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Severe asthma: An overview

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Severe asthma represents less than 10% of all asthma, but these patients are responsible for a disproportionate share of the health care costs and morbidity associated with the disease. A significant challenge in the diagnosis and management of severe asthma is the ability to identify accurately the patients most at risk for adverse outcomes, such as medication side effects, emergency department visits, hospitalization, near-fatal events, or disability from persistent symptoms or chronic lung function abnormalities. To improve the treatment of these patients, we must improve our understanding of the mechanisms responsible for severe disease. To achieve this goal, it is imperative to develop a common definition of severe asthma to allow adequate characterization of the disease clinically and provide the opportunity to compare results from many studies. Several severe asthma phenotypes have been described in the literature on the basis of the age of patients, age of disease onset, corticosteroid resistance, chronic airflow obstruction, and evidence for eosinophilic airway inflammation on biopsy. These phenotypes have led to an emerging interest in the use of noninvasive methods to monitor airway inflammation in severe asthma. Treatment algorithms based on markers of airway

inflammation may decrease measures of health care utilization in severe asthma. (*J Allergy Clin Immunol* 2006;117:487-94.)

Key words: Severe asthma, definition, phenotype, eosinophils, sputum, exhaled nitric oxide

THE SEVERE ASTHMA PROBLEM

Asthma is a common disease that is rising in prevalence worldwide, with the highest prevalence in industrialized countries.¹ It is estimated that nearly 300 million people in the world have asthma.¹ In the United States, more than 20 million people report symptoms consistent with or a diagnosis of asthma, and nearly 5000 people die each year with asthma reported as the underlying cause of death.^{2,3} Although asthma prevalence had steadily risen in the United States, there is evidence that the annual rate of increase may have stabilized in more recent years.² Concurrently, there has been a rise in outpatient visits with a fall in inpatient hospitalizations, suggesting that the development and implementation of guideline-based therapy (National Asthma Education and Prevention Program [NAEPP]^{4,5} and Global Initiative for Asthma [GINA]⁶) may be improving outcomes. Despite these favorable trends in overall asthma prevalence and health care outcomes, there remains a subset of patients with asthma with severe disease that is responsible for a disproportionate share of the health care costs associated with the disease.⁷⁻¹⁰ Although severe asthma likely represents less than 10% of all asthma, these patients manifest significant morbidity associated with the disease, resulting in important individual health-related and economic consequences.

A significant challenge in the management of severe asthma is the ability accurately to identify, characterize, and then treat these patients. Although this would seem to be an obvious task, uncertainty arises when one factors in the myriad of issues that can affect the classification of a patient with asthma as having severe disease. These include unintentional undertreatment, patient adherence with prescribed medical regimens (the so-called “difficult patient”), and comorbid medical conditions that mimic asthma (such as vocal cord dysfunction). In purest terms, the true patient with severe asthma remains symptomatic with frequent exacerbations despite adherence to an

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Abbreviations used

ATS:	American Thoracic Society
ENFUMOSA:	European Network for Understanding Mechanisms of Severe Asthma
EOS:	Eosinophil
FeNO:	Fraction of exhaled nitric oxide in ppb
GINA:	Global Initiative for Asthma
ICS:	Inhaled corticosteroid
NAEPP:	National Asthma Education and Prevention Program
NHLBI:	National Heart, Lung, Blood Institute
OCS:	Oral corticosteroid
OR:	Odds ratio
SARP:	Severe Asthma Research Program
TENOR:	The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens

appropriate treatment regimen that includes multiple asthma medications. This discussion examines our current understanding of true severe asthma and the methods used to assess disease severity both initially and longitudinally, to identify patients with severe asthma at risk for adverse outcomes, and to assess response to therapy and the clinical stability of disease.

