Advances in the care of adults with asthma and allergy in 2007

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In 2007 the National Asthma Education and Prevention Program published the Expert Panel Report 3, updating its 1997 and 2002 guidelines for the diagnosis and management of asthma with new emphasis on assessment and attainment of control. This review focuses on the Journal articles published in 2007 pertaining to risk and impairment in adult asthma and interventions to improve its control. (J Allergy Clin Immunol 2008;121:839-44.)

Key words: Asthma, adults, atopy, health disparities, therapeutics, adherence, inhaled corticosteroids, omalizumab, pregnancy, menopause

As in previous years,1-4 this summary highlights reports published in the Journal during 2007 on clinical advances in adult asthma and allergy, whereas the companion review provides the pediatric perspective. Especially relevant to both was the release of the Expert Panel Report 3 (EPR-3) of the National Asthma Education and Prevention Program5,6 with its new emphasis on maintaining asthma control through evaluating impairment and risk. Much of the clinical research published in last year’s Journal involved these areas and emerging therapeutics, as outlined. Key advances are summarized in Table I.

RISK FACTORS FOR ASTHMA OR RESPIRATORY SYMPTOMS

Atopy

Several studies produced evidence that further implicates atopy as a risk factor for asthma. Burgess et al7 report an association between allergic rhinitis and subsequent development of asthma in an Australian birth cohort. The presence of allergic rhinitis before age 7 years increased the risk of asthma 7-fold before adolescence, 4-fold at age 13 years, and 2-fold at 44 years; the association diminished thereafter. The strength of this study was its longitudinal nature and duration, whereas its major limitation was the use of self-reported or caretaker-reported allergic rhinitis and asthma as surrogates for physician-diagnosed disease. The investigators speculate that aggressive treatment of allergic rhinitis in early life might favorably alter subsequent asthma development and severity. The association of allergic rhinitis with asthma was also studied by Arbes et al8 by using data from the National Health and Nutrition Examination Survey, a US population-based survey that included skin prick tests with 10 allergens (cat, Alternaria, white oak, short ragweed, dust mite, Russian thistle, Bermuda grass, perennial rye, German cockroach, and peanut) in subjects 6 to 59 years old. Researchers found 56% of asthma cases in these relatively young individuals attributable to atopy with the percentage of atopic-associated asthma higher in male subjects, subjects with the highest education (perhaps because allergic rhinitis is more commonly recognized within this group9), and urban-dwellers. Sensitivity to cat, Alternaria, or white oak was independently and positively associated with asthma. In addition, Naqvi et al10 have found that higher IgE levels predict development and severity. The association of allergic rhinitis with asthma in early life might favorably alter subsequent asthma development and severity. The association of allergic rhinitis with asthma was also studied by Arbes et al10 by using data from the National Health and Nutrition Examination Survey, a US population-based survey that included skin prick tests with 10 allergens (cat, Alternaria, white oak, short ragweed, dust mite, Russian thistle, Bermuda grass, perennial rye, German cockroach, and peanut) in subjects 6 to 59 years old. Researchers found 56% of asthma cases in these relatively young individuals attributable to atopy with the percentage of atopic-associated asthma higher in male subjects, subjects with the highest education (perhaps because allergic rhinitis is more commonly recognized within this group9), and urban-dwellers. Sensitivity to cat, Alternaria, or white oak was independently and positively associated with asthma. In addition, Naqvi et al10 have found that higher IgE levels predict development and severity.

Menopause

Real et al12 found that lung function diminishes over the transition to menopause. In 1274 European women age 45 to 56 years taking no exogenous sex hormones, FEV<sub>1</sub> (−120 mL; 95% CI, −177 to −63 mL) and forced vital capacity values were significantly lower and respiratory symptoms higher among women who failed to menstruate during the previous 6 months, independent of smoking history. The correlation was even stronger among women with body mass index <23 kg/m<sup>2</sup>. Although the authors postulated hormonal changes were implicated, the cross-sectional design of this study does not allow causal inferences.

Environment

Dust mites and endotoxin. Rowe et al13 investigated whether the timing of exposure to allergen affects sensitization. Their study, which involved a birth cohort of 200 high-risk Australian
infants, found only transient dust mite IgE production in the first months of life, in contrast with elevated levels of mite-specific IgE by 2 years of age, suggesting dust mite contact in the postnasal period is more allergenic than prenatal exposure. Exposure to high levels of dust mite during infancy increases the risk of asthma at age 7 years and late-onset wheeze, according to Cele- don et al,14 who studied a birth cohort of children with atopic par-
ents. Paradoxically, exposure to endotoxin appeared to increase both the risk of atopy in infancy and of wheezing between 1 and 7 years of age, which contradicts the hygiene hypothesis.

