

Asthma end points and outcomes: What have we learned?

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In spite of the wide prevalence of asthma and its substantial consequences, the diagnosis and assessment of asthma has not been standardized, and the goals of therapy currently are not being achieved. Our purpose is to help delineate what the most important asthma end points are and what kinds of strategies we should use to guide therapy. Comparison of numerous studies reveals that asthma measures used routinely in the clinic, such as spirometric lung function, do not uniformly correlate with asthma control. We cannot improve outcomes until we determine which measures reveal the underlying disease process most clearly and at the same time offer ease of performance during routine office visits. We propose that by standardizing the way we collect and analyze data from our daily practice, we can better define which measures reflect true asthma control. Such measures most likely address a spectrum of changes occurring in the pathophysiology of asthma, notably distal airway inflammation and hyperresponsiveness. Inflammation may provide the best opportunity for

assessment and treatment, because if it is adequately addressed, airway sensitivity may improve, thereby reducing airway obstruction and subsequently minimizing exacerbations. The fraction of exhaled nitric oxide as a measure of inflammation is suggested as offering the best combination of disease evaluation and practical implementation for improved asthma outcomes. (*J Allergy Clin Immunol* 2006;118:S1-S15.)

Key words: Asthma, asthma treatment, lung function measures, clinical outcomes

Asthma is a chronic disorder in which the airways are characterized by inflammation, hyperresponsiveness, and intermittent obstruction. Although the precise cause of asthma is unknown, its manifestations appear to result from the interaction between the genetic makeup of the individual and the environment to which he or she is exposed. Asthma occurs in all races, and its prevalence has increased more than 30% since the late 1970s.¹ In the United States, by 2003, asthma affected almost 20 million persons, including more than 6 million children.² Asthma can develop at any time throughout life, although most cases begin before age 25 years.¹ In 2003, in the United States the asthma prevalence rate for boys under 18 years of age was 27% higher than the rate among girls, but among adults, prevalence rates were 77% greater among women than men.²

The economic effect imposed by asthma is considerable. The Centers for Disease Control and Prevention projection for the cost of asthma in the United States in the year 2000 was \$14.5 billion.³ Direct medical expenses from hospital care and physicians' services cost more than \$8 billion.³ Indirect costs, including lost school and work days and deaths from asthma, are estimated at \$4.6 billion.³ In addition, asthma can seriously impinge on quality of life in terms of restricted activities, avoidance of triggers, and fear of exacerbations. The cost of these issues cannot be estimated for individual patients with asthma.

In spite of the wide prevalence of asthma and its substantial consequences, the diagnosis and assessment of asthma has not been standardized. In part, standardization has not occurred because of wide interindividual variation in the natural history of asthma, symptoms produced, and response to therapy. In addition, objective physiologic measures of the disease often do not correlate with symptoms, resulting in diverse clinical end points. Our purpose here is to help delineate what the most important asthma end points are and what kinds of strategies we should use to guide asthma therapy.

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Abbreviations used

ACT:	Asthma Control Test
ATAQ:	Asthma Therapy Assessment Questionnaire
EIB:	Exercise-induced bronchoconstriction
eNO:	Exhaled nitric oxide
FP:	Fluticasone propionate
FRC:	Functional residual capacity
HRQL:	Health-related quality of life
ICS:	Inhaled corticosteroid
PEF:	Peak expiratory flow
RV:	Residual volume

We will describe how traditional lung function measures relate to clinical outcomes and how methods for evaluating the airway, such as closing volume and closing capacity, serve in assessing clinical outcomes. We will also explore what recent studies suggest about measures, such as exhaled nitric oxide (eNO) and sputum eosinophils, as a guide to treatment and disease progression. In addition, we will examine how being more rigorous in the way we collect and analyze a composite of objective and subjective measures can help guide asthma therapy and why we recommend individualization of therapy.

PHYSIOLOGIC MEASURES: WHAT INSIGHT INTO CLINICAL OUTCOMES DO WE GAIN FROM EVALUATION OF LUNG FUNCTION?

Measures of lung function obtained by means of spirometry have traditionally been among the most widely accepted methods for evaluating asthma, with FEV₁ as the most helpful. FEV₁ is the volume of air that can be forcibly expired during the first second of expiration after a maximal inspiration. Although some studies have demonstrated significant correlation between FEV₁ and asthma symptoms, other studies show discordance between this measurement of lung function and symptoms. Herein we review concordant and discordant studies and suggest potential mechanisms explaining the lack of consistent results.

Studies showing correlation of lung function with clinical outcome

Correlation between FEV₁ and asthma symptoms was demonstrated in a study by Kavuru et al,⁴ which examined the potential advantage of salmeterol, 50 µg, and fluticasone, 100 µg (combined in the ADVAIR Diskus 100/50 powder delivery device; GlaxoSmithKline, Philadelphia, Pa), over salmeterol or fluticasone alone at the same doses. Those treated with the combination had a significantly greater improvement (mean change, $P \leq .003$) in FEV₁ (0.51 L) compared with that seen with placebo (0.01 L), salmeterol (0.11 L), and fluticasone (0.28 L). Patients in the combination product group were less likely to withdraw from the study because of worsening asthma

compared with those in the other groups ($P \leq .020$). Low dropout rates, representing better asthma control, thus correlated with better FEV₁ values.

Similar correlation between FEV₁ and asthma symptoms was seen in a study by Laviolette et al,⁵ in which montelukast, an oral leukotriene receptor antagonist, was administered concomitantly with inhaled corticosteroids (ICSs). Patients receiving montelukast (10 mg) in addition to inhaled beclomethasone (200 µg twice daily) demonstrated significant improvement in FEV₁ ($P < .001$), daytime symptoms score ($P = .041$), and nocturnal awakenings ($P = .027$) over those receiving inhaled beclomethasone alone.

Nelson et al⁶ showed correlation between FEV₁ and asthma exacerbations in a study comparing the efficacy and safety of a combination of fluticasone propionate (FP) and salmeterol through the Diskus inhaler (FP/salmeterol combination) versus montelukast added to FP (FP plus montelukast). Results showed that the FP/salmeterol combination provided significantly greater improvements than FP plus montelukast in FEV₁ ($P < .001$), as well as a significantly lower rate of asthma exacerbations ($P = .031$).

The Predicting Inhaled Corticosteroid Efficacy trial, conducted by the Asthma Clinical Research Network, used FEV₁ to assess steroid responsiveness and found that FEV₁ can be quite useful in this regard and does correlate with asthma control in this setting. Patients were stratified based on their FEV₁ response as good, fair, and poor responders. Those who were poor FEV₁ responders to ICSs showed no significant difference ($P = .33$) in control when the steroids were discontinued. Those who were good responders showed significant ($P = .028$) worsening of asthma (exacerbations) when ICSs were discontinued. An intermediate response was seen in fair responders on discontinuing ICSs.