DEFINITIONS OF SEVERE ASTHMA

The NAEPP and GINA guidelines both assess disease severity on the basis of nocturnal symptoms, use of short-acting bronchodilators, frequency of exacerbations that affect daily activities, and baseline pulmonary function measurements before treatment. Subjective elements (patient symptoms) and objective data (pulmonary function) are weighted equally in these classification schemes, yet respiratory symptoms have been shown to correlate poorly with measures of airway obstruction (FEV_1).¹¹⁻¹³ Multiple studies have shown that both patients and physicians inaccurately estimate disease severity, leading to under-treatment of patients.¹³⁻¹⁵ A recent analysis evaluating concordance between the NAEPP and GINA guideline classification schemes with subspecialty physician assessment found poor agreement among these methods of disease classification.¹⁶

In 2000, the American Thoracic Society (ATS) sponsored an expert workshop on refractory asthma to identify important issues in severe asthma, including the development of a consensus definition for severe asthma.¹⁷ The workshop definition differs from the traditional guideline-based assessment of disease severity through the incorporation of a requirement for ongoing treatment with high doses of corticosteroids and the addition of other elements of asthma control, such as health care utilization. The ATS definition is based on a combination of major and minor criteria that aim to identify subjects with inadequate asthma control despite appropriate treatment with corticosteroids, the true patient with severe asthma. Using this

TABLE I. ATS Workshop consensus for definition of severe/refractory asthma*

Major characteristics

1. Treatment with continuous or near continuous ($\geq 50\%$ of year) OCSs
2. Requirement for treatment with high-dose ICSs

Minor characteristics

1. Requirement for additional daily treatment with a controller medication (eg, long-acting β -agonist, theophylline, or leukotriene antagonist)
2. Asthma symptoms requiring short-acting β -agonist use on a daily or near-daily basis
3. Persistent airway obstruction ($FEV_1 < 80\%$ predicted, diurnal peak expiratory flow variability $> 20\%$)
4. One or more urgent care visits for asthma per year
5. Three or more oral steroid bursts per year
6. Prompt deterioration with $\leq 25\%$ reduction in oral or ICS dose
7. Near-fatal asthma event in the past

Definition requires 1 or both major criteria and 2 minor criteria.

*Requires that other conditions have been excluded, exacerbating factors have been treated, and patient is generally compliant.

definition, subjects with severe asthma must meet 1 of 2 major criteria—(1) the use of high-dose inhaled corticosteroids (ICSs) and/or (2) the requirement for very frequent oral corticosteroid (OCS) use—as well as 2 of 7 minor criteria: the use of additional controller medications, the presence of daily symptoms requiring rescue inhaler, reduced lung function, urgent care by a physician, recurrent exacerbations requiring OCSs, clinical deterioration with steroid withdrawal, and a history of near-fatal events (Table I).

It is important to note that the ATS workshop definition was developed by consensus and has not been subjected to prospective evaluation. Nonetheless, there is circumstantial evidence that a classification strategy that includes measures of health care utilization may more accurately identify patients with severe asthma. The combination of 2 methods of severity assessment (NAEPP with physician assessment) in The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) cohort identified the severe asthma subjects with the highest health care utilization.¹⁶ Another recent study showed physician assessment of severity to be positively associated with emergency department visits and inpatient hospitalizations.¹⁸ These studies suggest that measures of health care utilization are an important addition to the traditional measures of disease severity in asthma. The incorporation of these measures into the ATS workshop definition should improve our ability to identify the subgroup of severe patients who are responsible for the morbidity and mortality associated with severe disease.

PATHOBIOLOGY OF SEVERE ASTHMA

Most studies investigating the pathobiology of asthma have used research bronchoscopy to sample the airways in milder asthma. Multiple reviews have summarized the

cellular inflammatory events seen in milder asthma with prominent roles for T_H2-lymphocytes, eosinophils, and basophils in this inflammatory milieu.^{19,20} Aside from this inflammatory cellular response, however, is a well described architectural remodeling of the airway with implications for chronic airflow obstruction.²¹⁻²³ Far fewer studies have been performed in severe asthma, but results thus far suggest that the classic eosinophilic inflammation seen in milder asthma may not be a feature in all patients with more severe asthma.²⁴ Two important findings have been described in severe asthma: (1) the persistence of eosinophilic inflammation seemingly unresponsive to treatment with high-dose corticosteroids, and/or (2) the presence of neutrophilic inflammation.²⁵⁻³¹ These studies suggest significant heterogeneity in response to corticosteroids within the severe asthma group that may represent the lack of response or a shift in responsiveness to corticosteroids. This concept of different inflammatory phenotypes in severe asthma has major implications for the evaluation and treatment of these patients. The ability to identify these phenotypes by using a noninvasive method to tailor treatment may be important in the future treatment of severe asthma. Further investigation is clearly needed.

