

Advancing asthma care: The glass is only half full!

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Over the past 20 years, there has been a concerted effort in the United States to reduce morbidity related to chronic disease, including asthma. Attention was initially directed toward asthma in response to the recognition that asthma mortality was increasing and that the burden of disease was significant. These efforts to address asthma mortality led to many new initiatives to develop clinical practice guidelines, implement the asthma guidelines into clinical practice, conduct research to fill the gaps in the guidelines, and continuously revise the asthma guidelines as more information became available. An assessment of our progress shows significant accomplishments in relation to reducing asthma mortality and hospitalizations. Consequently, we are now at a crossroads in asthma care. Although we have recognized some remarkable accomplishments in reducing asthma mortality and morbidity, the availability of new tools to monitor disease activity, including biomarkers and epigenetic markers, along with information technology systems to monitor asthma control hold some promise in identifying gaps in disease management. These advances should prompt the evolution of new strategies and new treatments to further reduce disease burden. It now becomes imperative to continue a focus on ways to further reduce the burden of asthma and prevent its onset. (*J Allergy Clin Immunol* 2011;■■■:■■■-■■■.)

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Abbreviations used

BRFSS: Behavioral Risk Factor Surveillance System
CDC: US Centers for Disease Control and Prevention
EPA: US Environmental Protection Agency
ICS: Inhaled corticosteroid
LABA: Long-acting β -adrenergic agonist
NACI: National Asthma Control Initiative
NACPP: National Asthma Control Program
NAEPP: National Asthma Education and Prevention Program
NHLBI: National Heart, Lung, and Blood Institute

Over the past 20 years, there has been a concerted effort in the United States to reduce morbidity related to chronic disease, including asthma. Attention was initially directed toward asthma in response to the recognition that asthma mortality was increasing and that the burden of disease was significant. These efforts to address asthma mortality led to many new initiatives to develop management guidelines, implement the asthma guidelines into clinical practice, conduct research to fill the gaps in the guidelines, and continuously revise the asthma guidelines as more information became available.

The *Journal* has also participated in this effort to improve asthma care by publishing numerous original articles, along with review articles and editorials, to draw attention to the advances in asthma research and to discuss current controversies. For the past 10 years, the *Journal* has also published annual reviews on advances in childhood and adult asthma to summarize the key publications from each year, especially from the *Journal*.^{1,2}

Since the initial publication related to increased asthma mortality in New Zealand³ approximately 30 years ago, many changes have occurred to organize asthma care within countries and globally. The first version of asthma guidelines in the United States was introduced in 1991. Therefore 20 years later is a good time to appraise where we are in asthma care and what steps need to be taken to further improve asthma management in children and adults. Indeed, an assessment of our progress shows significant accomplishments, and it now becomes imperative to continue a focus on ways to further reduce the burden of asthma and prevent its onset.

PATHWAY TO SUCCESS

Reports in the early 1980s brought attention to increasing mortality, and this was a wakeup call to redirect asthma management.³ Over the next 10 years, studies with bronchoscopy and biopsy indicated that asthma was more than acute inflammation caused by allergen exposure or simply bronchospasm related to asthma triggers, such as an environmental irritant or exercise. These studies indicated that asthma was also a chronic inflammatory disease. The approach to asthma management transitioned

quickly from treatment that used predominantly bronchodilator-based management (theophylline) to one directed at anti-inflammatory (inhaled corticosteroid [ICS]) therapy. National guidelines were introduced in several countries to consolidate principles of asthma care and transition the treatment approach to a base of anti-inflammatory therapy.

Asthma guidelines

During the 1990s, a number of important developments occurred, including the introduction of asthma guidelines to translate research findings into clinical practice, more effective medications, and the introduction of managed care. The first publication of asthma guidelines from the National Asthma Education and Prevention Program (NAEPP) was introduced in the United States in 1991,⁴ followed by the development of international guidelines in 1992,⁵ and consequently the Global Initiative for Asthma guidelines in 1995.⁶ This was an attempt to unify treatment within countries and then to collaborate on a uniform approach to asthma management in countries with a similar socioeconomic base. The global guidelines took into account the varying economies and access to medication. Since that time, there have been continuing revisions of the asthma guidelines, with the most recent version of the US guidelines released in 2007.⁷ These revised guidelines emphasized asthma control and put forth 2 domains of control: (1) impairment to assess current symptoms and (2) risk to assess potential for future exacerbations, asthma progression, and adverse medication effects.⁷

New medications

Many new medications for the management of asthma were introduced in the United States during the 1990s. These medications included more potent ICSs (budesonide and fluticasone), long-acting β -adrenergic agonists (LABAs; salmeterol and formoterol), leukotriene modifiers (zafirlukast, zileuton, and montelukast), and subsequently combination therapy with ICSs and LABAs in a single delivery device. The efficacy of these new medications was remarkable, especially combination ICS/LABA therapy, and physicians increasingly recognized the ability of these new medications to reduce symptoms, exacerbations, and systemic steroid requirements. Concern has been raised regarding the potential increased risk of severe asthma-related exacerbations with LABA therapy, and attempts have been made to limit the use of LABA therapy.⁸ The only new medication that has been introduced in the past 10 years has been omalizumab (anti-IgE). This medication, although very effective in a proportion of patients with severe asthma, has limited application because of its high cost.

