

Advances in adult and pediatric asthma

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This year we present updates on the management and therapeutics of asthma and research on the relationship of airway remodeling to clinically irreversible disease and continue a discussion about the origins of asthma. Significant advances are occurring in our understanding of the natural history of asthma, including the application of biomarkers and genetics. These tools should assist the clinician in defining patients at risk for significant morbidity related to asthma. Incorporating this knowledge will help prompt the development of more effective management techniques and new medications. Meanwhile, more effective health care strategies must be developed to reduce the reported disparities in asthma care noted in our patient populations. (*J Allergy Clin Immunol* 2006;117:512-8.)

Key words: Asthma, airway remodeling, airway smooth muscle, obesity, adults, children, health disparities, therapeutics

In past *Advances* articles,^{1,2} we described research in the genetics of asthma, pharmacoeconomics, the origins of asthma, and management and therapeutics in children and adults. This year we present updates on management and therapeutics and research on the relationship of airway remodeling and continue a discussion about the origins of asthma.

PHYSIOLOGY: AIRWAY REMODELING

The irreversible obstruction in asthma noted in some patients is attributed to airway structural alterations resulting

Abbreviations used

ASM: Airway smooth muscle
BMI: Body mass index
ED: Emergency department
EIB: Exercise-induced bronchospasm
FeNO: Fractional concentration of nitric oxide in exhaled breath
ICS: Inhaled corticosteroid
LABA: Long-acting β -agonist

from airway remodeling.^{3,4} The extent of remodeling varies among individuals and might explain the variable course of asthma. Recent emphasis has focused on the inflammatory and immunologically mediated aspects of remodeling as the primary determinants of asthma phenotype, with renewed attention to airway smooth muscle (ASM).³

Pepe et al⁵ examined airway structural changes in subjects with severe compared with moderate asthma. ASM in subjects with severe asthma had greater area and less distance between ASM and the epithelial layer. Bergeron et al⁶ explored remodeling of the small peripheral airways, comparing peripheral and central airway transbronchial and endobronchial biopsy specimens in 12 patients with mild-to-moderate asthma before and after 6 weeks of hydrofluoroalkane-flunisolide. They found no significant difference between central and peripheral airways in collagen III, smooth muscle actin, or TGF- β -positive cells (ie, significant evidence that remodeling extends to the peripheral airways). Disappointingly, they found no clinically relevant change in spirometric or remodeling parameters with flunisolide treatment.

Hallstrand et al⁷ compared asthmatic adults with and without exercise-induced bronchospasm (EIB) and found evidence of remodeling in both groups, with more abnormalities in the EIB group related to injury to the airway epithelium and greater airway eosinophilia. Thus this study suggests that even in relatively mild asthma there is evidence of remodeling and injury to airway epithelium.

Limb et al,^{8,9} in 2 articles, observed that the severity of asthma in adulthood correlated with the severity of childhood allergic asthma and that many adults with moderate or severe allergic asthma had irreversible lung function deficits in adulthood. De Blic et al¹⁰ applied high-resolution computed tomography and biopsy analysis to

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assess airway remodeling in children with severe asthma, validating high-resolution computed tomography as a tool for quantifying airway remodeling. Mascia et al¹¹ found that irreversible airway obstruction occurred more frequently in patients with aspirin-exacerbated disease and hypothesized that irreversibility suggested remodeling. These studies suggest that remodeling might contribute to irreversibility of lung function and the need to identify the associated molecular and cellular characteristics.

ASSESSING CLINICAL ASTHMA

The clinical state must be accurately described to correlate histology with disease. A lack of consistency in the definitions of asthma¹² and its severity¹³ and control¹⁴ were reported. Appleton et al¹² compared the relative performance of reversibility criteria in different international guidelines in 4060 adults with and without a diagnosis of asthma. The different guidelines identified different groups of patients with asthma. Miller et al¹³ used Global Initiative for Asthma guidelines, National Asthma Education and Prevention Program Guidelines, lung function, medication use, and the independent assessment of severity by their physicians to categorize asthma severity and found inconsistency in assessment modalities.

