed in these patients. Barton et al[71] identified plasma urokinase plasminogen activator receptor *(PLAUR)* as a potential asthma susceptibility gene and associated *PLAUR* with lung function decrease, supporting a role for *PLAUR* in airway remodeling in asthma. Enomoto et al[72] reported that acute asthma exacerbations are associated with hypersecretion of epidermal growth factor and amphiregulin in the airway. They postulated that recurrent asthma exacerbations could contribute to airway remodeling through these factors, and prevention of these exacerbations could therefore prevent progression of remodeling.

Environmental effect

Studies regarding the environment continue to shed light on the potential role of environmental factors in asthma. Salam et al[73] reported that the arginase genes *ARG1* and *ARG2* are associated with childhood asthma. Furthermore, the association of the *ARG1* variation and asthma might depend on atopy and ambient ozone levels. Therefore both genetic (history of atopy) and environmental factors (ambient ozone) could influence the asthma risk associated with arginase variants. Wichmann et al[74] reported that exposure to particulate matter and volatile organic compounds arising from petrochemical plants but not from traffic density was associated with worse respiratory health in children. Thus clinicians need to consider the source of air pollution in considering potential health effects in children.

Ronmark et al[75] noted that the prevalence of allergic sensitization increased significantly from 1996 to 2006, whereas no increase in clinical symptoms was observed. They believed that the parallel decrease in parental smoking and respiratory tract infections indicated a different influence of environmental factors on allergic sensitization and clinical symptoms. Future studies will monitor whether the large increase in sensitization might predict an increase in clinical symptoms of allergic disease in the preteenage and teenage years. Traidl-Hoffman et al[76] expanded on this concept by reviewing the structural basis of allergenicity and the potential role of additional factors from the environment and the host that determine the outcome on the response to allergens. Schaub et al[77] reported that farm exposure during pregnancy increases the number and function of cord blood regulatory T cells associated with lower T_H2 cytokine secretion and lymphocyte proliferation on innate exposure. They suggest that perhaps maternal farm exposure might reflect a natural model of immunomodulation, shaping a child's immune system in early life.

Drug-response modifiers

Biologic factors could play a significant role in modifying the effect of therapeutic agents used for asthma management. Miller et al[78] reported that strained parent-child relations, and perhaps stress more generally, could bring about adverse outcomes in asthma by reducing cortisol's ability to regulate cytokine activity and subsequent airway inflammation. Wright,[79] in an accompanying editorial, indicated that it will be important to begin to understand factors related to developmental programming of glucocorticoid sensitivity during critical periods of development, which could play a role in the cause of inflammatory respiratory disorders, as well as subsequent morbidity.

Another investigation related to the neuroimmune connection came from Miller et al,[80] who reported that children with depressive symptoms manifest vagal bias when emotionally stressed. Those with depressive symptoms and an FEV_1 of less than 80% of predicted value manifest greater airway resistance. They suggest that screening for depressive symptoms might be helpful in asthma management. Consequently, psychosocial intervention and targeted use of antidepressants, anticholinergic asthma medications, or both might prove to be beneficial adjuncts in the treatment of depressed patients with asthma.

Biomarkers

Measurement of biomarkers of disease activity hold the promise of adding information to our assessment of asthma control. The most carefully evaluated biomarker to date is exhaled nitric oxide. Several new publications provide further insight into the application of FeNO measurements to clinical practice. Smith et al[81] conducted studies to evaluate the method to obtain clinically optimum FeNO levels. They concluded that optimum FeNO levels are best established by using the patient's personal best value as a reference rather than using predicted values based on reference equations. Therefore targeting treatment against predicted FeNO values is not justified.

Jackson et al[82] examined FeNO levels in children 6 and 8 years of age at high risk for the development of asthma and allergic disease. They observed that increases in FeNO levels were strongly correlated with allergic sensitization. They concluded that an increased FeNO level obtained in the evaluation of asthma in children should prompt an evaluation of allergic sensitization.

Fitzpatrick et al[83] reported that symptomatic children with mild-to-moderate and severe allergic asthma have significant nitrosative stress, as indicated by measures of nitric oxide oxidation products in airway epithelial lining fluid, despite corticosteroid treatment. They suggested that additional therapies to decrease airway nitrosative stress might be needed in these children to reduce ongoing symptoms.

Hollams et al[84] sought to identify biomarkers associated with asthma phenotypes in children. They reported that asthma in teenagers is predominantly driven by atopy acting in concert with a second tier of T_H2-independent immunoinflammatory mechanisms. Therefore they believed that atopy contributes directly to asthma risk and in addition creates susceptibility to atopy-independent proinflammatory mechanisms, which can act as cofactors in disease pathogenesis.

Genetics

The integration of genetics with a careful evaluation of clinical parameters of disease offers the opportunity to not only provide insight into the pathogenesis of asthma but also provide indicators of prediction for those who will have asthma. He et al[85] reported that a genetic variant in the region of the thymic stromal lymphopoietin gene *(TSLP)* is associated with the phenotypes of asthma and AHR. They suggested that *TSLP* could be a novel target for modulating allergic inflammation in the airways because it is accessible to small molecules or antibodies that inhibit its action.

