

*Editorials***Expert Panel Report 3: Moving forward to improve asthma care****William W. Busse, MD, and Robert F. Lemanske, Jr, MD** *Madison, Wis*

With advances in understanding asthma pathogenesis and pathophysiology, the availability of effective and safe therapies, and knowledge from well-designed clinical trials to test efficacy of therapeutic approaches in both children and adults, the burdens of asthma should continue to diminish. The goal of the 2007 update of the National Asthma Education and Prevention Program (NAEPP) Guidelines is to inform all providers involved in the care of asthma with an analyses and interpretation of these advances and to translate them into both comprehensive and logical recommendations that will enable asthma patients to better control their disease.¹ A projected consequence of these recommendations is that patients with asthma will lead a normal life with minimal interference and be able to achieve this outcome with the highest level of safety. This issue of the Journal contains our summary document of the updated 2007 NAEPP Guidelines for the Diagnosis and Management of Asthma. Implementation of this report in clinical care will determine the effectiveness of our efforts and identify new areas for future investigation.²

A number of key changes, both in terms of medical treatment and fundamental new approaches to overall asthma care, are part of the Expert Panel Report 3 (EPR-3) document. In the first report issued in 1991,³ the expert panel proposed a classification scheme to define asthma severity that was assessed using a composite analysis of the patient's clinical status: symptom frequency, activity limitations, the need for rescue therapy, and lung function

Abbreviations used

NAEPP: National Asthma Education and Prevention Program

EPR: Expert Panel Report

values. Based upon findings in these categories, patients could be classified as having intermittent or persistent asthma, and persistent disease was further divided into three levels: mild, moderate, or severe. This classification of asthma severity was intended to guide the intensity of initial treatment and was, in our view at that time, a reasonable approach to guiding asthma treatment. However, a key component of "asthma severity" was missing from this equation—the response of the patient to treatment. This facet of asthma treatment is addressed in the current document.

Along this line of reasoning, the original 1991 EPR-1 report listed goals for asthma treatment: minimize symptoms, achieve normal activity level, reduce the need for rescue bronchodilators, aim for normal or near-normal lung function, and prevent exacerbations of disease in the presence of medication safety. Our update has brought these 2 concepts of asthma treatment, severity and control, into the guidelines for care. EPR-3 defines asthma severity as "the intrinsic intensity of the disease process and the assessment used to initiate therapy." Asthma control, in contrast, refers to the "degree to which the manifestations of asthma severity are minimized by treatment and the goals of therapy met."

The ERP-3 further identifies 2 domains for both asthma severity and control: current impairment and future risk. Impairment is defined as the current frequency or intensity of symptoms or functional limitations; impairment is the "here and now" of the disease. Risk, in contrast, represents another, and likely distinct, more longitudinal feature of asthma that includes exacerbations, progressive loss of lung function, and adverse effects from medication. Impairment and risk are felt to be distinct, but linked, manifestations of asthma severity and control, and their component factors may respond differentially to treatment. In formulating treatment of asthma to achieve optimal "control," the domains of both impairment and risk need to be assessed and monitored. If an analogy of this approach is applied to the treatment of hypertension, impairment would represent day-to-day measures of blood pressure, whereas risk would include long-term complications in the

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Disclosure of potential conflict of interest: W. W. Busse has consulting arrangements with Genentech/Novartis, Isis, GlaxoSmithKline, Altana, Wyeth, Pfizer, Dynavax, Centocor, Johnson & Johnson, Hoffman LaRoche, Alza, CV Therapeutics, Takeda, Abbott, and Millenium; has received grant support from Novartis, Dynavax, Wyeth, Centocor, GlaxoSmithKline, Medicinova, Sanofi-Aventis, Dey, Pfizer, Astellas Pharma, Inflazyme, and Biowa/MedImmune; and is on the speakers' bureau for Novartis, Merck, AstraZeneca, and GlaxoSmithKline. R. F. Lemanske, Jr, has received grant support from Novartis, Merck, AstraZeneca, and GlaxoSmithKline; has received grant support from the National Heart, Lung, and Blood Institute; and is on the speakers' bureau for Merck, GlaxoSmithKline, and AstraZeneca. Received for publication September 5, 2007; revised September 13, 2007; accepted for publication September 13, 2007.