Asthma control has become an important target for asthma management. Up to 75% of asthmatic patients experience at least one uncontrolled asthma episode over a 3-year period.¹⁵ Li et al¹⁴ recommended that clinicians judge adequacy of control on the basis of symptoms, sleep disturbance, use of rescue medication, limitations of daily activity, patient and physician assessment, and lung function. Interestingly, Schatz et al¹⁶ used tools of patient-reported symptoms, quality of life, and asthma control and found these tools alone cannot be used to distinguish baseline severity from asthma control. Asthma control must be carefully defined and measured.

Improving self-management

We must find the best ways to monitor asthma control and to improve self-management. Cabana and Le¹⁷ stressed assessing the understanding and competencies of the patient or caregiver before initiating education and cultivating respect between clinicians and patients. Kim et al¹⁸ analyzed inhaled corticosteroid (ICS) use by adults with symptom reports. In adults with moderate or severe persistent asthma, ICSs were more likely to be taken in the morning and adherence decreased and variability of adherence increased over a 6-week period. Interestingly, there was no relation between cumulative adherence and final symptoms.

Rasmussen and colleagues¹⁹ developed a physician-managed, online, interactive asthma-monitoring tool and compared its use with monitoring by an asthma specialist or a general practitioner. The researchers studied patients with mild disease. Thus no difference in emergency department (ED) visits was observed and, interestingly, the

Internet group visited doctors more frequently. In another report the fractional concentration of nitric oxide in exhaled breath (FeNO) was studied as a noninvasive measure of disease activity. Although it is known that cigarette smoking suppresses FeNO, its noninvasive nature makes it of great potential for use in children. McSharry et al²⁰ characterized the short- and long-term effects of smoking on FeNO and found the effects were different and independent.

Health disparities and vulnerable populations

Asthma prevalence, especially morbidity and mortality, are higher in blacks than in whites. National concern is that some of the increased morbidity is due to differences in treatment afforded certain minority groups.²¹ Busse et al²² evaluated 169 inner-city black and Hispanic adults hospitalized with asthma and found that only 60% of patients had an evaluation for allergen sensitization. Although 91.5% of the sensitized patients recalled positive skin test responses to dust mite, only approximately half recalled medical advice on avoidance measures. Wisnivesky et al²³ reported a lack of an established asthma care provider and language barriers associated with increased risk of hospitalization or ED use. These studies do not provide comparisons with more affluent white populations.

However, a study by Litonjua et al²⁴ offers comparisons that suggest differences in treatment by race-ethnicity. The investigators evaluated total and specific IgE levels of white, black, and Hispanic women identified by hospitalization for delivery of a child. Black and Hispanic women were more likely to report a physician's diagnosis of asthma and less likely to report a diagnosis of hay fever or eczema. These women had higher mean total IgE levels and were more likely to be sensitized to aeroallergens. Their findings could represent either underdiagnosis by medical personnel (eg, fewer referrals to an allergist or other specialist) or underreporting of symptoms by patients. They also concluded that it was unlikely that genetics alone could explain the differences in sensitization, and they were more likely related to differences in housing and community environmental exposures.

Eldeirawi et al²⁵ examined the association of place of birth with asthma, wheezing in the past 12 months, and other allergic conditions in Mexican American children. They reported that children born in the United States had an increased risk of asthma and were more likely to have positive skin reactions to cat, house mite, *Alternaria alternata*, peanut, Bermuda grass, and short ragweed but were less likely to have a positive skin test response to German cockroaches. Gold and Acevedo-Garcia²⁶ commented on similar findings among immigrants to Sweden and among Southeast Asian immigrants to Australia. They concluded that unmeasured environmental and social differences, such as in acculturation, might be important for the development and persistence of asthma and should be studied, with careful attention to study design. Further studies are needed to address differences in health care by racial and ethnic group.

Pregnancy

The National Asthma Education and Prevention Program Expert Panel updated the guidelines on asthma management during pregnancy.²⁷ The Panel's review of existing studies led them to conclude that asthma exacerbations can be diminished with ICSs and that no completed studies have found an association of ICSs with adverse perinatal outcomes. They noted the bulk of data is on the ICS budesonide.