Ongoing management

Along with the introduction of guidelines and new asthma medications, the concept of asthma management consisting of a multifaceted ongoing approach to prevent exacerbations was introduced and implemented during the 1990s and dramatically changed the landscape for medical care. This period of time saw the merging of single-physician practices into multiple-physician practices and subsequently into multispecialty clinics. A major goal was to reduce inpatient care and thus reduce hospital costs. In the past 10 years, increased attention has been placed on the

management of asthma in children. This was prompted by the recognition that ICSs compared with as-needed short-acting β -agonists had a significant effect on improving asthma control.⁹ In addition, adverse effects of ICSs were limited to a small reduction in growth velocity during the first year of treatment.¹⁰ This effect appears to be persistent but not progressive.¹⁰ In regard to the efficacy of ICSs in asthma management, they have been shown to adequately control symptoms during the course of treatment, but symptoms recur when treatment is stopped. However, ICSs did not significantly alter the course of the disease based on this study.⁹

With the recognition that management with asthma needs to be an ongoing rather than an intermittent effort, support programs have been developed to assist patients in symptom monitoring and to provide asthma education through various resources. The certification of asthma educators has also established some consistency in information that is provided to patients, including features of environmental control. With the introduction of new medications and new insights in disease development, efforts have now been enhanced to increase the awareness of asthma and provide asthma education for clinicians and patients. Community programs have emerged to support health care advances, including school programs. In addition, efforts have been made to expand information related to work-related asthma.^{11,12} Healthy People 2000 goals made asthma a national priority.¹³ The objectives of Healthy People 2000 included the following: reduction in asthma hospitalizations (objective, 11.1) and reduction to no more than 10% of the proportion of patients with asthma who experience activity limitation (objective, 17.4).¹⁴ Asthma-specific Healthy People goals for 2010 were expanded considerably to promote and track adoption of appropriate asthma care, as established in the NAEPP Expert Panel Report guidelines and self-management education.¹⁵ The asthma objectives have been expanded and updated for the recently released Healthy People 2020 goals (<http://www.healthypeople.gov/2020/about/default.aspx>).

A major public health response has been directed to actions at the state and community level to support patient- and community-level interventions and to assess the effect of the environment on asthma¹⁶⁻¹⁸ by the US Centers for Disease Control and Prevention (CDC); the National Heart, Lung and Blood Institute (NHLBI); and the US Environmental Protection Agency (EPA) and other federal agency partners. The CDC's National Asthma Control Program (NACP) was created in 1999 to implement evidence-based interventions at the state and local levels; forge partnerships between federal agencies, state health departments, and nongovernmental organizations to support asthma programs in multiple settings (hospital systems, city health departments, school systems, and local chapters of national asthma organizations); and establish national and state asthma surveillance.¹⁹ In 2001, the Controlling Asthma in American Cities Project began, and by 2009, the NACP supported 34 states; Washington, DC; and Puerto Rico with grants and technical assistance to build and sustain programs that translate evidence-based practice into interventions. For example, the NACP in partnership with the Task Force on Community Preventive Services systematically reviewed the evidence of effectiveness of home-based, multitier, multicomponent environmental interventions in improving asthma-related morbidity. Findings indicated that this approach is effective in improving overall quality of life and productivity in children with asthma, and this home-based multifaceted approach is now being

implemented on the state and local levels with planned evaluation of its effect.

The NAEPP, sponsored by the NHLBI, not only develops the clinical practice guidelines but also supports a number of activities to enhance the education of health care professionals, patients, and the public about managing asthma. The NAEPP's National Asthma Control Initiative (NACI; <http://naci.nhlbi.nih.gov>), which was launched last year, is an effort to accelerate adoption of the key messages of the clinical practice guidelines in clinical practice, community settings, and among government and private insurer programs. The NACI program sponsors demonstration projects at the community level to develop educational tools, community champions, and partnership programs with professional societies and lay organizations; the Web site and newsletter provide up to date information about these projects.

The EPA supports a number of activities to enhance the integration of tailored environmental interventions to reduce exposures that worsen asthma with comprehensive medical care and community services for patients with asthma. Their Web site (www.AsthmaCommunityNetwork.org) offers community-based asthma programs and health practitioners a forum for exchanging information about and sharing resources for improving asthma care, including Internet tools to facilitate collaboration, problem solving, and sharing program activities and news about asthma-related events. The Web site is sponsored by the EPA in partnership with Allies Against Asthma and the Merck Childhood Asthma Network.

