

Advances in childhood asthma: Hygiene hypothesis, natural history, and management

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There is significant interest in early identification and intervention in childhood asthma. Current asthma guidelines identify inhaled corticosteroids (ICS) as the preferred initial long-term control therapy even in young children. ICS clearly improve asthma control in children with mild to moderate persistent asthma, but it is not clear that they can alter the natural history and progression of asthma. New insights regarding the origins of asthma and allergy and their natural history will continue to stimulate questions regarding the appropriate time for intervention and will stimulate the design of new treatment strategies and the discovery of new medications. (J Allergy Clin Immunol 2003;111:S785-92.)

Key words: Asthma, children, hygiene, risk factors, management, therapy, guidelines, allergy

In January 2002, Spahn and Szeffler¹ summarized key studies that formulated the current paradigm of asthma management for children. Several recent reports indicate that the rate of asthma mortality and morbidity has reached a plateau^{2,3}; however, significant racial and ethnic disparities for asthma health care utilization and mortality remain.³ The next challenge is to see a decline in asthma mortality and morbidity in all subgroups of asthma patients (Table I). It might be possible to influence these outcomes through a proactive approach for asthma based on early diagnosis and intervention. This review will summarize recent reports that relate to the origins and natural history of asthma and allergy, and therapeutic strategies directed at early intervention and improved management.

Inhaled corticosteroids (ICS) are now considered the cornerstone for managing persistent asthma even in young children.⁴⁻⁶ New medications and delivery systems have been introduced, including a nebulized ICS for children as young as age 1.⁷ New initiatives to improve medication labeling for young children have now made it possible to intervene at a very early age.^{8,9}

Abbreviations used

BAL:	Bronchoalveolar lavage
BDP:	Beclomethasone dipropionate
CFC:	Chlorofluorocarbon
ECO:	Expired carbon monoxide
ECP:	Eosinophilic cationic protein
FE _{NO} :	Expired nitric oxide
GI:	Gastrointestinal
HFA:	Hydrofluorocarbon
ICAM-1:	Intercellular cell adhesion molecule 1
ICS:	Inhaled corticosteroids
ISS:	Immunostimulatory DNA sequences
NHLBI:	National Heart, Lung and Blood Institute

ORIGINS OF ASTHMA AND THE "HYGIENE HYPOTHESIS"

Many questions have been raised regarding the reasons for the rise in prevalence of asthma and allergy despite improvements in health care and pharmacotherapy. In one recent example from Nottingham, UK of the rise in atopy, the prevalence of allergen sensitization in 18- to 80-year-old adults in 1991 was more than double in the youngest (ie, 18–27 year olds) when compared with the older 63- to 70-year-old adults (46% vs 21%, respectively).¹⁰ Nine years later, atopy prevalence for the different age groups remained essentially unchanged as they became older, suggesting that higher atopy prevalence in young adults was not the result of a decline in atopy rate with aging, but from a prevalence rise that began with those born between 1938 and 1946.

One proposition for this prevalence increase has been popularly called the "hygiene hypothesis." If naturally occurring infections and microbial exposures can essentially immunize against asthma, then reductions in these exposures over the past century may be a major factor in the global rise in these conditions. In the past year, prolific hygiene hypothesis-related research has continued to provide insights to these questions. In a large US study, previous hepatitis A, *Toxoplasma gondii*, and herpes simplex virus 1 infections were associated with less asthma, hay fever, and allergen sensitization, mirroring a similar study of Italian military cadets.¹¹ Recent evidence in a mouse model of asthma of a new asthma susceptibility gene for T-cell membrane proteins that is homologous to the human hepatitis A receptor implicates hepatitis A and its receptor as a possible gene-environment interaction in the development of asthma and allergy.¹²

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TABLE I. Consequences of poor asthma control

Mortality
Respiratory arrest
Hospitalization
Acute exacerbation
Emergency department visit
Course of systemic glucocorticoid therapy
Nocturnal symptoms
Breakthrough symptoms—spontaneous or activity induced
Variability in pulmonary function because of airway sensitivity
School absence
Reduced quality of life, for example:
reduced activity level
poor self-image
Progression as indicated by:
loss of pulmonary function
increasing symptoms
increasing medication requirements
Persistent inflammation
Airway remodeling and irrecoverable loss of pulmonary function
Adverse effects related to overuse of rescue therapy, for example,
bronchodilators and systemic glucocorticoids

