National Asthma Education and Prevention Program

Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma

Update on Selected Topics 2002

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Heart, Lung, and Blood Institute

National Asthma Education and Prevention Program

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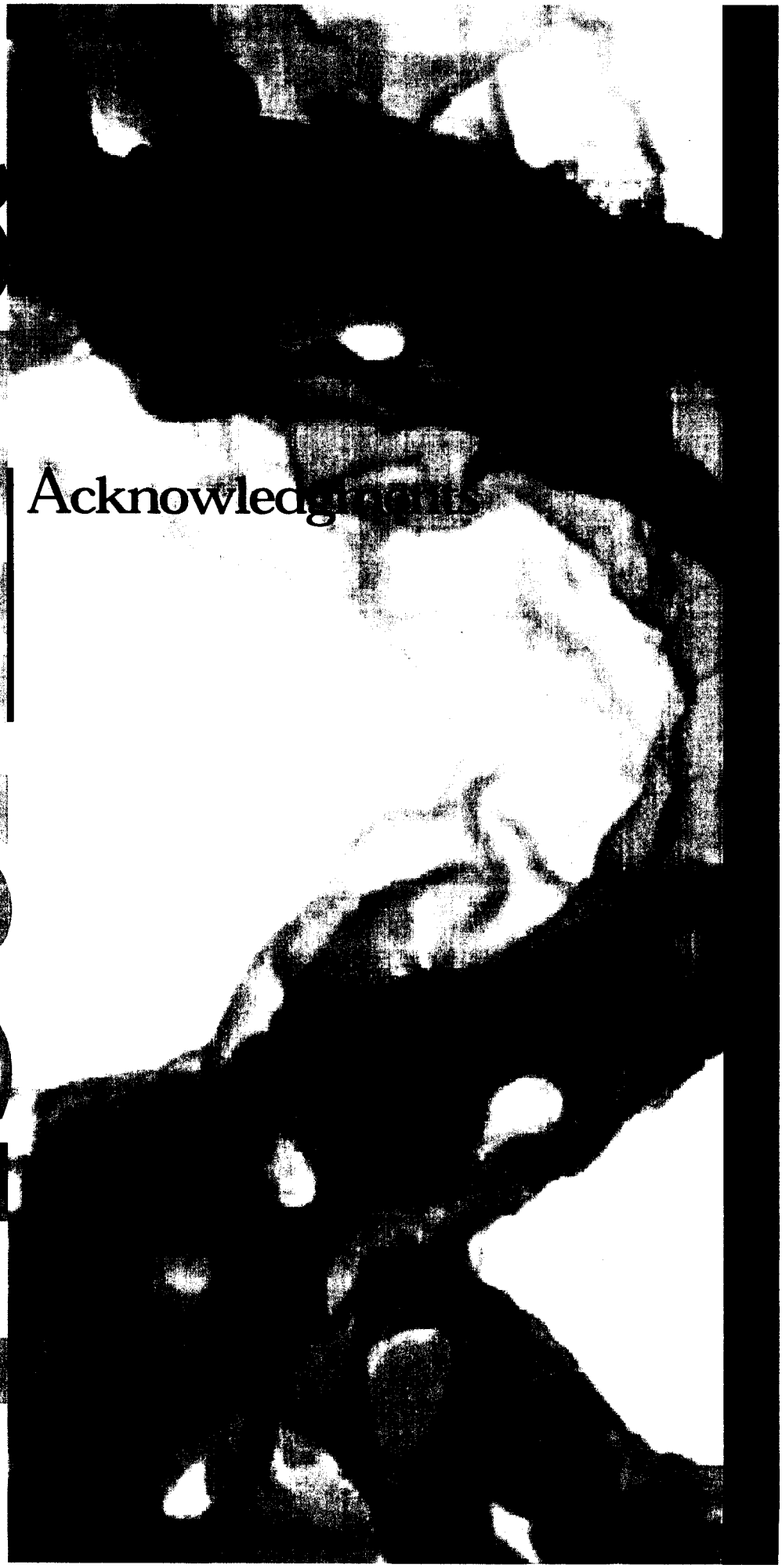

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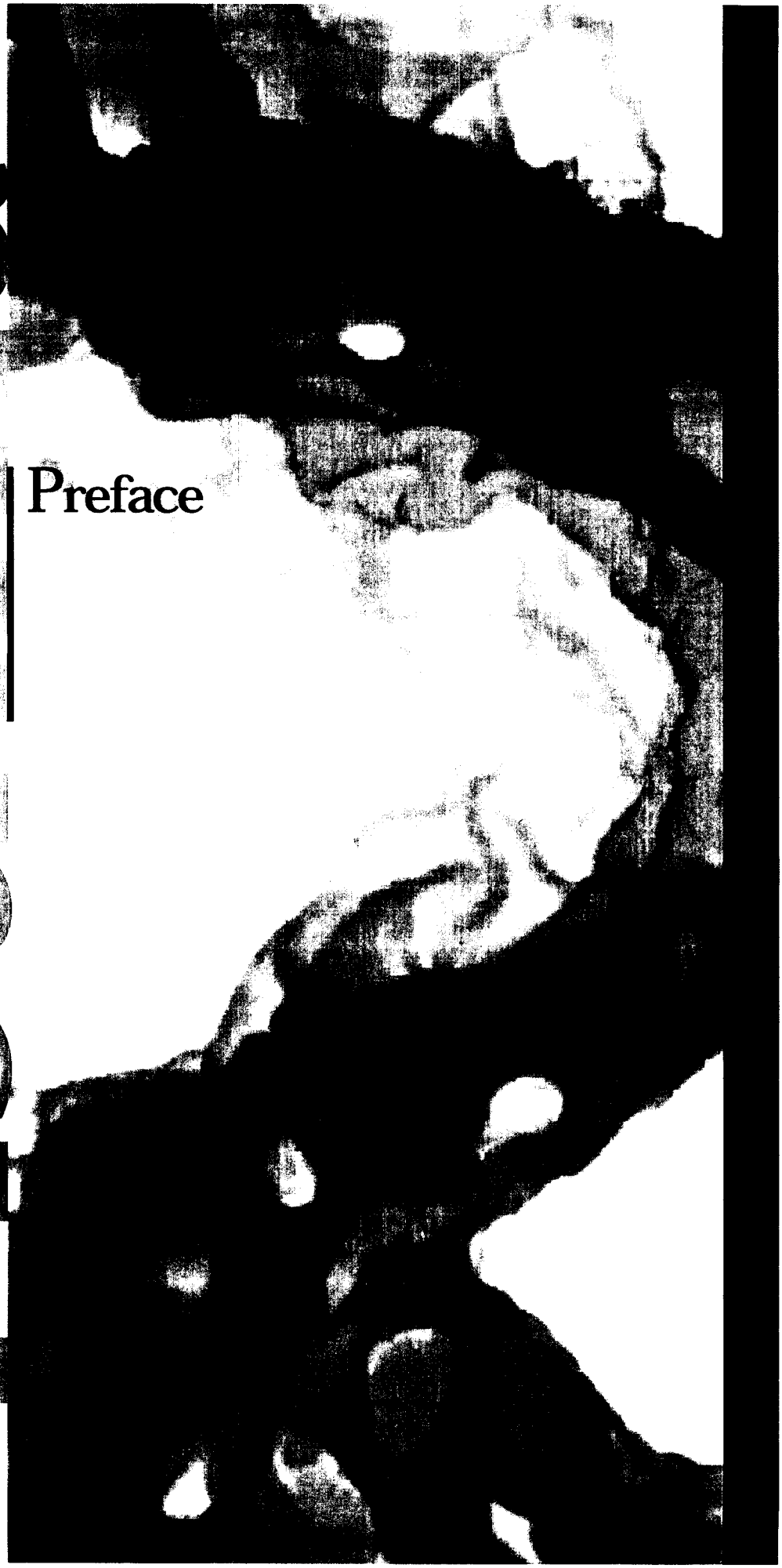
Preface



Preface

Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma—Update on Selected Topics 2002 (EPR—Update 2002) provides timely information on several selected priority asthma topics. It updates recommendations of the *Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma* (EPR-2).

The current update was developed using a new approach that will make the asthma guidelines a dynamic and timely guide for practicing clinicians. The National Asthma Education and Prevention Program (NAEPP) Science Base Committee regularly reviews the scientific literature as an ongoing process to identify topics that warrant a more in-depth and systematic review. For this update, the Committee has focused on a few of the more pressing asthma issues rather than updating all topics at once. This approach should provide more expeditious updates in the future, thus adding to the value of the guidelines as a living document.

The Committee recommends to the NAEPP Coordinating Committee when a review is warranted and, upon concurrence by the CC, an expert panel is convened. Expert panel members are independent thinkers who represent a multidisciplinary group of clinicians and scientists possessing expertise in clinical management. They make recommendations based on their interpretation of the best and most current evidence available.

The 2002 update to the asthma guidelines has been developed under the able leadership of Dr. William Busse, Panel Chair. The National Heart, Lung, and Blood Institute sincerely appreciates the work of Dr. Busse and all members of the Expert Panel in developing this report. Sincere appreciation also goes to the 40 organizations (professional societies, voluntary organizations, Federal agencies) that comprise the NAEPP-CC for their thoughtful review and comments in approving content of this report.

Ultimately, broad change in clinical practice depends on the influence of local physicians and other health professionals who not only provide state-of-the-art care to their patients, but also communicate to their peers the importance of doing the same. We are optimistic that over the next several years, the joint efforts of the NAEPP, its CC member organizations, and committed professionals at the local level will result in extensive implementation of the recommendations in the EPR—Update 2002 and EPR-2. We ask for the assistance of every reader in reaching our ultimate goal: improving asthma care and the quality of life for every patient with asthma and their families.

Publications from the NAEPP can be ordered through the National Heart, Lung, and Blood Institute Information Center, P.O. Box 30105, Bethesda, MD 20924-0105. Publications are also available through the Internet at http://www.nhlbi.gov.nhlbi/nhlbi.htm.

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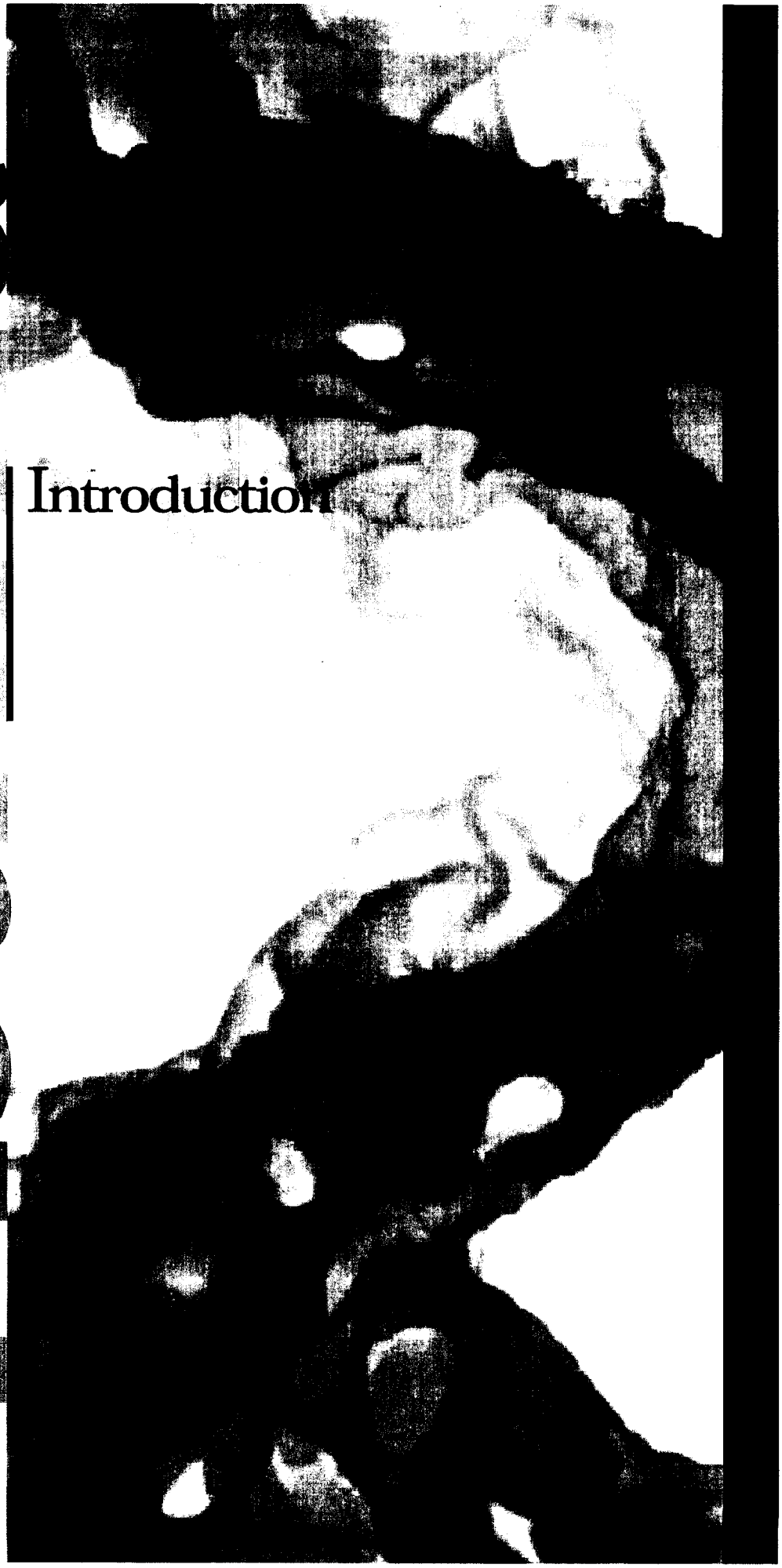
Asthma

Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma

Introduction



Introduction

Asthma is a chronic inflammatory disease of the airways that has created a significant public health burden. In the United States, more than 11 million people reported having an asthma attack in the year 2000, and more than 5 percent of all children younger than age 18 reported having asthma attacks. In 1999, asthma was responsible for 2 million emergency department visits, 478,000 hospitalization with asthma as a primary diagnosis, and 4,426 deaths. The rates of hospitalization have remained the same or lower since 1980 for all age groups, except children younger than age 15. Mortality rates have declined overall since 1995, but a disparity among ethnic groups remains: Asthma mortality is nearly 3 times higher in black males than in white males and 2.5 times higher in black females than in white females (Centers for Disease Control and Prevention).

Scientific advances over the last 15 years have led to a greater understanding of the mechanisms of asthma and the development of therapeutic approaches that can reduce morbidity and improve the quality of life among persons with asthma. To help health care professionals bridge the gap between current knowledge and practice, the National Heart, Lung, and Blood Institute's (NHLBI's) NAEPP has convened expert panels to prepare clinical practice guidelines for the diagnosis and management of asthma. The NAEPP Coordinating Committee, under the leadership of Claude Lenfant, M.D., director of the NHLBI, convened the first Expert Panel in 1989. The Panel was charged with developing a report that would provide a general approach to diagnosing and managing asthma based on current science. The NAEPP *Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma* (NAEPP 1991) was published in 1991. Recommendations for the treatment of asthma were organized around the following four components of effective asthma management:

- Use of objective measures of lung function to assess the severity of asthma and to monitor the course of therapy
- Environmental control measures to avoid or eliminate factors that contribute to asthma severity
- Comprehensive pharmacologic therapy for long-term management designed to reverse and prevent the airway inflammation characteristic of asthma, as well as pharmacologic therapy to manage asthma exacerbations
- Patient education that fosters a partnership among the patient, his or her family, and clinicians.

The NAEPP convened a second Expert Panel in 1995 to review the entire 1991 report and update it, if necessary, based on review of the literature published since 1991 and on clinical experience with implementation of the report's recommendations for clinical practice. The NAEPP *Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma* (EPR-2) was published in 1997.

The NAEPP recognizes that the value of clinical practice guidelines lies in their presentation of recommendations based on the best and most current evidence available. However, high-quality research on all areas of asthma management is not available, and scientific examination and discovery often is focused on only a few areas at any given time. The NAEPP concluded that an efficient approach to updating the clinical practice guidelines would be to identify selected questions that warrant intensive review and possible update, based on either the level of research activity reflected in the published literature or the level of concern or controversy in clinical practice. Position statements on these topics would be published as NAEPP *Expert Panel Report Updates*, and would be incorporated into the

Web-based version of EPR-2. Thus, the NAEPP *Expert Panel Report* is a dynamic document that will be updated continuously with position statements on topics of interest to the community of patients, clinicians, and organizations dedicated to improving asthma care.

The NAEPP charged its Science Base Committee with the responsibility for monitoring the scientific literature, identifying topics for review, determining the need for changes in the EPR-2, and preparing appropriate updates. The Science Base Committee is a multidisciplinary group of clinicians and scientists with expertise in asthma management. The group includes health professionals in the areas of general medicine, family practice, pediatrics, emergency and critical care, allergy, pulmonary medicine, pharmacy, and health education. The Science Base Committee reports to the NAEPP Coordinating Committee, which comprises representatives from 40 professional societies, voluntary organizations, and Federal agencies.

This report, the NAEPP *Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma—Update on Selected Topics 2002* (EPR—Update 2002), presents recommendations for the management of asthma that will help clinicians and patients make appropriate decisions about asthma care on the following topics:

- Medications
  - Long-term management of asthma in children:
    - Effectiveness of inhaled corticosteroids for children with mild or moderate persistent asthma compared with other medications
    - Safety of long-term use of inhaled corticosteroids
  - Combination Therapy: The addition of other long-term-control medications to inhaled corticosteroids
  - The effect of antibiotics on acute asthma exacerbations
- Monitoring
  - Written asthma management plans compared to medical management alone
  - Peak flow-based compared to symptom-based written action plans
- Prevention
  - Effects of early treatment on the progression of asthma.

The appendices to this report contain updated stepwise and dosage charts and a list of abbreviations and acronyms.

This report revises the EPR-2 Stepwise Approach for Managing Asthma to incorporate findings from the review of the scientific evidence. These guidelines are intended to inform, not replace, clinical judgment. Of course, the clinician and patient need to develop individual treatment plans that are tailored to the specific needs and circumstances of the patient. This report is not an official regulatory document of any Government agency.

Methods Used To Develop This Report

The NAEPP Science Base Committee met in April 1999 to identify priority areas for review and possible update of recommendations in EPR-2. The Committee used a modified Delphi technique to rank all major EPR-2 clinical recommendations according to whether major new studies had been published in that area or the area was of considerable clinical interest but lacking in consistent evidence at the time EPR-2 was developed. At the same time, the Agency for Healthcare Research and Quality (AHRQ), through its own routine process of soliciting questions from the medical community for the development of evidence reports, received questions on asthma from the American Academy of Pediatrics and the American Academy of Family Physicians. Several of the topics were comparable to those identified by NAEPP Science Base Committee, so the NHLBI worked with the AHRQ to develop a contract with an AHRQ Evidence-Based Practice Center. An AHRQ contract was awarded to the Blue Cross Blue Shield Association Technology Evaluation Center to conduct a systematic review of the evidence (SRE) on the topics listed earlier.

In August 1999, the AHRQ Evidence-Based Practice Center began to perform comprehensive review of the literature on each of the selected topics; to prepare evidence tables depicting study design, research

variables, and reported outcomes; and to summarize the literature findings in a narrative report. This report, however, was not intended to make judgments about the implications of the findings for clinical practice. The Evidence-Based Practice Center's methods for conducting the SRE are described in detail elsewhere (Blue Cross and Blue Shield Association Technology Evaluation Center) and are summarized here.

- The Evidence-Based Practice Center formed a Technical Advisory Group composed of asthma specialists and primary care physicians, including several members of the NAEPP Science Base Committee. The literature search included full-length reports published in peer-reviewed medical journals and articles in English or published in foreign languages with English abstracts. Studies that did not include control groups in the research design were excluded from review (except for those that dealt with the topic of adverse effects of inhaled corticosteroids), and most of the included trials were randomized. Specific criteria that defined patient populations of interest, outcomes of interest, types of interventions, and study design were established for each topic. A comprehensive literature search was performed using key text words and MeSH terms (Medical Subject Heading) to identify all relevant controlled clinical trials. (Key words included, for example, all long-term-control asthma medications, antibiotics in asthma, peak expiratory flow rate meter, action plan, and self-care monitoring.) Both the MEDLINE and EMBASE databases were searched for all articles published from 1980 through August 2000. In addition, the search included potentially relevant studies published before 1980 but referenced in the post-1980 literature.

- The search retrieved 4,235 English and 343 non-English language references. One member of the Evidence-Based Practice Center's study team reviewed abstracts; a second team member reviewed any excluded abstracts. On the basis of this abstract review, 668 full-length journal articles were retrieved and rated independently by two study team members against study selection criteria. Eighty-seven articles met the study selection criteria to be included in the SRE. Data from these 87 articles were abstracted for evidence tables by two reviewers and were recorded in an electronic database. Data elements included categories such as study design and methods, patient characteristics, lung function outcomes, symptom outcomes, medication outcomes, utilization outcomes, and adverse events.

- A quality assessment of the studies was performed to enable sensitivity analysis comparing the results and conclusions reached from all included studies with the results and conclusions of a subgroup of higher quality studies. Quality was assessed on three domains: concealment of treatment allocation during randomization, double-blinding, and handling of withdrawals and exclusions. Quality also was assessed on domains deemed pertinent to asthma research, such as establishing reversibility of airway obstruction, controlling for other medication use, reporting compliance, addressing seasonality, and a priori reporting of power calculations.

- A meta-analysis was performed to assess the benefits of adding long-acting inhaled $beta_2$ agonist medication to inhaled corticosteroids as treatment of moderate persistent asthma.

In February 2001, the Evidence-Based Practice Center submitted a draft report of the SRE to the AHRQ. The NAEPP Science Base Committee, serving as an Expert Panel, met in March to review the Evidence-Based Practice Center's report and to interpret the implications for clinical practice and the recommendations included in EPR-2. The Expert Panel reached consensus on whether the evidence supported the recommendations made in EPR-2 or indicated a need for revision. The Expert Panel then assigned writing committees to develop position statements on each of the topics. Each Panel member was assigned to one of the writing committees. The Expert Panel noted that, for some topics, significant studies had been published in the 7-month period between the Evidence-Based Practice Center's search of the literature and the submission of its report. The Expert Panel agreed that the writing committees would include their own review of additional literature published since August 2000 and use MEDLINE searches as appropriate. The distinction between the two literature reviews is noted in the position statements by separating discussion of the Evidence-Based Practice Center's SRE and the Expert Panel's *Additional Literature or Information*. Further, the

source and level of the evidence used to justify Panel recommendations for sustaining or revising EPR-2 are noted in parentheses following the recommendation. (That is, the level of evidence is categorized A, B, C, or D according to the description below. If the source of the evidence is from the SRE, the category is preceded by the notation "SRE"; if the source is the Expert Panel's additional literature, there is no prefix.) The system used to describe the level of evidence is as follows (Jadad et al. 2000):

- **Evidence Category A: Randomized controlled trials (RCTs), rich body of data.** Evidence is from end points of well-designed RCTs that provide a consistent pattern of findings in the population for which the recommendation is made. Category A requires substantial numbers of studies involving substantial numbers of participants.

- **Evidence Category B: RCTs, limited body of data.** Evidence is from end points of intervention studies that include only a limited number of patients, post hoc or subgroup analysis of RCTs, or meta-analysis of RCTs. In general, Category B pertains when few randomized trials exist, they are small in size, they were undertaken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent.

- **Evidence Category C: Nonrandomized trials and observational studies.** Evidence is from outcomes of uncontrolled or nonrandomized trials or from observational studies.

- **Evidence Category D: Panel consensus judgment.** This category is used only in cases where the provision of some guidance was deemed valuable, but the clinical literature addressing the subject was insufficient to justify placement in one of the other categories. The Panel consensus is based on clinical experience or knowledge that does not meet the criteria for categories A through C.

As the Expert Panel members reviewed the scientific evidence and considered revisions to EPR-2, they identified areas that require further investigation to either fill important gaps found in the data or to pursue promising areas of research revealed by study findings. Each position statement includes recommendations for further research.

The Expert Panel prepared draft position statements in its respective writing committees during summer and fall 2001, and the drafts were edited during the winter. A series of drafts were discussed in three telephone conference calls (June 2001, October 2001, and February 2002) among the full Panel membership. Final agreement on each position statement was reached during these calls, including the specific recommendations within the position statements to either retain or revise EPR-2. A vote confirmed the unanimous agreement of the Panel. In March 2002, a draft was mailed to the NAEPP Coordinating Committee members for their review, comment, and approval. In April 2002, the Expert Panel reviewed the Coordinating Committee's suggested edits by e-mail and by telephone conference call and incorporated suggestions that were within the scope of the Coordinating Committee's approval. Expert Panel members' agreement on the final text was unanimous. The NAEPP EPR—Update 2002 was released in June 2002.

This report was funded by the NHLBI, National Institutes of Health. Expert Panel members disclosed relevant financial interests to each other prior to their deliberations. Expert Panel members and reviewers participated as volunteers and were compensated only for travel expenses related to the Expert Panel meeting.

In summary, the NAEPP *Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma—Update on Selected Topics 2002* represents the NAEPP's ongoing effort to keep recommendations for clinical practice up to date and based on systematic review and consideration of the best available scientific evidence, as well as on the collective expertise of the Expert Panel and Coordinating Committee members in asthma management. The NAEPP hopes that this report will assist clinicians and patients as they work together to achieve asthma control.