THE SEVERE ASTHMA PHENOTYPE

There are few published reports on the clinical aspects of severe asthma. Differences in the definition of severe asthma and the respective control groups among these studies make comparisons difficult.³¹⁻³⁷ Three large research projects are currently investigating severe asthma: the National Heart, Lung, Blood Institute (NHLBI)-sponsored Severe Asthma Research Program (SARP), the European Network For Understanding Mechanisms of Severe Asthma (ENFUMOSA), and the observational TENOR study. Although these ongoing studies have used different definitions of severe asthma, the collective results from these large studies will provide the most comprehensive assessment of severe asthma to date.

Table II summarizes selected publications that address key aspects of the severe asthma phenotypes: (1) differences in severe asthma in children and adults,³²⁻³⁴ (2) the effect of age of onset on severe disease,^{31,32} (3) the concept of resistance to corticosteroid therapy and variability in disease,³³ the subset of subjects with (4) chronic airflow obstruction^{35,36} and/or (5) eosinophilia on airway biopsy,³¹ and (6) the spectrum of patients with severe asthma that has been published in a prospective comprehensive protocol by the ENFUMOSA investigators³⁷ (the ENFUMOSA group predates the SARP group and has published their initial data analysis, and the SARP group is preparing to submit their first collaborative manuscript in early 2006). In addition, the more recent studies have begun to explore the significance of measures of atopy (serum IgE and eosinophilia), exhaled nitric oxide, and sputum eosinophilia as potential biomarkers of disease severity.^{31,35-37}

Children versus adults

Severe asthma in children and adults is clearly different. Although many papers have analyzed severe disease in children or severe disease in adults, Jenkins et al³² studied a large group of subjects of all ages to contrast manifestations of the disease in childhood versus adult asthma. The subjects in this study were clearly patients with severe asthma in that the majority were on chronic OCS therapy (mean dose, 20-30 mg daily) and 25% had been intubated for an asthma exacerbation in the past. Well demonstrated by this study, and supported by the study by Chan et al³³ and the TENOR study,³⁴ is the sex switch from a male predominance in childhood severe asthma to female predominance in adult severe asthma.³²⁻³⁴ Although pulmonary function has been reported to be preserved in children with severe asthma,³⁸ the OCS-dependent children in the study by Jenkins et al³² had low baseline FEV₁ percent predicted. In addition, children with the longest duration of disease had the greatest annualized decline in lung function. In a cohort of children followed longitudinally in Australia, one predictor of severe airway obstruction in the adults was low baseline FEV₁ as a child.^{39,40} These data suggest that children with asthma with low lung function and long duration of disease are likely to progress to severe asthma, either during childhood or as adults.

Age at disease onset

Jenkins et al³² also analyzed adults in their cohort with respect to age at onset of disease. Adult subjects with asthma who had onset of their asthma in adulthood had a shorter duration of disease but similar decrement in lung function, suggesting that disease duration alone did not explain the degree of airway obstruction in these subjects with severe disease. Miranda et al³¹ reported similar results in adult subjects with asthma with onset of disease after the age of 12 years (late-onset asthma) who had marginally worse lung function despite a shorter overall duration of disease. This late-onset group was less atopic by skin test, tended toward lower IgE levels, and had fewer symptoms with allergen exposures, suggesting a nonallergic phenotype. Ten Brinke et al³⁵ also evaluated age of disease onset in their study on chronic airflow obstruction and found that adult-onset disease was a risk factor for chronic airway obstruction (odds ratio [OR], 3.3). These studies suggest that there may be important differences in pathophysiologic mechanisms in early-onset compared with late-onset asthma.

Corticosteroid resistance and disease lability

Severe asthma is defined by continuous symptoms and pulmonary function abnormalities despite treatment with high doses of corticosteroids. This observation has led to the concept of a lack of response or a shift in the dose-response curve to corticosteroids in some patients with severe disease. The study by Chan et al³³ is an early attempt to evaluate the response to corticosteroids in severe

