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## Foreword

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Asthma is a disease of high prevalence, morbidity, and cost, and of a low but persistent rate of mortality. All of the consequences of asthma can be reduced by adequate treatment; however, population surveys have consistently shown that asthma is both underrecognized and undertreated. This led to the development of national and international guidelines for diagnosis and management of asthma.

The foundation of the US guidelines, proposed in 1997 by the National Asthma Expert Panels (NAEP), was an evidence-based review of literature, supplemented by a consensus of experts on issues for which the evidence was incomplete.<sup>1</sup> The guidelines state specific goals for treatment: to reduce symptoms, to reduce the frequency and severity of exacerbations, to maintain nearly normal pulmonary function, to enable physical activity, and to meet patient goals and expectations of care. These goals were to be achieved with minimal risk of toxicity, that is, through the prescription of medications with the best therapeutic index (the highest ratio of clinical effectiveness to risk of adverse effects).

To what extent are the goals laid out in the NAEP guidelines achievable? And what treatments should be used to achieve them? We look to clinical trials and observational studies to answer these questions, and the purpose of this supplement is to describe their attributes and

to suggest criteria for their review. We unapologetically endorse an evidence-based approach. This approach emphasizes disciplined application of predefined criteria for selecting studies for assessment and review. These criteria might include a demonstrable relationship between the subjects enrolled and the population to whom the findings are to be generalized, careful and complete description of methods and materials, selection of clinically relevant outcomes, and application of appropriate methods of statistical analysis. Applying these criteria boils down to a series of questions: are the subjects chosen representative of the population to be treated? do the outcomes measured assess functions that are both reflective of the effects of the disease and important to patients? do the methods of statistical analysis actually measure the likelihood that the changes observed might have been a chance occurrence?

Another criterion for selecting studies for an evidence-based review might also include a priori definition of the magnitude of difference regarded as clinically meaningful. The importance of this criterion is underappreciated. Simply demonstrating a statistically significant difference between 2 treatments in a study, especially in a study of a large population, does not mean the difference is clinically important. Generating this criterion is ultimately a question of judgment, so it is hard to set firm rules for determining whether investigators were justified in selecting, say, a difference in change in FEV<sub>1</sub> of 7.5% as clinically important. At the moment, it is enough simply to require evidence that this judgment was made *before* the investigators reviewed their findings.

The 1997 Guidelines, like their 1991 predecessor, divided asthma treatments into 2 general categories: short-term relievers (short- or intermediate-acting bronchodilators) and long-term controllers. The long-term controller medications that were most strongly endorsed were the inhaled corticosteroids. Suissa and Ernst<sup>2</sup> recently reviewed international observational experience with inhaled corticosteroids, detailing many of the stud-

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ies that showed an association between increases in their use and reductions in the rates of hospitalization and mortality from asthma. In countries in which inhaled corticosteroid use has increased, asthma outcomes have improved in parallel.

In this supplement, Richard Beasley notes that, in contrast to the experience in most Western countries, the mortality rate from asthma in United States has not declined. It has instead remained stable. This failure of US asthma mortality rates to decline may be explained by a lower rate of use of inhaled corticosteroids than in other Western countries. The reasons for this decreased use are not fully known, but may reflect concerns of providers, patients, or both, about the safety of these medications. These concerns persist, despite their lack of clear substantiation in the literature.

Does this mean that the arduous development of consensus-based guidelines was a waste of effort? The simple publication of guidelines, however they were developed, does not ensure a change in the general quality of care. The most difficult task for their successful implementation is probably their dissemination. Until now, the methods for dissemination have largely targeted health care workers, instructing them about the methods for diagnosis and management. The methods for dissemination have not focused on the education of patients of the importance to recognize and seek adequate care.

The Asthma in America study<sup>3</sup> demonstrates how far the implementation of the NAEP's guidelines has to go. In this systematic cross-sectional telephone survey, 2500 patients with asthma were questioned as to their attainment of the goals of asthma management. Their control fell well short. Nine percent had been hospitalized and 23% had sought emergency department care in the previous year. Twenty-five percent of adults reported that they had missed work, and 49% of children had missed school because of their asthma. More than half reported they curtailed their activities, and 30% reported being awakened 1 or more times per week because of cough or wheeze.

This population survey confirms the impression that patients underrecognize the severity of their asthma. Of those with symptoms meeting the NAEP's criteria for "moderately severe" asthma, 61% stated that their asthma was "well controlled" or "completely controlled." Among those with symptoms meeting the criteria for "severe persistent asthma," 32% thought their asthma was "well" or "completely" controlled. The reason for this patient acceptance of incomplete control of asthma symptoms is unclear. It is entirely possible that patients accommodate to chronic impairment, so that the threshold is moved higher for a disturbance in function to register as a symptom or complaint. But the survey provides a clue to another possible explanation. Even though fewer than 12% of those with symptoms of moderate or severe asthma had taken a long-term controller medication in the previous month, most patients believed that not much more could be done for their condition than was already being done. Their underestimation of the severity of their condition could thus be seen as an almost heroic acceptance of the

burdens of a condition for which they believed not much can be done. Their expectations of care are low. Their failure to rate their disease as severe may reflect an unwillingness to "give in" to it. But this toughness is not just unnecessary—regular treatment with a long-term controller could greatly improve their lives. It is also risky. Though low overall, the risk of death from asthma increases with the severity of the disease.

Seen this way, the Asthma in America survey makes a case for a change in the strategies for implementing guidelines. So far, implementation has focused on physicians, nurses, and other providers of care. Patients have not been targeted for education in the goals of care, even though they are the ones whose lives are affected.