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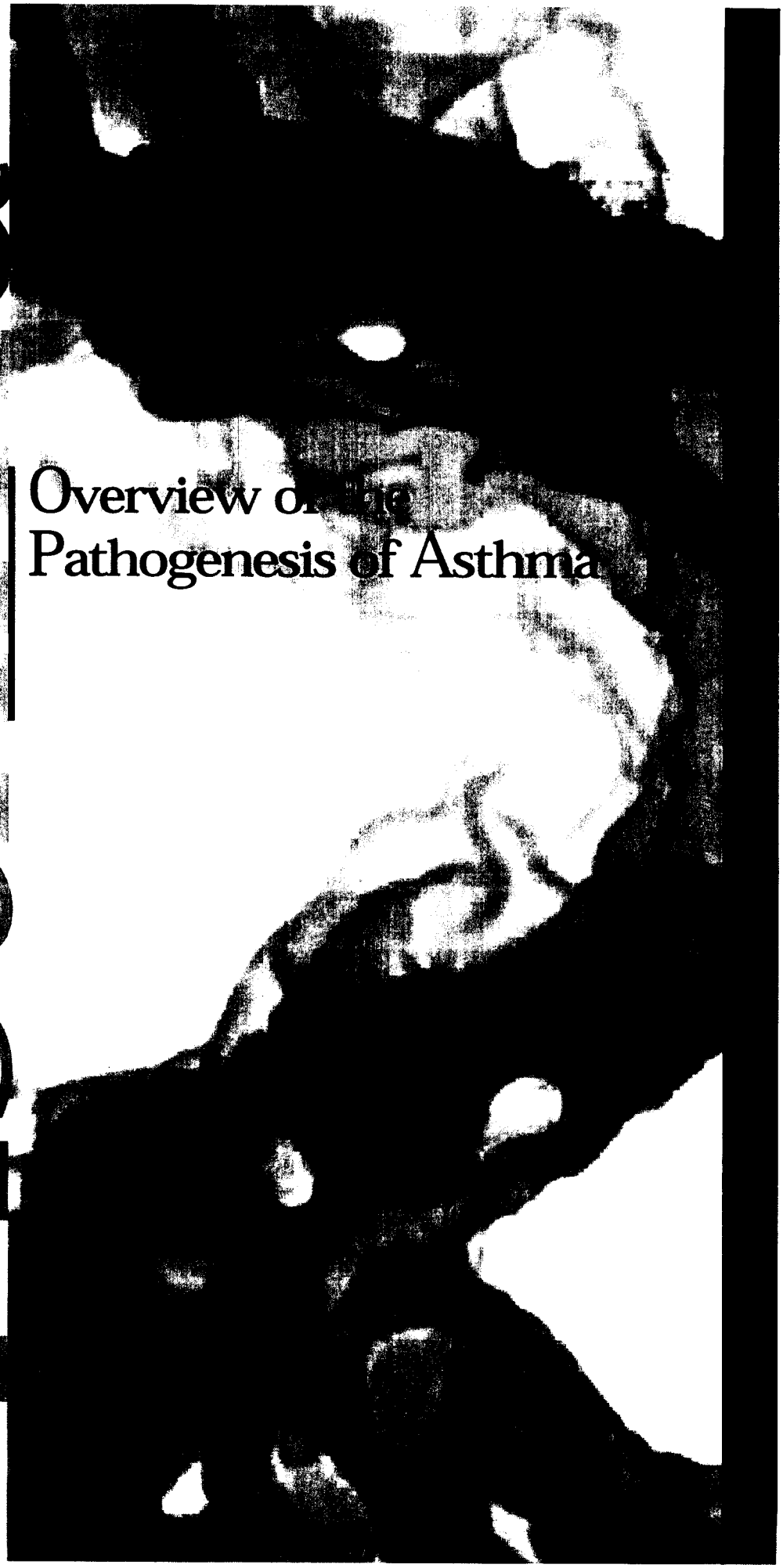
Asthma

Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma

Overview of the Pathogenesis of Asthma



Overview of the Pathogenesis of Asthma

An overview of current insights into the pathophysiology of asthma is presented here in order to provide a context in which recommendations regarding asthma treatment were made for the *EPR—Update 2002.*

The working definition of asthma, as proposed in the EPR-2 in 1997 (page 3)—

> *Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T lymphocytes, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli (NHLBI 1997).*

—continues to capture the features of asthma and underscores the importance of airway inflammation to the pathogenesis, pathophysiology, and treatment of this disease. Important additions to this definition include recent observations that reversibility may be incomplete in some patients with asthma, and other individuals with features of chronic bronchitis may manifest some degree of reversibility in airflow obstruction (Bousquet J. et al. 2000). Nonetheless, the study of asthma pathogenesis and its treatment continues to focus on inflammation as a target to control and regulate airflow obstruction and the resulting symptoms.

Recent studies have begun to categorize airway inflammation into phases, which although somewhat arbitrary in demarcation, provide insights into the possible progression of the disease as well as its management. Acute symptoms of asthma usually arise from bronchospasm and require and respond to bronchodilator therapy. Acute and chronic inflammation can affect not only the airway caliber and airflow but also underlying bronchial hyperresponsiveness, which results in susceptibility to bronchospasm. Treatment with anti-inflammatory drugs can, to a large extent, reverse some of these processes; however, the successful response to therapy often requires weeks to achieve and, in some situations, may be incomplete. Finally, some patients may have persistent airflow limitations for which no current therapy has been found to be effective. Therefore, the paradigm of asthma has been expanded from bronchospasm and airway inflammation to include airway remodeling in some patients. The concept that asthma may be a continuum of these processes that can lead to moderate and severe persistent disease is of critical importance to understanding this disease's pathogenesis and pathophysiology. As these questions undergo a constant evaluation, current treatment recommendations also must be reassessed.

Inflammation of Asthma

Airway inflammation in asthma is found in patients with mild, moderate, and severe disease. Although there are some universal features of this inflammatory response in the airway, the specifics of the bronchial reaction show variations, which are dependent upon the disease's severity, treatment, and duration. Infiltration of the airway by inflammatory cells such as activated lymphocytes and eosinophils, denudation of the epithelium, deposition of collagen in the subbasement membrane area, and mast cell degranulation are often, but not always, features of mild or moderate persistent asthma. In fatal disease and severe persistent asthma, other conditions occur, such as occlusion of the bronchial lumen by mucus, hyperplasia and hypertrophy of the bronchial smooth muscle, and goblet cell hyperplasia.

The cellular profile of inflammation in asthma provides evidence for the nature of the immune reaction of injury and remodeling or repair, the potential mechanisms by which such responses occur, the resulting alteration in physiology, and the possible therapeutic targets necessary to regulate, reverse, or prevent such events. IgE antibodies have been found to have a relationship to the severity of asthma and the airway's early response to allergens. The ability to synthesize IgE antibodies to environmental allergens (i.e., atopy) remains a major risk factor in asthma pathogenesis. Synthesized IgE binds to mast cells and basophils via high-affinity IgE receptors, and the bridging of these attached molecules signals the cells to release preformed and newly generated mediators, including histamine and cysteinyl leukotrienes, to rapidly contract airway smooth muscle. In addition, the mast cell can produce a variety of cytokines, including interleukin (IL)-1, -2, -3, -4, and -5 along with granulocyte-macrophage colony-stimulating factor, interferon (IFN)-γ, and tumor necrosis factor-α. The generation of these pro-inflammatory proteins suggests that mast cells can contribute to both acute and chronic inflammation.

Eosinophilic infiltration of the airway remains a consistent feature of acute inflammation and also is found in mucosal airway tissue from many patients with chronic, persistent asthma. The granule proteins of the mature eosinophil are sources of inflammatory mediators, including major basic protein, which can injure airway epithelium, enhance bronchial responsiveness, and affect the regulation of acetylcholine release. In addition, the eosinophil can release cysteinyl leukotrienes, such as C_4, to contract airway smooth muscle. The production of eosinophils and their release from the bone marrow are regulated by IL-5. Migration of these cells to the airway involves an interaction of eosinophil surface-bound integrins, β_1 and β_2, with endothelial cell and matrix tissue counterligands. Finally, recently identified families of chemokines (RANTES) eotaxin, and macrophage inflammatory protein-1α, participate in the migration of these cells to the airway. Although the eosinophil is a feature of asthma pathology that is known to be affected by anti-inflammatory therapy in a manner that improves airway physiology, its precise role in the pathophysiology of asthma is still under investigation.

An Imbalance Between Th1 and Th2 in the Origins of Asthma

The role of lymphocytes in the inception and progression of asthma continues to be of considerable importance. Since the 1997 EPR-2, there has been interest in the idea that an imbalance in T-helper (Th) 1 and Th2 cytokines may help explain and even predict the subsequent development of asthma. Airway inflammation in asthma may represent a loss of normal balance between two "opposing" populations of Th lymphocytes. Two types of Th lymphocytes have been characterized: Th1 and Th2. Th1 cells produce IL-2 and IFN-γ, which are critical in cellular defense mechanisms in response to infection. Th2, in contrast, generates a family of cytokines (IL-4, -5, -6, -9, and -13) that can mediate allergic inflammation. The current "hygiene hypothesis" of asthma illustrates how this cytokine imbalance may explain some of the dramatic increases in asthma prevalence in Westernized countries. This hypothesis is based on the assumption that the immune system of the newly born is skewed towards Th2 cytokine generation. Following birth, environmental stimuli such as infections will activate Th1 responses and bring the Th1/Th2 relationship to an appropriate balance. There is evidence that the incidence of asthma is reduced in association with certain infections (*M. tuberculosis,* measles, or hepatitis A); exposure to other children (e.g., presence of older siblings and early enrollment in childcare); and less frequent use of antibiotics. Furthermore, the absence of these lifestyle events is associated with the persistence of a Th2 cytokine pattern. Under these conditions, the genetic background of the child, with a cytokine imbalance toward Th2, will set the stage to promote the production of IgE antibody to key environmental antigens, such as house dust mite, cockroach, *Alternaria*, and possibly cat. Therefore, a gene-by-environment interaction occurs in which the susceptible host is exposed to environmental factors that are capable of generating IgE, and sensitization occurs. Precisely why the airways of some individuals are susceptible to these allergic events is not established.

There also appears to be a reciprocal interaction between the two subpopulations in which Th1 cytokines can inhibit Th2 generation and vice versa.

Allergic inflammation may be the result of an excessive expression of Th2 cytokines. Alternately, the possibility that the loss of normal immune balance arises from a cytokine dysregulation in which Th1 activity in asthma is diminished has been suggested in recent studies. The focus and actions of cytokines and chemokines to regulate and activate the inflammatory profile in asthma has provided ongoing and new insight into the pattern of airway injury that may lead to new therapeutic targets.

Because of the importance of IgE to the pathogenesis of allergic diseases and inflammation, the development of humanized monoclonal antibodies has become a possible treatment. Early studies in asthma have indicated that this approach can reduce serum IgE, inhibit the immediate and late airway response to inhaled antigen, and allow for a withdrawal of inhaled corticosteroids without deterioration in lung function or precipitation of an asthma exacerbation. The findings of anti-IgE monoclonal antibody therapy support the importance of IgE-mediated responses in asthma and suggest that IgE-regulated processes may encompass processes that influence inflammation other than mast-cell-dependent responses.

In addition, monoclonal antibodies against IL-5 recently have been tested in asthma. Anti-IL-5 has reduced circulating concentrations of eosinophils and their presence in sputum. However, despite the reduction (but not elimination) of eosinophils, there was no change in the development of the late-phase response to an inhaled antigen. These preliminary studies have raised questions about the specific role of IL-5 in mechanisms of airflow obstruction and of eosinophils in the pathophysiology of asthma. It appears to be an omnipresent cell in asthma, but how it participates in the disease process is not yet clear.

A soluble IL-4 receptor (IL-4R) has been developed for inhaled administration. This molecule acts as a decoy and is capable of binding to IL-4 and thus acting as an antagonist for that molecule. Although early studies that administered nebulized IL-4R showed that inhaled corticosteroid doses can be reduced without a loss of asthma control or lung function, subsequent trials with this molecule have failed to demonstrate effectiveness in asthma control.

A number of lessons can be learned from these early studies directed toward a single cytokine. Although modification of features of allergic inflammation can be seen in animals with genes that have "knocked out" selected cytokines, similar benefits have not necessarily been seen in human asthma. These findings underscore the relevancy of multiple factors regulating inflammation in asthma and the redundancy of these processes. Moreover, these clinical studies in human asthma also serve to indicate that phenotypes of asthma exist and that these phenotypes may have very specific patterns of inflammation. Nonetheless, as more clinical trials with modifiers of inflammation in asthma are performed, it is likely that a more comprehensive insight into the mechanisms of this disease will occur.

In summary, recent evidence continues to underscore the importance of immune factors in the development of asthma and resulting inflammation processes. Insight into the mechanisms of these processes will be important for future therapy. In the meantime, asthma therapy continues to focus on controlling underlying airway inflammation.

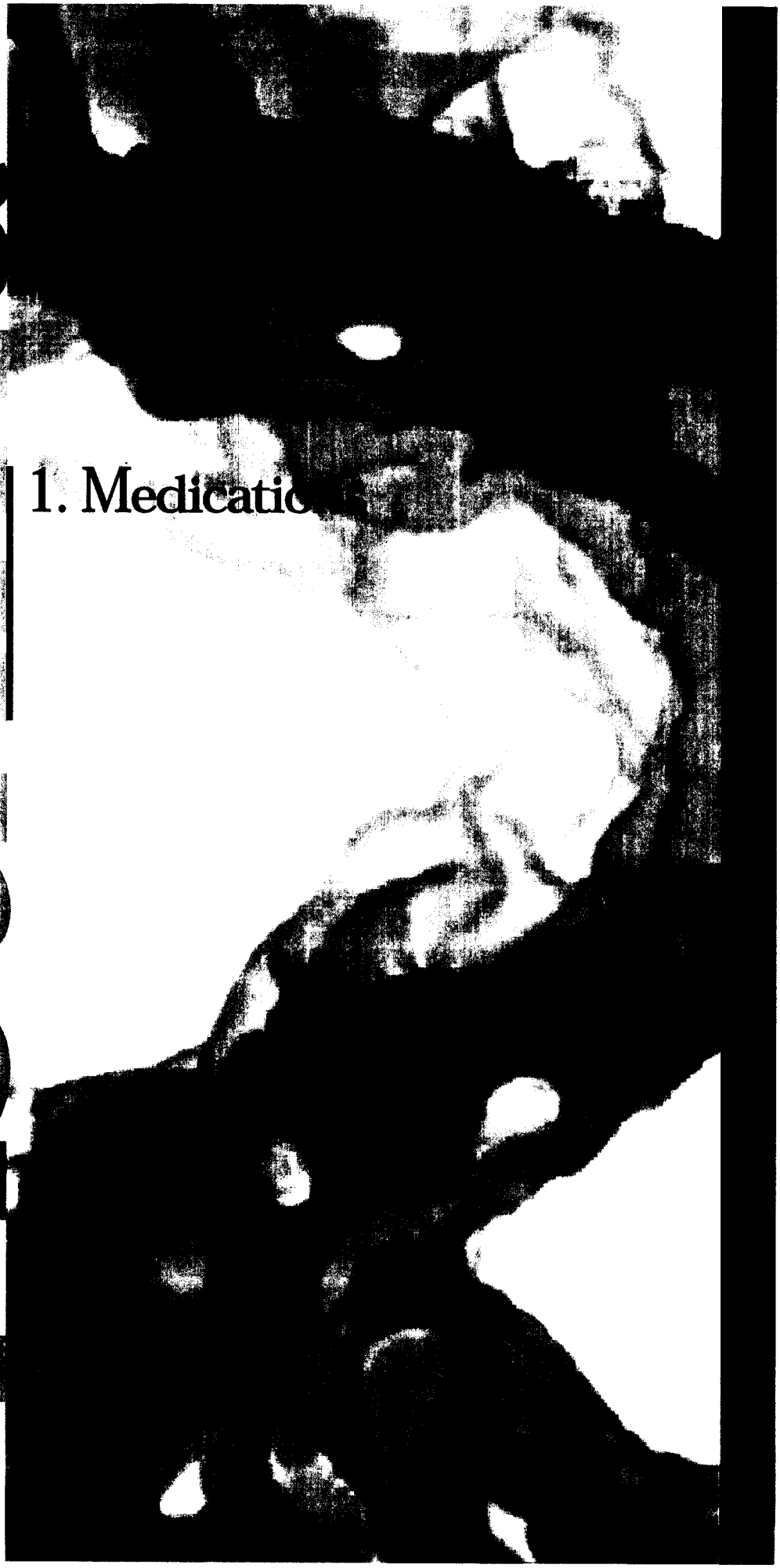
References

Bousquet J, Jeffery PK, Busse WW, Johnson M, Vignola AM. Asthma. From bronchoconstriction to airways inflammation and remodeling. *Am J Respir Crit Care Med* 2000;161(5):1720–45.

Asthma

Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma

1. Medicatio



1. Medications

Several clinical questions were considered by the NAEPP Expert Panel regarding medications used in asthma therapy, including questions about the effectiveness of inhaled corticosteroids compared to other long-term-control medications in the management of asthma in children, the safety of long-term use of inhaled corticosteroids in children, the use of combination therapy in treating moderate persistent asthma, and the use of antibiotics in treating acute exacerbations of asthma. This section on medications will present each clinical question separately, and each discussion will include a statement of the specific question; a summary answer to the question; the rationale for the question; a summary of the SRE, as well as additional literature considered by the Expert Panel after the systematic review was completed; recommendations for updating the EPR-2 and recommendations for future research.

Long-Term Management of Asthma in Children: Effectiveness of Inhaled Corticosteroids Compared to Other Medications

Question

Does chronic use of inhaled corticosteroids improve long-term outcomes for children with mild or moderate persistent asthma, in comparison to the following treatments?

- ***"As-needed" beta$_2$-agonists?***
- ***Long-acting beta$_2$-agonists?***
- ***Theophylline?***
- ***Cromolyn/nedocromil?***
- ***Combinations of above drugs?***

Leukotriene modifiers (leukotriene receptor antagonists [LTRAs] and 5-lipoxygenase inhibitors) were not included in the SRE because no published data meeting minimal inclusion criteria for children were available to compare this class of compounds directly to any other long-term-control medications, including inhaled corticosteroids. Studies on LTRAs in children that were published subsequent to the SRE were considered by the Expert Panel as additional information and included in the comprehensive review of the question.

Summary Answer to the Question

Strong evidence establishes that inhaled corticosteroids improve long-term outcomes for children of all ages with mild or moderate persistent asthma, compared to as-needed beta$_2$-agonists, as measured by prebronchodilator forced expiratory volume in 1 second (FEV_1), reduced hyperresponsiveness, improvements in symptom scores, fewer courses of oral corticosteroids, and fewer urgent care visits or hospitalizations (SRE-Evidence A). Studies comparing inhaled corticosteroids to cromolyn, nedocromil, theophylline, or LTRAs are limited, but available evidence shows that none of these long-term-control medications is as effective as inhaled corticosteroids in improving asthma outcomes (SRE-Evidence B; Evidence B, C). (See Appendix A, Stepwise Approach for Managing Asthma, for the definition of asthma severity classifications.) A revision to the EPR-2 stepwise approach to therapy is recommended. The Expert Panel recommends the following therapy for children with mild persistent asthma:

- For children older than 5 years of age, the preferred therapy is inhaled corticosteroids (low dose) (SRE-Evidence A). Alternative therapies (listed alphabetically because there are insufficient data to enable ranking) include cromolyn, LTRAs, nedocromil, or sustained-release theophylline (SRE-Evidence A, B; Evidence A, B).

- For children 5 years of age and younger, no studies compare inhaled corticosteroids to other long-term-control medications. Therefore, recommendations are based on extrapolations of studies in older children. The preferred therapy is low-dose inhaled corticosteroids, with nebulizer, dry powder inhaler (DPI), or metered-dose inhaler (MDI) with holding chamber, with or without a face mask. Alternative therapies (listed alphabetically) include cromolyn or LTRA (SRE-Evidence B).

Rationale for the Question

The NAEPP recognizes the need for continual appraisal of the benefits and potential risks of asthma medications in children. The EPR-2 recommends inhaled corticosteroids, cromolyn, and nedocromil as preferred treatment, with acknowledgement of a potential but small risk of adverse events with the use of inhaled corticosteroids. The NAEPP considers it important to update information regarding the effectiveness and safety of inhaled corticosteroids in children. A review of evidence on the safety of inhaled corticosteroids is presented in another section. To enrich the evaluation of effectiveness, the SRE searched the literature for studies comparing the effectiveness of inhaled corticosteroids used as monotherapy to short-acting beta$_2$-agonists taken as needed, and to other long-term-control medications used as monotherapy in children with mild or moderate persistent asthma. Such a review enables the NAEPP to consider the most appropriate position of various medications in the stepwise approach to asthma management, based on the current evidence. At the time that the EPR-2 was published, the following long-term-control medications were available for treatment in children: inhaled corticosteroids, long-acting inhaled beta$_2$-agonists (salmeterol), theophylline, cromolyn, nedocromil, and leukotriene modifiers (zafirlukast and zileuton); not all were approved for use in children younger than 5 years of age. Since the publication of the EPR-2, a third leukotriene modifier, montelukast, has become available for children 2 years of age and older, and a nebulized form of inhaled corticosteroids has become available for children as young as 1 year of age. The DPI forms of salmeterol and fluticasone, available for older children, also were approved down to 4 years of age.

Systematic Review of the Evidence

The following description of the SRE is an adaptation of the evidence report, including direct excerpts, submitted by the Blue Cross Blue Shield Association Evidence-Based Practice Center. (See Introduction, Methods.)

Methods of Literature Search

This question addresses long-term outcomes of treatment for children with mild or moderate persistent asthma. Outcomes of primary interest are those that indicate the progression of underlying disease; short-term measures of symptom control cannot adequately address this question. Of the available measures, longitudinal determination of postbronchodilator FEV_1 provides the best available measure of lung growth (CAMP Research Group 2000). Epidemiologic studies often use prebronchodilator FEV_1, which has been one of the strongest correlates with long-term outcomes. Peak expiratory flow (PEF) also can indicate long-term progression; both prebronchodilator FEV_1 and PEF are more subject to short-term changes in control and, of the two, PEF is the more variable measure. Other outcome measures, such as symptoms, medication use, and utilization measures, also are likely to correlate with long-term progression of disease over time, but are highly subject to changes in short-term control of bronchospasm.

In addition to the eligibility criteria for selecting studies related to all topics in the SRE (described in the Introduction), the following criteria were used to select studies for this question:

- Study design is a comparative or crossover clinical efficacy trial, with a concurrent control group.

- Study compares the use of inhaled corticosteroids vs. placebo; OR compares inhaled corticosteroids vs. no treatment control; OR compares inhaled corticosteroids vs. alternative medication for mild asthma (as-needed beta$_2$-agonists, theophylline, cromolyn, nedocromil, or combinations of these medications); OR compares *the addition of* inhaled corticosteroids to other medication for mild asthma (as-needed beta$_2$-agonists, theophylline, cromolyn, nedocromil, or combinations of these medications).

- Includes at least 10 evaluable, similarly treated patients per study arm or crossover phase with mild or moderate persistent asthma, with the following defined limits:
  - FEV_1 more than 60 percent of predicted; PEF variability more than 20 percent

  OR
  - Symptoms more than 2 times a week to daily

  OR
  - Nocturnal symptoms more than 2 times a month

  OR
  - Population cannot be classified into the above categories but appears to include primarily persons with mild or moderate persistent asthma

  OR
  - Population is mixed, but the majority appears to consist of persons with mild or moderate persistent asthma.

- Study duration is of at least 12 weeks.

- At least 90 percent of included patients have not been treated with other long-term-control medications (LTRAs, long-acting inhaled $beta_2$-agonists, inhaled corticosteroids) for at least 4 weeks before beginning to take inhaled corticosteroids.

- Enrolls only patients younger than 18 years of age or stratifies outcomes for patients younger than 18 years of age.

- Study addresses relevant outcomes.

Summary of Findings

Studies

Ten studies enrolling 2,210 patients met the inclusion criteria for this question. Three of the studies were based in the Netherlands (Hoekstra et al. 1996; Van Essen-Zandvliet et al. 1992; Verberne et al. 1997); two were from Scandinavia (Jonasson et al. 1998; Agertoft and Pedersen 1994); two from the United Kingdom (Storr et al. 1986; Connett et al. 1993); two from the United States (CAMP 2000; Tinkelman 1993); and one from Canada (Simons 1997). Nine of the 10 studies were randomized, double-blind, parallel-group trials. The most robust of these, the Childhood Asthma Management Program (CAMP) Research Group (CAMP 2000), is a three-arm trial enrolling 1,041 patients followed for 4 to 6 years that compared inhaled corticosteroids to nedocromil and with placebo. At present, the CAMP trial is the "largest, longest, and most comprehensive multicenter treatment trial for asthma ever attempted in the United States"(CAMP 2000). The remaining eight randomized trials are considerably smaller in size (range: 14 to 102 patients per study arm) and duration of followup (range: 1 to 2 years). The tenth trial (Agertoft and Pedersen 1994) was not randomized. (See the key evidence tables in this section for a summary description of the 10 studies that met the eligibility criteria for evaluation.) Publications comparing the use of LTRA in children to other long-term-control medications were not available at the time of the SRE.

Results of Studies

Inhaled Corticosteroids Compared to As-Needed $Beta_2$-Agonists

Children Older than 5 Years of Age

The evidence of the efficacy of inhaled corticosteroids in children older than 5 years of age was obtained from six trials, five of which were placebo controlled and randomized. These six trials enrolled a total of 790 patients treated with inhaled corticosteroids and 652 controls. The most robust evidence is from the CAMP trial, which contributed 40 percent (311) of the total inhaled corticosteroid patients and 64 percent (418) of the total controls, documented the longest duration of treatment (4 years), used the most complete outcome measures, and reported in the greatest detail the study design and statistical analysis.

Overall, these studies demonstrate that inhaled corticosteroids improve asthma control compared to as-needed $beta_2$-agonists without any other long-term-control medication. Inhaled corticosteroid-treated patients with mild or moderate persistent asthma demonstrate improvements in prebronchodilator FEV_1, reduced airway hyperresponsiveness, symptom scores and symptom frequency, less supplemental $beta_2$-agonist use, fewer courses of oral corticosteroids, and lower hospitalization utilization. The evidence does not

suggest, however, that inhaled corticosteroid use is associated with improved long-term postbronchodilator FEV_1 which is a surrogate measure of lung growth. The CAMP trial reported no difference in the change in postbronchodilator FEV_1 after 4 years of treatment (CAMP 2000). No study reported any statistically significant result that favored the as-needed $beta_2$-agonist control group.

Children 5 Years of Age or Younger
Two small trials (69 participants, combined) compared inhaled corticosteroid treatment to placebo in children younger than 5 years of age. The available evidence is scant, but the results reported appear to be consistent with those reported for children older than 5 years of age: that inhaled corticosteroids improve short-term control of asthma. No studies that examine the long-term impact of inhaled corticosteroids on lung function in this age group are available.

Inhaled Corticosteroids Compared to Alternative Long-Term-Control Medications

No comparison studies are available for children younger than 5 years of age.

Long-Acting Inhaled $Beta_2$-Agonist (Salmeterol)
The available evidence is inadequate to make definitive conclusions about relative effectiveness of inhaled corticosteroids and salmeterol in children with mild or moderate persistent asthma. Two randomized and double-blinded trials enrolled 116 (99 evaluable) children treated with inhaled corticosteroids, 112 (83 evaluable) children treated with salmeterol, and 80 (55 evaluable) children treated with placebo. One of these is a three-arm trial in which most comparisons were indirect and reported as inhaled corticosteroids vs. placebo and salmeterol vs. placebo. Of the statistically significant results reported, most were significant in only one of the two trials; however, all results clearly favored inhaled corticosteroids over salmeterol as monotherapy. In one of the trials, measurements of FEV_1 deteriorated over time in those children receiving monotherapy with salmeterol (Verberne et al. 1997).

Theophylline
One trial compared the effectiveness of 1 year of treatment with theophylline or low-dose inhaled corticosteroids in 747 patients, 185 of whom were children (Reed 1998). Although conclusions are limited because of the large numbers of withdrawals and the absence of additional trials, the data from this study support the superior effectiveness for low-dose inhaled corticosteroids compared to theophylline. The inhaled corticosteroids were significantly more effective in reducing symptoms, supplemental bronchodilators and systemic corticosteroid doses, bronchial hyperresponsiveness, and eosinophilia. No outcomes were significantly superior with theophylline, which caused more headaches, nervousness, insomnia, and gastrointestinal distress; and more patients discontinued treatment because of side effects that occurred while they were taking theophylline.

