SPECIAL SUPPLEMENT TO

MANAGED Care

Effective Asthma Management

Current Guidelines and Treatment Options

Based on a conference in Washington D.C. on Oct. 10, 2002.

HIGHLIGHTS

- 2002 Update From the National Asthma Education And Prevention Program
- Clinical and Economic Decision Making In Asthma Management
- Implementing an Asthma Management Program
- Improving Outcomes With Appropriate Utilization Of Asthma Therapies

Continuing medical and pharmacy education sponsored by Medical Education Resources Inc.

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MANAGED Care

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SPECIAL SUPPLEMENT

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Effective Asthma Management: Current Guidelines and Treatment Options

A CONTINUING EDUCATION ACTIVITY

Based on a conference held in Washington D.C. on Oct. 10, 2002.

About this publication

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SELF-STUDY CONTINUING EDUCATION ACTIVITY

Effective Asthma Management: Current Guidelines and Treatment Options

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Sponsorship
This activity is sponsored by Medical Education Resources Inc., a nonprofit medical education company in Littleton, Colo.

Target audience
This program has been designed to educate managed care pharmacists, pharmacy directors, and medical directors on recent and upcoming changes in asthma management guidelines, and to demonstrate ways to improve quality of care through providing examples of progressive and innovative asthma management programs.

Program overview
Managed care organizations are becoming increasingly aware of asthma's impact on the American health system. Despite a strong understanding of pathophysiology and pharmacotherapeutic advances relative to asthma, this disease affects more than 17 million people in the United States, resulting in more than 1.5 million emergency department visits, approximately 500,000 hospitalizations, and in excess of 5,000 deaths annually. As a result, the National Heart, Lung, and Blood Institute (NHLBI) and the National Institutes of Health (NIH) recently convened various expert panels to discuss and update current asthma-management guidelines and to provide recommendations as to how health plans can manage their asthmatic populations best.

The expert faculty members who have contributed to this supplement present pharmacotherapeutic options in asthma management and explain how the NHLBI guidelines have promoted early use of inhaled corticosteroids, narrowing the gap between actual and optimal care. Studies demonstrate that overuse of albuterol inhalers is often a marker of inadequate asthma control and an indication that patients are consuming a greater amount of expensive medical resources. The pathophysiology of chronic asthma supports the pharmacological basis for dual controller therapy, which addresses both the bronchoconstrictive and inflammatory components of this condition. Case studies detailing the development, implementation, management, and evaluation of successful asthma-management programs in two large managed care organizations are presented. Data regarding clinical and economic outcomes are discussed, as is the impact on pharmacy program cost and utilization. The faculty members delineate how a successful program can be implemented seamlessly in other managed care systems and outline recommendations for future asthma treatment options and guidelines.

Program faculty

Stuart Stoloff, MD
Clinical Professor
Family and Community Medicine
University of Nevada School of Medicine
Carson City, Nev.

Richard D. O'Connor, MD
Director, Dept. of Quality Management
Director, Dept. of Clinical Research
Staff Physician, Sharp Rees-Stealy Medical Group
Clinical Professor of Pediatrics
University of California San Diego School of Medicine
San Diego

Michael Belman, MD, MPH
Staff Vice President, Medical Director
Blue Cross of California
Woodland Hills, Calif.

H. Eric Cannon, PharmD
Director of Pharmacy Services
Intermountain Health Care
Salt Lake City

Robert P. Navarro, PharmD (moderator)
President
NavarroPharma, LLC
Southport, N.C.

Pharmacy accreditation
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This CME activity was planned and produced in accordance with the ACCME Essentials.

Learning objectives
On completion of this program, participants should be able to:

- Describe the clinical and economic burden of asthma.
- Explain the revised 2002 NHLBI and NIH asthma guidelines.
- Recognize the role of inhaled corticosteroids as outlined by the NHLBI guidelines.
- Apply the mechanisms of asthma pathophysiology to drug product selection.
- Explain how asthma management in managed care can be improved as demonstrated through managed care case studies.
- Develop new and improved guidelines for the treatment of asthmatic populations within their health plans.

Program completion time
Based on trials, the estimated time to complete this program is 2 hours.

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It is the policy of Medical Education Resources Inc. to ensure balance, independence, objectivity, and scientific rigor in all its educational activities. All faculty members participating in our programs are expected to disclose any relationships they may have with commercial companies whose products or services may be mentioned, so that participants may evaluate the objectivity of the articles. In addition, any discussion of off-label, experimental, or investigational use of drugs or devices is listed below as disclosed by the faculty.

The faculty reported the following:

Michael Belman, MD, has served as a consultant to AstraZeneca, and he has received grant/research support from GlaxoSmithKline.

H. Eric Cannon, PharmD, has no relationships with commercial companies for products that may be mentioned in his article.

Robert Navarro, PharmD, (moderator) serves as a consultant for GlaxoSmithKline.

Richard O'Connor, MD, owns stock in GlaxoSmithKline, AstraZeneca, Merck, Pfizer, Aventis, and Schering Corp. He has served as a consultant for GlaxoSmithKline, AstraZeneca, and Merck. He includes a discussion of off-label use in his article. The NIH update provides recommendations for medications and dosages not approved by the FDA, and this information is indicated in his presentation.

Stuart Stoloff, MD, is on the speakers' bureaus of GlaxoSmithKline, AstraZeneca, Merck, Pfizer, Aventis, and Schering. He has served as a consultant for GlaxoSmithKline, AstraZeneca, and Merck. His article includes a discussion of off-label usage. The NIH update provides recommendations for medications and dosages that are not approved by the FDA, and this information is included in his article.

INTRODUCTION

Updated Recommendations For Long-term Management of Asthma

ROBERT P. NAVARRO, PHARMD

President, NavarroPharma, LLC

ROBERT P. NAVARRO, PHARMD

In 1991, the National Asthma Education and Prevention Program (NAEPP) issued its first set of clinical practice guidelines for the diagnosis and treatment of asthma. These guidelines were grounded in a thorough review of the medical literature. Since then, the body of evidence has grown so much that the original guidelines have been updated twice. The 1997 update, released as the Expert Panel Report 2 (EPR-2), affirmed the importance of inhaled corticosteroids in the treatment of asthma. The 2002 update of EPR-2 presented new evidence-based recommendations for long-term management of asthma that reaffirm the value of low to medium doses of inhaled corticosteroids as the foundation of modern asthma therapy.

On Oct. 10, 2002, a distinguished faculty gathered in Philadelphia for a symposium dedicated to discussing the NAEPP's updated recommendations. The articles contained in this supplement are based on the proceedings of that symposium. Focusing on the most current treatment options for the asthma patient, this supplement is offered for continuing education credit for physicians and pharmacists.

According to a report from the Centers for Disease Control and Prevention, asthma-related mortality may have reached a plateau. That is a small victory, because despite the many advances in diagnosis and treatment made during the last decade, asthma still remains highly prevalent and imposes significant clinical, economic, and social burdens. The prevalence of asthma is approximately 6 percent nationwide but approaches 10 percent in some major cities. Blacks, women, and children still have more frequent asthma-related hospitalizations, office visits, and emergency department visits.

This special supplement presents comparative clinical data demonstrating the value of inhaled corticosteroids, alone and in combination with a long-acting beta agonist, to effectively manage asthma. Additionally, the relatively low value of leukotriene modifiers is shown through comparative clinical data.

The articles in this supplement also describe the successful results of asthma management programs in two large managed care organizations — Blue Cross of California and Intermountain Health Care. Both organizations achieved reductions in asthma-related medical care costs and utilization through distinctive physician-driven disease management programs.

Asthma continues to present a significant challenge for managed care organizations. Their support of physician-focused management with the use of inhaled corticosteroids as the cornerstone of therapy, as emphasized in the NAEPP guidelines, is likely to yield positive clinical and economic outcomes, along with improvement in the quality of the lives of patients and their families.

FACULTY PRESENTATION

NIH News: Update from the National Asthma Education and Prevention Program 2002

STUART STOLOFF, MD

Clinical Professor, Family and Community Medicine, University of Nevada School of Medicine, Carson City, Nev.

Although the number of deaths and the mortality rate from asthma increased gradually in the United States from 1980 through 1995, surveillance data recently reported by the Centers for Disease Control and Prevention (CDC) suggest that mortality rates may have started to plateau or even decline since then (Mannino 2002). In addition, hospitalization rates for asthma have gradually declined since peaking in the mid 1980s. However, these modest improvements constitute the only positive news about asthma. By all other measures, asthma continues to present a grave disease burden. Because of recent changes in the methodology used by the National Health Interview Service, it would be premature to state the direction in which prevalence trends are headed. Nonetheless, according to the most recent data from 1997, 26.7 million Americans have had a physician's diagnosis of asthma during their lifetime, and 11.1 million Americans have experienced at least one episode or attack of asthma during the previous 12 months. Between 1980 and 1999, the number of office visits (physician office or hospital outpatient department) for asthma increased from 5.9 million to 10.8 million. In addition, the number of emergency department (ED) visits for asthma increased by 36 percent between 1992 and 1999, to 1.99 million, while the rate of such visits (per 10,000 population) increased by 29 percent. Higher rates of hospitalizations, office visits, and ED visits have been noted among blacks, women, and children. Each year, about 14 million school-day absences by children and 14.5 million workday absences by adults are attributable to asthma.

STUART STOLOFF, MD

Although asthma is a disease that cannot be cured, it is manifestly a disease that can be treated — and in the physician's office. Appropriately treated, asthma never should result in ED visits or hospitalizations, let alone death. To reduce the morbidity and mortality from asthma, the National Asthma Education and Prevention Program (NAEPP) has issued an update to selected topics addressed in its most recent clinical practice guidelines, which were issued in 1997 as the Expert Panel Report 2 (EPR-2) (NAEPP 1997). The 2002 update is available in a quick reference format (2002a) or as a full report (2002b). EPR-2 itself reflected the stronger scientific research base that had accumulated during the 6 years since the Expert Panel issued its first report (NAEPP 1991) The 2002 update presents new, evidence-based recommendations on long-term management of asthma in children with mild or moderate persistent asthma, and combination therapy in those with moderate persistent asthma (NAEPP 2002). The panel has also revised its statement on the effects of early treatment on the progression of asthma. At the same time, EPR-2 has reviewed new evidence but has not changed the 1997 recommendations regarding the use of antibiotics (to treat acute exacerbations of asthma), and the use of written action plans and peak-flow monitoring. This article will discuss some of the evidence supporting these decisions.

Evaluating the guidelines: changing recommendations over time

The new position statements on these topics were developed by the EPR's Science Base Committee, and based on a systematic review of the literature conducted by the Blue Cross/Blue Shield Technology Evaluation Center (TEC). The TEC is an Evidence-based Practice Center working under contract to the Agency for Healthcare Research and Quality. Evidence was ranked according to its strength, as follows:

1. *Category A* — a substantial number of random-

TABLE 1 Classification of asthma severity: Clinical features before treatment or adequate control in adults and children >5 years of age

	Symptoms/day	Symptoms/night	PEF* or FEV_1†	PEF variability
Severe persistent	Continual	Frequent	≤60%	>30%
Moderate persistent	Daily	>1 night/week	>60%–<80%	>30%
Mild persistent	>2 days/week but <1x/day	>2 nights/month	≥80%	20%–30%
Mild intermittent	≤2 days/week	≤2 nights/month	≥80%	<20%

PEF = peak expiratory flow ; FEV_1 = forced expiratory volume in 1 second
* Percentage of personal best
† Percentage of predicted value
SOURCE: NAEPP *Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma — Update on Selected Topics 2002.* NIH Publication No. 02-5075.

ized, controlled trials enrolling a substantial number of subjects and providing a rich body of data;
2. *Category B* — randomized, controlled trials enrolling a limited number of subjects and providing a limited body of data, and making use of post hoc analyses;
3. *Category C* — nonrandomized studies and observational trials;
4. *Category D* — panel consensus judgment.

The principle that guides treatment decisions in the EPR-2 update is to seize control of the patient's symptoms quickly by using drug therapy appropriate for the severity of the asthma. The patient's severity classification is determined by the single most-severe feature present before treatment (Table 1).

After asthma control (Table 2) has been established, drug therapy may be adjusted downward to the smallest dose necessary to maintain control. This "step-down" approach has been shown to enhance patients' adherence to therapy.

Medication recommendations

Low to medium doses of inhaled corticosteroids (ICSs) are the foundation of modern asthma therapy. As the dose of an ICS is increased, particularly above 400 mcg/day, the benefits appear to diminish and systemic side effects begin to increase (Barnes 1998). In fact, asthma symptoms are more easily controlled when lower steroid doses are maintained. Moreover, in a pediatric population, the dose-response curve reaches a plateau around 400 mcg, which means that doubling the dose of an ICS does not double its benefit (Bisgaard 1997). In addition, systemic activity may increase as doses are increased to levels that exceed 400 mcg/day. Table 3 provides the comparative daily dosages for ICSs as estimated in the 2002 update; note that these recommendations may differ from those in the products' package inserts. The pharmacodynamic and pharmacokinetic properties of the drugs were reviewed by the committee, and the recommended doses were based on the data from the literature.

