Last year’s “Advances in pediatric asthma” concluded with the following statement: “Perhaps new directions in personalized medicine and improved health care access and communication will help maintain steady progress in alleviating the burden of this disease in children, especially young children.” This year’s summary will focus on recent advances in pediatric asthma that show significant accomplishments in reducing asthma morbidity and mortality over the last 10 years and discuss some pathways to further reduce asthma burden, as indicated in Journal of Allergy and Clinical Immunology publications in 2011. Some of the recent reports continue to shed light on methods to improve asthma management through steps to reduce asthma exacerbations, identify features of the disease in early childhood, alter asthma progression, intervene with nutrition, and more effectively implement the asthma guidelines. As new information evolves, it is also time to consider a revision of the asthma guidelines based on key studies that affect our management of the disease since the last revision in 2007. Now is also the time to use information recorded in electronic medical records to develop innovative disease management plans that will track asthma over time and enable timely decisions on interventions to maintain control that can lead to disease remission and prevention. (J Allergy Clin Immunol 2012;129:60-8.)

Key words: Airway remodeling, asthma, asthma control, asthma exacerbations, asthma impairment, asthma risk, asthma severity, early intervention in asthma, biomarkers, environment, genetics, inhaled corticosteroids, leukotriene receptor antagonists, long-acting β-adrenergic agonists, omalizumab, personalized medicine, severe asthma, therapeutics, tiotropium

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Last year’s “Advances in pediatric asthma” article included a discussion of studies related to the natural history of asthma, individualization of asthma therapy, reduction in asthma exacerbations, management of asthma in the inner city, and new uses of some available medications. In addition, the review by Apter on adult asthma focused on health care delivery and quality, asthma management, and the role of environmental exposures and their interaction with genetics.

This review will highlight 2011 Journal publications that provide new information to better understand the early development of asthma and the prevention of asthma exacerbations. The implementation of strategies for early intervention and a personalized approach to asthma management could further reduce the burden of asthma. Several key studies published in other journals will also be included to highlight these important advances. This past year, a new series of 6 reviews was introduced in the Journal in September 2011 related to the current status of asthma. The opening article in this series, entitled “Advancing asthma care: The glass is only half full!” indicates areas of accomplishment from the past 30 years along with areas that now must be addressed to continue to improve asthma care.

LOOKING BACK: ACCOMPLISHMENTS

The asthma series to date has included 4 of the 6 planned publications in 2011. The first article highlights the accomplishments in reducing asthma mortality and morbidity related to hospitalizations (Fig 1). This is an impressive accomplishment but certainly not a time to enter a comfort zone because the burden of disease is still significant, especially as it affects young children and certain populations, such as African Americans, and contributes to a high cost of care and school absence. Despite accomplishments in certain areas, the total incremental cost of asthma to society is estimated at $56 billion, with productivity losses caused by morbidity accounting for $3.8 billion and productivity losses caused by mortality at $2.1 billion, for 2007.

The second review by Holgate points out what we have learned from the studies of new medications that affect key pathways considered significant in asthma pathogenesis. He makes the case for a different approach to drug discovery based on acquiring a greater understanding of asthma stratification, the relevant pathways involved, and the development of appropriate diagnostic tests enabling the targeting of selective treatments to...
those asthma phenotypes most likely to respond. He suggests that the epithelium is at the forefront of asthma pathogenesis and should be an emphasis for therapeutics that increase the airways’ resistance against the inhaled environment rather than focusing only on suppression of inflammation.

The third article in the asthma series, which is by Busse, reviews important steps related to the diagnosis and treatment of asthma that must now be addressed. He emphasizes the point that although clinical information is important for management, we must now incorporate objective measures of airflow limitation and bronchial hyperresponsiveness in management. Important areas to address include prevention of asthma exacerbations and severe asthma. These 2 areas of need will require the development of novel approaches that could affect the overall management of asthma.

