

Consider the child: How early should we treat?

Andrew H. Liu, MD *Denver, Colo*

Epidemiologic and natural history studies of asthma have found that, for most people who develop asthma, clinical manifestations of the disease occur in the early childhood years. Both asthma persistence and severity during early childhood predict disease persistence into later childhood and adulthood, at which point asthma remission is uncommon. Current pathogenesis paradigms suggest that early intervention, before serious pathologic changes occur, may lead to optimal outcomes. Early intervention might optimize lung growth and immune development, and mitigate asthma persistence and severity. In this overview, categories for early intervention strategies for asthma will be based on the level of disruption of asthma pathogenesis. "Early interventions" target asthma shortly after its onset, "secondary preventions" aim to prevent lung targeting of disease processes in the vulnerable host, and "primary preventions" strive to promote healthful immune development and lung growth by keeping pro-asthmatic immune responses from occurring. This review will discuss recent clinical studies that exemplify early intervention and prevention strategies. (*J Allergy Clin Immunol* 2004;113:S19-24.)

Key words: Asthma, allergy, atopy, cysteinyl leukotrienes, respiratory syncytial virus

One way to conceptualize early interventions for asthma begins with an asthma pathogenesis schema (Fig 1). A combination of environmental exposures and biologic vulnerabilities provides a milieu of causes for asthma. Biologic vulnerabilities can be categorized as immune or pulmonary in nature. Pathogenic immune responses to common environmental exposures can cause asthma. Respiratory exposures implicated in this causal environment include inhaled allergens, respiratory viral infections, and chemical and biological air pollutants such as environmental tobacco smoke (ETS) and endotoxin, respectively. In the predisposed host, immune responses to these common exposures can be a stimulus for pathogenic inflammation and aberrant repair processes in the airways. In the early years, airflow limitation and the phenomenon of bronchial hyperresponsiveness (BHR) develop. Recent studies further suggest that, when these

Abbreviations used

AIT:	Allergen-specific immunotherapy
ASM:	Airway smooth muscle
BDP:	Beclomethasone dipropionate
BHR:	Bronchial hyperresponsiveness
CAMP:	Childhood Asthma Management Program study
CysLTs:	Cysteinyl leukotrienes
ETAC:	"Early Treatment of the Atopic Child"
ETS:	Environmental tobacco smoke
ICS:	Inhaled corticosteroids
IFN- γ :	Interferon-gamma
Ig:	Immunoglobulin
LRTI:	Lower respiratory tract infection
PEAK:	"Prevention of Early Asthma in Kids"
RSV:	Respiratory syncytial virus

pathogenic processes occur in the growing lung in early life, airway growth and development proceed abnormally, leading to architecturally altered lungs at mature ages. Once asthma has developed, ongoing exposures appear to worsen asthma and drive disease persistence. Infants and young children with pulmonary predispositions for asthma are at increased risk for persistent and severe disease when these immune pathologic processes develop. Lung-specific risk factors in infants and young children include smaller airways at birth (eg, due to premature birth, male sex, ETS exposure in utero) and BHR.

With this understanding of asthma development and risk factors, early management strategies for asthma can be categorized as follows:

1. "Early intervention" can be applied soon after clinical asthma has occurred, with the goals of reducing asthma symptoms and exacerbations safely, while mitigating immune pathogenic and aberrant repair processes to allow for normal lung growth and development to proceed.
2. "Secondary prevention" strategies target at-risk infants and young children to prevent lung targeting of disease processes. Examples of at-risk children include those born prematurely or with early manifestations of atopy.
3. "Primary prevention" aims to promote immune development in a manner that keeps pro-asthmatic immune responses from developing.

The inception of treatment at a young age presents challenges not as strongly considered with older patients. Safety is of particular concern, as young, growing children are generally considered to be particularly vulnerable to adverse effects, and drug testing in young children

From the Division of Allergy & Immunology, Department of Pediatrics, National Jewish Medical & Research Center, and University of Colorado Health Sciences Center, Denver, Colorado.

A. Liu served as a speaker and consultant for GlaxoSmithKline, Merck, and AstraZeneca.

Reprint requests: Andrew H. Liu, MD, Pediatric Allergy & Immunology, National Jewish Medical & Research Center, 1400 Jackson St (K1023), Denver, CO 80206.

