Continuing education credit for physicians and pharmacists sponsored by The Chatham Institute

Supported by an educational grant from Genentech, Inc. and Novartis Pharmaceuticals Corporation
Asthma is one of the most common illnesses in the United States and is a major driver of health care utilization costs. It also can be a challenge to manage. Disease severity, as defined by guidelines, does not necessarily correlate with patients’ self-reported symptoms, meaning that vigilance is imperative to reducing poor outcomes.

The purpose of this publication is to provide P&T committees with an understanding of how asthma functions as a disease syndrome, examine unmet needs with respect to treatment, discuss the extent of its burdens on society, and focus on what can be done to alleviate those burdens.

This peer-reviewed publication is a digest of current and evolving guidelines for treatment, existing and emerging therapeutic approaches to care, and strategies for managing patients and their conditions. In consolidating this information, it serves as a valuable tool for formulary committees and is an important contribution to the medical literature.

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P&T DIGEST

Asthma

Continuing education credit is offered to physicians and pharmacists who read pages 6 through 58 of this publication, complete the post-test on pages 60–61, and submit the evaluation form on page 59. Estimated time to complete this activity is 3 hours.

Target audiences
Practicing physicians and pharmacists; formulary committee members; and managed health care professionals, including medical directors, chief medical officers, pharmacy directors, and other clinical executives.

PURPOSE AND OVERVIEW
Asthma is one of the most common illnesses in the United States, affecting an estimated 16 million people. With an economic burden of more than $16 billion annually, asthma is the fifth most costly chronic disease in the United States. Importantly, asthma is believed to be underdiagnosed and undertreated, leading to lack of disease control and poor outcomes, even in the population that is treated. In addition, disease severity, as defined by guidelines, does not necessarily correlate with patients’ self-reported symptoms, making it challenging to manage the condition.

The purpose of this publication is to provide P&T committees with an understanding of how asthma functions as a disease syndrome, examine unmet needs with respect to treatment, discuss the extent of its burdens on society, and focus on what can be done to alleviate those burdens. This publication synthesizes best-practice information for managed care decision makers, who will be able to use it to develop treatment protocols and formulary recommendations and disseminate it to providers to improve the collective health of their populations. The information herein also is valuable to health care providers, who must stay abreast of current treatment approaches. The success of treatment depends on the clinician’s ability to accurately diagnose patients and encourage adherence to therapy.

The need for this educational activity was based on a review of current medical literature and faculty perception of significant issues. The review articles herein were commissioned for this publication and have been independently peer reviewed.

Educational objectives
After reading this publication, participants should be able to:
- Describe the clinical and economic burdens of asthma
- Understand the significance of unmet needs among people with asthma
- Summarize current treatment guidelines and reasons why guidelines are not followed
- Identify various recommended treatments for asthma, understand their mechanisms of action, and describe emerging therapeutic approaches
- Elucidate strategies for therapeutic compliance and the consequences of noncompliance with drug-therapy regimens
- Discuss National Committee for Quality Assurance guidelines for care of patients with asthma

CONTINUING EDUCATION
This activity is sponsored by The Chatham Institute.

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INTRODUCTION

Successful control of asthma involves understanding the effects of allergy, sinusitis, and gastroesophageal reflux on asthma severity. For practitioners, it also means balancing medications in combination to improve efficacy and safety. Disease severity, as defined by guidelines, does not necessarily correlate with self-reported symptoms, meaning vigilance is imperative to improving outcomes.

As a lifelong, life-threatening condition that can fall out of control in an instant with certain kinds of exposures, asthma may be challenging to manage. Successful asthma management has different meanings for physicians, patients, health plans, and purchasers of health care benefits.

For physicians, successful asthma management means establishing disease control and minimizing risk of long-term side effects. It also means persuading patients to remain on their prescribed regimens, as some do not understand that if they stop therapy, the asthma may return and become uncontrollable. Properly managed patients, ideally, never need to visit the emergency room or to be hospitalized, and are able to live without any significant impairment.

To patients, proper management means better quality of life, fewer lost days at school or work, fewer emergency medical visits, and the fundamental ability to breathe. Properly managed patients are not overly concerned about quality of life, do not feel sick, can exercise freely, and use no emergency inhalers.

For managed care plans, it means higher member satisfaction and better scores on the National Committee for Quality Assurance’s Health Plan Employer Data and Information Set (HEDIS). It also means lower costs related to emergency treatments and no deaths.

For employers and public-sector purchasers, successful management means improved employee production, fewer work absences, and assurance that dollars invested in health care are being put to optimal use.

With our dramatically increased understanding of asthma, guidelines have evolved and excellent medications have emerged, making asthma management, to a large extent — in the hands of properly educated physicians — a matter of routine. This indicates that caregivers are starting to gain positive control of this chronic, often debilitating, and occasionally fatal syndrome of diseases. Because further advancements are on the near horizon, even stronger control of asthma may be possible.

Burdens of asthma

The medical community has increased its focus on asthma because the associated societal burdens have increased greatly. Asthma’s prevalence has virtually doubled since the mid-’80s (Redd 2002) and is probably linked to the rising prevalence of allergies, together the most common underlying cause of asthma. More than 70 percent
of people who have asthma suffer from allergies (NLM 2005).

Annually, asthma accounts for about 1.5 million ER visits and 500,000 hospitalizations (ALA 2004a). The annual asthma death rate has doubled in the past 20 years, stabilizing at about 5,000 per year in the past decade (NCHS 2001). Direct costs of asthma treatment now exceed $11 billion annually (ALA 2004b).

Severity categorization

Asthma severity categorization has developed in the past 10 years. Specifically, guidelines from the National Asthma Education and Prevention Program (NAEPP), which is administered and coordinated by the National Heart, Lung and Blood Institute, can help physicians who are not asthma specialists to manage the condition more effectively. Thus, based on easily recognized symptom profiles and pulmonary function tests, patients can be classified as mild persistent asthmatics, mild intermittent, moderate persistent, and severe persistent; an algorithm indicates approximate treatment levels for each of these categories. Physicians are urged to bring the patient under complete control, and then step down the treatment to the lowest level that keeps the patient well.

The NAEPP (1997) advises that the presence of one severity indicator in any category (e.g., >1 nocturnal awakening per week) is enough to place a patient in that category, adding that the patient should be assigned to the most severe category in which any feature occurs. Thus, physicians try to treat the worst symptom, get the patient under complete control, and then progressively reduce the treatment intensity. Because asthma is extremely variable, characteristics and categories may overlap and change over time (NAEPP 2002).

Any patient at any level of severity can experience mild, moderate, or severe exacerbations. Some patients with intermittent asthma may experience severe and life-threatening exacerbations, separated by long, asymptomatic periods of normal lung function. One result of this variability is that severity, as defined by guidelines, does not necessarily correlate with patients’ self-reported symptoms at any given time (Diette 2004). This disparity raises the chances that a patient will be misclassified in a lower severity level than warranted — thus directing the physician to use less aggressive medications than might be warranted by the patient’s disease.

Classifying the severity of the patient’s asthma, then, is the first step toward controlling the condition. It can be helpful to the physician (and, under ideal circumstances, the rest of the asthma care team), the patient, and the members of the patient’s support system (relatives, significant others, and friends) to recognize the nature of the patient’s problem and then to learn what can and should be done about it. Classification also alerts physicians with limited formal asthma training or related experience that they may need to refer the patient to a specialist, preferably before the condition worsens and the patient needs emergent, episodic care. Yet, controlling asthma goes far beyond arbitrary classification schema, which act only to provide guidelines for treatment.

Controlling asthma

Understanding the principles of asthma and its treatment and following the NAEPP guidelines potentially make asthma care a straightforward proposition. Though some health providers apply the NAEPP guidelines universally, many use them only haphazardly, perhaps because some physicians who treat asthmatics may not understand the guidelines or the syndrome itself.

The inflammation that occurs in asthma patients’ airways results from both allergic and nonallergic processes, and is an ongoing problem. Thus, patients may be asymptomatic but still exhibit airway hyperresponsiveness reflecting airway inflammation. Such asthmatics can become sick quite suddenly when they develop an upper respiratory infection or sinusitis, or are exposed to allergens. Underlying airway reactivity exaggerates any new inflammation, and much greater symptoms are evoked.

In part because asthma is not a single disease but a syndrome, achieving control can be quite difficult unless the whole picture is kept in focus. Understanding asthma effectively — and controlling it — means:

- Considering degrees of disease severity (NAEPP guideline classification)
- Understanding the role of allergy in asthma, and evaluating for allergies all patients who have persistent asthma (any patient who wheezes >2 days per week should be evaluated for allergies)
- Recognizing contribution of concomitant sinusitis and/or gastroesophageal reflux to asthma severity
- Balancing the many medication options, taking into account the mode of action of the products, account dosing parameters, side effects, and variable responses to treatment

Theoretically, asthma could be managed in almost any physician’s office. Given the complexity of the factors listed above, however, and reliable estimates that a substantial share of patients with diagnosed asthma are undertreated, any asthmatic patient who suffers from more than moderate disease should consult with a specialist.

In the long run, this approach is cost-effective. Most asthma specialists never send a patient to a hospital for
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asthma care, yet the incidence of hospitalization and ER visits for such treatment has not changed in the past 10 years — despite the availability of better medications and clear treatment guidelines. Dollars spent on acute and hospital care would be put to better use by involving an asthma specialist earlier in the process.

What separates asthma specialists from others who treat asthma is that they recognize the following: the major role that allergies play in this condition and that they must be controlled; that sinusitis exists in approximately two thirds of moderate to severe asthmatics (CDC 1995); that gastroesophageal reflux and laryngopharyngeal reflux are present in a substantial portion of asthmatics; and that unless the sinus and esophageal conditions are controlled along with management of the allergic component, the asthma will be much more difficult to manage.

Conventional therapy

Conventional asthma treatment focuses on anti-inflammatory agents and bronchodilators. These are quite different medications, the use of which is presented clearly in the guidelines that provide the basic principles of asthma management. Bronchodilators open airways and provide short-acting relief of flare-ups; anti-inflammatories, such as corticosteroids, act as long-term controllers reducing underlying airway reactivity and inflammation. Understanding this dichotomy makes management of asthma a much simpler proposition.

Monitoring asthma control using peak-flow meters and observing conditions under which patients experience exacerbations will continue to necessitate much attention in managing asthma.

Difficult-to-treat asthma

About 30,000 moderate-to-severe asthmatics currently take omalizumab (Xolair), a monoclonal antibody therapy that blocks immunoglobulin E (IgE), an underlying cause of allergic asthma symptoms. No long-term outcomes studies are yet available for this relatively new therapy but, in my clinical estimation, it is reasonable to expect that about one third of patients will respond dramatically, a third will respond fairly well, and another third will not respond at all. It is probable that those patients who do benefit will be those who have the most severe asthma. Therefore, using this type of medication to treat patients with difficult-to-manage asthma, without having to administer huge doses of conventional medication for maintenance — thereby minimizing the possibility of introducing serious long-term side effects in those patients — may make sense.

Other medications that are being examined for possible use in asthma include other anticytokines and even modifications of the old theophylline products, phosphodiesterase subtype 4 inhibitors. Nevertheless, in the next decade, inhaled steroids — using safer molecules as they become available — will continue as the medication of choice, in combination with bronchodilators in various modes that may be delivered once daily or combined with the inhaled corticosteroid. Leukotriene modifiers are relatively safe, are taken by mouth, are not corticosteroids, and are moderately effective for the mild-moderate asthmatic. Such attributes make these medications extremely popular, especially because they also are indicated for treatment of allergic rhinitis, a frequently encountered concomitant disease.

Forecast

On the horizon are new guidelines, new approaches to asthma management, safer medications, and increased attention to disease control; in the immediate future, however, what has worked well for years will continue to work well. In many cases, the key to treating patients with recalcitrant asthma is not to change their asthma management, but to manage their sinusitis and their gastroesophageal reflux disease. Increasing the dosage of conventional medications would probably improve asthma control, but at the eventual cost of serious long-term side effects.

In the short term:

• Researchers must try to improve the safety of currently available medications as therapy for persistent, difficult-to-treat asthma in nonresponders
• Practitioners must balance medications in combination therapy to improve their efficacy and safety
• Patients should be taught how their medications work and be encouraged to remain compliant

All stakeholders need to watch for unexpected side effects developing in large patient populations with continued use. The trend will be to use safer drugs and lower doses of medicines in combination therapy, so that no one medicine is used at more than a minimum dose.

DIGEST MISSION SUMMARY

The purpose of this publication is to provide P&T committees with an understanding of how asthma functions as a disease syndrome, the extent of its burdens on society, and what can and must be done to alleviate those burdens. We are privileged to have the contributions of several well-known specialists in the field of asthma care.

Michael Blaiss, MD, of the University of Tennessee at Memphis, discusses the prevalence of asthma and its economic implications. Blaiss explores the demographic characteristics of asthma; analyzes treatment and control
statistics and utilization data; explores both the direct and indirect costs of the disease burden; assesses the economic effects of uncontrolled asthma on employers, including the effects of absenteeism and presenteeism; and ascertains the economic implications for purchasers and payers.

Undertreatment of asthma contributes to a lack of control of the condition, even in cases in which both patient and physician are convinced that control exists. Aidan A. Long, MD, of Massachusetts General Hospital, explores this phenomenon, defining — among patients who have been prescribed therapy for asthma — the unmet needs in asthma control. He establishes the extent of the problem, outlines the inherent issues, and discusses the implications of meeting — or not meeting — those needs, particularly for payers.

Because new national guidelines for the diagnosis and treatment of asthma are forthcoming, a review of the current guidelines is timely. Jill Ann Ohar, MD, of the Wake Forest University School of Medicine, summarizes current guidelines, hypothesizes about why they are often ignored, and discusses how that could play into future guidelines development.

Gaining positive control of active asthma depends on prescribing effective therapy. Mani Kavuru, MD, of East Carolina University, reviews current asthma therapy options — describing specific therapies, pharmacology, indications, appropriate dosage, limitations of existing therapies, and adverse reactions. Kavuru reviews inhaled corticosteroids, short-acting and long-acting bronchodilators, anticholinergic bronchodilators, leukotriene modifiers, theophylline, and biologic anti-IgE therapy.

Stephen P. Peters, MD, PhD, of Wake Forest University School of Medicine, picks up where Kavuru leaves off, describing novel treatment approaches that recently have become available and investigating some that are in developmental stages. He also discusses appropriate evaluation of patients who may be candidates for these options.

Among the most effective ways to control asthma is within the framework of a disease management program. Craig Jones, MD, of the University of Southern California, discusses the principles of effective disease management and then presents a case study of a program that is designed to prevent the development of active asthma, identify uncontrolled asthma among patients receiving care, and involve patients in the control of their asthma.

One major reason that patients fail to achieve control of their asthma is lack of compliance. H. William Kelly, PharmD, of the University of New Mexico, discusses compliance rates as well as strategies to foster better adherence to asthma-treatment regimens. Kelly will relate the effect of compliance to clinical and financial outcomes.

Michael Foggs, MD, of Advocate Health Centers, in Chicago, focuses on HEDIS requirements for the management of patients with asthma and explores trends in HEDIS compliance among health plans, as all plans that participate in the NCQA program must document continuity of care for patients. Foggs also raises questions about how the existing HEDIS asthma measure can be improved to heighten clinical outcomes.

CONCLUSION

With an increased scientific understanding of asthma, the potential for better care of patients with this condition is right before us. It is important that the treatment and payer communities come together to recognize where we are not following through on that potential and to then address those situations accordingly. We hope that the articles in this publication evaluate successes and appropriately frame failures for managed care decision makers, and that they will provide useful information that ultimately will result in better clinical and financial outcomes.

REFERENCES


Asthma: Prevalence And Economic Implications

MICHAE L S. BLAISS, MD

University of Tennessee Health Sciences Center, Memphis

SUMMARY

Increased prevalence of asthma has expanded the burdens of poor clinical outcomes and high treatment costs. Hospitalizations and emergency department visits, which carry significant economic implications, are related to lack of adequate disease control. Health care resource utilization rises as asthma control decreases.

Asthma is believed to affect more than 5 percent of the United States population. During the past quarter century, prevalence has risen markedly, expanding the burdens of poor clinical outcomes and costs of treatment. Uncontrolled asthma accounts for greater severity, which in turn increases per-capita direct costs of treatment.

The next several pages provide a statistical snapshot of asthma: prevalence, demands on health care utilization, and the ramifications for third-party payers and employer purchasers.

EPIDEMIOLOGY

Prevalence

Asthma affects as many as 300 million people worldwide (Figure 1), a number that is likely to rise by another 100 million over the next two decades (Masoli 2004).

Michael S. Blaiss, MD

1 Michael S. Blaiss, MD, is clinical professor of pediatrics and medicine at the University of Tennessee Health Sciences Center in Memphis. He has presented at more than 250 meetings around the world on such topics as allergic rhinitis, asthma, socioeconomic subjects in allergy and asthma, and issues in compliance. He has written for several peer-reviewed journals and allergy textbooks. Blaiss received his medical degree from the University of Tennessee Center for Health Sciences. After completing his residency at Le Bonheur Children’s Medical Center, he completed a fellowship in allergy and immunology at Ochsner Medical Foundation in New Orleans.

FIGURE 1

Global prevalence of clinical asthma

Proportion of population (%)*

- >10.0
- 7.6–10.0
- 5.1–7.5
- 2.6–5.0
- 0–2.5
- No standardized data available

SOURCE: MASOLI 2004
In the United States, approximately 16 million people currently have asthma (CDC 2004), while 30 million have experienced asthma symptoms at some point (ALA 2005a). Nearly a third of those with asthma are children under age 18. Asthma in adults is more common among women than men, affecting 7 million women versus just under 5 million men (ALA 2005a).

Asthma is the third most prevalent chronic disease in the United States, trailing only hypertension and mood disorders (Figure 2).

Asthma prevalence in the United States has been measured in varying ways. This has made some comparisons difficult, though an upward trend is clear. Prevalence by self-report more than doubled from 1980 to 1996, reaching 7.2 percent of the population (Redd 2002). Since then, current asthma has risen slightly, to 7.3 percent (NCHS 2005a).

Through 1996, the National Health Interview Survey asked respondents whether anyone in the family had asthma during the previous 12 months. Figure 3A depicts the percentage of people answering “yes.” After 1996, the question was changed to ask about lifetime, medically diagnosed asthma (Figure 3B). Post-1996 data, therefore, should not be compared with 1980–1996 data.

Asthma is more prevalent among non-Hispanic black Americans than in the white or Latino populations (Figure 3C). Black Americans also suffer from more severe exacerbations and a higher rate of emergency department visits and hospitalizations (CDC 2004).

**Mortality**

Although deaths from asthma are relatively rare, more than 4,000 occurred annually during the period from 1999 to 2002 (ALA 2005a), a statistic worth public health
PREVALENCE

concern in light of the preventable nature of asthma attacks. Moreover, the mortality rate has risen in the past two decades, particularly among black Americans and those 75 or older (Table 1). It also is currently higher in women than in men.

PUBLIC HEALTH AND HEALTH CARE UTILIZATION

Among children, the climb in prevalence has been steep; it advanced 160 percent from 1980 to 1995 (Fuhlbrigge 2002). Asthma is the third leading cause of hospitalization in the United States for those who are under the age of 15 (ALA 2005c).

Despite the rising prevalence rates, it is believed that asthma is underdiagnosed in the United States (Gergen 2003). Several studies have indicated that even patients who are identified as asthmatic may have been given a diagnosis of lesser severity than warranted. Fuhlbrigge’s survey (2002) of patients with asthma found that self-reported severity was heavily weighted toward moderate to severe persistent disease — 77 percent — compared with 11 percent reporting mild intermittent asthma. Halterman (2002) found that health care providers frequently underestimated asthma severity in children. Currently, up to 15 percent of patients have severe asthma (Weissler 2000).

Public health consequences

Hospitalizations and emergency department visits place a large burden on health resource utilization, and both are related to lack of adequate disease control. Asthma was responsible for 484,000 U.S. hospitalizations in 2002 (NCHS 2005b) and was the third leading cause of preventable hospitalization in the United States. Yet, only 28 percent of patients with asthma have action plans specifying steps for its management and control (NAEPP 1997).

The trend of asthma-related hospitalizations is somewhat checkered. Although hospital discharge rates per 10,000 fell from 19.6 in 1988 to 16.9 in 2002 — a 14 percent decline (ALA 2005a) — rates remained disproportionately high among women, children, the elderly, and black Americans (Table 2).

