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Advances in Adult Asthma Diagnosis & Treatment and HCEDQ in 2008

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Abstract

In 2008 the Journal reported new findings in management of asthma. Dosing schedules of inhaled steroids have been modified and individualized. New more costly propellants are replacing ozone-depleting chlorofluorocarbons. An association of asthma with pneumococcal disease has been observed. Smoking bans in public places are eliminating second-hand smoke and reducing asthma-related ED visits among adults. In contrast to these advances, however, disparity in asthma morbidity persists: blacks compared with whites have a 4-fold greater risk of an asthma-related ED visit.

Keywords

asthma; adults; genetics; inhaled corticosteroids; exhaled breath condensate; nitric oxide; chlorofluorocarbon; short-acting beta-agonists; health literacy

Introduction

Past *Advances* have considered new insights regarding management, therapeutics, and the environment.^{1–6} This year is no exception as we describe research in adults with asthma presented in the Journal that is especially relevant for clinicians, along with pertinent studies from other journals.

Management

Biomarkers

Biomarkers are quantifiable indicators of a biological state, such as current control of asthma. Such markers if validated could support or guide management decisions. The fractional excretion of nitric oxide (FE_{NO}) and the pH of exhaled breath condensate (EBC) are two readily measured, although not necessarily inexpensive, noninvasive markers that have received attention. FE_{NO} increases with eosinophilic airway inflammation and during asthma exacerbations. It is reduced by anti-inflammatory therapy.⁷ A low or acidic pH of EBC has been associated with asthma exacerbations.⁸ This low pH is thought to promote airway conversion of nitrite to nitric oxide and thus result in increased FE_{NO}.^{9–11}

FE_{NO} and EBC were compared with other biomarkers relevant to asthma: skin test results and methacholine challenge. Craig et al¹² used data from several studies performed by the Asthma Clinical Research Network, a multi-center network funded by the National Heart

Lung & Blood Institute of the National Institutes of Health. All subjects, mean age 32 and age range 12 to 65 years, had asthma defined by a positive methacholine challenge or 12% improvement after bronchodilator. All subjects underwent skin testing with a panel of allergens that included mite (*Dermatophagoides pteronyssinus*, *D. farinae*); molds (*Alternaria*, *Aspergillus*, *Penicillium* species); dog; cat; pollens (ragweed, grass mix, tree mix, weed mix); and cockroach. The researchers found 95% of subjects had at least 1 positive skin test and the number of positive skin tests correlated with higher IgE and FE_{NO} levels and lower PC₂₀.

However, Szeffler et al¹³ conducted a randomized, double-blind, parallel group multi-center trial comparing FE_{NO} as a biomarker of airway inflammation to guide management decisions compared with conventional clinical assessment using standard guidelines based on the National Asthma Education and Prevention Program Expert Panel Report (EPR).¹⁴ Conventional management resulted in good control; using FE_{NO} to guide management resulted in higher inhaled corticosteroid (ICS) doses without a clinically significant improvement in asthma control.

These findings are supported by Levesque and Hauswirth and colleagues^{9, 15} who studied EBC pH and FE_{NO} levels in healthy African Americans. Because asthma is prevalent in African Americans and associated with significant morbidity, the validity of these measures for this population should be determined.¹⁶ Although in other groups, variables such as serum total IgE, sex, and URI symptoms contributed to the variability of FE_{NO}, in this African American cohort, they contributed less than 50% of the variability. These researchers did not find the expected correlation between EBC pH or nitrite with FE_{NO}, leading the authors to conclude that EBC pH and nitrite are not significant determinants of FE_{NO} in healthy subjects. Together with the findings of Szeffler et al, these results suggest that these biomarkers may have limited utility for assessing clinical asthma control.

Another potential biomarker discussed in the Journal in the past year is malondialdehyde in EBC as a noninvasive measure of exposure to air pollution. Malondialdehyde is a reactive aldehyde that has been evaluated as a biomarker of pulmonary oxidative stress in occupational settings. Romieu et al¹⁷ found that malondialdehyde levels were positively associated with ozone and particulates less than 2.5 mcg/m³, inversely with FVC and FEV₁, and positively with IL8 levels from nasal lavage. Because EBC malondialdehyde was related both to air pollution exposure and changes in lung function as well as inflammatory markers like IL8, the investigators hypothesized that EBC malondialdehyde¹⁷ may be an important biomarker for the effect of exposure on asthma.

