What the asthma end points we know and love do and do not tell us

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Asthma is a disorder characterized by common features of reversible airflow obstruction and bronchial hyperreactivity in the setting of airway mucosal and submucosal inflammation. However, the clinical manifestations are syndromic and not unimodal. There is marked variability in severity of symptoms, natural history, risks of adverse outcomes, pathologic characteristics, and response to therapy. Understanding the relationship between these factors has been complicated by the variability of outcomes and the lack of correlation between them. There is a striking absence of correlation among the pathologic, physiologic, and clinical manifestations of the asthmatic disorders. Lung function tends to correlate poorly with clinical outcomes, and there is only modest correlation between clinical outcomes. Response to therapy is variable both externally (between patients) and internally, depending on which outcome is evaluated. A more complete understanding of the variability of disease and the genetic and environmental causes of the variability likely will change how we approach asthma and its therapy. (J Allergy Clin Immunol 2005;115:S539-45.)

Key words: *Asthma, control, severity, outcomes, phenotypes, variability, asthma-related quality of life*

Asthma is characterized by reversible airflow obstruction and bronchial hyperreactivity (BHR), but the clinical presentations and responses to therapy are variable. It is apparent that asthma is a syndrome with variable physiologic, pathologic, and clinical manifestations. The phenotypes represent the visible effects of the interactions between the genetic makeup and environment. Asthma phenotypes appear to be different in terms of control, severity, response to therapy, natural history, risk for adverse outcomes, the relationship among features of the disease, and the relationship between various outcomes.

Initial guidelines made a superficial effort to recognize this dramatic variability by grossly estimating severity. However, because the bulk of adverse outcomes appear to be related to underdiagnosis, inadequate therapy, and poor adherence, and because most patients respond favorably to inhaled corticosteroids and β-agonists, an improved understanding of the various asthma syndromes was not of major importance in the initial approach to improving asthma outcomes. Newer pharmacotherapy, better understanding of the pathophysiologies of asthma, and the beginnings of characterization of the genetics of the response to the environment and therapy make investigations of the variability of disease a new frontier in asthma research and treatment. One of the first changes in this new era is a refined focus on control instead of severity as the primary asthma measure and an integration of patient-derived outcomes into the dimensions of control.

Abbreviations used
BHR: Bronchial hyperreactivity
HRQOL: Health-related quality of life

GENERAL QUALITY OF LIFE OF PATIENTS WITH ASTHMA

Most of the variability that is observed in asthma can be explained by genetic differences among asthmatic patients. Asthma is monitored on the basis of several outcomes and therefore is recognized more as a syndrome rather than a disease. Currently, outcomes monitored in asthma vary greatly and do not correlate with one another. Although several outcomes are assessed for each patient, the primary concern of most primary care physicians and patients is the burden of the disease or the health-related quality of life (HRQOL). A recent study[1] illustrated that patients with asthma experienced twice as many unhealthy days a year compared with individuals who have never had asthma. There were twice as many days with activities limited, twice as many mentally unhealthy days, and more than twice as many physically unhealthy days.[1] In total, patients in the United States with asthma experience approximately 150 million unhealthy functioning days a year. The current review will examine frequently used asthma end points and what we can learn from them.

CHARACTERISTICS OF THE IDEAL ASTHMA MEASURE

Choosing outcomes to measure in the assessment of asthma control requires an understanding of what is an ideal measure and the various dimensions of control.