Studies showing discordance between lung function and clinical outcome

Lung function in terms of FEV₁ is not always helpful, however, in assessing a meaningful clinical outcome. In a study by Shingo et al,⁷ data from more than 1500 patients in two 1-year clinical trials with montelukast were analyzed to investigate the relationship between pulmonary function measurements, FEV₁, and peak expiratory flow (PEF) versus patient-reported end points of daytime symptoms and "as-needed" β-agonist use. As would be expected, there was good correlation (pairwise Pearson correlation coefficient = 0.74) between FEV₁ and PEF. Weak correlations were demonstrated, however, between FEV₁ and daytime symptoms (correlation coefficient = -0.13) and between FEV₁ and β-agonist use (correlation coefficient = -0.22). Weak correlations between PEF and daytime symptoms (correlation coefficient = -0.19) and between PEF and β-agonist use (correlation coefficient = -0.23) were also demonstrated. Canonical correlations, which capture the relationship between 2 sets of variables, were also calculated and also showed weak correlation between FEV₁ and PEF versus daytime

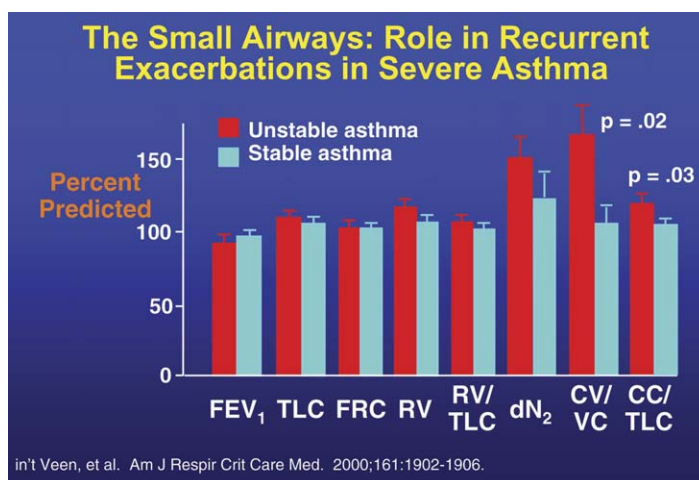


FIG 1. In a comparison of 2 groups of patients with asthma, there were significant increases in both closing volume (CV; $P = .024$) and closing capacity (CC; $P = .030$) in those with difficult-to-control asthma over those with stable asthma, highlighting the role of these measures of small airway function. No significant difference in FEV₁, total lung capacity (TLC), FRC, or RV was noted between the 2 groups. Adapted with permission from in't Veen JC, Beekman AJ, Bel EH, Sterk PJ. Recurrent exacerbations in severe asthma are associated with enhanced airway closure during stable episodes. *Am J Respir Crit Care Med* 2000;161:1902-6.¹⁰

symptoms and as-needed β -agonist use. The authors concluded that their findings highlight the need to measure multiple parameters in the control of asthma, including both measurements of airway function and symptoms.

Moy et al⁸ retrospectively analyzed health-related quality-of-life (HRQL) data in asthmatic subjects from 2 clinical trials. HRQL data included patient answers to such questions as presence of nighttime symptoms and impairment of daily activities. The study found that FEV₁ and PEF did not correlate well with HRQL at any level of asthma severity but that intensity of shortness of breath predicted HRQL at all levels of asthma severity.

In the Optima study, O'Byrne et al⁹ evaluated the effects of treating mildly asthmatic patients with budesonide, a low-dose ICS, with or without the addition of formoterol, a long-acting β -agonist. Patients who were previously receiving ICSs, as well as those who were not, improved with respect to reduced risk of exacerbations and reduced risk of poorly controlled days but showed little improvement in FEV₁.

Potential mechanisms to explain lack of concordance

The relationship between lung function as measured by FEV₁ thus does not uniformly track with patient symptoms. Possible reasons for this discordance might be uncovered by considering what FEV₁ is actually measuring versus what we now know about the pathophysiology of asthma. Two significant components in the pathogenesis of asthma, namely small peripheral airway reactivity and inflammation, might not be adequately gauged by FEV₁.

Small peripheral airway reactivity

A study by in't Veen et al¹⁰ compared 2 groups of severely asthmatic patients, one whose asthma was stable

versus one with recurrent exacerbations, to determine whether enhanced airway closure might be a risk factor for recurrent exacerbations. Multiple physiologic parameters were measured, including FEV₁, total lung capacity, functional residual capacity (FRC), residual volume (RV), and 2 measures of small airway disease, closing volume and closing capacity. They found no significant difference in FEV₁, total lung capacity, FRC, or RV between the 2 groups but noted significant increases in both closing volume ($P = .024$) and closing capacity ($P = .030$) in those with difficult-to-control asthma over those with stable asthma, highlighting the role of these measures of small airway function (Fig 1).

Wagner et al¹¹ compared small (peripheral) airways resistance in healthy and asthmatic subjects. Direct measurement of resistance was made by wedging a bronchoscope into a nondependent segment of the right lower lobe and inserting a catheter with a pressure transducer. The study found that peripheral airway resistance was significantly increased in asthmatic subjects over that seen in healthy subjects, despite normal spirometry.

Wagner et al¹² later performed a similar study using the wedged bronchoscope technique in which they instilled histamine through a catheter to determine directly the histamine responsiveness of the smallest airways. They found that the resistance of the smallest peripheral airways increased with histamine challenge in both healthy and asthmatic subjects but that the peripheral airways of the asthmatic subjects were more sensitive to histamine challenge than were those of healthy control subjects.

Although FEV₁ captures the function of airways throughout the lung, it is relatively insensitive to changes in small airway caliber and thus might disproportionately represent larger airways. Improvements seen in asthma

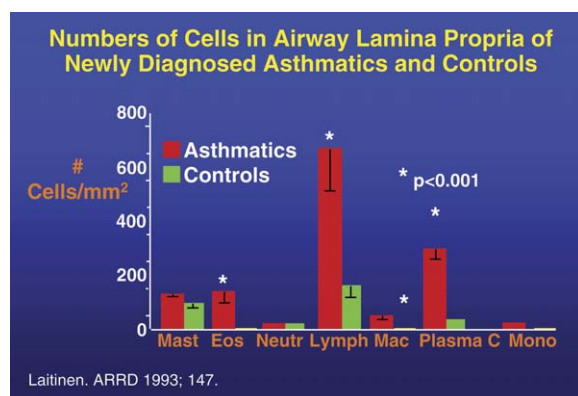


FIG 2. Bronchial biopsy specimens from patients with newly diagnosed asthma showed significantly increased numbers of eosinophils, lymphocytes, macrophages, and plasma cells (all $P < .001$) in the lamina propria. Reprinted with permission from Laitinen LA, Laitinen A, Haahtela T. Airway mucosal inflammation even in patients with newly diagnosed asthma. *Am Rev Respir Dis* 1993;147:697-704.¹³

symptoms might occur primarily because of dilation of small airways, which leads to decreased air trapping. Subsequent decreases in RV and potentially in FRC can occur. These alterations might in turn result in a decrease in the work of breathing because of increased curvature of the diaphragm and better mechanical efficiency. Ultimately, dilation of the small airways can correlate with improvements in symptoms, specifically shortness of breath, and yet not necessarily be measured adequately by FEV₁.

Inflammation

Laitinen et al¹³ investigated airway mucosal inflammation in bronchial biopsy specimens from patients with newly diagnosed asthma and found that even at this clinically early stage of the disease, significantly increased numbers of eosinophils, lymphocytes, macrophages, and plasma cells (all $P < .001$) were present in the lamina propria (Fig 2). Thus even when asthma is considered mild on the basis of lung function measurements and symptoms, inflammation is present.