TABLE II. Selected studies of severe asthma phenotypes

Study	Groups studied	N	Percent on OCS	Age (y)	Sex % F or F:M	Duration of asthma (y)	Percent intubated	Prebronchodilator % FEV ₁	Blood EOS	IgE	Positive skin test results	FeNO (ppb)	Airway EOS (%)
Jenkins et al ³² 2003	All severe Age ≤18 y Age >18 y	125 150	75% 80%	13 34	38%* 68%	10* 22	23 28	74 ± 2* 57 ± 2	259 266	505* 205	82% 88%		
Chan et al ³³ 1998	Severe <18 y Steroid sensitive Steroid insensitive	164 61 21	51%	14	55%	12 11 12		77 (61-90) Post-OCS 93 (84-104) 63 (55-71)*	176	208	73%		
TENOR ³⁴ 2004	Difficult to treat 6 to 12 years old 12 to <18 years old >18 years old	770 497 3489		10 15 49	34% 43% 71%			87 ± 20 84 ± 22 74 ± 23		183 224 85			
ten Brinke et al ³⁵ 2001	All severe (postbronchodilator) FEV ₁ <75% FEV ₁ >75%	66 70	35% 30%	49* 42	62%* 77%	27* 15		47 ± 15 85 ± 18	158 200	109 79	58% 59%	11 (2-76) 8 (2-202)	In sputum 3.2 (0-55)* 0.5 (0-59)
Bumbacea et al ³⁶ 2004	All severe (postbronchodilator) FEV ₁ <50% FEV ₁ >80%	37 29		44* 30	65%* 86%	25* 15	43* 17	38 (16-50) 98 (81-121)	410* 150	133 127	54% 55%	21 ± 2.4* 13 ± 2.3	
Miranda et al ³¹ 2004	All severe Onset <12 y Onset >12 y	50 30	75% 75%	29* 42	56% 59%	26* 14	21-56% 20-31%	56 ± 3 48 ± 4	108 56	98%* 76%			% EOS ⁺ 36%* 63%
ENFUM OSA ³⁷ 2003	Mild-moderate: low ICS + no exac/ past y Severe: OCS/high ICS + exac/ past y	158 163		41 43	1.6:1 4.4:1*	20 21		89 ± 18 72 ± 23*	4.1% 4.4%	148 109*	75% 60%*	9 (7-7.3) 10 (7-13)	

Because of the compilation of data from multiple studies, data are presented in various formats. Age and asthma duration are presented as mean values. Sex is expressed as % female subjects or ratio female:male. Prebronchodilator FEV₁ % predicted is presented as mean ± SEM, mean (range), or mean ± SD. Blood eosinophil counts are expressed as cells × 10⁶/L or % cells. IgE is expressed as IU/mL. + *Skin tests* denotes the percentage of subjects with >1 skin test response on prick testing or by RAST.

Exac, Exacerbation.

**P* < .05 in the respective study.

asthma through the evaluation of a subset of subjects with severe asthma who were treated with OCSs for an asthma exacerbation during an inpatient observation period. These subjects had more bronchial hyperresponsiveness and greater airflow obstruction at baseline compared with the subjects without exacerbation. A >15% increase in FEV₁ after corticosteroid therapy was used to identify a group of steroid-sensitive subjects who were compared with the steroid-insensitive patients. There were no differences in asthma duration or precorticosteroid FEV₁ between the steroid-sensitive and steroid-insensitive

group; baseline FEV₁ did not predict the lack of response to steroids. Further analysis of the latter group revealed that nearly half of the steroid-insensitive patients with asthma manifested >30% variability in daily FEV₁ measurements, reminiscent of the “brittle” patient with asthma described by Turner-Warwick⁴¹ in 1977. The possible mechanisms for steroid resistance in asthma range from molecular defects in the glucocorticoid genes and signaling pathways to lack of specificity of corticosteroids for the type of inflammation present in the severe asthma.^{42,43}

Chronic airflow obstruction

Persistent airway obstruction has been emphasized in the definition of severe asthma in all guidelines, but lung function is only 1 element in the ATS workshop definition, reflecting the concept that not all patients with severe asthma have low FEV₁. The subset of patients with severe asthma who manifest chronic airflow obstruction is likely different than those with preserved lung function, and 2 recent studies have addressed this issue clinically and with reference to biomarkers.^{35,36} The initial study by ten Brinke et al³⁵ compared subjects with severe disease with postbronchodilator FEV₁ < 75% predicted (mean, 47% predicted) to those with normal baseline lung function. The study by Bumbacea et al³⁶ is similar, but widened the gap between the chronic airflow obstruction group (FEV₁ < 50% predicted) and the unobstructed group (FEV₁ > 80%). The low FEV₁ groups in both studies were older with longer duration of disease. Measurement of lung volumes and diffusion capacity in both studies showed an elevated residual lung volume consistent with air trapping, but normal gas diffusion capacity (inconsistent with emphysema). The low FEV₁ group in the ten Brinke study³⁵ had more airway responsiveness to histamine, but this result is difficult to interpret because only 45% of the cohort underwent testing because of low pretest FEV₁. Bronchial wall thickening seen on high resolution computed tomography scans was associated with chronic airway obstruction in the study by Bumbacea et al,³⁶ and this may prove to be a valuable tool to assess disease severity or remodeling in the future.