Nedocromil
The CAMP trial found no differences between nedocromil and placebo in lung function or symptom outcomes, although courses of oral corticosteroids and urgent care visits were reduced (CAMP 2000). The primary analysis in this study compares two medications—nedocromil and inhaled corticosteroids—to placebo, rather than to each other. However, the magnitude of the effect of inhaled corticosteroids on all clinical outcomes, along with the marginal effect of nedocromil on just two, supports the conclusion that inhaled corticosteroids are more effective than nedocromil in reducing the frequency and severity of symptoms, supplemental $beta_2$-agonist use, and the frequency of hospitalizations due to asthma.

Additional Literature/Information

Additional data were reviewed to include information that was published since the SRE was performed and to consider leukotriene modifiers.

Inhaled Corticosteroids

A recent study confirmed the effectiveness of inhaled corticosteroids in improving symptoms, airway hyperresponsiveness, and lung function in children 2 to 5 years of age (Nielsen and Bisgaard 2000).

Cromolyn and Nedocromil

A consideration of the precise relationship of cromolyn and nedocromil among other long-term-control medications in the treatment of persistent asthma continues to be difficult based on the few available comparison studies. These two medications have distinct properties but similar mechanisms of action. They have been shown to provide symptom control greater than placebo in some clinical trials (Konig 1997; Petty et al. 1989) and to confer protection against exacerbations of asthma leading to hospitalization, particularly in children (Donahue et al. 1997) and emergency department visits (Adams et al. 2001). These results, along with the excellent safety profile, justify consideration of these medications as treatment options. However, when data regarding the efficacy of cromolyn recently were systematically reviewed (Tasche et al. 2000), the authors concluded that insufficient evidence existed to conclude that cromolyn had a beneficial effect on maintenance treatment of childhood asthma. Compared to placebo, nedocromil reduces urgent care visits as well as the need for prednisone, which are meaningful clinical outcomes. However, nedocromil is no different than placebo on all other outcome measures (CAMP 2000). Overall, nedocromil is significantly less effective in improving outcome measures than inhaled corticosteroids (CAMP 2000). Nedocromil has not been adequately studied in children younger than 5 years of age.

As a result of these disparate findings on cromolyn and nedocromil (i.e., some, but limited effectiveness and strong safety profile), the Expert Panel's opinion is that cromolyn for children of all ages and nedocromil for children older than 5 years of age could be considered in the treatment of persistent asthma, but they are not preferred therapies (SRE-Evidence A; Evidence B, C).

Leukotriene Modifiers

Leukotriene modifiers comprise two pharmacologic classes of compounds: 5-lipoxygenase pathway inhibitors (e.g., zileuton), and LTRAs (e.g., zafirlukast and montelukast). Only zafirlukast (for children as young as 7 years of age) (Pearlman et al. 2000; Weinberger 2000) and montelukast (for children as young as 2 years of age) (Knorr et al. 1998; Knorr et al. 2001) are approved for use in children. Zileuton has been demonstrated to control asthma more effectively than placebo (Israel et al. 1996) and comparably to theophylline (Schwartz et al. 1998) in adult patients with persistent symptoms; studies in children have not been reported yet.

The LTRAs have been demonstrated to provide statistically significant but modest improvement in lung function when used as monotherapy in both adults and children as young as 6 years of age and in asthma control outcomes other than lung function in patients as young as 2 years of age (Pearlman et al. 2000; Knorr et al. 1998; Knorr et al. 2001; Israel et al. 1996; Schwartz et al. 1998; Altman et al. 1998; Busse et al. 2001; Kemp et al. 1998; Nathan et al. 1998; Tashkin et al. 1999; Bleecker et al. 2000; DuBuske et al. 1997). In general, these studies included patients with either mild or moderate persistent asthma, although the classification of severity was not always clear in the studies, nor consistently applied. When comparing overall efficacy of LTRAs to inhaled corticosteroids in adult patients with persistent asthma, most outcome measures significantly and clearly favored inhaled corticosteroids (Busse et al. 2001). Therefore, based on the available data comparing LTRAs to inhaled corticosteroids, the Expert Panel concludes that inhaled corticosteroids should be the preferred treatment option for mild persistent asthma in adults and, by extrapolation until published comparison data become available, for children (Evidence B, C). (See Medications: Combination Therapy for recommendations on the use of LTRAs in moderate asthma.) Due to the lack of randomized controlled trials (RCTs) in children less than 12 years of age, zileuton cannot be recommended for use in children.

Long-Acting Inhaled Beta$_2$-Agonists

In a recent study, 164 patients ages 12 through 65 years whose asthma was well controlled on 400 mcg twice daily of inhaled corticosteroids were randomly assigned to continue inhaled corticosteroids or switch to long-acting inhaled beta$_2$-agonists, 42 mcg twice daily. During the 16-week study, clinical outcomes did not differ significantly. However, those

on long-acting inhaled beta$_2$-agonists experienced significantly more treatment failures (24 percent vs. 6 percent) and asthma exacerbations (20 percent vs. 7 percent) than those remaining on inhaled corticosteroids (Lazarus et al. 2001). These results, favoring use of inhaled corticosteroids over long-acting beta$_2$-agonists as monotherapy, support the findings of the studies in children that were noted in the SRE.

Recommendations for EPR Update

The Expert Panel recommends revising EPR-2, based on review of the SRE and additional data and clinical experience. The following key changes are described:

- Based on the SRE, inhaled corticosteroids are the preferred treatment for initiating therapy in children of all ages with persistent asthma (SRE-Evidence A, B). Thus, the Expert Panel no longer recommends consideration of an initial therapeutic trial with cromolyn or nedocromil. Current scientific evidence demonstrates the superiority of inhaled corticosteroids.

- LTRAs are available for children as young as 2 years of age, and studies have demonstrated improved outcomes (Evidence B). LTRAs are an alternative—although not preferred—treatment (Evidence B) and are considered if patient circumstances regarding administration of inhaled corticosteroids warrants selection of oral treatment (Evidence D).

- Based on epidemiologic study of wheezing in early childhood, it is the opinion of the Expert Panel that the initiation of long-term-control therapy should be considered strongly for infants and young children who in the past year have had more than three episodes of wheezing that lasted more than 1 day and affected sleep, and who in addition have identifiable risk factors for the development of asthma (Evidence D). This is in addition to previously recommended indications for initiating long-term-control therapy (i.e., children requiring symptomatic treatment more than 2 times a week or experiencing severe exacerbations less than 6 weeks apart).

Specifically, the Expert Panel recommends that the text of EPR-2 be revised to read as follows in the EPR-2 sections: The Medications and the Stepwise Approach for Managing Asthma; the blue text indicates new text.

Recommended changes to The Medications (pages 59 through 67 in EPR-2)

Key Points: The Medications (page 59 in EPR-2):

- **Cromolyn and nedocromil:** Used as alternative, but not preferred, medications for the treatment of mild persistent asthma (Evidence A, B). Can also be used as preventive treatment prior to exercise or unavoidable exposure to known allergens.

- **Long-acting inhaled beta$_2$-agonists:** Long-acting bronchodilator used concomitantly with inhaled corticosteroids is the preferred combination therapy for long-term control and prevention of symptoms in moderate and severe persistent asthma (Evidence A, B). Also prevents exercise-induced bronchospasm (EIB).

- **Leukotriene modifiers:** The leukotriene receptor antagonists (LTRAs) montelukast (for patients ≥ 2 years of age) and zafirlukast (for patients ≥ 7 years of age), or the 5-lipoxygenase inhibitor zileuton (for patients ≥12 years of age), are alternative, but not preferred, therapies for the treatment of mild persistent asthma (Evidence B). Leukotriene modifiers also may be used with inhaled corticosteroids as combination therapy in the treatment of moderate persistent asthma (Evidence B).

Corticosteroids (page 60 in EPR-2)

Insert after the third sentence.

The evidence of the efficacy of inhaled corticosteroids in children older than 5 years of age was obtained from six trials, five of which were placebo controlled and randomized (see EPR Update-2002 for complete references). Overall, these studies demonstrate that inhaled corticosteroids improve asthma control compared to as-needed beta$_2$-agonists without any other long-term-control medication (Evidence A). Inhaled corticosteroid-treated patients with mild or moderate persistent asthma demonstrate improvements in pre-bronchodilator FEV_1, reduced airway

hyperresponsiveness, symptom scores and symptom frequency, less supplemental beta$_2$-agonist use, fewer courses of oral corticosteroids, and lower hospitalization utilization. The evidence does not suggest, however, that inhaled corticosteroid use is associated with improved long-term postbronchodilator FEV_1, which is a surrogate measure of lung growth. No study reported any statistically significant result that favored the as-needed beta$_2$-agonist control group. Studies comparing inhaled corticosteroids to cromolyn, nedocromil, theophylline, or LTRAs are limited, but available evidence shows that none of these long-term-control medications appear to be as effective as inhaled corticosteroids in improving asthma outcomes (Evidence A, B).

Cromolyn Sodium and Nedocromil (page 60 in EPR-2)

Replace the third paragraph of text with the following.

Cromolyn sodium and nedocromil have been shown to provide symptom control greater than placebo in some clinical trials (Konig 1997; Petty et al. 1989) and to confer protection against exacerbations of asthma leading to hospitalization, particularly in children (Donahue et al. 1997) and emergency department visits (Adams et al. 2001) These results, along with the excellent safety profile, justify consideration of these medications as treatment options. However, when data regarding the efficacy of cromolyn recently were systematically reviewed (Tasche et al. 2000), the authors concluded that insufficient evidence existed to conclude that cromolyn had a beneficial effect on maintenance treatment of childhood asthma. Compared to placebo, nedocromil reduces urgent care visits as well as the need for prednisone, which are meaningful clinical outcomes. However, nedocromil is no different than placebo on all other outcome measures (CAMP 2000). Overall, nedocromil is significantly less effective in improving outcomes measures than inhaled corticosteroids (CAMP 2000). Nedocromil has not been adequately studied in children younger than 5 years of age. As a result of these disparate findings on cromolyn and nedocromil (i.e., some, but limited effectiveness and strong safety profile), the Expert Panel's opinion is that cromolyn for children of all ages and nedocromil for children older than 5 years of age could be considered in the treatment of persistent asthma, but they are not preferred therapies (Evidence A, B, C).

Leukotriene Modifiers (page 65 in EPR-2)

Replace the second paragraph of text with the following.

Three leukotriene modifiers—montelukast, zafirlukast and zileuton—are available as oral tablets for the treatment of asthma. Leukotriene modifiers comprise two pharmacologic classes of compounds: 5-lipoxygenase pathway inhibitors (e.g., zileuton), and LTRAs (e.g., montelukast and zafirlukast). Only zafirlukast (for children as young as 7 years of age) and montelukast (for children as young as 2 years of age) are approved for use in children. Zileuton has been demonstrated to control asthma more effectively than placebo (Israel et al. 1996) and comparably to theophylline (Schwartz et al. 1998) in adult patients with persistent symptoms; studies in children have not been reported yet.

The LTRAs have been demonstrated to provide statistically significant but modest improvement in lung function when used as monotherapy in both adults and children as young as 6 years of age and in asthma control outcomes other than lung function in patients as young as 2 years of age (Pearlman et al. 2000; Knorr et al. 1998; Knorr et al. 2001; Israel et al. 1996; Schwartz et al. 1998; Altman et al. 1998; Busse et al. 2001; Kemp et al. 1998; Nathan et al. 1998; Tashkin et al. 1999; Bleecker et al. 2000; DuBuske et al. 1997). In general, these studies included patients with either mild or moderate persistent asthma, although the classification of severity was not always clear in the studies, nor consistently applied. When comparing overall efficacy of LTRAs to inhaled corticosteroids in adult patients with persistent asthma, most outcome measures significantly and clearly favored inhaled corticosteroids (Busse et al. 2001).

Insert as the final paragraph.

Therefore, based on the available data comparing LTRAs to inhaled corticosteroids, the Expert Panel concludes that inhaled corticosteroids should be the preferred treatment option for mild persistent asthma in adults, and by extrapolation until published com-

parison data become available, for children (Evidence B, C). Five published studies evaluated the addition of leukotriene modifiers to fixed doses of inhaled corticosteroids; none compared the combination to increasing the dose of inhaled corticosteroids. Limitations of these studies preclude definitive conclusions, but they reveal a trend showing improvement in lung function and, in some, symptoms from the combination of leukotriene modifiers and inhaled corticosteroids compared with a fixed dose of inhaled corticosteroids alone.

Figure 3–1. Long-Term-Control Medications (page 63 in EPR-2)

Long-Acting Inhaled Beta$_2$-Agonists. Add in "Therapeutic Issues" column: Treatment of choice in combination with inhaled corticosteroids for treatment of moderate persistent asthma in adults and children over 5 years of age.

Leukotriene Modifiers. Add: Montelukast tablets: long-term control and prevention of symptoms in mild persistent asthma for patients ≥2 years of age. May also be used with inhaled corticosteroids as combination therapy in moderate persistent asthma. Zafirlukast: Change age zafirlukast to ≥7 years of age. And add: May also be used with inhaled corticosteroids as combination therapy in moderate persistent asthma. Zileuton: add: May also be used with inhaled corticosteroids as combination therapy in moderate persistent asthma.

Figure 3–2. Quick-Relief Medications (page 64 in EPR-2)

Short-Acting Inhaled Beta$_2$-Agonists. Add: Levalbuterol

Recommended changes to The Stepwise Approach to Managing Asthma; mild persistent asthma (step 2 care) (pages 85 through 97 in EPR-2).

Revisions of EPR-2 on moderate persistent asthma (step 3 care) are presented in the section "Medications: Combination Therapy."

Figure 3–4b. Stepwise Approach for Managing Asthma in Adults and Children Older than 5 Years of Age: Treatment (page 85 in EPR-2)

Step 2
Mild Persistent
One daily long-term-control medication
Preferred treatment:
Inhaled corticosteroids (low dose)
Alternative treatment (listed alphabetically):
Cromolyn
OR
Leukotriene modifier (only LTRAs are recommended for use in children)
OR
Nedocromil
OR
Sustained release theophylline to serum concentrations of 5–15 μg/mL.

Step 3 and Step 4
Please refer to the Medications: Combination Therapy on page 56 of this report.

Key Recommendations box for managing asthma in school-age children and adolescents (page 97 in EPR-2)

- Pulmonary function testing should use appropriate reference populations. Adolescents compare better to childhood than to adult predicted norms.
- When initiating daily long-term-control therapy for mild or moderate persistent asthma, the choice of medication includes consideration of treatment effectiveness, the individual patient's history of previous response to therapies, the ability of the patient and family to correctly use the medication, and anticipated patient and family adherence with the treatment regime (Evidence D).
- Adolescents (and younger children when appropriate) should be directly involved in establishing goals for therapy and developing their asthma management plans.
- Active participation in physical activities, exercise, and sports should be promoted.

- A written asthma management plan should be prepared for the student's school and should include plans to ensure reliable, prompt access to medications. Either encourage parents to take a copy to the child's school or obtain parental permission and send a copy to the school nurse or designee (Evidence D).

Figure 3–6. Stepwise Approach for Managing Infants and Young Children (5 Years of Age and Younger) With Acute or Chronic Asthma Symptoms (page 96 in EPR-2)

Step 2
Mild Persistent
One daily long-term-control medication
Preferred treatment:
Low-dose inhaled corticosteroids (with nebulizer OR MDI with holding chamber with or without a face mask OR DPI)
Alternative treatment (listed in alphabetical order):
Cromolyn (nebulizer is preferred; or MDI with holding chamber)
OR
Leukotriene receptor antagonist.

Step 3
Moderate Persistent
Preferred treatments:
Low-dose inhaled corticosteroids and long-acting inhaled beta$_2$-agonists
OR
Medium-dose inhaled corticosteroids
Alternative treatment:
Low-dose inhaled corticosteroids and either LTRA or theophylline.

If needed (particularly in patients with recurring severe exacerbations):
Preferred treatment:
Medium-dose inhaled corticosteroids and long-acting beta$_2$-agonists.
Alternative treatment:
Medium-dose inhaled corticosteroids and either LTRA or theophylline.

Special considerations for managing asthma in different groups: infants and young children (5 years of age and younger), key recommendations (pages 94 through 97 in EPR-2)

- Diagnosing asthma in infants is often difficult, yet underdiagnosis and undertreatment are key problems in this age group. Thus, a diagnostic trial of inhaled bronchodilators and anti-inflammatory medications may be helpful.

- Treatment for infants and young children with asthma has not been adequately studied. Recommendations for treatment are based on extrapolations from studies in older children and adults.

- The initiation of long-term-control therapy should be strongly considered in the following circumstances, in the opinion of the Expert Panel (Evidence D):

  - Infants and young children who had more than three episodes of wheezing in the past year that lasted more than 1 day and affected sleep AND who have a high risk of developing persistent asthma as indicated by either (a) a physician diagnosis of atopic dermatitis or a parental history of asthma OR (b) two of the following conditions: physician-diagnosed allergic rhinitis, greater than 4 percent peripheral blood eosinophilia, or wheezing apart from colds (Martinez et al. 1995; Martinez 1995; Castro-Rodriguez 2000).

  - Infants and young children consistently requiring symptomatic treatment more than 2 times per week should be given daily long-term-control therapy.

  - Infants and young children who have severe exacerbations (requiring inhaled beta$_2$-agonist more frequently than every 4 hours over 24 hours) that occur less than 6 weeks apart.

- When initiating daily long-term-control therapy, inhaled corticosteroids are the preferred treatment (SRE-Evidence B). Alternative treatment options (listed here in alphabetical order because there are insufficient data to enable ranking) include cromolyn and LTRA (montelukast) (Evidence B). The initial choice of long-term-control medication includes consideration of treatment effectiveness, the individual patient's history of previous response to therapies, the ability of the patient and family to correctly use the medication, and anticipated patient and family adherence to the treatment regimen (Evidence D).

- Response to therapy should be carefully monitored. Once control of asthma symptoms is established and sustained, a careful step down in therapy should be attempted. If clear benefit is not observed within 4 to 6 weeks, alternative therapies or diagnoses should be considered (Evidence D).

Diagnosis

Several studies show that as many as 50 to 80 percent of children with asthma develop symptoms before their fifth birthdays. Diagnosis can be difficult in this age group and has important implications. On the one hand, asthma in early childhood is frequently underdiagnosed (receiving such labels as chronic bronchitis, wheezy bronchitis, recurrent pneumonia, gastroesophageal reflux, and recurrent upper respiratory tract infections), and thus many infants and young children do not receive adequate therapy. On the other hand, not all wheezes and coughs are caused by asthma, and caution is needed to avoid giving infants and young children inappropriately prolonged asthma therapy. Episodic or chronic wheezing, coughing, and breathlessness also may be seen in other less common conditions, including cystic fibrosis, vascular ring, tracheomalacia, primary immunodeficiency, congenital heart disease, parasitic disease, and foreign body aspiration.

Among children 5 years of age and younger, the most common cause of asthma-like symptoms is viral respiratory infection. At present, the relative contributions of airway inflammation, bronchial smooth-muscle abnormalities, or other structural factors in producing wheeze with acute viral upper respiratory infections are unknown. There appear to be two general patterns of illness in infants and children who wheeze with acute viral upper respiratory infections: a remission of symptoms in the preschool years and persistence of asthma throughout childhood. No clear markers are available to predict the prognosis of an individual child; however, in infants and young children under 5 years of age with frequent wheezing (for example, more than three episodes in the past year that lasted more than 1 day and affected sleep), risk factors significantly associated with persistent asthma at 6 years of age include having either (a) parental asthma history or a physician diagnosis of atopic dermatitis or (b) two of the following conditions: physician-diagnosed allergic rhinitis, peripheral blood eosinophilia, or wheezing apart from cold (Evidence C) (Castro-Rodriguez et al. 2000; Martinez 1995). Although currently not established, it is conceivable that early recognition and treatment of these high-risk children could result in secondary prevention of childhood asthma.

Diagnosis is complicated by the difficulty in obtaining objective measurements of lung function in this age group. Essential elements in the evaluation include the history, symptoms, physical examination, and assessment of quality of life. A therapeutic trial with medications listed in figure 3–5d also will aid in the diagnosis.

Treatment

Figure 3–6 illustrates the Expert Panel's recommendations for a stepwise approach to managing acute and chronic asthma symptoms, regardless of the prognosis for the wheezing infant or young child.

It is the opinion of the Expert Panel that, in general, daily long-term-control therapy should be initiated in infants and young children consistently requiring symptomatic treatment more than 2 times per week and in infants and young children who experience severe exacerbations (requiring inhaled beta$_2$-agonist more frequently than every 4 hours over 24 hours) that occur less than 6 weeks apart. It is the opinion of the Expert Panel that the initiation of long-term-control therapy should also be strongly considered in infants and young children who had more than three episodes of wheezing in the past year that lasted more than 1 day and

affected sleep AND who have risk factors for developing persistent asthma: either (a) parental history of asthma or a physician diagnosis of atopic dermatitis or (b) two of the following conditions: physician-diagnosed allergic rhinitis, greater than 4 percent peripheral blood eosinophilia, or wheezing apart from colds (Evidence D).

The following have been Food and Drug Administration (FDA)-approved for young children: the inhaled corticosteroids budesonide nebulizer solution (approved for children 1 to 8 years of age) and fluticasone DPI (approved for children 4 years of age and older); the long-acting beta$_2$-agonist salmeterol DPI (approved for children 4 years of age and older); and, based on safety data rather than efficacy data, the LTRA montelukast 4 mg chewable tablet (approved for children 2 to 6 years of age).

At present, there are few studies of medications in children younger than 3 years of age. A therapeutic trial of anti-inflammatory medications should be monitored carefully. Treatment should be stopped if a clear beneficial effect is not obvious within 4 to 6 weeks. Inhaled corticosteroids have been shown to be effective in long-term clinical studies with infants; in contrast, cromolyn has inconsistently demonstrated symptom control in children younger than 5 years of age (Tasche et al. 2000). A LTRA (montelukast) 4 mg chewable tablet has shown some effectiveness in children 2 to 5 years of age (Knorr et al. 2001). Sustained-release theophylline is not recommended as an alternative long-term-control medication for young children with mild persistent asthma because it may have particular risks of adverse side effects in infants who frequently have febrile illnesses, which increase theophylline concentrations. Theophylline may be considered as adjunctive therapy in young children with moderate or severe persistent asthma if there are cost considerations, but only if serum concentration levels will be carefully monitored.

In deciding when to initiate daily long-term-control therapy, the clinician must weigh the possible long-term effects of inadequately controlled asthma vs. the possible adverse effects of medications given over prolonged periods. There is evidence that anti-inflammatory treatment can reduce morbidity from wheezing in early childhood (Connett et al. 1993). Long-term studies in children 5 to 12 years of age at the time of enrollment conclude that inhaled corticosteroids improve health outcomes for children with mild or moderate persistent asthma and that the potential albeit small risk of delayed growth from the use of inhaled corticosteroids is well balanced by their effectiveness (CAMP 2000). Further, available long-term data indicate that most children treated with recommended doses of inhaled corticosteroids achieve their predicted adult heights (Agertoft and Pedersen 2000). It is noted that the long-term prospective studies on growth involved budesonide, and that the retrospective analyses included studies on beclomethasone, but the results have been generalized to include all inhaled corticosteroid preparations. Although different preparations and delivery devices may have a systemic effect at different doses, all short-term studies on numerous preparations suggest that the effect of inhaled corticosteroids on growth is a drug class effect. In children with demonstrable adverse effects related to inhaled corticosteroid therapy, other options (cromolyn, LTRA, nedocromil, or theophylline) for initiating and maintaining long-term-control therapy are available. **Thus, based on high-quality evidence, the Expert Panel recommends long-term-control therapy for children with mild or moderate persistent asthma because it provides control and prevention of asthma symptoms (SRE-Evidence A). However, evidence to date is insufficient to permit conclusions regarding whether early vs. delayed intervention with daily long-term-control medication will alter the underlying course of the disease.** Although a preliminary study suggests that appropriate control of childhood asthma may prevent more serious asthma or irreversible obstruction in later years (Agertoft and Pedersen 1994), these observations were not verified in a recent long-term randomized controlled trial in children ages 5 to 12 years (CAMP 2000). The best available evidence does not support the assumption that children 5 to 12 years of age with mild or moderate persistent asthma have a progressive decline in lung function that can be prevented by early initiation of long-term-control medications. Observational prospective data from other large groups of children suggest that the timing of the CAMP intervention was too late, as

most loss of lung function in early childhood asthma appears to occur during the first 3 to 5 years of life (Martinez et al. 1995). However, it has not yet been determined whether early recognition of children at high risk of developing persistent asthma coupled with early therapeutic intervention will either prevent the loss of lung function or prevent the development of persistent disease. Currently, critical prospective studies to address these issues are in progress.

Recommendations for treating infants and young children at different steps of care include:

- **The patient's response to therapy should be monitored carefully. When benefits are sustained for 2 to 4 months, a step down in therapy should be attempted. If there are no clear benefits within 4 to 6 weeks, treatment should be stopped and alternative therapies or diagnoses should be considered (Evidence D).**

- **For step 2 care (mild persistent asthma), daily long-term-control therapy with an inhaled corticosteroid is the preferred option; cromolyn and LTRA are alternative therapies, (SRE-Evidence A, B; Evidence B). A trial of LTRA in children 2 years of age or older can be considered in situations in which inhaled medication delivery is suboptimal due to poor technique or adherence (Evidence D).**

- **When inhaled corticosteroids are introduced in step 2 care, doses should be in the low range. Inhaled corticosteroids are now available in both MDI and nebulizer preparations. (See figures 3–5b and 3–5c in EPR-2 for discussion of equivalency among preparations.)**

- For step 3 care (moderate persistent asthma), there are no data available that compare treatments in step 3 care for infants and young children whose asthma is not well controlled on low doses of inhaled corticosteroids. Recommendations are based on expert opinion and extrapolation from studies in older patients. (See Medications: Combination Therapy.) **There are two main choices for step 3 care therapy: adding long-acting inhaled beta$_2$-agonists to low-dose inhaled corticosteroids (SRE-Evidence B; extrapolation from studies in older children) OR increasing the dose of inhaled corticosteroids within the medium-dose range (Evidence D).** Alternative but not preferred options are adding either a LTRA or theophylline (if serum concentrations are monitored) to low-to-medium doses of inhaled corticosteroids (Evidence D).