In the fourth article in this series, Martinez reviews the natural history of asthma and indicates that persistent asthma might result from complex interactions between immune responses to allergens and respiratory tract viruses. He indicates that a major unmet need is the design and conduct of primary prevention studies that specifically test whether viral infections enhance allergic sensitization and chronic changes characteristic of asthma. The fifth article, which is by Jackson et al, discussed asthma exacerbations, reviewing their origin, effect, and prevention. The author discusses risk factors for exacerbations, the benefits and limitations of current therapy, and potential new avenues of treatment for the future. The 2 remaining articles in this series, one on severe asthma by Barnes and another on personalized medicine for asthma by Weiss, will complete this series and hopefully stimulate additional research to guide asthma care over the next 10 years.

In addition to the asthma series, there have been three 2011 Journal theme issues devoted specifically to asthma, including one on the burden of the disease (August 2011), another on airway remodeling (September 2011), and a third related to a discussion of the asthma guidelines (November 2011). A question related to the asthma guidelines is whether it is time to revise the 2007 version of the Expert Panel Report. The answer to that question is that 5 years have passed, and there are key studies that should now be considered for their potential to affect clinical practice. When such an update takes place will be determined by the National Heart, Lung, and Blood Institute (NHLBI)’s National Asthma Education and Prevention Program (NAEPP).

NEW INFORMATION TO SUPPLEMENT THE ASTHMA GUIDELINES

The August 2011 theme issue was devoted to a discussion of methods to reduce the burden of asthma. Asthma exacerbations pose the greatest risk for asthmatic patients and incur the greatest asthma-related treatment costs for the health care system. Inhaled corticosteroids (ICSs) taken on a regular basis are very effective in reducing the risk of asthma exacerbations, and the combination with long-acting β-adrenergic agonists (LABAs), both as main-tenance and also as rescue therapy, has a significant further beneficial effect. In addition, leukotriene receptor antagonists, omalizumab, sputum eosinophil–adjusted therapy, and anti–IL-5 in patients with sputum eosinophilia can contribute to reducing asthma exacerbations. In addition, administrative, survey, and telephone information can be used to define asthma severity, impairment, risk, and quality of care applied to methods to improve asthma outcomes in large health care systems. It is also hoped that advances in genetic discoveries will help identify patients at risk for asthma and for the development of certain phenotypes of asthma. The availability of such a tool would prompt a more proactive preventative approach to management.

Early onset, natural history, and intervention

Several studies evaluated the immune response to risk factors for asthma development. Miller et al evaluated risk factors for
severe human rhinovirus and reported that human rhinovirus was a frequent cause of bronchiolitis and frequent upper respiratory tract infections among previously healthy term infants requiring hospitalization or unscheduled outpatient visits. They noted substantial viral genetic diversity by season and year. Cakebread et al. reported that primary bronchial epithelial cells from asthmatic donors have a normal response to exogenous IFN-β. Therefore it might be used to limit virus-induced exacerbations by attenuating the inflammatory response.

Custovic et al. reported that allergen-specific IgG antibody but not IgG3 antibody levels could significantly modify the association between cat-specific IgE and childhood wheezing, with the risk of symptoms decreasing with increasing IgG levels. They suggest that measurements of allergen-specific IgG antibody might improve the diagnostic accuracy of specific IgE antibody measurements. Sternthal et al. noted that lower maternal childhood socioeconomic status was associated with increased cord blood IgE levels and repeated wheeze, prompting public health interventions to address poverty reduction and housing policies that might reduce asthma disparities.

The role of the environment in asthma development remains a source of controversy. Omland et al. studied farming students to determine whether their environment during childhood and as adults was a factor in the subsequent onset of asthma. They noted that exposure to swine and dairy confinements, welding, smoking, and bronchial hyperresponsiveness are risk factors for non-allergic asthma and that being born and raised on a farm reduces the subsequent risk for asthma. Motika et al. conducted population-based studies of asthma and atopy in the Hutterites of South Dakota and observed that asthma has increased over a 10-13-year period among female Hutterites and that atopy has become a significant risk factor for asthma. They questioned whether this was related to changes in environmental exposures that are either sex limited or that elicit a sex-specific response. An accompanying editorial by Grabenhenrich and Kiel suggested that future studies should incorporate information on soft factors, such as health care use, symptom perception, and labeling, as well as access and interest in health-related information, to determine their role in the presentation of allergic diseases. Loss et al. investigated the farm milk effect and responsible milk components in the Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the European Community (GABRIEL). Advanced Study, a multidisciplinary study to identify the genetic and environmental causes of asthma in the European Community, and concluded that the protective effect of raw milk consumption on asthma might be associated with the whey protein fraction of milk. In addition, Collins et al. reported that bronchial hyperresponsiveness was more common and more severe in girls, which was not explained by differences in lung function or atopic status.