Genetic polymorphisms such as *ADAM33*,¹⁸ *FCER19*, *CRHR1*,²⁰ and *ARG121* are biomarkers that have received attention for association with asthma susceptibility, its control, or response to therapy, although subsequent studies are not always able to reproduce the original finding.^{22, 23} This past year in the Journal Tavendale et al²⁴ reported a genome wide association study of 60 patients from Scotland in which increased susceptibility and poor control of asthma were associated with a polymorphism at the *ORMDL3* locus. This gene belongs to a family of genes encoding transmembrane proteins of the endoplasmic reticulum, but a biological mechanism explaining this association has not been identified. Whether or not future studies will support this result, it is clear that asthma is a complex disease with genetic and environmental influences and their relative importance will require much study.

Practice

CFC-free inhalers—Chlorofluorocarbon (CFC) is being eliminated as propellant in short-acting β_2 -agonists (SABAs) as mandated by the United Nations Environmental Programme's

Montreal Protocol to reduce depletion of the ozone layer.²⁵ 26 The plume, taste, care and cleaning of the new inhalers, mostly containing hydrofluoroalkane (HFA) propellant is different from CFC-containing inhalers.²⁵ Most concerning is that because there will now be no generic SABA. The cost of HFA SABAs is significantly higher and will most affect those without health insurance or medication coverage.²⁷

Communicating with patients—Barely more than half the US adult population has adequate reading and quantitative skills.²⁸ The average adult reads between the 7th and 9th grade levels.²⁹ Low literacy, which is found in all patient groups is frequently unrecognized³⁰⁻³² and can contribute to ineffective communication.³⁰⁻³³ Limited reading comprehension and numerical skills have been shown to compromise communication in asthma.³⁴⁻³⁶ Smith and Frew evaluated the reading levels of AAAAI Tips to Remember, educational pamphlets for patients, and found readability scores requiring completion of high school and frequently some college education.²⁹ This observation reminds us of the importance of providing materials that are understandable for all patients and of confirming comprehension of recommendations. Since low literacy is widespread and screening may threaten vulnerable patients, we do not favor screening for low literacy until its benefit is proven; rather all patients likely will benefit from the simplest explanation.³⁷

For research and possibly improving patient care directly, valid and efficient measurement of patients' asthma symptoms and quality of life is necessary. Several brief questionnaires have been validated,³⁸⁻⁴¹ but not necessarily in diverse urban populations which have the highest asthma morbidity. Patino et al⁴² validated such an instrument, the Asthma Control and Communication Instrument, written at a 5th grade reading level, for measuring clinically important disease status in blacks and whites. It is designed to be taken in the waiting room and then handed to the doctor at the beginning of the interview to prompt communication. Whether its use improves asthma outcomes or patient or provider satisfaction requires further study.

To measure health-related quality of life, Juniper et al⁴³ compared results from delivery by interactive voice-response (IVR) with the validated paper version of two questionnaires, the Standardized Asthma Quality of Life Questionnaire⁴⁴ and the Mini Rhinoconjunctivitis Quality of Life Questionnaire.⁴⁵ The asthma questionnaire was given in Germany and Italy and the rhinoconjunctivitis questionnaire to Kaiser Permanente patients in San Diego. A few hours separated the delivery of the written from IVR format and only patients reporting unchanged symptoms were included. Neither questionnaire achieved the preset standard of concordance between formats. Authors concluded it is important to test the validity of IVR questionnaires and to use only one method of data collection in research.

Finally, while patients' perceptions are extremely important for patient care, it is well to remember, as illustrated by Marsden et al⁴⁶ that objective measures and self-report of symptoms like cough may differ; measuring both is important.

Special populations

Pregnancy—Uncontrolled asthma during pregnancy has been thought to be associated with congenital malformations. Blais et al⁴⁷ linked data from 3 large Canadian data bases to form a cohort of 4344 pregnancies in order to better determine the risk of congenital malformations in women with an asthma exacerbation during the first trimester. Among 321 women with such an exacerbation, 41 (13%), compared with 9% (357 out of 4023) who did not have an exacerbation delivered infants with congenital malformations, for an increased odds ratio of 1.48 (95% CI, 1.04-2.09). There was no increase in major malformations (e.g. life-threatening, major cosmetic, or requiring hospitalization in the first year of life) associated with a first trimester exacerbation of asthma.