How can we improve on guideline implementation? The message needs to be focused on the specific goals of therapy: reduction in the symptoms and exacerbations of asthma. The first "target group" for implementation of guidelines is still the clinicians who provide care. The messages should be simple and memorable. First, it is important to recognize the patients at risk. These include patients who use more than 2 canisters of a short-acting bronchodilator per month or those who have had 2 or more unscheduled visits (or ED visits or hospitalizations) for asthma in a year (the "rules of 2"). Second, reliance on perception and reporting of symptoms commonly leads both patients and providers to underestimate disease severity. Some objective measure of lung function, preferably by spirometry, must be done when the diagnosis is first made and after any important change in symptom severity or treatment. Third, selection of the prescribed therapy should be supported by scientific studies and clinical trials. Fourth, whatever therapy is selected, the focus of follow-up visits should be on whether the goals of therapy have been achieved and whether side effects have occurred. And finally, patients should be enlisted as partners in their own care, armed with the knowledge and skills necessary to care for themselves.

Most reviews prompted by the publication of Guidelines have evaluated the third of the aforementioned questions: the selection of the therapy prescribed. The 1980s was the decade of long-acting theophyllines in the United States. These medications produce improvements in lung function and reductions in symptoms, but have a small demonstrable effect on airway mucosal inflammation and little effect on bronchial hyperreactivity. These medications were hard to use; the narrowness of their therapeutic window and the severity of their potential toxicities restricted their greater use. And while symptom control may have improved in individual patients, the overall morbidity of asthma did not. In fact, deaths from asthma appeared to be on the rise throughout the 1980s. Another commonly used class of medications was the cromones—cromolyn and nedocromil. These drugs have few side effects and little known toxicity—hence their common use was in children—but have modest therapeutic benefit compared with the improvements in all asthma outcomes brought by treatment with inhaled corticosteroids. The message of the 1991 NAEP guidelines, echoed in 1997,

remains consistent: the preferred primary controller therapy is an inhaled corticosteroid. For patients with mild persistent asthma, the 1997 guidelines added to its list of alternative therapies the leukotriene receptor antagonists. This therapeutic class was designed from knowledge of the potent bronchoconstrictor effect of leukotrienes in laboratory models. Large clinical trials have shown this class of therapy to have some effect in improving asthma control, improving pulmonary function, and reducing the frequency of exacerbations of asthma.

The area in which there appears to be some need for further change is in the recommendations for treatment of patients whose symptoms are not adequately controlled with inhaled corticosteroids. Joseph Spahn addresses this topic in his review in this supplement. For asthma that is more severe than mild persistent asthma, and for mild persistent asthma that is uncontrolled by low-dose inhaled corticosteroid therapy, the 1997 guidelines suggest either increasing the dose of the inhaled corticosteroid or adding a long-acting bronchodilator. This recommendation was based on 2 studies<sup>4,5</sup> showing that in patients with asthma uncontrolled on a low or moderate dose of an inhaled corticosteroid, the addition of a long-acting beta-agonist was more effective in improving asthma control than was doubling the dose of the inhaled corticosteroid. Many studies<sup>6,7</sup> have since confirmed this finding and have additionally shown that adding a long-acting  $\beta$ -agonist also reduces the frequency of asthma exacerbations.<sup>7</sup> In general, these studies suggest that the dose-response curve to inhaled corticosteroids is relatively flat. Doubling the dose had little effect on either lung function or symptom control, especially in contrast to the addition of a long-acting bronchodilator.

This supplement also presents data from observational studies. This approach to studying asthma has been used for years. Retrospective data analysis suggested the association of viral illnesses with acute asthma in the 1970s. And the association of the use of inhaled fenoterol with an increase in asthma mortality in New Zealand was described more than a decade ago.<sup>8</sup> A new use of the observational approach is its application to analyzing medical and pharmacy claims. An advantage of this approach is that it allows the evaluation of therapies in more generalizable populations that may not be included in randomized controlled trials. This approach has been used, for example, to assess benefits from the addition of salmeterol xinafoate to inhaled corticosteroid therapy. The enhancement in benefit, even when defined only in terms of the costs of care (for ED visits, unscheduled office visits, etc) was well worth the additional cost. In contrast, the leukotriene receptor antagonists have only a modest effect when added to the treatment of patients taking an inhaled corticosteroid, and, in the economic analyses, add cost without adding significant clinical benefit.

The goal of this supplement is to encourage the reader to explore and understand the medical literature on

asthma. Our approach is to question the population studied, the outcomes selected, the methods and materials used, and the statistical tests employed in published studies to determine whether the authors' conclusions are justified. We believe it especially important to ask not just whether results are statistically significant, but whether they are clinically meaningful. This is especially true of large studies that demonstrate a small but statistically significant effect. And even if the effect size is great enough to qualify as clinically meaningful, it must be asked whether the finding is generalizable to the actual patients for whom the treatment is recommended.

An evidence-based practice of medicine rests on a disciplined, regimented approach to the review of the literature. It enables sound judgment of approaches to treating patients and reduces unnecessary variations in care that may adversely affect outcome. The evidence-based approach underlying the 1997 NAEP Guidelines for the Diagnosis and Management of Asthma provides direction for care. The guidelines delineate clearly the goals of treatment, propose specific questions for assessing disease activity, urge objective measurement of lung function, outline an algorithm for selecting medications for patients with persistent disease, and emphasize the need to provide patients with the knowledge and skills necessary to participate as partners in their own care. The guidelines are neither fixed nor immutable. New evidence will be weighed by the standards and processes reviewed in this supplement, and the guidelines will be refined and revised in response to data meeting the rigorous criteria for "evidence-based" medical practice.

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