Crimi et al¹⁴ examined the relationship between airway inflammation and airway hyperresponsiveness in allergic asthma. In this study there was weak correlation ($r = -0.49$) between baseline FEV₁ and induced sputum eosinophils. Even with better sampling of the airway with bronchoalveolar lavage, correlation between FEV₁ and bronchoalveolar lavage eosinophils remained weak ($r = -0.49$).

Hamid et al¹⁵ examined the inflammatory process in the central and peripheral airways of surgically resected lungs from asthmatic and nonasthmatic subjects. Sections of lung were examined with mAbs to detect T cells, total eosinophils, activated eosinophils, mast cells, neutrophils, and macrophages. All airways from asthmatic subjects demonstrated significantly increased

numbers of T cells and eosinophils over those seen in nonasthmatic subjects ($P < .001$). In addition, a similar but more severe inflammatory process was found in peripheral versus central airways in asthmatic subjects.

Kraft et al¹⁶ examined inflammation in bronchial biopsy specimens from patients with nocturnal asthma and nonnocturnal asthma. Tissue from proximal endobronchial biopsy specimens was compared with tissue from distal alveolar transbronchial biopsy specimens for each patient obtained at 4 AM and 4 PM. This study found that at 4 AM, alveolar eosinophils were significantly increased in subjects with nocturnal asthma over numbers seen in subjects with nonnocturnal asthma. Both groups showed more inflammation in the alveolar tissue than in the proximal airways. Additionally, it was noted that correlation between the percentage overnight decrease in FEV₁ and numbers of eosinophils within the proximal airways was weak, but the decrease in FEV₁ correlated more strongly ($r = -0.54$) with numbers of eosinophils in the alveolar tissue.

A second study by Kraft et al¹⁷ suggested that numbers of CD4⁺ lymphocytes, the putative principal orchestrating cell in eosinophil recruitment, are increased in the alveolar tissue at night in subjects with nocturnal asthma versus in subjects with nonnocturnal asthma.

Sutherland et al¹⁸ examined the relationship of distal lung inflammation to spirometry and plethysmography and found that the degree of eosinophilic alveolar inflammation correlated well with thoracic gas volume ($r = 0.65$) but not with FEV₁. In a study now in press, Kraft et al¹⁹ evaluated the effect of montelukast on proximal and distal lung function and symptoms in 19 subjects with mild asthma. Improvement in air trapping, represented by RV, but not in FEV₁ correlated with improvement in symptoms, including morning shortness of breath, wheeze, and chest tightness ($r = 0.60-0.67$, $P = .002-.023$).

Symptoms thus might be influenced by accumulation of eosinophils and other inflammatory cells in the distal lung, a location not necessarily reflected in FEV₁ measurements. This discrepancy between events taking place within the tissue and what lung function studies can actually measure might account for discordance between lung function and clinical outcome.

Conclusions

FEV₁ can correlate with exacerbation and asthma control, although not uniformly because it does not represent the full spectrum of changes in the pathophysiology of asthma. Hyperresponsiveness of the distal airways and the presence of distal lung inflammation are potential mechanisms explaining the lack of concordance with FEV₁ values versus exacerbations, symptoms, and quality of life. Other physiologic end points should be considered in clinical trials, such as lung volumes and measures of distal lung inflammation, which might better reflect the changes occurring in the small peripheral airways and alveolar tissue.

TABLE I. Information drawn from a national survey, Asthma in America, indicates that the goals of asthma therapy as described by the Global Initiative for Asthma are not being achieved

Goal	Reality
No missed work or school	49% of children and 25% of adults missed school or work because of asthma
No sleep disruption	30% of patients reported nocturnal awakenings at least once a week
Maintenance of normal activity levels	48% report that asthma interferes with recreation, 36% with normal physical exertion, and 25% with social activities
No (or minimal) need for emergency department visits, hospitalizations, or other unscheduled office visits	32% of children and 19% of adults required emergency department visits; 55% of children and 36% of adults had unscheduled office visits
Normal or near-normal lung function	35% report having had a lung function test in the past year; 28% have peak flowmeters, and 9% report using them at least once a week

Copyright GlaxoSmithKline. Used with permission. Asthma in America: a landmark survey. National survey data. 1997-2006 GlaxoSmithKline. Available at: <http://www.asthmainamerica.com/cities/national.html>.²⁰

CLINICAL MEASURES: SHOULD WE INDIVIDUALIZE OR STANDARDIZE TREATMENT PROTOCOLS?

The goals of asthma therapy currently are not being achieved (Table I).²⁰ Although ample information regarding asthma outcomes is available to providers through the daily observation and care of asthmatic patients, we have not yet developed a standard protocol for diagnosis and assessment of patients with asthma that can be used over time. We propose that by standardizing the way we collect and analyze data from our daily practice, we can improve the quality of life for asthmatic patients, decrease costs associated with asthma care, and make management of asthma more efficient. In contrast, the information obtained from this assessment should be used in an individualized approach to guide treatment decisions to address the numerous variables that influence response.

Benefits of standardizing the diagnosis of asthma

The diagnosis of asthma is often delayed for a number of reasons, including fear of overtreatment, fear of generating anxiety in the patient, fear of unfair labeling of the patient, and misperception of asthma as an acute episodic disease rather than a long-term chronic disorder. Early and aggressive diagnosis of asthma offers multiple benefits over deferring the diagnosis.

Some argue that by avoiding an asthma diagnosis, unnecessary treatment will be avoided. However, by delaying the diagnosis in a patient who actually has asthma, valuable time is lost in controlling the disease. Our studies²¹ showed that patients who were unaware of having asthma had about half the adherence rates of those who were aware of their diagnosis. A timely diagnosis of asthma provides educational opportunities that increase the likelihood of patients taking their medications and following through with environmental controls.

Some physicians argue that the diagnosis of asthma might produce anxiety in the patient. Contrary to this idea, studies have shown that patients and parents of pediatric

patients are more anxious if they do not know what the disorder is and are receiving inconsistent messages about their condition.

Some health care providers avoid making a diagnosis of asthma to prevent unnecessary labeling of the patient by insurance companies, the military, and peers. However, it is more economically sound to diagnose asthma when it exists. For example, wheezers without diagnoses miss more school, and managed care organizations with the highest asthma prevalence rates have the lowest emergency use for asthma care. In our studies²² undiagnosed asthma resulted in double the cost of diagnosed asthma.

When asthma remains undiagnosed and untreated, its natural history tends to appear as an acute episodic disease, reinforcing such a general misconception of asthma among primary care practitioners. When asthma is more accurately understood as a long-term chronic disorder, we can teach specific protocols for standard diagnosis to primary care practitioners. In this way we can likely obtain earlier diagnoses and earlier referral to asthma specialists when needed. Earlier appropriate treatment might then lead to fewer acute episodes, better quality of life for the asthmatic patient, and lower costs of care. Standardized diagnosis will also help prevent missing patients who need asthma treatment and are not now receiving it.