Bakhireva et al²⁸ compared 654 infants born to asthmatic women with 303 infants born to nonasthmatic women. The mean birth weight of full-term infants born to mothers who used systemic corticosteroids was lower than that of infants of mothers who exclusively used β -agonists and that of nonasthmatic control subjects. No difference in the incidence of small for gestational age weight was observed. However, birth length was slightly shorter in the systemic steroid group. These data underline the importance of limiting the need for systemic steroids. One study limitation is that it is not clear whether the systemic steroid or the severity of asthma disease requiring systemic steroids is responsible for the finding of lower birth weight.²⁹ Another limitation is the possibility that the study is underpowered for assessing small but clinically significant effects of ICSs on small for gestational age birth weight.

REPORTS RELEVANT TO CHILDHOOD ASTHMA AND RESPIRATORY DISEASES

An April 2005 theme issue was devoted to pediatric asthma and highlighted the challenges we face in applying genetics and biomarkers to identify the onset of asthma, measure progression, and monitor treatment response.³⁰

Natural history of childhood asthma: Predisposing factors

Several studies supported the hygiene hypothesis. Juhn et al³¹ evaluated a birth cohort by examining mode of delivery and asthma status during the first 7 years of life. The mode of delivery was not associated with subsequent risk of development of childhood asthma or wheezing episodes. To evaluate the relationship of farm exposure to asthma prevalence, Adler et al³² conducted a cross-sectional, population-based survey among rural kindergarten through grade 12 school children. Farm-reared children were less likely to have a history of wheezing or a diagnosis of asthma. Farm residence beginning during the first 5 years, but not later, was associated with decreased rates of ever having asthma. However, cross-sectional studies cannot demonstrate causality, and Norwegian studies using a birth cohort did not find a protective effect of early respiratory tract infections or day-care attendance on the subsequent development of asthma.^{33,34}

Another area of controversy relevant to the hygiene hypothesis relates to the association of vaccine administration and antibiotic use on the development of atopic

disease in children. Enriquez et al³⁵ reported a significant and dose-dependent negative relationship between vaccination refusal and self-reported asthma or hay fever only in children with no family history of the condition and for asthma in children with no exposure to antibiotics during infancy. Vaccination refusal was also significantly and negatively associated with self-reported eczema and current wheeze. A prospective study is needed to validate these observations. Johnson et al³⁶ observed an association of atopy with antibiotic use approaching statistical significance; however, the association was concentrated among children with less than 2 pets in the home and children breast-fed for 4 or more months. Although these conclusions might appear to suggest that antibiotic use in early life contributes to increased risk for atopy in certain subgroups of children, the essentially cross-sectional nature of the study precludes drawing conclusions about cause and effect.

Simpson et al³⁷ evaluated the association of IgE-mediated sensitization with asthma and lung function, noting an increased risk of current wheeze and reduced lung function with increasing IgE levels to mite, cat, and dog and the sum of IgE to these 3 allergens. Brussee et al³⁸ examined the effect of allergen exposure at 3 months of age on the development of sensitization, wheeze, and physician-diagnosed asthma in the first 4 years of life in a birth cohort of children with and without an atopic mother, concluding that early house dust mite and cat allergen exposure might lead to sensitization and with cat allergen exposure to persistent wheeze. Early mite and dog allergen exposure might lead to asthma and persistent wheeze, respectively, but only in subgroups defined by maternal atopy.

Erwin et al³⁹ studied antibodies to cat and dust allergens and their relationship to wheezing in New Zealand children in a nested case-control study. They suggested that induction of tolerance to cat allergen is an allergen-specific phenomenon that cannot be attributed to endotoxin exposure.

Primary prevention

Arshad⁴⁰ provided a perspective on primary prevention of asthma and allergy, stating that exclusive breast-feeding and avoidance of exposure to environmental tobacco smoke can be safely recommended. Additionally, for children at high risk of allergy, maternal exclusion diet during lactation and protein hydrolysate as a supplement or alternative for children who could not breast-feed seems to provide further protection. The preventive effect of avoidance of house dust mite allergen alone during pregnancy or after birth is disappointing. However, prospective randomized studies evaluating a combined food and house dust mite allergen avoidance regimen show some protection against atopic dermatitis in infancy and asthma in later childhood. Chan-Yeung et al⁴¹ evaluated the effectiveness of a multifaceted intervention program for the primary prevention of asthma. The program was effective in reducing the prevalence of asthma by 7 years of age, prompting further work in this area.

