Advances in Asthma, Allergy, and Immunology Series 2007

Advances in pediatric asthma

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Because the outcomes experienced in adult asthma often result from pathophysiology that begins in early childhood, this year's summary focuses on recent advances in pediatric asthma. This past year, we have learned that early intervention with inhaled corticosteroids in childhood asthma reduces morbidity but does not alter the natural history of asthma. Theme issues over the last year focused attention on severe asthma and black box warnings. Both of these themes significantly affect the management of childhood asthma. Responsiveness to asthma treatment is heterogeneous even among patients with asthma of similar severity. This heterogeneity calls attention to the importance of assessing control and adjusting treatment accordingly. We are now moving toward an individualized approach to asthma therapy and searching for biomarkers and genetics as a resource to guide treatment. To improve asthma control, we must continue to obtain information on early asthma, severe asthma, asthma exacerbations, and methods to improve asthma control. Evaluation and management of severe asthma in children include verification of the diagnosis, assessment for coexisting illnesses, and identification of effective treatment strategies directed to adherence, medication delivery, and combination therapy. Application of biomarkers and genetics could be useful tools in individualizing our approach to the management of childhood asthma. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: *Asthma, severe asthma, early intervention in asthma, biomarkers, therapeutics*

The Advances series has included a summary of published literature related to adult and pediatric asthma.[1] This year's summary focuses on childhood asthma. Updates to the asthma guidelines were recently released focusing on asthma control and early intervention.[2]

Abbreviations used
BDR: Bronchodilator response
eNO: Exhaled nitric oxide
FVC: Forced vital capacity
ICS: Inhaled corticosteroid
LABA: Long-acting β_2-adrenergic agonist
LT: Leukotriene
LTRA: Leukotriene receptor antagonist
SIT: Specific immunotherapy

Another area receiving attention is the use of biomarkers to assist in predicting and monitoring medication response, as well as the application of genetics to asthma care. This review highlights 2006 Journal publications and several other studies that affect our current understanding of childhood asthma (Table I).

EARLY ASTHMA

Several recent publications reshaped our thinking around the early course of asthma in children. Haland et al[3] reported findings on a prospective birth cohort study of healthy infants in which they measured lung function shortly after birth, concluding that reduced lung function at birth was associated with an increased risk of asthma at 10 years of age. Illi et al[4] followed 1314 children from birth to 13 years of age and reported that the chronic course of asthma characterized by airway hyperresponsiveness and impairment of lung function at school age is determined by continuing allergic airway inflammation beginning in the first 3 years of life.

Two groups evaluated early intervention with inhaled corticosteroids (ICSs), noting their effect in reducing morbidity during therapy but no effect on altering the course of asthma.[5,6] Marks et al[7] examined early life exposures in the development of asthma and allergic disease and tested house dust mite avoidance and dietary fatty acid modification throughout the first 5 years of life, concluding that neither prevented the onset of asthma, eczema, or atopy.

To study the protective effects of environmental exposures, Perkin and Strachan[8] reported that unpasteurized milk consumption was the exposure mediating the protective effect on allergic sensitization in farm children. Similarly, Campo et al[9] evaluated relationships among high endotoxin exposure, pet ownership, atopy, and wheezing in high-risk infants, reporting that pet ownership

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TABLE I. Key advances in pediatric asthma in 2006

1. Early intervention with inhaled corticosteroids in childhood asthma reduces morbidity but does not alter the natural history of asthma.
2. Symptom questionnaires are predictive of subsequent asthma episodes in people older than 10 years but not in young children.
3. In children with asthma, FEV_1/FVC is a more reliable inclusion criterion for clinical studies as well as an assessment measure for clinical control.
4. Evaluation and management of severe asthma in children include verification of the diagnosis, assessment for coexisting illnesses, and identification of effective treatment strategies directed to adherence, medication delivery, and combination therapy.
5. Responsiveness to asthma treatment is heterogeneous even among patients with asthma of similar severity. This heterogeneity calls attention to the importance of assessing control and adjusting treatment accordingly.
6. We are now moving toward an individualized approach to asthma therapy and searching for biomarkers and genetics as a resource to guide treatment.

or endotoxin did not independently modify aeroallergen sensitization or wheezing during infancy. High endotoxin exposure in the presence of multiple dogs was associated with reduced wheezing in infants but did not effect sensitization.