The studies by ten Brinke et al³⁵ and Bumbacea et al³⁶ explored the presence of biomarkers in severe asthma; fraction of exhaled nitric oxide (FeNO) and blood eosinophilia were assessed in both, induced sputum in the former only.^{35,36} It is difficult to compare FeNO results caused by differences in presentation of the data in each study (one is shown as median [range], the other in graphic format). The overall mean/median values for FeNO seem low in both studies, but the low FEV₁ group is reported to have a significantly greater FeNO than the nonobstructed group in the study by Bumbacea et al.³⁶ These authors also reported greater blood eosinophil counts in the low FEV₁ group with an OR of 6.26 in chronic obstruction. None of these findings were replicated in the ten Brinke study,³⁵ which may reflect the less severe degree of chronic airflow obstruction in the low FEV₁ group. ten Brinke et al³⁵ induced sputum in a subset of their subjects and report a positive association between sputum eosinophilia $\geq 2\%$ and low lung function (OR, 7.7). These 2 studies, taken together, suggest that chronic airflow obstruction in severe asthma is related to duration of disease and may be manifested by increased airway hyperresponsiveness and computed tomography scan evidence of airway thickening. In these subjects with severe asthma with low lung function, increased eosinophils in serum and/or sputum may suggest ongoing eosinophilic inflammation that is resistant to corticosteroid therapy with resultant airway remodeling.

Eosinophils on biopsy

Early pathologic studies by Wenzel et al³⁰ led to the description of subgroups of severe asthma on the basis of the presence (or absence) of eosinophils in endobronchial mucosal biopsies. Correlation of these early pathologic results with more recent clinical data led to the description of eosinophil (EOS)⁺ and EOS⁻ severe asthma phenotypes.³¹ Overall, 2/3 of the subjects with severe asthma studied by Miranda et al³¹ had elevated airway eosinophilia despite chronic treatment with high doses of OCSs. There were far fewer EOS⁺ subjects in the early-onset severe asthma group (36%) compared with the late-onset group (63%), despite evidence for less atopy in this latter group (fewer skin test responses, lower IgE). The presence of eosinophils on biopsy (EOS⁺) was associated with an increased prevalence of near-fatal events (intubation) in early-onset disease, but was not seen in the late-onset group. There was a trend toward lower lung volumes in late-onset asthma. These observations suggest a clinically labile early-onset allergic phenotype that may be consistent with a classic T_H2 inflammatory response, but the lack of EOS⁺ on biopsy suggests that this allergic response may be well controlled by steroids. Late-onset disease, on the other hand, was characterized by lower lung function and ongoing eosinophilic airway inflammation despite corticosteroid use. The association of decreased FEV₁ and increased eosinophils on biopsy in the late-onset group is in agreement with the findings of ten Brinke et al³⁵ and Bumbacea et al,³⁶ who showed that high eosinophil counts in sputum and blood were associated with chronic airflow obstruction in older subjects with asthma.^{35,36} Ten Brinke et al⁴⁴ have recently challenged the existence of the EOS⁺ phenotype in a follow-up study in which they were able to eliminate airway eosinophils with high-dose parenteral corticosteroid treatment, suggesting that the persistence of eosinophilic inflammation in these patients with severe asthma is a result of inadequate dosages of corticosteroids.

ENFUMOSA and SARP

To improve our understanding of pathophysiologic mechanisms in severe asthma, 2 large multicenter prospective collaborations are ongoing; the NHLBI-sponsored SARP and the European Network (ENFUMOSA). One of the goals of these studies is to explore the severe asthma phenotypes discussed, but it is likely that many new phenotypes will be described from the subjects in these studies. Both networks are performing standardized comprehensive clinical evaluations (questionnaires, lung function and atopy testing) and assessing airway inflammation, using both noninvasive (FeNO, sputum induction) and invasive (investigative bronchoscopy) methods. This thorough assessment of a large number of subjects from a clinical to biologic level will greatly increase our knowledge in this field. As publications begin to appear from these investigators in the near future, it is important to note that the definitions of *severe asthma* and *control*

groups are different for SARP and ENFUMOSA, and this may lead to disparate results.