TABLE 2 Components of asthma control

1. Preventing chronic and troublesome symptoms (e.g., coughing or breathlessness at night, in the early morning, or after exertion)
2. Maintaining (near) "normal" pulmonary function
3. Maintaining normal activity levels (including exercise and other physical activity)
4. Preventing recurrent exacerbations of asthma and minimizing the need for ED visits or hospitalizations
5. Providing optimal pharmacotherapy achieved with minimal or no adverse effects
6. Meeting patients' and families' expectations of satisfaction with asthma care

SOURCE: NAEPP *Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma.* NIH Publication No. 97-0491.

ICS preferred for long-term management of asthma in children

The Science Base Committee considered whether the chronic use of ICSs improves long-term outcomes for children with mild or moderate persistent asthma, as compared with other asthma medications ("as-needed" $beta_2$ agonists, long-acting $beta_2$ agonists [LABAs], theophylline, cromolyn or nedocromil, or a combination of these drugs). Due to the lack of pediatric data comparing treatment with an ICS to that with a leukotriene modifier (also known as a leukotriene receptor antagonist [LTRA]), data were used from adult studies comparing treatment with LTRA and placebo to generalize pediatric use recommendations.

Based on a review of the evidence, ICSs now are the preferred treatment for initiating therapy in children of all ages with persistent asthma (evidence categories A and B). Previously, EPR-2 recommended that treatment for children start with an initial trial of cromolyn sodium because it is safe. Yet a recent meta-analysis, while confirming that cromolyn is safe, found that it otherwise is equivalent to placebo (Tasche 2000). Furthermore, when cromolyn is given as 20 mg q.i.d. by nebulization, its av-

erage wholesale price approaches $100 per month. For these reasons, an initial therapeutic trial with cromolyn/nedocromil no longer is recommended.

LTRAs now are available for children as young as 2 years and have demonstrated improved outcomes (evidence category B) (Israel 1996, Malmstrom 1999, Spector 1994). This class represents an alternative, not the preferred therapy (evidence category B). The lack of published data and clinical experience with LTRAs made it difficult for the Science Base Committee to establish a position for LTRAs.

The Expert Panel believes long-term control therapy should be considered for infants and children who in the past year have had more than three episodes of wheezing lasting more than 1 day and affecting sleep, if these patients also have risk factors for the development of asthma. These risk factors are physician-diagnosed atopic dermatitis, a parental history of asthma, or two of the following: physician-diagnosed allergic rhinitis, peripheral blood eosinophilia, or wheezing apart from colds (Martinez 1995). This advice augments the recommendation set forth in EPR-2 for starting long-term control therapy, namely, in infants and children requiring symptomatic treatment more than 2 times per week (a sign of persistent asthma) or experiencing severe exacerbations less than 6 weeks apart.

The decision to favor ICSs over LTRAs was based in part on a study showing that low-dose fluticasone propionate was more effective than montelukast as first-line maintenance therapy for adults with persistent asthma (Busse 2001). In this study, 533 subjects taking only short-acting beta$_2$ agonists were randomized to fluticasone 88 mcg (two puffs of 44 mcg twice daily) or montelukast 10 mg once daily. After 24 weeks, fluticasone 88 mcg was significantly more effective in improving lung function. The increase in FEV$_1$ from baseline was 22.9 percent in the fluticasone group versus 14.5 percent in the montelukast group ($p<.001$), and the mean change from baseline in morning PEF was 68.5 L/min in the fluticasone group versus 34.1 L/min in the montelukast group ($p<.001$). The improvements in morning PEF were significantly greater in the fluticasone group as early as day 2. Patients receiving fluticasone also scored better on other outcome variables, including nocturnal awakenings, use of rescue inhalers, and symptom-free days.

The role of LTRAs in maintenance therapy appears to be minimal, being limited to patients with aspirin sensitivity or nasal polyposis, or those in whom an ICS is insufficient to control moderate persistent asthma. In any case, LTRAs are an alternative and not the preferred therapy for the treatment of persistent asthma in the pediatric age group.

Limited long-term adverse effects of ICS

Once the use of an ICS has been proposed to control persistent asthma in a child, parents often want to know

TABLE 3 Estimated comparative daily dosages for inhaled corticosteroids

	Low daily dose		Medium daily dose		High daily dose	
Drug	Adult	Child	Adult	Child	Adult	Child
Beclomethasone CFC						
42 or 84 mcg/puff	168–504 mcg	84–336 mcg	504–840 mcg	336-672 mcg	>840 mcg	>672 mcg
Beclomethasone HFA						
40 or 80 mcg/puff	80–240 mcg	80–160 mcg	240–480 mcg	160–320 mcg	>480 mcg	>320 mcg
Budesonide DPI						
200 mcg/inhalation	200–600 mcg	200–400 mcg	600–1200 mcg	400–800 mcg	>1200 mcg	>800 mcg
Inhalation suspension for nebulization	—	0.5 mg	—	1.0 mg	—	2.0 mg
Flunisolide						
250 mcg/puff	500–1000 mcg	500-750 mcg	1000–2000 mcg	1000–1250 mcg	>2000 mcg	>1250 mcg
Fluticasone						
MDI: 44, 110, or 200 mcg/puff	88–264 mcg	88–176 mcg	264-660 mcg	176–440 mcg	>660 mcg	>440 mcg
DPI: 50, 100, or 250 mcg/inhalation	100–300 mcg	100–200 mcg	300-600 mcg	200–400 mcg	>600 mcg	>400 mcg
Triamcinolone acetonide						
100 mcg/puff	400–1000 mcg	400–800 mcg	1000–2000 mcg	800–1200 mcg	>2000 mcg	1200 mcg

SOURCE: *NAEPP Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma — Update on Selected Topics 2002.* NIH Publication No. 02-5075.

whether the drug will affect the child's growth or cause other adverse effects. The Science Base Committee addressed the question of whether ICSs produce long-term adverse effects, such as suppressed vertical growth, low bone mineral density, ocular toxicity, and suppression of the hypothalamic-pituitary-adrenal (HPA) axis, in children.

The committee concluded that, although low to medium doses of ICS may decrease growth velocity, the effects are small, nonprogressive, and may be reversible (evidence categories A, B, C). Likewise, ICSs have no major adverse effect on bone mineral density in children (evidence category A), and no significant effect on the incidence of subcapsular cataracts or glaucoma (evidence categories A, C). Neither do they have any clinically significant effect on HPA axis function (evidence categories A, C).

New evidence showing that the side effects associated with long-term ICS usage are limited comes from the Childhood Asthma Management Program (CAMP) Research Group (CAMP 2000). In CAMP, 1041 children with mild-to-moderate asthma, ranging in age from 5 to 12 years, were randomized to budesonide 400 mcg/day (200 mcg twice daily), nedocromil 16 mg/day (8 mg twice daily), or placebo. The subjects' mean age was 9 years at study entry, and their asthma had been diagnosed about 5 years previously. The children were treated for 4 to 6 years (mean, 4.3 years). No significant difference in bone density, as measured by dual-energy X-ray absorptiometry (DEXA), was observed among the three groups. Although the mean increase in height was 1.1 cm less in the budesonide group than in the placebo group, this small difference was transient, occurring mostly in the first 6 to 12 months after ICS introduction. This decrease in growth velocity was not sustained, and it was projected that the children in the budesonide group would attain final heights similar to those of the children in the other groups.

Another recent study confirmed that children with asthma who receive long-term ICS treatment attain their normal adult height (Agertoft 2000). This study followed 142 children treated with budesonide (mean daily dose, 412 mcg; range, 110–877 mcg) for an average of 9.2 years, matching them with 51 healthy siblings and 18 control patients with asthma who never received an ICS. As in the CAMP study, a reduction in the annual growth rate was observed during the first year of treatment, but this reduction was transient and did not adversely affect final adult height. The average adult height was 173.2 cm in the budesonide group, 173.9 cm in the control group, and 172.3 cm in the sibling group. The adult height of the budesonide-treated patients equaled their predicted adult height, and there was no significant correlation between measured and target adult height and treatment duration, cumulative budesonide dose, sex, age at study onset, age of adult height attainment, or duration of asthma at study onset.

Benefit to early intervention?

The 2002 update also addresses the question of whether early intervention with long-term control therapy (i.e., an ICS) in patients with mild or moderate persistent asthma prevents the progression of asthma, as measured by changes in lung function or symptom severity. Thus far, the evidence is insufficient to allow conclusions about the benefits of early versus delayed treatment. In CAMP, the benefits of budesonide compared with placebo included 43 percent fewer hospitalizations (2.5 vs. 4.4 per 100 person-years), 45 percent fewer urgent visits to a caregiver (12 versus 22 per 100 person-years), less oral steroid use, less use of rescue albuterol, fewer symptoms, more episode-free days, and decreased airway hyperresponsiveness. Budesonide was not better than placebo, however, in terms of improved lung function, as measured by percentage of predicted FEV_1 attained after bronchodilator administration (a measure that minimizes the effects of airway constriction and is less variable than the value when measured before bronchodilator use).

We know that if an ICS is stopped, asthma symptoms and airway hyperresponsiveness return (evidence category A). In CAMP, the subjects were about 3 years old when their asthma emerged, and they had asthma symptoms for an average of 4 years by the time they entered the study at an average age of 9. This suggests that the deficit in lung function in patients with asthma occurs earlier than was believed — underscoring the importance of identifying and treating asthma at an early age. When asthma symptoms started prior to age 3, deficits in lung growth were identified by age 6, and lung function abnormalities were still evident at ages 11 to 16 (Martinez 1995). Children with symptomatic asthma beginning after age 3, however, did not demonstrate deficits in lung function at age 6 and older.

Early intervention can improve asthma control and normalize lung function, but it remains to be determined if an ICS or a drug of any class can prevent the irreversible airway obstruction that may occur with asthma (evidence categories A, B).

Out of concern for branding a child with a stigma or due to insurance implications, physicians may be reluctant to diagnose asthma in a very young child, but they should be no less willing to diagnose asthma than to diagnose diabetes or any other chronic disease. As with any other diagnosis, if the physician is worried about making the wrong diagnosis, the patient should be referred to a practitioner specializing in the care of such individuals.

Benefits of combination therapy

Another question considered by the Science Base Committee was whether the addition of a long-term control agent improves outcomes for patients with moderate persistent asthma who already are receiving an ICS. Strong evidence indicates that combining an ICS and a LABA improves lung function and reduces symptoms and the use of short-acting $beta_2$ agonists. For patients with mild-to-moderate persistent asthma that is not controlled by a low- or medium-dose ICS, the preferred treatment is to add an inhaled LABA instead of increasing the ICS dose (evidence category A). A recent meta-analysis showed that adding salmeterol to an ICS results in improved lung function, greater symptom control, and a reduced need for rescue medication. Exacerbations of asthma were no greater when salmeterol was added to a moderate dose of an ICS than when the dose of the ICS was doubled (Shrewsbury 2000). Outcomes also may be improved by adding an LTRA or theophylline to an ICS, or even by doubling the dose of the ICS, but the evidence in this arena is not as substantial (evidence category B), and the addition of theophylline or an LTRA is a nonpreferred alternative in the treatment algorithm.

In cases of severe persistent asthma, no evidence supports adding montelukast as a third long-term control agent (evidence category C). Robinson and colleagues recruited 100 adults with continuing symptoms of moderate or severe persistent asthma to evaluate the benefit associated with add-on therapy with montelukast (Robinson 2001). All the patients were taking an ICS, and the vast majority were receiving a high dosage. Most of the patients also were receiving an additional medication (LABA, theophylline, or oral corticosteroid, or some combination of these). Patients were randomized to either 2 weeks of additional treatment with montelukast or placebo, after which they were reversed to receive 2 weeks of placebo or montelukast. The 2-week treatment periods were chosen because of previous reports suggesting that montelukast was associated with rapid onset and offset of bronchodilator effects. No significant improvements in symptoms or lung function were observed among patients treated with montelukast, nor was any subgroup of montelukast responders apparent.

Likewise, in patients whose symptoms were suboptimally controlled with a low to moderate dose of an ICS, the combination of fluticasone and salmeterol (administered as fluticasone 100 mcg and salmeterol 50 mcg in 1 inhalation twice daily) provided significantly greater asthma control than did adding montelukast 10 mg once daily to fluticasone 100 mcg in 1 inhalation twice daily (Nelson 2000).