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J Allergy Clin Immunol 2007;120:1012-4.
0091-6749/\$32.00

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doi:10.1016/j.jaci.2007.09.016

absence of appropriate treatment such as stroke, cardiac disease, or renal compromise. Consequently, monitoring and treating to reduce symptoms and need for rescue bronchodilators is important, and attention to asthma risk is essential for “best care.”

Asthma has considerable heterogeneity, a feature of this disease that needs to be considered in its treatment. This heterogeneity is reflected in many aspects, including the age of the patient. To more fully incorporate this feature in the formulation of treatment plans, 3 age-bracket categories are now considered: 0 to 4 years, 5 to 11 years, and ≥ 12 years. These age groupings were chosen for a number of reasons. First, evidence available demonstrating safety and efficacy for many medications is age-dependent (eg, many clinical trials have enrolled patients ≥ 12 years of age only, and it is unknown if these results are applicable to children 5 through 11 years of age; furthermore, few trial data are available for children less than 5 years of age). Second, issues related to drug delivery are often age-dependent (eg, the ability of a child and/or their caregivers to use nebulizers vs metered dose inhalers vs dry powder inhaler devices). Third, approval of medications by the US Food and Drug Administration is based on age. Fourth, lung function measurements, used to classify asthma severity (impairment domain) and control (risk domain), are usually not possible in children less than 5 years of age, and interpretations of these tests may require special consideration for children 5–11 years of age. Finally, the characterization of various wheezing phenotypes is frequently age-dependent, with different patterns among children 0–4 years of age compared to 5–11 years, or children 12 years of age or older and adults [eg, severe episodes of virus-induced wheezing (risk domain) with periods of no symptoms in between episodes (impairment domain) are most frequently seen in preschool children].

Another new feature of EPR-3 is an expansion of the step-wise approach to 6 treatment steps. In persistent asthma, steps 2 through 4, inhaled corticosteroids (ICSs) remain the preferred foundation for anti-inflammatory therapy, with additions of other medications as noted in previous versions of the guidelines. Two new steps have been added to sharpen the focus of the recommendations at each progressively higher level of treatment, because previous guidelines had multiple actions within some of the steps. For treating patients with more severe disease (the new steps 5 and 6), the EPR-3 adds new recommendations regarding the role of omalizumab, the monoclonal antibody directed against IgE. Omalizumab is a recently approved treatment that represents novel mechanisms of action and distinct clinical outcomes. Omalizumab improves asthma control, both in the domains of impairment (symptoms, need for rescue therapy) and risk (exacerbations). Its mechanisms of action are directed towards a reduction in IgE; it is recommended in patients with allergic disease, but it has no direct effects on lung function, a clinical profile distinct from other previous treatments.

What is not included in the updated EPR-3 guidelines? There has been recent interest in 3 areas of treatment. First is the concept that “adjustable” treatment with combination

therapy (ie, budesonide and formoterol) provides an effective method to reduce asthma exacerbations. In this model, patients use extra doses of the combination therapy as “rescue” treatment in addition to using the same medication on a scheduled basis and, as a consequence, reduce the frequency of asthma exacerbations compared to more commonly used treatment regimens.⁴ This approach is consistent with many patients’ desires to use the “least amount” of medication by focusing on administration of medicines primarily when they are symptomatic. Observations with this approach are still new and will need ongoing assessment before more definitive recommendations can be provided.

A second area of interest is the possibility that some patients with mild persistent asthma may need only intermittent treatment. A number of small studies have begun to address this possibility and found that under the right conditions in the right patient, intermittent therapy is effective, and control can be achieved in areas of both impairment and risk.⁵ However, the utilization of this approach on a wide scale and the clinical phenotypes appropriate for these types of recommendations are still in need of further study.