Other indoor allergens and pollutants. Analyses of indoor air quality by Kattan et al15 using data from the National Cooperative Inner-City Asthma Study reveal high concentrations of NO2, a byproduct of gas appliances, and environmental tobacco smoke. In this setting, exposure to NO2, but not environmental tobacco smoke, increases the risk of asthma symptoms, especially in colder months, suggesting that control of NO2 exposure might reduce asthma morbidity. The study data also indicate higher morbidity from asthma among children with cockroach sensitivity and exposure. However, a related study of adults from East Har-
lem by Wisnivesky et al16 found no association of sensitization to indoor allergens including cockroach, dust mite, cat, mold, or mouse with asthma morbidity. The investigators conclude that identifying and modifying other risk factors will be necessary to improve asthma morbidity among urban adults.

Social environment
Mosnaim et al12 show that caregiver language preference can determine whether a child with symptoms has diagnosed asthma. The investigators distributed surveys for caregivers to 14,177 His-
panic Chicago schoolchildren age 6 to 12 years. Caregivers of children with diagnosed asthma were more likely to have com-
pleted the survey in English, whereas children of caregivers who completed the survey in Spanish were more likely to have un-
diagnosed—and presumably untreated—asthma symptoms. However, the study does not distinguish whether language itself, or other collinear acculturation, social, or economic barriers that were not considered, account for this outcome.

Gene-environment interactions
To understand better the interaction of environment and family history (ie, physician-reported asthma in a first-degree relative) on asthma morbidity, Kuiper et al18 have examined the potential contribution of environmental factors, such as exposure to secondhand smoke, mite, cat, dog, and breast milk. They prospectively followed 221 Dutch infants with a family history of asthma and 308 infants without such a history during the first 2 years of life. Exposure to parental smoking and increased levels of Der p 1 in dust samples from the infants’ homes magnified the family history effect, whereas breast-feeding reduced it.

NEW INSIGHTS INTO MANAGEMENT AND COMMUNICATION WITH PATIENTS

Adherence
Rand et al19 compared adherence to an inhaled corticosteroid (ICS) versus montelukast tablets and discovered, not surprisingly, that participants with asthma were more likely to use the pill than the inhailer. An unexpected finding was that even when ICS (fluticasone) use was suboptimal, a dose-response relationship could be observed with regard to the amount of ICS used and both asthma rescue-free days and FEV1 percent predicted (FEV1,pp) when baseline FEV1,pp was <86%. The dose-response relation-
ship also was observed in the 36-week open-label period, suggest-
ing that fluticasone is more effective than montelukast, and that more ICS is prescribed than may be needed or used. Williams et al20 explored the role of unconventional socioen-
vironmental barriers to adherence by tracking the ICS prescrip-
tion-writing data and pharmacy claims. Among African American patients, residential crime rates were negatively associ-
ed with adherence, independent of other socioeconomic factors. Thus, neighborhood characteristics, which are not traditionally included in medical studies, may be important determinants of health.21 Likewise, steps to improve the quality of neighborhood life should lead to better self-management of chronic illness such as asthma and outcomes.

Baptist et al22 conducted a case-control chart-review study of hospital admissions for asthma to compare patients who leave hospitals against medical advice (AMA) with those who had a medically approved discharge. AMA patients were younger and were more likely to be male, be poor, lack commercial medical insurance or receive Medicaid, or have had an intensive care unit admission for asthma. They were also more likely to have a relapse. For patients at risk for AMA discharge, successful pro-
vider-patient communication to determine and address the precip-

tants is important.

Special situations: Pregnancy
Enriquez et al23 studied 140,299 pregnancies from the Tennes-
see Medicaid program, of which 6.5% of the women had asthma. Of these, 23% had an asthma hospitalization or emergency department visit, with these adverse events occurring twice as frequently in black women. Maternal asthma was associated with low-birthweight infants and, in a dose-dependent manner, with hypertensive disorders of pregnancy, membrane-related

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<th>TABLE I. Key advances in the care of adults with asthma and allergy in 2007</th>
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<td>1. EPR-3 recommends careful assessment of asthma control.</td>
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<td>2. Atopic children are at increased risk for developing asthma.</td>
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<td>3. Lung function diminishes over the time of transition to menopause.</td>
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<td>4. NO2, produced by gas stoves, is likely an important indoor pollutant associated with asthma symptoms.</td>
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<td>5. Sensitization to cockroach, dust mite, cat, mold, and mouse was not associated with asthma morbidity in urban adults.</td>
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<td>6. The language preference of parents influences whether a child with symptoms is diagnosed with asthma.</td>
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<td>7. Although patients are less likely to take all of their prescribed ICSs compared with montelukast, patients still benefited more from ICSs.</td>
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<td>8. Hospitalized patients discharged AMA after an admission for asthma are more likely to have a relapse.</td>
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<td>9. Except for patients with the most severe asthma, omalizumab is not cost-effective.</td>
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<td>10. Women prescribed ICSs during pregnancy may not fill more than 1 prescription.</td>
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disorders, preterm labor, antepartum hemorrhage, and cesarean section. Of women who used ICS, only 28% filled more than 1 prescription.