Other risk factors for asthma were reported in the past year. Lowe et al. reported a strong relationship between increasing maternal body mass index during early pregnancy and increased risk of asthma in the child, which they did not believe was due to complications of pregnancy. In addition, Turner et al. reported that reduced fetal size from the first trimester is associated with increased risk for asthma and obstructed lung function in childhood. Martin et al. observed that childhood eczema and rhinitis are strongly associated with the incidence and persistence of adult atopic but not nonatopic asthma. Lange et al. examined the link between maternal and paternal psychosocial stress and asthma outcomes in young children and concluded that both paternal and maternal psychosocial factors can influence asthma morbidity in young Puerto Rican children. Chen et al. reported that an approach that focuses on the psychological qualities that low-socioeconomic-status children develop to adapt to stressors might represent a practical and effective starting point for reducing health disparities.

Lodge et al. evaluated skin prick tests to individual allergens up to age 2 years and concluded that house dust mite sensitization at age 1 or 2 years in wheezing and eczematous children at increased familial allergy risk might predict asthma and point to a high-risk group. In an accompanying commentary, Marks indicated that we have a long way to go before we can instruct concerned parents on methods to prevent asthma development in their children because of the heterogeneity of the disease and the failure to identify thresholds for environmental exposure leading to sensitization and consequent asthma development.

Profiling for asthma risk was prompted by the introduction of the Tucson Respiratory Center Asthma Predictive Index. To date, this index has been a useful tool for pediatricians in assessing risk for asthma. Leonardi et al. studied this test in Leicester and concluded that the predictive performance of the test was modest and comparable with that of a simple question regarding the frequency of preschool wheeze.

Guilbert et al. sought to determine the relationship of virus-specific wheezing illness and lung function in a longitudinal cohort study of children at risk for asthma. They concluded that viral wheezing illnesses in early life caused by rhinovirus are the most significant predictors of decreased lung function up to 8 years in a high-risk birth cohort. It is not clear whether the low lung function is a cause, effect, or both of rhinovirus-induced wheezing illnesses.

Nurmatov et al. conducted a systematic review and meta-analysis of nutrition and food intake on the risk of children with allergy. They concluded that the available epidemiologic literature is weak but nonetheless supportive with respect to vitamins A, D, and E; zinc; fruits and vegetables; and a Mediterranean diet for the prevention of asthma. However, these are primarily hypothesis-generating observations and must be validated with carefully designed prospective studies.

**Asthma as a progressive disease**

The September 2011 theme issue was devoted to airway remodeling. Al-Muhsen et al. reviewed the structural alterations in airway remodeling in asthmatic patients. They indicated that recent investigations have changed our understanding of asthma from a purely inflammatory disease to a disease in which both inflammatory and structural components are equally involved. Asthmatic subjects experience an accelerated decrease in lung function compared with healthy subjects, which is proportionally related to the duration and severity of their disease. Koppelman and Sayers indicate that certain single nucleotide polymorphisms spanning ADAM33, ESR1, PLAU, and VEGF have been associated with an excess decrease in lung function in asthmatic subjects carrying the rare alleles. These genes have overlapping functions in proteolytic pathways in the airways. Hopefully, longitudinal studies with remodeling phenotypes and genome-wide association studies will identify novel susceptibility genes that could lead to targeted therapeutics for remodeling in asthmatic subjects. In addition, Durani et al. discuss the effect of available asthma treatment on airway remodeling and indicate that there is a paucity of information about which
treatments or interactions are most likely to regulate the process of airway remodeling. It is also unclear regarding the appropriate time to begin intervention to modify remodeling, particularly the components to target and how to monitor the effect of interventions. New therapies, including anti-IgE, anti–IL-5, and anti–TNF-α, should be evaluated for their effect on airway remodeling.