Obesity—Obesity and asthma have been statistically linked mostly by cross-sectional studies. Mosen et al⁴⁸ performed a large cross-sectional study of Kaiser Permanente-enrolled asthmatic adults. They found after controlling for known confounders that high BMI was associated with lower quality of life, poorer asthma control, and asthma-related hospitalizations. It would not be unexpected that obese individuals would report more symptoms, e.g. lower quality of life, more shortness of breath, and it is not surprising clinicians would respond to these symptoms, but as the authors note, a cross-sectional study cannot address mechanistic questions. Prospective studies that account for variables in the social and physical environment are needed to clarify the pathophysiology linking asthma and obesity.⁴⁹⁻⁵¹

Urban underrepresented minority groups—National data reveal that rates of asthma-related emergency department visits over that past 10 years have been stable or declining.^{52, 53} However, rates remain high in children less than 10 years. Most disturbing is the disparity between blacks and whites of all ages. In 2005, the most recent year in this report, the average risk of an asthma-related ED visit was 4-fold greater for black compared with white persons. While the rate of asthma-related ED use by white individuals decreased between 1998 and 2005, since 2000 it has actually increased for black patients. Miller et al⁵⁴ used factor analysis, a statistical method of summarizing relationships among a large set of variables,⁵⁵ to explore factors determining future asthma morbidity in children who had an ED visit for asthma. Although the analysis used a cohort of children, it may be applicable in adults. The investigators found four latent factors: (1) current symptom severity, (2) quality of care (e.g., using an ICS, evaluation by an asthma specialist, having peak flow meter and/or action plan, or received asthma education), (3) previous severe disease, and (4) sociodemographic (e.g. having a usual source of urgent care and a primary care provider, race, parental education level, ability to fill prescriptions, a follow-up appointment within 2 weeks of the index ED visit). The sociodemographic latent factor was directly related to the quality of care factor and inversely to current symptom severity. It was reassuring that investigators found the quality of care was better for those with current severe symptoms and previous severe disease, but disturbing that it was worse for those with adverse sociodemographic rating, i.e., more likely to be poor.

In another study, O'Connor et al⁵⁶ found urban children from low-income neighborhoods are exposed to higher air pollutant concentrations which is associated with more respiratory symptoms and lower lung function. Together these studies demonstrate that eliminating health disparity will require addressing complex barriers not only within health care delivery systems but also determining and addressing larger economic and social barriers that will require public policy change.^{33, 57}

Therapeutics

Inhaled corticosteroids

ICSs are often prescribed in combination with a long-acting beta-agonist. There is evidence that chronic stimulation use of beta-agonists can result in increased bronchoconstriction or lack of response to therapy.⁵⁸ Cooper et al,⁵⁹ using human precision-cut lung slices demonstrated attenuated relaxation with repeated stimulation with albuterol. However, pretreatment of the lung slices with dexamethasone prevented albuterol-induced β_2 -agonist receptor desensitization. The study suggests that desensitization with prolonged treatment with albuterol could be reversed or prevented with dexamethasone. Their findings support the benefit of combining steroid and beta-agonist over individual therapy, but also raise the question of whether ICS alone under various settings may be as efficacious as combined therapy.

Zeiger et al⁶⁰ conducted an economic analysis of data from a retrospective cohort study among members of Kaiser Permanente Southern California health plan of direct medical costs and asthma-related utilizations. They found a single controller ICS was associated with the lowest total and asthma-drug costs compared with a single controller alternative (leukotriene antagonist) or combination therapy. Limitations of the study include the homogeneous relatively affluent patient population, and possible confounding by severity. These studies underline the importance of ICSs and support the most recent EPR recommendations.¹⁴

Another timely question is whether ICS regimens dosing may be modified to permit adjustable or as-needed dosing for some patients. Boushey et al⁶¹ compared an as-needed with a regular schedule in patients with mild asthma and found the two regimens did not differ in morning peak flow, the primary outcome, or in rates of asthma exacerbations. Busse et al⁶² compared a fixed-dose ICS schedule to an adjustable schedule in patients with moderate to severe asthma, using an algorithm derived from the EPR guidelines. The adjustments were limited (two puffs twice daily, four puffs twice daily or 2 puffs once daily) and use of medication was recorded by diary. After 6 months, there was no difference between groups in asthma exacerbations, the primary outcome, asthma symptoms, or lung function.