Antibiotics not indicated

Unless there is a high risk of a bacterial infection, the available evidence (from two randomized, controlled trials) suggests there is no benefit from adding antibiotics to standard care for acute exacerbation of asthma (evidence category B). The recommendation in EPR-2 remains unchanged: antibiotics are not recommended for treatment of acute asthma exacerbations except for treating comorbid conditions on an as-needed basis.

No change in recommendations regarding education

The Expert Panel continues to recommend that written action plans be part of the effort to involve patients in self-management (evidence categories B, C), especially patients with moderate or severe persistent asthma and patients with a history of severe exacerbations. However, the evidence was insufficient to support or refute the use of written action plans, compared with medical management alone (evidence category B). Neither did the evidence support or refute written action plans based on peak-flow monitoring, as compared with symptom-based plans.

Countering this evidence, the Victorian Asthma Mortality Study Group recently reported a 7 percent reduction in risk of death from asthma among patients with a written action plan (Abramson 2001). In contrast, the risk of death was 30 percent greater among patients who received only oral instructions. Use of a peak-flow meter during the previous year was associated with a 35 percent reduced risk of death from asthma.

The goals of asthma therapy, as set forth in the Expert Panel's 2002 update, are for the patient to experience minimal or no chronic symptoms during the day or night, minimal or no exacerbations, no limitations on activities, no days of school or work missed because of asthma, minimal use of inhaled short-acting $beta_2$ agonists, and minimal or no adverse effects from medication.

These goals can be met if physicians employ the five "Rs" for teaching their patients how to self-manage asthma.

1. **Reach agreement on goals.** Because the clinician's goals may not be the same as the patient's goals, the clinician must elicit and address the patient's concerns about asthma. Once this has been accomplished, a realistic written treatment plan can be designed.
2. **Rehearse skills.** The clinician must teach the patient how to use the various devices for administering asthma medications, and the patient must be able to demonstrate proficiency with the devices.
3. **Repeat messages.** Every office visit should be viewed as an opportunity to repeat key messages

about asthma management and to demonstrate skills.

4. **Reinforce.** Asthma care must be integrated into the patient's daily life if it is to succeed. A patient diary can be useful.
5. **Review.** The clinician should ask open-ended questions to identify any barriers to patient adherence.

Conclusion

The 2002 update to the Expert Panel's 1997 guidelines expands the role of ICSs in controlling persistent asthma. An ICS is the preferred treatment for all forms of persistent asthma, including for patients as young as 5 years of age (supplanting an initial trial of cromolyn or nedocromil). If greater symptom control is needed, adding a LABA is preferred to increasing the dose of the ICS; no additional benefit accrues from adding montelukast to a regimen of an ICS and a LABA.

When low or moderate doses of an ICS are employed, adverse effects are minimal; in children, any effect on the growth rate occurs early in the course of treatment and is transient.

References

Abramson MJ, Bailey MJ, Couper FJ, et al. Are asthma medications and management related to deaths for asthma? *Am J Respir Crit Care Med.* 2001;163:12–18.

Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. *N Engl J Med.* 2000;343:1064–1069.

Barnes PJ, Pedersen S, Busse WW. Efficacy and safety of inhaled corticosteroids. New developments. *Am J Respir Crit Care Med.* 1998;157(3 Pt 2):S1–S53.

Bisgaard H. Use of inhaled corticosteroids in pediatric asthma. *Pediatr Pulmonol Suppl.* 1997;15:27-33.

Busse W, Raphael GD, Galant S, et al. Low-dose fluticasone propionate compared with montelukast for first-line treatment of persistent asthma: a randomized clinical trial. *J Allergy Clin Immunol.* 2001;10:461–468.

CAMP (The Childhood Asthma Management Program) Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med.* 2000;343:1054–1063.

Israel E, Cohn J, Dubé L, Drazen JM. Effect of treatment with zileuton, a 5-lipoxygenase inhibitor, in patients with asthma. A randomized controlled trial. Zileuton Clinical Trial Group. *JAMA.* 1996;275:931–936.

Malmstrom K, Rodriguez-Gomez G, Guerra J, et al. Oral montelukast, inhaled beclomethasone, and placebo for chronic asthma. A randomized, controlled trial. *Ann Intern Med.* 1999;130:487–495.

Mannino DM, Homar DM, Akinbami LJ, Moorman JE, Gwynn C, Redd SC. Surveillance for asthma — United States, 1980-1999. In: *Surveillance Summaries*, March 29, 2002. MMWR 2002;51(No. SS-1):1–13.

Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med.* 1995;332:133–138.

NAEPP (National Asthma Education and Prevention Program). *Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma.* Bethesda, Md.: National Institutes of Health. 1991. NIH Publication No. 91-3642.

NAEPP (National Asthma Education and Prevention Program). *Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma.* Bethesda, Md.: National Institutes of Health. 1997. NIH Publication No. 97-0491. Available at: «http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm». Accessed Oct. 24, 2002.

NAEPP (National Asthma Education and Prevention Program) Expert Panel. *NAEPP Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma — Update on Selected Topics 2002.* Bethesda, Md.: National Institutes of Health. July 2002a. NIH Publication No. 02-5075. Available at: «http://www.nhlbi.nih.gov/guidelines/asthma/execsumm.pdf». Accessed Oct. 20, 2002.

NAEPP (National Asthma Education and Prevention Program). *Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma. Update on Selected Topics 2002. J Allergy Clin Immunol.* 2002b;110(5): S141–S219. Available at: «http://www.nhlbi.nih.gov/guidelines/asthma/». Accessed Nov. 30, 2002.

Nelson HS, Busse WW, Kerwin E, et al. Fluticasone propionate/salmeterol combination provides more effective asthma control than low-dose inhaled corticosteroid plus montelukast. *J Allergy Clin Immunol.* 2000;106:1088–1095.

Robinson DS, Campbell D, Barnes PJ. Addition of leukotriene antagonists to therapy in chronic persistent asthma: a randomised double-blind placebo-controlled trial. *Lancet.* 2001;357:2007–2011.

Spector SL, Smith LJ, Glass M. Effects of 6 weeks of therapy with oral doses of ICI 204,219, a leukotriene D4 receptor antagonist, in subjects with bronchial asthma. ACCOLATE Asthma Trialists Group. *Am J Respir Crit Care Med.* 1994;150:618–623.

Shrewsbury S, Pyke S, Britton M. Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA). *BMJ.* 2000;320:1368–1373.

Tasche MJA, Uijen JHJM, Bernsen RMD, de Jongste JC, van der Wouden JC. Inhaled disodium cromoglycate (DSCG) as maintenance therapy in children with asthma: A systematic review. *Thorax.* 2000;55:913–920.

FACULTY PRESENTATION

Setting the Gold Standard: Clinical and Economic Decision Making In Asthma Management

RICHARD D. O'CONNOR, MD

Director, Department of Quality Management, Sharp Rees-Stealy Medical Group, San Diego

The accumulation of scientific evidence has led to a steady evolution of the asthma guidelines that were originally issued by the National Institutes of Health. Many aspects of these guidelines have been revised during the decade since they were first issued. In the original guidelines (NAEPP 1991), a "step-up" approach to therapy was advocated — the clinician was to initiate therapy and then intensify it to the next level if the patient's response was inadequate. By 1997, the advice provided in the second *Expert Panel Report* (EPR-2) became the opposite: use "step-down" therapy — the clinician should initiate treatment sufficiently intense to seize control of the patient's symptoms, and then step down to the lowest level sufficient to maintain control (NAEPP 1997). In 1991, inhaled corticosteroids (ICSs) were not recommended for patients with mild asthma, but in 1997 treatment with ICSs was extended to this group. Even more recently, low-dose ICS therapy has been recommended as the preferred treatment for children with mild persistent asthma (NAEPP 2002).

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EPR-2 has placed increased emphasis on the role of inflammation in asthma. This is due to an increased awareness and understanding of the pathogenesis of asthma. This understanding has become the basis for treatment recommendations for daily use of anti-inflammatory treatment (i.e., an ICS) and the foundation for management of persistent asthma.

Largely because of the importance attached to ICSs in the 1991 and 1997 guidelines, the use of ICSs in the United States began to rise dramatically in the early 1990s; prescriptions rose from about 5.4 million in 1991 to 17 million in 2000 (Scott–Levin 1991–2000). Unfortunately, prescriptions for ICSs have declined since that time, and this decline has been paralleled by an equally dramatic increase in prescriptions for leukotriene modifiers. These drugs include the leukotriene receptor antagonists zafirlukast, which is a specific inhibitor of both leukotriene D_4 and leukotriene E_4; montelukast, an inhibitor of leukotriene D_4; and zileuton, an inhibitor of 5-lipoxygenase, which is an enzyme leading to the biosynthesis of the entire leukotriene pathway. Zafirlukast and montelukast are considered bronchoconstrictor protection drugs, as the primary biologic activity of the cysteinyl leukotrienes in humans is bronchoconstriction.

Prescriptions for leukotriene modifiers increased from 1 million in 1997 (following Food and Drug Administration approval in late 1996 of zafirlukast) to 14 million in 2001, by which time montelukast and zileuton had been on the market for about 3 years (Scott-Levin 1997–2001). Global sales of montelukast surpassed $1 billion in 2001, during which time its U.S. sales grew by 58 percent, and montelukast ended the year as the leading prescribed asthma controller in the United States (Merck 2002).

This article will present evidence showing that, compared with leukotriene modifiers, ICS therapy is not only better for patients in terms of clinical response but it also is the least expensive option. Much of this information is drawn from observational studies. Many of these studies were methodologically similar, identifying an "index event" in pharmacy records — namely, the initiation of specific drug regimens for patients with asthma — and then searching medical records to determine health care utilization rates during a specified period before and after the index event.

Done well, observational studies complement the data provided by rigorous randomized controlled trials (RCTs). In addition, such studies often provide data that

are unavailable from RCTs, such as data about patients who are typically excluded from RCTs but nevertheless constitute a substantial proportion of patients who are seen in clinical practice. Moreover, reports about observational studies are deemed important enough by the editors of leading journals that they allocate a considerable amount of space to them. For example, observational studies accounted for 68, 74, and 87 percent of the feature articles and brief communications published in the *Annals of Internal Medicine*, the *New England Journal of Medicine*, and the *British Medical Journal* during January and February 1998 (Ray 2002). Physicians have been using information from observational studies without appreciating how important they have become to the practice of medicine.

ICSs are the only class of medication for which good epidemiologic data exist to suggest a reduction in mortality, hospitalizations, and emergency department (ED) visits attributed to asthma, despite increasing risk of illness. In a Canadian study, patients with asthma who used more than six canisters of an ICS per year had a mortality rate from asthma that was 50 percent less than that for patients who did not use an ICS (Suissa 2000). In Israel, during a period when the prevalence and severity of asthma did not decrease, the asthma mortality rate declined, and this decline was paralleled by an increase in ICS sales (correlation, –0.631; p=.016) (Goldman 2000). In Northern England, patients with asthma who received at least 13 canisters of a short-acting beta$_2$ agonist (SABA) per year had a relative risk of death that was 51.6 times greater than that for patients receiving fewer than three SABA prescriptions (Lanes 2002). Yet among patients who received more than one prescription per month of a SABA — an indication of the severity of the disease — regular use of an ICS reduced the relative risk of asthma to 0.4, compared with the reference population of those patients using less than three canisters of SABA annually.

Increased use of ICSs also has been associated with decreases in medical service utilization. In Sweden, a retrospective study was conducted using hospitalization data covering 71 percent of the country between 1978 and 1991 (Gerdtham 1996). Between 1978 and 1985, no trend upward or downward was observed for the number of bed-days due to asthma. After 1985, despite increased asthma prevalence, there was a significant downward trend in bed-days, and the reduction in bed-days correlated significantly (p<.01) with an increase in ICS sales.

Another Swedish study, conducted in Göteborg (Sweden's second largest city), also credited increased use of anti-inflammatory treatment, mostly ICSs, with a decrease in hospitalization due to asthma in children ages 2 to 18 years (Wennergren 1996).

In the United States, use of ICSs also has been shown to reduce the risk of asthma-related hospitalization. In a retrospective cohort study using data from an HMO in eastern Massachusetts, 742 (4.4 percent) of 16,941 eligible patients were found to have been hospitalized because of asthma during a 3-year period (October 1991 through September 1994) (Donahue 1997). The risk of hospitalization increased sharply in patients receiving more than three SABA canisters per year, which, as previously noted, is a marker of disease severity. Among patients receiving ICSs, the relative risk of hospitalization was reduced by 50 percent, and the protection afforded by ICSs was most pronounced among patients who received the largest amount of beta$_2$ agonists.

Similar results were seen in a retrospective case-control study in Canada, in which first-time users of an ICS were compared with first-time users of theophylline (Blais 1998). Regular use of an ICS was associated with a 40 percent to 80 percent reduced rate of hospitalization, compared to the regular use of theophylline, depending on when use of the ICS began.