Surveillance

Population-level surveillance has also developed in an attempt to identify trends in asthma mortality and morbidity at both the national and local levels. The national surveillance program has also been created to systematically track prevalence, morbidity, health care use, and mortality. The first asthma surveillance summary was published in a *Morbidity and Mortality Weekly Report* supplement series²⁰ in 1998. It brought together in one publication existing national data on asthma prevalence, morbidity, and mortality. At that time, there were no state-level data on asthma and minimal national-level data. State- and local-level surveillance was initiated in 1999.¹⁹

In 1999, the Behavioral Risk Factor Surveillance System (BRFSS) added questions about asthma control and medication use. In 2001, additional details on adult asthma control characteristics were obtained through a BRFSS optional module. Another BRFSS optional module with child prevalence questions was introduced in 2005. The National Asthma Survey, which was piloted in 2003 in 4 states, and a national sample provided extensive additional details on asthma management. Use of the detailed National Asthma Survey questionnaire has been expanded through its implementation as a BRFSS Asthma Call-Back Survey since 2005. The number of states conducting the Asthma Call-Back Survey has increased each year to 39 states in 2010. There has also been an increase in publications using national and state surveillance data. Two additional national surveillance summaries were published in 2003 and 2007.

State-level data are readily available on the NACI Program's Web site (<http://www.cdc.gov/asthma/asthmaadata.htm>). Asthma surveillance data have also been published in several journals (http://www.cdc.gov/asthma/links_data.html). These efforts are

intended to prompt a proactive approach to asthma management by monitoring population-level changes in asthma morbidity and mortality at the national, state, and local levels.

Asthma research

Asthma research expanded over the past 30 years to include several new areas of investigation, including better methods to conduct clinical trials and test interventions, effectiveness research to understand real-world application of clinical trials information, and pharmacogenetics discovery to identify new methods to individualize asthma management.

During the 1980s, studies related to asthma were mainly directed by pharmaceutical industries and were largely regulatory in nature. During the 1990s, there was a move toward evidence-based medicine and the introduction of National Institutes of Health asthma networks to address gaps in asthma management, including inner-city asthma.²¹⁻²⁸ With the emergence of key asthma network studies, it was possible to identify comparative efficacy of medications, explore variability in treatment response, and obtain information on areas of need, including inner-city asthma, severe asthma, and early development of asthma.²¹⁻²⁹ Also, studies were reported that demonstrated the role of intermittent ICSs in place of continuous daily dosing of these medications to minimize the risk of adverse effects.³⁰⁻³²

In addition, information from key asthma cohorts emerged to show the variable course of asthma.³³⁻⁴⁰ Also, there is increasing recognition of the importance of comparative effectiveness research to assess the benefits of medications in real-world settings through trials conducted outside the academic research setting and in community settings and to evaluate the uptake and implementation of guidelines-based care.⁴¹

In summary, the recognition of increased asthma mortality in the early 1980s prompted an ongoing effort to reduce mortality, reduce asthma exacerbations, and improve overall asthma control. In the 1990s, there was a dramatic transition away from bronchodilator therapy as core management to anti-inflammatory therapy as the preferred long-term controller. National and global guidelines emerged to help consolidate information, change the focus of management from episodic to ongoing disease management, and identify gaps in management. Concerted efforts were developed to provide a mechanism to conduct therapeutic research beyond the regulatory requirements for medication approval. Systems were also developed to monitor asthma not only for asthma-related mortality but also for asthma morbidity. This information also identified health disparities in mortality and morbidity. All of this has paved the way for defining methods to improve health care by recognizing the gaps in management and finding better interventions, especially for disadvantaged populations.

CURRENT STATUS OF ASTHMA CARE

Overall, we can feel a sense of accomplishment in reducing mortality and hospitalizations caused by asthma in the United States. Measurement of asthma prevalence changed with the redesign of the National Health Interview Survey in 1997 (Fig 1). There was a rapid increase from 1980 to 1996 of asthma 12-month period prevalence by an average of 3.8% per year. After the redesign, the most comparable measure, current asthma prevalence, was introduced in 2001 and still demonstrates increasing

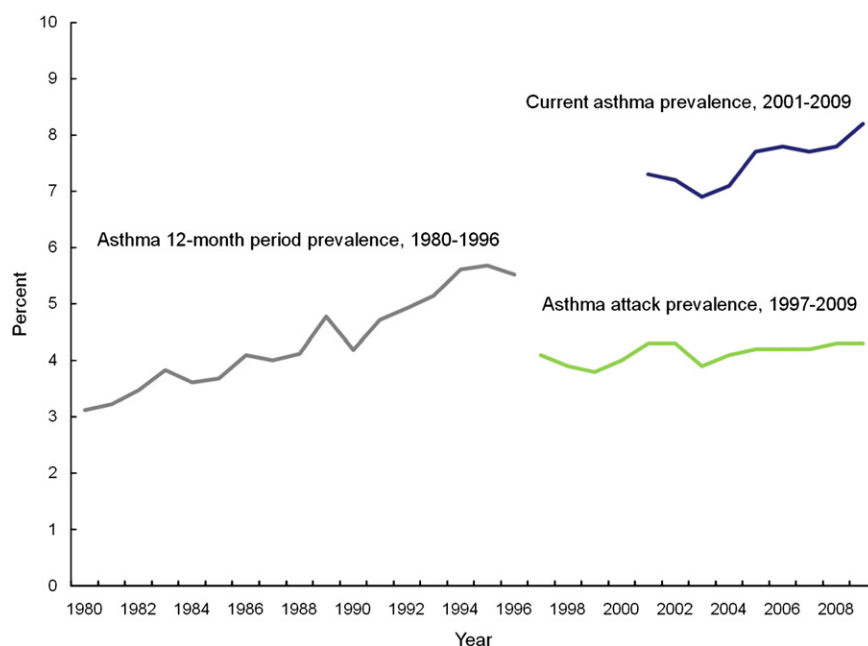


FIG 1. Asthma prevalence in the United States, 1980-2009. Source: National Health Interview Survey, National Center for Health Statistics, CDC.

prevalence, although at a lower rate (average, 1.4% per year). The growing proportion of the US population with current asthma, 8.2% (24.6 million persons) in 2009, presents a continuing challenge to adapt and improve effective prevention and disease management strategies.