Comparative studies in older children and adults consistently favor combination therapy over increasing doses of inhaled corticosteroids. Because studies indicate that the potential for side effects of inhaled corticosteroids, though small, appears to be dose related and has been demonstrated in this age group at the medium-dose range of inhaled corticosteroids (Bisgaard 2002), the approach of adding long-acting inhaled beta$_2$-agonists to a lower dose of inhaled corticosteroids is one preferred option (Evidence B-extrapolating from adult studies). On the other hand, there are no data on long-acting beta$_2$-agonists in children under 4 years of age, and studies in infants and young children have shown medium doses of inhaled corticosteroids to be effective in treating moderate and severe asthma (Connet 1993, de Blic 1996, Bisgaard 1999, Nielsen 2000). The few studies available in this age group that have directly compared different doses of inhaled corticosteroids have shown that increasing the dose is most effective in reducing asthma exacerbations (Bisgaard 1999) and less consistently effective in improving other outcomes (Bisgaard 1999, Baker 1999, Kemp 1999). These results also have been found in studies of adults. Therefore, it is the opinion of the Expert Panel that using medium doses of inhaled corticosteroids as monotherapy for moderate asthma is another preferred treatment option.

For all treatments, it is essential to monitor the child's response to therapy. If there is no clear response within 4 to 6 weeks, the therapy should be discontinued and alternative therapies or alternative diagnoses considered. If there is a clear and positive response after 2 to 4 months, a step down in therapy should be undertaken to the lowest possible doses of medication required to maintain asthma control (Baker 1999; Kemp, Skoner, Szefler et al. 1999).

- Exacerbations caused by viral respiratory infections may be intermittent yet severe. **Consider systemic corticosteroids if the exacerbation is moderate to severe or at the onset of a viral respiratory infection if the patient has a history of severe exacerbations.**

- **Consultation with an asthma specialist should be *considered* for infants and young children requiring step 2 care; consultation is *recommended* for those requiring step 3 or step 4 care.**

- Several delivery devices are available for infants and young children. The dose received may vary considerably among devices and age groups. (See figure 3–3 for a summary of therapeutic issues regarding aerosol delivery devices.) The child's caregivers must be instructed in the proper use of appropriately sized face masks, spacers/holding chambers with face masks, and spacers/holding chambers for medication delivery to be effective and efficient. For children 2 years of age and younger, nebulizer therapy with mask may be preferred for administering aerosol medications. Children between 3 and 5 years of age may begin therapy with MDI and spacer/holding chamber alone, but if the desired therapeutic effects are not achieved, they may require a nebulizer or an MDI plus spacer/holding chamber and face mask.

Recommendations for Future Research

- How do LTRAs and inhaled corticosteroids compare in safety and efficacy in both the short term and long term in the treatment of mild persistent asthma in children younger than 5 years of age?

- Do anticipated differences in adherence to medication regimens (for example, inhalation therapy vs. oral tablet dose therapy) translate into significant clinical differences in overall asthma control?

- What is the best form of adjunctive therapy in children with moderate persistent asthma who are not adequately controlled on inhaled corticosteroid therapy alone? Long acting beta$_2$-agonists? LTRAs? Theophylline?

- Can response to various long-term-control medications be predicted prior to initiating treatment? Phenotype and genotype characterizations and definitions are needed to address this question.

- What is the most effective way of treating children who have only viral-induced asthma symptoms?

- Is drug delivery using an MDI with spacer equal in efficacy to nebulizer treatments in childhood asthma?

- Can early recognition and treatment of an infant or young child at high risk of developing asthma prevent development of persistent asthma?

Key Evidence Tables

Table 1-1. Inhaled Corticosteroids vs. No Inhaled Corticosteroids

Citation/Study Type	Study Arm	Number Enrolled	Number Evaluable	Mean Age +/- SD	Estimated Disease Severity	
Children older than 5 years						
Childhood Asthma Management Research Group 2000a	Placebo	418	411	9 +/- 2.2	Mild or Moderate	
Randomized, parallel-arm, double-blinded, placebo-controlled trial	BUD	311	306	9 +/- 2.1	Mild or Moderate	
Jonasson, Carlsen, Blomqvist 1998	Placebo	40	40	9.6	Mild	
Randomized, parallel-arm, double-blinded, placebo-controlled trial	BUD 1 BUD 2 BUD 3	40 42 41	40 42 41	10.2 10.0 9.8	Mild Mild Mild	
Simons 1997	Placebo	55	52	9.5 +/- 2.4	Mild or Moderate	
Randomized, parallel-arm, double-blinded, placebo-controlled trial	BDP	81	67	9.6 +/- 2.6	Mild or Moderate	
Hoekstra, Grol, Hovenga et al. 1998	Placebo	19	15	11 +/- 1.8	Mild or Moderate	
Randomized, parallel-arm, double-blinded, placebo-controlled trial	FP	15	25	10.6 +/- 1.8	Mild or Moderate	
Agertoft and Pedersen 1994	Placebo	62	NR	6.1	Mild or Severe	
Parallel-arm-controlled trial	BUD	216	NR	6.2	Mild or Severe	
van Essen-Zandvliet, Hughes, Waalkens et al. 1992	Placebo	58	17	10.9 +/- 1.9	Mild or Severe	
Randomized, parallel-arm, double-blinded, placebo-controlled trial	BUD	58	29	11 +/- 1.9	Mild or Severe	
Children younger than 5 years						
Storr, Lenney, Lenney 1986	Placebo	14	13	3.4 +/- 1.5	Unable to estimate	
Randomized, parallel-arm, double-blinded, placebo-controlled trial	BDP	15	15	3.6 +/- 1.2	Unable to estimate	
Connett, Warde, Wooler et al. 1993	Placebo	20	19	1.9 +/- 0.5	Unable to estimate	
Randomizitrolled trial	BUD	20	17	1.7 +/- 0.6	Unable to estimate	

Key:
BDP = beclomethasone dipropionate
FP = fluticasone propionate
SD = standard deviation
BUD = budesonide
NR = not reported
Sx = symptom
FEV_1 = forced expiratory flow volume in 1 second
PC20 = provocative concentration of bronchoconstrictor that induces a 20% drop in FEV_1
PEF = peak expiratory flow
X = outcome reported

Study Duration (weeks)	Lung Function Outcomes FEV_1	PEF	PC20	Sx/Meds	Utilization Outcomes	Comments
224	X	X	X	X	X	
224	X	X	X	X	X	
12	X	X	X	X		Not stated how patients with moderate-severe asthma were excluded.
12 12 12	X X X	X X X	X X X	X X X		
52	X	X	X	X	X	
52	X	X	X	X	X	
12	X	X	X			
12	X	X	X			
270.4 (mean)	X				X	Control patients were those patients who declined recommendation to take inhaled corticosteroids. Inhaled corticosteroid-free period after diagnosis is referred to as the run-in period, equal to at least 1 year.
192.4 (mean)	X				X	
95.3 (median)	X	X	X		X	
95.3 (median)	X	X	X		X	Pharmaceutical company supplied study medication.
26				X		Study took place over an 18-month period in an attempt to eliminate seasonal bias.
26				X		
26				X	X	Patients treated for up to 6 months, included in analysis if treated at least 5 weeks.
26				X	X	Study medication adjusted to 200–400 mcg 2x/day budesonide or 1–2 puffs 2x/day placebo depending on clinical need.

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01-E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

Table 1-2a. Inhaled Corticosteroids vs. Long-Acting Inhaled Beta$_2$-Agonists

Citation/Study Type	Study Arm	Number Enrolled	Number Evaluable	Mean Age +/- SD	Estimated Disease Severity	
Verberne, Frost, Roorda et al. 1997	Salmeterol	35	25	10.6 +/- 2.9	Mild or Moderate	
Randomized, parallel-arm, double-blinded, controlled trial	BDP	35	32	10.5 +/- 2.3	Mild or Moderate	
Simons 1997	BDP	81	67	9.6 +/- 2.6	Mild or Moderate	
Randomized, parallel-arm, double-blinded, placebo-controlled trial	Salmeterol	80	58	8.8 +/- 2.1	Mild or Moderate	

Table 1-2b. Inhaled Corticosteroids vs. Theophylline

Citation/Study Type	Study Arm	Number Enrolled	Number Evaluable	Mean Age +/- SD	Estimated Disease Severity	
Tinkelman, Reed, Nelson, et al. 1993	Theophylline	93	69	11.9 +/- 2.8	Mild or Severe	
Randomized, parallel-arm, double-blinded, placebo-controlled trial	BDP	102	76	11.9 +/- 2.7	Mild or Severe	

Table 1-2c. Inhaled Corticosteroids vs. Nedocromil

Citation/Study Type	Study Arm	Number Enrolled	Number Evaluable	Mean Age +/- SD	Estimated Disease Severity	
Childhood Asthma Management Program Research Group 2000a	Placebo	418	411	9 +/- 2.2	Mild or Moderate	
Randomized, parallel-arm, double-blinded, placebo-controlled trial	BUD	311	306	9 +/- 2.1	Mild or Moderate	

	Study Duration (weeks)	Lung Function Outcomes FEV_1	PEF	PC20	Sx/Meds	Utilization Outcomes	Comments
	48	X	X	X			
	48	X	X	X			
	52	X	X	X		X	
	52	X	X	X		X	

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01-E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001

	Study Duration (weeks)	Lung Function Outcomes FEV_1	PEF	PC20	Sx/Meds	Utilization Outcomes	Comments
	36	X	X	X	X	X	
	36	X	X	X	X	X	

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01-E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001

	Study Duration (weeks)	Lung Function Outcomes FEV_1	PEF	PC20	Sx/Meds	Utilization Outcomes	Comments
	224	X	X	X	X	X	
	224	X	X	X	X	X	

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01-E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

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Long-Term Management of Asthma in Children: Safety of Inhaled Corticosteroids

Question

What are the long-term adverse effects of chronic inhaled corticosteroid use in children on the following outcomes?

- ***Vertical growth?***
- ***Bone mineral density (BMD)?***
- ***Ocular toxicity?***
- ***Suppression of adrenal/pituitary axis?***

Summary Answer to the Question

Strong evidence from clinical trials following children for up to 6 years suggests that the use of inhaled corticosteroids at recommended doses does not have long-term, clinically significant, or irreversible effects on any of the outcomes reviewed. Inhaled corticosteroids do improve health outcomes for children with mild or moderate persistent asthma, and the potential but small risk of delayed growth is well balanced by their effectiveness (SRE-Evidence A, B). Updated text is recommended for the EPR-2 incorporating the results of the SRE, but this update does not change the EPR-2 statements.

Rationale for the Question

Inhaled corticosteroids have been proven to be beneficial in the treatment of mild or moderate persistent asthma in children. Because this class of compounds has the potential for producing adverse side effects, however, a SRE on the potential long-term adverse effects would help guide consideration of potential risks and benefits in the therapeutic decisionmaking process.

Systematic Review of the Evidence

The following description of the SRE is an adaptation of the evidence report, including direct excerpts, submitted by the Blue Cross Blue Shield Association Evidence-Based Practice Center. (See Introduction, Methods.)

Methods of Literature Search

To be eligible for consideration in the SRE, each study was required to meet the following criteria:

- It reported on inhaled corticosteroid treatment.
- The treatment duration/observation was at least 1 year.
- For prospective studies:
  - Enrolled only patients younger than 18 years of age.

  OR
  - Stratified outcomes for patients younger than 18 years of age and reported baseline demographics for the stratified subgroup.
- For retrospective studies:
  - Enrolled children and/or young adults younger than 40 years of age and indicated that a substantial proportion of the exposure to inhaled corticosteroids had been during childhood.
  - Study design was a comparative clinical trial, cohort study, case control study, or cross-sectional study.
- Reported on a group of at least 25 evaluable, similarly treated asthma patients per study arm.
- For growth outcomes:
  - Studies of short-term growth were restricted to randomized clinical trials.
  - Studies of long-term growth were restricted to studies that assessed final attained adult height and controlled for confounding variables.
  - For bone density, studies were restricted to controlled trials.
  - For subcapsular cataract, clinical series studies were also included.

- For hypothalamic-pituitary-adrenal (HPA) axis function, studies also were included that used a pre-post single-arm design, where baseline HPA axis function was measured before initiation of inhaled corticosteroids.

Summary of Findings

Studies

The SRE addressed the long-term adverse effects of chronic inhaled corticosteroid use in children on four outcomes: vertical growth; bone mineral density; ocular toxicity, including posterior subcapsular cataract and glaucoma; and suppression of adrenal/pituitary axis. (See the key evidence tables in this section for a description of the studies reviewed for vertical growth [three retrospective cohort/studies on final height]; bone-mineral density [two cross-sectional studies and one randomized controlled trial]; and HPA axis function [six studies, including three randomized controlled trials]). The difficulties of systematically assessing adverse effects are well known. Most clinical trials are not designed to specifically address adverse effects and thus may be statistically underpowered and of insufficient duration to detect long-term adverse effects. In addition, the results of this evidence review do not apply to adults. For the adult population, particularly elderly adults, adverse effects may differ qualitatively and quantitatively. For example, although effects on vertical growth are not a concern for adults, ocular toxicity is likely to occur more frequently as age increases.

Results of Studies

The available evidence suggests that the use of inhaled corticosteroids at recommended doses does not have frequent, clinically significant, or irreversible effects on any of the outcomes reviewed. It is possible that chronic use of inhaled corticosteroids initiated in childhood and continued through adulthood might have cumulative effects that increase the relative risk of certain conditions—such as osteoporosis, cataracts, or glaucoma—in later life. However, none of the available studies had sufficient followup duration or numbers of patients to assess this possibility definitively. It is also likely that the probability of adverse effects is related to inhaled corticosteroids dosage. No studies identified in the published literature, however, were designed to test the dose-response relationship of inhaled corticosteroids to adverse effects.

Vertical Growth

The long-term prospective studies on growth involved budesonide, and the retrospective analyses included studies on beclomethasone, but the results have been generalized to all inhaled corticosteroid preparations. Although different preparations and delivery services may have a systemic effect at different doses, all short-term studies of numerous preparations suggest that the effect of inhaled corticosteroids on growth is a drug class effect.

Evidence addressing three measures of vertical growth in children was found: short-term growth velocity measured over a period of 1 year or less, growth velocity and change in height measured over longer duration (4 to 6 years), and final attained adult height. The evidence on short-term growth velocity is from a published meta-analysis, which pooled data from 5 randomized controlled trials representing 855 subjects, with a mean age of 9.5 years (Sharek and Bergman 2000). Evidence on growth velocity and height over a longer period of time is from the CAMP trial, comparing inhaled corticosteroids (budesonide), nedocromil, and placebo in 1,041 children with mild or moderate persistent asthma, who were followed for 4 to 6 years (CAMP 2000). For final attained adult height, evidence is from three retrospective cohort studies that adjusted for the potential confounding factor of parental height (Agertoft and Pedersen 2000; Silverstein et al. 1997; Van Bever et al. 1999). Together, these three studies included a total of 243 patients with asthma treated with inhaled corticosteroids, 154 asthmatic patients who had not been treated with inhaled corticosteroids, and 204 nonasthmatic controls.

Evidence on growth velocity when evaluated during the first year of therapy is consistent in showing a difference in height averaging approximately 1 cm between children treated with inhaled corticosteroids and controls. The magnitude of this change in height (≈0.5→1.5 cm) has varied between studies using different inhaled corticosteroid preparations, indicating that either the study design or specific steroid preparation/

dose may be important considerations (Doull et al. 1995; Allen et al. 1998; Verberne et al. 1997). In the only trial extending beyond 1 year (CAMP 2000), a difference consistent with this magnitude also occurred during the first year of the study. However, in subsequent long-term followup, the difference in growth velocity was not maintained; all groups had similar growth velocity at the end of treatment. At the end of the 4- to 6-year treatment period, there was still an approximately 1 cm difference in cumulative growth between the study groups, but a slight difference in bone age suggests the potential for catchup for the inhaled corticosteroid group.

The evidence on final adult height appears to be fairly consistent as well. However, this evidence is based on cohort studies that are subject to selection bias and the confounding effects of severity of asthma cannot be adjusted. Some comparisons in these studies also were limited by small sample size. Of the three studies, two showed no difference, and one showed a difference in final attained adult height between inhaled corticosteroid users and nonusers. However, the difference was much less than would be expected if a 1 cm/year growth velocity difference noted in the 1-year studies were maintained over several years.

Bone Mineral Density

The CAMP study followed children with mild or moderate persistent asthma and a mean age of approximately 9 years who were treated for 4 to 6 years with inhaled corticosteroids. This study, with large numbers, randomization, and assessment of longitudinal changes, provides strong evidence that there is no effect of inhaled corticosteroids on bone mineral density (BMD) in the doses given and in the duration in the study (CAMP 2002). One retrospective study of 30 young adults found a significant correlation between BMD and dose of inhaled corticosteroids among female patients (Ip et al. 1994). Such studies are subject to potential confounding because of unmeasured differences between groups that are risk factors for low BMD. In addition, the clinical significance of any observed differences in BMD are unknown. Subtle differences in BMD would not have a clinical impact until they were added to other risk factors such as aging, and it is uncertain whether differences observed during young adulthood would persist into old age.

Posterior Subcapsular Cataract and Glaucoma

Studies that report on the occurrence of posterior subcapsular cataracts consist mostly of small cohorts and cross-sectional studies (Allen et al. 1998; Tinkelman et al. 1993; Agertoft et al. 1998; Simons et al. 1993; Nassif et al. 1987; Abuekteish et al. 1995), with the exception of the CAMP study. The expected incidence rate of subcapsular cataract in any population of normal young children and adults is none. These studies are sufficient to rule out a large effect of inhaled corticosteroids on the short-term incidence of cataract, but they are not capable of detecting a small increase in risk of an event that has a baseline risk of essentially zero. In addition, several of the clinical trials that evaluated development of cataracts were of relatively short duration.

Two of these studies also reported on measurements of ocular pressure (Tinkelman et al. 1993; Nassif et al. 1987). The limited data available show no relationship between glaucoma or increased intraocular pressure and inhaled corticosteroids.

Effect on Hypothalamic-Pituitary-Adrenal Axis Function

Two types of evidence on the effects of inhaled corticosteroids on HPA axis function have been reported: three case reports of iatrogenic Cushing syndrome that were possibly related to inhaled corticosteroids (Zimmerman et al. 1998; Taylor et al. 1999; Priftis et al. 1991; Hollman and Allen 1988) and six controlled clinical trials regarding HPA axis function (Tinkelman et al. 1993; Nassif et al. 1987; Scott and Skoner 1999; Ribeiro 1993; Price et al. 1997; Gonzalez Perez-Yarza et al. 1996). Each study evaluated from one to three different measures of HPA axis function, with followup for at least 1 year after initiation of treatment.

The case reports show that systemic effects can occur in clinically detectable ways, with a strong case for causality indicated in the case studies by the accompanying laboratory tests and response when inhaled corticosteroids were withdrawn.

In the controlled clinical studies, four studies of serum control values identified no differences. However, three other studies used more sensitive tests of cortisol, such as 24-hour urinary cortisol, and two showed a statistically significant effect of inhaled corticosteroids. It should be noted that these statistically significant results occur as comparisons of mean values between groups. Few or no patients in most studies produce laboratory values out of the normal range. However, the clinical significance of these more sensitive indicators of adrenal function is unknown.

The results of the case reports appear to be causally attributable to inhaled corticosteroids based on clinical presentation, consistency with laboratory findings, and clinical response to reduction or withdrawal of treatment. Although the studies show that, on average, persons may only have clinically insignificant effects of inhaled corticosteroids on the HPA axis, some individuals may be acutely susceptible to their effects.

Additional Literature/Information

Since the release of the EPR-2, a FDA-based committee convened to review the safety of inhaled corticosteroid therapy, with particular emphasis on growth effects. The FDA committee recommended inserting the following cautionary wording in package inserts for all (both nasal and oral) inhaled corticosteroid medications: "A reduction in growth velocity in children or teenagers may occur as a result of inadequate control of chronic diseases such as asthma or from use of corticosteroids for treatment. Physicians should follow closely the growth of adolescents taking corticosteroids by any route and weigh the benefits of corticosteroid therapy and asthma control against the possibility of growth suppression if an adolescent's growth appears slowed (http://www.fda.gov)."

Two additional studies on the effect of inhaled corticosteroids were completed after the SRE; the studies involved primarily adults but included some children and thus were considered by the Expert Panel. One report pertaining to the risk of cataract formation among patients 3 to 90 years of age was based on a large retrospective cohort study in the United Kingdom-based General Practice Research Database population, with a nested case-control analysis among users of inhaled corticosteroids and patients without previous steroid use who were younger than 90 years of age. All users of inhaled corticosteroids were at a marginally increased risk of cataract formation (risk ratio = 1.3) compared to patients who did not use corticosteroids. Among individuals 40 years of age or older, the risk ratio increased as numbers of inhaled corticosteroid prescriptions increased after controlling for other variables. These trends were not evident for those individuals younger than 40 years of age (Jick et al. 2001).

A prospective cohort study on bone loss in women 18 to 45 years of age reported that bone-density loss at the total hip and the trochanter—but not at the femoral neck or spine—increased with the number of puffs per day of an inhaled corticosteroid (Israel et al. 2001). However, the clinical significance of these findings is uncertain because the rate of loss reported was small, any association of this small loss with increased risk of bone fracture has not been established, and the rates varied among the women taking the inhaled corticosteroids.

Recommendations for EPR Update

Based on this information from the SRE and additional studies, the Expert Panel recommends the following text (the blue text indicates new text) as an update to pages 71 through 73 of EPR-2 (The Medications, Special Issues on Safety, Systemic Adverse Effects). This text updates—but does not change—the EPR-2 recommendations.

Linear Growth

A reduction in growth velocity in children or adolescents may occur as a result of inadequate control of chronic diseases such as asthma or from the use of corticosteroids for treatment. Overall, however, the available cumulative data in children suggest that, although low-to-medium doses of inhaled corticosteroids may have the potential of decreasing growth velocity, the effects are small, nonprogressive, and may be reversible (SRE-Evidence A, B, C).

The long-term prospective studies on growth involved budesonide, and the retrospective analyses included studies on beclomethasone, but the results have been generalized to include all inhaled corticosteroid preparations. Although different preparations and delivery devices may have a systemic effect at different doses, all short-term studies on numerous preparations suggest that the effect of inhaled corticosteroids on growth is a drug-class effect. When high doses of inhaled corticosteroids are necessary to achieve satisfactory asthma control, the use of adjunctive long-term-control therapy should be initiated in order to reduce the dose of inhaled corticosteroids and thus minimize possible dose-related long-term effects on growth. Physicians should monitor the growth of children and adolescents taking corticosteroids by any route and weigh the benefits of corticosteroid therapy and asthma control against the possibility of growth suppression or delay if a child's or an adolescent's growth appears slowed.

Bone Mineral Density

Low-to-medium doses of inhaled corticosteroids appear to have no serious adverse effects on BMD in children (SRE-Evidence A) (CAMP 2000). A small, dose-dependent reduction in BMD may be associated with inhaled corticosteroid use in patients older than 18 years of age (SRE-Evidence C; Evidence B) (Ip et al. 1994; Israel et al. 2001), but the clinical significance of these findings is not clear.

Cataracts

In children, low-to-medium dose inhaled corticosteroid therapy has no significant effects on the incidence of subcapsular cataracts or glaucoma (SRE-Evidence A, C) (CAMP 2000; Jick et al. 2001). High (greater than 2000 mg) cumulative lifetime doses of inhaled corticosteroids may increase slightly the prevalence of cataracts as suggested in two retrospective studies of adult and elderly patients (SRE-Evidence C; Evidence C) (Cumming et al. 1997; Jick et al. 2001).

Hypothalamic-Pituitary-Adrenal Axis Function

The available evidence indicates that, on average, children may experience only clinically insignificant, if any, effects of low-to-medium dose inhaled corticosteroids on the HPA axis (SRE-Evidence A, C). Rare individuals, however, may be more susceptible to their effects even at conventional doses.

Recommendations for Future Research

- What are the long-term effects of inhaled corticosteroid therapy on BMD and cataract formation if it is initiated at a young age and continued for prolonged periods of time?
- Are potential growth effects of inhaled corticosteroid therapy more pronounced during certain developmental periods (e.g., first 3 years of life, preadolescence)?

Key Evidence Tables

Table 1-3. Differences in Adult Target Height in Cohort Studies

Study	Group (n) Comparison	Difference in (Adult Target) Height (cm)[1]
Silverstein, Yunginger, Reed et al. 1997	All asthmatics (n = 153) vs. nonasthmatics (n = 153)	0.2
	All corticosteroid users (n = 58) vs. noncorticosteroid asthmatics (n = 95)	-1.2
	Males: All corticosteroid users (n = 30) vs. noncorticosteroid asthmatics (n = 45)	-1.8
	Females: All corticosteroid users (n = 28) vs. noncorticosteroid asthmatics (n = 50)	-0.8
	Oral corticosteroid users (n = 40) vs. never used corticosteroids (n = 95)	-1.4
	Inhaled corticosteroid users (n = 18) vs. never used corticosteroids (n = 95)	-0.9
Van Bever, Desager, Lijssens et al. 1999	All inhaled corticosteroid users (n = 43) vs. never used corticosteroids (n = 42)	-2.54[2]
	Males: Inhaled corticosteroid users (n = 23) vs. never used corticosteroids (n = 26)	-3.09[2]
	Females: Inhaled corticosteroid users (n = 20) vs. never used corticosteroids (n = 16)	-1.99
Agertoft and Pedersen 2000	All inhaled corticosteroid users (n = 142) vs. noncorticosteroid using asthmatics (n = 18)	+0.5
	All inhaled corticosteroid users (n = 142) vs. healthy sibling control group (n = 51)	-0.6
	Males: All inhaled corticosteroid users (n = 86) vs. healthy sibling control group (n = 24)	-0.6
	Females: All inhaled corticosteroid users (n = 56) vs. healthy sibling control group (n = 27)	-0.8

[1] A negative number indicates that corticosteroid users had lower attained adult height than the comparison group, controlling for parental height.