TABLE 1 Beclomethasone vs. montelukast

	Placebo	Montelukast†	Beclomethasone†
Primary endpoints			
Percent change from baseline in AM FEV$_1$	0.7	7.4	13.1
Change from baseline in daytime asthma symptom score	–0.17	–0.41	–0.62
Secondary endpoints			
Percent change from baseline in total daily beta-agonist use	0.0	–23.9	–40.0
Change from baseline in AM PEFR, L/min	0.8 L/min	23.8 L/min	39.1 L/min
Change from baseline in PM PEFR, L/min	0.3 L/min	20.8 L/min	32.1 L/min
Change from baseline in nocturnal awakenings, nights/wk‡	–0.5	–1.7	–2.4
Worsening asthma episodes, % of days	26.1	15.2	9.7

† p <.001 compared with placebo
‡ Patients with nocturnal asthma only
FEV$_1$=forced expiratory volume in 1 second; PEFR=peak expiratory flow rate
SOURCE: Malmstrom 1999

Finally, a study conducted in Alberta, Canada, demonstrated that use of an ICS after discharge from an ED for treatment of asthma resulted in a 45 percent reduction in the rate of subsequent ED visits for asthma treatment, compared with the same rate for nonusers of ICS (Sin 2002). No dose-response relationship was observed, with rates of subsequent ED visits during a 2-year period being similar among patients receiving low, medium, or high doses of ICS.

Clinical and economic consequences of ICSs

When EPR-2 was issued in 1997, the position of leukotriene modifiers was unclear, because they were so new to the market. At the time, monotherapy with these agents was a common practice, and it still is in some parts of the country. Nevertheless, the first head-to-head comparison of montelukast with an ICS, beclomethasone, showed that, by every measure, patients who were randomized to beclomethasone 200 mcg b.i.d. had superior outcomes compared to patients treated with montelukast 10 mg q.d. (Malmstrom 1999). This 12-week study enrolled 895 patients (age range, 15 to 85 years) with chronic asthma and forced expiratory volume in one second (FEV_1) values between 50 percent and 85 percent of the predicted normal FEV_1.

Similar results were obtained when montelukast was compared head-to-head with low-dose fluticasone (Busse 2001). In this study, 533 patients with persistent asthma (FEV_1 between 50 and 80 percent of the predicted normal value) who remained symptomatic while taking SABAs alone were randomized to montelukast 10 mg q.d. or fluticasone 88 mcg (two puffs of 44 mcg twice daily) for 24 weeks. The percentage change from baseline FEV_1 was 22.9 percent in the fluticasone group versus14.5 percent in the montelukast group; morning peak expiratory flow (PEF) increased by 68.5 L/min in the fluticasone group versus 34.1 L/min in the montelukast group. The percentage of symptom-free days improved to 32.0 percent in the fluticasone group versus 18.4 percent among montelukast-treated patients. When patients were stratified according to severity of airway obstruction at baseline, as measured by percentage of predicted normal FEV_1, patients with milder asthma (>70 percent of predicted FEV_1) treated with low-dose fluticasone showed significantly greater improvements in morning and evening PEF than did patients treated with montelukast.

Fluticasone also has been compared head-to-head with zafirlukast (Kim 2000). This study enrolled patients with persistent asthma (60 percent to 85 percent of predicted FEV_1) who previously were maintained on a low-dose ICS (triamcinolone 400-800 mcg/day or beclomethasone 168-336 mcg/day). Patients were randomly switched to fluticasone 88 mcg b.i.d. or zafirlukast 20 mg b.i.d. for 6 weeks. The percentage of patients who experienced an asthma exacerbation was about 2 percent in the fluticasone group but 7 percent in the zafirlukast group (p=.035).

In another study in which montelukast 10 mg q.d. was compared with a combination product, fluticasone 100 mcg/salmeterol 50 mcg given twice daily, none of the patients who were treated with the combination product (n=211) experienced an asthma exacerbation, compared with 5 percent of the montelukast group (n=212) (p<.001) (Calhoun 2001).

In a retrospective study using the Texas Medicaid database, a population of patients with asthma who were not taking any medication except an ICS during a 6-month period was identified (Smith 2001). Patients who then began using an ICS in the next month and continued use for 12 months (n=99) were matched with patients whose continued therapy did not include an ICS (n=297). In the steroid group, utilization of medical services decreased after the ICS was added: visits to physician offices or clinics declined by 10 percent, ED visits by 57 percent, and hospitalizations by 58 percent. In contrast, utilization increased among the patients in the nonsteroid group: hospitalizations increased by 8 percent, visits to physician offices or clinics by 42 percent, and ED visits by 90 percent.

Similar results were found in a retrospective cohort analysis of medical and pharmacy claims from four managed care organizations (two in the Northeast, one in the Midwest, one in the West) (Pathak 2002). This study identified 781 patients with asthma who had no claim for an ICS or a leukotriene modifier during a 9-month period but who then received new prescriptions for fluticasone 44 mcg or 110 mcg (n=284), montelukast 5 mg or 10 mg (n=302), or zafirlukast 20 mg (n=195) during the next 9 months. The need to alter therapy by switching or adding additional medications was lowest in the fluticasone group (7 percent) compared to montelukast and zafirlukast groups (32 percent and 43 percent, respectively). The fluticasone group also had the lowest risk-adjusted treatment costs for the 9-month period, $528, compared with $967 and $1,359 for the montelukast and zafirlukast groups, respectively.

In a retrospective multivariate analysis of asthma-related costs in a managed care setting (Armstrong 2002), researchers found that use of albuterol was substantially higher in patients treated with leukotriene modifiers than it was in patients using fluticasone (10.07 canisters/year vs. 4.63, p<.0001), and annual costs were also higher in the leukotriene group ($1,092 vs. $511, p=.0001).

Sometimes it is suggested that patients be started on an ICS until they are stabilized and then switched to an oral agent in the form of a leukotriene modifier. This

strategy has been subjected to a retrospective analysis of data from three major health plans covering approximately 4 million members, and it has been found wanting, because hospitalization rates increase when a leukotriene modifier is substituted for an ICS as single-controller therapy (Stempel 2002b). The 2-year study identified patients who were stabilized on an ICS during the first year but who switched to a leukotriene modifier during the second year (n=285). These patients were matched with a cohort continuously treated with ICS for 2 years (n=570).

During the first year, asthma-related hospitalizations were similar in both groups (1.1 percent among those who would switch to a leukotriene modifier, 1.4 percent among those who would continue to use an ICS). In the second year, the rate of asthma-related hospitalization was 2.5 percent (n=7) in the leukotriene modifier cohort but 0.6 percent in the ICS cohort (n=3). The odds risk of hospitalization was 7.1 for patients switched to a leukotriene modifier.

Another question that often arises in clinical practice is whether a patient whose asthma is not well controlled on an ICS is likely to benefit from the addition of a long-acting beta$_2$ agonist (LABA) to the current ICS dose. A large European study, Formoterol and Corticosteroids Establishing Therapy (FACET), addressed this question (Pauwels 1997). FACET enrolled 852 patients who were stabilized on a relatively high dose of budesonide, 800 mcg b.i.d. (total daily dose, 1600 mcg). These patients were randomized to four groups: budesonide 100 mcg b.i.d. (total daily dose, 200 mcg) plus placebo, budesonide 100 mcg b.i.d. plus formoterol 12 mcg b.i.d. (total daily dose, 24 mcg), budesonide 400 mcg b.i.d. (total daily dose, 800 mcg) plus placebo, or budesonide 400 mcg b.i.d. plus formoterol 12 mcg b.i.d. At the time this study was designed, the addition of a LABA was controversial, because it was feared that LABA would put the patient at risk of a catastrophic exacerbation by masking initial exacerbations. This concern proved unfounded. Outcomes (exacerbations, symptoms, lung function) were improved significantly by adding the LABA to either dose of the ICS.

The unexpected results of FACET led to another study, Oxis and Pulmicort Turbuhaler in the Management of Asthma (OPTIMA), which examined the effects of adding a LABA to low doses of an ICS, budesonide, in patients with mild persistent asthma (O'Byrne 2001). In this study, patients who had not used an ICS for at least 3 months (n=698) were randomized to budesonide 100 mcg b.i.d., budesonide 100 mcg b.i.d. plus formoterol 4.5 mcg b.i.d., or placebo. Another group of patients who had been treated with a low-dose ICS (at least 400 mcg of inhaled budesonide or its equivalent for at least 3 months) (n=1272) were randomized to budesonide 100 mcg b.i.d., budesonide 100 mcg b.i.d. plus formoterol 4.5 mcg b.i.d., budesonide 200 mcg b.i.d., or budesonide 200 mcg b.i.d. plus formoterol 4.5 mcg b.i.d. In the ICS-free group, patients receiving budesonide alone had a 60 percent reduced risk of the first severe asthma exacerbation, compared with patients receiving placebo. These patients also experienced a reduced rate of exacerbations, asthma symptoms, nocturnal awakenings, and SABA use, along with an increase in FEV_1. Adding formoterol to budesonide produced further improvements in lung function. In the group of patients who previously received an ICS, the addition of formoterol was more effective than doubling the dose of the ICS for reducing asthma exacerbations and improving asthma control. Patients receiving budesonide 200 mcg b.i.d. had a 19 percent reduced risk of a first severe exacerbation, compared with patients receiving budesonide 100 mcg b.i.d., but adding formoterol to either dose of budesonide reduced this risk by 43 percent.

Fears that use of a LABA might mask worsening asthma were addressed in a study that compared rates and characteristics of asthma exacerbations in patients receiving a low dose of fluticasone plus salmeterol to those in patients receiving a higher dose of fluticasone only (Matz 2001). This study randomized 925 patients who were receiving fluticasone 88 mcg b.i.d. to either fluticasone 88 mcg b.i.d. plus salmeterol 42 mcg b.i.d. or fluticasone 220 mcg b.i.d. for 24 weeks. The percentage of patients with one or more exacerbations was lower in the group of patients whose ICS regimen was augmented with salmeterol (8.8 percent) than it was in the group of patients whose ICS dose was increased (13.8 percent, p=.017). In addition, the lower dose of fluticasone plus salmeterol was more protective than the higher dose of fluticasone in preventing asthma exacerbations, as measured by the time to first exacerbation (p=.049). If salmeterol had masked the recognition of worsening asthma, an increase in the frequency of asthma exacerbations would have been expected, but this was not the case. Exacerbations were recognized at the same time in each group. Although the investigators did not stress this point, patients receiving the lower dose of fluticasone plus salmeterol improved faster following an exacerbation than did those receiving only the higher dose of fluticasone, as was shown by decreased use of a rescue medication in the former group.

Choosing a second controller: LABA or leukotriene modifier?

We have just seen that adding a LABA to an ICS results in better outcomes than simply increasing the dose of the ICS. Now we will examine studies showing that the addition of a LABA to an ICS regimen produces superior clinical and pharmacoeconomic results than does the

TABLE 2 Acute care visits by asthma regimen

	SABA	Leukotriene modifier	ICS	ICS plus leukotriene modifier	ICS plus salmeterol	Fluticasone plus salmeterol
Percentage of patients with ≥1 visit in 1 year	65.2	56.0	38.5	37.7	31.4	18.6
Acute care visits annually per patient	2.8	3.6	2.1	3.1	1.9	1.3

SOURCE: Sharp Rees-Stealy Medical Group, San Diego

addition of a leukotriene modifier.

In a 12-week study, fluticasone 100 mcg/salmeterol 50 mcg b.i.d. combined in a single formulation was compared with fluticasone 100 mcg b.i.d. plus montelukast 10 mg q.d. (Nelson 2000). The study enrolled 447 patients who were symptomatic at baseline despite low-dose ICS therapy. Prior to randomization, all patients had a 3-week run-in period with fluticasone 100 mcg b.i.d., which resulted in a 3 percent improvement in predicted normal FEV_1 but still left patients with an FEV_1 that was 70 percent of predicted. After treatment, FEV_1 increased by 15 percent in the fluticasone/salmeterol group, versus 8 percent in the fluticasone plus montelukast group. In addition, in the fluticasone plus montelukast group (n=225) exacerbations were experienced by 2 percent (4/225) of patients, versus 6 percent (13/222) in the fluticasone/salmeterol group (p=.031).

If an RCT shows better lung function, one can expect that in clinical practice, patients with better lung function will need to use albuterol less frequently as rescue medication, which should be reflected in the pharmacy-refill request rate for albuterol. Also, if an RCT shows a reduction in exacerbations, one can expect that administrative databases will show a decline in visits to the ED and, ideally, a decline in the hospitalization rate.

Observational data from four recent studies (Wang 2001, O'Connor 2002, Stempel 2002a, Krishnan 2002) show these real-world confirmations of RCT results. (In these studies, all inhaled steroid preparations [beclomethasone, triamcinalone, flunisolide, budesonide, and fluticasone] and salmeterol were administered separately.)