Coupled to this observation of increasing prevalence of asthma is the current estimate of substantial costs related to asthma. Barnett and Nurmagambetov⁴² evaluated data from the Medical Expenditure Panel Survey and reported that over the years 2002-2007, the incremental cost of asthma was \$3259 per person per year. For 2007, the total incremental cost of asthma to society was \$59 billion, with productivity losses caused by morbidity accounting for \$3.8 billion and productivity losses caused by mortality accounting for \$2.1 billion.

Reductions in both asthma hospitalization and death rates have occurred over the past decade despite the challenge of increasing prevalence (Fig 2). However, racial disparities in hospitalization and mortality remain a challenge. Asthma hospitalization rates among the black population remain consistently higher than among the white population (Fig 3, A). In 2008, hospitalization rates were 3.6 times as high among black versus white patients, the largest disparity during the period shown from 1980 to 2008.

Although asthma death rates among the black population are also much higher, the relative disparity has decreased from a high of 3.1 times higher death rates among black compared with white patients in 2004 to 2.8 times in 2007 (Fig 3, B). These striking disparities represent a challenge for implementing effective asthma control measures among disparate populations with likely different needs and obstacles.

Although less dramatic, sex disparities also exist. In 2008, asthma hospitalizations were 1.5 times higher among female than male patients (Fig 4, A). The increase in asthma death rates in the 1980s was disproportionately borne among female patients, with relative disparities reaching 1.4 times higher rates among female compared with male patients, a difference that

has persisted despite decreasing death rates during the last decade (Fig 4, B).

Although this information has not been quantified in full publications, clinicians have recognized a reduction in the number of patients receiving oral glucocorticoid therapy as part of the maintenance schedule. This has significantly reduced the number of patients suffering the consequences of adverse effects of systemic steroid therapy, including osteoporosis, cataracts, and growth suppression. This observation has been particularly remarkable for children and has changed the spectrum of the disease. This has been largely attributed to the introduction of new medications, organization of treatment into guidelines, and better systems of management.

Currently, there is a focus on asthma control and an emerging interest in prevention, initially on preventing symptoms and then moving toward preventing progression. However, available research and surveillance show a continued underuse of evidence-based management strategies to control asthma, and thus there is room for improvement. This is an important step for addressing disparities in health care. National data exist for persons with asthma who report receiving components of self-management education and show that only a low-to-moderate percentage have received the basic elements of asthma education (Table I).⁴³

Steps have been taken to achieve better monitoring systems for asthma, including new tools, such as electronic medical records and health care provider surveillance systems. This level of systematic monitoring also has practice-level implications that strive to improve quality of care by tracking outcomes.

Along with the changes in practice management, the concept of personalized medicine has also emerged, and early indicators suggest that this could significantly advance asthma management because there are variable responses to asthma treatment. Although clinicians readily use a personalized approach to selecting a medication, dose, and delivery system to relieve and prevent asthma symptoms, they do not currently use patients'