Furthering the concept that gastrointestinal microbes may influence the development of asthma and allergy, some investigators have identified differences in the gastrointestinal flora of infants who develop allergic disease. Allergic infants were gastrointestinal tract–colonized with more clostridia and *Staphylococcus aureus*, whereas nonallergic infants had more enterococci, bifidobacteria, and bacteroides.^{13,14} Even differences in the vaginal microflora of pregnant women have been associated recently with wheezing outcomes in early childhood.¹⁵ Meanwhile, in rural Africa, parasitic infestation with schistosomiasis¹⁶ or ascaris/hookworm¹⁷ has been associated with less allergen sensitization and asthma. In the schistosomiasis study, peripheral blood cells from nonallergic patients demonstrated greater schistosome-specific IL-10 production in vitro,¹⁶ raising interest in the potential disease-mitigating role of IL-10–producing cells.¹⁸ Mechanistically, IL-10 can differentially regulate IL-4–stimulated B cells to produce IgG₄ instead of IgE, block mast cell degranulation, and downregulate IL-4 and IL-5 production. “Regulatory” IL-10–producing CD4⁺ CD25⁺ T lymphocytes, capable of abrogating autoimmunity and transplant rejection in some animal models, may also have a role in alleviating and preventing atopic inflammatory diseases.

Indeed, a recent study of Finnish medical registries revealed asthma prevalence to be higher in children with autoimmune diseases (ie, celiac disease, rheumatoid arthritis, type 1 diabetes).¹⁹ Similarly, a study of the prevalence of childhood asthma and type 1 diabetes in 28 different countries found a strong positive correlation of the prevalence of these 2 conditions.²⁰ These reports suggest that the immune processes underlying childhood asthma and autoimmune diseases might be similar, and that the hygiene hypothesis may also be relevant to autoimmunity.

Leading hygiene hypothesis insights have also been gained through the study of naturally occurring endotoxin exposure. Endotoxin might be one example of how potent microbial *component* exposures may influence immune development without the potential harm of infections. An extensive history of endotoxin studies in humans, in basic research, and in rodent asthma models has identified fundamental factors underlying outcomes from endotoxin exposure. Timing of exposure relative to disease development (eg, early life exposure), dose of exposure, nature of the stimulus, co-exposures, and genetics underlying the response are all expected to contribute.²¹ Longitudinal prospective birth cohort studies on endotoxin exposure in infancy and allergic and asthma outcomes are in their early stages but already suggest that endotoxin exposure in infancy is associated with less atopic dermatitis, as possible evidence of an effect on the allergic march of early childhood.²² However, in this and another birth cohort study of infants in Boston, greater endotoxin exposure was associated with more wheezing in infancy.²³

Endotoxin clinical studies may be particularly helpful as a prototypical gene–environment interaction with health versus disease outcomes, as the specific receptors for endotoxin and the associated cell signal cascades have been elucidated. For example, the importance of genetic polymorphisms in one of endotoxin’s receptor/enhancer proteins, CD14, their functional consequences for CD14 expression, and their association with less allergen sensitization and IgE have been reviewed.²⁴ Soluble CD14 is in high levels in breast milk, and breast-fed infants with atopic dermatitis were associated with lower sCD14 in the breast milk of their mothers, piquing interest in the possible role of maternally transferred sCD14, both pre- and postnatally.²⁵

European investigators of farm/non-farm communities have recently reported a collective of important associations between endotoxin exposure and outcomes in children: (1) farm children were exposed to more endotoxin (as measured in house dust, barn dust, and mattress dust)^{26,27}; (2) greater endotoxin exposure was associated with less allergen sensitization, hay fever symptoms, and atopic asthma, in a dose-dependent manner²⁶; (3) farm children’s blood expressed higher amounts of CD14 and Toll-like receptor 2²⁸; (4) early life exposures to farm barns and unpasteurized milk had strong associations with low asthma and allergy prevalences²⁹; and (5) high levels of endotoxin exposure were associated with an increased prevalence of nonatopic wheeze.²⁶ This is a set of hypothesis-generating observations for future longitudinal, prospective and interventional studies, on the role of noninfectious and naturally occurring endotoxin exposure to mitigate allergic manifestations, including the common allergy-associated asthma. At high levels of endotoxin exposure, asthma in endotoxin-sensitive individuals, similar to that seen in occupational forms of endotoxin-mediated asthma, will be manifest.