An additional important benefit of early and aggressive asthma diagnosis is the opportunity it allows for consistent assessment of a wide variety of significant factors, such as disease triggers (viral, exercise, and seasonal aeroallergen), timing of the disease (adult vs pediatric), and lung function. In a recent study by Yawn and Yawn,²³ a chart review of more than 500 school-aged asthmatic patients found that only 9% had documentation regarding asthma triggers; asthma severity was documented in only 4% of patient charts, and nighttime symptom frequency was recorded in only 33% of patient charts. Clearly, instituting a standardized approach to diagnosis would increase the probability of identifying factors that could help achieve asthma control, as well as provide a consistent view of the patient.

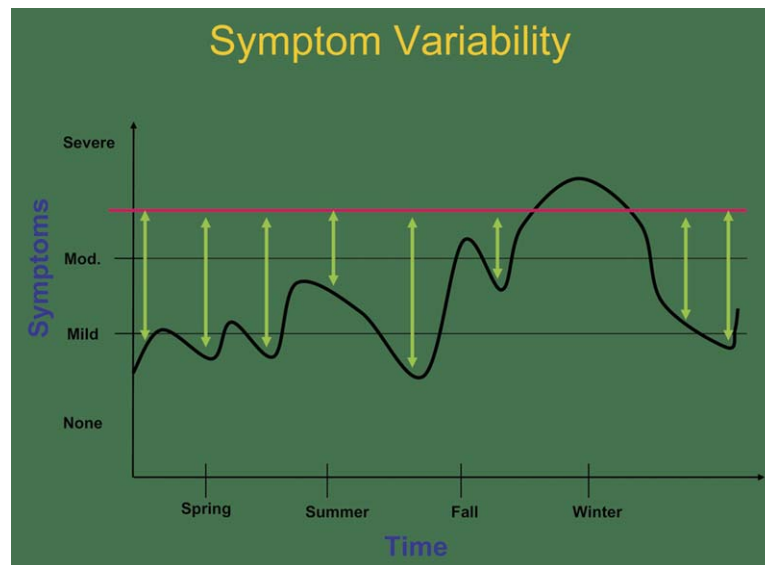


FIG 3. Although asthma is routinely classified as intermittent, mild, moderate, or severe, the severity of asthma changes over time.

Benefits of standardizing the assessment of asthma

Standardization of asthma assessment helps to clarify the multifaceted nature of asthma control. Because asthma is a variable disorder, control requires addressing a broad range of issues, including inconsistency in the severity of a patient's asthma over time and the presence of comorbid conditions and asthma triggers. In addition, there are disparate perspectives of what control should mean and how best to assess the risks of adverse outcomes.

Although asthma is routinely classified as intermittent, mild, moderate, or severe, the severity of asthma changes over time (Fig 3). Calhoun et al²⁴ assessed the variability of severity control among patients with persistent asthma. Patients included in the study all met the criteria for moderate or severe persistent asthma at baseline. Yet over a 12-week period, the mean percentages of treatment weeks that patients met all criteria for various categories were as follows: intermittent, 9%; mild, 14%; moderate, 71%; and severe, 6%. On the basis of morning PEF, patients were classified as having intermittent mild asthma on 52% of days, and on the basis of days per week for albuterol use or asthma symptoms, patients spent 59% of weeks in the intermittent category and 45% of weeks in the mild category.

Thus, neither single end points nor multiple end points at single points in time adequately represented asthma severity. Treating the patient based on a rigidly established label of intermittent, mild, moderate, or severe asthma thus might result in undertreatment or overtreatment.

The assessment of asthma is further complicated by the existence of comorbid conditions, such as rhinosinusitis and gastroesophageal reflux, in addition to seasonal changes that might trigger asthma, affect response to medications, or both. For example, Busse et al²⁵ studied

more than 400 asthmatic patients to determine the effectiveness of montelukast treatment in improving the control of asthma symptoms during the allergy season in patients with coexisting seasonal allergic rhinitis. Montelukast treatment resulted in significant improvement from baseline in the daytime asthma symptom score and in β -agonist use, nighttime symptoms, and PEF rates ($P = .002$). The improvements seen in this study might not have occurred during another time of year in the absence of coexisting symptoms of allergic rhinitis. Thus short-term asthma assessments might be influenced by factors other than asthma alone.

Asthma assessment is meaningful only insofar as it can tell us whether a patient's asthma is controlled and thus influence treatment decisions. How, though, do we define control? From the physician's perspective, asthma control is defined in objective terms, such as lung function measures, eNO levels, use of oral steroids, low cost of interventions, and numerous questions about symptoms: wheezing, breathlessness, chest tightness, cough, time of day or night symptoms occur, and what activities, allergens, or weather types trigger symptoms. In addition, we have a checklist of negatives for uncovering quality-of-life issues; that is, controlled asthma should result in no exercise limitations, no nocturnal awakenings, no school/work absences, no alteration in daily activities, no unscheduled medical care, and no uncontrolled upper respiratory symptoms.

For physicians, our definition of control seems to cover the entire scope of asthma control, but our tests, checklists, and questions do not reach the crux of quality-of-life issues for the patient. From the standpoint of a child with asthma, control means being able to play outside, stay at a friend's house without being bound by a medication schedule or inhaler, and keeping up with friends. An adult

TABLE II. Physicians tend to view asthma control in objective terms, but for the patient, control is defined by not having to live life around asthma

Asthma control: patient vs physician definition	
Physician's perspective	Patient's perspective
No non-upper respiratory tract-related exacerbations	I do not need steroids
Oral steroids ≤ 1 time/y	I am not afraid of getting a cold
No exercise limitations	I am not afraid of forgetting my inhaler
No nocturnal awakenings	I can exercise and I am losing weight
No school/work absences	I can sleep through the night
No alteration in daily activities	I can go to school/work every day
No unscheduled medical care	I can keep up with my friends
No uncontrolled upper respiratory tract symptoms	I do not live my life around asthma
	My sinuses are not always a problem

with asthma wants to be able to exercise, to go to work every day, to go out for a drink, and to keep weight off by avoiding steroids. Control for anyone with asthma means being free of the fear of getting a cold or forgetting his or her inhaler, not worrying about triggering an asthma attack by activity, and being able to laugh without wheezing or coughing. We need to understand the patient's perspective of the disease (Table II). For a patient, the luxury of being able to sleep with ease through the night is not conveyed by the physician's phrase "no nocturnal awakenings." For the patient, control is defined by not having to live life around asthma.

The assessment of asthma control is obscured by another problem as well. The control of some chronic diseases is based on a single strategy, which, although broad, is well defined. Pain control, for example, is based on the strategy of relieving symptoms. The control of hypertension is based on the strategy of minimizing the risk of cardiovascular effects. Asthma control, on the other hand, cannot be based entirely on one or the other but requires a strategy that includes both relief of symptoms and minimization of risk.

Furthermore, no ideal measure of asthma control exists, no single test that is simple, practical, meaningful, discriminatory, responsive to change, reflective of short- and long-term control, and applicable to patients, clinicians, and researchers. Such a test, such as the use of hemoglobin A_{1C} levels in the assessment of diabetes mellitus control, would simplify the identification of a patient as either controlled or impaired.