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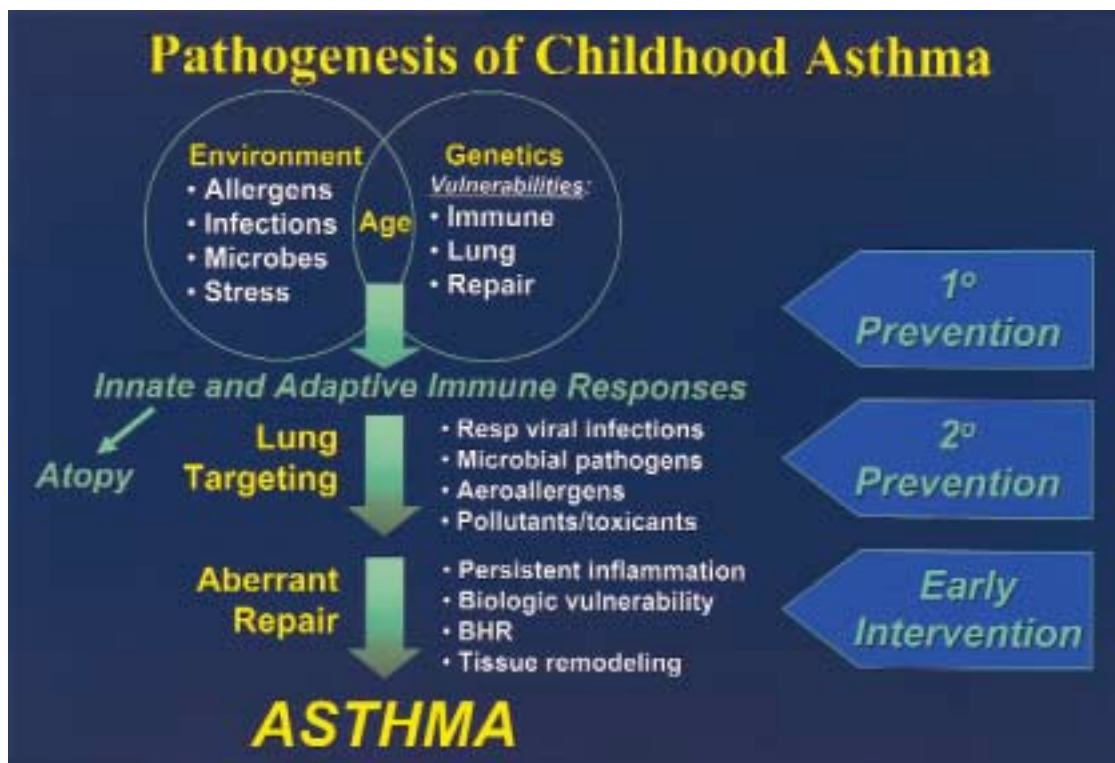


FIG 1. Early intervention to disrupt asthma pathogenesis. A combination of environmental exposures and biologic vulnerabilities provide a setting of causation for asthma. Pathogenic immune responses to common respiratory exposures target disease processes to the lungs. Persistent inflammation and aberrant repair processes in the airways, especially during the early years of greatest lung growth, may underlie the establishment of chronic persistent disease. In this pathogenic context, early intervention strategies for asthma can be categorized as: (1) "Early intervention" soon after clinical asthma is observed, to lessen or end aberrant immune and repair processes and allow for normal lung growth and development to proceed; (2) "Secondary prevention" for at-risk infants and young children to prevent lung targeting of disease processes; and (3) "Primary prevention" to promote immune development in a manner that keeps pro-asthmatic immune responses from developing.

to assess such concerns is typically limited. Therefore, the goal should be to obtain a balance between providing effective treatments during these early years of greatest lung growth and immune development, while maintaining a high level of patient safety.

EARLY INTERVENTION WITH CONVENTIONAL ASTHMA CONTROLLERS

Currently, treatment regimens for asthma target the airway inflammation, which is known to be present even in asymptomatic periods, and is linked to histopathologic and lung functional evidence of aberrant repair processes, so-called airway "remodeling." The mainstays of conventional asthma and allergy "controller" medications have anti-inflammatory actions. Some of these medications have been carefully studied for their safety in young children, and have approval from the US Food and Drug Administration for use in young children.