Because animals in homes is associated with greater endotoxin content in dust,³⁰ it is intriguing to find that 2 recent longitudinal, prospective birth cohort studies in US metropolitan communities have found less asthma in

children raised with pet dogs,³¹ and less allergen sensitization with increasing numbers of pet cats, dogs, or both in early life.³² Two studies have recently associated high levels of cat allergen in dust with less allergen sensitization^{33,34} and have suggested an allergen-specific mechanism. However, the Ownby study, strengthened by its prospective study design, found that pet cat and dog exposures were associated with less allergen sensitization to all tested common inhalant allergens (ie, dog, cat, mite, alternaria, grass, ragweed), suggesting a more generalized mechanism of protection against atopy. Thus, endotoxin exposure may have an atopy-mitigating role in modern metropolitan homes as well.

The hygiene hypothesis research is evolving from the association-type “ecological” studies to longitudinal prospective studies with biomarkers of immune response and development, providing greater validity to this naturally occurring phenomenon. The movement of hygiene hypothesis-related concepts to clinical interventions is also underway. The use of “immunostimulatory DNA sequences (ISS)” as Th1-inducing adjuvants is conceptually derived from unmethylated CpG motifs in bacterial DNA. ISS conjugates to allergen (ie, Amb a1) are being developed as immunotherapy for allergic asthma and hay fever, with promising results.³⁵⁻³⁷ Recently, ISS-allergen conjugates were shown to induce stronger antibody and Th1-type immune responses, while reducing mast cell degranulation, anaphylactogenic potential, and delayed arthus-type reactions than either allergen alone or allergen mixed with ISS but not conjugated.³⁵ Using a different approach, a randomized controlled birth cohort trial of oral lactobacillus supplementation for mothers of exclusively breast-fed infants in the first 6 months of life found that the prevalence of atopic dermatitis by age 2 was reduced 3-fold in those receiving supplementation (15% vs 47%, $P = .01$).³⁸ Lactobacillus supplementation was associated with higher concentrations of the anti-inflammatory cytokine TGF- β_2 in breast milk.

With these and other private sector initiatives in developing microbe-derived products for immune modulatory therapies, combined with studies to better understand if and how naturally occurring microbial exposures might lower the likelihood of asthma and allergies, a clearer picture is likely to emerge in the near future. In the meantime, for general pediatrics, it is important to note that current epidemiologic evidence finds that neither childhood immunizations^{39,40} nor antibiotic use⁴¹⁻⁴³ are associated with a greater prevalence of allergy and asthma.

THE NATURAL HISTORY OF ASTHMA

New directions in the management of childhood asthma include early recognition and early intervention with environmental control and administration of long-term control therapy.^{1,9} Hopefully, this movement will result in improved methods to diagnose and alter the natural history of asthma. Inhaled glucocorticoid therapy improves asthma control, but it is not clear whether this treatment can prevent progression of asthma.^{44,45}

Several prospective studies in the past year have helped to clarify the development of allergen sensitization in the early childhood years and its relationship to asthma development. Two studies found that food allergen sensitization in the first 2 years of life was associated with asthma at ages 7 and 22 years.^{46,47} For allergen sensitization to egg, milk, or both in the first year of life, sensitivity and specificity for asthma at age 22 years was 57% and 89%, respectively.⁴⁸ At age 7, food allergen sensitization was not associated with asthma; however, the combination of food allergen sensitization by age 2 and inhalant allergen sensitization by age 7 (“persistent sensitization”) was associated with a significantly higher prevalence of asthma and bronchial hyperresponsiveness.⁴⁶ For seasonal inhalant allergens, a group of infants born in Stockholm, Sweden during an unusually high birch pollen season (in 1993, birch pollen counts were 10 to 50 times higher than in 1992 and 1994) were compared with those born in relatively low birch pollen years.⁴⁹ At age 5, those born in 1993 had higher prevalences of allergen sensitization to birch and allergic asthma. For example, for allergic asthma at age 5, the prevalence for children born during birch pollen season in 1992 (low pollen counts), 1993 (high), and 1994 (low) was 8.4%, 12.2%, and 8.8%, respectively.