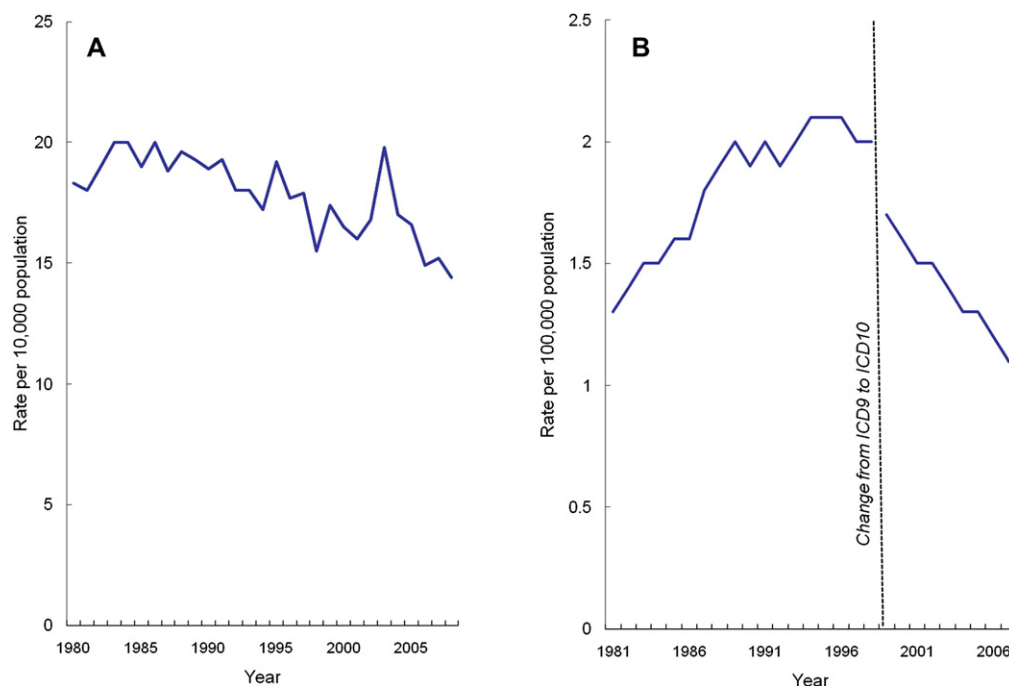


FIG 2. **A**, Asthma hospitalizations per 10,000 population, United States, 1980–2008. **B**, Asthma deaths per 100,000 population, United States, 1981–2007. Note: Asthma hospitalizations are first listed by using International Classification of Diseases (ICD)–9–CM code 493. Asthma deaths include those with the underlying cause coded as ICD-9 code 493 from 1981–1998 and ICD-10 codes J45–J46 from 1999–2007. Source: National Hospital Discharge Survey, Mortality Component of the National Vital Statistics System, National Center for Health Statistics, CDC.

characteristics, biomarkers, and genetics to select and adjust treatment. Generally, treatment is still based most often on symptom presentation. Even basic tools, such as spirometry, are not readily incorporated in assessing asthma control, monitoring the course of asthma, and adjusting therapy accordingly. Although spirometry is incorporated in asthma care conducted by most subspecialists, it has not been readily adapted in the course of asthma management in primary care.

There are several other interesting trends that will affect asthma management in the near future. There are increasing public health concerns regarding the effect of the environment on respiratory health, and measures are being taken to institute control procedures and alert the public to hazards, such as publication of pollen counts, and to incorporate asthma-friendly environmental policies into public housing, as well as school structure and rehabilitation. Current targets have been set to reduce hospitalizations and urgent care use by developing a systematic approach to managing chronic diseases, including asthma, by health care providers. The concept of a medical home has been introduced to help coordinate medical care, self-management education, and programs to link families to the services they need to support the treatment plan.

Unfortunately, there are no new asthma medications on the horizon. However, observations have been made regarding the beneficial effects of medications that were not directly approved for asthma management, including vitamin D and tiotropium.^{44–46} Steps are also being taken to obtain better insight into the origins of asthma, the natural history of asthma, and the relationship of genetics to the risk of asthma and to the variations in response to treatment and identification of easily measured biomarkers

that can be used to predict response to medications and monitor disease activity.

In summary, we are now at a crossroads in asthma care. We have recognized some remarkable accomplishments in reducing asthma mortality and morbidity and closing some gaps in health disparities with the introduction of new medications and management systems. The availability of new tools to monitor disease activity, including biomarkers and epigenetic markers, along with information technology systems to monitor asthma control, hold some promise in identifying gaps in disease management and should prompt the evolution of new strategies and new treatments to further reduce disease burden.

CHALLENGES FOR THE NEXT 10 YEARS

How do we go beyond measures of asthma mortality and hospitalizations?

Efforts are now being made to provide precise definitions and methods for measuring key asthma outcomes based on the work of the National Institutes of Health Asthma Outcomes Task Force held in 2010 (report in preparation). This will allow comparison across data in studies and facilitate pooling of data for meta-analysis.

Although it is important to continue monitoring critical asthma outcome measures, it would also be useful to assess the effect of asthma on the lives of all asthmatic patients. Some health care systems are already taking steps to monitor asthma control in their patients and prompt treatment adjustments to their clinicians. Indeed, disease severity is a combination of the level of asthma control along with the number and dose of medications used to