Inhaled corticosteroids

Inhaled corticosteroids (ICS) have broad anti-inflammatory mechanisms of action that account for their effec-

tiveness in asthma treatment.¹ Some of the strongest evidence linking airway inflammation with remodeling comes from the effect of ICS on airway basement membrane thickness in asthma. For example, a double-blind parallel group study evaluated the use of inhaled beclomethasone dipropionate (BDP) 500 µg twice daily in mildly asthmatic adults.² After 4 months, patients receiving BDP had reduced thickness of type III collagen deposits in the bronchial lamina reticularis and reduced granulocytes-macrophage colony-stimulating factor expression in the bronchial epithelium.²

When used on a long-term basis in asthmatic children, do ICS improve asthma outcomes? In the NIH/NHLBI-sponsored Childhood Asthma Management Program study (CAMP), 1041 children aged 5 through 12 years with mild to moderate asthma were randomized to receive 200 µg of inhaled budesonide twice daily, 8 mg of nedocromil twice daily, or placebo, for approximately 5 years.³ During treatment, those who received the ICS had global improvement in their asthma relative to the nedocromil and placebo groups. One unexpected finding was that, after discontinuation of study medication, the improvement in BHR (measured by methacholine bronchoprovocation chal-

lenges) in the ICS-treated group declined within 4 months to resemble the degree of BHR in the control and nedocromil groups. Because the CAMP cohort reported a mean asthma duration of approximately 5 years at the start of the study, the lack of more substantial and prolonged effect of ICS on BHR in the CAMP study has supported the hypothesis that optimal outcomes from anti-inflammatory therapy in asthma might only occur if such therapies are initiated soon after asthma onset. NIH/NHLBI has supported a study to test this hypothesis, "Prevention of Early Asthma in Kids" (PEAK).

Cys-leukotriene antagonists

A well known feature of airway remodeling in asthma is the airway smooth muscle (ASM) hypertrophy and hyperplasia.⁴ One mechanism by which this occurs is thought to involve cysteinyl leukotrienes (CysLTs). CysLTs (LTC₄, LTD₄, and LTE₄) are formed from the actions of the 5-lipoxygenase and a membrane-bound 5-lipoxygenase activating protein in the arachidonic acid pathway.⁴ There are few studies that have investigated the effects of CysLTs on the process of airway remodeling.⁴ Preliminary evidence of *in vitro* research on rat and rabbit airway tissues suggests that CysLTs promote ASM mitogenesis. Using human ASM, Panettieri et al⁴ studied the effects of the CysLTs (LTD₄) human ASM cells. They found that LTD₄ alone had no effect on DNA synthesis; however, LTD₄ combined with epidermal growth factor (produced with epithelial injury), increased human ASM cell proliferation and growth in a dose-responsive manner by acting through the CysLT receptors on ASM.⁴ This suggests that CysLTs have an important role in airway remodeling and especially ASM hypertrophy and hyperplasia in patients with asthma.

The importance of this observation becomes clearer when considering the immune abnormalities observed in young children with recurrent wheezing problems, typically in response to common respiratory viral infections. Elevated CysLT levels have been found in the nasal lavage of infants with virus-induced wheezing,⁵ and also in bronchoalveolar lavage fluid from young children with persistent wheezing.⁶ Could overproduction of CysLTs in response to common respiratory viral infections in young children underlie early ASM hypertrophy and hyperplasia, BHR, and exaggerated responses to bronchodilators? A clinical study that opens the door to this line of inquiry in young children is a double-blind, randomized, placebo study examining the effects of administering 5 mg of montelukast tablets or matching placebo to 130 infants aged 3 to 36 months (median age, 9 months) who were hospitalized with respiratory syncytial virus (RSV) bronchiolitis.⁷ Montelukast or placebo was administered within 7 days of the start of symptoms, for a 28-day period. While all infants continued to have daily or nightly symptoms for the first 12 days of treatment, infants given montelukast were symptom-free on 22% of the days compared with only 4% of the placebo group (Fig 2).⁷ Lung symptoms, such as daytime cough and exacerbations related to RSV bronchiolitis, were reduced or delayed with the use of montelukast com-

pared with placebo.⁷ This suggests that montelukast may promote optimal outcomes by preventing the development of chronic changes (perhaps ASM hypertrophy and hyperplasia) that lead to persistent symptoms after virus-induced wheezing. Important follow-up studies of this seminal observation will be needed to determine if such an intervention is truly effective, and if so, what are the optimal parameters of its use?