One of the contributing features to airway remodeling is local tissue susceptibility, such as the interface formed by the bronchial epithelium. Xiao et al. reported that the bronchial epithelial wall is compromised such that it allows passage of allergens and other agents that lead to immune activation and end-organ expression of asthma. Knight et al., in an accompanying editorial, comment that despite this new knowledge, we do not understand whether the abnormalities in protein expression described in these studies are a cause or effect of the disease process.

Of interest, there is renewed attention being placed on asthma as a risk factor for chronic obstructive pulmonary disease (COPD). deMarco et al. reported that in addition to cigarette smoke, the main risk factors for COPD among young adults are airway hyperresponsiveness, a family history of asthma, and respiratory tract infections in childhood. They suggest the need for a definition of COPD that is not exclusively based on spirometric results. Another recent report by Gershon et al. based on health administrative data from Ontario, Canada, indicates that 1 in 4 persons are likely to be given a diagnosis of and receive medical attention for COPD during their lifetime. Concern was raised by Mannino and Martinez that lifetime risk for both asthma and COPD are increasing and that perhaps COPD will actually increase rather than decrease over time because of this asthma link and the increasing lifetime age. If there is a link between asthma and COPD, perhaps as a unique phenotype of childhood asthma, then early diagnosis and treatment directed at COPD is a direction that needs to be followed.

Severe asthma

Another area of concern in pediatric asthma is severe asthma. It is recognized as heterogeneous, and until recently, it has been difficult to classify the various subtypes. Work from the NHLBI’s Severe Asthma Research Program indicates that similar to adults, there are unique clusters that can be identified in children. They are similar but somewhat different than those in adults and need validation in a larger clinical setting. In another report the Severe Asthma Research Program reported that investigative bronchoscopy, with proper precautions, could be performed safely in subjects with severe asthma, in this case primarily subjects older than 18 years. If treatment can then be effectively related to specific cluster types, this would merit extension of such bronchoscopic studies to younger age groups. Another observation of interest is the recognition that tiotropium, a long-acting anticholinergic agent, can improve lung function in patients with severe uncontrolled asthma treated with high-dose ICSs and LABAs. The next logical step is to conduct studies for specifically labeling this medication for use in the treatment of asthma and extending those studies to children.

Obesity and nutrition

Holguin et al. sought to compare the associations between body mass index categories with several parameters across age and noted that asthmatic subjects are differentially affected by obesity based on whether they had asthma onset early (<12 years of age) or later in life. Obesity and increased asthma severity are likely to be associated in subjects with late-onset asthma. Therefore obesity affects specific clinical phenotypes, and not all asthmatic subjects are alike. Forno et al. reported that compared with children of normal weight, overweight/obese children show a decreased response to ICSs on measures of lung function and emergency department visits/hospitalizations for asthma.

Ly et al. reviewed the available literature on the gut microbiota, probiotics, and vitamin D with regard to asthma, obesity, and allergy. They comment that certain gut microbial strains attenuate immune responses associated with chronic inflammation in experimental models. Probiotics, although limited by design features, thus far have not shown a consistent preventive or therapeutic effect on asthma and obesity. However, vitamin D might be important in gut homeostasis and in signaling between the microbiota and the host. In a brief report, Majak et al. provided the results of a double-blind prospective study with vitamin D to show that it improved pulmonary function and reduced asthma exacerbations in children. Similarly, Keet et al. reported that the vitamin D/wheeze relationship was strongest for nonatopic subjects and older subjects, suggesting that vitamin D might modify the risk of allergic and respiratory disease through multiple mechanisms, prompting future prospective trials.

Is it time to revise the asthma guidelines?

The November 2011 theme issue was devoted to the asthma guidelines. An editorial in this issue addressed the question of revising the 2007 NAEPP’s Expert Panel Report 3 published in 2007. On the basis of the amount of new information available on asthma and key studies that can modify the current management approach, new medications, and new information on early onset of asthma, it is time to consider a revision of the guidelines. For example, Thomas et al. reviewed current knowledge regarding step-up and step-down care in the asthma management recommendations. They introduced 3 new concepts of approach for adjusting asthma therapy, including (1) step-up long-term, (2) step-up short-term, and (3) step-up intermittent therapy. They also identified areas in which more studies are needed to assist clinicians in making decisions around medication adjustment to achieve asthma control.