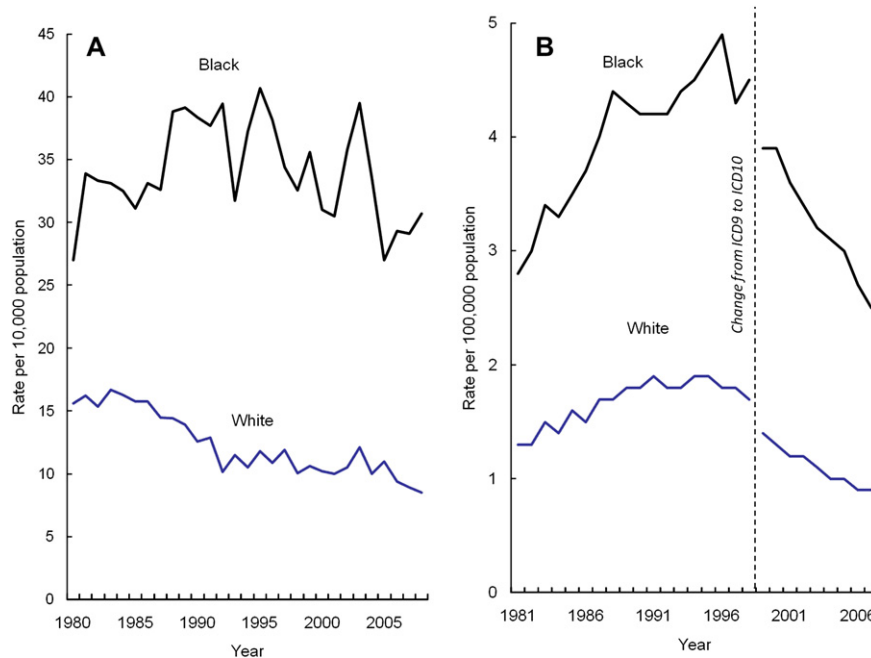


FIG 3. **A**, Asthma hospitalizations per 10,000 population by race, United States, 1980-2008. **B**, Asthma deaths per 100,000 population by race, United States, 1981-2007. Note: Asthma hospitalizations are first listed by using International Classification of Diseases (ICD)-9-CM code 493. Asthma deaths include those with the underlying cause coded as ICD-9 code 493 from 1981-1998 and ICD-10 codes J45-J46 from 1999-2007. Source: National Hospital Discharge Survey, Mortality Component of the National Vital Statistics System, National Center for Health Statistics, CDC.

achieve that control. Useful tools for health care providers to assess the effect of asthma and the proportion of patients considered to have severe disease and to require systemic steroids will be helpful. Identifying those patients who are significantly affected by asthma and refractory to conventional treatment could direct them to studies that evaluate the efficacy of new treatment strategies, such as immunomodulator therapy.

Will techniques of “personalized medicine” move from the bench to the clinic to the home setting?

Currently, risk of disease is gauged by family history. Symptom expression is used to assess asthma severity and control. Use of asthma action plans and education programs have helped patients manage their own disease. The asthma self-management concept has expanded. However, many patients with asthma still do not benefit from a comprehensive management program, and despite application of such a program, there are still unpredictable and severe exacerbations that lead to urgent care.

Combining a system of careful follow-up and communication through electronic medical records along with periodic measurements of pulmonary function, there is the capability of monitoring disease activity and the natural history of the disease in individual patients, including remission, progression, and relapse.^{36,38} However, these are still prominent features of the disease, and perhaps the identification of more subtle monitors of disease activity, such as biomarkers and epigenetic markers, could prompt a more effective treatment strategy to actually prevent exacerbations and progression. There is a continuing debate on whether chronic obstructive pulmonary disease might reflect the evolution of a certain phenotype of asthma. Therefore identifying these patients

early in the course of the disease could theoretically lead to more effective early intervention strategies to prevent chronic obstructive pulmonary disease. The definition of asthma phenotypes and identification of specific phenotype-related interventions will also be important.

To date, exhaled nitric oxide levels and sputum eosinophil numbers have been prototypic markers of disease activity and targets of therapeutic intervention. Strategies to reduce sputum eosinophil numbers by using methods to monitor and adjust glucocorticoid therapy have been shown to significantly reduce asthma exacerbations.⁴⁷ However, use of sputum eosinophil measurement has been limited to clinics with readily available procedures. Exhaled nitric oxide levels, on the other hand, are easier to measure, although still requiring special training, equipment, and maintenance. These can be used in the clinic setting to obtain on-site results for clinical decisions. The results of studies incorporating periodic measures of exhaled nitric oxide have been less impressive in reducing exacerbations compared with sputum eosinophil numbers.^{48,49}

Although there is limited additional value of measurements of exhaled nitric oxide for monitoring and adjusting therapy over a guidelines-based approach, measures of exhaled nitric oxide can be used as a predictor of ICS response in children but not necessarily in adults.^{50,51} Furthermore, a recent study with a combination of urinary leukotriene and exhaled nitric oxide measurement, including the ratio of these 2 biomarkers, might help direct the selection of either ICS or leukotriene receptor antagonist therapy for first-line long-term controller therapy in children.⁵² Exhaled nitric oxide levels can also be used as a measure of medication adherence for ICS therapy, although further studies are needed because exhaled nitric oxide levels might also be