In contrast to hospitalizations, emergency department visits showed a single pattern: up (Table 3). The number of visits nationally rose 36 percent from 1992 to 2002, to nearly 2 million (Mannino 2002, NCHS 2005b). In 2002, more than twice as many blacks (37.2 percent) as whites (14.5 percent) suffered exacerbations that landed them in the emergency department (CDC 2004). The rate of emergency visits per 10,000 population climbed 29 percent, to 73.3. Again, blacks and people under 34 years of age had significantly higher rates (174 and 142, respectively), compared to other race and age groups (Mannino 2002).

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<td>3.2</td>
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* Data for males and females, and by age group, are for all races and are age- and sex-adjusted. Pre-1999 data age-adjusted to 1940 U.S. standard population. Data for 1999–2002 age adjusted to 2000 U.S. standard population.

SOURCE: ALA 2005A

<table>
<thead>
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<td>19.7</td>
<td>30.8</td>
<td>22.5</td>
</tr>
</tbody>
</table>

SOURCE: ALA 2005A
Office visits have remained relatively stable since the early 1990s, at 9.5 million (Gergen 2003). Nearly 54 percent of patients with current asthma regularly have appointments with their physicians. More than one quarter of white patients and more than a third of black patients have had urgent visits (CDC 2004).

The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study of patients with severe or difficult-to-treat asthma also showed a relatively high degree of health care resource utilization, in terms of office visits, emergency visits, and steroid bursts. In addition, almost one fifth to one sixth had missed 1 or more days of school or work because of their disease (Figure 4).

Given that high utilization rates — particularly for urgent visits, hospitalizations, and emergency department visits — can be decreased with appropriate management of the disease, it is not surprising that third-party payers and clinicians have focused on optimal dis-

### TABLE 3

**Emergency department visits**

<table>
<thead>
<tr>
<th>Year</th>
<th>Total</th>
<th>White</th>
<th>Black</th>
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<td>1999</td>
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<td>17.4</td>
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<td>81.3</td>
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</table>

**Source:** ALA 2005B

### FIGURE 5

**Total costs of asthma**

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Costs (in billions of dollars)</th>
</tr>
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<tbody>
<tr>
<td>1990</td>
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<tr>
<td>1998</td>
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<tr>
<td>2004</td>
<td>$16.1</td>
</tr>
</tbody>
</table>

**Sources:** WEISS 1992, WEISS 2001, ALA 2005B

### FIGURE 6

**Proportion of asthma costs**

- Total: $16.1 billion
- Direct costs: $11.5 billion (71%)
- Indirect costs: $4.6 billion (29%)

**Source:** ALA 2005B

---

**Utilization**

Office visits have remained relatively stable since the early 1990s, at 9.5 million (Gergen 2003). Nearly 54 percent of patients with current asthma regularly have appointments with their physicians. More than one quarter of white patients and more than a third of black patients have had urgent visits (CDC 2004).

The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study of patients with severe or difficult-to-treat asthma also showed a relatively high degree of health care resource utilization, in terms of office visits, emergency visits, and steroid bursts. In addition, almost one fifth to one sixth had missed 1 or more days of school or work because of their disease (Figure 4).

Given that high utilization rates — particularly for urgent visits, hospitalizations, and emergency department visits — can be decreased with appropriate management of the disease, it is not surprising that third-party payers and clinicians have focused on optimal dis-
The value of pharmacy expenditures

In the mid-1990s, as public health officials and clinicians emphasized the use of pharmacotherapy as a means for controlling asthma, various studies identified pharmaceutical therapy as the largest source of direct treatment costs for the disease — relegating hospitalization to second place (Blaiss 2003). Cisternas (2003) found that half of direct treatment expenditures stemmed from pharmaceutical use and less than one third were the result of hospitalization and non-emergency department (e.g., physician-office) visits.

The pharmacoeconomic equation is simple:

\[ \text{A large and increasing prevalence} + \text{High rates of hospitalization and emergency room visits} = \text{A significant economic burden from uncontrolled disease} \]

The increased proportion of direct expenditures attributable to pharmacotherapies should be viewed in the context of total health care costs and disease control. Per-person direct and indirect costs for patients escalate with disease severity. Blaiss (2003) found that costs of mild asthma totaled $2,646; for those with moderate asthma, costs reached $4,530, and that they were nearly 3 times higher, $12,813, for severe asthma.

Health care utilization rises as asthma control decreases (Vollmer 2002), and the segment of patients with difficult-to-treat asthma — whether caused by proximity to asthma triggers, severe or frequent exacerbations, or multidrug regimens, account for a large portion of health care resource use (Sullivan 2003).

Indirect costs, as measured in terms of the drain on productivity, also affect the pharmacoeconomic picture. From 1980 to 1996, absentee days from work caused by asthma increased from 6.2 million to 14.5 million. Absentee days from school rose a similar amount, from 6.6 million to 14.0 million (Mannino 2002). Nearly one quarter of children have their activities limited by asthma (Gergen 2003), and almost 15 percent of adults do (Mannino 2002).

What's next for asthma pharmacotherapy? In part, this depends on one’s answer to another question: What type of asthma is it? Asthma is now thought to be not one, but a group of diseases, with varying etiologies and outcomes (Gergen 2003). Understanding the multiple inflammatory and immunological mechanisms thus may provide new therapies (Stirling 2000), and these may, in turn, treat asthma that is not currently susceptible to proper control and complications related to the disease (Storms 2003). Payers will need to evaluate emerging therapies in this context of unmet needs.

### TABLE 4  Components of direct and indirect costs

<table>
<thead>
<tr>
<th></th>
<th>Estimates, in millions of dollars</th>
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</thead>
<tbody>
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</tr>
<tr>
<td>Hospital Care</td>
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</tr>
<tr>
<td>Inpatient</td>
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</tr>
<tr>
<td>Emergency Room</td>
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</tr>
<tr>
<td>Outpatient</td>
<td>$492</td>
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<td>Physicians’ Services</td>
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<tr>
<td>Inpatient</td>
<td>$377</td>
</tr>
<tr>
<td>Outpatient</td>
<td>$897</td>
</tr>
<tr>
<td>Medications</td>
<td>$2,842</td>
</tr>
<tr>
<td><strong>Indirect Costs</strong></td>
<td></td>
</tr>
<tr>
<td>School days lost</td>
<td>$1,389</td>
</tr>
<tr>
<td>Loss of work</td>
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<td>Outside employment</td>
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<td>Housekeeping</td>
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<tr>
<td>Mortality</td>
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</table>

**SOURCE:** ALA 2005B
CONCLUSION

The increasing prevalence of asthma exacts a significant toll on individual and public health and quality of life. Asthma also has significant economic implications, including costs associated with health care utilization and missed school and work days. Given the magnitude of asthma prevalence, its cost, and the effects of uncontrolled disease, the implications are clear: Controlled disease equals better clinical and financial outcomes. Rodrigo (2004) documented that controlling severe asthma has the potential to reduce costs.

Beyond direct treatment, studies have increasingly analyzed interventions that can lead to improved outcomes across the board, both clinical and economic. An inner-city asthma intervention proved cost-effective and improved clinical outcomes in those with high asthma severity (Sullivan 2002). Better health-related quality of life scores are correlated with lower costs (Eisner 2002). A Dutch study found that self-management strategies proved cost-effective (Schermer 2002). All these strategies point to the need to improve control of asthma.

REFERENCES


Weiss KB, Sullivan SD. The health economics of asthma and asthma health care utilization. J Manag Care Pharm. 2003;9:534–543.


Addressing Unmet Needs In Asthma Care

AIDAN A. LONG, MD
Massachusetts General Hospital, Boston
Harvard Medical School

SUMMARY
Unmet needs stem from factors that contribute to poor disease control. The benefits of controlling asthma include decreased morbidity and mortality, improved patient and caregiver quality of life, and more effective resource utilization and reduced costs. Establishing positive control of asthma will ensure that health care dollars are spent efficiently to manage asthma proactively.

Asthma is characterized by airway inflammation and hyperresponsiveness that often presents as dyspnea, wheezing, chest tightness, and/or coughing. The disease is as individual as affected patients, with severity fluctuating throughout a patient’s life. In the United States and globally, asthma is poorly controlled and underestimated. Factors contributing to poor disease control and lack of diagnosis are known as asthma’s unmet needs, many of which have been defined. Several, including socioeconomic, bio-

logic, variability, and environmental factors, as well as patient perceptions and adherence, are examined here.

For patients and caregivers, especially parents of asthmatic children, benefits of asthma control include decreased patient morbidity and mortality, as well as better patient and caregiver quality of life. For clinicians, particularly in a managed care setting, the benefits of asthma control include more effective resource utilization, cost reductions, and better patient quality of life.

Establishing control of asthma ensures that health care dollars are spent efficiently on proactive management, instead of struggling with asthma-related sequelae on a reactive basis. Spending is better applied to restoring and maintaining health on a broad basis than to urgent, episodic care or treating advanced disease in a smaller, but needier, population. For payers and employers, reducing absenteeism and keeping employees on the job and functioning at a higher level makes more sense than dealing with absenteeism and presenteeism.

IDENTIFYING UNMET NEEDS
Despite the availability of effective therapies, asthma exacts a severe national burden through patient morbidity and mortality, rising health care costs, and employee presenteeism and absenteeism. Since 1980, the number of people in the United States who report having asthma has more than doubled, with the greatest rise in children up to 4 years old. Annually, asthma ac-

1 Aidan A. Long, MD, is assistant professor of medicine at Harvard Medical School. Among his present positions, Long is clinical director of allergy at Massachusetts General Hospital in Boston and codirector of the Partners Asthma Center. Long earned his medical degree from University College Cork, National University of Ireland, completed his residency at St. Vincent’s Hospital and University College in Dublin, Ireland, and then completed a fellowship in allergy and immunology at McMaster University Medical Center in Hamilton, Ontario. A fellow of the American Academy of Allergy, Asthma, and Immunology, Long has published numerous peer-reviewed articles. He also is the lead author of a U.S. Agency for Healthcare Quality and Research Evidence Report/Technology Assessment (no. 54), Management of Allergic and Nonallergic Rhinitis.

2 A growing concern among U.S. employers, presenteeism is defined by AON Consulting as “workers who remain on the job but who are not as productive as usual due to stress, depression, injury, illness or something as simple as a migraine headache” (Lowe 2004).
counts for 1.9 million emergency department (ED) visits and 484,000 hospitalizations. Asthma was responsible for 4,261 deaths in 2002 (NCHS 2005).

A relatively small group of difficult-to-treat or severely affected patients account for much of the morbidity, mortality, and costs associated with asthma. Dolan (2004) embarked on a study of 4,756 patients (≥6 years old) with physician-diagnosed severe or difficult-to-treat asthma. Eligible patients have been receiving asthma care for at least 1 year, have a smoking history of <30 pack years, and have been high users of health services or medication in the past year. Overall, 48 percent were classified with severe asthma according to National Asthma Education and Prevention Program (NAEPP) guidelines, 48 percent had moderate asthma, 3 percent mild asthma; 96 percent were deemed to have difficult-to-treat asthma because of their need for multiple drugs or the occurrence of frequent or severe exacerbations. This study is continuing, but from the data thus far, patients with severe asthma have the highest health care utilization in the previous 3 months ($P < .001$).

To improve diagnosis and treatment, the National Heart, Lung, and Blood Institute (NHLBI) established the NAEPP in 1997. NAEPP guidelines classify asthma severity by clinical features and lung function (Table 1) and recommend daily medication regimens (Table 2, page 18). Though diagnosis and treatment guidelines are widely available, the evidence suggests that they are not being properly implemented.

Despite the increased prevalence of asthma from 1980 to 1996, the reported rate of asthma episodes or attacks decreased from 1997 to 1999. Also, since 1995, mortality and hospitalization rates have decreased, but outpatient and ED visits have increased (Mannino 2002). Decreases in the frequency of asthma-related episodes, hospitalizations, and mortality may, in part, be attributed to treatment guidelines and new treatment options.

Other important contributing factors to poor control are the failure to properly diagnose asthma and patient nonadherence with therapy. Even when the guidelines are adhered to and patients comply with treatment, there is wide variability in outcomes. One inherent limitation of the guidelines relates to disease variability in asthma.

Current guidelines classify patients with persistent asthma as mild, moderate, or severe, on the basis of lung function, asthma symptoms, nighttime awakenings, and

<table>
<thead>
<tr>
<th>Classification</th>
<th>Symptoms</th>
<th>Nighttime symptoms</th>
<th>Lung function</th>
</tr>
</thead>
</table>
| **Mild intermittent** | • ≤2 per week  
• Asymptomatic and normal PEF between exacerbations  
• Exacerbations are brief (lasting a few hours to a few days); intensity varies  | ≤2 times monthly  | • FEV₁ or PEF ≥60 percent predicted  
• PEF variability <20 percent |
| **Mild persistent**     | • >2 per week but <1 per day  
• Exacerbations may affect activity level | >2 times monthly  | • FEV₁ or PEF ≥80 percent predicted  
• PEF variability 20–30 percent |
| **Moderate persistent** | • Daily symptoms  
• Daily use of inhaled short-acting β₂-agonists  
• Exacerbations affect activity  
• Exacerbations ≥2 times per week; may last days  | >1 time weekly  | • FEV₁ or PEF >60 percent to <80 percent predicted  
• PEF variability >30 percent |
| **Severe persistent**    | • Continual symptoms  
• Limited physical activity  
• Frequent exacerbations  | Frequent  | • FEV₁ or PEF ≤60 percent predicted  
• PEF variability >30 percent |

FEV₁ = forced expiratory volume in 1 second, PEF = peak expiratory flow.

SOURCE: NAIPEP 1997
exacerbations (NAEPP 1997). Yet, the guidelines do not address symptom severity that fluctuates over time.

**Guideline limitations**

The recommendations set forth in the guidelines are based on the findings of randomized, placebo-controlled trials in small subsets of the asthmatic population. Patients in such trials tend to be more compliant and receive more education on proper use of inhalers and treatments than other patients (Barnes 2004). Minorities and underprivileged persons tend not to be well represented in these types of controlled studies, on which treatment-guideline recommendations are founded. The rate of asthma among African-Americans is 2 to 3 times that of white Americans, with similar disparities for mortality, hospitalizations, and ED visits (Redd 2002).

**Socioeconomic factors**

Socioeconomic factors have long been thought to underlie differences observed between asthma prevalence and outcomes in white and black populations in the United States. Nelson and colleagues (1997) examined the prevalence of asthma in a socioeconomically homogeneous, middle class, multiethnic population of schoolchildren in Southfield, Mich. — a city with a middle-class population where only 4 percent of blacks and 7 percent of whites live below federal poverty limits. Researchers identified patients with "physician-diagnosed" asthma and patients with "probably undiagnosed" asthma. Access to medical care and environmental conditions were similar across the study population. It was found that after adjusting for maternal education and sex, prevalence of physician-diagnosed asthma and probable asthma were independently associated with race (black). Overall, the lifetime prevalence of asthma was 9.5 percent (12 percent black, 6 percent white). The lifetime prevalence of probable undiagnosed asthma was 16.6 percent in the black population and 10.8 percent in the white population. Possibly, biologic factors, as well as unmeasured socioeconomic factors have long been thought to underlie differences observed between asthma prevalence and outcomes in white and black populations in the United States. Nelson and colleagues (1997) examined the prevalence of asthma in a socioeconomically homogeneous, middle class, multiethnic population of schoolchildren in Southfield, Mich. — a city with a middle-class population where only 4 percent of blacks and 7 percent of whites live below federal poverty limits. Researchers identified patients with "physician-diagnosed" asthma and patients with "probably undiagnosed" asthma. Access to medical care and environmental conditions were similar across the study population. It was found that after adjusting for maternal education and sex, prevalence of physician-diagnosed asthma and probable asthma were independently associated with race (black). Overall, the lifetime prevalence of asthma was 9.5 percent (12 percent black, 6 percent white). The lifetime prevalence of probable undiagnosed asthma was 16.6 percent in the black population and 10.8 percent in the white population. Possibly, biologic factors, as well as unmeasured socioeconomic factors have long been thought to underlie differences observed between asthma prevalence and outcomes in white and black populations in the United States.
nomic factors, may contribute to the racial disparities observed among asthma patients.

**Biological factors**

Studies have documented a heritable component between certain phenotypes and asthma incidence (Holloway 1999, Holgate 1999). Due to asthma's variability, researchers often study the genetic component through phenotypes that can be measured objectively (e.g., inflammation, airway hyperresponsiveness). These measures are not asthma-specific, however. For clinicians, use of an asthma phenotype to evaluate asthma's genetic basis is confounded by multiple definitions of the same phenotype across studies. To date, genetic linkage and association studies have identified more than 25 asthma or phenotype across studies. To date, genetic linkage and association studies have identified more than 25 asthma or.

**Variability factors**

The term asthma variability refers to the fact that patient symptoms and severity are likely to fluctuate over time. Calhoun (2003) looked at variability of severity in patients who had not received maintenance treatment. Eighty-five patients in trials of therapy for moderate or severe persistent asthma at baseline were randomized to placebo for 12 weeks. Within the placebo group, severity classification varied significantly over the 12 weeks. At baseline, all patients met NAEPP criteria for moderate or severe persistent asthma. Over the 12 weeks, the mean percentage of time that patients met all criteria for intermittent, mild, moderate, or severe asthma were 9, 14, 71, and 6 percent, respectively. When severity was assessed by days per week with albuterol use or asthma symptoms, patients spent 59 and 45 percent of time, respectively, in the intermittent and mild categories. The researchers concluded that asthma control cannot be assessed by looking at a specific point in time. Conceptualization of guidelines that would be responsive to short-term fluctuations in asthma severity is difficult.

**ESTABLISHING ASTHMA CONTROL: ARE GUIDELINES ENOUGH?**

The current guidelines classify asthma severity based on daytime symptoms, nighttime symptoms, and lung function. As described above, many patients vary significantly over time with respect to disease severity. Further, these parameters of asthma often fail to predict risk of future exacerbations. Additional measures to assess asthma control are being studied.

**Airway hyperreactivity (AHR)**

Sont (1999) conducted a 2-year, prospective, randomized, parallel trial of 75 adults with mild to moderate asthma. Patients were evaluated every 3 months for forced expiratory flow volume in 1 second (FEV₁) and AHR to methacholine. Patients were instructed to keep diaries of symptoms, beta₂-agonist use, and peak expiratory flow (PEF). In one arm of the study, treatment with inhaled corticosteroids (ICS) was adjusted using a stepwise approach based on AHR. Bronchial biopsies were obtained at study entry and endpoint. Patients receiving treatment with the stepwise AHR treatment strategy had 1.8-fold fewer mild exacerbations than the reference group, and FEV₁ was significantly improved in the AHR strategy group (P<.05). Patients in the AHR strategy group had greater reduction in thickness of the subepithelial reticular layer than the reference strategy group [95 percent confidence interval; 1.7µm (0.2–3.1 µm)]. Changes in AHR in both groups correlated with biopsy eosinophil counts (r=−0.48, P=.003). More effective asthma control may be achieved if AHR is reduced along with an overall improvement in lung function. The data suggest that current guidelines may be insufficient for managing patients because they fail to utilize measures of inflammation as markers of severity and progression.

**Nitric oxide**

Exhaled nitric oxide (NO), related to airway inflammation, has received attention as a possible marker of asthma control and a means for adjusting treatment. In general, increases in expelled NO correspond to deterioration in asthma control (Jones 2001). To evaluate these findings and their implications on ICS usage, Smith (2005) randomized patients to have their ICS dose adjusted on the basis of expelled NO or using a treatment algorithm based on conventional guidelines. Researchers reported a 40 percent reduction in required ICS in patients monitored by exhaled NO without compromising major clinical outcomes, e.g., exacerbation rates.

**Sputum eosinophil count**

Sputum eosinophil counts (SEC) also have been proposed as a possible marker of underlying asthma disease control. A randomized controlled trial assessed whether a strategy that adjusted therapy so as to minimize eosinophil-related inflammation resulted in fewer exacerbations than a standard management strategy (Green 2002). Overall, the SEC was 63 percent lower (P=.002); patients had significantly fewer severe asthma exacerbations (35 vs. 109; P=.01); and significantly fewer patients...
were admitted to hospital with asthma (1 vs. 6, \(P = .047\)) in the sputum management group than patients in the guideline management group. Daily doses of oral or inhaled corticosteroids did not differ between the groups. These findings suggest that measures of control based on SECs may reduce exacerbations and admissions without the need for additional anti-inflammatory treatment.