ICS are the cornerstone of asthma management as the preferred long-term controller for managing asthma in all age groups. After low-dose ICS as initial therapy in subjects with mild persistent asthma, a step-up approach is to double the dose. However, 2 recent reviews suggest that doubling the dose of ICS might not provide clinically relevant therapeutic advantage in adults and children. The recently reported “Global strategy for asthma management and prevention in children 5 years and younger” summarized the available information on managing asthma in this age group, including the challenges in the diagnosis, efficacy, and safety of drugs and delivery devices and the lack of new therapies for this age group. In addition, Zeiger et al. reported that a 10-point or greater change in the Test for Respiratory and Asthma Control in Kids score, which is used to monitor asthma control status in children less than 5 years of age, is a meaningful change over time. This is useful information as we attempt to provide better monitoring tools in this age group.
In a pharmacoeconomic analysis of a recent NHLBI Childhood Asthma Research and Education Network study in older children with mild-to-moderate persistent asthma, low-dose fluticasone had lower cost and higher effectiveness compared with montelukast, especially in those with more airway inflammation, as indicated by increased levels of exhaled nitric oxide and more responsivity to methacholine. In addition, information is now available related to step-down therapy from low-dose ICSs. In another NHLBI Childhood Asthma Research and Education Network study, Martinez et al reported that an as-needed low-dose ICS combined with albuterol reduces the risk of a breakthrough asthma exacerbation when compared with stopping ICS therapy and treating only with as-needed albuterol.

Guilbert et al provided follow-up data on linear growth in young children treated for 2 years with ICS therapy. Linear growth was not significantly different in those children; however, post hoc analysis revealed that children who are younger in age and of lesser weight relative to the entire cohort had significantly less linear growth. In addition, Elmallah et al reported increased systemic exposure of ICSs with the use of an antistaticvalved holding chamber compared with a conventional (static) chamber and recommended initiation of a lower-dose ICS or a reduction in the dose as asthma control is achieved. In regard to combination therapy, a recent review by the US Food and Drug Administration indicated concern regarding increased risk of LABA therapy and suggested that further studies are needed to see whether combination ICS/LABA therapy administered in a single device reduces such risk.

As previously noted, tiotropium has been shown to be effective for severe asthma when added to high-dose ICS and LABA therapy, and this could be a useful supplementary therapy. Gate man et al also reported that tiotropium was as effective as salmeterol in those with the B16-Arg/Arg polymorphism and moderate persistent asthma. Busse et al also reported that monovalent activated 2009 H1N1 pandemic influenza vaccine was safe and provided overall seroprotection as a surrogate of efficacy in patients with mild and severe asthma.

**Systems management**

Control of symptoms in inner-city children of low socioeconomic status is more difficult; however, Scott et al demonstrated the ability to achieve and maintain control in this high-risk population using an intensive, accessible, guidelines-defined mobile asthma clinic system. Gruchalla, in an accompanying editorial, commented that health care initiatives must take notice of disease-specific management programs that can be operationalized for high-risk underserved populations and are successful.

Another source of intervention in children with asthma includes school-based programs. Bruzzese et al reported that an Asthma Self-Management for Adolescents program, a school-based intervention for adolescents and medical providers, is efficacious in improving self-management and reducing asthma morbidity and urgent health care use in low-income urban minority adolescents. Taking another direction, Ducharme et al indicated that provision of a written action plan in the emergency department significantly increased patients’ adherence to ICSs and oral corticosteroids and asthma control, as well as physician’s recommendations for maintenance ICSs and medical follow-up.

Another key step is community translation of a management program. Cloutier and Wakefield demonstrated that general pediatricians can successfully implement an organized asthma management program based on the NAEPP’s asthma guidelines to improve outcomes for large numbers of children. Yet another step is to implement continuous quality improvement and care-coordination steps to address pediatric health disparities. Lob et al reported that such activities result in data-driven clinic-wide improvements in symptom documentation, health care use, and review of action plans. All of these steps taken together hold promise for continued reduction of the burden of asthma in children.