A bronchoalveolar lavage (BAL) study of infants and children necessitating bronchoscopy for “unusual” asthma found that allergic asthmatics had increased BAL eosinophils, associating eosinophilic airway inflammation with the allergic asthmatic phenotype even in early childhood.⁵⁰ BAL eosinophils, however, were at low levels in infants younger than age 30 months. Furthermore, increased BAL neutrophils were found in childhood asthma of greater persistence and longer duration. Finally, the effect of infant breast-feeding on asthma outcomes was well studied in the past year, but with inconsistent findings. A prospective birth cohort study of about 2,600 Australian children found that exclusive breast-feeding for longer than 4 months was associated with less doctor-diagnosed asthma at age 6, regardless of maternal asthma history.⁵¹ However, a longitudinal study of about 1,000 New Zealand children to age 26 found that infants breast-fed for 4 weeks or longer had a higher prevalence of allergen sensitization and asthma that was independent of maternal asthma or hay fever history.⁵² Considering this lack of consensus on the relationship between infant breast-feeding and asthma, general pediatrics should continue to favor infant breast-feeding for its many other benefits.

Rasmussen et al⁵³ sought to determine the risk factors for single and multiple hospitalizations for asthma. From a population-based, unselected birth cohort of 1,037 New Zealanders who answered questionnaires and underwent lung function, airway responsiveness, and allergy testing on 7 occasions, the authors identified frequent respiratory symptoms, airway hyperresponsiveness, atopy, and low lung function as indicators of high risk for hospitalization for asthma, especially in relation to multiple hospitalizations. Another feature of asthma associated with significant morbidity is nocturnal symptoms. Strunk et

al⁵⁴ examined the database of the National Heart, Lung and Blood Institute's (NHLBI) Childhood Asthma Management Program obtained during the 28-day period before randomization to study treatment. They noted that nocturnal awakenings occurred in one third of these children with mild-to-moderate asthma. A nocturnal awakening was an indicator of increasingly severe asthma in the 3 days after a nocturnal episode. In addition, those with a positive skin test response to dog and a high level of dog allergen in the home had a greater risk of night awakening caused by asthma, as did those with a positive skin test response to cat and a high level of cat allergen in the home. These studies added to the available literature are beginning to help us profile the patient at risk for persistent asthma, and for significant morbidity.

MANAGEMENT OF CHILDHOOD ASTHMA

Asthma guidelines currently recommend intervention at several points.^{1,5,6} First, there is intervention with bronchodilators for treating symptoms with addition of systemic glucocorticoids for significant exacerbations. Second, intervention with long-term control therapy is recommended when symptoms occur more than twice per week, when nocturnal symptoms occur more than twice per month, and when pulmonary function with either FEV₁ or peak expiratory flow is less than 80% predicted or if within-day peak flow variability exceeds 20%. In addition, when significant acute exacerbations recur in young children within 6 weeks, then intervention with long-term controller therapy should be considered. Another opportunity for intervention with long-term therapy is in the young child at risk of persistent asthma with frequent exacerbations—for example, more than 3 within a 1-year period.⁵ Castro-Rodriguez et al⁵⁵ introduced the concept of an Asthma Predictive Index, suggesting that frequent wheezing during the first 3 years of life, along with either 1 major risk factor (parental history of asthma or eczema in the child) or 2 of 3 minor risk factors (eosinophilia >4%, wheezing without colds, and allergic rhinitis), was associated with the persistence of asthma.