Adding LABA reduces use of rescue medication

In a study called Foundation I (which examined data from 33,939 asthmatic patients enrolled in four different health plans, collected during a 6-month period), albuterol refills were requested by 57 percent of patients using fluticasone plus salmeterol combination therapy versus 77 percent and 75 percent of patients using any other ICS plus salmeterol or an ICS plus a leukotriene modifier, respectively (data on file).

A follow-up study, Foundation II, was conducted to gather data during a 12-month interval. Patients who used montelukast as their second controller (n=360) averaged 7.4 requests for albuterol refills, versus 4 and 4.9 such requests by users of fluticasone plus salmeterol (n=121) and any other ICS plus salmeterol (n=844), respectively (data on file).

Similar results were found in an analysis of 919 patients drawn from 14 United HealthCare (UHC) plans (Stempel 2002a). Patients receiving fluticasone plus salmeterol (n=261) averaged 2.79 SABA canisters per year, versus 3.29 and 4.45 in the cohort receiving any ICS (including fluticasone) plus salmeterol (n=703) and the ICS-plus-montelukast group (n=216), respectively.

Finally, analysis of a database from a physician practice group in San Diego, Sharp Rees-Stealy, showed the same results: the highest use of rescue medication always occurred in patients using leukotriene modifiers as the second controller added to their asthma regimen — 5 canisters per year in the ICS-plus-montelukast cohort versus 3.0 and 3.5 in the fluticasone-plus-salmeterol and the ICS-plus-salmeterol cohorts, respectively (O'Connor, unpublished data, 2001).

ED visits and hospitalizations reduced by adding LABA

In Foundation II, the rate of ED visits declined by 68 percent in the cohort receiving fluticasone plus salmeterol, compared with declines of 37 and 38 percent in the ICS-plus-salmeterol and the ICS-plus-leukotriene modifier cohorts, respectively. Likewise, in the UHC study, the ED visit rate declined by 52 percent in the fluticasone-plus-salmeterol group and by 28 percent in the ICS-plus-montelukast cohort group; it increased by 2 percent in the cohort receiving added montelukast. In the San Diego physician practice, clear differences exist in the rate of acute-care visits depending on agents selected; utilization rates were lower in the patient cohort treated with fluticasone plus salmeterol than they were in any other regimen (Table 2).

The choice of asthma medication regimen also affects hospitalization rates. In the Foundation II study, no patients in the fluticasone-plus-salmeterol cohort were hospitalized during the 12 months after combined treatment began. The UHC data were similar: hospitalization

TABLE 3 Total asthma-related costs per patient

Study	Fluticasone + salmeterol	ICS + salmeterol	ICS + leukotriene modifier
Foundation I (6 months) (Wang 2001)	$408	$460	$560
Foundation II (12 months) (O'Connor 2002)	$975	$1,089	$1,268
UHC (12 months) (Stempel 2002a)	N.A.	$952	$1,552
Sharp Rees-Stealy (12 months) (Krishnan 2002)	$889	$1,055	$1,846

rates of 1.1, 1.9, and 4.6 percent in the fluticasone-plus-salmeterol, ICS-plus-salmeterol, and ICS-plus-montelukast cohorts, respectively; the difference between the fluticasone-plus-salmeterol and the ICS-plus-montelukast groups was statistically significant (p=.030).

Higher asthma-related costs with leukotriene modifiers

In Foundation I, Foundation II, and the UHC studies, asthma-related pharmacy costs were highest in the group of patients receiving leukotriene modifiers as the second controller. In Foundation I, the 6-month risk-adjusted mean cost to the insurer per member was $385 in the ICS-plus-leukotriene cohort, $352 in the ICS-plus-salmeterol cohort, and $297 in the fluticasone-plus-salmeterol group ($p \leq .0001$ for all pair-wise comparisons) (Wang 2001). In Foundation II, the annual risk-adjusted mean pharmacy cost per member also was significantly higher ($996) in the ICS-plus-leukotriene cohort and lowest ($814) in the fluticasone-plus-salmeterol cohort (O'Connor 2002).

Similar results were seen in the UHC study, and for both studies asthma-related costs included office visits, ED, hospitalization, and pharmacy. In the UHC Study, the annual risk-adjusted mean asthma-related pharmacy cost per patient was $987 in the group receiving ICS plus montelukast, but it was only $606 in the group receiving ICS plus salmeterol ($p<.001$) (Stempel 2002a).

In some cases, the use of a more expensive drug may result in lower health care costs overall, but that was not the case in these studies. In every instance, patients who received a leukotriene modifier as their second controller also incurred the highest total asthma-related costs (Table 3). The values reported represent the financial cost to the health plan.

Conclusion

For patients with persistent asthma of any degree of severity, an abundance of evidence has established ICSs as preferred therapy. ICSs have consistently been shown to produce better clinical and economic outcomes than do leukotriene modifiers. If a second long-term controller needs to be added to a patient's medication regimen, better results are achieved, by every measure — clinical outcomes, utilization of medical services, asthma-related pharmacy costs, asthma-related total costs — by augmenting the ICS with a LABA rather than with a leukotriene modifier.

References

Armstrong EP, Malone DC. Fluticasone is associated with lower asthma-related costs than leukotriene modifiers in a real-world analysis. *Pharmacotherapy*. 2002;22(9):1117–1123. Available at: «www.medscape.com/viewarticle/441922».

Blais L, Suissa S, Boivin JF, Ernst P. First treatment with inhaled corticosteroids and the prevention of admissions to hospital for asthma. *Thorax*. 1998;53:1025–1029.

Busse W, Raphael GD, Galant S, et al. Low-dose fluticasone propionate compared with montelukast for first-line treatment of persistent asthma: a randomized clinical trial. *J Allergy Clin Immunol*. 2001;10:461–468.

Calhoun WJ, Nelson HS, Nathan RA, et al. Comparison of fluticasone propionate-salmeterol combination therapy and montelukast in patients who are symptomatic on short-acting beta(2)-agonists alone. *Am J Respir Crit Care Med*. 2001;164:759–763.

Data on file. Health Benchmarks, Inc. Woodland Hills, Calif.

Donahue JG, Weiss ST, Livingston JM, Goetsch MA, Greineder DK, Platt R. Inhaled steroids and the risk of hospitalization for asthma. *JAMA*. 1997;277(11):887–891.

Gerdtham UG, Hertzman P, Jonsson B, Boman G. Impact of inhaled corticosteroids on acute asthma hospitalization in Sweden 1978 to 1991. *Med Care*. 1996;34:1188–1198.

Goldman M, Rachmiel M, Gendler L, Katz Y. Decrease in asthma mortality rate in Israel from 1991–1995: is it related to increased use of inhaled corticosteroids? *J Allergy Clin Immunol*. 2000;105(1 Pt 1):71–74.

Kim KT, Ginchansky EJ, Friedman BF, et al. Fluticasone propionate versus zafirlukast: effect in patients previously receiving inhaled corticosteroid therapy. *Ann Allergy Asthma Immunol*. 2000;85:398–406.

Krishnan AA, O'Connor RD, O'Donnell JC, Bowers B, Davis EA. Economic impact of treatment options in management of asthma [abstract]. *Am J Respir Crit Care Med*. 2002;165:8.

Lanes SF, Garcia Rodriguez LA, Huerta C. Respiratory medications and risk of asthma death. *Thorax*. 2002;57:683–686.

Malmstrom K, Rodriguez-Gomez G, Guerra J, et al. Oral montelukast, inhaled beclomethasone, and placebo for chronic asthma: a randomized, controlled trial. Montelukast/Beclomethasone Study Group. *Ann Intern Med*. 1999;130:487–495.

Matz J, Emmett A, Rickard K, Kalberg C. Addition of salmeterol to low-dose fluticasone versus higher-dose fluticasone: an analysis of asthma exacerbations. *J Allergy Clin Immunol*. 2001:107:783–789.

Merck Annual Report 2001. Whitehouse Station, NJ: Merck & Co., Inc. 2002. Available at: «http://www.anrpt2001.com/12.htm».

NAEPP (National Asthma Education and Prevention Program). *Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma*. Bethesda, Md.: National Institutes of Health. 1991. NIH Publication No. 91-3642.

NAEPP (National Asthma Education and Prevention Program). *Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma.* Bethesda, Md.: National Institutes of Health. 1997. NIH Publication No. 97-0491. Available at: «http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm». Accessed Oct. 24, 2002.

NAEPP (National Asthma Education and Prevention Program) Expert Panel. *NAEPP Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma—Update on Selected Topics 2002.* Bethesda, Md.: National Institutes of Health. July 2002. NIH Publication No. 02-5075. Available at: «www.nhlbi.nih.gov/guidelines/asthma/execsumm.pdf». Accessed Oct. 20, 2002.

NAEPP (National Asthma Education and Prevention Program). *Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma. Update on Selected Topics 2002. J Allergy Clin Immunol.* 2002;110(5): S141–S219. Available at: «http://www.nhlbi.nih.gov/guidelines/asthma/». Accessed Nov. 30, 2002.

O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. *Am J Respir Crit Care Med.* 2001;164(8 Pt 1):1392–1397.

O'Connor RD, O'Donnell JC, Pinto LA, Wiener DJ, Legorreta AP. Two-year retrospective economic evaluation of three dual-controller therapies used in the treatment of asthma. *Chest.* 2002;121:1028–1035.

Pathak DS, Davis EA, Stanford RH. Economic impact of asthma therapy with fluticasone propionate, montelukast, or zafirlukast in a managed care population. *Pharmacotherapy.* 2002;22:166–174.

Pauwels RA, Löfdahl CG, Postma DS, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. *N Engl J Med.* 1997;337:1405–1411.

Ray JG. Evidence in upheaval: incorporating observational data into clinical practice. *Arch Intern Med.* 2002;162:249–254.

Sin DD, Man SFP. Low-dose inhaled corticosteroid therapy and risk of emergency department visits for asthma. *Arch Intern Med.* 2002;162:1591–1595.

Smith MJ, Rascati KL, Johnsrud MT. Costs and utilization patterns associated with persistent asthma: a comparison of Texas Medicaid patients with and without continuous inhaled corticosteroid treatment. *J Manag Care Pharm.* 2001;7:452–459.

Scott-Levin. Source Prescription Audit (SPA) from Verispan. 1991–2000.

Scott-Levin. Source Prescription Audit (SPA) from Verispan. 1997–2001.

Stempel DA, O'Donnell JC, Meyer JW. Inhaled corticosteroids plus salmeterol or montelukast: effects on resource utilization and costs. *J Allergy Clin Immunol.* 2002a;109:433–439.

Stempel DA, Pinto L, Stanford RH. The risk of hospitalization in patients with asthma switched from an inhaled corticosteroid to a leukotriene receptor antagonist. *J Allergy Clin Immunol.* 2002b;110:39–41.

Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med.* 2000;34:332–336.

Wang SW, Liu X, Wiener DJ, Sennett C, Bowers BW, Legorreta AP. Comparison of prevalence, cost, and outcomes of a combination of salmeterol and fluticasone therapy to common asthma treatments. *Am J Manag Care.* 2001;7:913–922.

Wennergren G, Kristjansson S, Strannegard IL. Decrease in hospitalization for treatment of childhood asthma with increased use of antiinflammatory treatment, despite an increase in prevalence of asthma. *J Allergy Clin Immunol.* 1996;97:742–748.

FACULTY PRESENTATION

An Asthma Management Program in Managed Care

MICHAEL J. BELMAN, MD, MPH

Staff Vice President, Medical Director, Blue Cross of California

A well-designed asthma management program promises to improve patient care while reducing costs. No matter how well it is structured and funded, however, no disease management (DM) program can do anything but fail unless it succeeds at the most critical interface, which is where the physician delivers care to the patient.

Most managed care organizations (MCOs) regard clinical practice guidelines as essential tools for their participating physicians. Indeed, guidelines are medical power tools for knowledgeable physicians, and MCOs typically consider them to be the cornerstone of any effective DM program. But guidelines have practical value only if they are applied effectively. Simply creating and disseminating new guidelines is insufficient to alter physicians' behavior.

If an MCO strives to achieve its organizational goals by having its physicians implement practice guidelines, it must establish an infrastructure to support their use. Physicians must become familiar with the guidelines that the MCO wants implemented, understand the benefits of applying those guidelines — to their patients and their medical business — and incorporate the guidelines' recommendations into their clinical practice.

This article will discuss the targeted interventions and physician incentive programs that Blue Cross of California (BCC) implemented to increase physicians' compliance with guidelines and, as a result, improve asthma care provided to patients in their plans.

Identifying a need

A study conducted among faculty members, fellows, and residents at the University of Iowa (Doerschug 1999) demonstrated that even asthma specialists lacked familiarity with the details of the asthma guidelines issued in the second Expert Panel Report of the National Asthma Education and Prevention Program (EPR-2) (NAEPP 1997).

