# SECTION 1, INTRODUCTION

Asthma is a chronic inflammatory disease of the airways. In the United States, asthma affects more than 22 million persons. It is one of the most common chronic diseases of childhood, affecting more than 6 million children (current asthma prevalence, National Health Interview Survey (NHIS), National Center for Health Statistics, Centers for Disease Control and Prevention, 2005) (NHIS 2005). There have been important gains since the release of the first National Asthma Education and Prevention Program (NAEPP) clinical practice guidelines in 1991. For example, the number of deaths due to asthma has declined, even in the face of an increasing prevalence of the disease (NHIS 2005); fewer patients who have asthma report limitations to activities; and an increasing proportion of people who have asthma receive formal patient education (Department of Health and Human Services, Healthy People 2010 midcourse review). Hospitalization rates have remained relatively stable over the last decade, with lower rates in some age groups but higher rates among young children 0–4 years of age. There is some indication that improved recognition of asthma among young children contributes to these rates. However, the burden of avoidable hospitalizations remains. Collectively, people who have asthma have more than 497,000 hospitalizations annually (NHIS 2005). Furthermore, ethnic and racial disparities in asthma burden persist, with significant impact on African American and Puerto Rican populations. The challenge remains to help all people who have asthma, particularly those at high risk, receive quality asthma care.

Advances in science have led to an increased understanding of asthma and its mechanisms as well as improved treatment approaches. To help health care professionals bridge the gap between current knowledge and practice, the NAEPP of the National Heart, Lung, and Blood Institute (NHLBI) has previously convened three Expert Panels to prepare guidelines for the diagnosis and management of asthma. The NAEPP Coordinating Committee (CC), under the leadership of Claude Lenfant, M.D., Director of the NHLBI, convened the first Expert Panel in 1989. The charge to that Panel was to develop a report that would provide a general approach to diagnosing and managing asthma based on current science. Published in 1991, the "Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma" (EPR 1991) organized the recommendations for the treatment of asthma around 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 precipitate asthma symptoms or exacerbations
- Patient education that fosters a partnership among the patient, his or her family, and clinicians
- 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

The NAEPP recognizes that the value of clinical practice guidelines lies in their presentation of the best and most current evidence available. Thus, the Expert Panels have been convened periodically to update the guidelines, and new NAEPP reports were prepared: The "Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma" (EPR—2 1997) and

"Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma—Update on Selected Topics 2002" (EPR—Update 2002). The "Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma—Full Report, 2007" (EPR—3: Full Report 2007) is the latest report from the NAEPP and updates the 1997 and 2002 reports. The EPR—3: Full Report 2007 is organized as follows: Section 1—Introduction/Methodology; Section 2—Definition, Pathophysiology and Pathogenesis of Asthma, and Natural History of Asthma; Section 3—The Four Components of Asthma Management; Section 4—Managing Asthma Long Term; and Section 5—Managing Exacerbations of Asthma. Key points and key differences are presented at the beginning of each section and subsection in order to highlight major issues.

This report presents recommendations for the diagnosis and management of asthma that will help clinicians and patients make appropriate decisions about asthma care. Of course, the clinician and patient need to develop individual treatment plans that are tailored to the specific needs and circumstances of the patient. The NAEPP, and all who participated in the development of this latest report, hope that the patient who has asthma will be the beneficiary of the recommendations in this document. This report is not an official regulatory document of any Government agency. It will be used as the source to develop clinical practice tools and educational materials for patients and the public.

## OVERALL METHODS USED TO DEVELOP THIS REPORT

### Background

In June 2004, the Science Base Committee of the NAEPP recommended to the NAEPP CC that its clinical practice guidelines for the diagnosis and management of asthma be updated. In September, under the leadership of Dr. Barbara Alving, M.D. (Chair of the NAEPP CC, and Acting Director of the NHLBI), a panel of experts was selected to update the clinical practice guidelines by using a systematic review of the scientific evidence for the treatment of asthma and consideration of literature on implementing the guidelines.

In October 2004, the Expert Panel assembled for its first meeting. Using EPR—2 1997 and EPR—Update 2002 as the framework, the Expert Panel organized the literature searches and subsequent report around the four essential components of asthma care, namely:
(1) assessment and monitoring, (2) patient education, (3) control of factors contributing to asthma severity, and (4) pharmacologic treatment. Subtopics were developed for each of these four broad categories.