[2] $p < 0.05$

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01-E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

Table 1-4. Effects of Inhaled Corticosteroids on Bone Mineral Density

Citation	Treatment Arm	Number Enrolled	Number Evaluable	Treatment Duration (years)	Bone	P Value	Comment
Agertoft, Larsen, and Pedersen 1998	Budesonide 504 mcg per day	157	157	3.0 (minimum)	Total body BMD: 0.92 g/cm²		No significant difference between groups or between boys and girls in bone mineral capacity or total bone calcium
	Nonsteroid asthma therapies	111	111	3.0 (minimum)	Total body BMD: 0.92 g/cm²	NS	Mean treatment time 4.4 (3–6) years
Ip, Lam, Yam, et al. 1994	Beclomethasone or budesonide	30	30	3.3	Spine: 0.944	0.041	Stratified by sex, all differences significant for females but not for males
					Femur Neck: 0.769	0.007	
					Trochanter: 0.676	0.034	
					Ward's Triangle: 0.729	0.016	
	Normal control subjects, matched by sex, age, BMI, menopausal status	30	30	NA	Spine: 1.011		
					Femur Neck: 0.835		
					Trochanter: 0.724		
					Ward's Triangle: 0.729		
Childhood Asthma Management Program Research Group 2000a	Budesonide 400 mcg/day	311	311	4–6	Change in spine BMD: 0.17 g/cm²	0.53 vs. placebo	
	Nedocromil 16 mg/day	312	312	4–6	Change in spine BMD: 0.17 g/cm²	0.15 vs. placebo	
	Placebo	418	418	4–6	Change in spine BMD: 0.18 g/cm²		

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01–E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

Table 1-5. Effects of Inhaled Corticosteroids on HPA Function

Citation	Treatment Arms	Measure of HPA Axis Function	
Randomized Clinical Trials			
Scott and Skoner 1999	BUD 500 mcg/day (n = 132) vs. conventional treatment (n = 57)	Serum cortisol at baseline and 12 mo. ACTH-stimulated cortisol at baseline and 12 mo. Percentage of patients from normal to abnormal stimulation test between baseline and 12 mo.	
Price, Russell, Hindmarsh et al. 1997	FP 50 mcg/day (n = 36) vs. cromolyn 20 mg/day (n = 27)	Urinary cortisol geometric mean ratio between patient groups at 6 and 12 mo.	
Tinkelman, Reed, Nelson et al. 1993	BDP 84 mcg/day (n = 102) vs. theophylline (n = 93)	Serum cortisol at baseline, 6 and 12 mo. ACTH-stimulated cortisol at baseline, 6 and 12 mo.	
Cross-Section Studies			
Gonzales Perez-Yarza, Mintegui, Garmendia et al. 1996	Budesonide or beclomethasone mean dose 676 +/- 280 mcg/day (range, 226–1800) (n = 250) vs. normal controls (n = 108)	Urinary cortisol Number of abnormal ACTH stimulation tests in subset with urinary cortisols below 1 standard deviation	
Nassif, Weinberger, Sherman et al. 1987	Beclomethasone 358 mcg/day (n = 17) vs. Beclomethasone 726 mcg/day (n = 14) vs. asthmatic control group (n = 20) and normal control groups (n = 21)	Serum cortisol Urinary cortisol	
Single Arm Pre-Post Study			
Ribiero 1993	Budesonide 200 mcg/day (n = 47)	Serum cortisol at baseline and 12 mo. ACTH-stimulated cortisol at baseline and 12 mo.	

	Results	P Value	Comments
	BUD (0, 12 mo): 320, 300 Conventional (0, 12 mo.): 250, 315	"No significant differences"	Subset of full trial
	BUD (0, 12 mo.): 695, 655 Conventional (0, 12 mo.): 690, 720	"No significant differences"	Subset of full trial
	BUD: 24% Conventional: 21%	"Not different"	
	Ratio of urinary cortisol at 6 mo.: 0.85 Ratio of urinary cortisol at 12 mo.: 0.96	NS: 95% CI includes 1 NS: 95% CI includes 1	
	BDP 336 mcg/day (0, 6, 12 mo.): 328, 306, 309 Theophylline (0, 6, 12 mo.): 309, 322, 334	Not stated: "similar"	
	BDP 336 mcg/day (baseline): 726 (6, 12 mo. NA) Theophylline (baseline): 723 (6, 12 mo. NA)	Not stated: "almost identical"	
	BUD/BDP: 58.69 nmol/m_2/day Control: 81.98 nmol/m_2/day	$p < 0.05$	
	BUD/BDP group: 2 abnormal tests (3.1%) Control group: Not done	Not applicable	One of the two patients with abnormal test had chronic oral corticosteroids.
	BDP <450 mcg/day: 403 BDP >450 mcg/day: 353 Asthmatic controls: 353 Normal controls: 367	Not specifically stated: presumed NOT statistically significant	
	BDP <450 mcg/day: 22 mcg/g creatinine BDP >450 mcg/day: 16.5 mcg/g creatinine Asthmatic controls: 43 mcg/g creatinine Normal controls: 29.5 mcg/g creatinine	Text: "Statistically significant" from controls	
	Basal cortisol (0, 12 mo.): 497, 497	Not stated, presumed not statistically significant	
	4-hr. stimulated cortisol (0, 12 mo.): 1104, 1131 5-hr. stimulated cortisol (0, 12 mo.): 1242, 1380	$p = 0.02$ for increase from baseline, both tests	

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01-E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

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Combination Therapy: Addition of Other Long-Term-Control Medications to Inhaled Corticosteroids

Question

In patients with moderate persistent asthma who are receiving inhaled corticosteroids, does addition of another long-term-control agent improve outcomes?

Summary Answer to the Question

Strong evidence consistently indicates that long-acting inhaled beta$_2$-agonists added to low-to-medium-dose inhaled corticosteroids improve outcomes (SRE-Evidence A). Adding a leukotriene modifier or theophylline to inhaled corticosteroids or doubling the dose of inhaled corticosteroids also improves outcomes, but the evidence is not as substantial (SRE-Evidence B). The EPR-2 recommendations for moderate persistent asthma have been revised: The preferred treatment for adults and children older than 5 years of age is the addition of long-acting inhaled beta$_2$-agonists to low-to-medium-doses of inhaled corticosteroids. Adjunctive therapy combinations have not been studied in children younger than 5 years of age. For this age group, it is the opinion of the Expert Panel that there are two preferred options for treating moderate asthma: either the addition of long-acting inhaled beta$_2$-agonists to a low dose of inhaled corticosteroids or medium-dose inhaled corticosteroids as monotherapy.

Rationale for the Question

There are an increased number of studies evaluating combination therapy primarily as a result of the development of fixed-dose combinations of the long-acting inhaled beta$_2$-agonists and inhaled corticosteroids (salmeterol plus fluticasone propriionate, now FDA-approved, and formoterol plus budesonide, under development). The ongoing preference to minimize the dose of corticosteroids, especially for patients taking high doses, and to reduce the possibility of adverse side effects, has stimulated studies of adjunctive therapies. The question of interest is whether, for patients requiring more than low doses of inhaled corticosteroids, equal or better asthma control could be achieved by adding an additional medication rather than by increasing the dose of inhaled corticosteroids. An extensive body of literature addressing the question of adjunctive therapy has become available since the publication of EPR-2 and has thus warranted Expert Panel Review.

Systematic Review of the Evidence

The following description of the SRE is an adaptation of the evidence report, including direct excerpts, submitted by the Blue Cross Blue Shield Association Evidence-Based Practice Center. (See Introduction, Methods.)

Methods of Literature Search

The SRE divided the studies into three study design categories:

1. The addition of a long-term-control medication to a fixed dose of inhaled corticosteroids compared with the same dose of inhaled corticosteroids alone. This design simply assesses whether combination therapy is better than monotherapy with inhaled corticosteroids. The potential bias from this study design is seen when patients can be controlled on inhaled corticosteroids alone, resulting in a negative study because of the inability to improve.

2. The addition of a long-term-control medication to inhaled corticosteroids with subsequent downward titration of the dose of inhaled corticosteroids to the lowest dose that maintains control. This design is even more problematic because it may be raising a fundamentally different question—i.e., "Can the other long-term-control medication act as a substitute for the inhaled corticosteroids following initial control of the asthma?" However, if the goal is simply to lower the dose of inhaled corticosteroids by some increment (usually half), then the study design addresses the primary question more directly.

3. The addition of the long-term-control medication compared with increasing the dose of inhaled corticosteroids to improve asthma control. This design most directly addresses the question, because eligible patients first demonstrated a lack of adequate control during an open run-in period on inhaled corticosteroids. The definition of inadequate control varied among studies, however, and this variance could introduce some bias.

In addition to the eligibility criteria for selecting studies related to all topics in the SRE (described in the Introduction), the criteria for selecting studies for this question were as follows:

- Study comparisons included:
  - Inhaled corticosteroids alone compared to inhaled corticosteroids plus leukotriene modifiers, or long-acting beta$_2$-agonists, or theophylline

  OR
  - Two different long-term-control medications in patients using inhaled corticosteroids

  OR
  - The addition of an alternative medication to an increased dose of inhaled corticosteroids for patients already on inhaled corticosteroids.
- Treatment duration was at least 4 weeks.
- At least 90 percent of patients in the study were on inhaled corticosteroids, or the subgroup of patients on inhaled corticosteroids was analyzed separately, and this subgroup otherwise met the eligibility criteria for this question.
- No more than 10 percent of the patients in the population or in a subgroup were on oral corticosteroids.

Summary of Findings

Studies

The majority of the studies reviewed by the SRE fit into study design categories 1 and 3. Thirty-nine studies involving 45 comparisons and a total of 9,020 patients were selected for the SRE. (See the key evidence tables in this section.) Overall, 34 of the 45 comparisons evaluated the addition of a long-acting beta$_2$-agonist to inhaled corticosteroids. All but one of the studies were randomized trials. The following comparisons were made:

- Twenty-six compared the addition of a drug to a fixed dose of inhaled corticosteroids (18 [3,163 patients] compared long-acting inhaled beta$_2$-agonists; 4 [234 patients] compared theophylline; and 4 [885 patients] compared LTRAs).
- Four compared a titrated dose of inhaled corticosteroids after the addition of a drug (3 [268 patients] compared long-acting inhaled beta$_2$-agonists; 1 [226 patients] compared LTRA).
- Fifteen compared a low-to-moderate dose of inhaled corticosteroids with an additional drug to high-dose inhaled corticosteroids (13 [4,285 patients] compared long-acting inhaled beta$_2$-agonists and 2 [252 patients] compared theophylline).
- No studies were found that compared long-acting oral beta$_2$-agonists.
- No studies meeting SRE quality criteria were found that compared the addition of cromolyn or nedocromil.

Results of Studies

Addition of long-acting inhaled beta$_2$-agonists

A sufficient number of quality studies in both design categories 1 and 3 were completed to enable meta-analyses of lung function and as-needed short-acting beta$_2$-agonist use outcomes in each category. (See the key evidence tables in this section for a description of eligible studies.) Both the systematic review and meta-analyses confirmed the superiority of combination therapy to inhaled corticosteroids monotherapy. In particular, the findings of the meta-analysis for the addition of long-acting inhaled beta$_2$-agonist compared with increasing the inhaled corticosteroid dosage were consistent with a previously reported meta-analysis (Shrewsbury et al. 2000). In addition to similar findings on lung function, Shrewsbury and colleagues had access to the original data and were able to assess the rate of asthma exacerbations, reporting a positive benefit of the combination

therapy. The data are robust and convincing that the addition of long-acting inhaled beta$_2$-agonists to inhaled corticosteroids improves lung function and asthma control in patients inadequately controlled with low-to-medium doses of inhaled corticosteroids.

Of note is the paucity of pediatric trials in the database. One pediatric study by Verberne et al. (1998) was completed in older children (mean 11 years of age). Following a 6-week run-in, 120 patients were randomized to either low-dose inhaled corticosteroid—beclomethasone dipropionate (BDP) (400 mcg/day), medium-dose BDP (800 mcg/day), or low-dose BDP plus the long-acting inhaled beta$_2$-agonist salmeterol for 1 year. No significant difference was found among any of the three arms in postbronchodilator FEV_1 or PC20 FEV_1 methacholine provocation. These results suggest that the children's asthma was adequately controlled with low-dose inhaled corticosteroids and that the addition of the long-acting inhaled beta$_2$-agonist neither improved nor worsened airway responsiveness. Thus, due to the design, this study cannot refute the potential benefit of the drug combination for those children inadequately controlled on low-dose inhaled corticosteroids alone.

A multicenter double-blind trial of salmeterol as added therapy for children who were not well controlled with inhaled corticosteroids (mean dose of 750 mcg/day) demonstrated significant improvement in morning PEF and symptom-free days in the long-acting inhaled beta$_2$-agonist plus inhaled corticosteroid group, compared to the placebo plus inhaled corticosteroid group (Russell 1995). Although this study did not compare the addition of a long-acting inhaled beta$_2$-agonist to an increased dose of inhaled corticosteroids, the patients were already receiving doses of inhaled corticosteroids ranging from 400 to 2,400 mcg a day. Thus, this study established a need for further asthma control in children already receiving inhaled corticosteroids; it also more directly addresses the question posed by the SRE.

Addition of long-acting oral beta$_2$-agonists

No studies were found.

Addition of cromolyn/nedocromil

No studies meeting the quality criteria of the SRE were found. No new studies since the publication of the EPR-2 were found.

Addition of theophylline

Six studies evaluated the addition of theophylline, including two more recent studies that compared the addition to increased inhaled corticosteroid dosage. The results indicate that the combination of drugs and the increased dose of the inhaled corticosteroids result in equivalent outcomes, suggesting that theophylline has only a modest steroid-sparing effect. None of the four studies (two in children 6 to 19 years of age) comparing the addition of theophylline to a fixed dose of inhaled corticosteroids met the quality criteria of the SRE, because all had study-design and statistical problems. No studies were found that included children younger than 6 years of age.

Addition of leukotriene modifiers

Five published studies evaluated the addition of leukotriene modifiers to fixed doses of inhaled corticosteroids; none compared the combination to increasing the dose of inhaled corticosteroids. Two of these studies used pranlukast, an LTRA unavailable in the United States, and one used zafirlukast in a dose four times the dosage recommended on the package label. None of the studies included children younger than 12 years of age. The most relevant of the five studies (Laviolette et al. 1999), which contributed the most patients and had the longest duration, failed to meet the definition of high quality for the SRE because it met only one of the quality indicators (double blinding). Limitations of these studies preclude definitive conclusions, but they reveal a trend showing improvement in lung function and, in some, symptoms from the combination of leukotriene modifiers and inhaled corticosteroids compared with a fixed dose of inhaled corticosteroids alone.

Addition of an adjunctive agent and down titration of the inhaled corticosteroids

This group of studies is discussed separately, as some of the trials were designed to ask a fundamentally different question (i.e., could the adjunctive therapy ultimately replace inhaled

corticosteroid therapy?). An example is the study that attempted to wean patients from the inhaled corticosteroids after beginning a long-acting inhaled beta$_2$-agonist until they had an exacerbation or the inhaled corticosteroid therapy was discontinued (McIvor et al. 1998). Ten of the 13 patients in the long-acting inhaled beta$_2$-agonist arm experienced an exacerbation only after discontinuing their inhaled corticosteroids, providing further evidence that the long-acting inhaled beta$_2$-agonist should not be used as a substitute for anti-inflammatory therapy. One trial attempted to wean patients from the inhaled corticosteroids after addition of the LTRA montelukast, with the goal of maintaining adequate asthma control (Lofdahl et al. 1999). The mean percentage reduction in the dose of inhaled corticosteroids was 47 percent—a 17 percent increase over placebo—and 40 percent of patients were able to discontinue their inhaled corticosteroids compared with 29 percent in the placebo arm, which was not statistically significant. Thus, data are inconclusive about the "steroid sparing" effect of adjunctive therapy, and data show that patients cannot be entirely weaned from inhaled corticosteroids. In addition, data from these studies are insufficient to determine the relative "steroid-sparing" effect of the various adjunctive therapies. Finally, none of the studies included children younger than 5 years of age.

Additional Literature/Information

In addition to reviewing studies published after the SRE, the Expert Panel considered four other issues relevant to the question of the use of combination therapy for the treatment of persistent asthma: the effect of the different combinations on the rate of exacerbations of asthma; the comparison of different combinations to determine relative effectiveness; the use of combination therapy in children 5 years of age and younger; and the use of combination therapy in severe persistent asthma.

Studies Published After the SRE

The addition of montelukast to inhaled corticosteroids was evaluated in 279 children 6 to 14 years of age with moderate asthma whose symptoms were not completely controlled on 400 mcg budesonide daily (Simons et al. 2001). This study was a double-blinded, randomized, placebo-controlled, crossover trial with a 4-week open-label run-in period to establish the need for adjunctive therapy. Each treatment period also consisted of 4 weeks. The trial had sufficient power (95 percent) to detect a 4.4-percent difference between the placebo and the active drug in the primary end point, FEV_1 percent predicted. In the intention-to-treat analysis, no significant difference was found between the placebo and montelukast for the primary end point (1.3 percent difference). A post hoc censure of the data revealed a statistically significant 1.9 percent difference between the active drug and the placebo. Other significant differences reported in favor of montelukast were a decrease in beta$_2$-agonist usage (.33 puffs/day difference) and exacerbation days that also were defined by beta$_2$-agonist usage—an improvement in morning and evening PEFs (9.7 L/min and 10.7 L/min, respectively). It was not indicated whether these were intention-to-treat analyses. Outcomes found to be the same at the end of the study included worsening asthma, global evaluations, number of asthma attacks requiring intervention, and quality of life.

Another study compared the addition of theophylline to low-dose BDP (400 mcg daily) with increasing the dose of BDP to 1,000 mcg daily or maintaining patients on the low-dose BDP alone for 7 months (Lim et al. 2000). The study found no difference between the high-dose inhaled corticosteroids and the theophylline group for any outcome, thus confirming the SRE findings.

Effect of Combination Therapy on the Rate of Exacerbations of Asthma

Reduction in the rate of asthma exacerbations has been suggested as a surrogate for an anti-inflammatory effect. Compared with placebos, leukotriene modifiers have been reported to reduce the number of exacerbations treated with prednisone (zileuton, zafirlukast, and montelukast package inserts). Both of the long-acting inhaled beta$_2$-agonists—formoterol and salmeterol—have been reported to reduce exacerbations of asthma when administered in conjunction with inhaled corticosteroids (Pauwels et al. 1997; Shrewsbury et al.

2000). In one study, the addition of formoterol to either low-dose (100 mcg bid) or high-dose (400 mcg bid) budesonide significantly reduced both mild and severe exacerbations. Further, fewer exacerbations occurred in the high-dose inhaled corticosteroid group compared with the lower dose group, though statistical analysis was not done (Pauwels et al. 1997). A meta-analysis of studies in which the addition of salmeterol to a lower dose of inhaled corticosteroids was compared with a higher dose of inhaled corticosteroids demonstrated that exacerbations were significantly lower with the combination therapy (Shrewsbury et al. 2000).

It has been suggested that this reduction in exacerbations may be attributed to an enhanced corticosteroid effect due to priming of the glucocorticoid receptor by the long-acting inhaled beta$_2$-agonist (Eickelberg et al. 1999). Two recently published studies (Lazarus et al. 2001; Lemanske et al. 2001) also are pertinent to the issue of using asthma exacerbation as an outcome. In the first trial, those patients adequately controlled on low-dose inhaled corticosteroids were left on the inhaled corticosteroids, switched to the long-acting beta$_2$-agonist salmeterol, or switched to placebo. Although the conventional outcomes (morning and evening PEFs) for the salmeterol and inhaled corticosteroid arms were not different, the salmeterol group had a significantly greater number of exacerbations and treatment failures—again demonstrating that the long-acting inhaled beta$_2$-agonists cannot substitute for inhaled corticosteroids (Lazarus et al. 2001). The companion study evaluated the ability to reduce the dose of inhaled corticosteroids following the introduction of a long-acting inhaled beta$_2$-agonist in those patients initially suboptimally controlled on the inhaled corticosteroids (Lemanske et al. 2001). In this group, the dose of inhaled corticosteroids was reduced by one-half in those patients responding to the addition without any significant change in asthma control, yet a significant treatment failure rate was noted when the inhaled corticosteroids were stopped.

Although clinical studies in the SRE suggest that the addition of a long-acting inhaled beta$_2$-agonist to a low-to-medium dose of inhaled corticosteroids is the most effective treatment for moderate persistent asthma (step 3 care), there may be situations where both the addition of a long-acting inhaled beta$_2$-agonist and an increase in the dose of inhaled corticosteroids are indicated. The studies of Sont et al. (1999) and Pauwels et al. (1997) support the added benefit of a higher dose of inhaled corticosteroids in reducing asthma exacerbations. Thus, for patients considered to be at higher risk for exacerbations (suggested by a history of repeated short courses of prednisone, emergency department visits, or hospitalizations), both the addition of a long-acting inhaled beta$_2$-agonist and an increase in the dose of inhaled corticosteroids may be indicated.

Comparison of Combinations To Determine Relative Effectiveness

Not included in the SRE were direct comparative studies of the effectiveness of the various drugs used as adjuncts to inhaled corticosteroids. Studies comparing the long-acting inhaled beta$_2$-agonist to sustained-release theophylline are numerous (Davies et al. 1998), and generally involve patients receiving inhaled corticosteroids. A meta-analysis of these studies (Davies et al. 1998) demonstrated that both pulmonary function and asthma symptoms showed more improvement with the long-acting inhaled beta$_2$-agonist as adjunctive therapy than with theophylline. In the three published studies included in the meta-analysis, between 50 percent and 97 percent of the subjects were receiving regular inhaled corticosteroid therapy (Fjellbirkeland et al. 1994; Muir et al. 1992; Paggiaro et al. 1996).

A comparison of the addition of the long-acting beta$_2$-agonist salmeterol to the addition of the LTRA zafirlukast (Busse et al. 1999) also examined a mixed population; however, this study was not included in the SRE because more than 80 percent of the patients in both arms were using inhaled corticosteroids, rather than 90 percent required by the SRE selection criteria. The study otherwise met the criteria for a high-quality study and should be considered. The results indicate that salmeterol improved both pulmonary function and asthma symptoms significantly more than did zafirlukast.

Another direct comparison of long-acting inhaled beta$_2$-agonists and a leukotriene modifier as combination therapy was published after the SRE (Nelson et al. 2000). This study also met the SRE criteria for high quality and should be considered. The investigators evaluated patients who were still symptomatic on low-dose inhaled corticosteroids (fluticasone 88 mcg bid), before and after the addition of the long-acting beta$_2$-agonist salmeterol or the LTRA montelukast over 3 months. Those patients receiving salmeterol plus fluticasone, compared with those on montelukast and fluticasone, had greater improvement in pulmonary function and in some asthma symptoms, and experienced significantly fewer exacerbations.

Although the addition of sustained-release theophylline or a leukotriene modifier to treatment with inhaled corticosteroids generally is not as effective as the addition of a long-acting inhaled beta$_2$-agonist, there may be circumstances when these combinations would be indicated for selected patients. Among the considerations favoring one of these alternative combinations would be the patient's intolerance of the side effects of the long-acting inhaled beta$_2$-agonist, marked preference for oral therapy, demonstration of superior responsiveness to the alternate class of drug, as well as financial considerations (theophylline is the least expensive). Finally, although the recently marketed fixed-dose combination of fluticasone propionate and salmeterol in a DPI may provide an advantage in terms of ease of use (one inhaler instead of two), there is no evidence of superiority of this particular combination over that of other inhaled corticosteroids and long-acting inhaled beta$_2$-agonists.

Combination Therapy in Children 5 Years of Age and Younger

None of the adjunctive therapy combinations have been adequately studied in children 5 years of age and younger. Indeed, only one study, a study adding the long-acting inhaled beta$_2$-agonist salmeterol to inhaled corticosteroids, included patients as young as 4 years of age (Russell 1995). The lower age limit of all other combination therapy studies in children is 6 years of age (Simons et al. 2001; Meltzer et al. 1992; Nassif et al. 1981). The data are thus inadequate to provide definitive recommendations on combination therapy in young children, and recommendations must be extrapolated from studies in older children and adults, which support the combination of inhaled corticosteroids and long-acting inhaled beta$_2$-agonists. Because patients in this age range may be at greater risk for systemic effects from high doses of inhaled corticosteroids, the use of combination therapy seems prudent when goals of therapy are not attained with low or the lower range of medium doses of inhaled corticosteroids. However, as noted in the section on effectiveness of long-term-control medications, there are no data available on the use of long-acting inhaled beta$_2$-agonists in infants and young children, whereas studies of medium doses of inhaled corticosteroids demonstrate effectiveness in this age group.

The following medications have been FDA-approved for young children: the inhaled corticosteroids budesonide nebulizer solution approved for children 1 to 8 years of age and fluticasone DPI approved for children 4 years of age and older; the long-acting inhaled beta$_2$-agonist salmeterol DPI approved for children 4 years of age and older; and, based on safety data rather than efficacy data, the LTRA montelukast 4 mg chewable approved for children 2 to 6 years of age.

Combination Therapy in Patients With Severe Persistent Asthma

Current recommendations for treatment include adding oral systemic corticosteroids if a patient cannot achieve and maintain control with high doses of inhaled corticosteroids and long-acting bronchodilators. An alternative approach may be to add a third long-term-control medication to a combination of medium-to-high-dose corticosteroids and long-acting inhaled beta$_2$-agonists in severe persistent asthma. However, few trials regarding this approach and of sufficient quality are available. A double-blind, crossover trial of LTRA (10 mg montelukast or placebo) in 72 adults with severe persistent asthma found no benefit from the addition of montelukast to other medication (Robinson et al. 2001). In this study, the concurrent medication varied among the patients: All patients received medium-to-high-dose inhaled

corticosteroids; 85 percent also received either theophylline, a long-acting inhaled beta$_2$-agonist, or both; and 47 percent also received oral systemic corticosteroids. No attempt was made to eliminate the oral corticosteroids. The treatment period of 14 days for LTRA and 14 days for placebo was relatively short, although leukotriene modifiers usually produce a rapid response. This study indicates that there is no additional benefit to adding LTRA as a third medication. Similar controlled clinical trials have not been conducted to evaluate other long-term-control medications added to the combination of medium-to-high doses of inhaled corticosteroids and long-acting inhaled beta$_2$-agonists in severe persistent asthma. Until more research is conducted, recommendations for managing severe persistent asthma are based on extrapolations from studies of the combination of inhaled corticosteroids and one other long-term-control medication in treating moderate persistent asthma.

Recommendations for EPR Update

Based upon the assessment of evidence provided by the SRE and the additional evidence considered by the Expert Panel, the following changes to step 3 care in EPR-2 are recommended:

- The preferred treatment for those adults and children older than 5 years of age whose asthma is inadequately controlled on low-dose inhaled corticosteroids is combination therapy: the addition of a long-acting inhaled beta$_2$-agonist (SRE-Evidence A) to a low-to-medium dose of inhaled corticosteroids. Scientific evidence from studies of children older than 12 years of age and adults indicates that patients with moderate persistent asthma benefit from two different types of daily medication in order to achieve and maintain optimal control of their asthma: (1) medication aimed at suppressing underlying airway inflammation and (2) a medication whose primary action is bronchodilation. This approach is preferred to increasing the dose of inhaled corticosteroids.

  The exception is indicated for those patients who experience recurring severe exacerbations that require oral prednisone, emergency department visits, or hospitalizations. For these patients, increasing the dose of inhaled corticosteroids along with the addition of a long-acting inhaled beta$_2$-agonist should be considered (SRE-Evidence B).

  For children 5 years of age or younger, combination therapy has not been adequately studied. Therefore, recommendations for step 3 care for this age group are based on extrapolations of data from older children and adults, as well as expert opinion. For children 5 years of age and younger with moderate persistent asthma, there are two equally preferred options: low-dose inhaled corticosteroids and a long-acting beta$_2$-agonist (Evidence B, extrapolation from studies in older children and adults) OR inhaled corticosteroids as monotherapy with an increase of the dose within the medium-dose range (Evidence D).