These researchers constructed a 31-item test to gauge physicians' understanding of EPR-2 and distributed it to asthma specialists and primary care physicians, including faculty members and residents. The mean score among test completers was 60 percent. As a group, asthma specialists had a score of 78 percent — a C+. Fellows in asthma specialties scored 69 percent, followed by internal medicine faculty members (67 percent), and family medicine faculty members (63 percent).

Overall, higher test scores correlated with the extent of physician training. The study results indicated that physicians at all levels of training, even the asthma specialists, tended to underestimate disease severity. Most commonly, they failed to recognize daily symptoms as a sign of at least moderate persistent asthma, daily use of beta$_2$ agonists as a sign of uncontrolled asthma, and weekly nocturnal symptoms as a sign of moderate persistent asthma.

Guidelines tend to be complex, and even physicians who accept the evidence base on which the guidelines are constructed may not fully understand how they should be applied. This lack of immediate understanding is only one of the elements accounting for variation in clinical practice patterns from one clinician to the next. The proliferation of guidelines and exponential increase in randomized clinical trials has produced a mass of evidence that no physician can master unaided. Prompts, reminders, and feedback are critical to enable physicians to use guidelines appropriately.

Asthma guidelines are intended to help clinicians bring a patient's asthma under control. Asthma control is defined as preventing chronic and troublesome symptoms, maintaining normal (or near-normal) pulmonary function tests, maintaining normal activity levels, preventing recurrent exacerbations, minimizing side effects, and satisfying patient expectations with respect to care.

To foster physician support for implementation of clinical practice guidelines relevant to asthma control, BCC implemented a number of programs.

BCC's first such program was launched in 1997. As more than 90 percent of the BCC membership has a pharmacy benefit, the captured pharmacy claims were used as a means to monitor use of asthma medications. In this quarterly, targeted asthma-controller intervention, BCC reviews those pharmacy claims, identifying members who received three or more canisters of a beta$_2$ agonist during the previous 6-month period. BCC then further refines the target group by identifying members

who failed to fill a prescription for an asthma controller (i.e., an inhaled corticosteroid (ICS), leukotriene modifiers, or mast cell agents.) To the physician of each plan member who meets these two criteria, BCC sends a letter containing details of the member's pharmacy history, along with additional information about the member's use of controllers and a form that can be faxed back to the health plan if the physician has any concerns about the member in question.

BCC also calculates the percentage of members receiving asthma controllers and beta$_2$ agonists on a quarterly basis. Figure 1 shows how this targeted effort improved rates of controller use over the course of 3 years. BCC saw positive results in both health maintenance organization (HMO) and preferred provider organization (PPO) populations.

Nevertheless, because overall compliance with NAEPP asthma-controller guidelines remained suboptimal, BCC developed a more intensive intervention to further improve the rate of controller use among its plan members. First, the MCO applied Health Plan Employer Data and Information Set (HEDIS) criteria to define the denominator (patients with persistent asthma) in a simple equation. These criteria included any of the following: four asthma-dispensing events, one emergency department (ED) visit with asthma as the principal diagnosis, one hospitalization with asthma as the principal diagnosis, or at least four outpatient visits and two asthma-dispensing events. The equation's numerator consisted of patients with at least one prescription for a controller medication ICS, leukotriene modifier, cromolyn, or nedocromil).

Once members with asthma were identified using HEDIS criteria, BCC took the following corrective interventions:

- sent letters to participating physicians, listing the names of the members identified using the HEDIS criteria;
- phoned office staff members to alert them to the posting of the letters and to reinforce the importance of controller use;
- through the pharmacy benefits manager, informed physicians of patients who may not be complying with therapy; and
- sent letters to members, offering them an age-appropriate gift — either an asthma-inhaler kit or a video game — to encourage ICS use.

Figure 2 shows how BCC's HEDIS scores improved between 2001 and 2002, in three age categories.

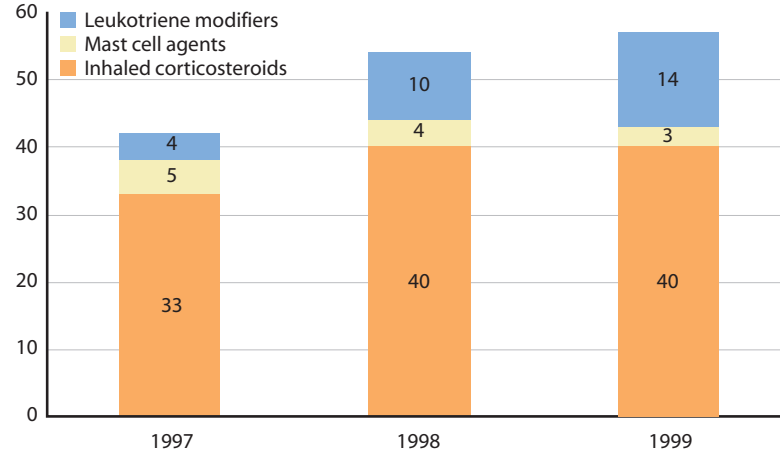
Disease management program

Subsequently, BCC began a DM program, which integrates pharmacy and medical-claims data, to identify plan members with asthma, reduce ED visits, and reduce inpatient stays. BCC's DM program stratifies patients according to risk, using a logistic-regression model, which incorporates medical-claims and pharmacy-claims data to predict ED visits and hospitalizations. The model also incorporates clinical care patterns based on claims and pharmacy data (e.g., a life-threatening event involving a patient not using anti-inflammatory medication).

The intervention for the low-risk patients focuses primarily on education. Low-risk patients receive an educational booklet, seasonal and quarterly mailings about asthma, and treatment guidelines; their physicians receive a "physician practice tool" (PPT) — a laminated set of nationally accepted guidelines. Moderate-risk patients receive the same materials as the low-risk patients, along with an asthma kit that includes a peak-flow meter and a spacer; their physicians also receive the PPT. High-risk patients receive the same materials as the moderate-risk patients, plus an asthma action plan and telephone calls from nurses to make sure the patients understand their disease state and know what to do in the event of a crisis; their physicians receive the PPT and are notified that their patients are at high risk. Within the high-risk group, a subset (those with multiple admissions or ED visits) is identified, and these patients are assigned nurse case managers. In addition, children aged 2 to 4 years within this subset are offered a free nebulizer. Historically, staff models and HMO models have had more success with DM programs, in terms of reducing ED visits and inpatient stays, than have PPO models.

FIGURE 1 Asthma controller use

Percentage of patients using relievers who also are receiving long-term controllers



SOURCE: Blue Cross of California.

FIGURE 2 BCC — HEDIS 2002

Appropriate medication for asthmatic members

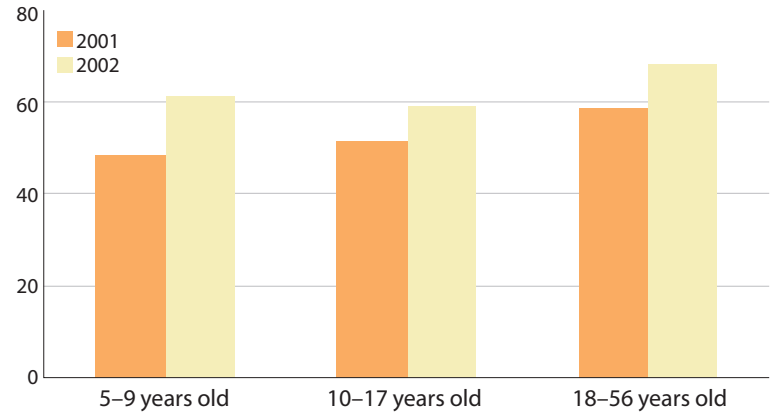


FIGURE 3 Asthma disease management

Pharmacy

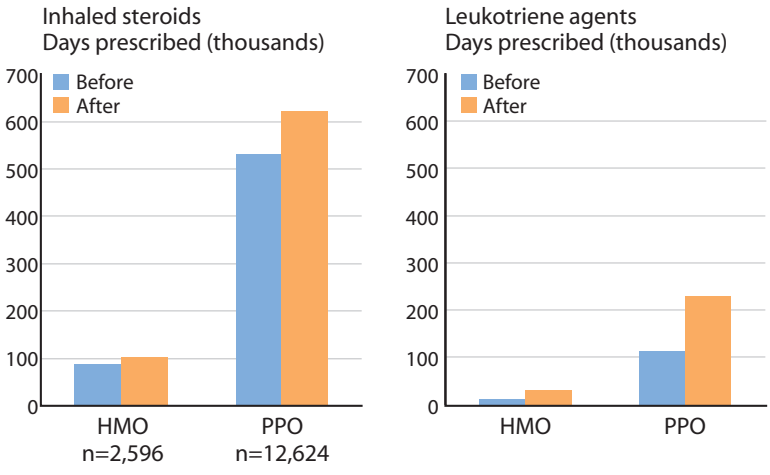
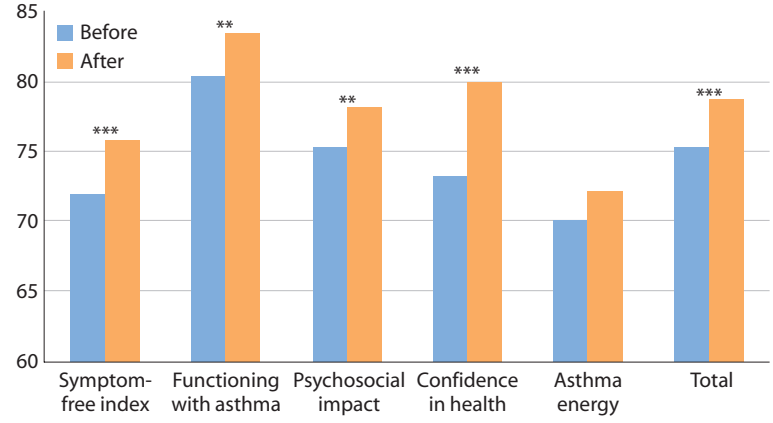


FIGURE 4 Asthma disease management: HRQoL

Health-Related Quality of Life — adults (n=412)



* $p<.05$; ** $p<.01$; *** $p<.001$

SOURCE FOR FIGURES 2–4: Blue Cross of California.

Shortly after BCC launched this intervention, however, ED visits significantly declined in both the HMO and PPO asthma populations, but inpatient admissions per 1000 asthmatics were significantly reduced only in the PPO population. In addition, use of anti-inflammatory drugs increased significantly (Figure 3), and asthma-related quality-of-life scores improved in both the children and adult populations (Figure 4). Although patients' knowledge of peak-flow meters and spacers increased, their use of these devices did not change.

Financial incentives

All methods of paying physicians have limitations. Fee-for-service practice provides too much financial incentive for too few practitioners, while capitation provides too little incentive for too many practitioners. Salaries alone may not provide incentive to encourage physicians to outperform their colleagues. To address this inequity, payers have developed reimbursement mechanisms that blend aspects of fee-for-service and capitation (Robinson 1999). Yet a DM program that is regarded as successful from the perspective of the members and the plan may not be viewed as successful by providers who no longer are receiving reimbursement for inpatient stays or office visits. If physicians perceive that they will lose revenue due to cost-reducing practice changes, they cannot be expected to eagerly implement the guidelines that are responsible for their lost revenue.

To compensate for physician-reward systems that are weak or even negative, health plans need to assign high priority to the design of better incentives (Newhouse 2002). BCC recently undertook this task for its HMO physicians. In the past (1994–2001), BCC graded physician groups on a 100-point scale comprising the following components: annual on-site audit (20 points), grievance and appeals (15 points), turn-around time for return of information related to appeals (5 points), transfers for quality (10 points), satisfaction survey results (30 points), and a preventive health audit

(20 points). Groups with average and above-average scores received a modest financial bonus.

BCC eventually replaced this grading system and is now replacing this system with a program with an expanded bonus based entirely on quality. Much of the BCC's new incentive plan (the HMO Shared Risk Incentive Program) is based on nationally recognized guidelines or HEDIS measures. A survey of California primary care physicians conceptually supports this change in the incentive program, linking greater job satisfaction in physicians with incentives that are based on quality of care and patient satisfaction (Grumbach 1998). By contrast, incentives intended to limit referrals or spur productivity tend to influence physicians negatively, resulting in compromised care and quality.

In addition, patients hold a negative view of physician bonus systems that are based on cost controls, but bonus systems based on both cost controls and quality of care are viewed more favorably (Gallagher 2001).