Finally, there is emerging interest and data on the use of biomarkers to define specific asthma phenotypes that would facilitate individualized treatment recommendations. Two leading biomarker candidates include exhaled nitric oxide⁶ and sputum eosinophils.⁷ Both biomarkers have been assessed in asthma management protocols and show promise. However, the translation of these approaches into clinical practice to establish and maintain control using various stepwise approaches will require additional evaluations.

Beginning more than 15 years ago, the NAEPP developed and released 3 sets of asthma guidelines that reflected basic and clinical knowledge to the greatest extent possible based on the evidence available. The first set of guidelines (EPR-1), released in 1991, focused on asthma as an inflammatory disease of the lung.³ As a result, new emphasis was placed on anti-inflammatory medications and their role as “controllers” in asthma management. In 1997, EPR-2 was released, and in this report the emphasis was on the potential importance of early recognition and treatment of asthma being important in conserving loss of lung function over time.⁸ More recent findings in childhood studies have brought this concept into question; for example, studies demonstrate a clear benefit of ICSs in improving control of asthma, but they have not demonstrated an effect on the underlying severity or progression of disease.⁹ Further research is essential to understand the mechanisms of asthma progression and how it might be altered. However, the third set of guidelines emphasizes the importance of monitoring lung function over time in children and young adults because such declines may not be detected without longitudinal assessment, and the declines may put the patients at higher risk of exacerbations. Thus, although the EPR-3 report continues to reinforce the themes of the previous 2 reports, it introduces a number of new concepts: evaluations of severity and control in the context

of 2 domains, impairment and risk; treatment recommendations being separated into 3 age groups rather than 2; and stepwise paradigms divided into 6 steps rather than 4.

Members of the expert panel who have contributed to the current EPR-3 report were impressed by the body of knowledge on asthma, both quantitatively and qualitatively, that has accumulated in the last decade. Based on this prodigious amount of data, the report was formulated to be both a scientific comprehensive review of this new evidence for individuals who desired to know precisely what information contributed to various recommendations and a summary report, published with this issue of the *Journal of Allergy and Clinical Immunology*, that condenses these detailed findings into a more “user-friendly” format.² The overarching goal of these updated guidelines continues to be the desire to provide recommendations that will establish and maintain the best care possible for both children and adults with asthma.

REFERENCES

1. National Heart, Lung, and Blood Institute and the National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR 3): Guidelines for the Diagnosis and Management of Asthma. Available at: <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm>. Accessed October 3, 2007.
2. National Heart, Lung, and Blood Institute and the National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Summary Report 2007. *J Allergy Clin Immunol* 2007;120:S93-138.
3. Sheffer AL. Guidelines for the Diagnosis and Management of Asthma. National Heart, Lung, and Blood Institute National Asthma Education Program Expert Panel Report. *J Allergy Clin Immunol* 1991;88:425-534.
4. O'Byrne PM. Acute asthma intervention: insights from the STAY study. *J Allergy Clin Immunol* 2007;119:1332-6.
5. Boushey HA, Sorkness CA, King TS, Sullivan SD, Fahy JV, Lazarus SC, et al. Daily versus as-needed corticosteroids for mild persistent asthma. *N Engl J Med* 2005;352:1519-28.
6. Smith AD, Cowan JO, Brassett KP, Herbison GP, Taylor DR. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. *N Engl J Med* 2005;352:2163-73.
7. Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Bradding P, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002;360:1715-21.
8. Murphy S, Bleecker ER, Boushey H, Brown C, Buist AS, Busse W, et al. Guidelines for the diagnosis and management of asthma. National Asthma Education and Prevention Program, editor. Bethesda (MD): National Institutes of Health; 1997. p. 1-150.
9. Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szeffler SJ, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006;354:1985-97.