- Alternative—but not preferred—approaches that may be considered include doubling the dose of inhaled corticosteroids within the medium-dose range (this is an alternative but not preferred option for older children and adults; for children 5 years of age and younger, increasing the inhaled corticosteroid dose is an equally preferred option); adding sustained-release theophylline; or adding a leukotriene modifier (SRE-Evidence B). Leukotriene modifiers or theophylline may be considered if the patient displays intolerance of long-acting inhaled beta$_2$-agonists, has a marked preference for oral therapy, and demonstrates superior responsiveness to the alternative class of drug through a therapeutic trial. Other issues may include financial considerations (theophylline is the least expensive).

- The recommendations for the use of nedocromil and long-acting oral beta$_2$-agonists as alternatives to increasing the dose of inhaled corticosteroids are untenable at this time due to lack of data and should be removed as therapeutic options.

Specifically, the Expert Panel recommends that step 3 in figure 3–4b, Stepwise Approach for Managing Asthma in Adults and Children Older Than 5 Years of Age, be revised as follows with the revision noted in blue text.

Figure 3–6. Stepwise Approach for Managing Infants and Young Children (5 Years of Age and Younger) With Acute or Chronic Asthma. (See Medications: Effectiveness in Children on page 25 of this report for revisions to step 3.)

Figure 3–4b. Stepwise Approach for Managing Asthma in Adults and Children Older Than 5 Years of Age: Treatment (pages 84 through 85 in EPR-2)

Step 3: Moderate Persistent
Daily Medication:
Preferred treatment:
Low-to-medium-dose inhaled corticosteroids and long-acting inhaled beta$_2$-agonists
Alternative treatment (listed alphabetically):
Increase inhaled corticosteroids within medium-dose range
OR
Low-to-medium-dose inhaled corticosteroids and either a leukotriene modifier OR theophylline

If needed (particularly in patients with recurring severe exacerbations)
Preferred treatment:
Increase inhaled corticosteroids within medium-dose range and add a long-acting beta$_2$-agonist
Alternative treatment:
Increase inhaled corticosteroids within medium-dose range and add either a leukotriene modifier
OR
Theophylline

Step 4: Severe Persistent
Daily Medication:
Preferred treatment:
High-dose inhaled corticosteroids

AND

Long-acting inhaled beta$_2$-agonists

AND, if needed

Corticosteroid tablets or syrup long term (1 to 2 mg/kg/day; generally do not exceed 60 mg/day). (Make repeat attempts to reduce systemic corticosteroids and maintain control with high-dose inhaled corticosteroids.)

The text in EPR-2 on pages 93 and 94 regarding step 3 and step 4 care for adults and children older than 5 years of age should be revised as follows, with the blue text indicating new text. (See Medications: Effectiveness in Children on page 25 for revisions to step 3 for children 5 years of age and younger.)

Step 3: Moderate Persistent Asthma
Consultation with an asthma specialist may be considered because the therapeutic options at this juncture pose a number of challenging risk-benefit outcomes. Before increasing therapy, however, the clinician should review the patient's inhaler technique and adherence, as well as determine whether environmental factors are contributing to the patient's worsening asthma. If a step-up in therapy is required, there are at least four options for initiating step 3 therapy.

- **Add a long-acting inhaled beta$_2$-agonist to a low-to-medium-dose of inhaled corticosteroids** (SRE-Evidence A, B). *This is the preferred treatment.* Early investigations suggested that the addition of a long-acting inhaled beta$_2$-agonist to a low (Greening et al. 1994) or medium (Woolcock et al. 1996) dose of inhaled corticosteroids resulted in greater improvement in lung function and overall asthma control than doubling the dose of inhaled corticosteroids. Since that time, numerous studies have confirmed the superiority of combination therapy over increasing the dose of inhaled corticosteroids, even for reducing severe asthma exacerbations (SRE 2001, Shrewsbury et al. 2000). Use of combination therapy has not been shown to mask worsening of inflammation and asthma. Indeed, the combination has consistently been shown to reduce the number of severe asthma exacerbations (Pauwels et al. 1997; Shrewsbury et al. 2000). This approach has proved so successful that it has spawned the development of two fixed-dose combinations of long-acting inhaled beta$_2$-agonists and inhaled corticosteroids in one inhaler, one currently marketed. The fixed-dose combination may be easier to use and hence facilitate adherence to the regimen, but there is no evidence of clinical superiority over using the inhaled corticosteroids and long-acting inhaled beta$_2$-agonists in separate inhalers.

OR

- **Increase the dose of inhaled corticosteroids *and* add a long-acting inhaled beta$_2$-agonist** (SRE-Evidence B). This approach should be reserved for those patients experiencing recurring severe exacerbations requiring oral prednisone, emergency department visits, or hospitalizations. In a 1-year trial of combination therapy, the addition of long-acting inhaled beta$_2$-agonists to either low-dose or high-dose inhaled corticosteroids significantly reduced both mild and severe exacerbations (Pauwels et al. 1997). In addition, fewer exacerbations occurred in the high-dose inhaled corticosteroid group compared with the lower-dose group, although statistical analysis was not done.

OR

- Give inhaled corticosteroids as monotherapy by increasing the dose within the medium-dose range (SRE-Evidence A, B). This approach is another preferred treatment option for young children; it is an alternative, but not preferred, treatment option for older children and adults. Studies of adults in which the dose of inhaled corticosteroids was at least doubled consistently demonstrate improved lung function and other outcomes in those patients not completely controlled on low-to-medium-doses of inhaled corticosteroids, but these results are consistently less effective than adding a long-acting inhaled beta$_2$-agonist (SRE-Evidence A, B).

OR

- **Add a leukotriene modifier or theophylline to inhaled corticosteroids** (SRE-Evidence B; Evidence B). The addition of leukotriene modifiers and theophylline has produced modest improvement in lung function and some other outcomes in patients not completely controlled on inhaled corticosteroids. The addition of theophylline, however, has not been shown to be more effective than doubling the dose of inhaled corticosteroids (Evans et al. 1997; Ukena et al. 1997). The leukotriene modifiers have produced improvements in lung function and in some but not all measures of asthma control in patients incompletely controlled on inhaled corticosteroids (Laviolette et al. 1999). In addition, the leukotriene modifiers allow slightly more patients to be taken off inhaled corticosteroids than does placebo (11 percent difference) (Lofdahl et al. 1999). The addition of the leukotriene modifiers to inhaled corticosteroids has not been compared with doubling the dose of inhaled corticosteroids. Direct comparisons of the addition of a leukotriene modifier or a long-acting inhaled beta$_2$-agonist to therapy for patients incompletely controlled on inhaled corticosteroids show significantly greater improvement in lung function and other measures of asthma control for patients receiving the long-acting inhaled beta$_2$-agonist and inhaled corticosteroid combination (Busse et al. 1999; Nelson et al. 2000). Thus, although the combination of inhaled corticosteroids and either theophylline or leukotriene modifier is not the preferred approach, considerations favoring one of these alternative combinations would be the patient's intolerance of the side effects of the long-acting inhaled beta$_2$-agonist, marked preference for oral therapy, and demonstration of superior responsiveness to the alternative class of drug, as well as financial considerations (theophylline is the least expensive).

Specific issues for children. **Recommendations on combination therapy for children younger than 12 years of age with moderate persistent asthma are based on extrapolations from studies in older children and adults and on expert opinion** (Evidence B, D). None of the adjunctive therapy combinations have been adequately studied in children younger than 12 years of age, and they have not been studied at all in children younger than 4 years of age. One negative study of combination therapy in children with mild or moderate persistent asthma failed to establish a need in the study participants at baseline for more therapy than low-dose inhaled corticosteroids and thus did not sufficiently address the question of combination therapy (Verberne et al. 1998). In one study in children 4 to 16 years of age with moderate or severe asthma, the addition of a long-acting beta$_2$-agonist produced a clear benefit compared to placebo (Russell et al. 1995). In a recent crossover comparison of children 6 to 14 years of age on inhaled corticosteroids, no significant difference was found with the addition of the LTRA montelukast in the primary outcome measure FEV_1, but a small reduction in as-needed short-acting

beta$_2$-agonist use (.33 puffs/day) in favor of LTRA was found. No difference was found for worsening asthma, asthma attacks, or quality of life (Simons et al. 2001). Studies of the addition of theophylline to inhaled corticosteroids in children 6 to 19 years of age showed both a benefit (Nassif et al. 1981) and no benefit (Meltzer et al. 1992). Neither of these theophylline studies is of high enough quality to generate a recommendation. Finally, there is only one study on adjunctive therapy that included children as young as 4 years of age, and there are no studies in children younger than 4 years of age.

Step 4: Severe Persistent Asthma

Patients with severe persistent asthma require high doses of inhaled corticosteroids and a long-acting inhaled beta$_2$-agonist and, if needed, an oral corticosteroid (Evidence B). It is the opinion of the Expert Panel that consultation with an asthma specialist is recommended for patients with severe persistent asthma. Evidence to date does not support using a third long-term-control medication added to inhaled corticosteroids and long-acting inhaled beta$_2$-agonists in order to avoid using systemic corticosteroid therapy (Evidence C). A study found no benefit for the addition of an LTRA to high doses of inhaled corticosteroids and, for most patients in the study, another medication (either theophylline, a long-acting beta$_2$-agonist, oral corticosteroid, or a combination) (Robinson et al. 2001). Similar studies of other long-term-control medications added to the combination of medium-to-high doses of inhaled corticosteroids and long-acting inhaled beta$_2$-agonists in severe persistent asthma are not available.

Patients whose asthma is not controlled on high doses of inhaled corticosteroids and the addition of long-acting inhaled beta$_2$-agonists also will need oral systemic corticosteroids on a regularly scheduled, long-term basis. For patients who require long-term systemic corticosteroids:

- Use the lowest possible dose (single dose daily or, preferably, on alternate days).
- Monitor patients closely for corticosteroid adverse side effects (see component 3-Medications).
- When control of asthma is achieved, make persistent attempts to reduce systemic corticosteroids. High doses of inhaled corticosteroids are preferable to systemic corticosteroids because inhaled corticosteroids have fewer systemic effects.
- Recommend consultation with an asthma specialist.

Recommendations for Future Research

The Panel recommends the following research to clarify treatment options:

- Long-term studies to examine the effect of adjunctive therapy on possible loss in pulmonary function and the natural history of asthma—hospitalization, exacerbations, and decline in pulmonary function.
- Studies of noninvasive markers that would give a composite picture of both disease activity (e.g., inflammation) and disease control. These could be used as surrogate markers for overall asthma control to guide therapy. Ideally, such markers would be more efficient than gauging a patient's response to therapy following a relatively long therapeutic trial.
- Long-term studies to examine the importance of the greater suppression of inflammation achievable with higher doses of inhaled corticosteroids compared with adjunctive therapy. Low doses of inhaled corticosteroids usually are sufficient for improvement in lung function and control of asthma symptoms but may not suppress inflammation to the same extent as higher doses. Studies to assess the value of maximum suppression of inflammation vis-à-vis therapeutic control will contribute to understanding the appropriate use of inhaled corticosteroids and adjunctive therapy.
- Evaluations of adjunctive therapies in children younger than 12 years of age.

Key Evidence Tables

Table 1-6. Meta-Analysis: Lung Function Outcomes for Studies Comparing the Addition of Long-Acting Beta$_2$-Agonists to a Fixed Dose of Inhaled Corticosteroids

Meta-Analysis	Effect Size Estimate	95% CI	Test for Homogeneity P-Value	Treatment Effect Estimate	95% CI
FEV_1: Combined Studies (n = 14)	0.334	0.241, 0.428	0.10	0.17 L 3.71% pred	0.12, 0.22 2.67, 4.75
FEV_1: Sensitivity analysis by quality: Studies that meet all generic quality criteria except allocation concealment and meet most (>4) asthma-specific criteria (n = 3)	0.319	0.139, 0.499	0.14	0.17 L 3.43% pred	0.07, 0.26 1.54, 5.54
FEV_1: Sensitivity analysis by quality: Studies that meet all generic quality criteria except allocation concealment (N = 11)	0.368	0.257, 0.478	0.20	0.19 L 4.08% pred	0.13, 0.25 2.85, 5.30
PEF: Combined studies (n = 9)	0.581	0.417, 0.745	0.0034	24.68 L/min 7.26% pred	17.70, 31.65 5.21, 9.31
PEF: Sensitivity analysis by quality: Studies that meet all generic quality criteria except allocation concealment and meet most (>4) asthma-specific criteria (n = 4)	.0.643	0.460, 0.826	0.17	27.33 L/min 8.04% pred	19.55, 35.10 5.75, 10.32
PEF: Sensitivity analysis by quality: Studies that meet all generic quality criteria except allocation concealment (n = 8)	0.630	0.478, 0.781	0.06	26.77 L/min 7.88% pred	20.32, 33.19 5.98, 9.76

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01-E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

Table 1-7. Meta-Analysis: Medication Use Outcomes for Studies Comparing the Addition of Long-Acting Beta$_2$-Agonists to a Fixed Dose of Inhaled Corticosteroids

Meta-Analysis	Treatment Effect Estimate	95% CI	Test for Homogeneity P-Value
Puffs/day: Combined studies (n = 6)	-1.18	-1.56, -0.80	0.018
Puffs/day: Sensitivity analysis by quality: Studies that meet all generic quality criteria except allocation concealment and meet most (>4) asthma-specific criteria (n = 3)	-1.34	-1.87, -0.84	0.20
Puffs/day: Sensitivity analysis by quality: Studies meet all generic quality criteria except allocation concealment (n = 5)	-1.00	-1.34, -0.66	0.14

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01-E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

Table 1–8. Meta-Analysis: Lung Function Outcomes for Studies Comparing a Lower Dose of Inhaled Corticosteroids Plus Long-Acting Inhaled Beta$_2$-Agonists vs. an Increased Dose of Inhaled Corticosteroids

Meta-Analysis	Effect Size Estimate	95% CI	Test for Homogeneity P-Value	Treatment Effect Estimate	95% CI
FEV_1: Combined Studies (n = 8)	0.209	0.133, 0.285	0.93	0.11 L 2.32% pred	0.07, 0.15 1.48-3.16
FEV_1: Sensitivity analysis by quality: Studies that that meet all generic quality criteria except allocation concealment and meet most (>4) asthma-specific criteria (n = 4)	0.203	0.107, 0.299	0.94	0.11 L 2.25% pred	0.06, 0.16 1.19, 3.32
FEV_1: Sensitivity analysis by quality: Studies that meet all generic quality criteria except allocation concealment (n = 7)	0.212	0.134, 0.290	0.88	0.11 L 2.35% pred	0.07, 0.15 1.49, 3.22
PEF: Combined studies (n = 10)	0.310	0.192, 0.429	0.0002	11.6 L/min 3.4% pred	5.2-18.0 1.5-5.3
PEF: Sensitivity analysis by quality: Studies that meet all generic quality criteria except allocation concealment and meet most (>4) asthma-specific criteria (n = 4)	0.300	0.030, 0.569	0.000007	12.75 L/min 3.75% pred	1.28, 24.18 0.38, 7.11
PEF: Sensitivity analysis by quality: Studies that meet all generic quality criteria except allocation concealment (n = 7)	0.296	0.143, 0.449	0.00005	12.58 L/min 3.7% pred	6.08, 19.08 1.79, 5.61

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01–E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

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Use of Antibiotics To Treat Asthma Exacerbations

Question

Does routinely adding antibiotics to standard care improve the outcomes of treatment for acute exacerbation of asthma? Does the addition of antibiotics to standard care in the following populations improve the outcomes of treatment for an acute exacerbation of asthma: patients without signs and symptoms of bacterial infection; patients with signs and symptoms of a bacterial infection; patients with signs and symptoms of sinusitis?

Summary Answer to the Question

The available evidence (two randomized, controlled clinical trials) suggests no benefit from antibiotic therapy for asthma exacerbations, whether administered routinely or when suspicion of bacterial infection is low (SRE-Evidence B). No studies addressed the question of greatest relevance to contemporary clinical practice: whether the addition of antibiotics to standard care when signs and symptoms suggest the possibility—but do not clearly indicate the presence—of bacterial infection improves the outcomes of treatment for acute asthma exacerbations.

The EPR-2 recommendation has not been changed: Antibiotics are not recommended for the treatment of acute asthma exacerbations except as needed for comorbid conditions—e.g., for the patients with fever and purulent sputum, evidence of pneumonia, or suspected bacterial sinusitis.

Rationale for the Question

Asthma exacerbations often are associated with clinical signs of infection, such as purulence of expectorated sputum or nasal discharge. Most asthma exacerbations are associated with infection by a respiratory virus, especially rhinovirus (Nicholson et al. 1993; Johnston et al. 1995), but a small percentage of exacerbations are associated with infection by an atypical bacterium, like *Mycoplasma pneumoniae* or *Chlamydia pneumoniae* (Freymuth et al. 1999). It is widely believed that coincident bacterial sinusitis contributes to asthma exacerbations, and some clinicians have postulated that airway obstruction due to mucus plugging—common in asthma—predisposes patients to bacterial infection of nondraining regions of the lungs.

In the absence of clear signs of bacterial infection (e.g., lobar pulmonary infiltrate on chest radiography distinguishing viral from bacterial infections), infection is often difficult to manage. Viral infections commonly resemble bacterial infections in that they also cause neutrophilic inflammation of the upper and lower airways (Teran et al. 1997; Trigg et al. 1996; Fahy et al. 1995). This difficulty, coupled even with the remote possibility that bacterial infection may be associated with an asthma exacerbation, may account for the frequency with which antibiotics are prescribed in addition to inhaled bronchodilators, inhaled or systemic corticosteroids, and supplemental oxygen.

Systematic Review of the Evidence

The following description of the SRE is an adaptation of the evidence report, including direct excerpts, submitted by the Blue Cross Blue Shield Association Evidence-Based Practice Center. (See Introduction, Methods.)

Methods of Literature Search

In addition to the selection criteria for studies related to all topics in the SRE (described in the Introduction section), studies for this question were included in which standard care (asthma medications) plus antibiotics was compared with standard care alone in the treatment of acute asthma exacerbations. Patient populations included patients without signs and symptoms of bacterial infection, patients with signs and symptoms of bacterial infection, and patients with signs and symptoms of sinusitis.

Summary of Findings

Studies

Only two randomized, double-blind, placebo-controlled, parallel-group trials—with a total enrollment of 121 patients—have addressed the question of whether routinely adding antibiotics to standard care improves the outcomes of treatment for acute asthma exacerbations (Shapiro et al. 1974; Graham et al. 1982). (See the key evidence tables in this section.) Both trials studied patients hospitalized for asthma exacerbations. Both used a penicillin derivative whose activity against atypical bacteria was unknown. Shapiro and colleagues examined the effects of hetacillin (an analogue of ampicillin; 100 mg/kg every 24 hours for a minimum of 24 hours, then 225 mg four times per day for 6 days) in 50 children who did not exhibit clinical evidence of bacterial infection. Graham and colleagues examined the effects of amoxicillin (500 mg three times per day) in 60 adults and adolescents who experienced a total of 71 hospital admissions. Whereas the pediatric study explicitly excluded patients with clinical evidence of bacterial infection, the study of adults and adolescents excluded only patients with evidence of pneumonia on chest radiography. Thus, the populations in these studies consisted primarily of patients without signs or symptoms of bacterial illness, including suspected acute sinusitis.

In both trials, all patients received standard care that included high-dose oral or intravenous corticosteroids and regularly scheduled beta$_2$-agonist treatment. In the pediatric study, all patients were also treated with intravenous aminophylline followed by oral theophylline.

The study design and conduct for these two trials did not meet the SRE criteria for higher quality because of deficiencies in allocation concealment, subject withdrawal, and reporting of power calculations.

The outcomes analyzed included change in FEV_1, symptom scores, and length of hospital stay.

Results of Studies

Neither study reported an association—nor a trend towards an association—between antibiotic treatment and greater improvement in any asthma outcome. Therefore, available evidence suggests no benefit from the use of antibiotic treatment for asthma exacerbations either routinely or when the suspicion of bacterial infection is minimal. (See key evidence tables 1–11 and 1–12.)

Additional Literature/Information

A related question, for which clinical trials data are unavailable, should ask whether the use of an antibiotic active against *Mycoplasma* and *Chlamydia* would alter outcomes. Some recent studies using polymerase chain reaction (PCR)-based methods for detecting specific genomic sequences have suggested that chronic infection with these organisms may contribute to the severity of chronic asthma (Kraft et al. 1998). These highly sensitive methods have not yet been applied to the analysis of airway tissue or secretions obtained from patients suffering acute exacerbations. Thus, there is a theoretical basis for the concept that a subgroup of patients with asthma exacerbations may benefit from treatment with an antibiotic that is active against these atypical bacteria.

The EPR-2 statement that "the use of antibiotics is generally reserved for patients with fever and purulent sputum (discolored because of polymorphonuclear leukocytes, not eosinophils)" comes under scrutiny because low-grade fever also may accompany viral respiratory infections. Furthermore, a recent study shows that discoloration of sputum by polymorphonuclear leukocytes is observed in viral tracheobronchitis, and the sputum from patients suffering from uncomplicated asthma exacerbations commonly contains high numbers of polymorphonuclear leukocytes (Fahy et al. 1995).

Recommendations for EPR Update

No evidence supports changing the EPR-2 recommendation (SRE-Evidence B). The parenthetical statement on page 116 of EPR-2 ["(discolored because of polymorphonuclear leukocytes, not eosinophils)"] should be removed (Evidence C). The recommendation can otherwise stand and is as follows:

Antibiotics are *not* recommended for the treatment of acute asthma exacerbations except as needed for comorbid conditions. Bacterial, *Chlamydia,* or *Mycoplasma* infections infrequently contribute to exacerbations of asthma and therefore the use of antibiotics is generally reserved for patients with fever and purulent sputum and for patients with evidence of pneumonia. When the presence of bacterial sinusitis is suspected, treat with antibiotics.

Recommendations for Future Research

No studies addressed the question of greatest relevance to contemporary clinical practice—whether the addition of antibiotics to standard care when signs and symptoms suggest the possibility but do not clearly indicate the presence of bacterial infection improves the outcomes of treatment for acute asthma exacerbations. The two trials reviewed excluded the patients most likely to be treated with antibiotics and those with signs or symptoms suggestive of bacterial infection, including suspected acute sinusitis. Studies of the efficacy of antibiotic treatment in this group are needed.

Several studies are needed to clarify the role of antibiotics in the treatment of asthma exacerbations. Questions for research are as follows:

- What is the efficacy of antibiotic treatment in asthma patients most likely to be treated with antibiotics, such as those with signs suggestive of bacterial infection, including suspected acute sinusitis? The role of sinusitis in acute exacerbations of asthma has not been truly defined.
- What is the role of sinusitis in acute exacerbations of asthma or increased asthma severity?
- What is the efficacy of using an antibiotic active against atypical bacteria, given the possibility that such bacteria commonly contribute to asthma exacerbations?
- What would be the value of studies applying modern sensitive methods of detection of atypical bacteria (e.g., PCR-based methods) to samples of airway tissues or secretions obtained at the time of an asthma exacerbation?
- Do antibiotics such as macrolides have a non-antibiotic action (e.g., anti-inflammatory) that is beneficial in asthma patients?

Key Evidence Tables

Table 1-9. Study Characteristics

Citation	Study Design	Study Setting	Asthma Severity	Eligibility
Graham, Milton, Knowles et al. 1982	Randomized, double-blind, placebo-controlled, parallel group trial	Country: United Kingdom Funding: Government grant Tx setting: University Hospital, inpatient setting	Stated: Not specified Estimated: Unable to estimate	Eligibility assessed on admission to hospital with asthma exacerbation: • FEV_1 of 1.5L or less and/or PEF of 150 l/min • Reversibility of FEV_1 at least 15% spontaneously or after inhalation of $beta_2$-agonist Exclusions: Evidence of pneumonia on CXR, history of penicillin allergy
Shapiro, Eggleston, Pierson et al. 1974	Randomized, double-blind, placebo-controlled, parallel group trial	Country: United States Funding: Pharm Industry and Government grant Tx setting: Hospital, inpatient setting	Stated: Not specified Estimated: Unable to estimate	Eligibility assessed on admission to hospital with asthma exacerbation: • Severe bronchospasm, lack of response to subcutaneous epinephrine Exclusions: Clinical evidence of bacterial infection; recent use of antibiotics

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01-E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

Table 1–10. Study Parameters

Citation	Study Arm	Treatment	Comments
Graham, Milton, Knowles et al. 1982	Placebo	Placebo tablet 3 times per day Oral prednisolone (20–60 mg/day) and/or IV hydrocortisone (100–200 mg every 4 to 6 hours) Regularly scheduled beta$_2$-agonists and/or phosphodiesterase inhibitors Chest physiotherapy	60 patients enrolled with 71 exacerbations. Unit of analysis by exacerbations.
	Antibiotics	Amoxicillin 500 mg 3 times per day Oral prednisolone (20–60 mg/day) and/or IV hydrocortisone (100–200 mg every 4 to 6 hours) Regularly scheduled beta$_2$-agonists and/or phosphodiesterase inhibitors Chest physiotherapy	Culture-proven bacterial source of infection found in two patients on admission and two patients on discharge
Shapiro, Eggleston, Pierson et al. 1974	Placebo	Placebo 4 times per day for 6 days IV hydrocortisone (7 mg/kg/24 hr) for 24 hours, followed by oral prednisone IV aminophylline (15 mg/kg/24 hr) for 24 hours, followed by oral theophylline Nebulized beta$_2$-agonists q30 min x 4, then as needed	37 patients enrolled with 44 exacerbations, unit of analysis by exacerbation
	Antibiotics	Hetacillin (100 mg/kg/24 hr) for at least 24 hours, followed by oral hetacillin 225 mg 4 times per day for 6 days IV hydrocortisone (7 mg/kg/24 hr) for 24 hours, followed by oral prednisone IV aminophylline (15 mg/kg/24 hr) for 24 hours, followed by oral theophylline Nebulized beta$_2$-agonists q30 min x 4, then as needed	

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01–E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

Key Evidence Tables

Table 1-11. Lung Function Outcome

Citation	Study Arm	Number Enrolled	Number Evaluable	Study Duration (days) (median/range)	FEV_1 Baseline (mean)	
Graham, Milton, Knowles et al. 1982	Placebo	71*	32*	8 (3–16)	20.9 (<7.3–63)	
	Antibiotics	71*	37*	7 (3–25)	23.1 (<7.3–45.5)	
Shapiro, Eggleston, Pierson et al.1974	Placebo	50*	24*	2.9 (SD 1.4)	26.5 (SD 15)	
	Antibiotics	50*	20*	2.5 (SD 0.8)	28.3 (SD 11)	

Table 1-12. Symptoms/Utilization Outcomes

Citation	Study Arm	Number Enrolled	Number Evaluable	Study Duration (days) (median/range)	
Graham, Milton, Knowles et al. 1982	Placebo	34	32	8 (3–16)	
	Antibiotics	37	37	7 (3–25)	
Shapiro, Eggleston, Pierson et al. 1974	Placebo	24	24	2.9 (SD 1.4)	
	Antibiotics	20	20	2.5 (SD 0.8)	

	FEV_1 Final (mean)	P-Value	PEF Baseline (mean/range)	PEF Final (mean/range)	P-Value
	65.6 (31.5–108.5)		23.8 (<9.4–83.9)	72.8 (32.8–108.1)	
	52.3 (10–92.9)	0.039	23.8 (<9.4–47.3)	59 (16.7–95)	0.052
	49 (SD 17)		NR	NR	
	61 (SD 19)	NR	NR	NR	

*Unit of analysis was admission. Number enrolled represented total admissions in both groups, information not provided by group. Number evaluated represents total number of admissions included in analysis.

