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Abbreviations: NHLBI = National Heart, Lung and Blood Institute; RCT = randomized controlled trial

It should be a nonissue to agree that measuring sputum eosinophils is useful in the management of severe asthma. We would add that the clinical value is enhanced by additional measurements of total nonsquamous cell count (expressed as 1 million per gram of sputum selected from saliva), neutrophils, and other cellular indices.

Asthma is recognized as a chronic disease of the airways of the lungs, presenting with symptoms that are characterized by variable airflow limitation, airway hyperresponsiveness, and airway inflammation.¹ Because there is no unifying cause, its recognition depends on the presence of the physiologic abnormalities; symptoms are nonspecific and sometimes insensitive and airway inflammation is not always present.^{2,3} However, the severity of asthma is graded primarily by the inflammatory component of the disease, the minimum daily dose of corticosteroid required to maintain control, or the best results once factors that aggravate asthma have been excluded.⁴ The designation of severe asthma is now reserved for patients with severe refractory asthma, which is only controlled (or still uncontrolled) by high-intensity treatment of $\geq 1,000$ μg fluticasone equivalent or added ingested corticosteroid (in addition to long-acting β agonist or any other controller medications, if they are beneficial), which confer a risk of serious adverse effects of treatment.^{5,6} Severe refractory asthma needs to be distinguished from difficult asthma, which remains uncontrolled, despite high-intensity treatment, because of persisting aggravating factors that if removed might reduce the severity. Patients with severe refractory or difficult asthma should be assessed by a specialist and receive personalized treatment of the components and the causes or aggravating factors.

A problem with current asthma management strategies is that despite consideration of asthma as a

chronic inflammatory disease,¹ the importance of inflammation in its treatment, the recognition that the inflammation correlates poorly at best with the presence of abnormal functioning or symptoms, and the availability of good quality methods to measure it, the measurement of the inflammatory (bronchitic) component of asthma (or other airway disease) is generally not promoted in consensus documents or measured in practice.⁵⁻⁷ Of the measurements currently available, the most specific, comprehensive, and discriminative are sputum quantitative nonsquamous cell counts.⁷

When cell counts are performed on weighed sputum selected from the saliva, treated with dithiothreitol, and filtered to obtain a homogeneous suspension of cells, they provide a total and differential cell count, as well as a semiquantitative measure of free eosinophil granules and macrophage smokers inclusions. The cell counts have good test qualities, have known normal values (with mean and median values for eosinophils of 0%), and identify the presence, severity, and type of inflammation. Three types of cellular inflammation are recognized (eosinophilic, neutrophilic, or both), and there are several known environmental causes of these inflammations. For example, eosinophilic bronchitis (usually indicated by an increase in the percentage of eosinophils and a total cell count that remains in the normal range) can result from hypersensitivity to inhaled allergens or occupational chemical sensitizers as well as from unknown causes. The causes of neutrophilic bronchitis include cigarette smoke or atmospheric pollutants, which usually increase the percentage of neutrophils, or confirmed viral^{8,9} or suspected bacterial¹⁰ infections, which also increase the total cell count and are, therefore, more intense.

Identifying the presence and cellular features of the bronchitic component of asthma can improve management in a number of ways.⁷ Sputum eosinophilia will respond to adequate corticosteroid treatment. However, its persistence also raises the possibility that there might be one or more aggravating aspects of difficult asthma that need reevaluation, such as nonadherence, improper inhaler use, malingering, and avoidance of exposure to allergens or chemical sensitizers. Noneosinophilic inflammation is unlikely

to respond to an increase in steroid therapy and, absent eosinophils, suggests that the dose is excessive and can be reduced without a recurrence of an eosinophilic exacerbation. When eosinophils are in the upper normal range, a recurrence of sputum eosinophilia is likely if corticosteroid use is reduced. Serial measurements associated with adjustments to therapy can guide identification of the minimum corticosteroid dose required to maintain control of the eosinophilic inflammation and reduce exacerbations. A noneosinophilic neutrophilic bronchitis with a raised total cell count and neutrophils > 80% is suggestive of bacterial infection and should benefit from appropriate antibiotic therapy. The causes of airway inflammation are common and will vary from one time to another. Hence, exacerbations with different causes do not necessarily require the same treatment. Measurement of sputum cell counts helps to prevent misdiagnosis and mistreatment.

Specific studies on how the use of sputum cell counts can change the way severe asthma is managed are limited but impressively supportive. The support comes from two randomized controlled trials (RCTs) of eosinophilic asthma in which sputum eosinophils are used to guide corticosteroid treatment,^{11,12} from three studies of the effect of anti-IL-5 monoclonal antibody in severe refractory asthma,¹³⁻¹⁵ and from one retrospective longitudinal audit of prednisone-dependent severe refractory asthma.¹⁶

The first single-center, 1-year trial that examined the effect of treating asthma to reduce eosinophils to < 2% resulted in a significant reduction of severe exacerbations compared with a control group treated without sputum eosinophil counts.¹¹ The large number of exacerbations and their severity was probably a result of the policy at the time to further reduce corticosteroid use if control was maintained for 2 months. The second trial was a multicenter trial conducted over 2 years, and it differed in that the minimum dose of corticosteroid to maintain sputum eosinophils at < 3% was determined first and then maintained for the duration of the study.¹² Exacerbations were few and mild compared with the first study and were

reduced by about 50% compared with the group treated with the same best-guideline approach to treatment without sputum cell counts. The active treatment reduced eosinophilic exacerbations but had no effect on neutrophilic exacerbations, which were regarded as probably of viral cause. The benefits in both studies were achieved without any increase in corticosteroid dose over that required by the control group. The utility of using sputum eosinophils to decrease exacerbations in adults and children with moderate to severe asthma was recently confirmed in a systematic review and meta-analysis.¹⁷