**Patient perceptions**

A significant gap exists between patient-perceived asthma severity and actual severity. To gain understanding from the patient perspective, Rabe (2000) surveyed the extent to which the goals of the 1995 Global Initiatives for Asthma (GINA) guidelines were being met. These goals include control of symptoms, prevention of exacerbations, maintenance of near-normal pulmonary function, maintenance of normal activity levels, avoidance of treatment-related adverse events, prevention of irreversible airflow disruption, and mortality prevention.

Asthma patients were identified by telephone by screening nearly 74,000 households in seven European countries. The survey identified current asthma patients in 3,488 households; 2,803 patients completed the survey. Overall, only 5.1 percent of adults and 5.8 percent of children met the GINA criteria for asthma control. Forty-six percent of patients reported daytime asthma symptoms, and 30 percent of patients reported asthma-related sleep disturbances at least once weekly. Of those, a staggering 6.7 percent of children and 5.3 percent of adults reported nightly sleep disturbances. Coughing, wheezing, dyspnea, and chest-tightness episodes were reported by 52 percent of children and 57 percent of adults, with 36 percent and 28 percent of patients, respectively, requiring urgent care in the last year. Overall, the rate of overnight hospitalization was 7 percent. Only 61 percent of children and 45 percent of adults reported receiving a lung function test in the last year. In addition, only 30 percent of children and 29 percent of adults reported using a peak flow meter at least once weekly (Rabe 2000).

Despite the high frequency of asthma-related symptoms, health care visits, use of inhaled medications, and limitations on activity, 50 percent of patients in this study reported that they considered their asthma to be completely or well controlled. Clearly, the patient-perceived level of asthma control is significantly different from the clinical definition of control.

An earlier study by Kendrick (1993) study had similar findings. In this study, 255 patients with asthma were asked to define their severity using a visual analog scale (1-100, with 1 representing “no asthma” and 100 representing “most severe asthma”) and a coded peak flow meter (to prevent patient bias in the findings). The main outcome measure of interest to the researchers was the correlation between the analog scale and the PEF (measured as a percentage of predicted peak flow). Overall, 60 percent of patients were termed “poor discriminators,” as there was a low level of correlation between self-reported scores and simultaneous peak flow measurements (\(P > .05\)). Some of the poor discriminators gave only low ratings on the analog scale despite large changes observed during simultaneous peak flow rates. Other poor discriminators were aware that they had asthma but exhibited difficulty in judging their asthma severity.

Findings from these and other studies clearly demonstrate the need for patient education in the areas of self-reported asthma severity as well as treatment goals. Patients seem to be willing to accept less than complete control of symptoms as an outcome. Further, patients appear to be willing to accept some level of symptom exacerbation as normal and may dismiss such incidents at a physician interview. It is important, therefore, that patients are educated regarding the reporting of any symptom, even those that they consider mild.

**Patient adherence**

Adherence is a leading reason for poor control, despite highly effective treatments. About 50 percent of patients with chronic disease do not adhere to treatment regimens and medical advice (Meichenbaum 1987, Sackett 1979).

A review of studies measuring adherence with ICSs, inhalation techniques with different devices, and deposition of drug in the lung found that, overall, patients received the recommended dose of medication on 20 to 73 percent of days. Further, only 46 to 59 percent of patients were using efficient inhalation techniques. Lung deposition varied not only with the inhaler technique but also with particle size (Cochrane 2000).

If patients are not trained on proper use of medication-delivery devices, they cannot properly self-medicate and thus miss the treatment benefit. Such suboptimal treatment may lead patients to believe that their medication is ineffective, increasing the likelihood that they will discontinue use. Investigators looked at medication under-use and found that average compliance (ratio of doses taken to doses prescribed) was 63 to 92 percent; the percentage of underuse days was 24 to 69 percent (Cochrane 2000). The 92 percent compliance rate derived from a study employing an intensive patient education program (van der Palen 1997). Patients also may overmedicate to compensate for a suboptimal response achieved with poor dosing techniques. The trend to overmedicate may be higher with bronchodilators as benefits are more apparent to the patient with the short-acting agents.

The documented benefit of patient adherence to treatment regimens is overwhelming. In one study, asthma-related mortality dropped 21 percent with each added
canister of ICSs used in the previous year. Asthma mortality rates in the 3 months after discontinuation of an ICS were higher than those for patients continuing treatment (Suissa 2000). Another study examined the effect of ICS use on risk of a subsequent event necessitating hospitalization or ED treatment following discharge (Smith 2004). After controlling for demographic and resource variables, they found a 52 percent reduction in risk of a subsequent ED visit or hospitalization among patients filling an ICS prescription who had previously presented to the ED with an asthma-related event.

To evaluate the effect of adding a long-acting bronchodilator to an ICS-alone treatment regimen, Stempel (2005) examined refill rates for several ICSs either alone or combined with a long-acting bronchodilator. He found that when an ICS is paired with a long-acting bronchodilator in a single inhaler, the rate of refill is significantly higher ($P<.05$) than any of the individual agents alone, suggesting that patients may perceive more benefit when a bronchodilator — which exerts a more immediate effect on symptoms — is paired with an ICS, which tends not to have an immediate effect. However, refill rates for the combination product were still $<5$ per year, implying that a majority of the time, patients are not adherent.

**Environmental factors**

Environmental allergens can exacerbate asthma, with numerous triggers reported. Means of preventing asthma exacerbations by way of allergen avoidance have been studied intensively. Much research has been focused on the avoidance of dust mites in the home.

The need to employ avoidance measures that are both sufficient and patient-specific is exemplified by a recent study by Woodcock (2003). The effect of the use of allergen-impermeable bed covers was evaluated in a 1-year study involving 1,122 adults with asthma. Of interest to researchers were the mean morning PEF rate and the proportion of patients discontinuing ICS therapy as part of a phased reduction program during study months 7 through 12. After adjusting for baseline characteristics, no significant difference in mean morning PEF was found ($P<.001$). Further, there was no significant difference between the control and intervention groups in the proportion of patients discontinuing ICS treatment. The researchers concluded that use of an allergen-impermeable bed cover alone in an unselected group of asthma patients, as a way to avoid exposure to dust mite allergen, does not yield clinical improvements in asthma.

In a 2001 systematic review of 23 dust mite avoidance studies, researchers described approaches to reducing environmental exposure to dust mite allergens as moderately effective (Goetzsche 2001). There is a great need to identify means to effectively reduce environmental allergens and to document changes in asthma outcomes associated with those strategies. Comprehensive, patient-specific allergen-avoidance strategies are helpful.

A recent study examined effects of a patient-tailored, environmental intervention to reduce concentration of allergens and the effects on asthma-related morbidity in a population of 937 inner-city children (Morgan 2004). The children and caregivers received education on the technique and importance of allergen removal. Patients were provided with tools to replicate the model behavior demonstration. Intervention continued for 1 year, with 1-year follow-up. Patients in the intervention group had significantly fewer days with asthma symptoms than patients in the control group during the intervention year and follow-up period ($P<.001$). Further, reduced levels of cockroach and dust mite allergen were significantly correlated with fewer asthma complications ($P<.001$). These findings translate to 34 fewer days with symptoms of wheezing among patients in the intervention group compared to the control group. These findings support efforts to reduce environmental allergens and suggest a need to target each strategy to each patient’s allergic sensitization and environmental risk factors. Such targeted approaches may improve asthma outcomes and warrant further investigation.

**Recalcitrant asthma**

Despite all efforts, asthma, in some cases, remains difficult to control. A few patients experience significant asthma-related morbidity despite maximal medical therapy. Up to 5 percent have glucocorticoid-resistant asthma, suffering severe disease and poor symptom control regardless of high-dose oral glucocorticoid therapy.

Because airway inflammation and immune activation are important factors in chronic asthma, current guidelines focus on anti-inflammatory therapy, particularly inhaled glucocorticoids, but some patients fail to respond. Steroid-resistant asthma (SRA) may be defined by the failure to improve baseline morning prebronchodilator FEV$\text{I}$ by more than 15 percent, following 7 to 14 days of 20 mg twice daily oral prednisone. While some patients might respond to higher doses administered for longer periods, adverse effects argue against such a regimen.

SRA is characterized by higher levels of immune activation in the airways than that exhibited by patients with steroid sensitivity; further, glucocorticoids do not reduce the eosinophilia or T cell activation found in SRA patients; this persistent immune activation is associated with high levels of interleukin (IL)-2, IL-4 and IL-5 in the airways. SRA patients can have acquired steroid resistance (type I) or primary steroid resistance (type II) SRA.

When a patient presents with a history of this condi-
RATIONALE

The clinician must confirm that he or she is compliant and taking the oral steroid under strict supervision; checking morning serum cortisol after a course of steroid therapy is vital. Because Type I accounts for over 95 percent of SRA cases, the clinician should suspect poor adherence to therapy until this is proven not to be so (Leung 1997). Other factors unrelated to steroid resistance also contribute to severe asthma, and these recently have been reviewed in detail (Wenzel 2005).

SUMMARY

To gain better control of asthma, a comprehensive approach is essential. Health plans, researchers, clinicians, patients, and caregivers must ensure that asthma is adequately diagnosed, properly treated, and closely monitored. There are numerous unmet needs in asthma; only a few have been explored here. Nevertheless, it is evident from this review that a composite approach to defining asthma control that includes symptoms, functional limitations, use of rescue medications, adherence, lung function, and other markers where available, is necessary.

In particular, clinicians need to involve patients (and their caregivers) in their own care. Researchers must continue to develop new therapies to alleviate intractable asthma, and health plans have to impress on other stakeholders that scarce resources must be used optimally.

REFERENCES

Asthma Treatment Guidelines: Current Recommendations, Future Goals

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SUMMARY

Physicians have not fully implemented evidence-based guidelines, despite their worldwide availability. Adherence to guidelines can prevent hospitalization and disability as well as improve quality of life. Future generations of guidelines will need to add an emphasis on emerging clinical issues, such as risk markers and disease control.

Clinical practice guidelines are systematically developed statements to help practitioners and patients decide on appropriate health care for specific circumstances (Lohr 1992). Reliable guidelines are evidence-based — derived primarily from data in randomized, controlled clinical trials as well as clinical expertise; they are refereed by peers prior to release. Though they may be owned by a professional society or association, they generally are available on the Web or in society journals. The U.S. standard for asthma care is based on the National Heart, Lung, and Blood Institute Guidelines (NHLBI) Expert Panel Report 2 (sometimes referred to as the EPR-2 or National Asthma Education and Prevention Plan [NAEPP] guidelines) (NAEPP 1997, 2002). Internationally, the standard for guidelines is either those from the NAEPP or those from the joint NHLBI/World Health Organization (WHO) initiative — the Global Initiative for Asthma (GINA).

Two types of guidelines are in clinical use: those from professional societies and expert panels and those from health care organizations and third-party payer groups. Health plans issue guidelines to try to improve treatment processes and outcomes. Such guidelines tend to be drafted with the demographics of the plan’s membership in mind and, often, include an element of cost-effectiveness. Though geared toward specific populations (e.g., Medicare patients), health plan guidelines are derived from a combination of professional society recommendations, literature reviews, expert clinical opinions, and community standards of care.

An advantage of using national or international guidelines is that they can eliminate local discrepancies among protocols through use of evidence-based best practices. For health care professionals, relying on one set of guidelines for advice simplifies clinical practice — especially when a medical practice contracts with many health plans, each with unique expectations about patient care.

One objective of the GINA 2004 update was to “…assist health care professionals and public health officials in appreciating the magnitude of the asthma problem in their countries and to design and deliver effective asthma management and prevention programs in their communities” (GINA 2004). Despite the GINA initiative, the asthma epidemic is expanding worldwide and will likely worsen as the number of environmental triggers keeps pace with continued industrialization. A future generation of guidelines seeking to counter this trend with a heightened emphasis on disease control and adherence to updates can contribute substantially to resolving this problem.

U.S. and international guidelines

In 1989, the NHLBI initiated the National Asthma Education and Prevention Program. Two years later, an
expert panel generated a scientific report on the diagnosis and management of asthma. The report recognized that airway inflammation was important in the pathogenesis of asthma and recommended anti-inflammatory agents, inhaled corticosteroids, as the basis of therapy.

In 1995, a scientific committee met to review more than 5,000 medical literature abstracts and determined a need for an update. A second expert panel was convened, which issued a report in 1997. This version of the guidelines presented a stepwise approach that could be stepped up or down, and specified goals for therapy — controlling symptoms, reducing exacerbations, and minimizing asthma-related limitations of activity. The four-part stratification scheme it introduced — classifying patients as mild intermittent, mild persistent, moderate persistent, or severe persistent (see page 18) — is useful but sometimes confusing, because a patient’s classification can vary over time and classifications can overlap. In 2002, these guidelines were updated relative to medication use, monitoring symptoms, and prevention (NAEPP 2002).

Since then, scientific understanding of asthma has grown, and agents with new mechanisms of action have come to market. There also is increasing recognition that guidelines generally have neither been followed nor led to acceptable levels of disease control. Therefore, NAEPP is expected to issue a thorough update of its guidelines in 2006. Informed discussion in the medical community suggests that new guidelines will address the importance of disease control, rather than relying solely on a strict classification-based treatment scheme.

Internationally, in 1997, the WHO issued global guidelines on three chronic respiratory diseases — asthma, obstructive lung disease, and allergic rhinitis — and their effects on asthma. The guidelines were designed by specialists and are extremely useful to specialists, more so than to primary care physicians.

Primary care practitioners initiated an effort called the International Primary Care Airways Group (IPAG) task force. It was established in 2002 to develop evidence-based guidelines specifically designed for use in primary care settings. The first IPAG report was released in May 2005, and it emphasizes integration of primary and specialty care in managing chronic lung diseases.2

The commonly used asthma guidelines are listed in the Table. There are no glaring discrepancies between the key recommendations of these various guidelines. Classification systems in the United States are based on symptoms and spirometry. The British, Canadian, and Australian guidelines use severity categories similar to those in U.S. guidelines, but tend to emphasize individual control over classification (Colice 2004, Campbell 2004).

Use of asthma guidelines has been shown to affect outcomes favorably (Cloutier 2005). Specifically, hospitalization is reduced with initiation of inhaled corticosteroids (Donahue 1997).

If guidelines are to be implemented, the following must occur: physicians must know about them, read them, believe them, and then adhere to them. Also, the concept of control must be firm in the physician’s mind.

2 Physicians have free access to the IPAG handbook through the IPAG Web site, «http://www.ipagguide.org».

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**TABLE**

<table>
<thead>
<tr>
<th>Current asthma guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>United States</strong></td>
</tr>
<tr>
<td><strong>Worldwide</strong></td>
</tr>
<tr>
<td>Global Initiative for Asthma (GINA) issued worldwide guidelines in coordination with the NHLBI and a pocket guide for asthma management and prevention. The 50-page guidelines and the pocket guide were updated in 2004. These guidelines are available at: «<a href="http://www.ginasthma.com/download.asp?intId=94%C2%BB">http://www.ginasthma.com/download.asp?intId=94»</a>.</td>
</tr>
<tr>
<td><strong>Europe</strong></td>
</tr>
<tr>
<td>British Guidelines on the Management of Asthma. Issued by the British Thoracic Society and the Medical Specialty Society, these guidelines were published by the Scottish Intercollegiate Guidelines Network in 2003 and updated in 2004. They are also issued as a Quick Reference Guide. Available at: «<a href="http://www.sign.ac.uk/guidelines/published/support/guideline63/download.html%C2%BB">http://www.sign.ac.uk/guidelines/published/support/guideline63/download.html»</a>.</td>
</tr>
<tr>
<td><strong>Canada</strong></td>
</tr>
<tr>
<td><strong>Australia</strong></td>
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</tbody>
</table>
that depend on disease severity and progression. Goals for treatment of asthma are stated in NAEPP and the GINA guidelines. In clinical practice, however, emphasis is not always placed on achieving goals by monitoring asthma-related events and markers or by adjusting medications, doses, or educational efforts. Although treating to goal improves outcomes (Bateman 2004), it is not yet common practice.

A basic understanding of chronic asthma as an inflammatory disease is lacking among physicians and patients alike (Colice 2004). The causes of asthma exacerbations still are undergoing scientific scrutiny.

Frequency of exacerbations is associated with degree of airway hyperreactivity and peak flow variability. The NAEPP guidelines make clear that physicians must undertake to control the disease and prevent exacerbations with evidence-based preferred anti-inflammatory treatment, inhaled corticosteroids. Less-effective alternatives include leukotriene blockers and cromolyn/nedocromil (the latter especially for children under age 12). The 2002 NAEPP update stated that inhaled corticosteroids are safe and effective for children as young as age 4. There also should be a plan for a quick-relief medication (short-acting beta₂-agonist bronchodilators), in case exacerbations occur despite best efforts. Guidelines for asthma treatment depict progressive choices of control medication that depend on disease severity and progression.

**WHY GUIDELINES ARE NOT FOLLOWED**

There are many reasons for physician nonadherence to guideline recommendations — some valid, some not. Understanding of the guidelines varies with degree of specialization of practitioner (Colice 2004). Yet, understanding does not necessarily equate to adherence.

Individual physician-autonomy philosophies may negatively influence guideline usage. Differing treatment philosophies of individual physicians may include skepticism about outcomes research and evidence-based medicine in general, especially among seasoned clinicians, who may be unwilling to abandon practice traditions and office culture (Diamond 1998). But, even if the practitioner wishes to use the guidelines, issues surrounding patient care (setting, funding) can challenge the ability to implement guideline recommendations.

Demographic and other factors can influence physician adherence to guidelines (Cabana 2000). Physician age may present barriers, for example. Though younger and older practitioners suffer from time limitations and may suffer from lack of outcome expectancy, older practitioners are less comfortable with their peak-flow meter training and younger physicians feel less confident about correctly prescribing corticosteroids (Cabana 2000).

Non specialists, particularly those who are not part of an integrated health system or a health plan, may not know about the existence of certain guidelines. Further, guidelines can be too complex, with categories that are difficult to remember. The reasons that guidelines are not followed have been studied extensively. In asthma, possible explanations include (Putnam 2001):

- Inertia
- Underestimation of seriousness of asthma
- Misclassification of severity level in NAEPP guidelines
- Resistance to prescribe or use “steroids”

New evidence can prove a guideline wrong, and it eventually changes. For example, current guidelines recommend daily therapy for mild, persistent asthma. Prescription patterns show, however, that most patients in this category use these therapies sporadically. Clinical investigation has demonstrated that intermittent courses of inhaled budesonide or oral zafirlukast on an as-needed basis were as effective as daily doses of these medications (Boushey 2005). The NAEPP guidelines state that for mild, intermittent asthma, short-acting beta₂-agonists is the treatment of choice. Use of steroid inhalers, however, reduced the mortality rate (Donahue 1997).

Other new evidence concerns combination therapies. Combination therapies have been shown to allow lower dosing of corticosteroids through various mechanisms, including:

- Upregulation of steroid receptors by beta adrenergics
- Upregulation of beta adrenergic receptors by steroids
- Weak anti-inflammatory properties of beta adrenergics

These mechanisms allow lower dosing of corticosteroids via a dual mechanism rather than raising the corticosteroid dose (Roche 2004). Some patients who were uncontrolled on an inhaled corticosteroid (ICS) or controlled on an ICS and a long-acting beta₂-agonist were able to maintain control on a budesonide/formoterol combination inhaler when the dose and...
number of inhalations were reduced (Ind 2004).

Another reason for guideline nonadherence is that physicians and patients may not recognize dangerous symptom patterns that should serve as signals for stepping up care. Patients do not accurately gauge the severity of their disease (Luskin 2005). Neither patients nor physicians recognize the signs of escape from control. Patients are unable to sense large changes in lung function that put them at risk, so they do not contact their physicians. Education about symptom patterns that indicate loss of control and on the need for additional therapy can help to avert crises.

An effective educational solution for recognizing danger signals is Asthma Care Training for Kids (ACT), a major asthma initiative of the Asthma and Allergy Foundation of America. The ACT program is targeted to 7-12-year-old children with asthma and their parents, and functions to motivate the parent and child to learn self-management skills and work as a team with their physician to control the child's asthma. The ACT program is designed to work in tandem with regular medical care (CDC 2005).

**Effect of guideline adherence on control**

A minority of patients do not achieve goals on guideline-recommended first-line treatments. These patients should be switched to other medications. If the annoyance, stigma, or fear factor for corticosteroids is the rationale for nonadherence, then education and counseling can change patient behavior. Corticosteroids suppress the hypothalamic-pituitary-adrenal axis, but are very rarely the cause of clinically recognizable adrenal insufficiency (Colice 2004). Annoyances such as candidiasis can be controlled by means such as an inhaler spacer and alcohol-based mouthwashes, rather than switching to a less effective therapeutic category. If fears of steroid side effects are the issue, parents can be assured that children on corticosteroids at appropriate doses grow more slowly, but they grow for a longer period and catch up, potentially to a greater adult height than if they have uncontrolled asthma.

