

## Defining asthma phenotypes: Focusing the picture

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Over the past 30 years, we have witnessed the refinement of asthma care. Asthma guidelines were first developed to reduce asthma mortality and share information about best management techniques. The National Asthma Education and Prevention Program was formed by the National Heart, Lung and Blood Institute and released the first set of United States Expert Panel Report Guidelines for the Diagnosis and Management of Asthma in 1991. Since that time, there have been several revisions of the US guidelines, with the most recent version in 2007.<sup>1,2</sup> In addition, there have been international and then global guidelines developed in an attempt to harmonize management across countries. Individual countries have introduced and revised asthma guidelines as well.

Usually the guidelines are revised when there is a new medication or concept that results in a paradigm shift of asthma management along with a significant body of knowledge that changes asthma care. The most recent guidelines have focused on achieving asthma control. Recent contributions from the Journal to this body of knowledge were summarized earlier this year in the Advances Series on pediatric and adult asthma.<sup>3,4</sup>

In this issue of the Journal, Bousquet et al,<sup>5</sup> who participated in a meeting of the World Health Organization (WHO) in April 2009 to propose a uniform definition of severe asthma, summarize their evaluation of the concepts of asthma severity and control. They raise concern that the terminology applied today is not standardized and that certain terms are often used interchangeably. They propose that a common international approach is needed to define severe asthma, uncontrolled asthma, and when the 2 coincide. They conclude that severe asthma includes 3 groups, each carrying different public health messages and challenges: (1) untreated severe asthma, (2) difficult-to-treat severe asthma, and (3) treatment-resistant severe asthma.

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### EVOLVING CONCEPTS LEAD TO LOFTIER GOALS

Avenues for additional work include recognition of early asthma and appropriate steps for early intervention to alter the course of the disease as well as the appropriate management of severe asthma. The 2007 version of the National Asthma Education and Prevention Program Expert Panel 3 Report emphasized the importance of asthma control, a stepwise approach to asthma management, and early diagnosis and intervention.<sup>1,2</sup> The new National Asthma Education and Prevention Program asthma guidelines introduced several new terms that apply to asthma management, specifically assessment of severity, control, responsiveness, impairment, and risk.<sup>1,2</sup> Severity is defined as the intrinsic intensity of the disease process. Control is the degree to which the manifestations of asthma are minimized and the goals of therapy are achieved. Responsiveness is the ease with which control is achieved by therapy.

The heart of the review by Bousquet et al<sup>5</sup> is the introduction of new terminology to describe the patterns of severe asthma.<sup>5</sup> Before this report, an American Thoracic Society/European Respiratory Society Asthma Exacerbations and Control Task Force<sup>6</sup> took a bold step to put some order to definitions of asthma exacerbations and control.

The new terminology introduced by Bousquet et al<sup>5</sup> informs us that we should categorize those patients who are difficult to control as having the following:

1. Untreated severe asthma—asthma that is easily controlled once the appropriate medication and adequate adherence and technique are set in place. This may enable them to achieve a less severe form of asthma in the presence of adequate therapy to which they respond.
2. Difficult-to-treat severe asthma—characterized by a partial or poor response to treatment that reflects the presence of factors other than asthma alone, such as poor access to treatment, poor adherence, poor inhalation technique, environmental exposures, and psychosocial issues.
3. Treatment-resistant severe asthma—consisting of 2 categories of medications responsiveness:
  - a. Those who are partially or poorly controlled despite high-dose inhaled corticosteroid or a high-dose inhaled corticosteroid/long-acting  $\beta$ -adrenergic agonist combination and frequent or chronic use of systemic corticosteroids (previously called refractory or severe asthma).
  - b. Well controlled asthma that requires the highest level of recommended treatment to maintain control. These patients may still be at risk for severe exacerbations.