The steps used to develop this report include: (1) completing a comprehensive search of the literature; (2) conducting an indepth review of relevant abstracts and articles; (3) preparing evidence tables to assess the weight of current evidence with respect to past recommendations and new and unresolved issues; (4) conducting thoughtful discussion and interpretation of findings; (5) ranking strength of evidence underlying the current recommendations that are made; (6) updating text, tables, figures, and references of the existing guidelines with new findings from the evidence review; (7) circulating a draft of the updated guidelines through several layers of external review, as well as posting it on the NHLBI Web site for review and comment by the public and the NAEPP CC, and (8) preparing a final-report based on consideration of comments raised in the review cycle.

## Systematic Evidence Review Overview

### INCLUSION/EXCLUSION CRITERIA

The literature review was conducted in three cycles over an 18-month period (September 2004 to March 2006). Search strategies for the literature review initially were designed to cast a wide net but later were refined by using publication type limits and additional terms to produce results that more closely matched the framework of topics and subtopics selected by the Expert Panel. The searches included human studies with abstracts that were published in English in peer-reviewed medical journals in the MEDLINE database. Two timeframes were used for the searches, dependent on topic: January 1, 2001, through March 15, 2006, for pharmacotherapy (medications), peak flow monitoring, and written action plans, because these topics were recently reviewed in the EPR—Update 2002; and January 1, 1997, through March 15, 2006, for all other topics, because these topics were last reviewed in the EPR—2 1997.

### SEARCH STRATEGIES

Panel members identified, with input from a librarian, key text words for each of the four components of care. A separate search strategy was developed for each of the four components and various key subtopics when deemed appropriate. The key text words and Medical Subject Headings (MeSH) terms that were used to develop each search string are found in an appendix posted on the NHLBI Web site.

### LITERATURE REVIEW PROCESS

The systematic review covered a wide range of topics. Although the overarching framework for the review was based on the four essential components of asthma care, multiple subtopics were associated with each component. To organize a review of such an expanse, the Panel was divided into 10 committees, with about 4–7 reviewers in each (all reviewers were assigned to 2 or more committees). Within each committee, teams of two ("topic teams") were assigned as leads to cover specific topics. A system of independent review and vote by each of the two team reviewers was used at each step of the literature review process to identify studies to include in the guidelines update. The initial step in the literature review process was to screen titles from the searches for relevancy in updating content of the guidelines, followed by reviews of abstracts of the relevant titles to identify those studies meriting full-text review based on relevance to the guidelines and study quality.

Figure 1–1 summarizes the literature retrieval and review process by committee.

Figure 1–2 summarizes the overall literature retrieval and review process. The combined number of titles screened from cycles 1, 2, and 3 was 15,444. The number of abstracts and articles reviewed for all three cycles was 4,747. Of these, 2,863 were voted to the abstract Keep list following the abstract-review step. A database of these abstracts is posted on the NHLBI Web site. Of these abstracts, 2,122 were advanced for full-text review, which resulted in 1,654 articles serving as a bibliography of references used to update the guidelines, available on the NHLBI Web site. Articles were selected from this bibliography for evidence tables and/or citation in the text. In addition, articles reporting new and particularly relevant findings and published after March 2006 were identified by Panel members during the writing period (March 2006–December 2006) and by comments received from the public review in February 2007.

