

Clinical advances in adult asthma

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From October 2001 through September 2002, reports of clinical research on asthma in adults focused on the epidemiology of asthma, the investigation of pharmacologic and immunologic therapy in the context of new national guidelines, and discussions of medical economics. Epidemiologic findings include the observation that overall mortality has declined and hospitalizations have remained constant in the United States since 1995, although these rates are at least twice as high in Blacks. Socially and economically disadvantaged groups receive poorer health care for asthma. Young children who have fewer than 5 episodes of wheezing in conjunction with respiratory infections generally have a good prognosis and do not have compromised lung function as adults. Pharmacologic reports and the National Asthma Education and Prevention Program Update recommend low- to medium-dose inhaled steroids combined with a long-acting β -agonist as the preferred therapy for moderate persistent asthma. The use of chlorofluorocarbon-free medications for asthma is increasing. Medications comprise the largest cost category for asthma. (*J Allergy Clin Immunol* 2003;111:S780-4.)

Key words: Asthma, adult, disease management, epidemiology, drug therapy, medical economics, atopy, minorities, inhaled corticosteroids, health disparities, guidelines

In the United States, more than 7.4 million persons 15 years old or older reported having an asthma attack in 2000.¹ Although overall mortality rates have declined and hospitalizations have remained constant since 1995, these rates continue to be substantial and are at least 2 times higher for blacks. Thus asthma remains a significant problem for adults.

This update discusses important contributions to clinical research in asthma in adults, as reported in *The Journal of Allergy and Clinical Immunology* from October 2001 through September 2002. Key findings during this time are summarized in Table I. These findings can be categorized as related to the epidemiology of asthma, investigation of pharmacologic and immunologic therapy in the context of new national guidelines, and discussions of medical economics. Important background references are also included.

Adult asthma is one, but certainly not the only, disease target of the new Interest Section in Health Care Delivery and Quality (HCDQ) of the American Academy of Allergy Asthma and Immunology. The mission of the HCDQ Interest Section is to foster discussion, research, and clinical

Abbreviations used

CFC: Chlorofluorocarbon
HCDQ: Health Care Delivery and Quality
ICS: Inhaled corticosteroid
NAEPP: National Asthma Education and Prevention Program

innovation to improve the delivery of health care for allergic and immunologic diseases. As a result, our interest section's concerns overlap with those of many other clinical interest sections that are more disease focused. Research to improve the delivery and quality of health care as relevant to allergist-immunologists includes many areas: informatics, medical education, and behavioral science, which encompasses adherence and communication with patients. The impacts of the culture and socioeconomic status of patients and of the practices of the health system on patients' ability to obtain health care are also worthy of attention. National policy, medical economics, health disparities, and improving health delivery to vulnerable populations nationally and internationally are also topics of relevance to the HCDQ Interest Section. Finally, the methodology and ethics of clinical research and patient care are our concern. The articles from the past year summarized here address some of these topics as related to asthma. In the next years, we anticipate increasing the number and breadth of contributions in the area of health care delivery and quality.

EPIDEMIOLOGY OF ASTHMA

Natural history of asthma

Two articles in the past year, one from Australia and one from Italy, have added to what is known about the natural history of asthma, complementing an earlier article by Martinez et al² published in 1995. The first, by Phelan et al,³ described 479 children from Melbourne, Australia, who were randomly selected during a routine school medical examination at 7 years of age in 1964, before the availability of cromolyn or inhaled corticosteroids (ICS). Thus these children were not treated with what is now considered effective therapy. These subjects were followed prospectively, with the most recent evaluation in 1999 when the subjects were 42 years of age. Only 5% of the originally identified children who had fewer than 5 episodes of wheezing associated with a respiratory tract infection before the age of 7 years had persistent asthma at 42 years. The more frequently children had wheezing, the more likely they were to have symptoms as adults. Those with severe asthma in childhood tended to have a loss of lung function by the age of 14

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years, but the loss did not continue to progress. These findings suggest that those children with infrequent episodes do not require therapy to prevent progressive disease and loss of lung function. As Phelan et al³ noted, the major limitation of this study was that wheezing was assessed by parental recall in the early years, raising the possibility of recall bias.