Pneumococcal vaccine

Juhn et al⁶³ report an increased risk of serious pneumococcal disease (e.g., sepsis, bacteremia, meningitis, pneumonia, osteomyelitis) in individuals with asthma. Using a retrospective case-control design, these investigators identified residents of Rochester, Minnesota who developed serious pneumococcal disease and determined whether or not they had asthma. This increased risk persisted despite controlling for smoking exposure or high-risk conditions for invasive pneumococcal disease. These findings agree with the earlier reported positive association of asthma with invasive pneumococcal disease in Tennessee Medicaid recipients.⁶⁴ While a statistical association is not sufficient for proving that asthma increases the risk of serious pneumococcal infection or demonstrating the mechanism, this finding supports such a hypothesis.⁶⁵ Pneumococcal vaccination is currently not recommended for adults with asthma. These publications suggest that broadening the recommendations to include persons with asthma should be considered.⁶⁵

Aspirin

Although aspirin worsens asthma in the small percentage of persons with aspirin-exacerbated respiratory disease (AERD), new research suggests that in others it may have a beneficial effect. In two large cohorts of adults who did not have AERD, researchers found aspirin *reduced* the risk of developing asthma.⁶⁶ In the Physicians' Health Study, more than 22,000 male physicians between 40 and 84 years were randomized to 325 mg aspirin or placebo on alternate days and followed for 4.9 years. A 22% reduction in incidence of self-reported asthma was observed in the group receiving aspirin.⁶⁶ An earlier analysis of data from the Nurses' Health Study by the same authors had similar findings: those women who used aspirin frequently were less likely to have a new diagnosis of asthma.⁶⁷ It is speculated that the reduced incidence of asthma results from aspirin's anti-inflammatory effects. Understanding the mechanism behind this observation will be important for preventing asthma in high-risk individuals.

Menzies et al⁶⁸ considered whether aspirin could have an anti-inflammatory effect by decreasing thromboxane B₂ levels or increasing lipoxin levels which are thought to inhibit the inflammatory cascade mediated by leukotrienes. They conducted a double-blind placebo-controlled cross-over study of 15 adults with mild to moderate asthma who did not

have aspirin hypersensitivity, randomizing subjects to crossover treatment with 75 mg of aspirin or placebo daily for 3 weeks. Although serum thromboxane B2 levels decreased, there was no observed increase in serum lipoxin levels, no beneficial or deleterious effects on airway inflammation, and no measurable changes in histamine PC₂₀, nitric oxide, spirometry, or other parameters.⁶⁸ The study was limited in that the treatment period was only 3 weeks, subjects had relatively mild to moderate rather than severe asthma, there was no washout period, aspirin was given at low dose, and blood rather than lung thromboxane and lipoxin were measured. It is also possible the assumptions made for calculating the needed sample size could have led to a size too small to detect a difference. This is an important area for future investigation.

For the 5% to 10% of asthmatic aspirin-intolerant patients, aspirin is sometimes needed for its prophylactic anti-platelet effect in persons with cardiovascular disease. Shaker et al⁶⁹ conducted a cost-effectiveness analysis which found aspirin “desensitization” more cost-effective than using clopidogrel as an alternative agent in patients with moderate to severe AERD.

Montelukast and depression

New drugs generally are approved after studies in only several thousand patients who used the medication for a relatively short time, usually less than a year.⁷⁰ Thus, post-marketing experience is very important for recognizing and understanding slowly evolving, rare, or late-occurring associated events. In 2007 the FDA reported a possible association between the use of montelukast and behavior/mood changes, suicidal thinking, and suicide.⁷¹ In 2008 Holbrook et al⁷² conducted a secondary analysis of data from 3 studies conducted by the American Lung Association Asthma Clinical Research Network. Participants ranged in age from 6 to 25 years and asthma was generally mild. The studies collected quality of life using either Juniper Mini Asthma Quality of Life Questionnaires³⁸ or the Pediatric Asthma Quality of Life Questionnaires.⁷³ The third study used different questionnaires: the Center for Epidemiological Studies Depression Scale (CES-D)⁷⁴ and the SF-36.⁷⁵ Correlations between these quality of life instruments were calculated. The investigators found no evidence of an adverse effect on emotional well-being in those patients taking montelukast. This analysis is limited by the secondary nature of the analysis, the lack of use of a uniform validated questionnaire to assess depression and quality of life, the short follow-up, the possibility of selection-bias in that patients with significant psychiatric illnesses were excluded from the clinical trials, and the relatively low number of pediatric subjects.