**INSIGHTS THAT COULD AFFECT FUTURE MANAGEMENT**

**Environment**

There is increasing interest in the role that the environment can play in respiratory health. Baumann et al reported that living in close proximity to a high-traffic-density avenue in a periurban community in Peru was associated with an increased risk of asthma symptoms and an increased risk of atopy for adolescents. Bougault et al studied airway hyperresponsiveness in elite swimmers and noted that airway hyperresponsiveness measured based on results of methacholine and eucapnic voluntary hyperpnea challenge is transient and not associated with inflammation. This observation should be considered in managing exercise-induced bronchospasm.

There has been great interest in the relationship of immune development, genetics, and environmental exposure. Wood et al studied an inner-city birth cohort at high risk for allergy and asthma and noted that low cytokine responses at birth were associated with a higher risk for eczema, whereas a variety of adverse environmental exposures contributed to the risk of wheezing in infancy. Olmedo et al studied the relationship between asthma prevalence and murine and cockroach exposure and concluded that cockroach allergen exposure could contribute to the higher asthma prevalence observed in some compared with other New York City neighborhoods. An et al studied IgE levels in relation to sickle cell disease and noted that increased levels of total and allergen-specific IgE are a risk factor for asthma and that high IgE levels are a risk factor for acute chest syndrome but not pain rates.

Another source of environmental exposure is related to farming. Recent interest has grown around the role of environmental microorganism exposure and asthma. Ege et al reported that children living on farms were exposed to a wider range of microbes than were children in a reference group and that this exposure could explain the protective effect of the farming environment on the development of asthma in children. Germ, in an accompanying editorial, said that this observation offers hope for new conceptual breakthroughs that will lead to novel preventive strategies, but it also raises questions about the mechanisms of nature and range of microbial exposures that might alter the developmental biology of the lung and immune system. Ege et al subsequently reported that common genetic polymorphisms are unlikely to moderate the protective influence of the farming environment on childhood asthma and atopy, but rarer variants, particularly of the glutamate receptor, metabotropic 1 gene (GRM1), might do so. However, these findings must be replicated in other farming populations.
Huang et al\textsuperscript{76} provided data from a study in adults to show that composition of the bronchial airway microbiota is associated with the degree of bronchial hyperresponsiveness among patients with suboptimally controlled asthma, prompting further studies on the contribution of the microbiota in asthma pathogenesis. McLoughlin and Mills\textsuperscript{77} reviewed the role of gastrointestinal commensal bacteria on the immune responses that mediate allergy and asthma and indicated that early-life events are instrumental in establishing the microbiota, the composition of which is affected by various environmental and lifestyle changes. They suggest that interventional approaches to create a healthy microbiota could confer maximum tolerogenic immunomodulatory effects in the gut that could protect against systemic inflammatory disease. Weiss\textsuperscript{78} commented on this area of work and concluded that identification of good bacteria in the human gut microbiome is of primary scientific importance in understanding allergic disease but that the effort will be challenging given the size and diversity of the gut microbiome. The interrelationship of vitamin D in modulating signaling from gut bacteria to relevant immune cells is equally important. However, if this task can be accomplished, it holds promise that vitamin D could play a role in preventing asthma, allergic diseases, and autoimmunity disease. Arbes and Matsui\textsuperscript{79} proposed that oral bacteria could play a role in development of allergic disease, and this would require some well-designed prospective studies to understand the relationship between oral bacteria and the development of allergic diseases, including asthma. One area is to evaluate the association between periodontal disease and asthma, 2 prevalent chronic inflammatory diseases.

**Phenotypes-endotypes**

It has been proposed that better methods to characterize patients with asthma could lead to insights regarding genetic and biomarker associations, as well as direction to individualize interventions. Lotvall et al\textsuperscript{80} hypothesize that asthma is a syndrome that can be divided into distinct disease entities called “asthma endotypes.” Using defined criteria, they identified several subtypes that can be used in clinical study design and drug development to target existing and novel therapies. Bisgaard et al\textsuperscript{81} sought to explore endotyping of early childhood asthma and proposed a novel method based on the frequency and age of onset of troublesome lung symptoms analyzed longitudinally. This quantitative approach showed a stronger relation to an underlying genetic mechanism by the \textit{ORMDL3} genetic variant than qualitative characteristics. Savenije et al\textsuperscript{82} identified wheezing phenotypes in 2 birth cohorts using longitudinal latent class analysis. They demonstrated that the phenotypes could be associated with asthma, atopy, bronchial hyperresponsiveness, and lung function at age 8 years. The phenotypes will be used for further studies on genetic and environmental risk factors for asthma and allergic diseases. Understanding distinct determinants of disease development will lead to identification of targeted preventative and therapeutic strategies for the various phenotypes of childhood wheeze.\textsuperscript{83}