Smoking serves as an irritant that chronically fuels the inflammation of asthma. The guidelines call for smoking cessation and avoidance of secondhand smoke. Smoking cessation is an area that is underemphasized in guidelines and by physicians and patients (Putnam 2001). Cigarette smoking has been shown to reduce the anti-inflammatory action of glucocorticosteroids. The new GINA guidelines stress the importance of keeping the environment smoke-free for persons with asthma.

Some physicians are skeptical of the usefulness of guidelines. Others pick and choose what they will follow, based on clinical experience. Each new guideline adds something to the total asthma picture. Physicians will compare and contrast guidelines and ask themselves, “What in these guidelines differs from the others?”

**REVISING GUIDELINES**

Disease-specific guidelines updates tend to occur when evidence substantially changes current practices or when grant money to update them becomes available. Guidelines specific to a new treatment often are issued by a consensus panel underwritten by the manufacturer. When updates are implemented, the research covered by the consensus panel as preliminary evidence can be folded into the guidelines.

Protocols for updating guidelines have been adopted but are not always followed (Shaneyfelt 1999). These protocols include having experts from varied professional groups included in the update, as well as seeking patients’ views and preferences. Options for diagnosis and treatment should be presented and the key recommendations made clear. Cost and organizational barriers to implementing the guidelines should be discussed, and the guidelines should be tested among end users and should be peer-reviewed before being issued. Editorial independence from the funding body and potential conflicts of interests of the participants should be recorded (AGREE 2001).

In the case of the NAEPP guidelines, the fact that physicians routinely underestimate the stage of asthma (Colice 2004) certainly will have to be addressed. Several relevant topics may be considered when NAEPP guidelines are updated:

**Markers for risk of acute asthma.** In asthma and in chronic obstructive pulmonary disease, there is much controversy over markers that correlate with risk. Currently, the “rule of 2”4 is used to prevent exacerbations and the need for rescue medications.

**Emphasizing control rather than classification.** Intervention strategies based on a symptom-based disease-stratification system make asthma difficult to treat because severity is something of a moving target. Current GINA classification is based on etiology, severity, and pattern of airflow limitation.

**Refinement of classification system.** The current system fails to include measures of airway inflammation, which may lead to underdosing of appropriate anti-inflammatory therapy and consequent perpetuation of the asthma exacerbation cycle (Colice 2004). Suggestions have been made to incorporate methacholine chal-

4The “rule of 2” holds that young children should be treated with long-term medications if they have symptoms more than 2 times a week, awaken at night because of asthma more than 2 times a month, or use more than 2 canisters of a quick-relief medication per year.
lenge testing and sputum eosinophil counts into severity assessments. Categories may begin to be based on new genetic criteria as genetic information becomes available.

**New drugs, devices, and biologic interventions.** The emergence of omalizumab and phosphodiesterase (PDE4) inhibitors, and the clinical use of nitrous oxide as a marker of control are forcing a reexamination of longstanding clinical practices (Rosenwasser 2003, Smith 2005). For newer drugs and biologic therapies, more clinical experience is necessary to help to establish their appropriate place in therapy. Nitrous oxide devices are expensive, large, and difficult to calibrate but likely will become smaller and less expensive (Suissa 2000).

**Concern about long-acting beta<sub>2</sub>-agonist safety.** This has led to a U.S. Food and Drug Administration hearing. Results of the hearing likely will be incorporated into the updated guidelines.

**CONCLUSION**

Evidence-based guidelines have helped to modernize asthma treatment. Yet, much work remains to implement them, update them, and ensure that specialists and primary care practitioners use them in setting and achieving asthma control goals for the individual patient.

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Luskin A. What the asthma end points we know and love do and do not tell us. *J Allergy Clin Immunol*. 2005;115:5539–5545.


therapy is needed to complement environmental controls and patient education, selection of an appropriate drug regimen should be based on the understanding that asthma is a chronic inflammatory disorder.

This article discusses the classes of drugs most commonly used in the United States to control asthma as per the roles assigned to them (see page 18) by the National Asthma Education and Prevention Program: inhaled corticosteroids (ICSs), long-acting beta2-agonists (LABAs), methylxanthines, leukotriene modifiers, and cromones (Table 1). The newest class of asthma agents, the IgE blockers, is also discussed.

For most patients, inhaled short-acting beta2-agonists are the most important part of day-to-day asthma management. In patients with mild intermittent asthma who are asymptomatic between episodes, these agents are used at the patient’s discretion on an as-needed basis. In patients with persistent asthma, the anti-inflammatory agents discussed in the pages that follow complement as-needed therapy with short-acting beta2-agonists. Increased reliance on short-acting beta2-agonists may be a sign that the patient’s asthma is inadequately controlled.

Inhaled corticosteroids

The preferential status accorded to ICSs among the asthma therapies included in current treatment guidelines, is supported by epidemiologic data that show that reductions in mortality (Goldman 2000, Suisse 2000), hospitalizations (Blaiss 1998, Donahue 1997, Wennergren 1996), and emergency department visits (Sin 2002) are associated with ICS utilization. Because of the demonstrated efficacy of ICSs in controlling asthma symptoms, improving lung function, and reducing airway reactivity, daily ICS use has become the basis of...
### TABLE 1  Long-term control medications

<table>
<thead>
<tr>
<th>Generic name (trade name)</th>
<th>Formulations</th>
<th>Adult dosage</th>
<th>Child dosage (age &lt;12 years except as noted)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Corticosteroids — systemic</strong>  (for inhaled corticosteroids, see Table 2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>2, 4, 8, 16, 32 mg tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5 mg tablets 5 mg/5 cc, 15 mg/5 cc</td>
<td>2 puffs every 12 hours 1 blister every 12 hours</td>
<td>1–2 puffs every 12 hours 1 blister every 12 hours</td>
</tr>
<tr>
<td>Prednisone</td>
<td>1, 2.5, 5, 10, 20, 50 mg tablets 5 mg/cc, 5 mg/5 cc</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Long-acting beta₂-agonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmeterol (Serevent)</td>
<td>DPI 21 mcg/puff  DPI 50 mcg/blisterto</td>
<td>2 puffs every 12 hours 1 blister every 12 hours</td>
<td>1–2 puffs every 12 hours 1 blister every 12 hours</td>
</tr>
<tr>
<td>Formoterol (Foradil)</td>
<td>DPI 12 mcg/capsule</td>
<td>1 capsule every 12 hours</td>
<td>1 capsule every 12 hours</td>
</tr>
<tr>
<td><strong>Combined medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluticasone/salmeterol (Advair)</td>
<td>DPI 100/50, 250/50, 500 mcg/50 mcg</td>
<td>1 inhalation twice daily; dose depends on asthma severity</td>
<td>1 inhalation twice daily; dose depends on asthma severity</td>
</tr>
<tr>
<td><strong>Leukotriene modifiers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Montelukast (Singulair)</td>
<td>4 mg granules 4 or 5 mg chewable tablets 10 mg tablets</td>
<td>10 mg once every evening</td>
<td>4 mg granules (12–23 mo) 4 mg (2–5 years) 5 mg (6–14 years) 10 mg (≥15 years)</td>
</tr>
<tr>
<td>Zafirlukast (Accolate)</td>
<td>10 and 20 mg tablets</td>
<td>20 mg twice daily</td>
<td>10 mg twice daily (7–11 years)</td>
</tr>
<tr>
<td>Zileuton (Zyflo)</td>
<td>600 mg tablets</td>
<td>600 mg 4 times daily</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Cromolyn and nedocromil</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cromolyn</td>
<td>MDI 1 mg/puff  Nebulizer 20 mg/ampule</td>
<td>2–4 puffs 3 or 4x/daily. 1 ampule 3 or 4 times daily</td>
<td>1–2 puffs 3 or 4 times daily. 1 ampule 3 or 4 times daily</td>
</tr>
<tr>
<td>Nedocromil (Tilade)</td>
<td>MDI 1.75 mg/puff</td>
<td>2–4 puffs 2 or 4 times daily</td>
<td>1–2 puffs 2 or 4 times daily</td>
</tr>
<tr>
<td><strong>Methylxanthines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td>Liquids, sustained-release tablets, capsules</td>
<td>Starting dose of 10 mg/kg/day up to maximum of 300 mg; usual maximum 800 mg/day</td>
<td>Starting dose 10 mg/kg/day. Usual max for children: age &lt;1 year: 0.2 (age in weeks)+5 = mg/kg/day; age ≥1 yr: 16 mg/kg/day</td>
</tr>
<tr>
<td><strong>Anti-IgE therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omalizumab (Xolair)</td>
<td>Subcutaneous injection</td>
<td>150 to 375 mg every 2 or 4 weeks</td>
<td>NA</td>
</tr>
</tbody>
</table>

DPI=dry powder inhaler, MDI=metered dose inhaler, NA=not applicable.

SOURCE: NAEPP 2002, PRESCRIBING INFORMATION
therapy for persistent asthma of any degree of severity in adults and children.

Prior to the release of the last full set of guidelines by the NAEP, daily treatment with long-term control medications was reserved for patients with moderate or severe persistent asthma. When the guidelines were revised in 1997, daily treatment was extended to patients with intermittent persistent asthma as well. A recent 1-year study suggests that instead of daily treatment, as-needed use of a short course of inhaled or oral corticosteroids also may be effective therapy for mild persistent asthma in adults (Boushey 2005). These findings are likely to be taken into consideration during the next full update of the NAEP guidelines, slated for a 2006 release.

**Presumed mechanism.** The benefits of ICS therapy are believed to be manifestations of the multiple ways in which corticosteroids address the inflammation that underlies asthma, but the precise mechanism of the corticosteroids remains unknown. By activating the intracellular glucocorticoid receptor (GR), found in abundance within human lung tissue, corticosteroids affect numerous cells involved in the inflammatory process (Barnes 1998). Corticosteroids reduce the number of mast cells, circulating eosinophils, and dendritic cells, and they prevent macrophages and T-lymphocytes from releasing the cytokines that recruit and sustain other inflammatory cells. Corticosteroids also may produce beneficial effects in structural cells, including submucosal glands, airway smooth muscle, and endothelial and epithelial cells. It is believed that most of these effects (as well as the adverse effects associated with corticosteroid therapy) are mediated ultimately by the activated GR through transactivation or transrepression pathways.

The GR is found in numerous tissues throughout the body, which is why corticosteroids have the potential to produce a wide range of adverse effects — such as weight gain, Cushing syndrome, adrenal insufficiency, growth suppression, glaucoma, cataracts, reduced bone mineral density (BMD), and osteoporosis. Corticosteroid-induced osteoporosis and osteoporotic fractures are common in patients taking oral steroids over the long term, and bone loss apparently occurs at any dose (Kelly 2003).

**Transactivation and transrepression.** In the absence of a glucocorticoid, the GR is anchored to heat-shock proteins (so called because heat shock or other stress induces their synthesis). Once a corticosteroid diffuses into the cytoplasm, it binds to the GR and separates it from its chaperone. At this point, it is said that the GR is activated.

On dissociation from the chaperone, activated GR reveals another binding site, for a specific sequence of DNA in the nucleus that is known as a glucocorticoid response element (GRE). The newly formed complex of activated GR and glucocorticoid thus serves as a transcription factor itself. Translocated into the nucleus, GR binds to the GRE, activating transcription of GR-responsive genes. In any given cell, between 10 and 100 different genes may be regulated by steroids (Barnes 1998).

In addition, two transcription factors, nuclear factor-κB (NF-κB) and activator protein-1 (AP-1) appear to be susceptible to activated GR. Both are involved in the immune response, activated by inflammatory cytokines. Activated GR may downregulate NF-κB indirectly, by activating transcription of an NF-κB inhibitor. Or, it may do so directly, through transrepression — the physical interaction of monomeric activated GR with a component of NF-κB. Activated GR also interacts directly with AP-1 (Smith 1998).

Because the anti-inflammatory effects of corticosteroids now are thought to be mediated primarily through transrepression, whereas many side effects arise primarily (but not exclusively) from transactivation, favoring transrepression over transactivation may facilitate the design of novel corticosteroids with fewer side effects than currently available products (Barnes 1998). So far, it has not been shown that corticosteroids optimizing the transrepression:transactivation ratio provide clinical benefits (Hochhaus 2004).

Strategies intended to reduce the risk of systemic adverse effects focus on inhalation therapy to deliver corticosteroids to the lung tissue, keeping it there for as long as possible, and minimizing the amount of drug that can enter the systemic circulation through the gastrointestinal tract. Owing to corticosteroid deposition in the oropharynx, however, certain localized adverse effects (e.g., cough, dysphonia, and oral candidiasis [thrush]) are associated with ICS therapy on occasion, each being reported in clinical trials in about 5 percent of patients or fewer (Asmanex 2005, Advair 2004). In a recent observational study of patients treated with ICS (N=6,740), the prevalence of oropharyngeal disorders was 35 percent (Molimard 2004). These disorders were observed more frequently in users of fluticasone and budesonide (43 and 41 percent, respectively) than beclomethasone (28 percent). Gargling and abstaining from tobacco use were associated with reduced risk of oropharyngeal disorders.

The Childhood Asthma Management Program (CAMP) Research Group demonstrated that any side effects associated with long-term ICS utilization appear to be limited (CAMP 2000). In this study, children were randomized to budesonide 200 mcg twice daily, nedocromil 8 mg twice daily, or placebo, and were treated for 4 to 6 years. A small but transient decrease in growth velocity was observed in the budesonide group. Data from CAMP and similar studies still are inadequate, however, for determining whether children who use ICS throughout childhood attain their full adult height (Kelly 2003).
In CAMP, no significant difference in BMD was observed among the three treatment groups. A meta-analysis also found no statistically significant difference in lumbar spine BMD among asthma patients using ICS for at least 3 years (Sharma 2003).

Table 2 shows typical ICS dosages. Note that since 2002, when NAEPP released this table, the U.S. Food and Drug Administration has approved a new ICS, mometasone (Asmanex), which is administered once daily via an inhalation-driven dry powder inhaler. This product is reviewed by Peters on page 38.

**Limitations to ICS therapy.** Although ICSs safely and effectively control asthma in most patients, there are numerous barriers to their use. Though not generally regarded as serious, oropharyngeal adverse events (AEs) present a threat to continued therapy. When they do emerge, physicians often respond by altering the regimen, either by reducing the dose of the ICS or discontinuing the ICS, which may involve switching to another ICS or a different long-term controller (Kaliner 2005).

More importantly, it should be noted that a substantial number of patients with persistent asthma fail to respond adequately to an ICS. In one study, about a third of patients randomized to beclomethasone or fluticasone had a poor response, measured by FEV₁ and methacholine PC₂₀ (Szefler 2002). Likewise, in a head-to-head comparison of montelukast and beclomethasone, about 25 percent of patients receiving beclomethasone showed no improvement in FEV₁ (Malmstrom 1999). In addition, in revisiting data from a study evaluating six ICS-delivery device combinations, Szefler (2002) revealed that about 40 percent of subjects had a poor FEV₁ response, which was observed with each delivery device combination.

Whether a given ICS induces AEs or not, patients’ beliefs about ICS therapy may lead to a lack of compliance.

### TABLE 2
**Estimated comparative daily dosages for inhaled corticosteroids**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low daily dose</th>
<th>Medium daily dose</th>
<th>High daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adult</td>
<td>Child</td>
<td>Adult</td>
</tr>
<tr>
<td><strong>Beclomethasone CFC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>42 or 84 mcg/puff</td>
<td>168–504 mcg</td>
<td>84–336 mcg</td>
<td>504–840 mcg</td>
</tr>
<tr>
<td><strong>Beclomethasone HFA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 or 80 mcg/puff</td>
<td>80–240 mcg</td>
<td>80–160 mcg</td>
<td>240–480 mcg</td>
</tr>
<tr>
<td><strong>Budesonide DPI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Pulmicort Turbohaler)</td>
<td>200–600 mcg</td>
<td>200–400 mcg</td>
<td>600–1200 mcg</td>
</tr>
<tr>
<td>Inhalation suspension</td>
<td>0.5 mg</td>
<td>1.0 mg</td>
<td>2.0 mg</td>
</tr>
<tr>
<td>for nebulization (child dose)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Flunisolide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fluticasone</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Flovent) MDI: 44, 110, or 200 mcg/puff DPI: 50, 100, or 250 mcg/ inhalation</td>
<td>88–264 mcg</td>
<td>88–176 mcg</td>
<td>264–660 mcg</td>
</tr>
<tr>
<td>100–300 mcg</td>
<td>100–200 mcg</td>
<td>300–600 mcg</td>
<td>200–400 mcg</td>
</tr>
<tr>
<td><strong>Mometasone</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Asmanex) 220 mcg/ inhalation</td>
<td>220 mcg</td>
<td>220–440 mcg</td>
<td>&gt;440 mcg</td>
</tr>
<tr>
<td><strong>Triamcinolone acetonide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Azmacort) 100 mcg/puff</td>
<td>400–1000 mcg</td>
<td>400–800 mcg</td>
<td>1000–2000 mcg</td>
</tr>
</tbody>
</table>

CFC=chlorofluorocarbon, DPI=dry powder inhaler, HFA=hydrofluoroalkane, MDI=metered dose inhaler. 
**SOURCE:** NAEPP 2002, PRESCRIBING INFORMATION
with therapy. A recent study showed an inverse correlation between adherence and patients’ beliefs regarding development of tolerance to daily ICS therapy, the proper dose, and perceived lack of safety (Le 2005).

For all the above reasons, attention has turned to the development and use of other drug classes, notably the LABAs and the leukotriene modifiers, to complement ICS therapy. For certain difficult-to-treat patients, the addition of the new IgE blocker, omalizumab (Xolair), also may be appropriate.

**Long-acting inhaled beta₂-agonists**

The adrenoreceptors are divided into two groups, alpha and beta. It was discovered in 1967 that at least two different types of beta adrenoreceptors exist: beta₁, found predominantly in cardiac and gastrointestinal tissues; and beta₂, found predominantly in uterine and lung tissue. Stimulation of either subtype elevates intracellular levels of cyclic adenosine monophosphate (cAMP). In cardiomyocytes, elevated cAMP increases contractility. Acting through a different signaling pathway, elevated cAMP in bronchial smooth muscle results in relaxation.

The identification of the beta₁ and beta₂ adrenoceptor subtypes drove the development of asthma drugs that are highly selective agonists of the beta₂ receptors. Human beta₂ receptors account for about 30 percent of beta₂-adrenergic receptors in the heart, however. This raises the possibility that asthma drugs that are highly selective for the beta₂ receptor may produce unwanted effects in the heart as well.

In the NAEPP guidelines, LABAs are recommended to complement ICSs in patients with moderate or severe persistent asthma. The LABAs specified in the current guidelines are salmeterol (Serevent) and formoterol (Foradil), which act for up to 12 hours. This attribute makes them especially suited for controlling nocturnal asthma and exercise-induced asthma. On the other hand, some LABAs have slow onset of action. With salmeterol, significant improvement in pulmonary function is not seen until 2 hours after administration (Serevent 2004). Patients need to be aware that salmeterol cannot be used in place of short-acting beta₂-agonists for treatment of acute asthma exacerbations. A role may be emerging, though, for formoterol as a quick-relief medication (see the Peters article that begins on page 37).

**Combination treatment.** In the United States, a fixed dose of salmeterol 50 mcg is combined with three different doses of fluticasone (100, 250, or 500 mcg) in a single inhalation device (Advair). According to IMS Health, this product led asthma medications in the United States in wholesale sales in 2004 and ranked ninth in sales among all U.S. drugs (IMS 2005). Early concerns that a fixed-dose combination product would impede dosing flexibility apparently have been overcome by increased compliance stemming from greater convenience, and early fears that a LABA might mask deteriorating asthma have been unfounded.

In a 12-week placebo-controlled study (N=356), fluticasone 100 mcg/salmeterol 50 mcg provided greater asthma control than either agent administered separately (Kavuru 2000). In a 1-year study, salmeterol/fluticasone was more effective than fluticasone alone in helping a majority of patients achieve a high level of control of their asthma, defined by the virtual elimination of exacerbations and near-normal quality of life (Bateman 2004). In patients with persistent asthma (N=447), a greater percentage of those given salmeterol/fluticasone achieved a 12 percent or greater increase in FEV₁ than did those receiving low-dose fluticasone plus montelukast (54 percent vs. 32 percent), and at a lower daily cost (O'Connor 2004).