Pilot program targets PPO quality

Although most of BCC's recent efforts have focused on improving the quality of HMO services, 4.1 million of its 6.7 million members receive care through PPO plans. BCC's PPO members constitute 40 percent of the PPO market share in California. Thus, BCC is well positioned to develop and implement a quality improvement program for its contracting physicians. Known as the Physician Quality and Incentive Program (PQIP), this pilot effort specifically seeks to reduce the burden of illness and mortality associated with prevalent chronic conditions — asthma, cancer, diabetes, heart failure, and mental illness — and to assure the delivery of preventive-care services.

Key to the PQIP is an Internet-based PPO Physician Score Card containing 15 accepted indicators of quality that have been proven effective in the current medical literature. During the pilot program, the score card will be used to evaluate approximately 15,000 PPO physicians throughout California. They will have electronic access to data about their own performance as well as comparative data about average peer performance, categorized both geographically and by specialty.

A pilot program now is being launched in the San Francisco Bay-area counties. PPO physicians in this region will be eligible to participate in a Physician Recognition Program, which provides financial rewards for superior performance in the clinical, administrative, and pharmacy measures tracked on the score card.

Two of the clinical indicators — the use of long-term controllers and follow-up visits after asthma-related ED treatment — are specific to asthma. Among the other clinical indicators are rates of mammography, screening for cervical cancer and colorectal cancer, the use of angiotensin-converting enzyme inhibitors for patients with heart failure, retinal examinations and hemoglobin-A_{1c} monitoring for patients with diabetes, compliance with lipid-lowering therapy, childhood immunizations, and follow-up care after a mental health admission. Typically, each physician in the program will have a minimum of 10 patients in a given clinical category.

PQIP is supported by a substantial grant from the Robert Wood Johnson Foundation. BCC will use this funding to monitor and evaluate the program and make improvements as its most effective components are identified. The RAND organization, a nonprofit public-policy research institution, will assess the effectiveness of PQIP.

Conclusion

In principle, physicians accept valid guidelines for the diagnosis and treatment of asthma; the optimal process to ensure that physicians apply the guidelines in clinical practice remains unknown, however. Targeted interventions and DM programs vary in their effectiveness; no single program provides effective management of an asthmatic population.

Further progress in improving the care of asthma patients depends on advancements in information technology and multifaceted interventions, to change physician and patient behavior.

References

Doerschug KC, Peterson MW, Dayton CS, Kline JN. Asthma guidelines: an assessment of physician understanding and practice. *Am J Respir Crit Care Med.* 1999;159:1735–1741.

Gallagher TH, St Peter RF, Chesney M, Lo B. Patients' attitudes toward cost control bonuses for managed care physicians. *Health Aff* (Millwood). 2001;20:186–192.

Grumbach K, Osmond D, Vranizan K, Jaffe D, Bindman AB. Primary care physicians' experience of financial incentives in managed-care systems. *N Engl J Med.* 1998;339:1516–1521.

NAEPP (National Asthma Education and Prevention Program). *Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma.* Bethesda, Md.: National Institutes of Health. 1997. NIH Publication No. 97-0491. Available at: «http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm». Accessed Oct. 24, 2002.

Newhouse JP. Why is there a quality chasm? *Health Aff* (Millwood). 2002;21:13–25.

Robinson JC. Blended payment methods in physician organizations under managed care. *JAMA.* 1999;282:1258–1263.

FACULTY PRESENTATION

Appropriate Utilization of Asthma Therapies for Better Outcomes

H. Eric Cannon, PharmD

Director of Pharmacy Services, Intermountain Health Care, Salt Lake City

Successful disease management depends on the efficient integration of pharmacy and medical data. This article will discuss the experience of a western health care system, Intermountain Health Care (IHC), in reducing asthma-related medical care utilization via appropriate use of asthma therapies within its own physician-driven disease management program.

IHC is an integrated health care system consisting of 21 hospitals and 150 medical facilities and physician offices throughout Utah and Idaho. IHC employs 450 physicians (350 primary care physicians) and has 2,500 affiliated physicians. It provides health care for 498,000 members of health plans and 500,000 affiliates. IHC recently was ranked number one in *Modern Healthcare's* list of the top 100 integrated health care networks.

H. Eric Cannon, PharmD

In establishing its ethical priorities, IHC has given primacy to improving the quality of service delivered to the patient. Controlling costs is a secondary concern, because IHC believes that if high-quality medical care is provided through best practices, controlled costs will follow. Following from these considerations, IHC's disease management program for asthma comprises the standard components, as shown in Table 1.

The goals of IHC's asthma program are listed in Table 2. The guidelines for therapy used by IHC are similar to the most recent recommendations from the National Asthma Education and Prevention Program (NAEPP). One minor difference is that while the NAEPP guidelines mention leukotriene modifiers (montelukast, zafirlukast, zileuton) as an alternative or add-on therapy for persistent asthma, the IHC guidelines specify only the leukotriene receptor antagonists (montelukast and zafirlukast).

Physician education is one mechanism for supporting IHC's disease management program in asthma. In June 2002, a letter was sent to all physicians reminding them of the NAEPP's unequivocal recognition of inhaled corticosteroids as preferred first-line therapy. Physicians also were told that because the best control of patients' symptoms can be achieved via ICSs, it would be well worth a physician's time to teach

TABLE 1 Components of IHC disease management program for asthma

- Member identification
- Dissemination of evidence-based practice guidelines
- Risk stratification
- Matching interventions with needs
- Collaborative practice model (physician and support staff)
- Self-management education program
- Routine reporting and feedback process (includes patient, physician, and health plan updates)
- Information technology (use of Internet, distance monitoring)
- Methodology for process and outcomes measurement
- Physician champions

TABLE 2 Goals of the IHC asthma clinical program

- Provide a coordinated, integrated, and multidisciplinary system of care for asthma
- Summarize literature and — where a clear evidence base is lacking — provide expert advice regarding diagnosis and treatment for asthma
- Maintain near-normal lung function and activity levels
- Prevent chronic and troublesome symptoms and recurrent exacerbations by controlling the inflammatory process
- Provide optimal pharmacotherapy with minimal or no adverse effects
- Limit regular use of short-acting beta$_2$ agonists to ≤2 times per week
- Minimize the need for emergency-department visits and hospitalizations
- Promote patient participation in disease management by providing patient education tools

patients how to use an inhaler. Physicians had no financial incentive for doing so.

IHC also understands the importance of patient education. Whenever a patient visits an emergency department (ED), a care manager contacts the patient afterward. Care managers are based in both the clinics and the health plan. Most often, a health plan care manager will call the patient, but if the patient already has an ongoing relationship with a clinic-based care manager, then that manager will make the call. During September 2002, 80 such contacts were made.

Unfortunately, 29 percent of these patients refused any assistance or free educational services. This underscores the importance of ongoing patient education to reinforce and re-educate patients about the importance of daily use of controller therapy and the consequences of their failure to comply with therapy.

The imminent launch of a product combining fluticasone propionate and salmeterol in a single inhaled formulation gave IHC an opportunity to review its data on patients' adherence to asthma therapy. On average, patients were refilling their prescriptions for controller therapy three times per year. When combination therapy was examined, it was found that, during 2000, 911 patients in the IHC system were using fluticasone and salmeterol separately, at an average cost per year of $459, in direct dollars from the plan. At the same time, 550 patients were using fluticasone plus a leukotriene modifier, at an average annual cost of $557, and 540 patients were using fluticasone, salmeterol, and a leukotriene modifier, at an average annual cost of $892.

The combination product of fluticasone and salmeterol was added to IHC's formulary in April 2001, available in three doses of fluticasone (100 mcg, 250 mcg, or 500 mcg), each combined with a fixed dose of salmeterol (50 mcg). In order of increasing dose of fluticasone, IHC's cost per unit (one 28-day inhaler) was $83.99, $109.50, and $153.96. Based on an average of 2.94 prescriptions per year, it was estimated that the annual cost per patient for the combination product would be $344, versus $459 for fluticasone and salmeterol administered separately — an estimated annual savings of $115 per patient. Total annual savings for IHC were estimated at $104,927. On a monthly basis, switching patients to the new combination product would reduce pharmacy costs in every instance, in terms of simple cost minimization. These savings included one less brand dispensing fee of $2.

The fluticasone/salmeterol combination product was added to the IHC formulary because the published data indicated that it was safe and efficacious (Aubier 1999, Chapman 1999, Nelson 2000). Nevertheless, IHC was concerned about the financial impact of this action, and this fear was borne out, as shown by the steep ascent of the slope for the combination product, in Figure 1. At the time the combination product became available, many IHC physicians already were prescribing combi-

FIGURE 1 Medication cost trends

Total ingredient costs, in thousands of dollars

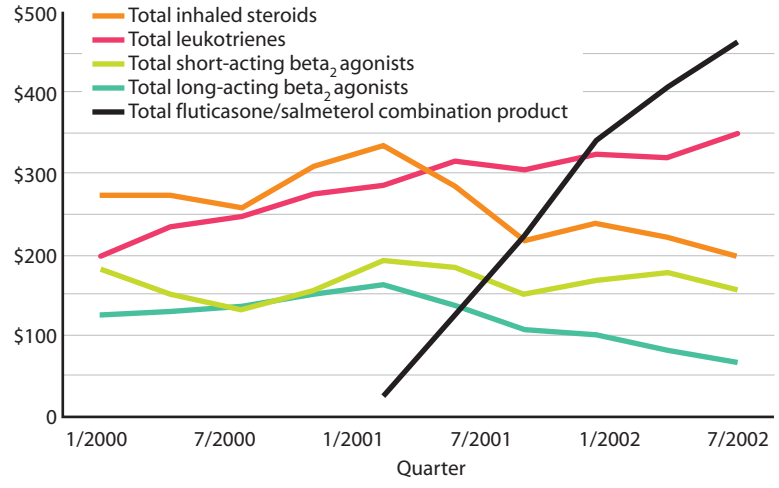


FIGURE 2 Medication costs (per member per month)

Asthma drug costs

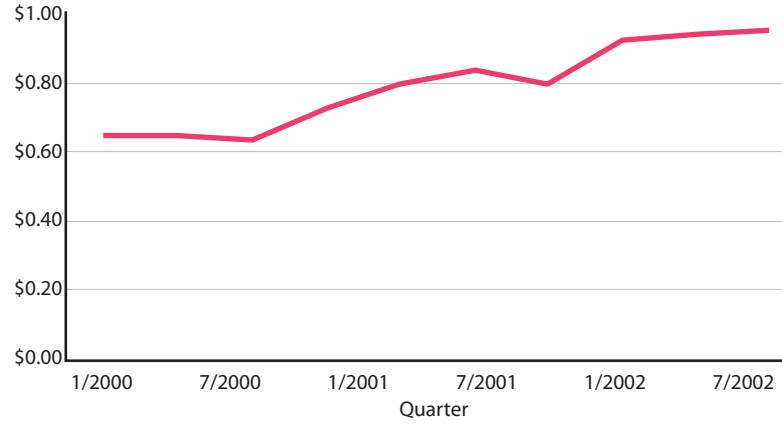


FIGURE 3 Controller use

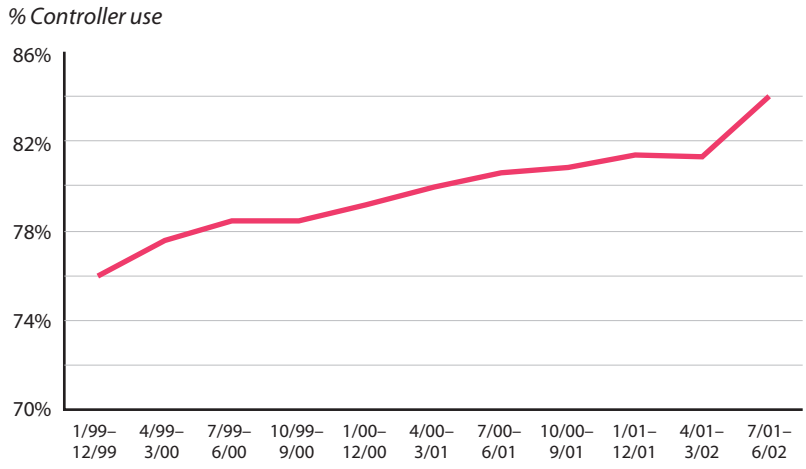


FIGURE 4 Inpatient rates

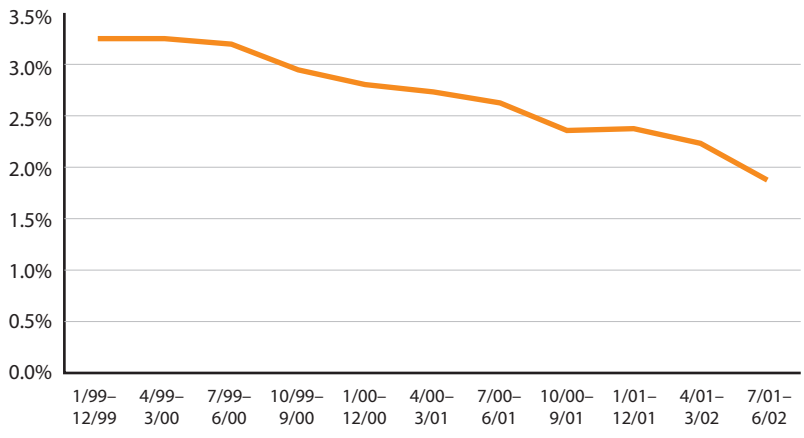
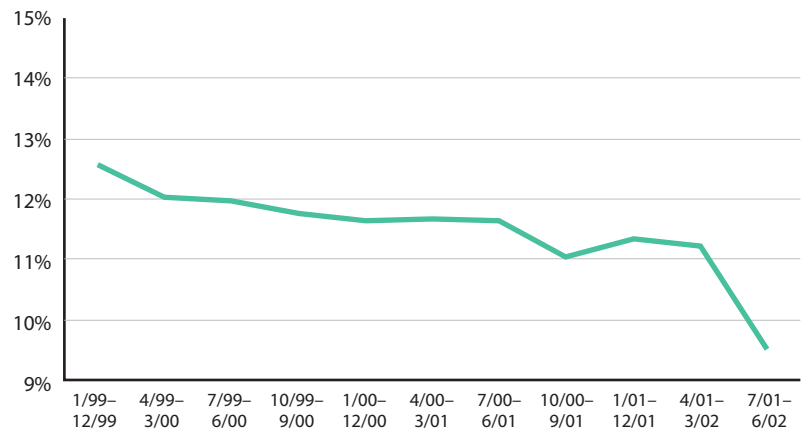


FIGURE 5 Emergency-department visit rates



nation therapy with fluticasone and salmeterol administered separately. Not surprisingly, ICS utilization and long-acting beta$_2$ agonist utilization have both decreased since the combination product became available.