ASTHMA MORBIDITY

Exacerbations

Inflammatory mediators induced by viral infections could adversely affect lung development.⁴² Friedlander and Busse⁴³ commented on the role of rhinovirus in asthma exacerbations. Risk factors for wheezing with colds include asthma and atopy, extremes in age, and perhaps having a deficient T_H1 response to rhinovirus. Lemanske et al⁴⁴ evaluated the relationship of viral respiratory tract infections during infancy to the development of subsequent wheezing, allergic diseases, or both in early childhood in children genetically at high risk for allergic respiratory diseases. They found that the most significant risk factor for the development of preschool childhood wheezing is the occurrence of symptomatic rhinovirus illnesses during infancy.

Johnston et al⁴⁵ examined whether asthmatic children requiring ED treatment for exacerbations after school return in September were more likely to have respiratory viruses present and less likely to have prescriptions for control medications than children with equally severe asthma not requiring emergency treatment. Human picornaviruses were detected in 52% of patients and 29% of control subjects. Those with exacerbations were less likely to have been prescribed controller medication. Stempel⁴⁶ commented that we must define the population at risk to reduce the risk of an exacerbation and avoid limiting the treatment to just this period of time.

Williams et al⁴⁷ reported that adding metapneumovirus to other viral causes increased the overall prevalence of viral infections among wheezing subjects younger than 3 years to almost 90%, confirming that viral respiratory tract pathogens are the dominant risk factor for wheezing exacerbations in early childhood.⁴⁸ Xepapadaki et al⁴⁹ observed that duration of airway hyperresponsiveness after a single natural cold is 5 to 11 weeks in atopic and nonatopic asthmatic children.

Persistent asthma

Although mild asthma is viewed as a benign disease, Bisgaard and Szeffler⁵⁰ indicate that available studies point to substantial morbidity in this population and support intervention with controller therapy. Gruchalla et al⁵¹ studied allergen sensitivities, allergen exposures, and associated morbidity, noting that geographic differences in allergen exposure and sensitivity exist among inner-city children. Cockroach exposure and sensitivity predominate in the northeast, whereas dust mite exposure and sensitivity are highest in the south and northwest. Cockroach allergen exposure appears to have a greater effect on asthma morbidity than dust mite or pet allergen in these children.

OBESITY AND ASTHMA

Our high-calorie diets and lack of exercise promote obesity, which has reached epidemic proportions in

children and adults in the United States and has been postulated to be associated with more severe asthma.^{52,53} Several mechanisms for a causal relationship have been proposed; most suggest obesity is a risk factor for asthma, although clearly asthma could limit exercise and predispose to obesity. One set of theories suggests increased production of inflammatory mediators in adipose tissue.⁵⁴⁻⁵⁶ Interestingly, Santamaria et al⁵⁷ evaluated the relationship between age, sex, body mass index (BMI), and exhaled nitric oxide and concluded that children, unlike adults, do not have a significant increase in exhaled nitric oxide levels with increasing adiposity. Other theories of the association of obesity to asthma point to structural and functional changes in the airways of obese individuals.⁵⁸

Lucas and Platts-Mills⁵⁹ suggest that lack of exercise and sedentary lifestyle might be partly responsible for the association between obesity and asthma and recommend including an exercise program in management. Calvert and Burney⁶⁰ found an increased risk of EIB in urbanized African populations in association with greater skin test sensitivity or increased BMI and proposed that increases in BMI of rural children in subsistence economies might lead to an increased prevalence of atopic disease. Randomized prospective intervention studies are needed to clarify the relationship of obesity to asthma control.

THERAPEUTICS

Biomarkers

Biomarkers might serve as predictors of response and monitors of response. Hartl et al⁶¹ reported that bronchoalveolar lavage CCR4⁺CD4⁺ and CXCR3⁺ cells and their ligands, thymus- and activation-regulated chemokine, macrophage-derived chemokine, and IFN- γ -inducible T-cell chemokine α chemoattractant, clearly differentiate asthmatic children from nonatopic children with chronic cough.