The National Asthma Education and Prevention Program's guidelines update addressed the needs of childhood asthma through a careful evidence-based review of critical issues, such as the time of intervention, the safety and limitations of ICS, and the preferred medication for additive therapy to ICS.^{5,6} Information related to asthma management for children younger than age 5 is weak because of the small number of studies. Therefore, many assumptions for treatment recommendations for young children are based on studies in adults.

Current studies substantiate the role of ICS as first-line therapy in the management of persistent asthma, but they also identify some limitations in the efficacy of ICS, such as failure to eradicate acute exacerbations or to prevent the recently described loss in pulmonary function.^{45,56} Treatment strategies must now address the limitations of ICS in preventing asthma progression and reversing pulmonary function in long-standing, poorly controlled asthma.

The preferred additive therapy for inadequate control with low-medium dose ICS is a long-acting β_2 -adrenergic agonist.^{5,6} Leukotriene antagonists, as well as cromolyn, nedocromil, and theophylline, are considered alternative first-line therapy to ICS and alternative additive therapy to long-acting β_2 -adrenergic agonists once ICS has been initiated.^{5,6}

One of the first steps in alleviating symptoms related to persistent asthma is to identify the patient's allergen sensitivity, assess exposure in the patient's environment, and make attempts to limit the allergen exposure. As this recommendation has never been adequately tested, Carter et al⁵⁷ assessed the efficacy of allergen avoidance as a treatment for asthma among inner city children in Atlanta. They documented a significant decrease in acute visits ($P < .001$) for asthma among children whose homes were visited. However, there was no significant difference between the active and placebo homes either in the effect on asthma visits or in allergen concentrations. When the children with mite allergy were considered separately, there was a significant correlation between decreased mite allergen and change in acute visits ($P < .01$); however, the avoidance measures for cockroach allergen appeared to be ineffective.

Several new classes of medications were introduced over the last 5 years, including the long-acting β_2 -adrenergic agonists and the leukotriene modifiers. The long acting β_2 -adrenergic agonists, salmeterol and formoterol, have a 12-hour duration of action and are currently approved for use in children age 4 and older. One of the oral leukotriene antagonists, montelukast, has emerged as a popular first-line, long-term control therapy in children with asthma because of the availability of dosage guidelines and the demonstration of safety in children as young as 6 months of age.

Arguments against the use of leukotriene receptor antagonists have centered around the limited evidence for anti-inflammatory effect. Phipatanakul et al⁵⁸ evaluated the effect of montelukast on upper and lower airway responses to intense cat allergen exposure in a double-blind, placebo-controlled, randomized, crossover trial in 18 participants ages 6 to 14 with cat-induced asthma. The participants were treated for 1 week and then exposed for 1 hour to cat allergen in an environmental exposure unit. Montelukast was significantly more effective than placebo in attenuating lower respiratory responses and extending challenge length when cat-sensitive children with mild persistent asthma were exposed to high levels of cat allergen. To examine the anti-inflammatory properties of leukotriene modifiers and their effect on bronchial hyper-responsiveness, Stelmach et al⁵⁹ in a double-blind, randomized, placebo-controlled trial, evaluated 39 children with mild-to-moderate atopic asthma. They were randomly allocated to receive montelukast or placebo for 6 weeks, and then inflammatory markers along with pulmonary function and airway responsiveness to histamine was measured. They found that montelukast resulted in a significantly decreased serum concentration in cytokine, intercellular cell adhesion molecule 1 (ICAM-1), and

eosinophilic cationic protein (ECP) and peripheral blood eosinophils, along with improvement in FEV₁ and reduction in histamine PC₂₀ over the treatment period.

Evidence for the role of ICS on improving asthma control was largely based on the results of the long-term NHLBI Childhood Asthma Management Program.⁴⁵ This study also demonstrated significant improvement in asthma control and reduction in airway responsiveness; however, there was no significant long-term effect on pulmonary function and airway responsiveness. This observation, combined with similar losses in asthma control measures, indicate that long-term outcomes of asthma may not be altered by even our best form of treatment.