In view of all these complex issues in the assessment of asthma control, we need a standardized approach, one followed by specialists and primary care practitioners alike. The approach we recommend is the *focused asthma visit*, the key to managing the composite of different end points needed to assess control (Table III). The thrust of this approach is the use of the same tests and the same questions consistently over long periods of patient follow-up. Only by examining the different aspects of control by addressing the same questions over time can we sort out the variables and answer the 2 most important assessment questions of all, the questions that underlie the very need

TABLE III. The focused asthma visit is a standardized approach that can be followed by specialists and primary care practitioners alike to facilitate the complexities of asthma management

Asthma-focused follow-up visit standardized evaluation
Established diagnosis of asthma?
Known allergies?
Medication history, including adherence and response?
Disease triggers?
Asthma-related medical visits in past year?
Comorbid disorders?
ACT results?
Depression screen?

for assessment: First, is the patient's asthma controlled? Second, is the patient at risk of adverse outcomes?

The focused asthma visit addresses the multifaceted nature of asthma control by using a variety of objective and subjective measures. The first category, objective measures, includes such physiologic parameters as lung function, bronchial reactivity, and inflammation. Consistent use of the same test or tests over time is the key to interpreting that portion of asthma control related to physiologic measures.

The second category of measures consists of standard screening for poor control at each office visit by means of the systematic collection of certain data, including medication use, side effects, and adherence. Adherence involves not only whether patients are taking prescribed medication but also whether they are using inhalers properly. Obtaining follow-up information on all exacerbations is important, including follow-up on telephoned orders for steroid bursts. Our own studies (internal communication, Dean Clinic; data from Deancare HMO, Asthma Therapy Assessment Questionnaire [ATAQ] protocol) have shown that outpatient exacerbations in primary care settings are just as serious and severe as those that result in emergency department visits. Standard screening also includes reviewing the symptoms responsible for the original diagnosis of asthma and any allergic

In the <u>past 4 weeks</u>, how much of the time did your <u>asthma</u> keep you from getting as much done at work or at home? ☐ None of the time ☐ A little of the time ☐ Some of the time ☐ Most of the time ☐ All of the time During the <u>past 4 weeks</u>, how often have you had shortness of breath (SOB)? ☐ Not at all ☐ Once or twice a week ☐ 3 to 6 times a week ☐ Once a day ☐ More than once a day During the <u>past 4 weeks</u>, how often did your <u>asthma</u> symptoms (wheezing, coughing, SOB, chest tightness, or pain) wake you up at night or earlier than usual in the morning? ☐ Not at all ☐ Once or twice ☐ Once a week ☐ 2 to 3 nights a week ☐ 4 or more nights a week	During the <u>past 4 weeks</u>, how often have you used your rescue inhaler or nebulizer medication (eg, albuterol, Ventolin, Proventi, Maxair, or Primatene Mist)? ☐ Not at all ☐ Once a week or less ☐ 2 or 3 times per week ☐ 1 or 2 times per day ☐ 3 or more times per day How would you rate your <u>asthma</u> control during the <u>past 4 weeks</u>? ☐ Completely controlled ☐ Well controlled ☐ Somewhat controlled ☐ Poorly controlled ☐ Not controlled at all
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FIG 4. The Asthma Control Test is a quick and helpful 5-question test, which takes less than 30 seconds to complete after the patient has experience with it. Reprinted with permission from QualityMetric, Providence, RI.

TABLE IV. A significant benefit of the focused asthma visit is that at the same time it demonstrates whether the patient is impaired, it also helps clarify the patient's risk for adverse outcomes

What do you want to know?

Is asthma controlled?

- Is the patient impaired?
- How should impairment be reversed or minimized?

Is the patient at risk?

- What are the risks for adverse outcomes?
- How can risks be addressed?

precipitators, as well as smoke exposure. Collection of data regarding disease triggers and comorbid disorders that might influence the patient's asthma is also important, as is information about any asthma-related medical visits in the last year and courses of antibiotics.

Obtaining symptom scores and insights into quality-of-life issues also form a significant part of the focused asthma visit. We recommend a standardized test, such as the ATAQ²⁶ or the Asthma Control Test (ACT),²⁷ which give a number that you can use to measure control. In our experience the ACT is a quick and helpful 5-question test that takes less than 30 seconds to complete after the patient has experience with it (Fig 4). Also in our practice, we have found a 2- or 3-question depression screen to be helpful because depression can be a complicating risk factor in most patients with severe asthma and in some with mild asthma. Questions about nocturnal awakenings and days

missed from school or work should be included, as well as incorporating questions to investigate the concept of "presenteeism," a bigger cost to the workplace than absenteeism. "Presenteeism" represents days the patient might be present at school or work but during which asthma symptoms prevent them from working up to par.

Instituting the focused asthma visit to collect and analyze standard data thus provides a snapshot, which, if recorded over time, will present an overview of the patient's asthma and show whether the patient's status is controlled or impaired. A significant benefit of this strategy is that at the same time it demonstrates whether the patient is impaired, it also helps clarify the patient's risk for adverse outcomes (Table IV). The asthmatic patient who is treated by a primary care physician is of particular importance in this regard because patients who are most at risk will benefit from referral to an asthma specialist. We offer a standard protocol to our primary care colleagues to enhance effective asthma management, which emphasizes particular awareness of patients who are obese, depressed, and/or nonadherent with their medications. These patients and others with poor control or significant asthma impairment need specialty referral.

We recommend the following protocol to primary care providers. Designate asthma as controlled if the ACT score is 20 or greater, the ATAQ demonstrates 0 to 1 barriers, there are no hospitalizations or emergency department/urgent care visits, there are no uncontrolled comorbidities, and there is greater than 50% adherence to controller medication. Under these conditions,

continue current therapy and see the patient back every 6 to 12 months. If the asthma is completely controlled for 12 months, consider decreasing the medication slowly. Otherwise, designate the patient's asthma as uncontrolled if the ACT score is 19 or less, the ATAQ demonstrates 2 or more barriers, there has been unscheduled asthma-related care in the past year, or adherence to controller medication is less than 50%. Under these conditions, address adherence as needed and increase medication. See the patient again in 1 to 2 months, and if the asthma remains uncontrolled on 2 successive visits, consider specialty referral.

Benefits of individualizing the treatment of asthma

The focused asthma visit can help standardize the assessment of asthma control and thereby allow us to deal with the vast heterogeneity of asthma. Presently, we do not know enough about the interaction of genetics and environment to understand the diversity we see in the control and natural history of asthma, including its severity, response to therapy, and risk for adverse outcomes. In addition, we cannot yet explain the variable relationship among features of the disease and the relationship between disparate outcomes. Because we do not yet understand these variables, our standardized assessment of asthma control must serve as a basis for designing individualized treatment (Table V). Clinical trials often underscore the need for individualized treatment by demonstrating unexplained differences in response. For example, in a study by Bateman et al,²⁸ which examined response to various medications, some patients achieved control with fluticasone alone, others with baseline plus oral steroids, and others with combinations of fluticasone and salmeterol. In about 30% of patients, however, control was not achieved, even with combination medications. In a study by Zeiger et al,²⁹ 44% of patients did not respond well to either montelukast or fluticasone alone, when judged on the basis of asthma-free days, and more than 50% did not respond well to either medication, as judged on the basis of FEV₁.