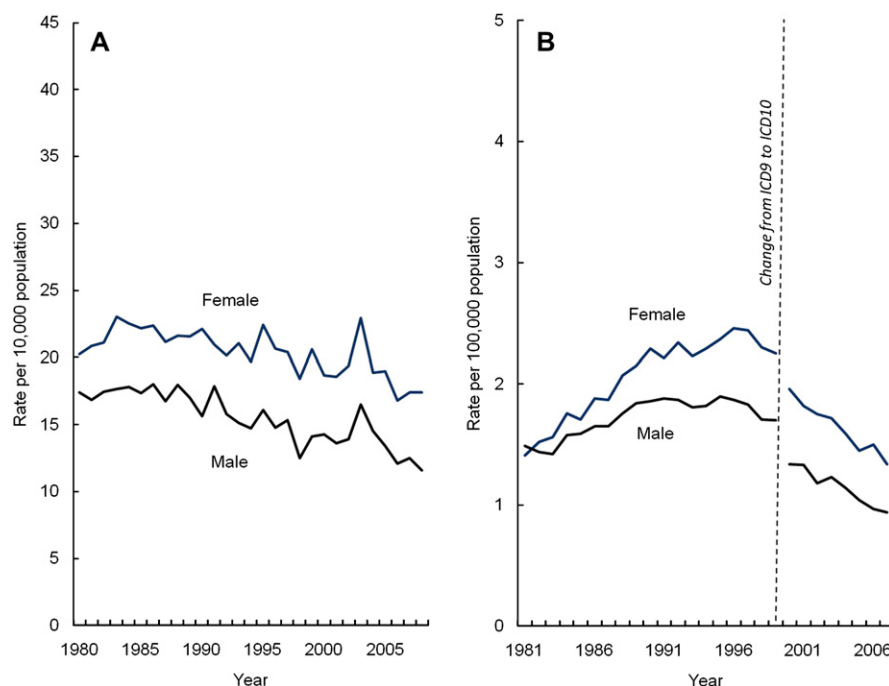


FIG 4. **A**, Asthma hospitalizations per 10,000 population by sex, United States, 1980-2008. **B**, Asthma deaths per 100,000 population by sex, United States, 1981-2007. Note: Asthma hospitalizations are first listed by using International Classification of Diseases (ICD)-9-CM code 493. Asthma deaths include those with the underlying cause coded as ICD-9 code 493 from 1981-1998 and ICD-10 codes J45-J46 from 1999-2007. Source: National Hospital Discharge Survey, Mortality Component of the National Vital Statistics System, National Center for Health Statistics, CDC.

TABLE I. Percentage of persons with current asthma* reporting receipt of self-management education, National Health Interview Survey, 2008

	Total (% [95% CI])	Children, 0-17 y† (% [95% CI])	Adults ≥18 y (% [95% CI])
Given an action plan	34.2 (31.1-35.9)	44.3 (40.0-48.8)	29.9 (27.2-32.8)
Taken a class to learn how to manage asthma	12.2 (10.7-13.8)	12.5 (10.0-15.7)	12.0 (10.3-13.9)
Taught to recognize early signs and symptoms of asthma attack	59.9 (57.3-62.5)	72.1 (68.1-75.8)	54.8 (51.5-58.0)
Taught how to respond to asthma attack	68.1 (65.6-70.6)	78.3 (74.2-82.0)	63.8 (60.8-66.8)
Taught how to use peak flowmeter	42.2 (39.7-44.7)	49.4 (45.1-53.6)	39.2 (36.2-42.2)
Given advice on environment control	49.3 (46.6-52.0)	50.6 (45.9-55.2)	48.8 (45.6-51.9)
Followed "most or all" advice about environment	60.7 (57.1-64.2)	81.2 (76.2-85.3)	51.6 (47.0-56.2)

Source: CDC.⁴³

*Persons reporting ever having received a diagnosis of asthma and still having asthma at the time of the survey.

†Percentage of parents reporting receiving this management education for their child's asthma.

increased because of other exposures, such as allergens in sensitized patients.

To date, monitoring daily peak flow has not been sufficiently sensitive and specific to identify impending asthma exacerbations⁵³ but still might be useful in assessing variability, an important indicator of unstable asthma.

Furthermore, information is emerging that the Asthma Predictive Index, identified as part of the Tucson Respiratory Study, can be useful in identifying young children with early respiratory tract illnesses suggestive of asthma or emerging asthma. A positive Asthma Predictive Index score might also be associated with a higher likelihood of beneficial effects from ICS therapy in young children with emerging asthma.^{31,54} Further refinement of these clinical tools and their application could help direct the selection and monitoring of asthma therapy, especially in children.

Exploration of genetic markers continues in relation to clinical application for asthma management. The most well-studied genetic marker to date for asthma has been associated with β -adrenergic polymorphisms. Early information suggested that the B16 Arg-Arg polymorphism therapy was associated with decreasing pulmonary function in those treated with regular short-acting β -agonists.⁵⁵ Because this method of treatment, namely regular use of short-acting β -agonists, is now rarely used and the marker has not been associated with deteriorating asthma control with combination ICS/LABA therapy, the clinical application of this genetic marker is not an essential component of asthma care. However, emerging information with filaggrin polymorphisms suggests that this marker, when identified in patients with atopic dermatitis, might carry a prognosis for higher risk of asthma.^{56,57} This combination of patients' characteristics and

genetics could prompt early intervention strategies that would provide improved control and perhaps lead to disease remission.

What changes can be expected from the public health perspective?

Continued efforts are being made to follow the epidemiology and effect of asthma through national, regional, and local statistics. This information can be used to identify areas of need. In particular, community statistics can be useful in identifying hot spots of asthma prevalence or areas of increased asthma burden to focus resources or identify effect factors, such as the environment, socioeconomic factors, or a combination thereof. This is one of the direct effects of the CDC's NACP that funds states for surveillance, coalition building, and interventions.¹⁹ Recent information from the Web sites of the NHLBI's NACI program and the EPA's Asthma Community Networks in addition to the CDC's programs reveals increasing effort to coordinate federal programs to broaden their reach to underserved communities and strengthen their ability to help clinicians and patients improve asthma management.

With the development of a global approach to asthma care, there can be more standardization of asthma management; however, various economic factors can lead to site- and community-specific medication selections or intervention strategies. Once again, statistical information to identify areas of high asthma prevalence and morbidity will be important to channel knowledge and resolution.