An area that requires additional research centers around the appropriate time to intervene with either environmental control, pharmacotherapy, or immune modulation.^{5,6} Stevenson et al⁶⁰ examined the national prevalence and demographic correlates of sensitivity to indoor allergens related to asthma in a cross-sectional survey of a representative sample of 4,164 US children aged 6 to 16 years who participated in the Third National Health and Nutrition Examination Survey from 1988 to 1994. The main outcome measures were sensitivity reactions to cockroach, dust mite, cat, and *Alternaria alternata* by skin prick testing. The authors reported that African American and Mexican American children were substantially more likely than white children to be sensitized to allergens important in asthma. These differences in indoor allergen sensitivity were consistent with racial differences in asthma morbidity. These observations, along with other reports, demonstrate racial disparity in housing and community, or that the 2 combined environmental factors play a role in determining national patterns of asthma morbidity. As indicated by Wahn and von Mutius,⁶¹ cross-sectional studies can only generate hypotheses, which must be supported by prospective, longitudinal, cohort studies. Well-controlled intervention studies should identify which nutritional, environmental, or lifestyle factors to consider for early intervention.

Because allergen exposure is difficult to control, we then turn to pharmacotherapy. John Warner and the Early Treatment of the Atopic Child (ETAC) Study Group⁶² examined the effect of an antihistamine, cetirizine, in preventing the onset of asthma in children ages 1 and 2 with atopic dermatitis in a double-blinded, randomized, placebo-controlled trial. The authors completed 18 months of treatment and followed the participants 18 months off treatment. Cetirizine delayed or, in some cases, prevented the development of asthma in a subgroup of infants with atopic dermatitis sensitized to grass pollen and, to a lesser extent, house dust mite. Egg sensitization was also noted as a high-risk factor for development of asthma. Studies focused specifically on sensitized groups are now needed to substantiate this observation.

Roorda et al⁶³ sought to determine whether there are subgroups of young children with recurrent asthma symptoms who are most likely to respond to ICS. They examined pooled data from 2 similar 12-week studies with inhaled fluticasone propionate and placebo. Chil-

dren with frequent symptoms, a family history of asthma, or both showed the greatest response to this treatment. Szeffler et al⁶⁴ compared the efficacy of switching from chlorofluorocarbon (CFC)-beclomethasone dipropionate (BDP) to a hydrofluorocarbon (HFA)-based BDP inhaler in children ages 5 to 11. They concluded that asthma control can be well maintained in children with switching from CFC-BDP plus spacer to an HFA-BDP Autohaler at doses as low as 100 to 200 µg/day.

Also, renewed interest has developed in the combination of medications in one formulation, such as an ICS and a long-acting β-adrenergic agonist, based on evidence of additive effects, convenience for the patient, and the potential to further reduce the risk for significant exacerbations.⁶⁵ However, combination therapy as a single entity is currently only approved for use in children age 12 and older.

To limit the adverse effects of short-acting β-agonists, the stereoisomer of albuterol, levalbuterol, was developed. Milgrom et al⁶⁶ studied the comparative safety and efficacy of levalbuterol and albuterol in asthmatic children ages 4 to 11 in a multicenter, randomized, double-blind study over a 21-day treatment period with medication administered 3 times a day. Levalbuterol was clinically comparable to 4- to 8-fold higher doses of racemic albuterol with a more favorable safety profile.

Pharmacotherapy in young children can also be a challenge because of limitations in the route of administration for inhaled medication administration and dependence on patient cooperation.⁶⁷ Information regarding the appropriate dose of medications for children younger than age 5 is available for some medications, but not all. Revised dosing guidelines for asthma medications in children appear in the recent update to the NAEPP guidelines.^{5,6} The updated guidelines suggest that first-line therapy could begin with low-dose inhaled glucocorticoid by nebulizer or alternatively, by a spacer/holding chamber and face mask.⁵ As indicated previously, a nebulized budesonide preparation recently was approved for use in children as young as age 1.⁷ Comparative studies are needed to determine whether an ICS administered by pressurized metered dose inhaler and spacer/face mask is equivalent to nebulized ICS administration. Other alternatives include the use of montelukast that is now available in a formulation that can be administered to children as young as age 2.