A report by the National Heart, Lung, and Blood Institute's Childhood Asthma Research and Education Network, using a cross-over design that included treatment with an ICS and a leukotriene receptor antagonist, indicated that children with low pulmonary function or high levels of markers associated with allergic inflammation, including FeNO, should receive ICS therapy.⁶² Buchvald et al⁶³ found that FeNO levels in healthy children, aged 4 to 17 years, is less than 15 to 25 ppb, depending on age and self-reported atopy. Smith et al⁶⁴ measured FeNO levels in a single-blind, placebo-controlled trial in adult patients with asthma to guide ICS therapy, determining that maintenance ICS doses might be significantly reduced without compromising asthma control.

The Childhood Asthma Research and Education Network study previously mentioned compared montelukast with fluticasone in children, using pulmonary function as a primary outcome measure for defining asthma response.⁶² However, this is only one indicator of response, and composite measures that adjust for baseline parameters and attempt to weigh the contribution of each variable to

TABLE I. Key advances

- Alterations of ASM contribute to remodeling.
- Differences in care of asthmatic patients on the basis of race-ethnicity is evident.
- Obesity is associated with asthma, but a causal relationship has yet to be identified.
- ICSs, particularly budesonide, are safe for mothers and their fetuses.
- A significant risk factor for the development of childhood wheezing is the occurrence of symptomatic rhinovirus illness during infancy.
- Biomarkers might be useful in selecting initial intervention with long-term control therapy for children with asthma.

allow comparison across studies for application to clinical practice should be developed.¹⁵ Larsen et al⁶⁵ point out that the method of pulmonary function measurement is highly dependent on the age of the child and the ability to cooperate. The measurement of pulmonary function in young children will become increasingly important as we attempt to define early onset of disease.

Methodology

Two discussions of methodology in studies of therapeutics deserve attention. Onder⁶⁶ reviewed the controversies and circumstances of potential benefits in the use of placebo-controlled trials in evaluation of therapeutics with respect to asthma. Suissa and Ernst⁶⁷ conducted an analysis to demonstrate how not taking account of time dependency in observational studies of a therapeutic agent can lead to misclassification of subjects and a biased result.

Cost-effectiveness

The Inner City Asthma Study group assessed the cost-effectiveness of an environmental intervention study and concluded that a targeted, home-based environmental intervention improved health and reduced service use in inner-city children with moderate-to-severe asthma.⁶⁸

ICSs

Concern about the adverse systemic effects of ICSs and differences in local delivery of ICSs are the underlying theme of many recent studies.⁶⁹ Approximately 25% of children with asthma have reduced lung growth, despite ICS therapy.^{70,71} Whelan et al⁷² found plasma concentrations of fluticasone were less with dry powder inhalers than with metered-dose inhaler. Ciclesonide, a nonhalogenated inactive ICS formulated with a hydrofluoroalkane propellant, is hydrolyzed to an active compound reported to have fewer systemic side effects at high doses.⁷³⁻⁷⁵

Wen et al⁷⁶ conducted a double-blind trial of prednisone and antiasthma herbal medicine intervention for 4 weeks and found FEV₁ improved in both groups, although it was slightly greater in the prednisone group. Omalizumab, anti-IgE therapy, remains a drug whose long-term benefits and risks remain to be defined along with its cost-effectiveness.⁷⁷⁻⁷⁹ Roflumilast, an oral once-daily

phosphodiesterase 4 inhibitor, showed only a very modest effect in a double-blind, 3-period crossover study of 24 patients.

Long-acting β -agonists

The most significant controversy involving therapeutics involves the safety and efficacy of long-acting β -agonists (LABAs). After a meeting of the Pulmonary Allergy Drug Advisory Committee in July 2005 to discuss whether LABAs should remain on the market, the US Food and Drug Administration issued an Advisory and amended their labeling to encourage concomitant ICS use.^{80,81} The January 2006 issue of the *Journal* is devoted to a detailed discussion of the topic of black-box warnings. Research is needed to address the safety of LABAs combined with ICSs for all patient groups, including African Americans.

CONCLUSIONS

As indicated in this review of 2005 *Journal* publications, significant advances (Table I) are occurring in understanding the natural history of asthma, including the application of biomarkers and genetics. These tools should assist the clinician in defining patients at risk for significant morbidity related to asthma. Incorporating this knowledge will help prompt the development of more effective management strategies and the development of new medications. Meanwhile, more effective health care strategies must be developed to reduce the reported disparities in asthma care noted in our patient populations.

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