SECONDARY PREVENTION STRATEGIES

RSV-induced bronchiolitis and future risk of asthma

Although almost all children have an RSV infection in the first few years of life, a subset will have a lower respiratory tract infection (LRTI) with wheezing as a result of RSV. In a longitudinal prospective birth cohort study (Tucson Children's Respiratory Study), 888 participants were followed closely for 3 years for the development of LRTIs and the respiratory pathogens associated with these episodes.⁸ The results showed that 519 (58.5%) patients were diagnosed with at least one LRTI, of which 472 (90.9%) had a pathogen identified from respiratory cultures.⁸ Of those, RSV was the most common (44%).⁸ Children with RSV-associated LRTIs were 4.3 times more likely to wheeze frequently by 6 years of age.⁸ However, it remains unclear if RSV-associated LRTI causes asthma, or if RSV reveals subjects who have aberrant, pro-asthmatic immune responses to common respiratory viruses.

Some children have a very high risk of severe bronchiolitis as a result of RSV. In particular, infants born prematurely, especially those who develop chronic lung disease of prematurity and/or congenital heart disease, have a high risk of requiring hospitalization due to RSV bronchiolitis (20–60%).⁹ They are also at increased risk of having greater airflow limitation in later childhood.¹⁰

Palivizumab, a genetically engineered monoclonal antibody specific for RSV, provides passive immunity against RSV.⁹ Palivizumab works by inhibiting and neutralizing fusion activities of the RSV isolates Type A and B.⁹ The IMPact-RSV study group examined the efficacy and safety of palivizumab used as prophylaxis for reducing the rate of hospitalizations in high-risk infants due to RSV.¹¹ In this randomized, double-blind, placebo-controlled study, 1502 premature infants (≤ 35 weeks) or infants with bronchopulmonary dysplasia were given either 5 monthly injections of palivizumab during the RSV months or placebo.¹¹ The results showed that 4.8% of children who received palivizumab prophylaxis were hospitalized for RSV bronchiolitis compared with 10.6% of those who received placebo.¹¹ The results of the IMPact-RSV study have been well replicated in similar studies, and now approximately 5 years post-release, this management strategy continues to appear quite safe.⁹ This exemplifies a secondary prevention approach of preventing severe infection due to RSV in infants with highly vulnerable lungs. Studies that ascertain the long-term benefits of severe RSV bronchiolitis prevention should be forthcoming. The value