Interventions to improve management

The EPR-3 emphasizes a multifaceted approach that includes expanding patient education to all points of contact, such as the pharmacy and schools. Basheti et al.24 and other pharmacists showed that taking 2.5 minutes to check inhaler technique at the pharmacy improved drug delivery and quality of life, although technique declined over a period of 3 to 6 months. A limitation was the small pharmacist sample size: 120 were contacted, but only 31 consented to participate, and 27 completed the study. It is possible that only pharmacists who were most enthusiastic about the intervention participated. Jones et al.25 enrolled 2185 children age 3 to 18 years to receive structured asthma management delivered from mobile clinics providing ongoing care at their schools. Although the investigators reported success in achieving control, maintenance was highly variable.

The EPR-3 also encourages clinician and health system support of the patient-clinician partnership. Borrelli et al.26 describe a promising patient-centered counseling approach to behavioral change called Motivational Interviewing that may be integrated into patient encounters to enhance motivation for behavioral change leading to improved self-management. Research is underway testing the efficacy of such an approach in asthma.

EPR-3 AND ASTHMA CONTROL

Poor asthma control is associated with higher morbidity and lower disease-specific quality of life.6,27 EPR-3 advises assessment of baseline asthma severity when initiating therapy, then monitoring asthma control while adjusting stepwise therapy to prevent functional impairment and minimize the risk of an exacerbation (Fig 1). EPR-3 has proposed using validated questionnaires to measure impairment.6,27 Schatz et al.28 demonstrated the reliability and validity of the Asthma Control Test administered by interactive telephone outreach and speech recognition technology. Liu et al.29 reported the development of the Childhood Asthma Symptom Scale, an 8-item tool previously validated for a large heterogeneous population of English- and Spanish-speaking children.40

Nevertheless, a study by Yoo et al.31 illustrates the limitations of self-reported outcomes, including questionnaires, for documenting asthma. Concordance of caretaker report with review of the medical record children followed at the Mayo Clinic found consistency of 89% for report of no asthma, but only 49% agreement for the presence of asthma. Caretakers tended to underreport the asthma status of their children.

Although tools that measure control of asthma are important for research and may be helpful in some clinical settings, a note of caution is warranted. They must be appropriate for the language and literacy of patients or caregivers, and they must address patients’ chief complaints. Even a validated tool for data collection could be perceived by patients as a substitute for direct involvement by the physician.32

THERAPEUTICS

Omalizumab

The potential steroid-sparing benefit of omalizumab, the first biologic antiasthma agent approved by the US Food and Drug Administration, has been tempered by its cost. The economic analysis from a societal viewpoint according to the US Panel on Cost-Effectiveness in Health and Medicine by Wu et al.33 found that except for patients with the most severe asthma, omalizumab is not cost-effective. Treatment with omalizumab costs more than $800,000 per quality-adjusted life-year gained, far in excess of the $50,000 per quality-adjusted life-year that is considered cost-effective in the United States. Krishnan and Gould34 point out that although EPR-3 now includes omalizumab as a treatment option (Fig 1), it is not very effective and does not represent a good value for the health care dollar. In addition, there are now concerns about its safety on the basis of postmarketing reports of anaphylaxis after administration.35,36

Controller and other medications

Menzies et al.37 also searching for a nonsteroidal anti-inflammatory for asthma, evaluated simvastatin on the basis of its anti-inflammatory and immune-modulating properties in other settings. Their month-long double-blind randomized crossover trial of 16 Scottish adults found no evidence of anti-inflammatory effect on exhaled nitric oxide levels or other parameters.38 The sample size was small, and subjects with more severe asthma dropped out during the run-in period when anti-inflammatory medications were discontinued before randomization.

Lung function declines more rapidly in patients with asthma than normal individuals over time. The study by de Marco et al.39 showed that ICS attenuates this decline in FEV1 in a dose-dependent manner. This effect was greatest in subjects with high serum IgE who used an ICS for at least 4 years, suggesting particular benefit in allergic asthma.