Even in studies that show good mean response in regard to such parameters as FEV₁ or symptoms, the total responses are reflected by a bell-shaped curve, indicating variability of that factor in different patients. Diversity of outcomes thus can be obscured by representing data in terms of the mean. In daily practice, however, patients representing the whole spectrum of response can be seen, and individual treatment plans must be devised for each.

Adherence is also variable among patients, and is, in fact, the most common reason that drug therapy fails. A study by Suissa et al³⁰ found that regular use of low-dose ICSs was associated with a 31% reduction rate in hospital admissions for asthma and a 39% reduction rate in readmissions and that reduction rates were sustained over long-term follow-up. Williams et al³¹ found, however, that in their study overall adherence to ICSs was only about 50%. Even more disturbing are the findings by Bender et al,³² who reviewed the literature regarding

TABLE V. Because we do not yet fully understand the natural history of asthma, genetic and environmental interaction, and the diversity of asthma response, our standardized assessment of asthma control must serve as a basis for designing individualized treatment

Defining and developing effective strategies for the individual patient

- Diagnose the condition and implement treatment early in the disease for optimal effectiveness
- Identify the severity of asthma and environment triggers that are contributing to disease
- Implement environmental modifications
- Use pharmacotherapy as necessary to safely and effectively control inflammation, manage exacerbations, and prevent symptoms
- Monitor the patient

Data from the National Asthma Education and Prevention Program. Expert Panel Report guidelines for the diagnosis and management of asthma update on selected topics 2002. Bethesda (MD): National Institutes of Health (NIH); 2003. NIH publication no. 02-5074.

intervention to correct the problem of poor adherence to ICS therapy. They found that in half the studies reviewed, experimental intervention did not change adherence, and behavior change reported by patients was often not accompanied by changes in treatment success. Successful asthma therapy must include addressing adherence on a case-by-case basis.

Individual variability must also be considered in regard to patient safety. For example, in a study by Israel et al,³³ wide variation was observed in susceptibility to total hip osteoporosis as a consequence of ICS use. Susceptible patients had decreased bone density, whereas those who were more resistant tolerated high doses of steroids without losing bone density. Safety concerns thus obligate us to consider in each individual case whether the benefits outweigh the risks.

Response to medications can vary greatly because of genetic factors that we cannot yet address in a standard regimen. For example, comparison of 3 studies, a study by Malmstrom et al,³⁴ Asthma Clinical Research Network trials,^{35,36} and the Childhood Asthma Management Trial,^{37,38} reveals the heterogeneity of outcomes in terms of percentage change in FEV₁ in response to ICS therapy documented at 12 weeks, 6 weeks, and 8 weeks, respectively. This interindividual variability in outcomes suggests that genetic factors can contribute to the therapeutic response to ICS treatment. Further analysis revealed that variation in one gene, corticotropin-releasing hormone receptor 1 (*CRHR1*), was predictive of response to ICS therapy in each of the 3 populations investigated.³⁹

Another significant genetic variation investigated in a study by Israel et al⁴⁰ involved patients with a polymorphism resulting in homozygosity for arginine rather than glycine at amino acid residue 16 of the β_2 -adrenergic receptor. These patients had a lower morning PEF rate during treatment with albuterol than during a placebo period, when albuterol use was limited. This subset of patients

thus might need to avoid albuterol. These cases serve as examples of potential genetic complexities that determine individual responses. Only by individualizing our treatment approaches can we accommodate unexpected reactions.

Other considerations that might be highly variable in different patients and therefore necessitate individualizing therapy include disease triggers, timing of office visits, and risk factors. Only by obtaining information on an ongoing basis regarding such factors as depression, non-adherence to medications, and comorbid conditions can we adjust therapy according to individual needs.

The best reason for individualizing therapy lies within the ultimate goal of asthma therapy: to achieve control and thereby restore or maintain the best possible quality of life for each individual patient. We might be setting our sights too low in this regard. We often focus on how much we have improved the patient's symptoms rather than on how much better he or she could still be. Individualizing therapy can help us aim higher: to minimize impairment and risk to the lowest point achievable and to raise the quality of life to the highest point possible for that individual.

Our control goals thus should include minimal or no chronic symptoms day or night, no nocturnal awakenings, minimal or no exacerbations, no limitations on activities, no missed school or work, near-normal pulmonary function, minimal use of inhaled short-acting β_2 -agonists, minimal or no adverse effects from medications, and minimal measurable inflammation. Overall, and most significantly, our goals should include that both the patient and the clinician rate the patient as being well.

Conclusion

Diagnosis, assessment, and treatment of asthma are complex, but we have the ability to improve current asthma outcomes. Instead of focusing on measuring and defining the severity of asthma, we should emphasize achieving control and addressing and modifying risks of adverse outcomes. We cannot standardize treatment because there are numerous factors that we do not yet understand sufficiently to incorporate into a standard protocol. We can and should standardize assessment by monitoring the patient's condition the same way during each office visit.

The standardization of diagnosis and assessment entails investing time, effort, and funds in the beginning but generates substantial rewards over time. Instituting standard questionnaires and standard objective measures of airway obstruction, inflammation, and bronchial reactivity can result in more efficient evaluation in the long run, with less time spent and fewer tests. Once the routine is established, complex treatment decisions are made easier. In addition, funds spent on prevention early on pay off eventually by reducing both direct and indirect costs.

Because many factors contribute to variable responses in asthmatic patients, treatment must be individualized. Standardizing diagnosis and assessment simplify the first part of the process of asthma control and pave the way for

improving the quality of life and satisfaction of each individual patient.

OTHER MEASURES: HOW SHOULD NEW RESEARCH REGARDING ASSESSMENT OF INFLAMMATION, REMODELING, AND DISEASE PROGRESSION AFFECT WHAT WE DO IN THE CLINIC?

Many potential asthma biomarkers (objective measures of lung dysfunction and inflammation) have been identified and used in clinical research investigating causal links and disease outcomes. Transformation of these biomarkers into clinically useful tests, however, has been lacking. We can use insights gained from clinical research to substantiate the use of biomarkers for asthma management in our daily clinical practice. Improved management can, in turn, lead to improved outcomes. Implementing these improvements rests on determining which biomarkers reveal the underlying disease process most clearly and at the same time offer ease of performance during routine office visits.

Biomarkers that improve clinical outcomes: Measures of inflammation

Two clinical trials that have been particularly helpful in distinguishing lung-specific biomarkers capable of improving clinical outcomes are those by Sont et al⁴¹ and Green et al.⁴² Both of these studies have compared the management of asthmatic patients using standard guidelines with management using additional biomarkers. Standard guidelines recommend that symptoms and lung function tests provide the basis for anti-inflammatory drug dosage adjustments. The strategies in the Sont and Green studies were to use as reference subjects patients followed in accordance with these recommendations. The reference subjects were compared with intervention subjects followed by using these recommendations, as well as by measures of inflammation.