At any dose of fluticasone, the maximum recommended daily dosage of fluticasone/salmeterol is 1 inhalation twice daily. This is because higher doses of salmeterol are associated with an increased risk of AEs in some patients (Advair 2004), but no greater efficacy as the dose-response curve flattens (Palmqvist 1999).

**Leukotriene modifiers**

The relatively new class of leukotriene modifiers comprises three agents: zileuton (Zyflo) and zafirlukast (Accolate), both of which were approved by the FDA in 1996, and montelukast (Singulair), approved in 1998. The pathway for leukotriene biosynthesis begins with arachidonic acid. Zileuton inhibits 5-lipoxygenase, the enzyme that converts arachidonic acid into intermediate products leading to synthesis of leukotrienes, including the potent bronchoconstrictor leukotriene D₄ (LTD₄). Zafirlukast and montelukast block the receptor for LTD₄.

Zileuton was discontinued by its original manufacturer in 2003, and supplies were exhausted by early 2004. The current manufacturer acquired worldwide rights to zileuton in 2004, and, with the FDA’s approval of its supplemental NDA in September 2005, plans to make zileuton available again. Even so, it is unlikely that zileuton ever will serve more than a minute subpopulation.

Because of its numerous advantages over the other leukotriene modifiers, montelukast dominates this class. According to IMS Health, in 2004 montelukast ranked 16th among all prescription drugs and second among all respiratory drugs (IMS 2005). Montelukast can be administered just once daily, in the evening, unlike zafirlukast (2 times daily) or zileuton (4 times daily). Montelukast also is available in various formulations (granules, chewable tablets, film-coated tablets) for pa-
tients as young as 1 year. Additionally, no evaluation or monitoring of liver transaminases is recommended for patients receiving montelukast, in contrast to zileuton.

The market prominence of montelukast belies the role ascribed to leukotriene modifiers by the NAEP guidelines. That is, they are not the preferred treatment for asthma of any degree of severity, but rather are listed as alternative treatments, on an equal footing with theophylline and cromolyn. This status follows from head-to-head studies in which patients receiving beclomethasone (Malmstrom 1999), low-dose fluticasone (Busse 2001a), or a fluticasone/salmeterol combination (Calhoun 2001) had better outcomes than patients randomized to montelukast, along with a head-to-head trial in which patients with persistent asthma who were randomized to low-dose fluticasone experienced a lower rate of asthma exacerbation than those receiving zafirlukast (Busse 2001b).

Nevertheless, a recent retrospective, observational study in the United Kingdom showed that 66 percent of patients for whom montelukast was prescribed in routine care reported an improvement in control (Barnes 2005). The majority of responders were patients with mild to moderate asthma, but even those with severe asthma reported improvement. On the other hand, a third of patients discontinued montelukast, primarily because of lack of effectiveness. If a patient does not respond within the first 1 to 3 months of treatment, discontinuation of a leukotriene modifier is warranted (Kavuru 1998).

Aspirin-induced asthma. In light of the market withdrawals of rofecoxib (Vioxx) and valdecoxib (Bextra), patients and physicians should be alert to the possibility of an increase in aspirin-induced asthma (AIA, also known as aspirin-exacerbated respiratory disease or aspirin sensitivity) as patients who used the withdrawn products now turn to aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) for pain relief. In susceptible patients, asthmatic attacks are precipitated by ingestion of an ASA molecule.

Aspirin-induced asthma is the same as that for moderate or severe persistent asthma. Because the cyst-LT1 receptor is selectively blocked by montelukast and zafirlukast, these agents are a rational treatment for patients with AIA. Although not widely practiced, oral aspirin desensitization has merit for some patients (e.g., those who need aspirin or NSAIDs to manage arthritis or thromboembolism, patients who are corticosteroid-dependent, or patients who need repeated polypectomies or sinus surgery) (Szczeklik 2003). Only experienced physicians possessing the equipment needed to treat the bronchospastic reactions that can occur during desensitization should attempt the procedure. Once patients have been desensitized, they can take aspirin and NSAIDs continuously without further risk of a respiratory reaction.

Methylxanthines

The methylxanthines are a group of closely related chemicals commonly encountered in beverages like coffee (caffeine), cocoa (theobromine), and tea (theophylline), from which theophylline derives its name. Theophylline differs from caffeine by having two methyl groups, instead of three, affixed to the basic xanthine molecule.

Theophylline acts primarily as a bronchodilator, albeit a weaker one than the beta2-agonists, but it also is known to inhibit migration of eosinophils into the airways during the late-onset response to allergens. This latter effect has been observed at a lower serum concentration than that required for bronchodilation (Page 1999).

A drawback of theophylline therapy is the need for serum monitoring. Improved lung function is observed at concentrations ranging from 5 to 30 mcg/mL, but adverse effects begin to emerge at concentrations of 15 mcg/mL and become common when exceeding 20 mcg/mL. The recommended levels are 5 to 15 mcg/mL.

Being inexpensive and available in oral formulations, theophylline once was a mainstay of maintenance therapy, but current guidelines relegate it to an alternative to low-dose ICSs for mild persistent asthma in adults, or a complement to medium-dose ICS in the treatment of moderate persistent asthma in adults and children ages 5 and above. Just as adding an LABA to an ICS may be more beneficial than increasing the dose of an ICS, so is adding low-dose theophylline to an ICS more beneficial than increasing the dose of the ICS (Evans 1997).
Anti-IgE therapy

For some patients with allergic asthma, anti-IgE therapies might offer a novel form of treatment. Presently, this class contains one member, omalizumab, which was approved in 2003 for patients age 12 and above with moderate to severe persistent allergic asthma that is resistant to ICS treatment.

Omalizumab is a humanized monoclonal antibody against IgE. In patients with IgE-mediated asthma, circulating IgE binds with receptors on the surface of mast cells and basophils. These cells release histamine, leukotrienes, and other mediators of the allergic response when bound molecules of IgE are crosslinked by an allergen. Omalizumab disrupts this process by selectively binding to the same site on the Fc portion of IgE that binds with its high-affinity receptor on the cell surface. Anti-inflammatory effects above and beyond those achieved by binding IgE have been observed (Djukanovic 2004).

Omalizumab is administered subcutaneously every 2 to 4 weeks, with the doses and dosing frequency determined by the patient’s body weight and the concentration of IgE in the serum at the start of treatment. If more than 150 mg is required, multiple injection sites must be used to limit the dose to 150 mg at any single site. Omalizumab must be administered in a physician’s office, and the patient must be observed afterwards, owing to the apparently very slight risk of anaphylaxis, which occurred during the first 2 hours after administration in three patients (<0.1 percent) in clinical trials. Injection-site reaction is the most common AE, being reported by 45 percent of omalizumab-treated patients (placebo, 43 percent); severe injection-site reactions were reported by 12 and 9 percent of patients receiving omalizumab and placebo, respectively.

For formulary committees, one important consideration with omalizumab is its cost. The drug costs in 1 year of treatment can be expected to be $10,000 and higher. For this reason, it will be important to identify the subset of patients with IgE-mediated asthma who are most likely to benefit from omalizumab therapy. Careful selection of patients, then, might reduce overall health care expenditures despite the drug’s acquisition cost.

Hospitalization is the primary driver of health care costs associated with asthma. Moreover, estimates of the share of people with asthma whose disease is considered to be severe disease range from 5 to 15 percent of all patients with asthma, but these patients command more than half of all spending on asthma (Barnes 1996, Weissler 2000). Pooled analysis of three phase 3 trials of omalizumab (two in adults, one in children) showed that it reduced the rate of hospitalization by 92 percent (0.26 vs. 3.42 hospitalizations per 100 patient-years; \( P < .002 \)) (Corren 2003).

The authors of one phase 3 trial suggest that the population of patients for whom omalizumab might be most appropriate would comprise difficult-to-treat patients with persistent symptoms that resist conventional corticosteroid therapy, need high-dose ICS therapy, or have developed adverse effects from corticosteroid use (Solèr 2001).

If omalizumab therapy is attempted, it is important to give it a fair trial — at least 12 weeks. In one study in which 64 percent of patients responded to omalizumab after 16 weeks of therapy (16-week placebo response rate, 48 percent), only 61 percent of the omalizumab responders showed a response after 4 weeks but 87 percent had responded after 12 weeks (Bousquet 2004).

The prescribing information for omalizumab warns about the potential for malignancy, based on the observation of malignant neoplasms in 0.5 percent (20/4127) of omalizumab-treated patients versus 0.2 percent (5/2236) of control patients during clinical trials (Xolair 2003). Additional clinical data have been obtained, and though the rates remain the same, 0.5 percent (25/5015) and 0.2 percent (5/2854), the malignancy rate among patients receiving omalizumab is comparable to that of patients receiving control (\( P > .05 \)) (Fernandez 2005). More importantly, when compared with cancer rates from NIH’s SEER database, the standardized incidence ratio of the observed-to-expected number of events is one third of expected in the control group and 0.98 in the omalizumab group — i.e., similar to that expected in the general population. Hence, the available data do not support a causal link between omalizumab and cancer.

CONCLUSION

Attempts to find satisfactory treatments for asthma stretch far back into medical history (see “Asthma Therapy Through the Ages,” page 35), but drug therapies that are safe and efficacious have been developed only recently. For most patients with persistent asthma, long-term control now can be achieved safely and effectively with an ICS complemented by an LABA or a leukotriene modifier. A subset of patients with difficult-to-control IgE-mediated asthma may benefit from add-on therapy with omalizumab, the first member of the new class of IgE blockers. The emergence of this new class should be reflected in the next revision of the NAEPP guidelines.

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Accolate (zafirlukast) [prescribing information]. Wilmington, Del.: AstraZeneca Pharmaceuticals. 2004.
Asthma therapy through the ages

Attempts to find a remedy for asthma span the ages (Cockcroft 1999), and the wide variety of remedies favored at different times and places points to the difficulty in finding a satisfactory treatment. For example, Chinese herbalists long have favored ginseng as a treatment for asthma, among many other ailments, and Chinese records indicate that plants containing adrenergic or anticholinergic agents have been used to treat asthma for at least 5,000 years. Two millennia ago, the Chinese were using the beta-agonist ephedrine to treat asthma. Around the same time, licorice was recommended by a Sanskrit medical compendium, the Caraka Samhita, a text summarizing the Indian body of medical knowledge known as the Ayurveda.

In the 17th century, Ayurvedic literature discussed the use of smoking preparations made from herbs of the Datura genus. Members of this genus, which includes jimsonweed (D. stramonium), contain the anticholinergic agent atropine. The Philadelphia physician Samuel Cooper experimented with jimsonweed preparations in 1797, and cigarettes containing jimsonweed leaves, among other herbal ingredients, were widely used in the 19th century to treat asthma. Strong coffee also was used then to relieve asthma symptoms.

Meanwhile, the pioneering English physician Thomas Willis (1621–1675) had attributed asthma to nervous origins, and he also associated bronchospasm with asthma. Following from Willis’s findings, in the early 20th century, drug treatment for asthma addressed bronchoconstriction (typically with ephedrine) and anxiety (typically with phenobarbital). Morphone, heroine, chloral hydrate, and a combination of morphine and atropine were employed widely to treat asthma paroxysm. (An atropine derivative, ipratropium, was developed in 1972 but has not become a component of routine asthma care, being more commonly used to treat patients with non-asthmatic chronic airflow limitations.)

The first effective treatment for the inflammation that underlies asthma was cortisone. It was discovered in 1949, but the adverse effects associated with cortisone therapy greatly hindered its use. Searching for a better-tolerated drug, an English physician of Armenian descent, Roger Altonyoun, embarked on an 8-year project that culminated with his discovery of cromolyn in 1965. Cromolyn was based on khellin, a plant-derived herbal remedy used for centuries in the Middle East as a vasodilator and bronchodilator.

During the course of his unorthodox research program, Altonyoun, an asthmatic, subjected himself to about 1,000 asthmatic attacks to test the effectiveness of investigational compounds (Howell 2005). Then, drawing on his experience with propellers as a pilot and flight instructor in the Royal Air Force during World War II, Altonyoun designed a novel dry powder inhaler, the Spinhaler, to deliver cromolyn. He and his colleagues also discovered nedocromil. Although these agents represented an improvement over oral corticosteroids, in terms of safety, they have only a minor role today because they did not prove to be adequate for long-term control of persistent asthma. For this purpose, contemporary pharmacotherapy turns primarily to inhaled corticosteroids.


Xolair (omalizumab) [prescribing information]. South San Francisco, Calif.: Genentech. 2003.

**NEW DEVELOPMENTS**

New Developments In Asthma Therapy

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**SUMMARY**

To address unmet needs, pharmaceutical companies are developing new products. This article reviews inhaled corticosteroids that target lung tissue more directly and combination products that enable an inhaled corticosteroid to be used at a lower dose. It also reviews a monoclonal antibody and a phosphodiesterase-4 inhibitor.

Although inhaled corticosteroids (ICSs) are the mainstay of contemporary pharmacotherapy for persistent asthma, the currently available ICSs have limitations. The glucocorticoid receptor (GR) is widely distributed, and ICSs are selective for GRs in addition to those found in lung tissue — hence, the propensity of oral steroids or high-dose ICSs to cause adverse events when the drugs enter the systemic circulation. In addition, the currently available ICSs are indicated for use at least twice daily, though some data support once-daily budesonide as introductory or maintenance therapy in patients with stable, mild to moderate asthma (McFadden 1999).

Moreover, as recently pointed out in several published reports, a substantial proportion of patients treated with an ICS fail to respond adequately (Israel 2002, Malmstrom 1999, Szefler 2002). In a successful trial, non-responders and partial responders will be more than offset by patients exhibiting a more robust response, enabling the trial to demonstrate efficacy. In clinical practice, however, where partial responders and non-responders are encountered individually, limitations of the drug will become apparent. Moreover, in routine practice, the conditions under which patients take their medications are less stringent than those in randomized clinical trials, making the reasons for a poor response to ICS therapy less clear. In clinical practice, it might be reasonable to invoke not only genetic predisposition, but also inadequate adherence with inhalation therapy, poor inhalation technique, or habitual smoking as reasons for ICS failure (Chalmers 2002, Chaudhuri 2003). Smoking is a common exclusion criterion for randomized controlled trials of asthma medications, thus complicating
New inhaled corticosteroids

Because of improvements in inhalation delivery devices, as well as alterations in corticosteroid molecules that result in hepatic inactivation, the oral bioavailability of many newer ICSs is minimal. With oral bioavailability of less than 1 percent, fluticasone propionate has been the leader in this regard, standing in sharp contrast to the oral bioavailability of oral steroids such as prednisolone or dexamethasone (>80 percent) and ICSs such as beclomethasone dipropionate (41 percent) and even budesonide (11 percent).

Two new ICSs — mometasone furoate and ciclesonide — also have oral bioavailability that is comparable to that of fluticasone. Hence, systemic exposure to any of these agents stems from their uptake in the lungs. Further reduction of systemic exposure depends on developing ways to inactivate an ICS extrahepatically or, alternatively, using a prodrug that is activated in the lung. Preliminary research has suggested that the former approach could be pursued with glucocorticoid lactone antedrugs, which are stable in lung tissue but are rapidly inactivated in plasma by human serum paraoxonase, an enzyme found only in the liver and plasma (Bigadike 2004); any clinical benefit from this approach has yet to be demonstrated, however. The latter approach is employed by ciclesonide, as will be discussed in the column at right.

Mometasone furoate. The U.S. launch of this product, which received U.S. Food and Drug Administration approval in March 2005, was expected before the end of 2005. Mometasone furoate is the first once-daily ICS available in the United States, and is indicated for maintenance therapy in patients age 12 and above. Mometasone is the active ingredient in a dermatological ointment (Elocon) and a nasal spray (Nasonex), both of which have been available in the United States since 1987 and 1997, respectively.

For patients currently maintained on a bronchodilator alone or an ICS, the recommended starting dose of mometasone is 220 mcg once daily; the highest recommended daily dose is 440 mcg once daily. For patients currently maintained on oral steroids, the recommended starting dose is 440 mcg twice daily, and the daily dose of 880 mcg represents the maximum daily dose. A daily dose of 1,600 mcg represents the lower limit for consistently detectable systemic effects, as measured by the area under the curve for 24-hour serum cortisol concentrations (Affrime 2000).

Ciclesonide. In October 2004, the FDA issued an approval letter for another once-daily ICS, ciclesonide, for treatment of persistent asthma of any degree of severity in patients age 4 and above. The company has not disclosed the nature of the additional data that the FDA has requested.

Approved in more than 20 other countries, ciclesonide was launched in the United Kingdom and Germany in early 2005. Approved dosages vary. In the United Kingdom (which served as the Reference Member State for the Mutual Recognition Procedure that will guide other European countries), the starting dose (and maximum dose) for patients age 18 and above is 160 mcg once daily, but 80 mcg may be used for maintenance. In Australia, the highest approved daily dose for patients ages 12 and above is 320 mcg; in Brazil and Mexico, it is 640 mcg.

The ciclesonide molecule is an inactive prodrug that is converted to an active metabolite capable of binding with the glucocorticoid receptor through esterase cleavage of isobutyrate (Richter 2005). The affinity of the active metabolite, desisobutyryl-ciclesonide, for the glucocorticoid receptor is about 100-fold higher than that of ciclesonide, and the active metabolite has an anti-inflammatory effect comparable to that of budesonide (Stoeck 2004).

The esterases that cleave the parent compound are found at the site of inflammation in lung tissue, possibly contributing to low oral bioavailability and a diminished propensity for systemic effects. In a study in which 18 patients with asthma inhaled ciclesonide 800 mcg and fluticasone 1,000 mcg in a crossover design, residual levels of both agents in the oropharynx were low after 30 minutes. Over the course of 1 hour, however, the oropharyngeal deposition of ciclesonide and its active metabolite was half that of the fluticasone (Richter 2005). Moreover, only 17 percent of the residual ciclesonide was converted to the active metabolite, which had a concentration that was only 8 percent that of the fluticasone.

The potential clinical relevance of these characteristics of ciclesonide is suggested by analysis of pooled data...
from two randomized, placebo-controlled trials of ciclesonide in patients with mild to moderate persistent asthma (N=1,015), which showed that the rates of oral candidiasis were comparable in the ciclesonide and placebo groups (0.9 and 0.4 percent, respectively), as were the rates of dysphonia (0.4 percent in each) (Pearlman 2005).

In patients with persistent asthma, once-daily treatment with ciclesonide 80 mcg or 160 mcg has been shown to be as effective as twice-daily fluticasone 88 mcg in improving FEV₁ (Magnussen 2005). Likewise, once-daily ciclesonide 160 mcg, administered in the morning or evening, has been shown to be as effective as twice-daily budesonide 200 mcg in improving FEV₁ (Gadgil 2005). In both studies, the incidence of adverse events was comparable in all treatment groups.

In contrast with measurements of lung function, health-related quality of life (QOL) assessments show the effects of therapy on physical, emotional, and social functioning, and QOL data appear to reveal a distinct feature of asthma (Luskin 2005). In 12-week studies, ciclesonide also has been shown to improve QOL in patients with severe persistent asthma (N=531) (Bernstein 2005), mild to moderate persistent asthma (N=1,015) (Nayak 2005), and pediatric patients (N=793) (Miller 2005). It also should be noted that asthma-specific QOL is inversely associated with overall costs and health care utilization, including emergency department visits and hospitalizations (Eisner 2002).

**Single-inhalation combination therapy**

At present, only one product offering an ICS and a long-acting beta₂-agonist (LABA) via a single inhaler is available in the United States — the combination of fluticasone and salmeterol (Advair), a top-selling drug in the United States. This fluticasone/salmeterol combination product (reviewed in detail by Kavuru, beginning on page 28) is supplied as a fixed 50 mcg dose of salmeterol together with 1 of 3 doses of fluticasone: 100, 250, or 500 mcg. Hence, increasing or decreasing the daily dose of fluticasone necessitates switching to a different inhaler.

Internationally, Advair is marketed as Seretide, which competes with another ICS/LABA combination provided in a single inhaler, budesonide and formoterol. In contrast to salmeterol, formoterol is a rapid-acting LABA. In Europe, formoterol is used as a rescue medication, owing to its rapid onset of action, 1 to 3 minutes, which is comparable to that of salbutamol (albuterol). In a large (N=18,124) open-label international study, formoterol was shown to have a safety profile similar to that of salbutamol (Pauwels 2003). This study enrolled patients ranging in age from 4 to 91 years, with asthma of all degrees of severity, using a wide range of maintenance therapies.