These new terms represent a step forward in categorizing severe asthma. They will still need some refinement to adapt to clinical trials and management plans to categorize patients for medication selection. This WHO panel recognized that the literature experience is primarily based on adults, and they attempted to draw into discussion the evolution of the disease in children. The panel also did a nice job in describing a number of features that contribute to

inadequately controlled asthma, including access to care, medication delivery, and a host of other factors.

After this 2009 WHO meeting, several studies appeared in the *Journal* that provided additional insight into severe asthma in children. Zeiger et al<sup>7</sup> evaluated data in The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimen (TENOR) Study and noted a significantly higher rate of asthma exacerbations in children versus adults despite specialist-prescribed optimal controllers and acute intervention with oral corticosteroids. Su et al<sup>8</sup> reported relationships between the intensity of an endogenous epigenetic control, that is, the balance of histone deacetylase and acetyltransferase activities, in healthy and atopic asthmatic children with the physiologic intensity of airway hyperresponsiveness. In addition, Fitzpatrick et al<sup>9</sup> reported that children with severe asthma have increased biomarkers of oxidant stress in the epithelial lining fluid that are associated with increased formation of glutathione disulfide and a shift in the glutathione redox potential toward the more oxidized state.

Additional publications emerging from the TENOR Study highlight some important features of poorly controlled asthma in children. They evaluated whether the level of impairment predicts risk for future asthma exacerbations.<sup>10,11</sup> One study reported that consistently very poorly controlled asthma is strongly predictive of future asthma exacerbations. Another report from TENOR noted that a recent severe exacerbation is an important independent predictor of a future severe exacerbation in children with severe/difficult-to-treat asthma.<sup>11</sup>

## WHO REPORT: MOVING FORWARD

We are currently moving toward an individualized approach to asthma management by prompting early recognition and early intervention, expanding the number of physicians who use spirometry, increasing the recognition of allergen sensitivity as a key player in asthma pathogenesis, addressing environmental concerns, and applying biomarkers such as exhaled nitric oxide in assessing disease activity related to allergic airway inflammation.<sup>3,12,13</sup> Genetic markers are emerging to predict disease onset and to characterize patients who may benefit from early intervention. However, none to date has been associated with a severe form of asthma. Perhaps breaking severe asthma into categories will help identify a genetic link. Also, a closer evaluation of gene-environment interactions could help in understanding the emergence of these various phenotypes.<sup>14,15</sup>

We now have the asthma guidelines that serve as a repository for asthma knowledge. We have several key task forces that have cried for better definition of asthma features. We will soon have a report from the National Institutes of Health Asthma Outcomes Task Force that will seek to define outcome measures that can be incorporated into all asthma research funded by the National Institutes of Health. Consequently, these definitions should be applied to pharmaceutical studies and investigator-initiated studies as well. That will help bridge some gaps between studies to harmonize asthma research. Those who are interested in advancing the care of asthma globally should read the WHO report<sup>5</sup> to get a better appreciation of the worldwide impact of asthma and the challenges we face in achieving total control.

If these new terms for severe asthma become useful in the research world, the next logical step would be to incorporate them into asthma guidelines and practice, including electronic medical

records. That will help assure communication across medical systems to facilitate the identification of patients with emerging, inadequately controlled, and severe asthma in health care systems. From a public health perspective, that effort would prompt the identification of problem areas, such as poor access to care, poor adherence, poor technique for inhaled medications, refractoriness to treatment, excessive exposure to environmental factors, and the need for a higher level of intervention. The patients, once carefully characterized, who do not respond to conventional steps in management could then move on to specialized care and studies in which the phenotypes can be refined and links to better tools and innovative treatment strategies could identify better management techniques.

Currently most medical record systems do not characterize the level of severity or, better yet, control, much less define patients by the subset of severe asthma. Introducing new terminology into asthma care not only should be applied to research studies but also should quickly transcend into clinical care if it proves useful for designing interventions that will decrease morbidity and improve overall asthma control.

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