In ENFUMOSA, the definition of severe asthma was based on use of high-dose corticosteroid therapy and 1 or more exacerbations in the past year, without reference to additional therapy, lung function, or daily asthma control.³⁷ The severe group was compared with a group of controlled asthma subjects on low-dose ICSs with no exacerbations in the past year. There was no difference in subject age or duration of asthma between the groups, but there was a striking sex disparity, with nearly 80% of the severe group women with an OR of 2.69 for severe disease. The severe group had lower lung function and less atopy (both IgE and skin test responses), but there was no difference in blood eosinophil counts. Although there was no difference in FeNO in the groups overall, the subjects with severe disease on OCSs had FeNO levels that were 3-fold that of the severe subjects on ICSs alone. This finding has important implications for the interpretation of FeNO levels as a measure of steroid responsiveness in patients with severe asthma. Historically, women with severe asthma reported greater sensitivity to aspirin and nonsteroidal anti-inflammatory drug (OR, 5.12), previous episodes of sinusitis (OR, 3.92), and menses-related symptoms (OR, 3.3). Associations with possible asthma triggers were less in men (aspirin sensitivity OR, 4.61), but the small number of male subjects in the study makes interpretation difficult. The ENFUMOSA study confirms the presence of chronic airflow obstruction and less atopy in adults with severe asthma, although it suggests that there may be important sex differences in clinical phenotypes in severe asthma.

The SARP group has used the ATS workshop definition of severe asthma that may capture a broader spectrum of severe asthma than the patients with severe asthma studied in ENFUMOSA. A comparison group of patients with "not-severe" asthma ranging from mild intermittent to moderate persistent asthma has been recruited as control groups. The variability of both the severe and not-severe groups in SARP should facilitate the description of additional clinical and inflammatory phenotypes in asthma that will improve our understanding of underlying mechanisms important in the heterogeneity of both milder and severe asthma.

USING NONINVASIVE BIOMARKERS TO IDENTIFY SEVERE ASTHMA PHENOTYPES IN THE CLINIC

Although these severe asthma phenotypes have yet to be replicated in large populations, it may be instructive to use these phenotypes, although acknowledging that they may evolve over time. By any definition of severe asthma, these patients are failing to respond to traditional therapy. They are symptomatic from their severe asthma and have significant comorbidity associated with the high-dose glucocorticoid therapy that does not control their disease. Possible etiologies for this failed clinical response to

steroids have been the subject of previous reviews.^{24,42,43}

The persistence of sputum and endobronchial eosinophilia despite corticosteroid therapy is a cardinal feature in a subset of patients with severe asthma. A noninvasive measure of airway eosinophilia is an attractive marker to assess ongoing eosinophilic inflammation and changes in this inflammation in response to changes in corticosteroid dose. Likewise, the absence of airway eosinophilia in another subset of patients with severe disease may discourage further escalation of corticosteroid therapy, prompting consideration of another therapeutic modality. This discussion focuses on 2 recent descriptions of the use of noninvasive markers of airway eosinophilia to titrate corticosteroid therapy in asthma: (1) sputum eosinophilia and (2) exhaled nitric oxide. Neither study has targeted treatment of subjects with very severe asthma, and thus, the applicability of these findings to severe asthma is unclear, although the concept of biomarkers as superior markers with which to guide steroid therapy may be sound.