In addition to being used as maintenance therapy, budesonide/formoterol is being investigated for use in providing acute relief. In a double-blind 1-year study, 2,760 patients with asthma were randomized to 1 of 3 regimens: budesonide 80 mcg/formoterol 4.5 mcg twice daily, plus the same formulation as needed for relief; budesonide 80 mcg/formoterol 4.5 mcg twice daily, plus terbutaline 0.4 mcg as needed; or budesonide 320 mcg plus terbutaline 0.4 mcg as needed (O’Byrne 2005). Patients ranged in age from 4 to 80 years, and their FEV₁ at baseline ranged between 60 and 100 percent of predicted. In the group using budesonide/formoterol for both maintenance and relief, the risk of severe exacerbation was 45 percent lower than that in the budesonide/formoterol-plus-terbutaline group and 47 percent lower than that in the high-dose budesonide-plus-terbutaline group. (Severe exacerbation was defined as hospitalization or an emergency department visit, treatment with oral steroids, or morning peak expiratory flow less than or equal to 70 percent of baseline on 2 consecutive days.) Rates of adverse events were similar among all treatment groups.

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**Generic-trade name conversions**

*For products discussed in this review*

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budesonide/formoterol (single inhaler)</td>
<td>Symbicort</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>Alvesco</td>
</tr>
<tr>
<td>Daclizumab</td>
<td>Zenapax</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Enbrel</td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>Asmanex</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>Xolair</td>
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<tr>
<td>Roflumilast</td>
<td>Daxas</td>
</tr>
</tbody>
</table>
Phase 3 clinical studies are complete for a pressurized metered-dose inhaler (pMDI) formulation of the budesonide and formoterol combination product. The manufacturer filed a new drug application (NDA) with the FDA in September 2005 for the device.

Separately, another fixed-dose combination product that combines ciclesonide and formoterol is in phase 2 trials.

Finally, it is worth noting that once-daily LABAs are being developed, with phase 2 data having been reported for one, (QAB149). Should such a product reach the market, we also could anticipate attempts to develop a once-daily ICS/LABA.

**New molecular targets**

Through various animal, *in vitro*, and *in vivo* models, a number of molecules have been identified as potential targets for new asthma drugs. Rationales have been offered for developing biologic response modifiers that would block IgE receptors and block tumor necrosis factor (TNF), IL-2, IL-4, IL-5, IL-9, IL-12, IL-13, and IL-15. (*Editor’s note: see the previous article for information about IgE blockade with omalizumab.*)

For the small percentage of patients with asthma that is refractory to ICS, blockade of TNF might be a therapeutic approach to consider. Etanercept is a fusion protein consisting of the Fc region of human IgG1 fused with the extracellular portion of two p75 TNF receptors. Etanercept binds with high affinity to TNF, preventing it from binding with its cell-surface receptors and activating the transcription factors that trigger induction of proinflammatory and immunomodulatory genes. In a small trial enrolling 10 patients who have asthma that is refractory to ICS, etanercept 25 mg twice weekly led to statistically significant improvement in lung function, airway hyperresponsiveness, and asthma quality of life after 10 weeks (Berry 2005). Additional clinical trials employing this approach and other approaches to block TNF (including the use of an anti-TNF monoclonal antibody) are in progress.

IL-4 presents an attractive theoretical target because, among other characteristics important in asthma, IL-4 promotes the differentiation of T_{H}0 lymphocytes into T_{H}2 helper cells. The T_{H}2 lymphocytes produce IL-4 as well as IL-5, IL-9, and IL-13, all of which are implicated in asthma pathogenesis, joined by other cytokines, IL-5 helps stimulate the development of eosinophils from CD34+ progenitor cells; IL-9 is associated with eosinophil function, IgE regulation, airway hyperresponsiveness, and mucous hypersecretion; and IL-13 is associated with IgE synthesis and eosinophil migration, and it is necessary for airway hyperresponsiveness and mucous hypersecretion. Thus, an agent that neutralizes excessive IL-4 could have broad advantages. Yet, despite showing early promise in clinical trials, development of an inhaled recombinant soluble IL-4 receptor (Nuvance) was discontinued after larger trials failed to demonstrate clinical benefit.

The reason for the failure of an agent directed at IL-4 alone may stem from the fact that IL-4 acts in concert with IL-13, through the IL-4/IL-13 signaling cascade. Targeting only IL-4 leaves IL-13 free to function, suggesting that simultaneous blockade of both interleukins may offer a more promising therapeutic approach (Corry 2002). Through the construction of novel “cytokine traps,” it may be possible to simultaneously block IL-4 and IL-13 with a single agent (Economides 2003). Such traps are designed to overcome an inherent difficulty in cytokine blockade, which is that many cytokines employ a multistep binding process. In the first step, the cytokine binds with low affinity to the alpha-component of the receptor complex. At this point, a second receptor component is recruited, and the two receptor components form a complex that binds the cytokine with much higher affinity. In an engineered cytokine trap, both receptor components are fused to the Fc portion of human IgG1. A trap that may have utility in asthma treatment incorporates the alpha-component of the IL-13 receptor complex (IL-13Ralpha1) and the alpha-component of the IL-4 receptor complex (IL-4Ralpha). The reason this fusion protein may block both IL-4 and IL-13 is that IL-13Ralpha1 is involved in the signaling of each interleukin.

Interest in developing drugs to counter IL-5 has been waning, in part because recent trials have shown that while blocking IL-5 with a monoclonal antibody reduces circulating and sputum eosinophils, it has no effect on the antigen-induced late airway asthmatic response (Leckie 2000). Clinical trials in asthma similarly have not been encouraging. Whether this is because IL-5 and eosinophils are less important in asthma pathogenesis than previously thought or because the agents used to date lack sufficient efficacy is not clear. Nonetheless, the latter is possible, because one recent study reported an incomplete reduction of airway eosinophilia after treatment with an anti-IL-5 antibody, mepolizumab, in spite of much larger reductions in circulating and sputum eosinophils (Flood-Page 2003, O’Byrne 2004).

Animal studies still suggest an important role for IL-5 in asthma pathogenesis, however. Two recent studies using two different strains of eosinophil-deficient transgenic mice (Humbles 2004, Lee 2004) suggest that eosinophils may be more important in promoting airway remodeling than had been previously thought (Wills-Karp 2004). If this possibility is confirmed, in-
interest in the development of more effective methods to deplete IL-5 and the resulting tissue eosinophilia could increase.

**PDE4 inhibitors.** Unlike theophylline, which non-selectively inhibits phosphodiesterase (PDE), new PDE inhibitors in clinical development as a treatment for asthma and chronic obstructive pulmonary disease (COPD) are selective for PDE4 receptors. PDE4 inhibitors are believed to act by blocking the hydrolysis of intracellular cAMP, thereby leading to elevated levels of cyclic adenosine monophosphate (cAMP), which inhibits many inflammatory and immunomodulatory cells (Hatzelmann 2000). The PDE4 inhibitor most likely to reach the market first is roflumilast. A marketing authorization application for roflumilast was submitted to European regulators in 2004 for asthma and COPD indications. Submission to the FDA of an NDA is expected shortly, pending analysis of a 12-month study completed in mid-2005.

**Daclizumab.** In 1997, the FDA approved the monoclonal antibody daclizumab for prevention of acute rejection in kidney transplants, to be used as part of an immunosuppressive regimen that includes cyclosporine and corticosteroids. Daclizumab is a humanized antibody against the alpha chain of the human interleukin-2 (IL-2) receptor, also known as CD25. CD25 is found primarily on activated T lymphocytes, as well as on activated B cells, macrophages, and a subset of nonactivated CD4+ T cells that act as regulatory T cells. By binding to CD25 on activated T cells, daclizumab inhibits IL-2–mediated activation of lymphocytes, preventing the release of cytokines associated with transplant rejection and autoimmune and inflammatory diseases. In 2003, the manufacturer resold all rights to daclizumab, except in transplantation, and these two companies are jointly pursuing development of daclizumab in the treatment of asthma and other respiratory disorders.

In a phase 2 study enrolling patients with moderate to severe persistent asthma (N=115), daclizumab was found to improve asthma control (Busse 2004). A posthoc analysis of a subset of patients who were refractory to ICS (n=33) showed that, compared with placebo-treated patients, the daclizumab-treated patients experienced improved asthma control, in the form of increased FEV₁ (+8.5 percent vs. –9.6 percent; P=.02), more asthma-free days (15 percent vs. 0 percent; P=.02), and increased PEF (+15.7 L/min vs. –13.5 L/min; P=.03) (Nelson 2005).

**Pharmacogenomic profiles**

The next breakthrough in asthma therapy may not be the development of a new drug class or of new drugs within existing classes. Instead, the emergence of pharmacogenomic tools offers the hope of using genetic information to identify patients who are likely to respond poorly to a given therapy or who are prone to experiencing adverse events. Genetic variation appears to explain why some patients respond poorly or adversely to beta₂-agonists, leukotriene modifiers, and ICSs.

For example, polymorphisms affecting the beta₂-adrenergic receptor appear to explain why some patients vary in their response to inhaled beta₂-agonists. In a retrospective study exploring the question of why some participants in a study of inhaled beta₂-agonists had experienced deterioration in peak expiratory flow rate (PEFR) after 16 weeks of albuterol treatment, it was found that the patients who were homozygous for arginine (arg) at the 16th amino acid residue of the beta₂-adrenergic receptor experienced a decline in the morning PEFR, whereas patients who were homozygous for glycine (gly) at that position evinced no such decline (Israel 2000). Results of a subsequent prospective, placebo-controlled clinical trial suggest that albuterol may be inappropriate for patients with the arg/arg genotype (Israel 2004). In these patients, morning PEFR was lower after 16 weeks of albuterol treatment, in comparison with placebo (–10 L/min; P=.02); in albuterol-treated patients with the gly/gly genotype, morning PEFR was higher (14 L/min; P=.02).

At present, clinicians have no convenient or inexpensive means to obtain genotypes pertinent to beta₂-agonists or any other aspect of asthma pharmacotherapy. Nonetheless, affordable pharmacogenomic assays are expected to be clinically available within the next 5 years, allowing clinicians to develop risk-benefit profiles for individual patients prior to the initiation of drug therapy (Wechsler 2005).

**CONCLUSION**

In the near future, a number of new drug treatments are likely to be approved for marketing in the United States. Some of these products expand treatment options within existing drug classes and hold out the promise of improving patient outcomes by improving adherence to therapy; other forthcoming products would be the first members of novel classes of drugs for treating patients with asthma. As these products become available, the challenge will be in determining how to use them appropriately amidst the currently available products. Over the longer term, physicians can look forward to using pharmacogenomic assays that may facilitate the tailoring of pharmacotherapy to a patient’s genetic profile. Such an approach could improve clinical outcomes, enhance patient satisfaction, and possibly reduce asthma-related health care spending.
NEW DEVELOPMENTS

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Adherence With Asthma Therapy

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SUMMARY

Patient nonadherence to asthma-treatment recommendations is associated with decreased control and increased health-resource utilization, morbidity, and costs. Nonadherence can include a set of complex interrelated behaviors. Further, patients differ in their beliefs about their health, routines, and goals, and thus their ability to adhere to a medication regimen. Overcoming obstacles to adherence through improved communication between patient and caregiver can improve management of asthma.

Nonadherence can be defined as lack of compliance to a prescribed course of treatment, and can include taking an incorrect dose, not filling prescriptions, not taking all prescribed doses, taking medication at the wrong times, and premature medication discontinuation. Literature analysis reveals that nonadherence to medication results in about 188 million medical visits annually (DiMatteo 2004). Estimates of nonadherence among patients with all chronic diseases range from 20 to 80 percent of the population, and the costs involved with failure to adhere to prescribed medications go beyond negative clinical outcomes for the patients. The waste of health care dollars from poor adherence has been estimated to be as high as $300 billion in the United States annually (DiMatteo 2004).

SCOPE OF NONADHERENCE

Studies show that noncompliance to the asthma guidelines (NHLBI 1997) is linked to decreased asthma control, increased risk of emergency department visits and hospitalizations, and higher morbidity and costs (Kelly 2001, Weinstein 2005). Mean (95 percent confidence interval) adherence across 41 pulmonary studies was 68.8 percent (61.1, 76.2) (DiMatteo 2004). Specific to asthma, patient nonadherence to inhaled corticosteroids and other preventive asthma therapies often exceeds 50 percent (Stempel 2001, Creer 1997, Carter 2003). These estimates were derived using subjective measures, such as a patient diary, and objective measures, such as prescription refill data and electronic medication monitors that are equipped with microprocessor technology. Although there are no acceptable guidelines for minimum adherence rate to ensure clinical benefit, 80 to 85 percent adherence to medication has been used as a standard (Creer 1997).

Nonadherence in asthma can include a set of complex interrelated behaviors, including medication compliance, attendance at follow-up appointments, avoidance of allergy trigger factors, recording of symptoms, and regular reviews. There are several types of nonadherence, as well as degrees of adherence (Rand 2000, Weinstein, 2005). In erratic nonadherence, the patient forgets to fill

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the prescription, forgets to take a dose, misplaces the medication, or fails to attend an appointment. Unwitting nonadherence refers to when the patient does not completely understand either the specifics of the treatment regimen or the necessity for compliance. In intelligent nonadherence, the patient rejects the diagnosis or treatment over concerns about adverse effects, taste, cost, lifestyle changes, or medication efficacy. The intelligent form of nonadherence is most troublesome, as it necessitates constant communication with patients to obtain an understanding of their beliefs and feelings about their illness and medications, and then to determine the reasons that lead patients to reject treatment. Yet, both unwitting and erratic nonadherence necessitate diligence on the part of the health care system.

Cost of nonadherence

In the United States, the average overall cost of health care expenses per person was estimated to be $5,440 in 2002 (Bender 2004). Considering an average of 3.1 physician office visits per person, the total physician office visits in the United States would exceed 880 million. Nonetheless, studies suggest that the physician advice offered at these office visits is largely wasted (DiMatteo 2004). Estimates suggest that as many as 188 million medical visits lead to poor outcomes because of patient nonadherence to physician advice. Monetary costs for this nonadherence, taking into consideration that this may not be a precise measurement, are estimated to be as high as $300 billion (DiMatteo 2004).

According to a recent World Health Organization (WHO) report, improvements in treatment adherence would have a greater impact on human health than development of new therapeutics (Sabate 2003). WHO estimates that treatment nonadherence is a larger problem in developing countries, where averages fall far below the 50 percent observed in developed countries. Within developed countries, race-ethnicity, lower socioeconomic status, and lower educational achievement are all predictors of lower adherence (Apter 2003).

The economic effects of nonadherence in United States is complicated by the fact that the various health care organizations (HMOs, insurance companies, hospitals, clinics, and medical centers) are sometimes in conflict. For example, insurance policies often determine the amount and type of health care a patient will receive. The pressure to see more patients in a shortened amount of office visit time does not allow for adequate monitoring of noncompliance. Such ill-informed and nonmotivated patients are more likely to end up requiring urgent care, including emergency department visits and hospital stays, which have been estimated to be as high as $2 billion (Cisternas 2003).

Health care costs related to nonadherence

Approximately 16 million persons in the United States have asthma (about 5 percent of the population), reflecting a 75 percent increase in prevalence from 1980 to 1994 (CDC 2004). Severe asthma exacerbations lead to more than 4,000 deaths and 480,000 hospitalizations per year (ALA 2005). Total costs to society for asthma in the United States exceed $16 billion, with more than 70 percent attributable to direct medical costs (ALA 2005). Thirty-seven percent of this expenditure is attributable to medical care of severe acute exacerbations (Weiss 2001). It is unknown how many of the some 13.7 billion ambulatory care visits for asthma per year are secondary to asthma exacerbations, but it is known that asthma results in an estimated 100 million restricted days annually and that the indirect costs to society — more than $4.6 billion for such disruptions as time lost from work or school — are driven primarily by exacerbations (Weiss 2000, ALA 2005).

Studies have shown that the cost increases are proportional to the severity of the asthma condition (Cisternas 2003). For example, annual costs of treatment were $2,316 for mild asthmatics, $4,088 for moderate asthmatics, and $11,066 for severe asthmatics. Patients with severe asthma are considered to be at greater risk for noncompliance because they require more medication to control their symptoms and are prone to secondary complications. These patients also have to cope with the long-term effect of the illness, which affects their work performance, employability, and ultimately their ability to pay for health care and medication (Weinstein 2005).

A Canadian study estimated that the economic burden of hospitalization as a result of nonadherence with controller therapy exceeded U.S. $1.6 billion (Iskedjian 2002).

Exacerbations of asthma are not only important clinical markers of inadequately controlled or worsening asthma, but also likely are the most important outcome from the humanistic and health economics viewpoint as well. A physician who thinks that the patient is not responding to the original treatment might misdiagnose an asthmatic patient who is nonadherent to therapy. This could lead to dangerous or costly complications. Milgrom (1996) found that asthma exacerbations were more commonly seen in nonadherent pediatric asthma patients requiring a prednisone burst.

CAUSES OF NONADHERENCE

While many factors influence a patient’s level of compliance, the literature shows evidence that three factors — patient factors, treatment regimen factors, and factors involving the health care system — affect adherence. Often, clinicians view medication nonadherence as aber-
Patient factors

Asthma patients differ regarding their beliefs about their health, their daily routine, their aspirations and goals, and thus their capacity to adhere to a medication regimen. Patients typically follow only those recommendations in which they really believe and those that they have the ability to carry out (DiMatteo 2004). Factors such as the patient’s age, daily schedule, and the number of other medications being taken for other complaints can make the task of adhering to their management plan more difficult. Poor communication skills, as a result of language barriers, age, or cultural background, also can lead to a patient not understanding what they need to do to adhere to therapy.

People bring into the consultation their beliefs and perceptions about the illness (Inui 1976). Exploring these beliefs about illness, discussing the advantages and drawbacks to taking medication, and working with the patient toward a resolution lead to better clinical outcomes (Janz 1984). A favorable attitude toward medication has a significant positive effect on adherence but does not completely mitigate the effects of racial or ethnic beliefs about health care treatment or delivery (Apter 2003).

The pediatric patient presents unique challenges relative to adherence; patient autonomy in caring for his or her disease varies over time, dependent on both developmental or maturational stage and family dynamics. A risk factor for asthma-related death in children and adolescents is broken family structure (Strunk 1987). Improvement in family communication has been associated with increased adherence and better asthma control (Gustaffson 1986). It is important for parents to provide the child with structure and support, enabling the child to participate in his or her own care to a degree that is developmentally appropriate. Parents may be too protective and the child may become rebellious. Parents may expect the child to accept too much responsibility for his or her total care. Also, if the child perceives that the parents are not committed to following the treatment program, it is unlikely that the child will adhere to it.

Elderly patients also present a distinctive set of adherence issues. Some studies have indicated that 25 to 50 percent of particular groups of elderly patients do not, or cannot, take all their medications as prescribed (Shimp 1985). Adverse reactions to medications, commonly observed in older people, further discourage adherence. The issue of drug interactions can increase the incidence of fear among the elderly regarding their medication. Other factors to consider include poor eyesight, strength, motor coordination, cognition, depression, and isolation. Older people also tend to underreport their symptoms. The presence of other underlying diseases may make asthma symptoms more difficult to identify (Williamson 1980).

Psychosocial factors increasingly are considered to be important influences on adherence and a risk factor for asthma death (Rea 1986). Some of these factors are psychiatric illness, drug abuse, social isolation, and refusal to accept asthma severity. Psychosocial factors are considered to contribute toward a large number of cases of near-fatal asthma. There is evidence that having a supportive family is associated with better self-management in adolescence (Evans 1993).

Drug-regimen factors

It is well known that the greater the number of medications prescribed, the less likely they are to be taken. Coutts (1992) measured compliance with inhaled medication in asthma and found that as medication dosing became more frequent, adherence decreased — from 71 percent for a twice-daily regimen to 18 percent for one prescribed 4 times a day. Physicians also have observed that asthma patients use their medication as prescribed most often when they are symptomatic, as there is an immediate connection between taking medication and symptom relief. Hence, adherence with reliever medication tends to be greater than adherence with preventive medication (Milgrom 1996). In fact, it has been observed that once symptoms resolve, continued adherence becomes increasingly difficult for many people with asthma. Patients will describe this as a balance between whether it is more difficult to take the medication or to have the symptoms.