The second article, authored by De Marco et al,⁴ used data from 18,873 Italian subjects. The design of this study was cross-sectional, with data obtained from a questionnaire mailed between 1998 and 2000 to a random sample of residents aged 20 to 44 years from all parts of Italy. Subjects completed a survey on respiratory symptoms, their medical history, and use of medications for asthma. The probability of remission was highest in the group with the youngest age of onset of asthma: 62.8% (95% CI 59%-67%) for groups with onset at less than 10 years, 40.3% (95% CI 32%-49%) for onset between 10 and 20 years, and 15% (95% CI 11%-21%) for onset at 20 years or later. Incidence peaked in male respondents at less than 10 years (4.38/1000 persons) and in female respondents at 30 years or older (3.1/1000 persons). These data were also subject to potential recall bias of self-reported data and selection bias (those who completed the survey were potentially different from those who did not).

Together, these articles from different parts of the developed world suggest that most children who wheeze are not significantly troubled by asthma as adults, particularly if there are few episodes and these episodes are related to a respiratory infection. The more severe the asthma is in childhood, the more likely it is that asthma will persist in adulthood and will be associated with loss of lung function. Those who develop asthma during their adult years are less likely to have a remission. One issue not addressed is whether the course of asthma is the same for persons from low socioeconomic groups and developing countries.

Vulnerable populations

Racial and ethnic minorities have at least twice the morbidity and mortality from asthma as whites.¹ In 2002, the Institute of Medicine addressed racism and discrimination in health care.⁵ In the Journal, Adams et al⁶ documented inadequate use of anti-inflammatory medication for all patients with asthma but particularly those who were socially and economically disadvantaged. The study was a cross-sectional, national, random-digit telephone survey conducted in 1998. The major limitation of this study was the possibility of error in drawing conclusions about diagnosis and severity from self-report, but the survey was concerning and supported other articles showing inadequacy of anti-inflammatory prescriptions among the overall population and among minority patients.⁷⁻⁹

Health disparities were also addressed specifically as they are related to asthma in an insightful review in the Journal by Strunk et al¹⁰ of a National Heart Lung and Blood Institute workshop. Together, these articles suggest the importance of developing research methods to

TABLE I. Key contributions to understanding asthma in adults from *The Journal of Allergy and Clinical Immunology* from 2001 to 2002

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- Overall mortality has declined and hospitalizations have remained constant for US citizens since 1995, but these rates are 2 times higher in blacks.
 - In socially and economically disadvantaged groups, asthma carries greater morbidity and mortality than in the general population, and these groups receive poorer health care for asthma.
 - New NAEPP guidelines recommend (1) low to moderate doses of ICSs with a long-acting β -agonist as the preferred treatment for adults with moderate persistent asthma, (2) that antibiotics not be routinely prescribed for an asthma flare associated with an upper respiratory infection, which is usually of viral origin, and (3) that a written action plan be given to patients.
 - Children with fewer than 5 episodes of wheezing associated with respiratory infections generally do not acquire persistent asthma and rarely have loss of lung function as adults.
 - The use of CFC-free medications is increasing.
 - Medications comprise the largest cost category for asthma.
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target treatment to minority and disadvantaged groups and to tailor interventions to individuals. Better understanding of the implications of socioeconomic status and studies of interventions to improve asthma outcomes for these patients are necessary.⁵ Importantly, the Institute of Medicine Report⁵ and the recent article by Strunk et al¹⁰ stressed the importance of recognizing and dismantling the barriers to obtaining care our health systems unintentionally rig for vulnerable patients. Also emphasized was the importance of strengthening the doctor-patient relationship to improve patient satisfaction and access to care; to better communicate knowledge of disease management to patients, addressing relevant patient health beliefs, attitudes, and adherence; and to remove barriers to health care that are part of the medical system.