**Genetics and epigenetics**

Linking genetics to characteristics of asthma could be helpful in identifying risk for specific phenotypes of asthma. Custovic et al\textsuperscript{84} reported that sensitization and wheezing might differ among children with different variants of the Toll-like receptor 2 gene. They propose that only subjects with particular genotypes might benefit from a specific intervention. Savenije et al\textsuperscript{85} demonstrated that \textit{IL1RL1} polymorphisms are associated with serum IL1RL1-a levels, blood eosinophil numbers, and asthma in childhood. Schaubberger et al\textsuperscript{86} identified genetic variation in the \textit{ATPAF1} gene that predisposes children of different ancestries to asthma, although not in those of Hispanic descent. Asthma severity was also associated with variants in and around \textit{ATPAF1}.

Loisel et al\textsuperscript{87} investigated the genetic architecture of sex differences in asthma risk and reported that \textit{IFNG} polymorphisms were associated with childhood asthma in a sex-specific manner. Ferreira et al\textsuperscript{88} identified 2 additional loci with genome-wide significant association with asthma risk, \textit{IL6R} and chromosome 11q13.5, and suggested the possibility that an \textit{IL6R} antagonist could be an effective asthma therapy. Tantisira et al\textsuperscript{89} identified a functional glucocorticoid-induced transcript 1 gene (\textit{GLCCI1}) variant that is associated with substantial decrements in response to ICSs in patients with asthma, including children.

Galanter et al\textsuperscript{90} identified several associations that appear to be population specific and show heterogeneity between the 2 populations studied, specifically Mexican and Puerto Rican subjects. Therefore caution is needed in applying the results from genetic studies in one Latino population to others. Yang and Schwartz,\textsuperscript{91} in a recent review, indicate that there is emerging evidence that certain epigenetic markers affect gene expression in the lung and are associated with certain lung diseases, including asthma, COPD, and interstitial lung disease. This information should also lead to novel diagnostic and therapeutic approaches for lung diseases.

**Indicators of disease activity**

In addition to genetics and epigenetics, an assessment of biomarkers can be used to identify and monitor disease activity. Von Jagwitz et al\textsuperscript{92} reported that a reduced, deaerated, exhaled breath condensate pH value might help identify asymptomatic children at high risk for asthma. A readily available biomarker is exhaled nitric oxide, and there are now American Thoracic Society guidelines for its clinical application.\textsuperscript{93} Sordilo et al\textsuperscript{94} demonstrated that allergen exposure increases fraction of exhaled nitric oxide (\textit{FENO}) production in sensitized subjects independent of asthma status, and sedentary behaviors are associated with higher \textit{FENO} levels.

Zeiger et al\textsuperscript{95} reported that \textit{FENO} appears clinically useful in identifying persistent atopic, nonsmoking asthmatic patients taking ICSs at risk for future uncontrolled asthma. However, studies are still needed to determine whether such \textit{FENO} information will improve future asthma care and outcomes. Stern et al\textsuperscript{96} indicated that fluctuations in \textit{FENO} levels and their cross-correlation to symptom scores provide information on asthma severity and control. They propose that new methods that quantify the complexity of asthma over time might provide additional information on predicting asthma exacerbations. Breton et al\textsuperscript{97} reported that DNA methylation in the \textit{ARG1} and \textit{ARG2} promoters is associated with \textit{FENO} levels in children with asthma and indicates a role for epigenetic regulation of nitric oxide.
production. On a review of biomarkers in the assessment of airways disease, Taylor\textsuperscript{98} states that successful application of a biomarker result is critically dependent on the specific question being addressed and the performance characteristics of the biomarker in relation to that question in the context of pretest probabilities.