On being presented with utilization data by IHC's underwriting department, one broker was quick to point to a 273 percent increase in costs for the new fluticasone/salmeterol combination product during the past year. The challenge for IHC thus became to demonstrate that the combination product was appropriate therapy. Although per member per month (PMPM) asthma medication costs have been steadily increasing, as shown in Figure 2, these costs appear to have stabilized. It should be noted that a substantial portion of the PMPM increase is due not just to increased use of the fluticasone/salmeterol combination product but to increased use of leukotriene modifiers. As discussed elsewhere in this supplement, a preponderance of evidence suggests that a great many of these patients should be switched from leukotriene modifiers to ICSs.

The percentage of IHC patients simultaneously using long-term control medications has steadily increased (Figure 3) as a result of IHC's recently implemented asthma management program. During the 12-month period ending in December 1999, only 76 percent (4347/5723) of eligible patients were using controllers, but in the 12-month period ending in June 2002, controller use increased to 84 percent (4868/5794).

IHC can point to continuing declines in the rate of hospitalizations (Figure 4) and ED visits (Figure 5), which offset concerns about increasing expenditures for a product with a seemingly higher average wholesale price (fluticasone/salmeterol combination product). During the 12-month period ending in December 1999, asthma-related inpatient services were used by 3.25 percent (188/5784) of the eligible population,

but by June 2002 the rate had declined to 1.87 percent (111/5933). ED visits were made by 12.6 percent (727/5784) of the eligible population during the 12-month period ending in December 1999, a rate that already was below IHC's organizational target of 13.1 percent. Further improvements have been made since then, with emergency services needed by only 9.5 percent (454/5933) of eligible patients during the 12-month period ending in June 2002.

These successes are attributed to the fact that the disease management process at IHC is physician-driven. IHC has a "physician champion" for asthma, who is willing to take the time to work one-on-one with IHC physicians. The care-process models and patient education materials are developed by the clinical programs in collaboration with treating physicians to make sure that IHC physicians perceive the materials as appropriate for their patients. The programs that are put in place are educational in nature; they are neither prescriptive nor imposed. Because IHC is an integrated system, it can generate integrated data that allow IHC to evaluate outcomes and illuminate opportunities for further improvement. The IHC experience demonstrates that — through good disease management, integration of data, and collaboration with physicians — cost-effective treatment can be provided for patients.

It has been the experience of IHC that, by following clinical evidence and providing therapy in line with national standards, improvements in the clinical quality of patient care and reductions in cost do follow. Using the combination of fluticasone/salmeterol provided IHC with opportunities to improve patient care. While it cannot be said that incorporation of fluticasone/salmeterol therapy was solely responsible for decreases in inpatient admissions and rates of emergency-department visitations, it is clear that it did not adversely impact the overall cost of patient care and treatment.

References

Aubier M, Pieters WR, Schlosser NJ, Steinmetz KO. Salmeterol/fluticasone propionate (50/500 microg) in combination in a Diskus inhaler (Seretide) is effective and safe in the treatment of steroid-dependent asthma. *Respir Med.* 1999;93:876–884.

Chapman KR, Ringdal N, Backer V, Palmqvist M, Saarelainen S, Briggs M. Salmeterol and fluticasone propionate (50/250 microg) administered via combination Diskus inhaler: as effective as when given via separate Diskus inhalers. *Can Respir J.* 1999;6:45–51.

Nelson HS, Busse WW, Kerwin E, Church N, Emmett A, Rickard K, Knobil K. Fluticasone propionate/salmeterol combination provides more effective asthma control than low-dose inhaled corticosteroid plus montelukast. *J Allergy Clin Immunol.* 2000;106:1088–1095.

CONTINUING EDUCATION ANSWER SHEET/STATEMENT OF CREDIT

Effective Asthma Management: Current Guidelines and Treatment Options

CME and CE Credit: Physicians and Pharmacists

To receive CME/CE accreditation, please send this completed form along with a $10 processing fee to the address below.

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EXAMINATION: Place an X through the box of the letter that represents the best answer to each question on pages 27 and 28. There is only ONE answer per question. Place all answers on this answer form:

	A.	B.	C.	D.	E.
1.	☐	☐	☐	☐	☐
2.	☐	☐	☐	☐	
3.	☐	☐	☐	☐	
4.	☐	☐	☐	☐	
5.	☐	☐	☐	☐	
6.	☐	☐	☐	☐	
7.	☐	☐	☐	☐	
8.	☐	☐	☐	☐	☐
9.	☐	☐	☐	☐	
10.	☐	☐	☐	☐	
11.	☐	☐	☐	☐	☐
12.	☐	☐	☐	☐	
13.	☐	☐	☐	☐	
14.	☐	☐	☐	☐	
15.	☐	☐	☐	☐	

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To receive credit, please answer all information requested below. This assures prompt and accurate issuance of your continuing education certificate.

Please rate this program as follows:

	Excellent	*Very good*	*Good*	*Fair*	*Poor*
Overall quality of program	5	4	3	2	1
Content	5	4	3	2	1
Relevance of content to objectives	5	4	3	2	1
Effectiveness of this format for learning	5	4	3	2	1
Value to me in my daily responsibilities	5	4	3	2	1

How long did it take you to complete this continuing education activity?

Hours _____ Minutes _____

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_____

Comments: _____

_____

Did you detect any bias in this presentation?

Yes ___ No ___ *If yes, please explain:*

_____

_____

CONTINUING EDUCATION QUESTIONS

Effective Asthma Management: Current Guidelines and Treatment Options

Accreditation: To receive credit for this continuing education activity, the physician and pharmacist must complete the following test. Continuing education certificates will be sent to those participants who receive a score of at least 70%.

Directions: Please tear out the combined answer sheet/assessment form on page 26. On the answer sheet, place an X through the box of the letter corresponding with the correct response for each question.

1. **According to the 2002 update to the 1997 Expert Panel Report, the preferred treatment for a 5-year-old with moderate persistent asthma would be:**
   a. Cromolyn.
   b. Inhaled corticosteroid.
   c. Leukotriene modifier.
   d. Long-acting beta$_2$ agonist.
   e. Short-acting beta$_2$ agonist.

2. **If a patient has mild to moderate persistent asthma that is not controlled on a low- or medium-dose inhaled corticosteroid, the preferred treatment, according to the 2002 update to the 1997 Expert Panel Report, is to:**
   a. Double the dose of the inhaled corticosteroid.
   b. Add a leukotriene modifier.
   c. Add cromolyn.
   d. Add a long-acting beta$_2$ agonist.

3. **Which statement best reflects the opinion of the Expert Panel's Science Base Committee regarding the effects of low to medium doses of an inhaled corticosteroid on growth?**
   a. Although low to medium doses of an inhaled corticosteroid may decrease growth velocity, the effects are small, nonprogressive, and may be reversible.
   b. Low to medium doses of an inhaled corticosteroid are associated with the failure of patients to fully attain their predicted final height.
   c. A permanent decrease in growth velocity is observed during the first 6 to 12 months of treatment with low to medium doses of an inhaled corticosteroid.
   d. The Science Base Committee lacked sufficient data to formulate an opinion on this matter.

4. **In a study by Robinson et al, add-on therapy with montelukast for patients with continuing symptoms of moderate or severe persistent asthma resulted in:**
   a. No significant improvements in symptoms or lung function.
   b. Significant improvements in symptoms and lung function.
   c. Significant improvements in symptoms but not in lung function.
   d. Significant improvements in lung function but not in symptoms.

5. **Which statement is true?**
   a. When used in combination with an inhaled corticosteroid, a long-acting beta$_2$ agonist masks worsening asthma.
   b. If additional control of asthma symptoms is required, adding a leukotriene modifier to an inhaled corticosteroid is just as effective as adding a long-acting beta$_2$ agonist.
   c. When added as a second controller, leukotriene modifiers reduce the use of rescue medication and the rates of asthma-related hospitalization and emergency department (ED) visits, compared with long-acting beta$_2$ agonists.
   d. Compared with combination therapy using inhaled corticosteroids and long-acting beta$_2$ agonists, combination therapy employing leukotriene modifiers is associated with greater rates of medical service utilization as well as higher asthma-related pharmacy costs and total costs.

6. **When montelukast was compared head-to-head with beclomethasone by Malmstrom et al, which of the following results was observed?**
   a. The percentage of days with worsening asthma episodes was lower in the beclomethasone group.
   b. The decrease from baseline in nocturnal awakenings was greater in the beclomethasone group.
   c. The change from baseline in morning PEFR was greater in the beclomethasone group.
   d. All the above.

7. Which approach to asthma therapy is recommended by the 1997 Expert Panel Report?
a. "Step-up" therapy.
b. "Step-down" therapy.
c. "Step-aside" therapy.
d. "Steady-state" therapy.

8. The only class of asthma medication for which good epidemiologic evidence exists to suggest reductions in mortality, hospitalizations, and ED visits is:
a. Inhaled corticosteroids.
b. Inhibitors of 5-lipoxygenase.
c. Leukotriene receptor antagonists.
d. Long-acting $beta_2$ agonists.
e. Short-acting $beta_2$ agonists.

9. In a test of physicians' knowledge of the 1997 Expert Panel Report, even asthma specialists:
a. Overestimated disease severity.
b. Underestimated disease severity.
c. Misunderstood the difference between zafirlukast and zileuton.
d. Misunderstood the difference between zafirlukast and montelukast.

10. According to a survey of primary care physicians in California, greater job satisfaction among physicians was associated with incentives based on:
a. Quality of care and patient satisfaction.
b. A reduction in ED visits and hospitalizations.
c. A reduction in pharmacy expenditures.
d. A reduction in referrals.

11. Use of a targeted mail intervention by Blue Cross of California was associated with:
a. An increase in member satisfaction.
b. An increase in use of asthma controllers.
c. A decrease in asthma-related hospital admissions.
d. A decrease in asthma-related ED visits.
e. All the above.

12. The interventions employed by the asthma disease management program of Blue Cross of California were associated with:
a. Increased use of anti-inflammatory agents.
b. A reduction in ED visits.
c. Improved asthma-related quality-of-life scores.
d. All the above.

13. Intermountain Health Care estimated that switching patients from fluticasone and salmeterol administered separately to a single product combining both drugs would produce which of the following effects?
a. Annual costs would increase by $15 per patient.
b. Annual costs would increase by $115 per patient.
c. Annual costs would decrease by $15 per patient.
d. Annual costs would decrease by $115 per patient.

14. A goal of the clinical program for asthma at Intermountain Health Care is to limit the use of short-acting $beta_2$ agonists to:
a. ≤2 times per day.
b. ≤2 times per week.
c. ≤2 times per month.
d. ≤2 times per year.

15. Although cause and effect cannot be proven, which of the following observations were made by Intermountain Health Care after the fluticasone/salmeterol combination product was added to its formulary in April 2001?
a. The rate of asthma-related hospitalizations declined further.
b. The rate of asthma-related ED visits declined further.
c. The percentage of eligible patients using long-term control medications increased further.
d. All the above.