Exposure to pets

The impact of exposure to pets, particularly in infancy, on the development of asthma is an area of active research.¹¹⁻¹⁵ In the period of our review, Jaakkola et al¹⁶ reported a careful study to address the contributions of current and past exposures to pets to the risk of development of asthma in adulthood. Jaakkola et al¹⁶ carried out a population-based incident case-control study of adults 21 to 63 years of age from South Finland. Subjects had a new history of asthmalike symptoms and demonstrated reversible obstruction in lung function. The analysis took into account selection bias: individuals with symptoms of asthma tend to remove pets from the home. This phenomenon could mask or reverse a relationship between pet exposure and the risk of asthma. In the adjusted analysis, they found the odds of development of asthma were increased with previous pet exposure and lower among subjects with current pet exposure. Parental atopy increased the risk of incident asthma. Jaakkola et al¹⁶ concluded that these data are consistent with the hypothesis that both keeping pets and parental atopy increase the risk of the subsequent development of asthma in

adults. They observe that their data are also consistent with the hypothesis that individuals with symptoms are more likely to avoid pet exposure. The Journal will continue to address the issue of pet exposure and sensitization in upcoming research presentations and editorials.

ASTHMA THERAPY AND THE NATIONAL ASTHMA EDUCATION AND PREVENTION PROGRAM GUIDELINES

The National Asthma Education and Prevention Program Update on Selected Topics—2002

The complete version of this update was published in the November 2002 issue of the Journal¹⁷ and is available at the Journal's website (<http://www.mosby.com/jaci>). The update is commendable not only for focusing on new research data that fills significant knowledge gaps but also for using a rigorous methodology to systematically identify and evaluate the quality of the research motivating their recommendations. The National Asthma Education and Prevention Program (NAEPP) Panel intends to continuously update and review relevant research in the coming years.¹⁷ For this most recent update, the NAEPP Panel focused on medications, patient monitoring, and disease prevention for extensive review of the evidence and revised recommendations. This review comments on aspects of the NAEPP update relevant to clinical asthma research on adults reported in the Journal over the past year.

Inhaled corticosteroids

The Panel now recommends low-to-medium doses of ICSs with a long-acting inhaled β -agonist for moderate persistent asthma.¹⁷ The Panel concluded that the evidence is stronger for the value of adding a long-acting β -agonist to ICS treatment than for adding a leukotriene modifier or theophylline.

Several recent articles in the Journal explored the role of ICSs in asthma relative to other therapy.^{6,18-21} Among these an article by Szefer et al²⁰ for the Asthma Clinical Research Network of the National Heart, Lung, and Blood Institute is important for its attempt to develop a methodology for comparing beneficial and adverse effects of one ICS with those of another. It is also noteworthy for examining the dose-response relationships of two ICSs, beclomethasone and fluticasone. Determination of such methods is important. Experiments were conducted in 30 adults between 18 and 55 years of age. These subjects had a variety of markers of moderate persistent asthma, including a baseline FEV₁ of 55% to 85% of predicted, at least a 12% or 200-mL improvement in FEV₁ in response to β -agonist, and a PC₂₀ of 8 mg/mL or less. Near maximal FEV₁ and PC₂₀ effects occurred at low to medium doses for fluticasone and at medium doses for beclomethasone. The two ICSs caused dose-dependent suppression of cortisol. The findings are provocative but limited by the small sample size, the lack of blinding, and the short observation time. It is unclear whether these results would also be

observed in a larger, more diverse patient group (the subjects were 80% male and mostly young adults, and their race or ethnicity was not described). Nevertheless, if this method of comparing beneficial and adverse effects can be validated in a more diverse population, ICSs can be compared and their optimal doses can be determined.

Antibiotics for asthma exacerbations

The NAEPP Panel¹⁷ recommends avoiding the routine use of antibiotics for exacerbations of asthma triggered by respiratory infections, because most of these are of viral origin. Antibiotics are recommended as needed for comorbid conditions, such as pneumonia and bacterial sinusitis.