Sputum eosinophils

In milder and severe asthma, sputum eosinophils increase during exacerbations, and elevated baseline sputum eosinophil counts predict exacerbation with steroid withdrawal.⁴⁵⁻⁴⁸ As such, regardless of the baseline inflammatory milieu in an individual with severe asthma, the presence of eosinophils (whether chronic or acute) would portend poor asthma control. A treatment strategy that titrates the dose of corticosteroid therapy with the goal of decreased airway eosinophilia or confirmation of the absence of eosinophilia should improve asthma outcomes. Green et al⁴⁹ performed a randomized trial comparing management of 74 subjects with asthma for 12 months by using either traditional guideline-based clinical indices of asthma control or a strategy designed to maintain sputum eosinophil counts at <3%. Subjects had moderate to severe asthma (mean FEV₁, 73-76%) with 76% of each group reported to have refractory asthma (not well defined). Subjects were randomly assigned to treatment groups after stratification by recent OCS use, baseline eosinophil count, and bronchial hyperresponsiveness to ensure equal representation of these elements in the 2 groups. Both sputum eosinophil counts and FeNO were lowered in the sputum management group, and there was improvement in bronchial hyperresponsiveness in this group. In addition, the sputum group had significant improvement in measures of health care utilization with fewer exacerbations and less need for OCS rescue therapy. Traditional measures of asthma control (symptoms, bronchodilator use, FEV₁) did not differ between the groups. These observations suggest that mechanisms that cause exacerbations and airway eosinophilia may differ from those that underlie symptoms and airflow obstruction. Given the current emphasis on health care utilization measures as an important element of asthma control in severe disease, a treatment strategy using sputum eosinophilia as a surrogate marker for airway eosinophilia seems reasonable, although the application of this technique to the real world would be difficult.

Exhaled nitric oxide

FeNO has been proposed as an even less invasive measure of airway eosinophilia that rises with acute exacerbation or loss on asthma control.^{46,50,51} The relationship between FeNO and airway eosinophilia has been controversial, particularly in severe asthma.⁵² A recent large study (n = 566), however, found a significant non-linear correlation between FeNO and sputum eosinophilia ($r^2 = 0.26$; $P < .001$).⁵³ In addition, concordant associations have been found between levels of FeNO (both low and high) and eosinophils on airway biopsies (normal and high, respectively).^{54,55} Several studies, however, have found that subjects with severe disease treated with chronic OCSs had the greatest FeNO measurements, suggesting that steroid therapy itself is a confounding element in the interpretation of FeNO levels in severe asthma.^{37,55,56}

Given that FeNO may be an indirect measure of airway eosinophilia, it has been evaluated in a single blind, placebo-controlled trial using FeNO to guide corticosteroid therapy in milder asthma.⁵⁷ Smith et al⁵⁷ studied 96 patients with mild to moderate asthma (FEV₁, 80-92% on low-dose to medium-dose ICSs) using standard guideline-based therapy or a treatment strategy designed to maintain FeNO levels < 35 ppb (50 mL/s flow rate). Patients with severe disease were effectively excluded by limits on recent exacerbations or a history of a near-fatal event. ICS doses were titrated to lower levels in the FeNO management group with a trend toward reduction in exacerbation rates compared with the traditional therapy group, but this did not meet significance. It should be noted that at the time of the first uncontrolled visit, the traditional therapy group that had poor asthma control clinically did not have an elevated FeNO level or sputum eosinophil count. Multiple reports suggest that the presence of airway eosinophilia may predict asthma exacerbations.^{31,35,36,45-49} As such, the traditional therapy group may have been less likely to exacerbate, and the true reduction in exacerbation rate with the FeNO strategy may have been underestimated. Although the reduction in health care utilization using a FeNO titration strategy was less impressive than that seen using sputum eosinophil counts, patients with asthma of differing severity were evaluated in these 2 studies, and the baseline rate of exacerbation in these groups of patients may have undervalued the FeNO strategy.

SUMMARY

Although patients with severe asthma reflect a small proportion of the general population of patients with asthma, they represent the cost and morbidity of the disease. The incorporation of measures of health care utilization and medication use into the definition of severe asthma is crucial to allow investigators and clinicians to identify the patients at highest risk for adverse outcomes. Observation of heterogeneity within the severe asthma group has led to multiple reports of asthma phenotypes.

The currently described severe asthma phenotypes are based on patient age (children vs adults), historical features (age of onset), resistance to usual therapy (corticosteroid dependence and resistance), physiologic impairments (chronic airflow obstruction), and airway inflammation (EOS⁻ and EOS⁺). The use of novel noninvasive biomarkers to assess disease severity and asthma control to guide therapy is an extension of the phenotypes described in this review. The ongoing large prospective ENFUMOSA, SARP, and TENOR cohorts are likely to identify additional phenotypes and will greatly increase our knowledge of pathophysiologic mechanisms important in severe asthma. This knowledge will facilitate the emerging role of immunomodulators and biologic therapies (antibodies and receptors antagonists) in the treatment of patients with severe asthma.

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