A recent study that compared nebulized budesonide to inhaled cromolyn by nebulizer clearly demonstrated superior asthma control with the nebulized budesonide formulation in measures of asthma exacerbations, symptom control, and time for supplementary medication. However, hospitalizations and emergency department visits were similar in both treatment groups.⁶⁸

Recent studies from the Tucson Children's Respiratory Study that have followed respiratory patterns in children for the first 15 years of life now indicate that children who wheeze during lower respiratory tract illnesses in the first 3 years of life and who still wheeze at age 6 ("persistent wheezers") have the lowest levels of lung

TABLE II. Key advances in pediatric asthma over the last year*

Origins and natural history of asthma
• Associations of microbial exposures with less atopy-associated asthma in children
• Associations of animal exposures in early life (farm animals and pet cats and dogs) with less asthma, atopy, or both in children
• No associations of childhood immunizations or antibiotic use with more asthma
• Refinement of early childhood patterns of allergen sensitization to inhalants and foods, as risk factors for asthma
Management of asthma in children
• Presentation of a profile of risk features for the development of asthma in a young child with frequent wheezing
• Introduction of medications approved for use in young children with asthma
• Identification of the limitations of inhaled corticosteroids in persistent asthma

*Based on literature available between October 2001 and September 2002.

function in later childhood.⁵⁶ Based on limited evidence, it is thought that a loss of pulmonary function over time is associated with airway remodeling.⁶⁹ It is also projected that the consequent alteration in lung growth could have an overall effect on long-term outcomes. It has been proposed that early intervention with ICS therapy can be effective in preventing the progression of the disease and the risk for irreversible changes in the airways; however, this remains to be proven. There is no doubt that intervention with ICS offers the best opportunity to improve asthma control.^{45,68}

The NHLBI Asthma Clinical Research Network described the significant variability in response to ICS in adults with reduced pulmonary function and persistent asthma.⁷⁰ It will be important to determine whether this variability in response to ICS is also present in children undergoing early intervention. A review by Payne and Balfour-Lynn provides a summary of our current understanding of the management of severe persistent asthma in children.⁷¹ They proposed that tools to measure airway inflammation, such as exhaled nitric oxide, induced sputum, BAL, and biopsy could assist in decisions centered around pursuing more aggressive forms of anti-inflammatory therapy or bronchodilator therapy. Other measures of airway inflammation, such as IL-4 and interferon gamma, can be measured in exhaled condensates.⁷² Zancanato et al⁷³ examined the effect of oral prednisone treatment on expired nitric oxide (FE_{NO}) and carbon monoxide (ECO) in 30 asthmatic children before and after a 5-day course of oral prednisone therapy for an acute asthma exacerbation. They reported a significant decrease in FE_{NO} but no significant change in ECO, suggesting this measure is less sensitive than FE_{NO}. Unfortunately, there is very little evidence in children that these indicators of airway inflammation can be reliably applied to asthma management decisions, especially for patients with refractory asthma.

The area of pharmacogenetics could provide information on the relationships of genetics to medication response.⁷⁴ Advances in this area could help define relevant asthma phenotypes and genotypes associated with a favorable response to medications and assist in defining individualized treatment approaches.

CONCLUSION

Based on the results of the long-term Childhood Asthma Management Program clinical trial in childhood asthma, the benefits of continuous long-term ICS on asthma control in children are clear. Studies are in progress to evaluate whether early intervention with ICS can alter the natural history of asthma. Indicators are rapidly being defined to identify the patient at risk for persistent asthma and thus identify the appropriate candidates for early intervention. Given the right medication and the patient profile, it may be possible to induce remission or even a "cure." It will also be very important to recognize patients at risk for severe asthma and to intervene more effectively to prevent asthma progression to severe levels and the consequent irrecoverable loss of pulmonary function.

The key advances in pediatric asthma over the last year are summarized in Table II. The goal should now be to strive for a reduction in asthma morbidity and mortality. A high proportion of asthma morbidity among inner city children appears related to nonadherence. Therefore, targeting management approaches to improve adherence or to derive more effective therapies could reduce morbidity in this patient population.⁷⁵

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