Von Mutius[86] and Vercelli,[87] in commentaries on gene-environment interactions, advise us that we must consider the complex interactions of genes and environment as an opportunity to better characterize the plasticity of genetic programs and to use this knowledge in prevention and treatment. There is a need to better develop tools for individual exposure assessment in all

environmental fields. As such, Flory et al[88] provided a confirmatory report regarding the interaction among the 17q12-21 variants, childhood smoke exposure, and pediatric asthma in a white population. However, they were unable to show an age-of-onset effect. They indicated that further prospective research is needed to explore the interaction between the 17q12-21 variants and age of onset of asthma. The 17q12-21 locus harbors the *ORMDL3* gene, which encodes a gene product of uncertain function that localizes in the endoplasmic reticulum.

Another gene of interest in developing allergy and asthma is the filaggrin gene *(FLG)*. Marenholz et al[89] reported that *FLG* mutations and food sensitization represent 2 distinct mechanisms interacting in the pathogenesis of asthma. They believed that in infants with eczema and food sensitization, genotyping of the *FLG* mutations allows the prediction of asthma before the onset of symptoms. This observation could facilitate the development of subgroup-specific interventions to prevent the progression from eczema to allergy that is commonly observed in the clinical setting.

ANOTHER STEP TOWARD PERSONALIZED MEDICINE

Some clinicians have expressed disappointment regarding the absence of new medications to manage asthma. However, this apparent quiescent period has allowed us the time to organize our approach to asthma management through the ongoing effort to revise the asthma guidelines, to better organize our overview of individual patients through the implementation of electronic medical records, and to identify unmet needs in our patient population. We are gradually moving from an approach based on evidence from clinical studies that speak to the average patient to addressing the needs of the outliers.

This new direction in medical care, often referred to as *individualized* or *personalized medicine*, will not only integrate genetics and biomarkers into clinical practice but will more importantly prompt us to develop new approaches to manage those at risk for disease and those who are not responding to conventional therapy. Another new trend in medicine is the closer attention being paid to public health and to improving chronic and acute disease management. As such, new programs are being developed through schools and communities to monitor disease activity and to assist children and adults in educating themselves to better prevent and manage illness.

Biomarkers, such as exhaled nitric oxide, are making their way into clinical practice, at least at a subspecialty level. Measurement of FeNO levels has served as an easily accessible biomarker that can help in diagnosing asthma, predicting response to ICS therapy, monitoring ICS adherence, and adjusting ICS dosing. However, FeNO levels might not serve to anticipate asthma exacerbations or provide an indication of asthma progression. Additional biomarkers might be useful in addressing these unmet needs.

In regard to genetics, considerable effort has been invested in understanding β-adrenergic polymorphisms and their role in asthma management. Arguments could be made for using a measurement of the Arg16 polymorphism of the β-adrenergic receptor in clinical practice to identify patients at risk for loss of asthma control on frequent use of short-acting β-adrenergic agonists. Alternatively, it might be a marker for a patient population at risk for more severe asthma that requires higher use of β-adrenergic agonists and a need for alternative treatment. As noted in this review, other genetic markers, such as *HLX1*, *TBX21*, *PLAUR*, *FLG*, *ORMDL3*, and *TSLP* variants, are emerging as genes that could be measured to predict disease onset and characterize patients who might benefit from early intervention.

The picture of asthma management is changing before our eyes and perhaps even faster than we realize it. The next challenge for the NAEPP Expert Panel will be to integrate this new information and move the asthma guidelines from a document that speaks to the average patient and their likely response to a therapeutic intervention into a practice guideline that integrates the new knowledge that can be applied to a more personalized approach. This step would identify relevant information that would help the clinician select treatment strategies that will perhaps prevent disease and achieve better control in those who are not responding to conventional approaches. This effort will bring together new advances in science, disease monitoring, and public health and should lead to the development of new approaches to asthma management that will ultimately reduce asthma morbidity and further reduce asthma mortality.

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Key advances in pediatric asthma, 2009

- **Because asthma is a complex disease that affects millions of persons, multifaceted comprehensive interventions that combine all evidence-based successful strategies are essential to finally closing the gap in asthma morbidity.**
- **New predictors of disease activity need to be identified that will be able to measure the continued fluctuation of disease, such as asthma exacerbations and periodic episodes of loss of control, that persists in highly adherent, well–treated populations.**
- **Better understanding of the functional effect of the associated polymorphisms for *HLX1* and *TBX21* could help identify critical pathways in the development of childhood asthma.**
- **Children with a currently high BMI are at increased risk of dyspnea and AHR at 8 years. However, a high BMI at an earlier age is not related to an increased risk if the child has become normal weight at 6 to 7 years.**
- **The outer area of the small airways is a major site of remodeling in patients with fatal asthma, potentially contributing to functional changes and the loss of airway-parenchyma interdependence observed in these patients.**
- **Genetic markers, such as *HLX1*, *TBX21*, *PLAUR*, *FLG*, *ORMDL3*, and *TSLP* variants, are emerging as genes that could be measured to predict disease onset and characterize patients who might benefit from early intervention.**

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