Another effort to understand predisposition to allergic disease occurred through the evaluation of cortisol circadian rhythm and stress response among infants at risk for the development of allergic disease. Ball et al[10] identified low basal levels of endogenous cortisol and greater cortisol stress response in infants of mothers with allergy, proposing that this abnormality might affect allergic immune responses. The effect of mild to moderate childhood asthma on lung growth was examined in the National Heart, Lung, and Blood Institute Childhood Asthma Management Program and showed that the FEV_1/forced vital capacity (FVC) ratio was diminished in children with asthma because of slower FEV_1 and greater FVC development with age.[11] Shapiro[12] addressed the question of predicting persistent asthma among young children with wheezing episodes, highlighting allergic sensitization and the presentation of allergic features such as rhinitis, eczema, and eosinophilia as well as decrease in lung function by age 3 years, female sex, tobacco smoke exposure, parental history of asthma, and early development of airway hyperresponsiveness manifested by coughing and wheezing during viral infections.

ASTHMA MECHANISMS

Chen et al[13] reported that stress, particularly among lower socioeconomic status children, was associated with higher morbidity and cytokine levels attributed to asthma inflammation. Ercan et al[14] examined the oxidant/antioxidant imbalance in asthma, reporting strong oxidative stress in children with asthma that increases with asthma severity. The val/val genotype at GSTP1 ile105val locus may be an important factor in determining the degree of oxidant injury.

Zeidler et al[15] demonstrated that natural exposure to cat allergen resulted in significant small airways obstruction and hyperresponsiveness with distal lung inflammation. Profita et al[16] reported that markers of inflammation including exhaled nitric oxide and measures of exhaled breath condensates detect nasal and bronchial inflammation.

ASTHMA EXACERBATIONS

McCoy et al[17] characterized patients with asthma episodes and exacerbations, reporting that episode frequency was highest in children younger than 10 years. Additional risk factors were smoking, African American ethnicity, low lung function, and past history of severe asthma. Symptom questionnaires were predictive of subsequent asthma episodes in people over age 10 years but not in young children. Johnston et al[18] studied the sequence of timing of September asthma hospitalization epidemics, identifying a precise relationship to school return after the summer vacation and speculating that school-age children transmit agents responsible for the epidemic. Measures to improve asthma control and reduce transmission of infections should be directed at children with asthma before school return.

SEVERE ASTHMA

The March 2006 theme issue focused on severe asthma, addressing pathogenesis and management.[19] Steps to be taken in the evaluation and management of severe asthma in children and adults include verification of the diagnosis, assessment for coexisting illnesses, and identification of effective treatment strategies directed to adherence, medication delivery, and combination therapy.[20]

de Marco et al[21] investigated prognostic factors of asthma severity, noting early deterioration of lung function, high IgE levels, and persistent cough/mucus hypersecretion as strong markers of moderate/severe asthma. Ueda et al[22] evaluated lung density on high-resolution computed tomography, noting that expiratory/inspiratory high-resolution computed tomography is useful for assessing small airways disease in asthma and that small airways involvement is associated with airway obstruction, airway hypersensitivity, and more severe disease.

Lemiere et al[23] sought to compare airway inflammation by using noninvasive and invasive methods in moderate and severe asthma. Sputum cell counts allowed the identification of a subgroup with severe asthma at risk for frequent asthma exacerbations. Fitzpatrick et al[24] identified features of severe versus mild-to-moderate asthma in school age children by using noninvasive assessments of

lung function, atopy, and airway inflammation, reporting that severe asthma in children is characterized by poor symptom control including higher frequency of severe exacerbations, despite high-dose ICS treatment, and is differentiated from mild-to-moderate asthma by lung function and exhaled nitric oxide (eNO).

ASTHMA CONTROL MEASURES

Stoloff and Boushey[25] discussed the difference among the terms *severity*, *control*, and *responsiveness*, emphasizing that initial treatment should be based on assessment of asthma severity but subsequent treatment based on level of control. Responsiveness to treatment is heterogeneous, however, even among patients with asthma of similar severity. This heterogeneity calls attention to the importance of assessing control and adjusting treatment accordingly. Application of a guidelines-based approach to management requires an awareness of asthma as causing current symptoms and functional impairment and risk of future adverse events.

Schatz et al[26] identified independent prospective determinants of future long-term asthma control among asthma severity, management, demographic, and comorbidity predictors, reporting that markers of asthma severity and other patient characteristics are inversely related to future asthma control, but effective management strategies are associated with improved asthma control, even after accounting for these high-risk characteristics. Inhaled corticosteroids, long-acting β-agonists, and asthma specialist care are associated with improved asthma control, even after accounting for markers of asthma severity.