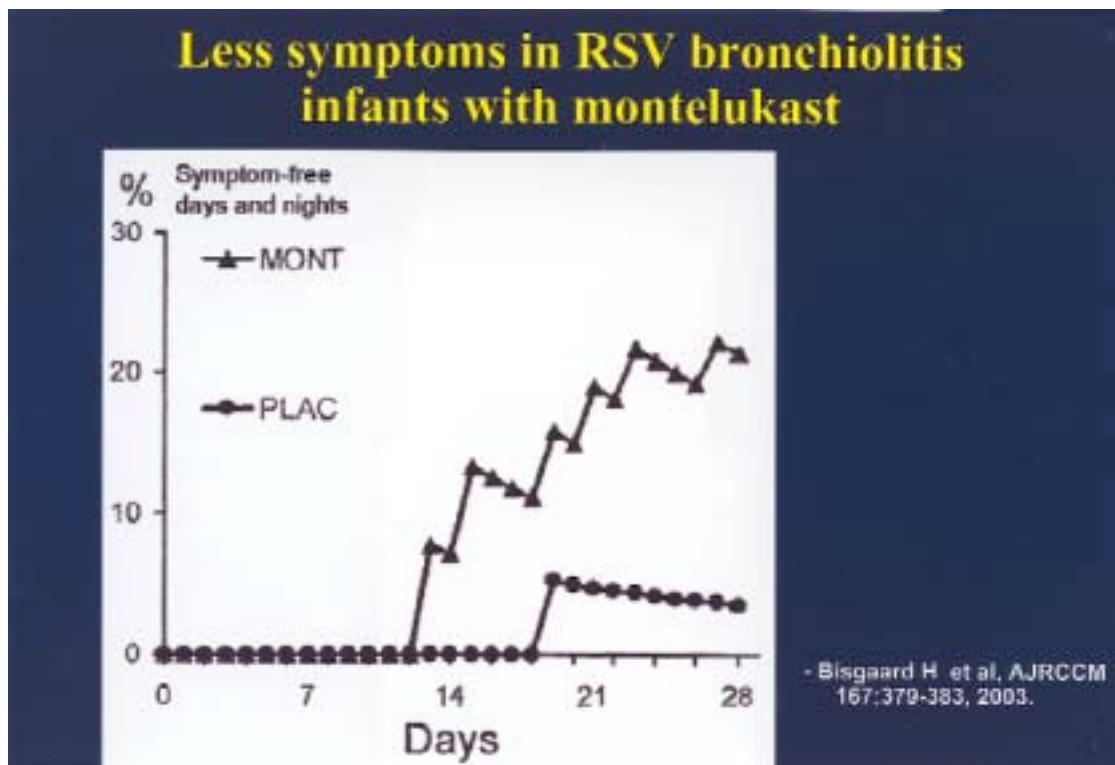


FIG 2. Montelukast in infants hospitalized with RSV bronchiolitis. In this randomized controlled trial of a 28-day course of montelukast for infants hospitalized with RSV-proven bronchiolitis ($n = 130$; ages 3-36 months; mean age 9 months), there initially was no significant improvement. However, 12 days after initiation of therapy, infants given montelukast (5 mg/day) were symptom-free on 22% of days and nights compared with only 4% in the placebo-treated group. (From Bisgaard H, et al. *Am J Respir Crit Care Med* 2003;167:379-83.)

of preventing RSV bronchiolitis in other children with significant risk factors for bronchiolitis (eg, young age during RSV season, low birth weight, male sex, ETS exposure) and/or asthma (eg, maternal history of asthma, infantile eczema) has not yet been determined.

Antihistamine trial to prevent asthma in infants with atopic dermatitis

Natural history studies of asthma have found that clinical and biological manifestations of atopy (eg, atopic dermatitis, elevated blood eosinophils, early inhalant allergen sensitization) in young children with recurrent wheezing are consistent risk factors for persistent asthma.¹² Interventions in young children with atopic dermatitis to prevent the "atopic march" to subsequent asthma exemplify secondary prevention strategies. The "Early Treatment of the Atopic Child" (ETAC) study tested this hypothesis with the antihistamine cetirizine in 566 children between 1 and 2 years of age with active symptoms of atopic dermatitis for at least 1 month.¹³ Participants were randomized to receive either cetirizine twice daily or placebo for 18 months; follow-up continued for an additional 18 months.¹³ Although there was no difference in cumulative prevention of asthma in either group, a subset of children with house-dust mite and/or grass pollen sensitivity who were treated with cetirizine

were approximately 50% less likely to have asthma symptoms compared with those receiving placebo.¹⁴ This exemplifies another secondary prevention approach to asthma by attempting to interrupt the allergic march before it reaches the lungs.

PRIMARY PREVENTION OF ATOPY AND ASTHMA

In modernized locales, there has been an increase during the last half of the century in the prevalence of atopic diseases, such as atopic dermatitis, allergic rhinitis, and asthma.^{15,16} Because this increase has occurred within the last two generations, it is unlikely to be the result of genetic changes.¹⁷ Therefore, it is believed that this is because of environmental and lifestyle changes. The popular but controversial "hygiene hypothesis" of allergic diseases and asthma accounts for this prevalence rise as the result of changes in public and personal hygiene, leading to significant reductions in microbial exposures.¹⁸ Microbial exposures in infancy and early childhood may drive immune development and maturation away from pro-allergic, pro-asthmatic immune responses. Naturally occurring infections and microbial exposures might essentially "immunize" against the development of asthma and allergic, as well as autoimmune, diseases. Some new therapies

based on the potential benefits of microbial exposures have been brought to bear on asthma prevention.