Patients’ preference for simpler therapy also may be reflected in the results of studies of refill rates for various categories of asthma medications. In one study, refill rates for leukotriene-receptor antagonists were substantially higher than those for long-acting beta,-agonists or inhaled corticosteroids (Figure, page 46). In another study, of British patients, refill rates for a leukotriene-receptor antagonist were significantly higher than for a beta,-agonist and an inhaled corticosteroid (Figure).

Health care system factors

Adherence and self-management are the joint responsibility of the patient and members of the asthma health care team. The asthma health care team includes the in-
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Insurance companies, health care organizations, and medical centers that provide clinical care. Because the insurance companies usually determine the type of health care a patient receives, there appears to be a conflict between the needs and objectives of these organizations (Bender 2004). The asthma health care team has a responsibility to ensure that the patient is receiving the best possible treatment, education, and advice to facilitate a good level of adherence. This would also lead to cost savings, as the price of an average emergency care episode is greater than the cost of long-term controller medication in most cases (Weiss 2001). With positive, open and nonjudgmental relationships, both health professionals and patients can keep to their part of the contract.

HOW TO IMPROVE ADHERENCE

There is no doubt that improving adherence in patients with severe persistent asthma will improve quality of care, reduce unnecessary emergency services, and prevent morbidity and mortality (Weinstein 2005). Fostering this necessitates multiple interventions that include monitoring records of medication refills, providing clear written instructions to the patients, encouraging patient self-monitoring of compliance, and developing social-support structure. Though adoption of various intervention methods may improve adherence to medication regimens over the short term, however, producing a measurable long-term effect on outcomes has been more difficult (Haynes 1987).

Strategies recommended by various investigators to improve compliance in asthma patients include measuring pharmacy refills, use of a self-help workbook; patient attendance at medical appointments, individual counseling sessions, follow-up telephone calls from a health educator; and physician-delivered behavioral strategies to parents of asthmatic children (Jerome 1987, Nides 1993, Berg 1997, Gallefoss 1999, Van Es 2001). These recommendations serve as the underpinnings of the strategies listed in the Table.
The National Institutes of Health–National Asthma Education and Prevention Program Expert Panel Report 2 (2002) recommends the development of a partnership between the health care provider and the patient as a general strategy for improving compliance to asthma therapy. Partnership involves eliciting the trust and involvement of the patient in the treatment decision-making process. Overcoming the obstacles to patient compliance by improved communication between patient, parent, and caregiver can significantly improve the chances of successful management of asthma. Treatment regimen can be further addressed by employing medications with mild side effects. Finally, educating patients on the importance and proper use of therapy is likely to improve nonadherence.

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Disease Management Considerations In Asthma

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SUMMARY

Disease management programs are of interest to employers, insurers, and health care organizations as strategies to improve long-term control of prevalent chronic health conditions. DM typically implies a model of care that includes structured health-risk assessments, integration and coordination of services, and careful tracking of patients on a community- or population-wide basis.

Current patterns of health care expenditures highlight an opportunity to improve resource utilization and the lives of patients with chronic disease. Studies suggest that 75 percent of the nation’s medical care costs are for people with chronic diseases (CDC 2004), with 76 percent of hospital admissions and nearly 90 percent of prescription costs attributable to the needs of the chronically ill (Johnson 2003).

This pattern is evident with asthma. More than half of Americans with asthma have poorly controlled disease, despite national guidelines for diagnosis and management. These findings suggest a need for better health care strategies for chronic health conditions and a shift in resource utilization from episodic care to preventive care.

Disease management (DM) programs provide integrated, expanded, and standardized therapeutic and educational interventions for the chronically ill. Effective DM programs are based on responsive networks of health care providers including specialists, primary care physicians, nurses, pharmacists, nurse-educators, and others who monitor and manage a distinct patient population. The ideal DM program can adapt quickly to changes in patient circumstances by monitoring patients’ progress, including disease control and exacerbations. The ability to store and track meaningful clinical data is important in identifying patients with poorly controlled health conditions and to offer them targeted interventions that help them avert health crises. Tracking patient data also allows evaluation of patient- or population-wide outcomes.

DM strategies have been adopted by insurers, employers, and government agencies to counter steep rises in health care costs for chronic conditions, such as diabetes, heart disease, and asthma (Diamond 2004). Plans that omit DM often lack sustained and effective medical care for high-cost patients, failing to provide such pre-
ventive interventions as cost-effective medications that help control active disease and reduce morbidity. Cost-effective treatment includes preventive interventions such as early counseling, encouragement of patients to control their disease, education, establishment of daily management plans, unhindered access to appropriate medications, and close follow-up and tracking to determine whether patients are achieving the goals of therapy.

To achieve these objectives, all stakeholders in the health care system should participate in DM. Nevertheless, many stakeholders remain unconvinced that DM is effective and economically feasible.

**Measuring DM’s effects**

Numerous variables make it difficult to measure DM’s effects on cost (Johnson 2003). Medical plans that offer DM programs generally pay a third party to manage the programs and pay extra nurses, pharmacists, and other health care workers to administer the program and offer ongoing communication and counseling. Whether asthma DM reduces overall costs is yet to be determined, but many small studies have shown asthma DM to be cost-effective in specific situations and have shown it to reduce emergency department visits, inpatient visits, and hospital stays (Weng 2005). Studies for tracking outcomes and accreditation are not yet standardized among the companies providing or certifying DM programs, making meta-analyses difficult (Johnson 2003).

Rigorous evaluation of DM’s effects should include measures of health status, morbidity, resource utilization, cost of care, functional status, and patient satisfaction. In one meta-analysis, DM programs were most appropriate and economically effective among severely ill enrollees (Krause 2005). These findings suggest that a cost-efficiency approach can target the intensity of DM resources based on level of disease severity and morbidity. In a pediatric asthma study in France, total medical resource utilization cost savings varied according to level of asthma severity (Laforest 2005, Van Ganse 2002). Return-on-investment (ROI) studies have been completed in diabetes, heart disease, and kidney failure. A common phenomenon — high patient turnover in a given plan — complicates DM evaluation, however, by making long-term tracking of outcomes problematic.

Several study designs are used to evaluate the effectiveness of a DM program, including the total population approach, survival-time analysis, and the time series analysis. The population approach is the most widely used model: it consists of a pre-test/post-test that addresses the clinical and financial performance of a DM program during a given period, usually 1 year.

Accreditation for DM programs is available through independent not-for-profit organizations, including the Joint Commission on Accreditation of Healthcare Organizations, National Committee for Quality Assurance, Disease Management Association of America (DMAA), and URAC (a continuous-quality-improvement standards organization). These bodies ensure that DM programs adhere to quality standards; they also monitor a program’s health impact and employ a strategy for ongoing outcomes assessment and quality improvement. They assure that a regular process of data analysis, reporting, and program improvement is used to support clinical operations.

**Components of DM**

At their most basic level, DM programs strive to help chronically ill patients manage their conditions in ways that reduce or delay the detrimental effects of the disease and diminish the need for medical care. In an asthma DM program, as in other DM systems, emphasis is placed on self-care, and enrollees are encouraged to be key participants in improving their health status.

According to the DMAA, DM can be defined as a system of coordinated care and communicators, with the goal of helping patients manage conditions that necessitate significant self-management. The DMAA definition includes the following six factors:

1. Population identification process
2. Evidence-based practice guidelines
3. Collaborative practice models to include physician and support-service providers
4. Patient self-management education (this may include primary prevention, behavior modification programs, and compliance/surveillance)
5. Process- and outcomes measurement, evaluation, and management
6. Routine feedback loop on the process (may include practice profiling and communication with patient, physician, health plan, and ancillary providers)

All six components must be present for a program to be considered a full-service DM program. Otherwise, the program is considered a support service for DM. The DMAA further defines a DM program as one that “supports the physician or practitioner/patient relationship and plan of care; emphasizes prevention of ex-

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2 About 150 different companies offer DM services to managed care organizations and employer purchasers. Some payers choose to build their own internal DM programs, as opposed to contracting with one of these companies for DM services.

3 Available at «http://www.dmaa.org/definition.html».
accerations and complications using evidence-based practice guidelines and patient empowerment strategies; and evaluates clinical, humanistic, and economic outcomes on an ongoing basis with the goal of improving overall health.”

APPLICATION OF DM TO ASTHMA

Treatment of asthma

Evidence-based guidelines exist for asthma treatment (NAEPP 1997, 2002), but they often are not implemented (Eisenberg 2004). The thorough assessment required at each visit is time consuming, complex, and based largely on detailed subjective information about the patient’s asthma and comorbid conditions. Development or adjustment of a patient’s daily management plan depends on a thorough assessment and subsequently necessitates detailed and repeated education. Long-term preventive care depends on adherence to the daily management plan, and engagement with preventive care depends on regular follow-up and reinforcement. Patient compliance is complicated by patients’ stopping medications once symptoms improve, by medication-related side effects, and by the fact that up to a third of patients may not respond to commonly used asthma controller medications. Alternative therapies for treatment that combine different mechanisms of action and enable a reduction in dose may be beneficial and may reduce the public health burden of this disease (Mickleborough 2004).

Treatment of asthma is complex because of the comparative difficulty of predicting acute episodes from severity class (Luskin 2005). Lung function correlates poorly with clinical outcomes, and disease activity and severity must be evaluated regularly based primarily on subjective (nonphysiologic) assessments of symptom frequency, use of rescue medications, severity of flare-ups, and the frequency of flare-ups and their impact on daily life. The course of asthma at any level of severity can change suddenly. Clinical findings don’t always reflect biologic or physiologic findings. Moreover, in asthma, self-awareness doesn’t relate either to biologic, physiologic, or clinical outcomes; denial of seriousness of disease is common.

Responses to therapies in one patient and among patients are highly variable. A given treatment might improve markers but not change exacerbation rates, and vice versa. There is a need to identify and control triggers and inducers. Genetic studies are helping predict which patients will respond to which drugs.

The importance of DM for asthma

DM programs can provide a systematic approach and infrastructure to facilitate thorough patient assessments, development of management plans, regular follow-up and education, as well as careful tracking of health status and patient outcomes. Asthma frequently is not diagnosed, and disease activity is characteristically variable, making it easy for patients to rely on a pattern of rescue or emergency care that involves reliever medications rather than prevention with environmental control and controller medications. Therefore, disease modification and disease control are imperative. Interventions in asthma that produce the clearest clinical benefit increase access to specialty care and increase access to controller (as opposed to rescue) medications. There is a need for education of the integrated care team and their patients, as well as a need for goals and written management plans for chronic and acute care.

Additionally, there is a need for outcomes to include clinical, biologic, and physiologic markers and humanistic (quality of life) and economic factors, and to improve therapies and increase the adherence rate. For asthma programs, a feedback loop must allow quick changes in the treatment approach. There must be a refined focus on control instead of severity as a primary measure and an integration of patient-derived outcomes into the definitions of control.

To achieve these objectives, the following should be improved: case identification, patient tracking and information systems, care coordination, and methods to efficiently evaluate clinical control of asthma.

Numerous approaches have been taken to asthma disease management. The author’s experience is detailed in the case study accompanying this article (see page 51). Under the program described in the case study, the majority of patients in all categories of asthma severity achieve clinical control of asthma by their third visit, with approximately 90 percent of ongoing participants achieving control by the sixth visit.

REFERENCES


Jones CA, Clement LT, Hanley-Lopez J, et al. The Breathmobile (Continued on page 53)
Case Study
The PADMAP experiment in Los Angeles

Lower socioeconomic groups and ethnic minorities are disproportionately underdiagnosed and affected by adverse outcomes and increased hospitalizations. In inner city areas, visiting the emergency department for primary care and receiving episodic health care can be a way of life (Grant 2000, Jones 2004).

The Pediatric Asthma Disease Management Program (PADMAP), funded by the Southern California Chapter of the Asthma and Allergy Foundation of America (So Cal AAFA) and the Los Angeles County Department of Health Services (LAC DHS), began in 2002 to meet the needs of an underserved population of inner-city youths in Los Angeles County. The program evolved from a community outreach effort, which used mobile clinics to deliver preventive asthma care to students at their schools in 1995. PADMAP’s goal is to establish and maintain a communitywide asthma DM program to shift inner-city children from acute episodic care to regular preventive care in accordance with national standards.

At present, PADMAP includes four Breathmobiles that regularly visit approximately 90 schools and three County Comprehensive Health Centers, as well as a Care Coordination Center and the Allergy & Immunology Clinic at the Los Angeles County + University of Southern California Medical Center. The Breathmobiles are 34-foot mobile clinics staffed by teams of four asthma care specialists. Each team includes an allergist (physician), two staff members (two RNs, or an RN and a respiratory therapist), and a patient service worker who assists families as a translator and with access to health care resources. A programwide computer network supports the use of an electronic tracking system, AsmaTrax, to track clinical data and care coordination. These resources are organized to systematically identify patients with poorly controlled disease, engage families in preventive care, track clinical outcomes, and ultimately achieve and maintain clinical control of asthma.

A primary objective of PADMAP is to help a lower socioeconomic urban population achieve and maintain clinical control of asthma. The definition of clinical control of asthma was abstracted from the National Asthma Education and Prevention Program’s Guidelines for the Diagnosis and Management of Asthma (NAEPP 1997). These goals are summarized as follows:

- No severe flare-ups of the patient’s asthma since the last visit that required emergency departments, in-patient stays, or systemic oral corticosteroids
- Lung function that is normal or optimal for patient
- No reported asthma-related limitations on patient’s activities and exercise

The goals of the PADMAP program are being met. The majority of patients in all categories of asthma severity achieve clinical control of asthma by their third visit, with approximately 90 percent of ongoing participants achieving control by the sixth visit. Consistent with other studies (Weng 2005), there have been significant reductions in inpatient and emergency department use (Jones 2005).

Most patients can maintain clinical control of their asthma at follow-up visits; careful tracking reveals a portion of the population with difficult-to-control asthma, however, despite ongoing care in accordance with current national guidelines. This DM approach allows for more intensive services to be appropriately targeted. Families enrolled in PADMAP tend to remain engaged in ongoing care, with rates for return visits consistently ranging from 70 to 75 percent.

In 2002, the program was the first to be awarded Disease-Specific Care Certification by the Joint Commission on Accreditation of Healthcare Organizations. Such certification is based on an assessment of compliance with relevant standards and criteria, effective use of clinical guidelines, and outcomes measurement. According to JCAHO (2004), “Certification demonstrates excellence in fostering better outcomes by the integration and coordination of care. The JCAHO’s quality-review programs for accreditation and certification represent the industry’s gold standard in health care.”

DM methods in PADMAP

Patient progress is tracked and recorded in a structured manner, providing a longitudinal view of important clinical elements whenever the family interacts with the health care team. The following are continually assessed:

- Clinical control of asthma, disease activity, and morbidity
- Presence and activity of comorbid conditions
- Environmental exposures
- Knowledge and understanding of treatment plan, medications, and appropriate techniques
DISEASE MANAGEMENT

- Knowledge and understanding of environmental intervention measures
- Adherence records
- Response to each therapeutic component (i.e., condition, medication)

Follow-up occurs at regular intervals, with the intensity and frequency necessary to achieve and maintain control. On the basis of longitudinal findings, therapy is adjusted to meet this objective as well as those of the patient and family.

If poorly controlled asthma is identified (see Table), assessments are made to adjust the treatment plan and pharmacotherapy and to supply directed education.

The basis for the PADMAP health care model is outlined in Figure 1. At present, PADMAP emphasizes identification of poorly controlled asthma and then engagement in ongoing specialty care supported by care coordination, routine patient contact, and careful clinical tracking on a communitywide basis. Clinical tracking is accomplished through the use of AsmaTrax, which provides the infrastructure for program evaluation and improvement. On a regular basis, data are analyzed to learn whether program objectives are being met. The

TABLE

<table>
<thead>
<tr>
<th>Measures to be taken in difficult-to-control asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Ensure that the patient understands the treatment plan, comorbidities, exposures, and triggers</td>
</tr>
<tr>
<td>• Reinforce the importance of following the daily asthma management plan</td>
</tr>
<tr>
<td>• Ensure that the patient understands the treatment rationale</td>
</tr>
<tr>
<td>• Determine patient’s understanding of medications (controllers vs. relievers)</td>
</tr>
<tr>
<td>• Ensure that the patient understands the goals of his or her therapy</td>
</tr>
<tr>
<td>• Consider the patient’s priorities in setting therapeutic goals</td>
</tr>
<tr>
<td>• Ask the patient to demonstrate understanding and technique of treatment</td>
</tr>
<tr>
<td>• Ask each patient, “Were you able to get your medications?” If not, ask why</td>
</tr>
<tr>
<td>• Explain regular follow-up to the patient, as well as measures of response to therapy</td>
</tr>
<tr>
<td>• Assess the patient’s desire and commitment to follow the plan</td>
</tr>
<tr>
<td>• Evaluate response to therapy and plan follow-up based on the evaluation</td>
</tr>
<tr>
<td>• Plan services and treatment with advanced therapeutics when necessary</td>
</tr>
</tbody>
</table>

FIGURE 1

PADMAP model for routine care to control active asthma

Application of disease management principles

Patient population

Routine care | No routine care

Identify poorly controlled asthma

Case identification and referral

Administrative data, direct health-status assessment

Newly identified patients

Contact and schedule initial visit

Assess and prioritize: care coordinators, staff team

Contact prior to each visit and for missed visits

Engage in long-term preventive care: care coordinators, staff team

Encounter with asthma DM specialty teams

Assessment, track clinical control of asthma, treatment plan, education, medications, schedule return visit

Bidirectional communication with PCPs

General care and maintenance asthma therapy; track clinical control

Identify poorly controlled asthma

DM=disease management, PCP=primary care practitioner.
results are used to adjust clinical operations as well as the program objectives and measures.

The routine process for program evaluation and improvement is outlined in Figure 2. In the PADMAP program, support for data management and analysis is provided by So Cal AAFA, while the LAC DHS supports clinical operations.

Current efforts are focused on expanding operations to the primary care setting to facilitate identification, treatment, and referral of poorly controlled asthma as part of a more comprehensive model. To achieve this, So Cal AAFA has supported the development of a kiosk-based survey system deployed in primary care settings. In the clinic setting, parents/patients complete the survey, scoring algorithms determine the score, and a report is printed telling patients: a) whether they are likely to have active asthma, b) whether asthma is poorly controlled, and c) whether they are likely to have moderate-to-severe disease activity. Survey answers are summarized. The family then brings this report to review with their provider. Positive reports can be forwarded electronically and automatically to an asthma care manager or coordinator. The goal is to help providers and families identify and treat poorly controlled disease in a systematic way. Patients who are unable to achieve and maintain clinical control can be referred to the specialty portion of the PADMAP care model.

**Conclusion**

Through a systematic approach, the use of DM principles and the objective of “treating to control” can help a population achieve greater rates of control than are observed with conventional health care operations. This is accomplished by evaluation to determine whether objectives are achieved and by modifying the health care process when needed to improve the success rate of clinical control and maintenance on an individual-patient and on a populationwide basis.

Success with PADMAP in Los Angeles shows that an asthma DM program is achievable on a large-scale basis by proper design and resource allocation, as well as by stratified care delivery that shifts patients from episodic care to long-term routine preventive care.

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**Figure 2**

Continuous model for program improvement based on evaluation of health status and process measures

**Objective**

**Performance measure:** relevant to objective

**Analysis and review:** objective achieved?

**Modification of health care process**

**Modify measures and methods**

**PADMAP asthma disease management program:** *Plan for program evaluation and improvement*

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**DISEASE MANAGEMENT**


HEDIS Requirements and Considerations For Managing Patients With Asthma

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Advocate Health Care, Chicago

SUMMARY

NCQA evaluates whether health plan members with persistent asthma are prescribed medications that are deemed acceptable by the NHLBI as primary therapy for long-term control of asthma. Data indicate that much work is needed to improve quality of care. Yet the question remains: Does HEDIS accurately identify components of care most germane to ensuring optimal clinical outcomes?

Nearly 2 decades ago, a concerted movement toward accountability and continuous quality improvement (CQI) in health care began. Since then, performance indicators have since become more sophisticated and more broadly utilized. With this, there is implicit agreement among stakeholders — payers, plans, providers, and patients — with the basic tenet of CQI: You cannot manage what you cannot measure, and you cannot improve what you cannot manage.

Payers’ demands for accountability provided the impetus for development of data gathering and reporting or-
Performance on HEDIS measures can be used to promote quality improvement and as the foundation for physician pay-for-performance programs. While these activities indicate significant progress relative to quality measurement, the question emerges as to whether HEDIS truly can improve patient care and quality of life and make a relevant contribution to asthma control.