Baatenburg de Jong et al[27] provided data supporting the observation that most children with persistent asthma well controlled by ICS have normal lung function and little or no bronchodilator response, calling into question the use of reduced lung function and presence of bronchodilator response as inclusion criteria for clinical trials in childhood asthma; however, they did not discuss the alternative of including FEV_1/FVC. Strunk et al[11] indicated that FEV_1/FVC is abnormal in children with mild to moderate asthma. Perhaps FEV_1/FVC is a more reliable inclusion criterion for clinical studies as well as asthma assessment for children.

Alternatively, methacholine responsiveness could be applied in clinical trials as an indicator of asthma and response to treatment. Covar et al[28] reported on the experience of conducting more than 8000 methacholine challenges. In 7% of the positive and incomplete challenges, participants reported having at least 1 symptom, such as chest tightness, shortness of breath, and cough, that was easily reversible with a bronchodilator treatment.

Measurement of eNO could be useful in measuring, predicting, and monitoring response to corticosteroids, because it is a surrogate marker specific for eosinophilic airway inflammation which is usually steroid-responsive. Thus, eNO may be used to guide steroid responsiveness and steroid requirements and may be useful in the management of severe or difficult-to-control asthma.[29] Infants and toddlers with eczema may also have elevated eNO, perhaps an early indicator of developing asthma.[30] Although one report indicated no change in eNO after exposure to an indoor swimming pool, another reported changes in daily measurements during a birch pollen season.[31,32] The handheld device (NIOX MINO, Aerocrine AB, Solna, Sweden) could expand the application for home monitoring and imminent acute asthma exacerbations.[32]

Another application of data from the National Heart, Lung, and Blood Institute Childhood Asthma Management Program was to assess the association of baseline lung function to future lung function and the variability with treatment.[33] This analysis demonstrated that baseline bronchodilator response, airway responsiveness, and level of FEV_1 are independent predictors of subsequent level of FEV_1 in childhood asthma. Baseline bronchodilator response was a particularly powerful predictor of lung function improvements while on ICS, whereas airway responsiveness was a better predictor in subjects not randomized to any controller medications.

ASTHMA THERAPY

The preferred long-term controller for the management of persistent asthma in all age groups is ICS. However, many parents and physicians are still apprehensive regarding potential adverse effects. Parents ask if their child needs to be on continuous ICS therapy. Physicians ask how they can decide whether to use an ICS or leukotriene receptor antagonist (LTRA). Answers to these questions appeared last year in a study that characterized the response to ICS and LTRA. Using pulmonary function as an indicator of response, this study concluded that children with low pulmonary function or high levels of markers associated with allergic inflammation, including elevated eNO, should receive ICS therapy instead of a LTRA.[34] A follow-up report using another marker of response, asthma control days, concluded that eNO as a predictor of response might help to identify individual children not receiving controller medication who achieve a greater improvement in asthma control days with an ICS compared with a LTRA.[35]

Elevated urinary leukotrienes are associated with a favorable pulmonary response to LTRA.[34] Because leukotrienes can be measured in exhaled breath condensates, Montuschi et al[36] studied the effect of montelukast, an LTRA, on exhaled leukotriene (LT) E_4, 8-isoprostane, and prostaglandin E_2 in children with asthma, along with measures of eNO, reporting that LTRA decreased exhaled LTE_4 in atopic children with asthma dependent on baseline exhaled LTE_4 values. Therefore, exhaled LTE_4 might help identify children with asthma most likely to benefit from LTRAs.

The January 2006 theme issue[37] focused on black box warnings, including the safety of long-acting β_2-adrenergic agonists (LABAs). This LABA warning prompts physicians to assess their benefits and risks carefully before prescribing. Although the safety of LABA when

combined with ICS is reassuring, it is generally recognized that LABA should not be used as monotherapy and that LABA should be limited to use with ICS in moderate to severe asthma.

Kumar et al[38] characterized the distribution and determinants of bronchodilator response (BDR) and bronchodilator hyperresponsiveness in rural Chinese children ages 8 to 15 years. They concluded that multiple factors affected BDR, including age, sex, height, body mass index, asthma status, and family history of asthma. Therefore, interpretation of clinical or research findings on BDR needs to take these factors into consideration.

Roberts et al[39] conducted a randomized, placebo-controlled study on the efficacy and safety of grass pollen specific immunotherapy (SIT) in 39 children ages 3 to 16 years with seasonal allergic asthma over 2 pollen seasons. SIT was associated with a substantial reduction in asthma symptom-medication score compared with placebo, along with significant reduction in cutaneous, conjunctival, and bronchial reactivity to allergen, with a trend toward less ICS use in the SIT group with similar levels of airway inflammation.