An ideal measure for asthma should be simple and practical, meaningful, and applicable to doctors, patients, health system managers, and researchers. It needs to be reflective of short- and long-term control. It should be

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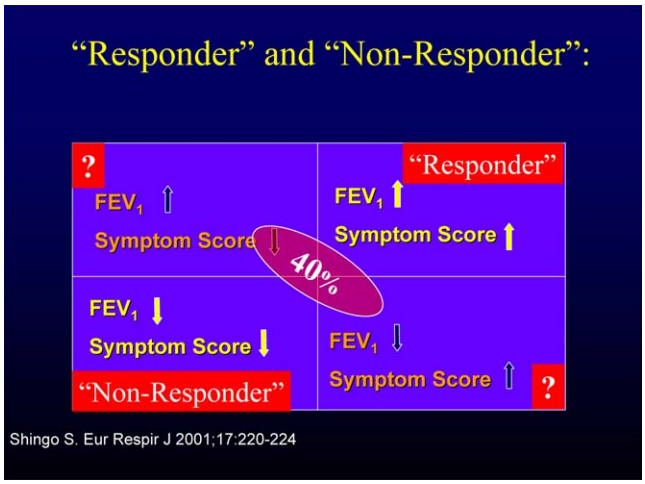

FIG 1. There is an approximate 40% divergence comparing positive or lack of response with lung function and symptoms as outcomes. Reprinted with permission from Shingo et al. Copyright © 2001 European Respiratory Society Journals Ltd. All rights reserved.[2]

selective of patients who are at risk of clinical worsening and those who have mild disease and will always remain minimally affected. It needs to be discriminatory and responsive to change. Because asthma is a syndrome rather than a disease, it has been and continues to be difficult to identify such an indicator.

DIMENSIONS OF ASTHMA CONTROL

There are various dimensions of control that take form from the various burdensome aspects of asthma. There are medical outcomes, including clinical, biologic, and physiologic markers; the humanistic outcomes, including quality of life (QOL) and satisfaction; and the economic outcomes, including costs to patients, society, health care systems, and the workplace. It is reasonable to differentiate these markers into physiologic, symptoms, QOL, medications, health care use, exacerbations, activities of daily living, and comorbidites.

Current favored measurements include the following: (1) FEV_1, (2) BHR, (3) symptom scores, (4) emergency department visits and hospitalizations as major drivers of health care use, (5) exhaled nitric oxide or other exhaled gases, (6) β-agonist use, (7) exacerbations, and (8) QOL. Because of the variability in these outcomes, it is likely that there is no single measurement that is the best indicator of asthma control, nor will one function as a universally applicable surrogate for all patients.

As understanding improves about these issues, we also must consider that control is a continuum versus a point in time, as analog versus digital, and variable between observers and that there is a disconnect between various control outcomes.

SYNDROMIC NATURE OF ASTHMA

The phenotype of asthma is clinically and pathologically variable between those with early-onset, late-onset, neutrophilic, and eosinophilic asthma. In addition to clinical and pathologic differences, there are also physiologic differences between patients. For example, there are subjects with hyperacute or brittle asthma with marked BHR and others for whom BHR is not a major feature. Correlating the pathologic changes with clinical and physiologic outcomes has been inconsistent. Furthermore, an overlooked variable is the individual response to therapy. Although BHR and reversible air flow obstruction are important characteristics of asthma, they do not predict the response to therapy. The outcomes monitored do not correlate well with each other or between observers.

RESPONDERS AND NONRESPONDERS

Simplistically, it would be helpful to characterize asthmatic subjects as responding or not responding adequately to a particular intervention. A widely held but incorrect belief is that patients either respond or not, and if they respond, they will improve in all important features of their disease (clinical, pathologic, and economic). However, evaluation leads to very different conclusions. Asthmatic patients can be separated into 2 groups on the basis of their FEV_1 and symptom score responses to therapy. If the FEV_1 and the symptom scores both go up, that patient might be considered a responder. In contrast, a nonresponder is a patient whose FEV_1 and symptom scores do not change or worsen. However, although 60% of asthmatic patients can be classified as either responders or nonresponders because their lung function and symptoms get better or not, 40% of asthmatic patients have divergent responses (Fig 1).[2] Thus in a large group of patients, symptoms improve in the absence of lung function improvement, or lung function improves without a parallel improvement in symptoms.

A study by Malmstrom et al[3] evaluated subjects with moderate asthma treated with the leukotriene modifier montelukast and evaluated FEV_1 as an outcome. One third