**Measurement of process vs. outcomes**

HEDIS indicators generally measure how frequently an event occurred. For example, this might be the percentage of individuals who received beta-blockers after a heart attack, the percentage of adults who have been screened for a number of cancers, or the percentage of children and adolescents who have received appropriate immunizations. These, and many others, are considered process measures, or what NCQA designates as Effectiveness of Care measures. Performing at or above national benchmarks on these measures presumes that reasonable to good quality of care is being delivered.

Nevertheless, many stakeholders are skeptical that the measurement of process is an accurate and reliable substitute for clinical outcomes and the effect of treatment on patient quality of life. Researchers have asked, “What are the utility, practicality, and target audiences for various HEDIS performance measurements?” (Press 2004).

While these questions have no simple answers, the trend is that health-status surveys and quality measurement will continue in the direction of indicators with relevance for patients and clinicians. In asthma treatment, new measures might include assessments of overall symptom control, or the effect of asthma on lost school or work days, reduced productivity, or increased health care resource utilization (ER, office visits, and avoidable hospitalizations).

**HEDIS asthma measure/medication overview**

The HEDIS measure Use of Appropriate Medications for People With Asthma evaluates whether health plan members with persistent asthma are prescribed medications deemed acceptable by the National Heart, Lung, and Blood Institute (NHLBI) as primary therapy for long-term control of asthma. The measure is collected separately for children (age 5–9), adolescents (age 10–17), and adults (age 18–56). A combined rate also is reported.

The HEDIS asthma indicator measures the percentage of individuals meeting a claims-based definition of persistent asthma who are dispensed at least one of a specified group of controller medications within the measurement year. Controller medications include:

- Inhaled corticosteroids (current gold standard)
- Nedocromil (infrequently used in clinical practice)
- Cromolyn sodium (infrequently used)
- Leukotriene modifiers
- Methylxanthines (infrequently used)
- Long-acting, inhaled beta2-agonists (beta2-agonists also are available as short-acting, sustained release, oral medications)

As stipulated in the HEDIS instrument, members are identified as having persistent asthma by having any of the following in the year prior to the measurement year:

- At least 4 occasions on which asthma medication was dispensed
- At least 1 ER visit with asthma as the principal diagnosis
- At least 1 hospitalization with asthma (ICD-9 code 493) as the principal diagnosis
- At least 4 outpatient asthma visits as one of the listed diagnoses AND at least 2 asthma medication-dispensing events

Specifically, the numerator of the measure captures health plan members who have been prescribed one or more controller medications in the measurement year; the denominator captures members who had persistent asthma in the year prior to the measurement year.

**HEDIS PERFORMANCE**

Year-2000 baseline rates for appropriate asthma medication prescribing indicate that much work remains to improve quality of care (Shih 2003). In the State of Health Care Quality: 2004, NCQA reports that huge “quality gaps” exist in health care delivery. These gaps reflect the difference in performance between the top decile of health plans and those meeting national averages. Asthma care is no different, with measurable disparities emerging when plans and populations are compared (Tables 1 and 2, pages 56 and 57 respectively).

National averages for appropriate medication use in people with asthma are improving, albeit slightly. The increase in medication usage was statistically significant only among commercial plans. Additionally, the performance gap between commercial and Medicaid plans is increasing — a trend plans and providers would like to see reversed. One important caveat: The specification for this measure changed in 2003 to exclude certain patients who may not have asthma from the denominator. This change may be responsible for some rate increases.

**Reasons for suboptimal performance**

Irregular use of inhaled anti-inflammatory asthma medication contributes to poor control of the disease. This lack of adherence may be due to patients’ mis-
understanding of the preventive role of these medications. When almost 600 parents of children with persistent asthma were interviewed, nearly 25 percent thought that the role of inhaled anti-inflammatory medication was to treat asthma symptoms, as opposed to addressing the disease’s root cause. This basic misunderstanding is associated with decreased daily use (Farber 2003).

Patterns of anti-inflammatory use vary widely among children with persistent asthma. This is due to significant variability in prescription dispensing for controller medications, as well as nonadherence. Among 13,352 children studied in three MCOs, significantly fewer of the younger children (age 3–5) were prescribed more than one controller medication ($P<.001$). Among all children who were dispensed six or more beta$_2$-agonists, only 39 percent received five or more controller medications. Adolescents and females were far less likely to receive at least five inhaled anti-inflammatory prescriptions ($P<.001$). The authors conclude that age, sex, and health plan affect the rate of prescribing for controller medications, with few children receiving controllers as recommended by national guidelines (Adams 2001).

**HEDIS and quality of care**

The question that remains is: Can HEDIS accurately identify components of care that are most germane to ensuring optimal clinical outcomes for patients with persistent asthma? For example, patients may have poor inhaler technique, or they may not recognize that a household pet is contributing to disease exacerbation. If providers concentrate only on the rate at which they prescribe controller medications, defined by HEDIS as a proxy for quality care, other potentially key determinants of enhanced outcomes may be overlooked.

Another issue with the HEDIS measure is potential misalignment of the numerator and denominator. As stated, the numerator counts members prescribed one or more controller medication(s) in the measurement year. The denominator captures members with persistent asthma in the year prior to the measurement year.

For patients with truly persistent and poorly controlled disease, this ratio will adequately assess processes of care and stand as a reasonable proxy for quality. Nonetheless, for patients with severe but infrequent exacerbations of symptoms resulting in either an ER visit or even hospitalization, the measure’s numerator and denominator may be misaligned fundamentally — depending on when in the year the exacerbation occurred. Patients with serious exacerbations rightfully may be prescribed an inhaled corticosteroid, the use of which is frequently tapered down as appropriate. These same patients, however, may not be long-term candidates for these medications, assuming that they have their disease under control, their symptoms have become extremely mild, or their disease has gone into remission. In this not-so-infrequent scenario, the current HEDIS measure would translate the care received as substandard even though it might have been entirely appropriate. This potential misalignment of the timing of events in the numerator and denominator of the indicator undermines the validity of the measure itself.

Another issue is that the HEDIS measure only considers the number of prescriptions dispensed. Though writing and dispensing a prescription is the first step toward treatment goals, simply filling a prescription does not equate with adherence or ensure quality care, nor does it necessarily promote optimal outcomes.

### TABLE 1

**Plan performance with the asthma effectiveness of care measure**

<table>
<thead>
<tr>
<th>Combined percentage of appropriate asthma medication use 2000–2004</th>
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</thead>
<tbody>
<tr>
<td><strong>Year</strong></td>
</tr>
<tr>
<td>2000</td>
</tr>
<tr>
<td>2002</td>
</tr>
<tr>
<td>2004</td>
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</table>

<table>
<thead>
<tr>
<th>Appropriate asthma medication use: commercial rates, 2000–2004</th>
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<tbody>
<tr>
<td><strong>Age group</strong></td>
</tr>
<tr>
<td>5–9</td>
</tr>
<tr>
<td>10–17</td>
</tr>
<tr>
<td>18–56</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Appropriate asthma medication use: Medicaid rates, 2000–2004</th>
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</thead>
<tbody>
<tr>
<td><strong>Age group</strong></td>
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<tr>
<td>5–9</td>
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<tr>
<td>10–17</td>
</tr>
<tr>
<td>18–56</td>
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</table>

**SOURCE:** NCQA 2005
There are differences in HEDIS criteria versus NHLBI criteria (the gold standard) for diagnosis of persistent asthma. In a cross-sectional study of 896 parents of children with asthma, all children met HEDIS criteria for persistent asthma by parent report. By comparison, the NHLBI criteria state that asthma is persistent if, within the last 2 months, nighttime asthma symptoms occurred more than 2 nights per month, or daytime asthma symptoms were experienced more than 2 days per week. On the basis of HEDIS criteria, 73 percent of the children studied would be diagnosed with persistent asthma, versus only 38 percent under the NHLBI diagnostic criteria. The authors conclude that HEDIS criteria are sensitive but not extremely specific and may include children who do not require use of controller medications (Cabana 2004).

Further, among patients with persistent and poorly controlled disease, it generally is believed that sustained use of controller medications — not just 1 prescription per year — will enable them to bring their disease under control. The HEDIS measure does not consider disease severity, and thus may not contribute to optimal therapy for seriously ill patients.

Intermittent use of controller therapy is being researched and debated. For example, some adult patients with mild yet persistent asthma have done well with only intermittent use of corticosteroids, which in all likelihood is how these medications are used outside the clinical environment in this population. A recent article in the *New England Journal of Medicine* reported that intermittent, short-course corticosteroid treatment produced similar and acceptable outcomes compared with daily therapy. Patients in the intermittent cohort used budesonide, on average, for only 0.5 week of the 1-year study period. Use of the corticosteroid was guided by asthmatic symptom expression (Boushey 2005). The article has been criticized, however, in that patients participated in a randomized controlled trial that does not equate with actual use (i.e., not a real-world scenario and no minors were included in the study groups).

Research such as that by Boushey suggests that treatment guidelines may need to be revisited and that more studies on optimal asthma control in varied patient subgroups needs to be conducted. As yet, there is no consensus on intermittent use of controller medications, but the standards of practice have indicated that sustained use is best, especially among such high-risk populations as extremely young children (Glauber 2001).

### HIGH-RISK POPULATIONS

The HEDIS measure excludes children under 5 years old, yet numerous studies suggest that this population may be highly appropriate for interventions that can reduce morbidity. Additionally, asthma onset prior to age 3 increases a child’s risk of serious, chronic disease. Despite these findings, extremely young children with asthma are less likely than children above age 5 to receive use of controller medications.

### CORTICOSTEROID USE

Examining HEDIS national averages for Use of Appropriate Medications for People With Asthma reveals superior performance among health plans that also have gone through NCQA’s voluntary accreditation process and that have agreed to release public “report cards” on their performance.

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<tr>
<td>18–56</td>
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<td>10–17</td>
<td>69.6</td>
<td>68.8</td>
<td>0.8</td>
</tr>
<tr>
<td>18–56</td>
<td>74.0</td>
<td>71.0</td>
<td>2.9</td>
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<table>
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<tr>
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<td>5.9</td>
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<tr>
<td>18–56</td>
<td>67.2</td>
<td>60.6</td>
<td>6.6</td>
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</table>

**SOURCE NCQA 2005**
controller therapy (Glauber 2001). Therefore, it might be advisable for HEDIS to include this vulnerable population in the measure’s next iteration.

Other high-risk groups include racial and ethnic minorities, especially where a language barrier exists, and persons with limited economic means. Such individuals tend to receive poorer quality of care and thus experience suboptimal clinical outcomes (Haltermann 2000). Specifically targeting all these high-risk individuals in a new HEDIS measure might be a prudent consideration.

**HEDIS measure and disease control**

Among thought leaders, there is debate about controlling the expression of asthma versus aggressively treating its underlying pathology. A shift is occurring from concentration on disease severity to measurement of control, regardless of clinical/pathological severity. This shift is due in part to the fact that patients and, certainly, physicians often have little or no control over external factors that can exacerbate asthma symptoms. The question many clinicians face is, “How well is asthma controlled in my patients?” Unfortunately, the HEDIS measure does little to answer this question and may not be robust enough to encourage proper control.

To help address this question, quality-of-life instruments, such as the Asthma Control Test, are emerging. Its use is supported by the American Lung Association and is validated in people with asthma who are 12 and older. It comprises five simple questions on expression-of-asthma symptoms (degree of control) as well as patient assessment of how asthma has affected their lives in the previous 4 weeks. It can be completed online or while waiting for an office visit. Patients’ scores on the control test will help their providers adjust treatment plans, initiate discussion about potentially problematic allergens and/or irritants to which the patient might be exposed, and develop individual patient benchmarks for improvement. Underscoring the trend toward measurement of asthma control in high-risk populations, this instrument is currently being validated in young children.

**EVOLUTION OF A NEW HEDIS MEASURE**

There is clear evidence of the necessity of measurement evolution and change. This will occur as new treatments emerge and as potentially better indicators are developed that accurately reflect quality of care and functional and clinical outcomes from the perspectives of the patient, provider, and payer.

Further, beyond simple prescription of a controller therapy is the issue of adherence. Poor adherence with inhaled anti-inflammatory therapy results in increased costs and unnecessary resource utilization such as ED and office visits as well as potentially avoidable hospitalizations (Berger 2004, Smith 2004). Dispensing controller medications and a higher controller-to-reliever ratio, are associated with a lower risk of ED visits in children with persistent asthma (Fuhlbrigge 2004). These studies point to the value in developing a new HEDIS measure(s) that includes the assessment of adherence as a possible means of achieving improved clinical outcomes and patient functionality, and reduced resource consumption.

The NHLBI is revisiting its asthma guidelines and will, in all likelihood, issue significant revisions in 2006. These guidelines are likely to have a profound effect on a new HEDIS measure(s) and will hopefully help to stimulate improvements in the processes of care that will result in better clinical and functional outcomes for all patients suffering from persistent asthma.

**REFERENCES**


If a score of 70 percent or better is not achieved, no credit will be awarded and the registrant will be notified. This activity is provided at no cost to the participant through an educational grant from Genentech Inc.

EXAMINATION: Place an X through the box of the letter that represents the best answer to each question on pages 60–61. There is only ONE correct answer per question. Place all answers on this form:

1. A. B. C. D. E.  
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PROGRAM EVALUATION
So that we may assess the value of this self-study program, we ask that you please fill out this evaluation form.

Have the activity’s objectives been met?

1. Describe the clinical and economic burdens of asthma □ Yes □ No

2. Understand the significance of unmet needs among people with asthma □ Yes □ No

3. Summarize current treatment guidelines and reasons why guidelines are not followed □ Yes □ No

4. Identify various recommended treatments for asthma, understand their mechanisms of action, and describe emerging therapeutic approaches □ Yes □ No

5. Elucidate strategies for therapeutic compliance and the consequences of noncompliance with drug-therapy regimen □ Yes □ No

6. Discuss NCQA guidelines for care of patients with asthma □ Yes □ No

Was this publication fair, balanced, and free of commercial bias? □ Yes □ No

If no, please explain: __________________
___________________________________
___________________________________

Please use the following scale to answer the next four questions:

Strongly Agree .......... 5
Agree .................. 4
Neutral .................. 3
Disagree .................. 2
Strongly Disagree ..... 1

Did this educational activity meet my needs, contribute to my personal effectiveness, and improve my ability to:

Treat/manage patients? 5 4 3 2 1 N/A

Communicate with patients? 5 4 3 2 1 N/A

Manage my medical practice? 5 4 3 2 1 N/A

Other ____________________________

Effectiveness of this method of presentation:

Very Excellent good Good Fair Poor

5 4 3 2 1

What other topics would you like to see addressed? __________________
___________________________________
___________________________________

To receive credit, complete the answer sheet/evaluation form and mail or fax the completed form to:
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CONTINUING EDUCATION POST-TEST
P&T DIGEST Asthma

On the combined answer sheet/evaluation form on page 59, please place an X through the box of the letter corresponding with the correct response for each question. There is only one correct answer to each question.

1. According to the National Heart, Lung, and Blood Institute, more than ________ asthma-related deaths occur each year in the United States.
   a. 4,000.
   b. 5,000.
   c. 6,000.
   d. 7,000.

2. The patient-perceived level of asthma control is ________ the clinical definition of control.
   a. Higher than
   b. About the same as
   c. Below

3. The following statements are true for the U.S. population except:
   a. Women are more likely than men to develop asthma.
   b. About 16 million people have asthma.
   c. Chronic asthma is less prevalent than are mood disorders.
   d. The majority of asthma sufferers are children under age 18.

4. A recent study of more than 6,000 patients treated with inhaled corticosteroids found the prevalence of negative side effects, such as thrush, in the oropharynx to be ________.
   a. 5 percent.
   b. 15 percent.
   c. 25 percent.
   d. 35 percent.

5. Asthma control should be defined in terms of ________.
   a. Frequency of exacerbations.
   b. Disease progression.
   c. Symptoms.
   d. Pulmonary function.
   e. All the above.

6. The mechanism of inhaled corticosteroid therapy is believed to involve:
   a. Enhancement of submucosal glands, airway smooth muscle, endothelial, and epithelial cells.
   b. Reduction in the number of mast cells, circulating eosinophils, and dendritic cells.
   c. Prevention of macrophages and T-lymphocytes from releasing cytokines.
   d. Activation of the intracellular glucocorticoid receptor.
   e. All the above.

7. Why is the worldwide asthma epidemic expected to worsen in the future?
   a. Increasing awareness of new treatments will prompt more people to report asthma symptoms to their physicians.
   b. Expanding industrialization will increase the amount of air pollutants that may trigger asthma.
   c. Too many physicians are not adhering to evidence-based treatment guidelines.
   d. Smoking rates and population growth are rising in poor countries where asthma is already a significant problem.

8. Though the prevalence of asthma is highest among black Americans, blacks are less likely than Latinos or whites to be hospitalized or receive emergency treatment for severe exacerbations.
   a. True.
   b. False.

9. According to HEDIS, a health plan member would be identified as having persistent asthma if he or she had at least 4 outpatient asthma visits and ________.
   a. At least 4 occasions on which asthma medication was dispensed.
   b. At least 1 emergency department visit with asthma as the principal diagnosis.
   c. At least 2 asthma-medication dispensing events.
   d. At least 1 hospitalization with asthma as the principal diagnosis.
   e. Any of the above.

10. What is the estimated cost of nonadherence to prescribed therapy for all chronic diseases in the United States?
    a. $200 million per year.
    b. $500 million per year.
    c. $300 billion per year.
    d. $600 billion per year.

11. What proportion of asthma cases are considered severe?
    a. Up to 11 percent.
    b. Up to 15 percent.
    c. Up to 28 percent.
    d. Up to 77 percent.

12. What is the recommended level of theophylline therapy?
    a. 0.5–5.0 mcg/mL.
    b. 5–15 mcg/mL.
    c. 15–25 mcg/mL.
    d. 20–30 mcg/mL.
13. Large-scale studies show that disease management for asthma reduces overall health care costs.
   a. True.
   b. False.

14. Which of the following asthma-related occurrences could be assessed as the basis for a HEDIS effectiveness of care measure?
   a. Lost school or work days due to the disease.
   b. Symptomatic control of the disease.
   c. Avoidable hospitalizations.
   d. Office visits.
   e. All the above.

15. All the following factors contribute to physicians’ nonadherence to asthma guideline recommendations except:
   a. Inability to access the most current guidelines.
   b. Lack of confidence in their ability to prescribe correct doses of corticosteroids.
   c. Discomfort relative to their peak-flow meter training.
   d. General skepticism about outcomes research and evidence-based medicine.

16. In a meta-analysis by Corren (2003), omalizumab, a humanized monoclonal antibody, reduced the rate of hospitalization
   a. Among adults and children with severe, persistent asthma by 92 percent.
   b. Among adults with severe, persistent asthma by 92 percent.
   c. Among children with moderate to severe asthma by 92 percent.
   d. Among adults and children with moderate to severe asthma by 46 percent.

17. Of the three forms of patient nonadherence, which is considered most troublesome?
   a. Erratic.
   b. Unwitting.
   c. Intelligent.
   d. All forms are equally troublesome.

18. Affordable assays allowing physicians to develop risk-benefit profiles for individual patients prior to initiation of drug therapy are expected to be clinically available
   a. Within a few months.
   b. Within 1 year.
   c. Within 3 years.
   d. Within 5 years.

19. Which of the following targets appear promising in the development of new therapies for asthma?
   a. Tumor necrosis factor.
   b. IL-2.
   c. IL-4.
   d. IL-5.
   e. All of the above except d.

20. Who administers the Asthma Control Test?
   a. The physician.
   b. The patient.

21. At any given time, half of all asthma patients in the United States are not using their prescribed preventive therapy.
   a. True.
   b. False.

22. In contrast to the relatively robust response to inhaled corticosteroids in clinical trials, the agent’s failures in clinical practice may be more common for the following reasons except the patient’s:
   a. Genetic predisposition.
   b. Inadequate adherence with inhalation therapy.
   c. Increased exposure to allergy triggers.
   d. Poor inhalation technique.
   e. Habitual smoking.

23. Which of the following drugs is the dominant leukotriene modifier?
   a. Zileuton.
   b. Zafirlukast.
   c. Montelukast.
   d. Fluticasone.

24. In asthma management and all disease management systems, primary emphasis is on
   b. Advance physician training.
   c. Evaluation of economic outcomes.
   d. Collaboration between physician and support service providers.

25. Under the Los Angeles PADMAP program, how many visits does it take for the majority of pediatric patients to achieve clinical control of their asthma?
   a. 3.
   b. 4.
   c. 5.
   d. 6.