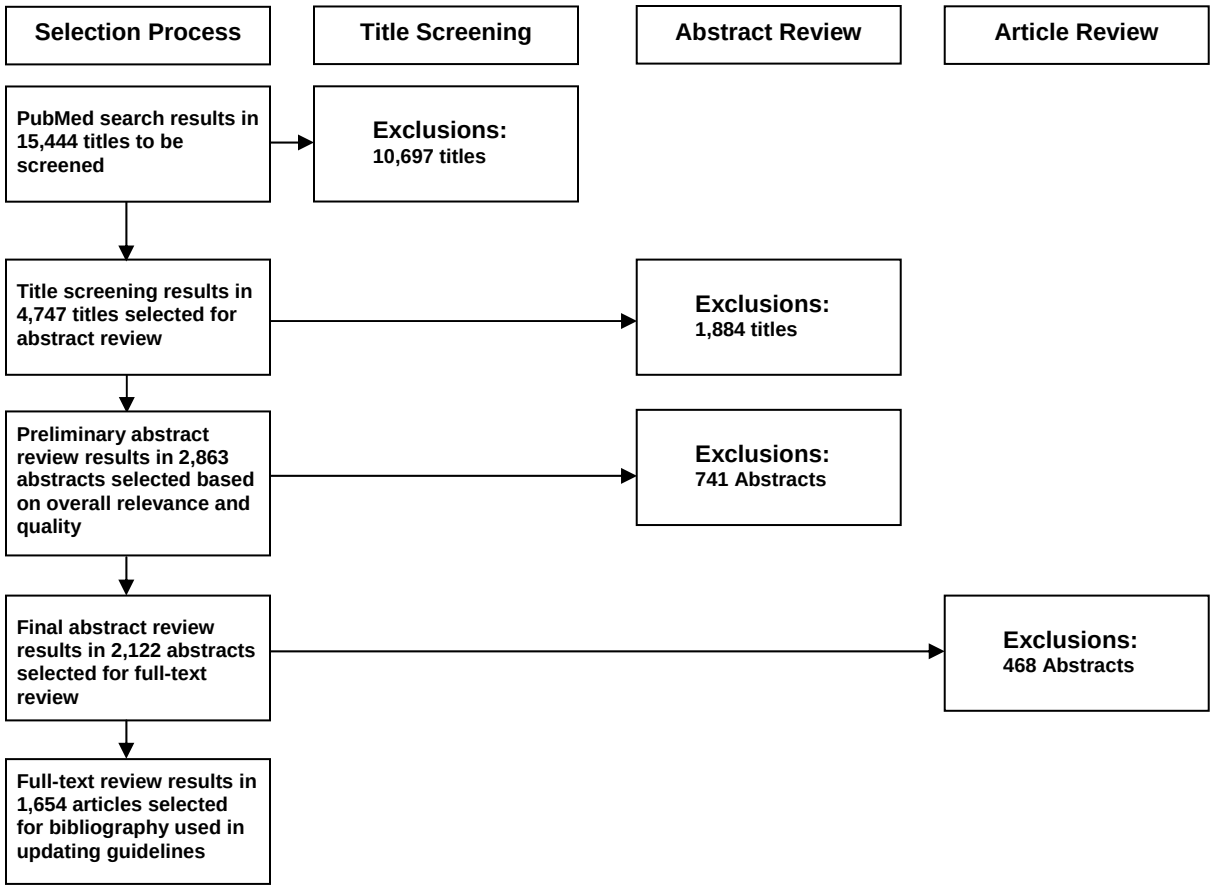
**FIGURE 1–1. LITERATURE RETRIEVAL AND REVIEW PROCESS: BREAKDOWN BY COMMITTEE**

| Committee | Citations<br><br>Screened for relevance to asthma guidelines | Abstracts<br>Reviewed by 2 independent reviewers; vote based on relevance to guidelines and quality of study | Full Text<br><br>Reviewed by primary reviewer with secondary review of articles rejected by primary reviewer | Evidence Tables | | |
|---|---|---|---|---|---|---|
| **Topics Covered** | **Number** | **Number** | **Number** | **Table Number** | **Table Title** | **Number of Cites** |
| Assessment and Monitoring | 3,996 | 758 | 214 | 1 | Predictors of Exacerbation | 31 |
| | | | | 2 | Usefulness of Peak Flow Measurement | 14 |
| Patient and Provider Education | 1,860 | 873 | 442 | 3 | Asthma Self-Management Education for Adults | 24 |
| | | | | 4 | Asthma Self-Management Education for Children | 27 |
| | | | | 5 | Asthma Self-Management Education in Community Settings | 35 |
| | | | | 6 | Cost-Effectiveness of Asthma Self-Management Education | 12 |
| | | | | 7 | Methods for Improving Clinician Behaviors: Implementing Guidelines | 6 |
| | | | | 8 | Methods for Improving Systems Support | 4 |
| Control of Factors Affecting Asthma | 2,574 | 1,108 | 195 | 9 | Allergen Avoidance | 11 |
| | | | | 10 | Immunotherapy | 8 |