On a broader scale, the public health response to increased application of guidelines-recommended care could further identify and address health disparities in asthma care. There are ongoing challenges to implement a guidelines-based approach into clinical practice and to increase public awareness of asthma control and for patients to work with clinicians to achieve control. Continued health care policy changes should help to improve reimbursement for physicians to provide this level of care and for patients to benefit from it. A carefully integrated plan to understand and address emerging public health challenges, such as increasing exposure to traffic pollutants, housing, climate change, and pollutant/allergen interactions, and to reduce secondhand tobacco smoke exposure should also prove helpful in reducing asthma burden.

Can we cure asthma by halting progression and preventing onset?

With the continued use and development of data bases for clinical outcomes, biomarkers, genetics, and the environment to help understand disease origins and natural history, we will be able to successfully develop early intervention strategies for control and prevention. Indeed, the Getting to Healthy People 2020 strategy places an emphasis on disease prevention.⁵⁸ It will be important to define genetic markers and environmental factors that place patients at risk for asthma to get to that point. If certain markers and environmental factors are associated with the development of asthma, especially severe asthma, this will prompt consideration for the use of immunomodulators at an earlier point in management.

Methods to monitor disease activity, such as epigenetics and biomarkers, will be important to assess the risk of disease persistence and progression. Information is also developing

related to the potential effect of the microbiome on asthma development.⁵⁹ However, it is not clear whether the organisms identified are causative or perhaps commensal because of a defect in the immune system related to asthma.⁶⁰ This story will continue to develop.

Currently, our early intervention strategies center around the use of short-acting β -adrenergic agonists to relieve symptoms and glucocorticoids to address airway inflammation. However, some studies suggest that this strategy is not sufficient to alter the course of the disease once glucocorticoid treatment is discontinued.⁶¹ If this is indeed true, then more effective strategies are needed to prevent progression and reduce the risk of asthma exacerbations. We must continue to try to understand the reasons for treatment failure to shed light on potential new treatment strategies, including new medications.

To date, the application of immunomodulator therapy in young children is viewed with great concern because of the potential effects on growth and development, including the immune system and the ability to maintain adequate host defense. However, a recent article related to omalizumab therapy and the reduction of fall exacerbations in inner-city children prompts questions related to the potential interaction of virus- and allergen-induced inflammation.^{24,62} Perhaps strategies designed to target periods of allergic inflammation will also reduce the risk of virus-induced asthma exacerbations. This area merits further study. Efforts to define severe forms of asthma and identify phenotypes could also lead to a more directed approach to management.^{26,27,63}

In regard to environmental control, it is apparent that airway inflammation and consequent symptoms of airway obstruction caused by inflammation can be related to allergy, virus, and air pollutants. However, there are no specific biomarkers that can be used to identify the driving force of the airway inflammation. Although exhaled nitric oxide levels and sputum eosinophil numbers are often associated with allergic airway inflammation, urinary leukotriene levels with tobacco smoke exposure, and sputum neutrophil numbers with infection or air pollution, it is not entirely clear on how to use these specific markers to set a direction in treatment for individual patients. If certain biomarkers could prove useful to differentiate the factors leading to airway inflammation, perhaps they could channel environmental control strategies that are more specific to the individual patient rather than generalized to all patients with asthma.

Can this effort extend to other national and global initiatives?

Indeed, asthma is considered a global public health problem. Concerted efforts within and beyond countries can help shed light on the epidemiology and management of asthma. This review has focused on information available in the United States, but asthma and allergies are being addressed in various worldwide efforts. As previously mentioned, the Global Initiative for Asthma guidelines seek to address asthma management for developed and developing countries. In addition, the World Allergy Organization is preparing a white book that will address the increasing prevalence of asthma and allergies to increase the visibility of this problem and to propose recommendations to improve management.

THE ASTHMA SERIES

This review is the first in a series of articles on the current status of asthma. The objective of this series is to highlight specific areas

important to advancing asthma care. Each review will summarize the current status of the area and future needs to advance the field. The next article in this series will focus on asthma pathophysiology. Dr Stephen Holgate will discuss the pathophysiology of asthma and the information that has developed after the evaluation of new medications intended to interrupt various pathways of inflammation. Dr William Busse will then discuss the advantages and limitations of our current tools and gaps that must be filled to improve the diagnosis and treatment of asthma.

Next in this series will be a discussion of the origins of asthma by Dr Fernando Martinez. Dr Martinez will summarize current knowledge on the disease's origins and natural history and the need for further studies to define the various pathways of this disease, as it presents in children and adults. This will be followed by a comprehensive discussion of the current state of severe asthma.

Dr Sebastian Johnston will follow with a topical review of asthma exacerbations. He will discuss our knowledge regarding the cause of asthma exacerbations and future steps that could be taken to reduce the frequency and effect of these exacerbations or periodic loss of control.

Dr Peter Barnes will analyze whether the pattern of severe asthma is changing and what determines whether asthma is severe. He will also discuss our current treatment strategies and the promise for new interventions.

Dr Scott Weiss will conclude the series with a timely discussion of genetics and the application of personalized medicine. He will identify steps that could be taken now to apply these principles and steps that could be taken in the future to advance therapy and improve the asthma guidelines.

We thank all of the invited experts for the time that they took to evaluate their areas for review and for a comprehensive discussion of these topics. We hope that these summaries will prompt further research that will lead to continuing advances in asthma care.

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