CLOSING COMMENTS

With each Advances review, we can follow the shift in approach to asthma management. We are moving toward goals of improving asthma control and identifying therapies that will induce remission, at least during treatment. We now recognize the limitations of current therapy in resolving asthma symptoms completely and altering the natural history of asthma.

An individualized approach to asthma therapy seeks to apply biomarkers and genetics as resources to guide treatment. eNO and β-adrenergic polymorphisms are prototypes for this approach. However, we must validate their application to clinical care.

Ideally, an individualized approach to asthma management will lead us to new information regarding driving factors in poorly controlled asthma and potential new targets for therapeutic intervention. Whether an agent that hits multiple targets, such as ICSs, or selective targets, such as anti-IgE, will remain within our current armamentarium will be topics for future research as we attempt to advance asthma care for children.

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REFERENCES

1. Apter AJ, Szefler SJ. Advances in adult and pediatric asthma. J Allergy Clin Immunol 2006;117:512-8.
2. 2006 GINA report: global strategy for asthma management and prevention. Available at: http://www.ginasthma.org. Accessed January 18, 2007.
3. Haland G, Lodrup Carlsen KC, Sandvik L, Sekhar Devulapalli CS, Munthe-Kass MC, Pettersen M, et al, for ORAACLE. Reduced lung function at birth and the risk of asthma at 10 years of age. N Engl J Med 2006;355:1682-9.
4. Illi S, von Mutius E, Lou S, Niggermann B, Gruber C, Wahn U, on behalf of the Multicentre Allergy Study (MAS) group. Perennial allergen sensitization early in life and chronic asthma in children: a birth cohort study. Lancet 2006;368:763-70.
5. Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szefler SJ, et al. Two year inhaled corticosteroid treatment on subsequent asthma in high-risk toddlers. N Engl J Med 2006;354:1985-97.
6. Murray CS, Woodcock A, Langley SJ, Morris J, Custovic A, for the IFWIN study team. Secondary prevention of asthma by the use of inhaled fluticasone propionate in wheezy infants (IFWIN): double-blind, randomized, controlled study. Lancet 2006;368:754-62.
7. Marks GB, Mihrshahi S, Kemp AS, Tovey ER, Webb K, Almqvist C, et al. Prevention of asthma during the first 5 years of life: a randomized controlled trial. J Allergy Clin Immunol 2006;118:53-61.
8. Perkin MR, Strachan DP. Which aspects of the farming lifestyle explain the inverse association with childhood allergy? J Allergy Clin Immunol 2006;117:1374-81.
9. Campo P, Kalra HK, Levin L, Reponen T, Olds R, Lummus ZL, et al. Influence of dog ownership and high endotoxin on wheezing and atopy during infancy. J Allergy Clin Immunol 2006;118:1271-8.
10. Ball TM, Anderson D, Minto J, Halonen M. Cortisol circadian rhythms and stress responses in infants at risk of allergic diseases. J Allergy Clin Immunol 2006;117:306-11.
11. Strunk RC, Weiss ST, Yates KP, Tonascia J, Zeiger RS, Szefler SJ, for the CAMP Research Group. Mild to moderate asthma affects lung growth in children and adolescents. J Allergy Clin Immunol 2006;118:1040-7.
12. Shapiro GG. Among young children who wheeze, which children will have persistent asthma? J Allergy Clin Immunol 2006;118:562-4.
13. Chen E, Hanson MD, Paterson LQ, Griffin MJ, Walker HA, Miller GE. Socioeconomic status and inflammatory processes in childhood asthma: the role of psychological stress. J Allergy Clin Immunol 2006;117:1014-20.
14. Ercan H, Birben E, Dizdar EA, Keskin O, Karaaslan C, Soyer OU, et al. Oxidative stress and genetic and epidemiologic determinants of oxidant injury in childhood asthma. J Allergy Clin Immunol 2006;118:1097-104.
15. Zeidler MR, Golden JG, Kleerup EC, Kim HJ, Truong DA, Gjertson DW, et al. Small airways response to naturalistic cat allergen exposure in subjects with asthma. J Allergy Clin Immunol 2006;118:1075-81.
16. Profita M, LaGrutta S, Carpagnano E, Riccobono L, DiGiorgi R, Bonanno A, et al. Noninvasive methods for the detection of upper and lower airway inflammation in atopic children. J Allergy Clin Immunol 2006;118:1068-74.
17. McCoy K, Shade D, Irvin CG, Mastronarde JG, Hanania NA, Castro M, et al. Predicting episodes of poor asthma control in treated asthmatics. J Allergy Clin Immunol 2006;118:1226-33.
18. Johnston NW, Johnston SL, Norman GR, Dai J, Sears MR. The September epidemic of asthma hospitalization: school children as disease vectors. J Allergy Clin Immunol 2006;117:557-62.
19. Bateman ED. Severity and control of severe asthma. J Allergy Clin Immunol 2006;117:519-21.
20. Wenzel S, Szefler SJ. Managing severe asthma. J Allergy Clin Immunol 2006;117:508-11.
21. de Marco R, Marcon A, Jarvis D, Accordini S, Almar E, Bugiani M, et al. Prognostic factors of asthma severity: a 9-year international prospective cohort study. J Allergy Clin Immunol 2006;117:1249-56.
22. Ueda T, Niimi A, Matsumoto H, Takemura M, Hirai T, Yamaguchi M, et al. Role of small airways in asthma: investigation using high-resolution computer tomography. J Allergy Clin Immunol 2006;118:1019-25.
23. Lemiere C, Ernst P, Olivenstein R, Yamauchi Y, Govindaraju K, Ludwig MS, et al. Airway inflammation assessed by invasive and noninvasive means in severe asthma: eosinophilic and noneosinophilic phenotypes. J Allergy Clin Immunol 2006;118:1033-9.
24. Fitzpatrick AM, Gaston BM, Erzurum SC, Teague WG. Features of severe asthma in school age children: atopy and increased exhaled nitric oxide. J Allergy Clin Immunol 2006;118:1218-25.
25. Stoloff SW, Boushey HA. Severity, control, and responsiveness in asthma. J Allergy Clin Immunol 2006;117:544-8.
26. Schatz M, Zeiger RS, Vollmer WM, Mosen D, Cook EF. Determinants of future long-term asthma control. J Allergy Clin Immunol 2006;118:1048-53.