Sont et al⁴¹ investigated whether adding a protocol aimed at reducing airway hyperresponsiveness to the standard recommended protocol led to better control and greater improvement in airway inflammation. The study consisted of a 2-year, single-blind, randomized, prospective parallel trial involving 75 adults with mild-to-moderate asthma. One group, serving as the reference, was assessed and treated with stepwise adjustment in controller medication, based on an algorithm similar to the asthma management guidelines of the National Institutes of Health/National Heart, Lung, and Blood Institute and the Global Initiative for Asthma.⁴³ The intervention group was additionally managed in accordance with results of methacholine bronchoprovocation, which is both the gold standard measure of airway hypersensitivity and a surrogate marker for inflammation. Patients in the intervention group had a 1.8-fold lower rate of mild exacerbations than did those followed by the guidelines protocol

alone (0.23 and 0.43 exacerbations per year per patient, respectively). In addition, bronchial biopsy specimens from those in the methacholine-managed group demonstrated a significant decrease ($-2.1 \mu\text{m}$, $P = .005$) in basement membrane thickness over the course of the study, whereas those in the reference group showed no significant decrease ($-0.4 \mu\text{m}$, $P = .3$). Those in the methacholine-managed group received significantly more ICSs, with a median difference in dose of 400 $\mu\text{g}/\text{d}$. The implication of this study is that adding a measure of airways hyperresponsiveness to the routine assessment of asthma control can reveal inadequately controlled features of asthma, leading to uptitration of prescribed controller therapy and improved asthma outcomes.

Green et al⁴² used British Thoracic Society asthma guidelines and compared a reference group, managed by these standard guidelines, with an intervention group that was additionally managed by normalization of induced sputum eosinophil counts. The study assessed 74 adult patients with moderate-to-severe asthma over 1 year. The sputum eosinophil count was 63% lower in the sputum management group versus the reference group; the sputum management group had significantly fewer severe exacerbations than did the reference group (35 vs 109, $P = .01$) and significantly fewer hospitalizations for asthma (1 vs 6, $P = .047$). There was no significant difference between the average daily doses of inhaled or oral corticosteroids between the 2 groups. The implication of this study is that adding a direct measure of airways inflammation to the routine assessment of asthma control can improve the uptitration and downtitration of prescribed controller therapy, leading to improved asthma outcomes.

Advantages and disadvantages of inflammation biomarkers

Both of these studies demonstrated that adding measures of inflammation to standard assessment protocols can result in better asthma control. Diminishing exacerbations in this way potentially increases patient safety and might decrease the costs and time involved in urgent care treatment. Although better control in the study by Sont et al⁴¹ required stepping up dosages of ICSs, it also suggests that with the use of inflammation measures, we can identify the subset of patients who need higher dosages and step up treatment only in that group. Furthermore, in the study by Green et al,⁴² better control was achieved without increasing total steroid use. The implication for clinical practice from these studies is that the additional measurement of inflammation might confer an educational advantage; that is, knowing that inflammation is present in the airway might improve provider practice and patient adherence.

On the other hand, the measures of inflammation used in these 2 studies are beneficial research tools but are difficult to implement in a busy clinic. Bronchoprovocation protocols are fairly involved and require expertise to induce airflow obstruction in a safe manner. Likewise,

sputum induction is not ideal for routine practice because it is a lengthy procedure and irritating to the airways. As the importance of assessing inflammation in the management of asthma is increasingly recognized, the need for a practical biomarker of inflammation has become apparent. One of the most promising new measures in this regard is eNO, a noninvasive and logistically feasible biomarker for inflammation.

eNO as an emerging inflammation biomarker for assessment

In the past few decades, nitric oxide has been recognized as an endogenously produced gas with diverse functions in the human body, including multiple roles in inflammation. It is produced by numerous cell types, including eosinophils and airway epithelial cells. Measurement of the fraction of nitric oxide in exhaled air (eNO) is helpful in the management of asthma; it has been found to be a marker of sputum eosinophilia,⁴⁴ bronchial wall eosinophilia (as assessed by means of biopsy),⁴⁵ and bronchial responsiveness.⁴⁶

A number of recent studies have been performed to determine whether measuring eNO improves asthma outcomes. A study by Smith et al⁴⁷ sought to determine whether the dose of ICSs could be titrated to the lowest effective dose by monitoring asthmatic patients with eNO. Patients (aged 12-75 years) were randomly assigned to groups for corticosteroid dose adjustment based either on eNO measurements or on conventional guidelines (control group). At the end of 1 year of follow-up, the mean daily dose of ICS for the eNO group was 270 $\mu\text{g}/\text{d}$ less than that for the control group, representing a significant difference ($P = .003$). No statistically significant difference in exacerbation rates was observed between the 2 groups.

Likewise, Pijnenburg et al⁴⁸ demonstrated improvement of asthma management in children by using eNO to titrate the dosage of ICSs. Patients (aged 6-18 years) were divided into 2 groups, one in which treatment decisions were based on eNO measurements and symptoms and one in which decisions were based on symptoms alone. Over 1 year, with similar corticosteroid dosages in the 2 groups, children in the eNO group achieved greater improvement in bronchial hyperresponsiveness, as measured by means of bronchoprovocation tests with methacholine (2.5 vs 1.1 doubling doses, $P = .04$.) In addition, children treated on the basis of symptoms alone demonstrated an increase in eNO levels (from 30.8 to 36.7 ppb, $P = .035$), suggesting increased airway inflammation. No significant overall change in eNO level was observed in those within the eNO group.

A second study by Pijnenburg et al⁴⁹ investigated whether eNO measurements could predict asthma relapse in children with well-controlled asthma in whom ICSs were discontinued. eNO was measured in 40 children (mean age, 12.2 years) before withdrawal of steroids and at 2, 4, 12, and 24 weeks afterward. They found higher eNO values in children with subsequent clinical relapse at 2 and 4 weeks. A 4-week eNO value of 49 ppb provided