**FIGURE 1–1. LITERATURE RETRIEVAL AND REVIEW PROCESS: BREAKDOWN BY COMMITTEE (CONTINUED)**

| Committee | Citations | Abstracts | Full Text | Evidence Tables | | |
|---|---|---|---|---|---|---|
| | Screened for relevance to asthma guidelines | Reviewed by 2 independent reviewers; vote based on relevance to guidelines and quality of study | Reviewed by primary reviewer with secondary review of articles rejected by primary reviewer | | | |
| **Topics Covered** | **Number** | **Number** | **Number** | **Table Number** | **Table Title** | **Number of Cites** |
| Pharmacologic Therapy: Inhaled Corticosteroids | 724 | 463 | 155 | 11 | Combination Therapy | 27 |
| | | | | 12 | Dosing Strategies | 37 |
| Pharmacologic Therapy: Immunomodulators | 141 | 63 | 28 | 13 | Anti-IgE | 17 |
| Pharmacologic Therapy: Leukotriene Receptor Antagonists | 364 | 130 | 56 | 14 | Monotherapy/Effectiveness Studies | 21 |
| Pharmacologic Therapy: Bronchodilators | 921 | 438 | 183 | 15 | Safety of Long-Acting Beta$_2$-Agonists | 18 |
| | | | | 16 | Levalbuterol | 7 |
| Pharmacologic Therapy: Special Situations | 3,187 | 222 | 107 | | No tables | |
| Complementary and Alternative Medicine | 171 | 134 | 81 | | No tables | |
| Managing Exacerbations | 1,407 | 616 | 261 | 17 | Increasing the Dose of Inhaled Corticosteroids | 5 |
| | | | | 18 | IV Aminophylline | 2 |
| | | | | 19 | Magnesium Sulfate | 5 |
| | | | | 20 | Heliox | 5 |

**FIGURE 1–2. LITERATURE RETRIEVAL AND REVIEW PROCESS: OVERALL SUMMARY**




## PREPARATION OF EVIDENCE TABLES

Evidence tables were prepared for selected topics. It was not feasible to generate evidence tables for every topic in the guidelines. Furthermore, many topics did not have a sufficient body of evidence or a sufficient number of high-quality studies to warrant the preparation of a table.

The Panel decided to prepare evidence tables on those topics for which an evidence table would be particularly useful to assess the weight of the evidence—e.g., topics with numerous articles, conflicting evidence, or which addressed questions raised frequently by clinicians. Summary findings on topics without evidence tables, however, also are included in the updated guidelines text.

Evidence tables were prepared with the assistance of a methodologist who served as a consultant to the Expert Panel. Within their respective committees, Expert Panel members selected the topics and articles for evidence tables. The evidence tables included all articles that received a "yes" vote from both the primary and secondary reviewer during the systematic literature review process. The methodologist abstracted the articles to the tables, using a template developed by the Expert Panel. The Expert Panel subsequently reviewed and

approved the final evidence tables. A total of 20 tables, comprising 316 articles are included in the current update (see figure 1–1). Evidence tables are posted on the NHLBI Web site.

## RANKING THE EVIDENCE

The Expert Panel agreed to specify the level of evidence used to justify the recommendations being made. Panel members only included ranking of evidence for recommendations they made based on the scientific literature in the current evidence review. They did not assign evidence rankings to recommendations pulled through from the EPR—2 1997 on topics that are still important to the diagnosis and management of asthma but for which there was little new published literature. These "pull through" recommendations are designated by EPR—2 1997 in parentheses following the first mention of the recommendation. For recommendations that have been either revised or further substantiated on the basis of the evidence review conducted for the EPR—3: Full Report 2007, the level of evidence is indicated in the text in parentheses following first mention of the recommendation. 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.