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01–E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

	Baseline Symptom Score (median/range)	Final Symptom Score (median/range)	P-Value	Hospital Length of Stay	P-Value
	11 (6–12)	4 (4–8)		8 (3–16)	
	11 (5–12)	5 (4–9)	NS	7 (3–25)	NS
	7.1 (mean) (SD 2.2)	2.5 (SD 2.0)		2.9 (SD 1.4)	
	7.1 (mean) (SD 1.8)	2.0 (SD 2.0)	NR	2.4 (SD 0.8)	

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01–E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

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Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01–EO44. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

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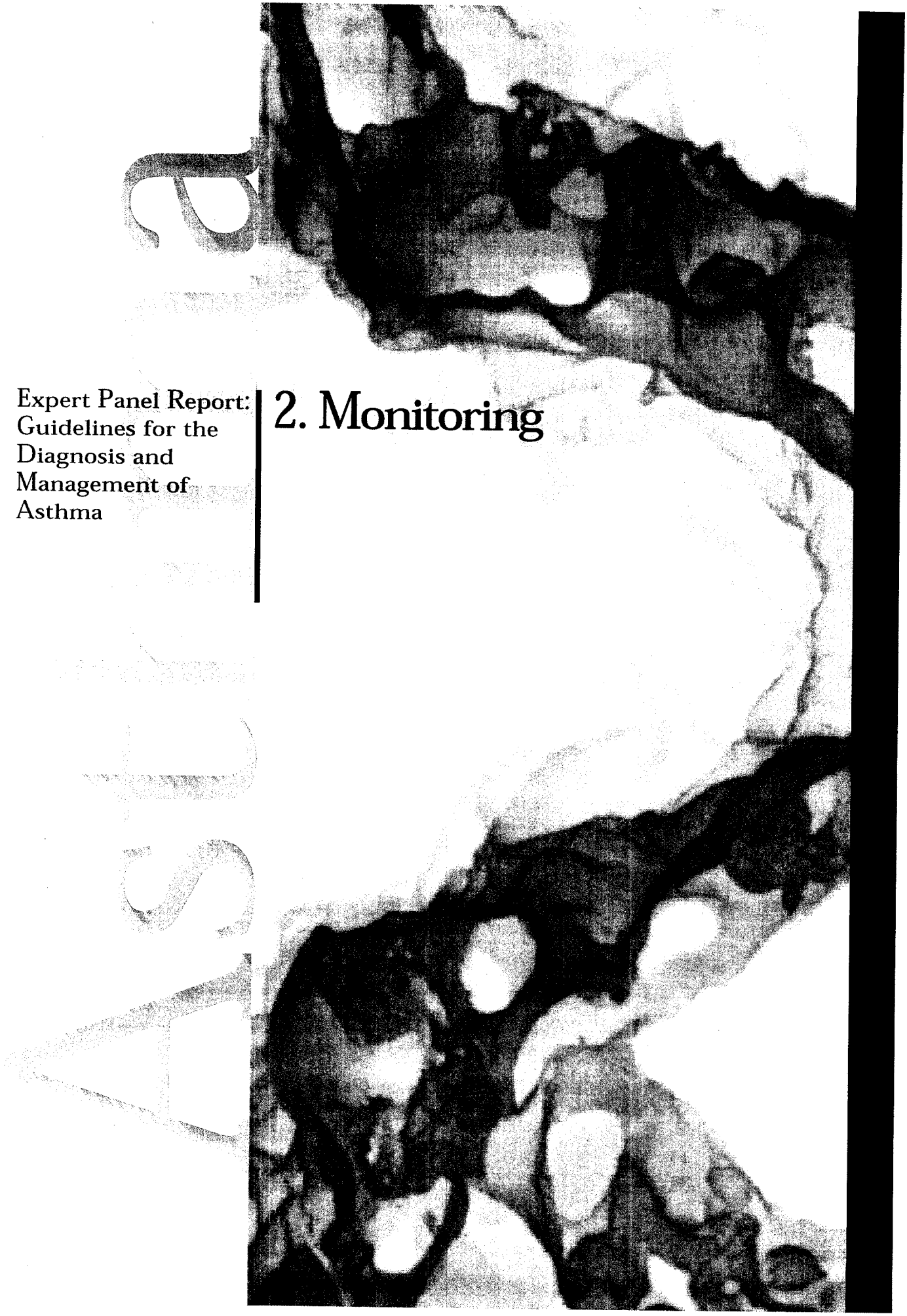
Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma

2. Monitoring



2. Monitoring

Two distinct questions have been raised regarding the use of written action plans in the management of asthma. First, does the use of written action plans make a difference in patient outcomes beyond those accomplished by appropriate medical/pharmacologic management? Second, is there a difference in patient outcomes between action plans based on symptom monitoring and those based on peak flow monitoring? This section of the EPR Update considers both questions.

Written Action Plans Compared to Medical Management Alone

Question

Compared to medical management alone, does the use of a written asthma action plan improve outcomes?

Summary Answer to the Question

Data are insufficient to support or refute the benefits of using written asthma action plans compared to medical management alone (SRE-Evidence B). Seven studies compared medical management with written action plans to medical management without action plans. Beyond including instructions on the action plan to the intervention groups, four of these studies did not include asthma education for either the intervention or control groups; three of the studies included similar but limited asthma education for both intervention and control groups. Only one study included children. Significant limitations in study designs and methods in these studies preclude conclusions. For example, the studies showing no benefits of written action plans did not have sufficient power for comparisons between treatment and control groups, and the two studies reporting significant improvements with action plans had potential biases in patient selection, withdrawals, data collection, or analysis.

However, a Cochrane review of 25 studies comparing asthma self-management education interventions for adults to medical care without such education also contrasted those studies with self-management interventions that included written action plans to those that did not. The self-management interventions that included written action plans had the greatest benefits, including reduced emergency department visits and hospitalizations and improved lung function.

The EPR-2 recommendations have not been changed: It is the opinion of the Expert Panel that use of written action plans as part of an overall effort to educate patients in self-management is recommended, especially for patients with moderate or severe persistent asthma and patients with a history of severe exacerbations (Evidence B, C).

Rationale for the Question

The use of written action plans is recommended in the EPR-2 and is widely accepted as good practice. Generally, the use of written action plans has been studied as part of self-management education (Gibson et al. 2000). In busy practices, however, physicians often provide their patients with action plans independent of other asthma education efforts. This question was posed in order to identify data that describe the effects of using written action plans, independent of other components of asthma education.

Systematic Review of the Evidence

The following description of the SRE is an adaptation of the evidence report, including direct excerpts, submitted by the Blue Cross Blue Shield Association Evidence-Based Practice Center. (See Introduction, Methods.)

Methods of Literature Search

For the purpose of the SRE, an action plan is a written algorithm that identifies specific clinical indicators that should alert patients to make adjustments in their medications and provides specific instructions on how to make these adjustments. EPR-2 recommends the use of both a daily self-management plan and an action plan for exacerbations. Generally, studies included in the SRE involved the use of one plan that combined the objectives of both. Typically, the plans divided steps for patient actions into different zones, in which recommended actions are correlated with differing acute signs and symptoms of worsening asthma. Most of the plans in the available studies used four-zone plans, some were three-zone plans that did not include directions for use of oral corticosteroids before seeking emergency care.

The evidence review examined studies in which the intervention used an action plan as defined above and, if asthma education was given to both treatment and control groups, the treatment group had no more than 1 additional hour of education for the action plan. The treatment/observation duration was at least 12 weeks, and the intervention and control groups received the same treatment, except that the intervention group also received a written action plan. Studies were excluded if the comparisons were confounded by additional treatment components in the intervention group—for example, optimization of medications in the intervention group only or education programs of more than 1 hour in the intervention group only. The literature review included randomized controlled trials (RCTs) in which at least 25 evaluable patients (not physicians) were randomly allocated to the intervention and control groups.

Summary of Findings

Studies

Seven studies involving more than 1,400 patients met SRE inclusion criteria for review; only one of the studies included children. (See the key evidence tables in this section.) None of the studies met SRE standards for high quality; each had significant limitations. None was conducted with sufficient power (i.e., adequate numbers of subjects in each study arm) to enable comparisons between treatment and control groups. In one study reporting reduced emergency department visits, data were unavailable to control for baseline differences that may have existed between treatment and control groups, and the reported effect may be attributed to a subset of high frequency users. In another study, the design involved clinicians who both provided plans and collected assessment data. Moreover, a large number of subjects were excluded from the analyses.

All seven studies compared medical management with written action plans to medical management without written action plans, and all used a peak flow meter-based plan. Three of the studies also included similar but limited asthma education for both the intervention and control groups, but the groups still differed as to whether written plans were used. In two trials, the control group used peak flow meters but without an action plan.

Results of Studies

Five trials documented no differences in outcomes, and two trials documented significant benefit of written action plans, especially in reducing emergency department visits. However, there were notable limitations to each of these trials, as described earlier. In summary, SRE study data were insufficient to support or to refute the advantages of using asthma action plans independent of self-management education when compared with medical management alone.

Additional Literature/Information

Evidence supporting the use of written plans as a component of self-management education is reported in a recent Cochrane Collaboration review (Gibson et al. 2000). The SRE question on action plans provides a clearer assessment of isolating the advantages of providing an action plan. The Cochrane review centered on the benefits of self-management interventions and regular medical review with the clinician vs. usual medical care. The Cochrane review, however, also contrasted those self-management interventions with written action plans to those without written action plans. The review included some of the same studies included in the SRE but overcame the limitations of study sample sizes by pooling data. Further, the set of 25 studies in the Cochrane review was larger than the 7 in the SRE due to the broader question under review.
In the Cochrane analysis that compared results of self-management interventions with action plans to those without, the interventions with written action plans demonstrated the greatest benefits, including reduced asthma-related hospital admissions (odds ratio 0.35, 95 percent confidence interval) and reduced emergency department visits (odds ratio 0.55, 95 percent confidence interval). In addition, patients who managed their asthma by adjusting medications according to a written action plan had better lung function than those whose medications were adjusted by a doctor during regular care visits. The review concluded that training in asthma self-management that involves self-monitoring by either peak flow or symptoms, coupled with regular medical review and a written action plan, appears to improve health outcomes for adults with asthma.

Additional evidence supporting written action plans coupled with regular patient education and medical review is available from a recent case control study (Abramson et al. 2001). This study does not fit the SRE review criteria because studies that qualified for this review were required to be RCTs allowing inferences of cause and effect, and they were required to provide an action plan independent of a multicomponent intervention including education. Although the Abramson study is not an RCT, it is a well-conducted study that compared 51 patients who died from asthma to 202 patients presenting to hospitals with acute asthma. The study reported that written action plans for patients with severe persistent asthma were associated with a 70 percent reduction in mortality risk. As such, the study supports the opinion that providing written action plans as part of asthma education is an important element of practice.

Recommendations for EPR Update

No data from the SRE, in which RCTs compared written action plans to medical management alone, indicate the need to change the EPR-2 action plan recommendations (SRE-Evidence B). Additional data from studies on action plans as a part of self-management education support the EPR-2 recommendations (Evidence B, C). The following blue text indicates revisions that should be incorporated into the text on pages 33 and 123 in EPR-2.

Component 1: Measures of Assessment and Monitoring; Periodic Assessment and Monitoring (page 33 in EPR-2)

Whether peak flow monitoring, symptom monitoring, or a combination of approaches is used, the Expert Panel believes that self-monitoring is important to the effective self-management of asthma. The nature and intensity of self-monitoring should be individualized, based on such factors as asthma severity, patient's ability to perceive airflow obstruction, availability of peak flow meters, and patient preferences.

It is the opinion of the Expert Panel that, regardless of the type of monitoring used, patients should be given a written action plan and instructed to use it. (See figure 4–5.) It is the opinion of the Expert Panel that including action plans as part of an overall effort to educate patients in self-management is the soundest approach and is especially indicated for patients with moderate or severe persistent disease or a history of severe exacerbations (Evidence B, C). It is the opinion of the Expert Panel that a plan is important in large part because it enhances clinician-patient communication. The plan should define a regimen that meets the medical needs of the patient

and should have a format that facilitates the patient's understanding and ability to take appropriate action to control the disease. Regardless of format, an effective plan should include the following:

- Explicit, patient-specific recommendations for environmental control and other preventive efforts that may be necessary to avoid or reduce the impact of exacerbations
- An algorithm of procedures that clearly describes how to use long-term-control and rescue medicines, given a set of specific circumstances and conditions, and clear instructions on how to make medicine adjustments when conditions change
- Steps the patient should take when medicines are ineffective or if an emergency situation arises
- Contacts for securing urgent care, if needed

As emphasized above, it is the opinion of the Expert Panel that a written action plan is considered part of ongoing efforts to provide self-management education and support appropriate to the severity of the patient's asthma, the patient's age, and related circumstances (Evidence B, C). The clinician should periodically review the plan, revise it as necessary, and confirm that the patient knows what to do if his or her asthma gets worse.

Component 4: Education for a Partnership in Asthma Care, Key Points (page 123 in EPR-2)

- Patient education should begin at the time of diagnosis and be integrated into every step of clinical asthma care.
- It is essential that education be provided by all members of the health care team. The principal clinician should introduce the key educational messages and negotiate agreements with patients; these messages should be reinforced and expanded by all members of the health care team.
- Teach asthma self-management, tailoring the approach to the needs of each patient. Maintain a sensitivity to cultural beliefs and practices.
- Teach and reinforce at every opportunity:
  - Basic facts about asthma
  - Roles of medications
  - Skills: inhaler/spacer/holding chamber use, self-monitoring
  - Environmental control measures
  - When and how to take rescue actions.
- Jointly develop treatment goals.
- To encourage an active partnership, provide all patients with a written daily self-management plan and an action plan for exacerbations. A written action plan is considered part of ongoing efforts to provide self-management education and support appropriate to the severity of the patient's asthma, the patient's age, and related circumstances (Evidence B, C). Action plans are especially important for patients with moderate-to-severe asthma and patients with a history of severe exacerbations. Provide appropriate patients with a daily asthma diary.
- Encourage adherence by promoting open communication; individualizing, reviewing, and adjusting plans as needed; emphasizing goals and outcomes; and encouraging family involvement.

Recommendations for Future Research

Research that may enhance the quality and effect of interventions fostering patient self-management would examine the following questions:

- Are some action plan formats more effective than others? What characterizes the most effective format?
- What alternative action plan formats are effective, given specific patient needs, including disease severity, literacy levels, languages spoken, ages, and unique management problems (e.g., comorbidities)?
- How much time and emphasis should be given to the development of action plans during the course of clinical counseling? In comprehensive education programs? In medical review?

- What are potential means of providing self-management interventions that include action planning to patients who are members of underserved populations (e.g., reaching them through worksites, community centers, or churches)?
- How effective are written action plans in treating children with asthma?
- How effective are written action plans in different caretaker situations (e.g., daycare, camps, or school)?

Key Evidence Tables

Table 2-1. Study Characteristics

Citation	Study Design	Study Setting	
Optimal medical management vs. optimal medical management + peak flow meter (PFM)-based action plan			
Jones, Mullee, Middleton et al. 1995	Randomized; parallel, controlled	Country: United Kingdom Funding: Pharm. ind. grant Tx Setting: Primary/specialty combination, university Multicenter	
Drummond, Abdalla, Beattie et al. 1994 (GRASSIC)	Randomized; parallel, controlled	Country: United Kingdom Funding: Academic grant Tx Setting: Specialty care, nonuniversity Multicenter	
Ayres, Campbell, Follows 1995	Randomized; parallel, controlled	Country: United Kingdom Funding: Pharm. ind. grant Tx Setting: Unknown Multicenter	
Cowie, Revitt, Underwood et al. 1997	Randomized; parallel, controlled	Country: Canada Funding: Hospital Tx Setting: Primary/specialty combination, university Multicenter	
Cote, Cartier, Robichaud et al. 1997	Randomized; parallel, controlled	Country: Canada Funding: Pharm. ind. grant Tx Setting: Specialty care, nonuniversity Multicenter	
Optimal medical management + (PFM) use (without action plan) vs. optimal medical management + PFM-based action plan			
Ignacio-Garcia and Gonzalez-Santos 1995	Randomized; parallel, controlled	Country: Spain Funding: Not specified Tx Setting: Specialty care, nonuniversity	
Charlton, Antoniou, Atkinson et al. 1994	Randomized; parallel, controlled	Country: Australia Funding: Pharm. ind. and government and university funding Tx Setting: Specialty care, nonuniversity	

	Eligibility	Comments
	Patient eligibility based on symptoms only Included patients using inhaled corticosteroids <1,000 mcg per day for at least 1 month Exclusions: Patients on oral steroids or using peak flow meters at home	Power based on several outcomes (FEV needed 23 patients, sixfold reduction in night wakening needed 21 per group, eightfold reduction in days off work or school needed 37 per group). 2-week course of oral steroids given before randomization to optimize lung function.
	Patient eligibility based on lung function and utilization Inclusion: FEV_1 reversibility 20% or greater Exclusion: Patients who already owned a PFM	Power based on the 569 randomized, but n varies for each outcome and in some cases is not specified as to exact n, just that n was > = 250; may not be powered for all outcomes. Patients included had less severe asthma on entry than those who already owned a PFM and were excluded, especially with regard to social and physical functioning.
	Patient eligibility based on lung function, symptoms, utilization Inclusions: PEF variability maximum 0.15%; nights/week with symptoms minimum 3; use of inhaled corticosteroids or sodium cromoglycate for a minimum of 3 months	Doctor also graded the overall and individual severity of symptoms as 0 = none and 3 = severe.
	Patient eligibility based on symptoms and utilization Inclusions: Treatment for an exacerbation of asthma in an ER or attending a university asthma clinic; history of receiving urgent treatment for asthma in the previous 12 months	Subjects were recruited by contacting those who had been treated for an exacerbation of asthma in an emergency room or those attending a university asthma clinic who had a history of having received urgent treatment for their asthma in the previous 12 months.
	Patient eligibility based on lung function and symptoms FEV_1 postbronchodilator 85–100% of predicted PEF minimum 85% of predicted; PEF variability minimum 0%; Methacholine Exclusion: Patients having previously taken part in an asthma educational program	In discussion "although the control group received more than the usual care treatment, none received book, none had written action plan; none had structured education or PFM at home after run-in." Run-in = 2–6 wks.; diagnosis of asthma included need to take daily anti-inflammatory agents; were excluded.
	Patient eligibility based on utilization only Inclusion: Patients from outpatient asthma clinic with asthma for 2 years	One doctor aware of the group assignment was responsible for assessment of all patients' condition, but the paper also says "in control group, the doctor assessing the patient was blinded with regard to registers of peak flow monitoring until end of study", random allocation by order of recruitment.
	Patient eligibility based on utilization only Inclusion: Patients who required admission for asthma or attended the outpatient department	Randomization was based on age, sex, whether they used asthma prophylaxis before study.

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01-E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

Table 2-2. Lung Function Outcomes: FEV_1

Citation	Study Arm	Number Enrolled	Number Evaluable	Treatment Duration (weeks)	
Usual care vs. peak flow meter (PFM)-based action plan					
Jones, Mullee, Middleton et al. 1995	Usual care	64	39	26	
	PFM-based action plan	63	33	26	
Drummond, Abdalla, Beattie et al. 1994 (GRASSIC)	Usual care	284	260	52	
	PFM-based action plan	285	250	52	
Ayres, Campbell, Follows 1995	Usual care	64	64	24	
	PFM-based action plan	61	31	24	
Cowie, Revitt, Underwood et al. 1997	Usual care	48			
	PFM-based action plan	46			
Cote, Cartier, Robichaud et al. 1997	Usual care	54			
	PFM-based action plan	50			
Usual care + PFM use alone vs. usual care + PFM-based action plan					
Ignacio-Garcia and Gonzalez-Santo 1995	Usual care + PFM use	44	35	28	
	Usual care + PFM-based action plan	50	35	28	
Charlton, Antoniou, Atkinson et al. 1994	Usual care + PFM use	43			
	Usual care + PFM-based action plan	48			

	Baseline FEV_1*	Final FEV_1	P-Value	P-Value Comparison	Comments
	85.4 +/- 17.5 % of predicted	81.2 +/- 18.3 % of predicted			
	87.1 +/- 16.9 % of predicted	83.2 +/- 18 % of predicted	NS	Absolute value, Tx vs. Ctl	
	78.1 % of predicted	75.4 +/- 27.7 % of predicted			95% CI for baseline FEV is 74.8-81.4.
	77.3 % of predicted	74.6 +/- 27.8 % of predicted	NS	Change, Tx vs. Ctl	95% CI for baseline FEV is 74.1-80.5.
	2 +/- 0.1 L (type predose)	2.2 +/- 0.1 L (type predose)			Unclear number of patients analyzed on each end point.
	2.3 +/- 0.1 L (type predose)	2.3 +/- 0.2 L (type predose)	NS	Absolute value, Tx vs. Ctl	Unclear number of patients analyzed on each end point.
	78 +/- 21.3 % of predicted				Number of subjects with <60% predicted was 10.
	82 +/- 20.5 % of predicted				Number of subjects with <60% predicted was 9.
	65.34 +/- 16.6 % of predicted (type predose)	65.48 +/- 24.7 % of predicted			
	69.03 +/- 24.0 % of predicted (type predose)	80.45 +/- 23.3 % of predicted	<0.0040	Absolute value, Tx vs. Ctl	

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01-E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

Table 2-3. Symptom Score Outcomes

Citation	Study Arm	Number Enrolled	Number Evaluable	Treatment Duration (weeks)	Baseline Daytime Symptom Score	Final Daytime Symptom Score	
Usual care vs. peak flow meter (PFM)-based action plan							
Jones, Mullee, Middleton et al. 1995	Usual care	64	45	26		4.95 (median; scale, 0-3)	
	PFM-based action plan	63	39	26		2.85 (median; scale, 0-3)	
Drummond, Abdalla, Beattie et al. 1994 (GRASSIC)	Usual care	284	67	52			
	PFM-based action plan	285	54	52			
Ayres, Campbell, Follows 1995	Usual care	64	64	24	1.91 +/- 0.6 (scale, 0-3)	1.39 +/- 1.11, (scale 0-3)	
	PFM-based action plan	61	61	24	1.77 +/- 0.6 (scale, 0-3)	1.38 +/- 0.12 (scale, 0-3)	
Cowie, Revitt, Underwood et al. 1997	Usual care	48	48	24			
	PFM-based action plan	46	46	24			
Cote, Cartier, Robichaud et al. 1997	Usual care	54					
	PFM-based action plan	50					
Usual care + PFM use alone vs. usual care + PFM-based action plan							
Ignacio-Garcia and Gonzalez-Santos 1995	Usual care + PFM use	44	35	28			
	Usual care + PFM-based action plan	50	35	28			
Charlton, Antoniou, Atkinson et al. 1994	Usual care + PFM use	43	37	52		0.22 (median; scale, 0-3)	
	Usual care + PFM-based action plan	48	42	52		0.26 (median; scale, 0-3)	

	P-Value	Final Nighttime Symptom Score	P-Value	Comments
		0.75 (median; scale, 0-3)		Symptom score across study was divided by number of days w/diary data X 28 to give a monthly rate; sx score day = cough; sx score night = wakening at night; median wheeze = 5.46; shortness of breath = 7.88; asthma restricting normal daily activities = 0.0
	NS[1]	0.35 (median; scale, 0-3)	NS[1]	Symptom score across study was divided by number of days w/diary data X 28 to give a monthly rate; sx score day = cough; sx score night = wakenings at night; median wheeze = 4.39; shortness of breath = 6.50; asthma restricting normal daily activities = 0.17.
				Night and day sx score outcome is only from a subgroup of patients reporting variation in outcome; 112/246 never reported sleep disturbances; 15/246 reported that their sleep was disturbed every night.
				Night and day outcome is only from a subgroup of patients reporting variation in outcome, controlled for peak flow, FEV_1, duration of asthma; 114/239 never reported sleep disturbances; 14/239 reported that their sleep was disturbed every night.
		0.69 +/- 0.13, (scale 0-3)		Sx score day = overall severity of asthma. Changes in: sleep disturbance scores 1.89 → 0.69; cough at rest 1.08 → 0.69; wheeze at rest was 1.25 → 0.67; difficulty breathing 1.47 → 0.96; cough with activity = 1.75 → 1.30.
	NS[1]	0.67 +/- 0.14 (scale, 0-3)		Sx score day = overall severity of asthma. Changes in: sleep disturbance scores 1.79 → 0.67; cough at rest 1.00 → 0.87; wheeze at rest was 0.97 → 0.74; difficulty breathing 1.41 → 0.85; cough with activity = 1.48 → 1.28. All comparisons in sx scores between groups NS.
				No significant differences in other indexes of asthma control, including waking with asthma, $beta_2$-agonist use, or self-rating of asthma severity differed among the groups at 3 months or at 6 months after entry.
				No significant differences in other indexes of asthma control, including waking with asthma, $beta_2$-agonist use, or self-rating of asthma severity among the groups at 3 months or at 6 months after entry.
				Nighttime symptoms = total nighttime awakenings over total study. (Values not reported by AHRQ)
				Nighttime symptoms = total nighttime awakenings over total study.
		0.25 (median; scale, 0-3)		Sx score day = wheeze day; Sx score night = wheeze night; daily score for activity restriction was 0.13.
	NS[1]	0.15 (median; scale, 0-3)	NS[1]	Sx score day = wheeze day; Sx score night = wheeze night; daily score for activity restriction was 0.06, $p < 0.05$ compared to control.

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01–E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

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Peak Flow-Based Compared to Symptom-Based Written Action Plans

Question

Compared to a written action plan based on symptoms, does use of a written action plan based on peak flow monitoring improve outcomes?

Summary Answer to the Question

Evidence neither supports nor refutes the benefits of written action plans based on peak flow monitoring compared to symptom-based plans in improving health care utilization, symptoms, or lung function. Just four studies, one including children, were available, and these studies had limitations (e.g., inadequate sample sizes and power to detect differences or potential bias in patient selection). The evidence does not clearly show that a peak flow-based action plan is better, but equivalent benefits have been demonstrated (Evidence B). Patient preferences and circumstances (e.g., inability to recognize or report signs and symptoms of worsening asthma) may warrant choosing peak flow monitoring.