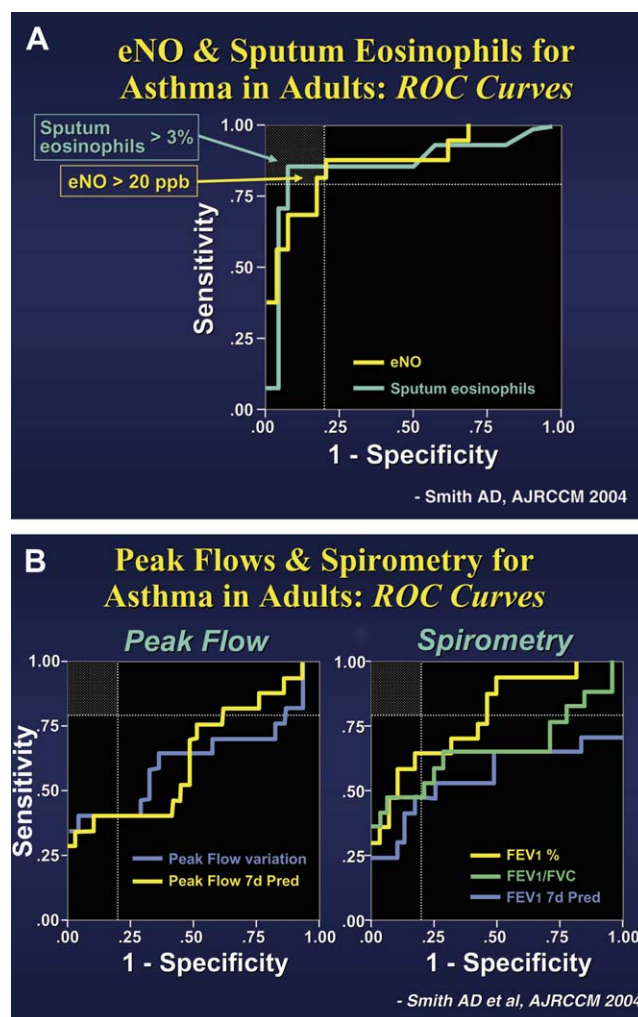


FIG 5. A, eNO and sputum eosinophil measurement for asthma in adults: receiver operating characteristic curves. Sputum eosinophil and eNO values correlated with each other and provided diagnostic accuracy. Levels of greater than 20 ppb for eNO and greater than 3% for sputum eosinophils were found to be highly predictive of asthma. **B,** Peak flows and spirometry for asthma in adults: receiver operating characteristic curves. Conventional tests were found to be poorly sensitive (0% to 47%) in comparison with sputum eosinophil and eNO measurement. Reprinted with permission from Smith AD, Cowan JO, Filsell S, McLachlan C, Monti-Sheehan G, Jackson P, et al. Diagnosing asthma: comparisons between exhaled nitric oxide measurements and conventional tests. *Am J Respir Crit Care Med* 2004;169:473-8.⁵⁴

the best combination of sensitivity (71%) and specificity (93%) as an objective predictor of relapse.

In another study that investigated the utility of eNO measurements in children, Buchvald et al⁵⁰ performed eNO measurements and standard exercise challenge tests on stable outpatient asthmatic children to determine whether eNO could predict exercise-induced bronchoconstriction (EIB). They found that EIB could be excluded with a probability of 90% at eNO levels of less than 20 ppb in children without current inhaled steroid treatment and at levels of less than 12 ppb in children with current treatment. These findings suggest that eNO can be used to screen for children unlikely to have EIB and thus reduce the need for exercise testing, in addition to identifying those who need pretreatment before exercise.

A second study by Buchvald et al,⁵¹ a multicenter trial involving 405 healthy children (aged 4-17 years), was performed to establish normal values of eNO and to assess the feasibility of the method in children. They determined that normal pediatric eNO values are less than 15 to 25 ppb, depending on age and self-reported rhinitis/conjunctivitis or hay fever and that the method was safe, simple, and reproducible. The success rate for test performance was almost 100% from the age of 10 years and upward.

In addition, the National Institutes of Health/National Institute of Allergic and Infectious Diseases is currently supporting a large study, the Asthma Control Evaluation: A Biomarker-Based Approach to Improving Asthma Control, through the Inner City Asthma Consortium to

“determine whether an asthma treatment strategy that measures eNO to indicate disease progression is more effective in treating asthma symptoms when combined with existing asthma treatment guidelines than treatment using the guidelines alone.”⁵² The study design is randomized and double-blind and involves a 46-week treatment period with an enrollment of 543 inner-city adolescents with poorly controlled asthma. It is expected that the study will be completed in 2006 and that it will help provide critical information in our understanding of the usefulness of eNO as an additional tool in asthma assessment and treatment.

A current advancement in logistic feasibility will undoubtedly add to eNO's clinical utility. Until recently, most eNO asthma monitoring was accomplished with stationary, chemiluminescence-based nitric oxide analyzers, such as the NIOX (Aerocrine Inc, New York, NY).⁵³ Although useful for asthma assessment in specialized settings, the instruments are sophisticated and cost prohibitive for many centers. A new generation of electrochemical analyzers is being developed, including one that was released in Europe in 2005 (NIOX MINO: <http://www.nioxmino.com>). These devices are more easily implemented for routine clinical use, appear to offer a more stable technology, and promise to be more affordable.

eNO as an emerging biomarker for diagnosis

In addition to its documented usefulness as a test for asthma assessment, eNO measurement is also emerging as a clinically useful tool for asthma diagnosis. Confirmatory tests for asthma diagnosis have been problematic, with no single, simple, and highly accurate test available. Early evaluations of eNO measurement are promising as a simple and reproducible confirmatory test in patients with a history of recurrent coughing and wheezing.

Smith et al⁵⁴ compared the performance of conventional diagnostic tests for asthma (ie, peak flow measurements, spirometry, and airway responses to inhaled bronchodilator and oral steroid) with that of eNO measurements and induced sputum eosinophil counts in patients aged 8 to 75 years. Conventional tests were found to be poorly sensitive (0% to 47%) in comparison with sputum eosinophil (86%) and eNO (88%) measurement. Sputum eosinophil and eNO values correlated well with each other and provided significantly better diagnostic accuracy than conventional tests on the basis of receiver operating characteristic curves. Levels of greater than 20 ppb for eNO and greater than 3% for sputum eosinophils were found to be highly predictive of asthma (Fig 5). Because eNO measurement is technically less demanding and quicker (1-2 minutes vs 30-45 minutes) than sputum induction and cell counting, eNO measurement offers the best overall clinical utility.

A similar study by Malmberg et al⁵⁵ performed on children 3 to 7 years of age compared the value of eNO, baseline lung function, and bronchodilator responsiveness in diagnosing newly detected probable asthma. Based on receiver operating characteristic curves, eNO was the best

method for discriminating between children with probable asthma and healthy control subjects (sensitivity of 86% and specificity of 92%). In this group of young children, an eNO value of greater than 10 ppb was found to be the best predictive cutoff point for the presence of asthma.

Biomarkers in disease progression

The next frontier in using biomarkers will extend from assessment and diagnosis of asthma to evaluation of disease progression. There is still a poor understanding of the natural history of asthma and whether it is progressive in all patients. Research is needed to address whether current biomarkers are reasonable indicators of disease progression.⁵⁶ Of particular concern is disease progression in children, which can result in substantial loss of lung function over time. Covar et al⁵⁷ identified a subset of children from the Childhood Asthma Management Program cohort (253/990 [25.6%] participants) who had a significant reduction (at least 1% per year) in postbronchodilator FEV₁ percent predicted over a 4-year period. The study identified risk factors in this group, including younger age, male sex, and higher postbronchodilator FEV₁ percent predicted. At the end of the study period, this subset of patients had lower spirometric measurements but similar methacholine reactivity and circulating eosinophil counts compared with the population who showed no decrease in lung function. There is concern that this subgroup of children with progressive decrease in airflow would go unnoticed without routine spirometric assessment during their early years. Spirometric measurement and comparison to determine which children with asthma are “falling off their growth curve” of predicted airways growth might be necessary. There is a clear need for improved understanding and outcomes in this population. The potential use of lung function, inflammation, and/or remodeling biomarkers in this setting to improve asthma outcomes has not been addressed.

Summary

Our understanding of the underlying disease process in asthma has been hampered by the nature of the disorder, namely the intermittent triggering of airway obstruction, combined with airway hyperresponsiveness and inflammation. We propose that highlighting inflammation as the key factor, however, provides the best opportunity for assessment and treatment, resulting in the best possible outcomes. If inflammation is adequately addressed, airway sensitivity might improve, reducing airway obstruction and thus making asthma exacerbations less severe and less frequent. The fraction of eNO as a measure of inflammation is suggested as the most promising of emerging biomarkers. It might provide the best combination of disease evaluation and practical implementation.

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