In addition to specifying the level of evidence supporting a recommendation, the Expert Panel agreed to indicate the strength of the recommendation. When a certain clinical practice "is recommended," this indicates a strong recommendation by the panel. When a certain clinical practice "should, or may, be considered," this indicates that the recommendation is less strong. This distinction is an effort to address nuances of using evidence ranking systems. For example, a recommendation for which clinical RCT data are not available (e.g., conducting a medical history for symptoms suggestive of asthma) may still be strongly supported by the Panel. Furthermore, the range of evidence that qualifies a definition of "B" or "C" is wide, and the Expert Panel considered this range and the potential implications of a recommendation as they decided how strongly the recommendation should be presented.

## PANEL DISCUSSION

The first opportunity for discussion of findings occurred within the "topic teams." Teams then presented a summary of their findings during a conference call to all members of their respective committee. A full discussion ensued on each topic, and the committee arrived at a consensus position. Teams then presented their findings and the committee position to the full Expert Panel at an in-person meeting, thereby engaging all Panel members in critical analysis of the evidence and interpretation of the data.

A series of conference calls for each of the 10 committees as well as four in-person Expert Panel meetings (held in October 2004, April 2005, December 2005, and May 2006) were scheduled to facilitate discussion of findings and to dovetail with the three cycles of literature review that occurred over the 18-month period. Potential conflicts of interest were disclosed at the initial meeting.

## REPORT PREPARATION

Development of the EPR—3: Full Report 2007 was an iterative process of interpreting the evidence, drafting summary statements, and reviewing comments from the various external reviews before completing the final report. In the summer and fall of 2005, the various topic teams, through conference calls and subsequent electronic mail, began drafting their assigned sections of the report. Members of the respective committees reviewed and revised team drafts, also by using conference calls and electronic mail. During the calls, votes were taken to ensure agreement with final conclusions and recommendations.

During the December 2005 meeting, Panel members reviewed and discussed all committee drafts.

During the May 2006 meeting, the Panel conducted a thorough review and discussion of the report and reached consensus on the recommendations. For controversial topics, votes were taken to ensure that each individual's opinion was considered. In July, using conference calls and electronic mail, the Panel completed a draft of the EPR—3: Full Report 2007 for submission in July/August to a panel of expert consultants for their review and comments. In response to their comments, a revised draft of the EPR—3: Full Report 2007 was developed and circulated in November to the NAEPP Guidelines Implementation Panel (GIP) for their comment. This draft was also posted on the NHLBI Web site for public comment in February 2007. The Expert Panel considered 721 comments from 140 reviewers. Edits were made to the documents, as appropriate, before the full EPR—3: Full Report 2007 was finalized and published. The EPR—3: Full Report 2007 will be used to develop clinical practice guidelines and practice-based tools as well as educational materials for patients and the public.

In summary, the NAEPP "Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma—Full Report 2007" represents the NAEPP's ongoing effort to keep recommendations for clinical practice up to date and based upon a systematic review of the best available scientific evidence by a Panel of experts, as well as peer review and critique by the collective expertise of external research/science consultants, the NAEPP CC members, guidelines implementation specialists, and public comment. The relationship between guidelines and clinical research is a dynamic one, and the NAEPP recognizes that the task of keeping guidelines' recommendations up to date is an increasing challenge. In 1991, many recommendations were based on expert opinion because there were only limited randomized clinical trials in adults, and almost none in children, that adequately tested clinical interventions

grounded in research findings about the disease process in asthma. The large gaps in the literature defined pressing clinical research questions that have now been vigorously addressed by the scientific community, as the size of the literature reviewed for the current report attests. The NAEPP is grateful to all of the Expert Panel members for meeting the challenge with tremendous dedication and to Dr. William Busse for his outstanding leadership. The NAEPP would particularly like to acknowledge the contributions of Dr. Gail Shapiro, who served on NAEPP Expert Panels from 1991 until her death in August 2006. Dr. Shapiro provided valuable continuity to the Panel's deliberations while simultaneously offering a fresh perspective that was rooted in observations from her clinical practice and was supported and substantiated by her clinical research and indepth understanding of the literature. Dr. Shapiro had a passion for improving asthma care and an unwavering commitment to develop evidence-based recommendations that would also be practical. Dr. Shapiro inspired in others the essence of what NAEPP hopes to offer with this updated Expert Panel Report: a clear vision for clinicians and patients to work together to achieve asthma control.

## References

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