It is likely that combinations of biomarkers or multiple biomarkers will be needed to assist in asthma management. For example, Innes et al.\textsuperscript{99} provided evidence that a specific mucin glycan phenotype (O-secretor) is associated with susceptibility to recurrent asthma exacerbations. Rabinovitch et al.\textsuperscript{100} reported that children exposed to secondhand smoke are at increased risk for severe asthma exacerbations, despite use of ICSs, and that urinary leukotriene E\textsubscript{4} levels identify children exposed to secondhand smoke at high risk for asthma exacerbations. Of interest, Verrills et al.\textsuperscript{101} using a proteomics approach, identified a panel of 4 blood-based biomarkers that could be used to discriminate between healthy control subjects, patients with asthma, and patients with COPD. In addition, Saud et al.\textsuperscript{102} provided proof-of-concept evidence that the analysis of excreted urine metabolites (metabolomics) can be used to differentiate patients with stable asthma from healthy control subjects and patients with asthma undergoing an asthma exacerbation.

Schroer et al.\textsuperscript{103} reported that dysregulation of glutathione-S-transferase pi, a predominant redox regulator in the lung, might contribute directly to an asthma phenotype through disruption of redox homeostasis, resulting in increased oxidative stress. Corren et al.\textsuperscript{104} reported on the effect of lebrikizumab, an anti–IL-13 receptor monoclonal antibody, in improving pulmonary function in asthmatic subjects, especially in a subgroup of participants with an increased serum periostin level. Periostin is considered a surrogate marker for IL-13 activity.

Another promising measure of disease activity is imaging of the lungs. Castro et al.\textsuperscript{105} review the potential effects of new techniques, such as computed tomography, magnetic resonance imaging, positron emission tomography, and single-photon emission computed tomography, in describing the underlying pathophysiology of asthma, especially severe asthma, in evaluating potential targets of intervention strategies.

**SUMMARY**

Indeed, it has been reassuring to see a reduction in mortality and hospitalization in the past 15 years; however, this achievement should prompt initiatives to further reduce the burden of asthma. This will take place through new therapeutic strategies, new medications, and early intervention combined with improved techniques to monitor the course of asthma in individual patients. We are now witnessing the application of biomarkers, such as exhaled nitric oxide, in clinical practice, and more are on the way. Although there have been some genetic markers of interest, application of specific markers to predict asthma, as well as the severity of asthma, await a level of verification before they will be used in clinical practice. Once these additional tools are in place, we will be able to intervene early and more effectively to reduce the effect of asthma, even in young children.

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**Key advances in pediatric asthma in 2011**

- The total incremental cost of asthma to society is estimated at $56 billion, with productivity losses caused by morbidity accounting for $3.8 billion and productivity losses caused by mortality at $2.1 billion, for 2007.\textsuperscript{4}
- The protective effect of raw milk consumption on asthma might be associated with the whey protein fraction of milk.\textsuperscript{22}
- Childhood eczema and rhinitis are strongly associated with the incidence and persistence of adult atopic but not nonatopic asthma.\textsuperscript{26}
- Viral wheezing illnesses in early life caused by rhinovirus are the most significant predictors of decreased lung function up to 8 years.\textsuperscript{32}
- In addition to cigarette smoke, the main risk factors for COPD among young adults are airway hyperresponsiveness, a family history of asthma, and respiratory tract infections in childhood.\textsuperscript{59}
- As-needed low-dose ICSs combined with albuterol reduce the risk of a breakthrough asthma exacerbation compared with stopping ICS therapy and treating only with as-needed albuterol.\textsuperscript{56}
- The composition of the bronchial airway microbiota is associated with the degree of bronchial hyperresponsiveness among patients with suboptimally controlled asthma.\textsuperscript{76}
- Sensitization and wheezing can differ among children with different variants of the Toll-like receptor 2 gene. Subjects with particular genotypes might benefit from a specific intervention.\textsuperscript{64}
- Exhaled nitric oxide measurement appears to be clinically useful in identifying persistent atopic, nonsmoking asthmatic patients taking ICSs at risk for future uncontrolled asthma.\textsuperscript{92}
- Children exposed to secondhand smoke are at increased risk for severe asthma exacerbations, despite use of ICSs, and urinary leukotriene E\textsubscript{4} levels identify children exposed to secondhand smoke at high risk for asthma exacerbations.\textsuperscript{100}

**REFERENCES**


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