Probiotics in primary prevention of atopic disease

Beneficial microbes in gut flora may be helpful in the prevention of atopic diseases.¹⁹ Probiotics enhance the barrier mechanisms of the gut, and may enhance early immune development to prevent atopy and asthma. In a randomized, placebo-controlled trial, Kalliomaki et al looked at the effects of probiotics in infants on preventing atopic disease.¹⁹ One-hundred fifty-nine pregnant women with a family history of atopic disease, allergic asthma, or allergic rhinitis were given either oral *Lactobacillus* GG or placebo daily.¹⁹ Postpartum, the infants or breast-feeding mothers were given daily *Lactobacillus* GG or placebo for six months. By 2 years of age, significantly less children who had received the probiotic had been diagnosed with atopic eczema.¹⁹ Interestingly, this effect was also observed in infants who were exclusively breast-fed, and whose mothers received the *Lactobacillus* supplementation. Further study of these and other infants to determine if *Lactobacillus* supplementation can also reduce asthma outcomes are needed and forthcoming.

IMMUNE MODULATION WITH ALLERGEN IMMUNOTHERAPY: FUTURE VISIONS

Allergen-specific immunotherapy (AIT) is effective for the treatment of persons with seasonal rhinoconjunctivitis, especially patients with disease that responds poorly to anti-allergic pharmacotherapy.²⁰ Recent studies suggest that AIT has immune modulatory effects beyond allergen-specific tolerance, and is relevant to airway allergic disease and asthma. Several studies have demonstrated that immunotherapy inhibits the early and late phase nasal responses after allergen provocation.²⁰ In a recent study, evidence of a decrease in the nasal mucosal number of CD4 T-lymphocytes and total and activated eosinophils 24 hours after immunotherapy was presented.²⁰ Furthermore, improvements in seasonal symptoms and medication requirements were associated with an increase in the expression of interferon (IFN)- γ in the allergen-stimulated nasal mucosa.²⁰ This suggests that AIT may promote T_H1 T-lymphocytes (IFN- γ) with downregulation of the effects of T_H2 cytokines, resulting in the suppression of immunoglobulin (Ig)E and eosinophils.²⁰

The effects of discontinuation of AIT for 3 to 4 years were also reported.²¹ Participants who had received active AIT remained in clinical remission for at least 3 years.²¹ Other studies have recently shown that AIT in children prevents additional sensitization to new aero-allergens ("neo-sensitization").²² A recent report also suggests that AIT in allergic rhinitis patients reduces the prevalence of new-onset asthma in these patients.²³ These findings suggest that earlier AIT can prevent the progression or development of multiple allergen sensitizations and asthma through lasting immune-modulatory effects.

An effort to improve AIT by combining it with mono-

clonal anti-IgE (omalizumab) was attempted in pediatric patients with seasonal allergic rhinitis in a double-blind, randomized, placebo-controlled, parallel group study.²⁴ A total of 221 patients, 6 to 17 years of age, with a clinical history of seasonal allergic rhinitis were included in the study.²⁴ The group receiving combination therapy had a 48% reduction in symptoms when compared with the group given AIT alone.²⁴ Anti-IgE also reduced rhinoconjunctivitis symptom scores and rescue medication use significantly.²⁴ This study suggests that combination immune modulatory therapies may be useful in certain cases of complex allergic disorders.²⁴

CONCLUSION

Although early intervention strategies to disrupt or prevent asthma are abundant, clinical studies that convincingly demonstrate their effectiveness in achieving these optimal outcomes are limited. Cumulatively, a number of clinical studies in young children and even infants have provided valuable insights and experience with the types of studies that will be needed. Early intervention and secondary and primary prevention studies target different patient populations based on their clinical manifestations of disease. Practically speaking, early intervention in children with early manifestations of asthma is well justified considering their ongoing symptomatology. In such cases, the potential efficacy and interest in attaining optimal outcomes can outweigh the risks of interventions that are relatively safe. In contrast, prevention strategies in young children or even infants before pulmonary manifestations of disease are challenging to rationalize, unless they are found to be very safe.

Asthma prevention is ideal and not necessarily unrealistic. Immunization strategies in infancy to prevent diseases with severe outcomes in a minority of the treated population have proven their value time and again in improving health. Once efficacy and safety of prevention strategies is established, their implementation to prevent what has become the most common and costly of chronic diseases in childhood will be welcome.

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