The EPR-2 recommendations have not been changed. It is the opinion of the Expert Panel that peak flow monitoring for patients with moderate or severe persistent asthma should be considered because it may enhance clinician-patient communication and may increase patient and caregiver awareness of the disease status and control (Evidence B).

Rationale for the Question

The EPR-2 contains descriptions of the data available to assess asthma-related outcomes associated with peak flow monitoring. The EPR-2 Panel made clear that studies conducted at the time of EPR-2 were limited in number and quality and that findings were contradictory. Some guidance was available in the existing research related to patients with moderate or severe asthma who might benefit most from peak flow monitoring. It was considered useful to search the literature for additional, more recent studies.

Efforts to teach, encourage, and persuade patients to use a peak flow meter can be costly. Review of the question would help discern whether physician and patient time, energy, and money are warranted in terms of disease-related outcomes.

Systematic Review of the Evidence

The following description of the SRE is an adaptation of the evidence report, including direct excerpts, submitted by the Blue Cross Blue Shield Association Evidence-Based Practice Center. (See Introduction, Methods.)

Methods of Literature Search

The evidence review included studies that lasted at least 12 weeks and that compared the use of a peak flow meter-based plan plus medical management vs. a symptom-based action plan plus medical management, different schedules of peak flow monitoring, or the use of peak flow monitoring for routine chronic management vs. acute exacerbations. The comparison of peak flow monitoring to symptom monitoring was considered a strong approach, as there is widespread agreement among clinicians that patients should closely monitor their asthma symptoms. Peak flow monitoring values are thought to be beneficial objective measures that help patients determine the need to adjust their medicines and identify potentially urgent situations. Their use in patient self-management is thus dependent on an action plan provided by a clinician. Therefore, all studies included in the SRE compared peak flow monitoring-based written action plans with symptom-based written action plans.

Summary of Findings

Studies

Four studies met SRE inclusion criteria to assess the differences in outcomes when using a peak flow monitoring-based written action plan or a symptom-based action plan. (See the key evidence tables in this section). None of the studies met SRE criteria for high quality. In addition, the studies included in the review had significant limitations (e.g., all four studies had insufficient power to detect differences

between treatment and control groups). Further methodological weaknesses were noted in the question on written action plans, because three of the studies were included in both reviews (Cowie et al. 1997, Cote et al. 1997, and Charlton et al. 1990).

Results of Studies

Three of the four studies documented no significant differences on any outcome measure between peak flow monitoring-based plans and symptom-based plans. One study reported a difference in total emergency department visits in favor of the peak flow monitoring-based plan (Cowie et al. 1997). These findings are presented in the key evidence tables in this section. However, the significant methodologic weaknesses of the studies, as noted earlier, limit the conclusions. For example, the study reporting reduced emergency department visits did not compare change from baseline among groups, and the data suggest the effect may be attributable to a subset of patients who had very high frequency of emergency department visits.

In summary, the available evidence neither supports nor refutes the use of peak flow monitoring-based action plans vs. symptom-based plans in improving outcomes.

Recommendations for EPR Update

Current EPR-2 recommendations should not be changed until there is clear evidence that one monitoring method is superior to another. The Expert Panel recommends the following blue text be incorporated into EPR-2.

Component 1: Measures of Assessment and Monitoring; Peak Flow Monitoring (pages 28 through 33 in EPR-2)

Peak flow monitoring can be used for short-term monitoring, managing exacerbation, and daily long-term monitoring. When used in these ways, the patient's measured personal best is the most appropriate reference value. Thus far, the few studies that have isolated a comparison of peak flow and symptom monitoring have not been sufficient to assess the relative contributions of each to asthma management. The literature does suggest which patients may benefit most from peak flow monitoring. (See box 1, Peak Flow Monitoring Literature Review.)

A systematic review of the evidence conducted in 2002 concluded that evidence at this time does not clearly show that a peak flow monitoring-based action plan is better than a symptom monitoring-based plan in improving outcomes, but it does show similar benefits (SRE-Evidence B). In the opinion of the Expert Panel, there are two distinct arguments for keeping the recommendations to consider peak flow monitoring for patients with moderate or severe persistent asthma: (1) peak flow monitoring appears to provide a way to enhance clinician-patient communication, and (2) either peak flow or symptom self-monitoring appears to increase patient awareness of the disease status and control, thereby helping patients "tune in" to their disease.

If this is the case, either method, if taught and followed correctly, may be equally effective (Evidence B). Patient preferences for objective measures or certain patient circumstances, such as inability to either perceive or report signs and symptoms of worsening asthma, warrant the use of peak flow monitoring. It is the opinion of the Expert Panel that the associated clinician and patient time, energy, and costs are, therefore, justified (Evidence D). This does not, however, change the recommendation that all patients with persistent asthma have a peak flow meter and know how to use it.

The Expert Panel concludes, on the basis of this literature and the Panel's opinion, that:

- **Patients with moderate or severe persistent asthma should learn how to monitor their PEF and have a peak flow meter at home.**

- **Peak flow monitoring during exacerbations of asthma is recommended for patients with moderate or severe persistent asthma to:**
  - Determine severity of the exacerbation.
  - **Guide therapeutic decisions** (see component 3, Managing Exacerbations, and figure 4–5) **in the home, clinician's office, or emergency department.**

- **Long-term daily peak flow monitoring is helpful in managing patients with moderate or severe persistent asthma to:**
  - **Detect early changes in disease status that require treatment.**
  - **Evaluate responses to changes in therapy.**
  - **Provide assessment of severity for patients with poor perception of air flow obstruction.**
  - **Afford a quantitative measure of impairment.**

- **If long-term daily peak flow monitoring is not used, a short-term (2- to 3-week) period of peak flow monitoring is recommended to:**
  - **Evaluate responses to changes in chronic maintenance therapy.**
  - **Identify temporal relationship between changes in PEF and exposure to environmental or occupational irritants or allergens. It may be necessary to record PEF 4 or more times a day (Chan-Yeung 1995).**
  - **Establish the individual patient's personal best PEF.**

- **The Expert Panel does not recommend long-term daily peak flow monitoring for patients with mild intermittent or mild persistent asthma unless the patient, family, and/or clinician find it useful in guiding therapeutic decisions. Any patient who develops severe exacerbations may benefit from peak flow monitoring (Evidence B).**

Limitations of long-term peak flow monitoring include:

- Difficulty in maintaining adherence to monitoring (Reeder et al. 1990; Chmelik and Doughty 1994; Malo et al. 1993), often due to inconvenience, lack of required level of motivation, or lack of a specific treatment plan based on PEF.

- Potential for incorrect readings related to poor technique, misinterpretation, or device failure.

Whether peak flow monitoring, symptom monitoring, or a combination of approaches is used, the Expert Panel believes that self-monitoring is important to the effective self-management of asthma. The nature and intensity of self-monitoring should be individualized, based on such factors as asthma severity, patient's ability to perceive or report airflow obstruction, availability of peak flow meters, and patient preferences.

Recommendations for Future Research

The utility of peak flow monitoring and the circumstances where it is beneficial continue to be salient issues in asthma self-management. The following questions for research deserve attention:

- Does peak flow monitoring provide benefits over symptom monitoring? Studies of adequate power are needed to settle the question.

- Which patients (e.g., those with more severe disease, of different ages, or with special circumstances or preferred language or literacy concerns) are most likely to benefit from peak flow monitoring? Studies in children are especially needed because children may not report symptoms as easily or readily as adults.

- What type of benefits can be accrued from peak flow monitoring?
  - Identification of precipitants to symptoms?
  - More timely adjustment of medicines?
  - Improved perception of airflow obstruction?

- Is peak flow monitoring more likely to be used by patients regularly instead of only during exacerbations? Short term vs. long term? What are the relative benefits of short term use in producing disease-related outcomes?

The SRE stimulates questions that go beyond those related to written action plans and peak flow vs. symptom monitoring. Answers to the following related and important research questions may enhance efforts to educate patients and foster self-management:

- Which components of self-management interventions are most powerful (i.e., account for the greatest variance in disease-related outcomes)?

- What is the minimum core of information and skills required in self-management interventions to produce desired outcomes?
- Which types of interventions (and which of their components) are most effective given the patient's disease severity?
- Which members of the health care team or education partners (e.g., teachers and social workers) best provide which components of self-management education?
- What new venues (e.g., worksites, community centers, churches) might provide greater access to patients who are members of underserved populations?

Key Evidence Tables

Table 2-4. Study Characteristics

Citation	Study Design	Study Setting	Eligibility	Comments
PFM-based action plan vs. symptom-based action plan				
Cowie, Revitt, Underwood et al. 1997	Randomized; parallel, controlled	Country: Canada Funding: Foothills Hospital, Calgary Tx Setting: Primary/specialty combination, university Multicenter	Patient eligibility based on symptoms and utilization. Inclusions: Treatment for an exacerbation of asthma in an ER or attending a university asthma clinic; history of receiving urgent treatment for asthma in the previous 12 months	Subjects were recruited by contacting those who had been treated for an exacerbation of asthma in an emergency department or those attending a university asthma clinic with a history of having received urgent treatment for their asthma in the previous 12 months.
Cote, Cartier, Robichaud et al. 1997	Randomized; parallel, controlled	Country: Canada Funding: Pharm. Ind., grant Tx Setting: Specialty care, nonuniversity Multicenter	Patient eligibility based on lung function and symptoms. FEV_1 Postbronchodilator 85–100% of predicted; PEF minimum 85% of predicted; PEF variability minimum 0%; Methacholine Exclusion: Previous enrollment in an asthma educational program	In discussion "although the control group received more than the usual care treatment, none received book, none had written action plan, none had structured education or PFM at home after run-in"; run-in = 2–6 weeks; diagnosis of asthma included need to take daily anti-inflammatory agents; were excluded.
Turner, Taylor, Bennett et al. 1998	Randomized; parallel, controlled	Country: Canada Funding: Pharm. Ind. + other, not specified Tx Setting: Primary care, nonuniversity	Patient eligibility based on lung function and symptoms. Inclusions: Methacholine PC20 maximum 7.9; using inhaled corticosteroids Exclusions: Previous PFM use; significant comorbid conditions	Patients were randomized after stratification for severity of airway responsiveness using values of PC20 methacholine <2 mg/mL or >2 mg/mL. 150 screened, 117 enrolled.
Charlton, Charlton, Broomfield et al. 1990	Randomized; parallel, controlled	Country: United Kingdom Funding: Clare Wand Fund, Scientific Foundation of RCP Vitalogap Tx Setting: Specialty care, nonuniversity	Patient eligibility based on symptoms only. Inclusion: Patients on repeat prescribing register	Patients were not randomly selected for participation. Letters were sent to patients on the repeat prescribing register, and invited them to make an appointment with a nurse.

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01-E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

Table 2-5. Lung Function Outcomes: FEV_1

Citation	Study Arm	Number Enrolled	Number Evaluable	Treatment Duration (weeks)	
Peak flow meter (PFM)-based action plan vs. symptom-based action plan					
Turner, Taylor, Bennett et al. 1998	Symptom-based action plan	48	48	24	
	PFM-based action plan	44	44	24	
Charlton, Charlton, Broomfield et al. 1990	Symptom-based action plan				
	PFM-based action plan				
Cowie, Revitt, Underwood et al. 1997	Symptom-based action plan	45			
	PFM-based action plan	46			
Cote, Cartier, Robichaud et al. 1997	Symptom-based action plan	45			
	PFM-based action plan	50			

Table 2-6. Symptom Score Outcomes

Citation	Study Arm	Number Enrolled	Number Evaluable	Treatment Duration (weeks)	
Peak flow meter (PFM)-based action plan vs. symptom-based action plan					
Turner, Taylor, Bennett et al. 1998	Symptom-based action plan	48	48	24	
	PFM-based action plan	44	44	24	
Charlton, Charlton, Broomfield et al. 1990	Symptom-based action plan				
	PFM-based action plan				
Cowie, Revitt, Underwood et al. 1997	Symptom-based action plan	45	45	24	
	PFM-based action plan	46	46	24	
Cote, Cartier, Robichaud et al. 1997	Symptom-based action plan	45			
	PFM-based action plan	50			

	Baseline FEV_1*	Final FEV_1	P-Value	P-Value Comparison	Comments
	78.7 +/- 18.9% of predicted	86.1 (mean) % of predicted			FEV_1 in L, mean (SD) was 2.86 (0.88).
	78.1 +/- 19.7% of predicted	83 (mean) % of predicted	NS	Absolute value, Tx vs. Ctl	FEV_1 in L, mean (SD) was 2.84 (0.86).
	79 +/- 18% of predicted				Number of subjects with <60% predicted was 8.
	82 +/- 20.5% of predicted				Number of subjects with <60% predicted was 9.

* FEV_1 pre- or postbronchodilator status unknown unless otherwise indicated.

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01–E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

	Baseline Daytime Symptom Score	Final Daytime Symptom Score	P-Value	Final Nighttime Symptom Score	P-Value	Comments
	9.1 (mean; scale, 0–24)	5.2 (mean; scale, 0–24)				Not sure if reported score is actually a mean; daytime score is really overall score where 24 is max and higher value = more asthma symptoms.
	8.2 (mean; scale, 0–24)	3.2 (mean; scale, 0–24)	NS[1]			Not sure if reported score is actually a mean; daytime score is really overall score where 24 is max and higher value = more asthma symptoms.

[1] Treatment comparison-absolute value, Tx vs. Ctl
[2] Treatment comparison not specified

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01–E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

References

Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01–E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

Chan-Yeung M. Assessment of asthma in the workplace. American College of Chest Physicians Consensus Statement. *Chest* 1995;108(4):1084–117.

Charlton I, Charlton G, Broomfield J, Mullee, MA. Evaluation of peak flow and symptoms only self management plans for control of asthma in general practice. *BMJ* 1990;301(6765):1355–9.

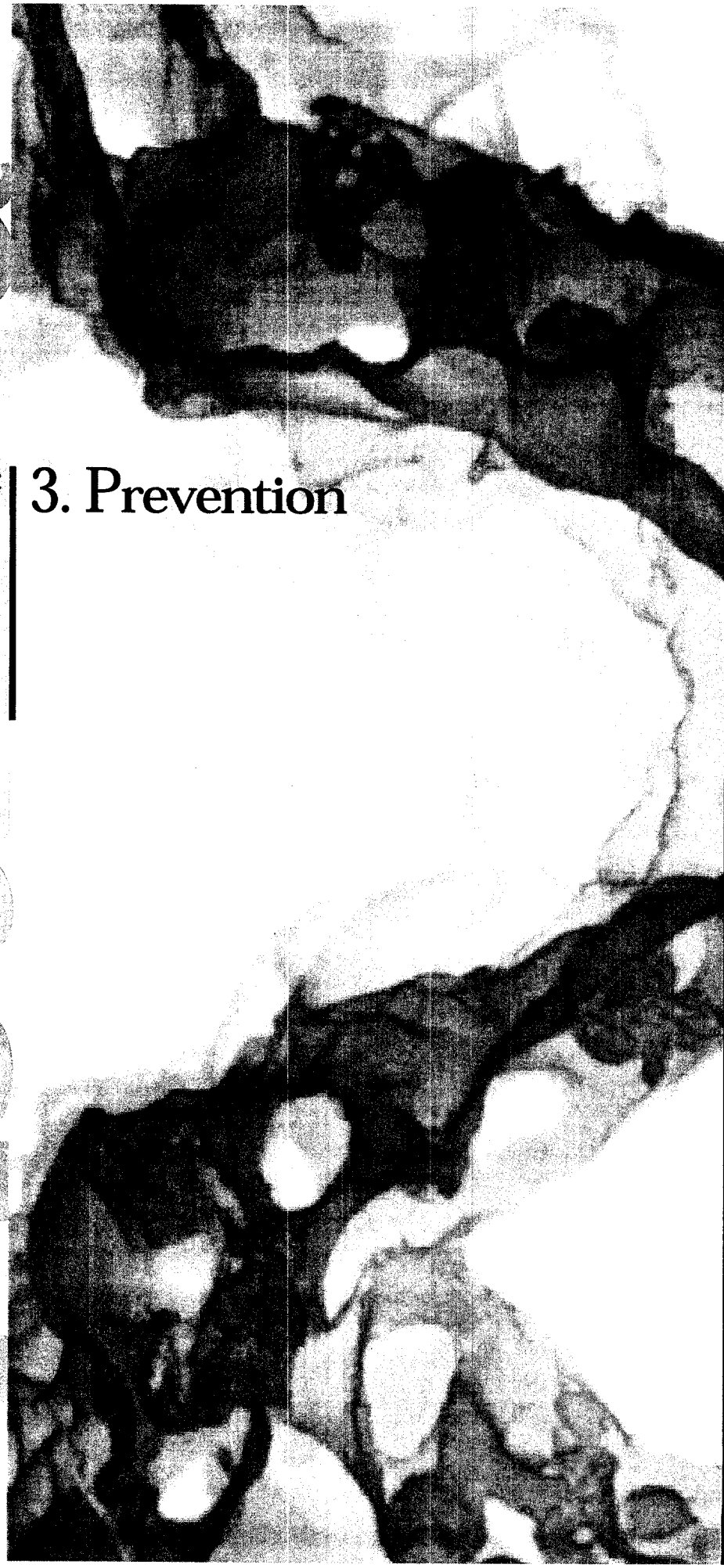
Cote J, Cartier A, Robichaud P, Boutin H, Malo JL, Rouleau M, Fillion A, Lavallee M, Krusky M, Boulet LP. Influence on asthma morbidity of asthma education programs based on self-management plans following treatment optimization. *Am J Respir Crit Care Med* 1997;155(5):1509–14.

Cowie RL, Revitt SG, Underwood MF, Field SK. The effect of a peak flow-based action plan in the prevention of exacerbations of asthma. *Chest* 1997;112(6):1534–8.

Turner MO, Taylor D, Bennett R, Fitzgerald JM. A randomized trial comparing peak expiratory flow and symptom self-management plans for patients with asthma attending a primary care clinic. *Am J Respir Crit Care Med* 1998;157(2):540–6.

Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma

3. Prevention



3. Prevention

In deciding when to initiate daily therapy for patients with asthma, clinicians consider the goals of controlling and preventing symptoms, as well as the possibility of preventing further progression of the underlying disease. This section of the EPR—Update 2002 addresses the question of whether early initiation of daily inhaled corticosteroid treatment is warranted to prevent progression of asthma.

Effects of Early Treatment on the Progression of Asthma

Question

For patients with mild or moderate persistent asthma, does early intervention of long-term-control therapy (i.e., inhaled corticosteroids) prevent progression of asthma as indicated by changes in lung function or severity of symptoms?

Summary Answer to the Question

Evidence regarding the benefits of early treatment of asthma in preventing the progression of disease is insufficient to draw conclusions. But available evidence does not support the assumption that children 5 to 12 years of age with mild or moderate persistent asthma experience a progressive decline in lung function (SRE-Evidence A). Further, the evidence indicates that although inhaled corticosteroids provide superior control and prevention of asthma symptoms during treatment of childhood asthma, symptoms and airway hyperresponsiveness worsen when treatment is withdrawn (SRE-Evidence A). This evidence suggests that the therapy controls but does not modify the disease in this age group. Studies in children younger than 3 years of age and in adults document declines in lung function. Studies of whether treatment can prevent these declines in lung function or symptom severity have not yet been conducted in young children and are inconclusive in adults. Revisions to the EPR-2 are recommended to reflect the new understanding of the progression of asthma.

Rationale for the Question

A common question confronting clinicians and patients is: At what point in the disease process—as reflected by the level of clinical signs and symptoms as well the duration of disease—should daily long-term-control therapy be initiated? Although the effectiveness of inhaled corticosteroids in controlling and preventing symptoms of asthma and improving pulmonary function is well documented, an important question is whether inhaled corticosteroids modify the natural history of the disease. If the progression of asthma is from airway inflammation to airway remodeling and some irreversible airway obstruction, then anti-inflammatory medication (i.e., inhaled corticosteroids) given early in the course of disease may interrupt this process and prevent permanent declines in lung function. In order for early initiation of inhaled corticosteroids to be more beneficial than delayed initiation, two assumptions must be valid: as a group, people with mild or moderate persistent asthma experience a progressive decline in lung function that is measurable and clinically significant, and treatment with inhaled corticosteroids prevents or slows this decline, in addition to controlling asthma symptoms. A SRE was conducted to evaluate the current literature on the effect of intervention of inhaled corticosteroids in altering the progression of disease.

Background Information

Addressing the question about the effect of inhaled corticosteroids on the progression of disease requires answering a series of questions: What is the progression of asthma? Does intervention alter the progression? When is the appropriate time to intervene? The Expert Panel's review of the literature on the progression of asthma is presented here as a context for interpreting the studies evaluated in the SRE.

Natural History of Persistent Asthma

Children

It has been well established that asthma is a variable disease: It can vary among individuals, and its progression and symptoms can vary within an individual's experience over time. It has been postulated that the persistence or increase of asthma symptoms over time is accompanied by a progressive decline in lung function. Recent research suggests that this may not be the case; rather, the course of asthma may vary markedly between young children, older children and adolescents, and adults, and this variation is probably more dependent upon age than symptoms.

A prospective cohort study in which followup began at birth revealed that in children whose asthma-like symptoms began before 3 years of age, deficits in lung growth associated with the asthma occurred by 6 years of age (Martinez et al. 1995). Continued followup on lung function measures taken at 11 to 16 years of age found that compared to the group of children who experienced no asthma symptoms for the first 6 years of life, the group of children whose asthma symptoms began before 3 years of age experienced significant deficits in lung function at 11 to 16 years of age, but the group whose asthma symptoms began after 3 years of age did not experience deficits in lung function.

A longitudinal study of children 8 to 10 years of age found that bronchial hyperresponsiveness was associated with declines in lung function growth in both children with active symptoms of asthma and children without (Xuan et al. 2000). Thus, symptoms neither predicted nor determined lung function deficits in this age group.

Baseline data from the Childhood Asthma Management Program (CAMP) study support the finding that the individual's age at the time of asthma onset influences declines in lung function growth. At the time of enrollment of children with mild or moderate persistent asthma at 5 to 12 years of age, an inverse association between lung function and duration of asthma was noted (Zeiger et al. 1999). Although the analysis did not distinguish between age of onset and duration of asthma, it can be inferred that because the average duration of asthma was 5 years and the average age of the children was 9 years, most children with the longer duration of asthma started experiencing symptoms before 3 years of age. The data suggest that these were the children with lowest lung function levels. After 4 to 6 years of followup, the children in the CAMP study, on average, did not experience deficits in lung growth (as defined by postbronchodilator FEV_1), regardless of their symptom levels or treatment they received (CAMP 2000).

These results suggest that most of the deficits in lung function growth observed in childhood asthma occur in children whose symptoms begin during the first 3 years of life, and the onset of symptoms after 3 years of age usually is not associated with significant deficits in lung function growth. Further, at least for children with mild or moderate persistent asthma, there do not appear to be deficits in lung function growth from 5 to 17 years of age.

Thus, the most promising target for interventions designed to prevent deficits in lung function and perhaps the development of more severe symptoms later in life would be those children who have symptoms before 3 years of age and are destined to develop persistent asthma. However, it is important to distinguish this group from the majority of children who wheeze before 3 years of age and do not experience any more symptoms after 6 years of age (Martinez et al. 1995). Until recently, no validated algorithms were available to predict which children among those with asthma-like symptoms early in life would go on to have persistent asthma. Data obtained from long-term longitudinal studies of children enrolled at birth generated such a predictive index. This predictive index identified the following risk factors for developing persistent asthma

symptoms among children younger than 3 years of age who had more than three episodes of wheezing during the previous year: either physician diagnosis of atopic dermatitis/eczema or a parental history of asthma or two out of three of the following asthma-associated phenotypes—peripheral blood eosinophilia, wheezing apart from colds, or physician-diagnosed allergic rhinitis. When the index was applied to a birth cohort that was followed through 13 years of age, 76 percent of the children who were diagnosed with asthma after 6 years of age had a positive predictive index; moreover, 97 percent of the children in this cohort who did not have asthma after 6 years of age had a negative asthma predictive index before 3 years of age (Castro-Rodriguez et al. 2000).

Adults

Accelerated loss of lung function appears to occur in adults with asthma. In a study of adults with asthma who received 2 weeks of high-dose prednisone if airflow obstruction persisted after 2 weeks of bronchodilator therapy, the degree of persistent airflow obstruction correlated with both the severity and the duration of their asthma (Finucane et al. 1985).

Two large prospective epidemiological studies evaluated the rate of decline in pulmonary function in adults with asthma. In an 18-year prospective study of 66 nonsmokers with asthma, 26 smokers with asthma, and 186 control participants with no asthma, spirometry was performed at 3-year intervals (Peat et al. 1987). Seventy-three percent of the study group underwent at least 6 spirometric evaluations. The slope for decline in lung function (FEV_1) was approximately 40 percent greater for the participants with asthma than for those with no asthma. This did not appear to be the result of extreme measurement produced by a few participants, because fewer than 25 percent of the participants who had asthma were measured with a slope less steep than the mean for those who did not have asthma. In another study, three spirometry evaluations were performed in 13,689 adults (778 who had asthma, 12,911 who did not have asthma) over a 15-year period (Lange et al. 1998). The average decline in FEV_1 was significantly greater in those who had asthma (38 mL per year) than those who did not have asthma (22 mL per year). Although, in this study, asthma was defined simply by patient report, the researchers noted that because the 6 percent prevalence rate for asthma did not increase in this cohort as they increased in age, it is likely that the subjects who reported having asthma did indeed have asthma rather than chronic obstructive pulmonary disease (COPD). It is not possible to determine from these studies whether the loss of pulmonary function occurred in those who had mild or moderate asthma or only in those who had severe asthma. Nevertheless, the data support the likelihood of potential accelerated loss of pulmonary function in adults who have asthma.

Taken together, these longitudinal epidemiological studies and clinical trials indicate that the progression of asthma, measured by declines in lung function, varies in different age groups. Declines in lung function growth observed in children appear to occur by 6 years of age and occur predominantly in those children whose asthma symptoms started before 3 years of age; children 5 to 12 years of age with mild or moderate persistent asthma do not appear to experience declines in lung function through 11 to 17 years of age. There is also evidence of progressively declining lung function in adults.

Data on the effect of interventions to influence the progression of asthma, measured by declines in lung function, airway hyperresponsiveness, or the severity of symptoms, were evaluated in the SRE.

Systematic Review of the Evidence

Methods of Literature Search

The following description of the SRE is an adaptation of the evidence report, including direct excerpts, submitted by the Blue Cross Blue Shield Association Evidence-Based Practice Center. (See Introduction, Methods.)

In addition to the eligibility criteria for selecting studies related to all topics in the SRE (described in the Introduction), the criteria for selecting studies for this question were as follows:

- Some or all patients started long-term-control medication (inhaled corticosteroids, leukotriene modifiers, cromolyn, nedocromil, or theophylline) during the study