Omalizumab

Omalizumab, anti-IgE therapy, is a new asthma medication with novel properties. Thus, post-marketing experience may be particularly important. In 2007 Limb et al⁷⁶ reported a series of 124 cases of anaphylaxis attributed to omalizumab, characterized by delayed onset and protracted progression of symptoms. A similar event was reported this year by Barry et al.⁷⁷ As Limb et al note, only 1% to 10% of all adverse events are ever reported, so it is possible other omalizumab events are unreported.⁷⁸ As electronic medical records and web-based reporting systems are more widely used, adverse drug reactions can be better studied.
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Environment

Rayens et al⁸⁰ compared asthma-related ED visits before and after implementation of a smoke-free law in Lexington-Fayette County, KY. Kentucky has one of the highest rates in the country of adult smoking and home exposure to secondhand tobacco smoke. Compared to the period before the implementation of this law, investigators found an overall rate of

decline of 22% in ED visits for asthma, primarily in adults, in the post-law period. The absence of significant effect for children was thought due in part to the fact that most smoke exposure for children occurs in the home while the new law affected public places, but not schools or child care facilities which were already no-smoking sites. Although the design is cross-sectional, the report contributes to the evidence that smoking bans can reduce asthma morbidity. Importantly, and as Rabinovitch points out in an accompanying editorial, such public health interventions targeting populations rather than individuals can make a remarkable contribution to improving health and longevity.⁸¹

Exposure to tobacco may be a marker for other environmental exposures that interfere with health. Kumar et al⁸² led a cross-sectional study of urban children and their caregivers in which secondhand exposure to tobacco smoke assessed by salivary cotinine levels was associated with other modifiable social exposures: poverty and depression.

Other modifiable indoor precipitants of asthma symptoms deserve mention. Salo et al⁸³ conducted a cross-sectional secondary analysis of data from the National Survey of Lead and Allergens in Housing, a survey of 831 housing units from 75 different locations throughout the United States. The investigators assessed the association between indoor levels of mite, dog, cat, cockroach, and mouse urine protein with asthma symptoms. They found high allergen levels were common and associated with socioeconomic status measures, the presence of smokers, pets, mold/moisture-related problems, and presence of cockroaches and rodents. Among subjects reporting a doctor's diagnosis of atopy and asthma, high allergen burden was associated with increased asthma symptoms. This evidence of gene-environment interactions was studied more explicitly by Hunninghake et al⁸⁴ who found dust mite allergen levels modify the effect of IL10 polymorphisms on allergy and asthma exacerbations.

Conclusions

This year's research continues the effort to improve patient care of asthma, a complex challenge that involves finding better markers of disease and disease activity, improving therapeutics, and understanding the needs of patients within the larger context of their lives, most of all of eliminating disparities in health and healthcare delivery.

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ABBREVIATIONS USED

AERD	Aspirin-exacerbated respiratory disease
CFC	Chlorofluorocarbon
EBC	Exhaled breath condensate
EPR	National Asthma Education and Prevention Program Expert Panel Report
FE_{NO}	Fractional exhaled nitric oxide
FEV₁	Forced expiratory volume in 1 second, percent predicted
FVC	Forced vital capacity
HFA	Hydrofluoroalkane

ICS	Inhaled corticosteroids
IVR	Interactive voice-response
SABA	Short-acting β_2 -agonist

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Table 1**Key Findings in the Care of Adults with Asthma in 2008**

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- Uncontrolled asthma particularly in the first trimester of pregnancy is associated with congenital malformations.
 - While the overall rate of asthma-related ED visits has not risen recently, blacks compared with whites have a 4-fold greater risk of an asthma-related ED visits.
 - β_2 -adrenergic receptor desensitization may occur with prolonged treatment with albuterol and reversed or prevented with steroids.
 - ICS is the preferred single controller regimen for asthma, associated with lower direct costs and asthma-related utilizations than a single leukotriene modifier or combination controllers.
 - Adults with asthma may be at increased risk for pneumococcal pneumonia or invasive pneumococcal disease.
 - Eliminating second hand smoke from public places is associated with reduced asthma-related ED visits in adults.
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