Chlorofluorocarbon propellants

In 1987 the United States signed the Montreal Protocol on Substances that Deplete the Ozone Layer, codified in the United States as the Clean Air Act.^{22,23} The United States agreed to phase out production and importation of chlorofluorocarbons (CFCs). CFC propellants remain only in essential respiratory medications. Wysowski and Swann²² of the Food and Drug Administration reported on the use of CFC propellants in the United States from 1996 to 2000 according to national data from the National Prescription Audit Plus, a pharmaceutical marketing research database owned by IMS HEALTH (Plymouth Meeting, Pa). This database is widely used by the pharmaceutical industry to monitor sales of their products. This survey showed that the outpatient prescriptions for CFC-free inhalant medications had increased 2-fold, with nasal steroids accounting for 80% of the increase. The Food and Drug Administration is considering whether to remove the "essential" designation for CFC-containing nasal steroids. As substitute propellants and dry powder inhalers become more available for asthma and chronic obstructive pulmonary disease, the use of CFC-containing formulations will be phased out.

Levalbuterol

Albuterol is a racemic mixture of (R)- and (S)-enantiomers. Levalbuterol, the (R)-enantiomer, was developed on the basis of the hypothesis, supported by animal studies, that such a preparation would have fewer side effects and be more efficacious than racemic albuterol. Some studies^{24,25} reported support of this hypothesis, but Lotvall et al²⁶ presented a double-blind placebo controlled crossover study of 20 adults with asthma comparing levalbuterol with racemic albuterol and did not find a difference. The editorial by Ahrens and Weinberger²⁷ in that same issue nicely summarized the problems with the earlier studies. Whether levalbuterol has different effects in children compared with adults and whether its use in adults and children warrant the use of this more expensive compound have not yet been established.^{28,29} More study of this drug is warranted.

Written action plan and peak flow monitoring

Although the NAEPP Panel admits that research data are insufficient to support or refute the benefits of a writ-

ten action plan for asthma, the Expert Panel continues to recommend a written action plan for patients with moderate or severe persistent asthma. They also continue to recommend consideration of peak flow monitoring as part of this plan. They are motivated in part by a Cochrane evidence-based review of 25 studies³⁰ (<http://www.update-software.com/>) comparing asthma self-management education for adults to care without such education and studies comparing self-management plans that were written to those that were not. Although evidence on the benefits of using peak flow monitoring as part of an action plan also remain inconclusive, the Panel recommends that peak flow monitoring be considered as a way of strengthening clinician-patient communication and increasing patient awareness of disease status.

ECONOMICS OF ASTHMA

In 1998 the annual cost of asthma was estimated at \$12.7 billion, with medications the single largest cost component.³¹ With resources for health care limited, the costs and benefits of choosing one therapy over another must be considered. The methods for these economic analyses and comparisons were recently reviewed in an excellent two-part series in the Journal by Weiss and Sullivan^{31,32} and in articles by Drummond et al³³ and O'Brien et al³⁴ and an earlier review by Eisenberg³⁵ in *JAMA: The Journal of the American Medical Association*.

Several articles during the past year discussed economic issues. One used the perspective of the managed care organization.³⁶ Although Stempel et al³⁶ contended in this article that their design allows observation of the "real world," the before and after retrospective design has limitations, as they concede. Only direct costs related directly to asthma were considered. The other provocative report considered direct and indirect costs from the perspective of the employer for the analysis.³⁷ As resources continue to become more limited for patients, health plans, and society, clinicians will need more economic reviews, including those with the perspectives of the patient and of society and those that analyze direct, indirect, and intangible costs according to the standards described by Weiss and Sullivan.^{31,32,37}

CONCLUSION

Information on the best health care delivery practices for adults with asthma is informed by research that encompasses many subject areas. Some of these are medical education; behavioral science as relevant to patient self-management, adherence, health beliefs of patients and providers, and patient-provider communication; health policy; social epidemiology and elimination of health disparities; ethics; medical economics; the methodology of clinical research; and informatics. The articles from this past year addressed some of these topics. In the next years we anticipate increasing the number and breadth of contributions to the area of health care delivery and quality.

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