27. Baatenburg de Jong A, Brouwer AFJ, Roorda RJ, Brand PLP. Normal lung function in children with mild to moderate persistent asthma well controlled by inhaled corticosteroids. J Allergy Clin Immunol 2006; 118:280-2.
28. Covar RA, Colvin R, Shapiro G, Strunk R. Safety of methacholine challenges in a multicenter pediatric asthma study. J Allergy Clin Immunol 2006;117:709-11.
29. Taylor DR. Nitric oxide as a clinical guide for asthma management. J Allergy Clin Immunol 2006;117:259-62.
30. Dinakar C, Craff M, Laskowski DL. Infants and toddlers without asthma with eczema have elevated exhaled nitric oxide levels. J Allergy Clin Immunol 2006;117:212-3.
31. Carroro S, Pasquale MF, Da Fre M, Rusconi F, Bonetto G, Zanconato S, et al. Swimming pool attendance and exhaled nitric oxide in children. J Allergy Clin Immunol 2006;118:958-60.
32. Vahlkvist S, Sinding M, Skamstrup K, Bisgaard H. Daily home measurements of exhaled nitric oxide in asthmatic children during natural birch pollen exposure. J Allergy Clin Immunol 2006;117:1272-6.
33. Tantisira KG, Fuhlbrigge AL, Tonascia J, Zeiger RS, Strunk RC, Szefler SJ, et al. Bronchodilation and bronchoconstriction: predictors of future lung function in childhood asthma. J Allergy Clin Immunol 2006;117: 1264-71.
34. Szefler SJ, Phillips BR, Martinez FD, Chinchilli VM, Lemanske RF Jr, Strunk RC, et al. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. J Allergy Clin Immunol 2005;115:233-42.
35. Zeiger RS, Szefler SJ, Phillips BR, Schatz M, Martinez FD, Chinchilli VM, et al. Response profiles to fluticasone and montelukast in mild-to-moderate persistent childhood asthma. J Allergy Clin Immunol 2006;117:45-52.
36. Montuschi P, Mondino C, Koch P, Barnes PJ, Ciabattoni G. Effects of a leukotriene receptor antagonist on exhaled leukotriene E_4 and prostanoids in children with asthma. J Allergy Clin Immunol 2006;118:347-53.
37. Szefler SJ, Whelan GJ, Leung DYM. Black box warning: wake-up call or over-reaction? J Allergy Clin Immunology 2006;117:26-9.
38. Kumar R, Wang B, Wand X, Chen C, Yang J, Fu L, et al. Bronchodilator responses in Chinese children from asthma index families and the general population. J Allergy Clin Immunol 2006;117:1257-63.
39. Roberts G, Hurley C, Turcanu V, Lack G. Grass pollen immunotherapy as an effective therapy for childhood seasonal allergic asthma. J Allergy Clin Immunol 2006;117:263-8.