Chipps et al.40 have conducted an analysis of data from The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens.41 a large cohort of difficult-to-treat children with asthma (≥2 urgent care visits or ≥2 prednisone bursts or prescribed more than 3 controller medications or using high-dose ICS or ≥5 mg prednisone/d in the past year), a study funded by the codevelopers of omalizumab. Investigators found that the subjects 6 to 17 years old who had the highest health care utilization and use were shorter and weighed more than their peers.40 Whether these deficits resulted from the disease, its treatment, or other factors is not clear from this cross-sectional analysis.

The safety of medications containing long-acting β-agonists continues to receive attention.42-44 Chinchilli35 reviewed a meta-analysis of the safety of salmeterol43 and discussed epidemiologic principles governing systematic reviews. One limitation of this meta-analysis is that findings reflect the results of 1 large study.42

The authors, by excluding unpublished studies such as abstracts of scientific meetings or data from pharmaceutical firms, may have omitted negative studies. By including only randomized placebo-controlled double-blind studies that compared salmeterol to placebo, only 19 of 5000 originally identified studies were included. Including other studies could have provided more data on adverse events of patients exposed to salmeterol.

Camargo et al.46 describe significant regional differences in the prescribing of EpiPens, considered to be surrogate for anaphylaxis prevalence. Noting that New England has the highest
frequency of EpiPen prescribing, whereas Hawaii the lowest, they theorize that sunlight-dependent vitamin D status could be an etiologic factor in anaphylaxis. Unanswered questions include, ‘‘Is the rate of epinephrine-prescribing truly reflective of the prevalence of anaphylaxis?,’’ ‘‘To what extent do other factors, especially social and economic, explain regional prescribing practices?’’ or ‘‘Would this regional difference persist if other brands of injectible epinephrine were included?’’ The data are provided by Dey (Napa, Calif), the manufacturer of EpiPen. It is well to remember that a statistical association, for example between vitamin D status and anaphylaxis occurrence, does not imply causality, as is noted by Taback and Simons in their editorial.

Kemeny et al remind us to be ever mindful of the placebo effect. In their double-blind crossover study of 55 adults with mild asthma, bronchial hyperreactivity to methacholine was significantly reduced in 18% of subjects by placebo bronchodilator.

Biomarkers for assessing success of therapy

Biomarkers continue to generate interest as tools for assessing asthma severity and control, although EPR-3 does not recommend them for clinical application, citing an insufficient current research consensus. Several novel biomarkers were described in early investigations in 2007. The difference between inspiratory and expiratory attenuation from high-resolution computed tomography of the chest, the air trapping index, was studied as a potential biomarker of active asthma, because it appears to reflect involvement of the small airways. A 3-month trial of ICSs

resulted in decreased airtrapping. Dragoni et al. propose that volatile organic compounds in exhaled breath are quantitatively different in healthy individuals and individuals with asthma and could be used for diagnosis and outcomes measurement. However, volatile organic compound concentrations failed to distinguish mild from severe asthma.

Bourdin et al. detect reticular basement membrane thickening compatible with airway remodeling in endobronchial biopsy specimens from individuals with severe asthma. When compared with bronchial specimens from subjects with mild asthma or chronic obstructive pulmonary disease, the biopsies from individuals with severe asthma showed greater basement membrane thickness. The obvious limitation of this approach for clinical assessment is its invasiveness. De Lange et al. used hyperpolarized helium-3 magnetic resonance to image airspaces and focal areas of airflow obstruction over time and with methacholine challenge in 10 individuals with asthma. Both recurrent and persistent regional ventilation defects were observed, suggesting the existence of regions of relatively fixed obstruction.

**FUTURE RESEARCH**

Simons reports that 65% of a random sample of abstracts presented at the 2000 American Academy of Allergy, Asthma & Immunology Annual Meeting were subsequently published as full-text articles in peer-reviewed journals, a higher ratio than is reported by many specialties and other subspecialties. She recommends continued monitoring of abstract performance, because determining the reasons for failure to publish may serve as opportunities for mentoring young investigators. Finally, in recounting the remarkable accomplishments of the Asthma and Allergic Disease Centers funded by the National Institute of Allergy and Infectious Diseases, Austen reminds us of the importance of research to the future of our field and of engaging and supporting the next generation.

**Conclusion**

This year’s research achievements and the EPR-3 update focus attention on asthma control. This requires attention to allergic and nonallergic factors, special life events including pregnancy and menopause, the indoor environment, social issues including language discordance with clinicians, and reasons for poor adherence. Further study of these factors will be the substrate for the research of the next generation.

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**REFERENCES**