In the two RCTs on the effect of mepolizumab^{13,14} and the RCT on the effect of reslizumab,¹⁵ the drugs reduced sputum eosinophils to close to zero. This was associated with a reduction of exacerbations compared with the placebo group in the first mepolizumab study and a prednisone-sparing effect and improvement in clinical outcomes in a small sample size in the second. In the larger reslizumab clinical trial, the reduction in sputum eosinophils was associated with an improvement in FEV₁ and in asthma control over a 5-month period in patients with moderate to severe asthma. The results of these three studies were in contrast to the negative results of five other trials, where the effect of the antieosinophil drug was not examined in patients with asthma and current sputum eosinophilia. In two of the five studies^{18,19} that measured sputum eosinophils and in the three RCTs, the greater the certainty that an increase in eosinophils was persistent, the greater the success of treatment (Table 1).

Clinical outcomes are significantly improved when patients who require daily prednisone are monitored using sputum cell counts.¹⁶ Sixty-three patients with asthma (36 men; mean age, 52 years; mean BMI, 29.1) were followed for a median period of 7 years (range, 0.25-26 y). Thirty-seven patients had associated chronic airflow limitation (postbronchodilator FEV₁/vital capacity < 70%). Twenty had never smoked. Forty-two percent were nonatopic. Significant comorbidities included gastroesophageal reflux disease (70%), nasal polyps and sinusitis

Table 1—Response to Anti-IL-5 and Eosinophil Phenotype

Study/Year	Intervention	Sputum Eosinophil at Entry	Success
Flood-Page et al ¹⁸ /2007	Mepolizumab	5% of patients had > 3% eos	X
Kips et al ¹⁹ /2003	Reslizumab	~30% of patients had > 3% eos	X
Haldar et al ¹⁴ /2009	Mepolizumab	All patients had > 3% eos on one occasion in 2 y	√
Castro et al ¹⁵ /2011	Reslizumab	All patients had > 3% eos at randomization	√√
Nair et al ¹³ /2009	Mepolizumab	All patients had > 3% eos on ≥ 3 occasions	√√√

√ = grade of success of intervention; eos = eosinophils; X = intervention unsuccessful.

(65%), and sensitivity to nonsteroidal antiinflammatory drugs (28%). Ethmoid and sphenoid sinusitis were the most important predictors of persistent airway eosinophilia.¹⁸ At the time of their initial assessment, the majority of the patients were not on daily prednisone (median daily dose, 0 mg; sputum eosinophils: mean, 18.8%; median, 5.3%; min, 0; max, 84%). Monitoring with the aim of keeping sputum eosinophils <2% resulted in higher doses of corticosteroids (median daily dose of prednisone was 10 mg and for inhaled corticosteroids was 1,000 µg of fluticasone equivalent), and this was associated with predictable significant adverse effects. Over the period of follow-up, despite decreasing the eosinophilic exacerbations to <0.2 y/patient, there were 22 noneosinophilic neutrophilic exacerbations. Overall, there was no significant loss of lung function over the period of follow-up (mean decrease in FEV₁, 27 mL/y).

The identification of a specific type of bronchitis helps in investigating the underlying mechanisms that lead to the bronchitis and, thus, in instituting specific therapies (Fig 1). Thus, sputum eosinophilia can be due to chronic eosinophilic pneumonia, vasculitis, hypereosinophilic syndromes, or chronic hyperplastic rhinosinusitis,^{20,21} and persistent neutrophilic bronchitis can be due to atypical infections, bronchiectasis, innate immune deficiency disorders, abnormalities in ciliary motility, *CFTR* gene abnormalities, and other causes.^{10,22} Identification of asthma driven by airway hyperresponsiveness without cellular bronchitis can help select patients for therapies such as bronchial thermoplasty directed at reducing the airway smooth muscle mass.

Quantitative sputum cell counts can be made available for clinical practice. In the past 6.5 years

since we have had a sputum database, we have carried out approximately 8,900 sputum cell count examinations. The inductions have been performed by technologists in the pulmonary function laboratory and the sputum examinations by certified technologists trained in cell morphology under the hospital laboratory medicine program. The specimens have almost entirely been from outpatients, requisitioned by hospital or outside respirologists. A similar service is now provided in at least another five Canadian academic centers, using the same standardized procedures. Surely, it is time to introduce this service elsewhere to help improve the treatment of severe asthma. It identifies the type of bronchitis that is contributing to the severity and helps select appropriate investigations and medications. By normalizing eosinophils and identifying the least treatment needed to maintain that state, lung function is improved and exacerbations reduced. What more could one ask for?

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Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following conflicts of interest: Drs Hargreave and Nair have a patent on a filter device provided in a kit to process and examine sputum for quantitative inflammatory cell counts and fluid phase indices. This has not been marketed, and there is currently no profit from this. Drs Hargreave and Nair's university hospital laboratory acts as a central laboratory to teach, control quality, troubleshoot, and examine sputum in multicenter drug trials. Drs Hargreave and Nair provide teaching videos for sputum induction and examination through e-learning at mhealth.ca.

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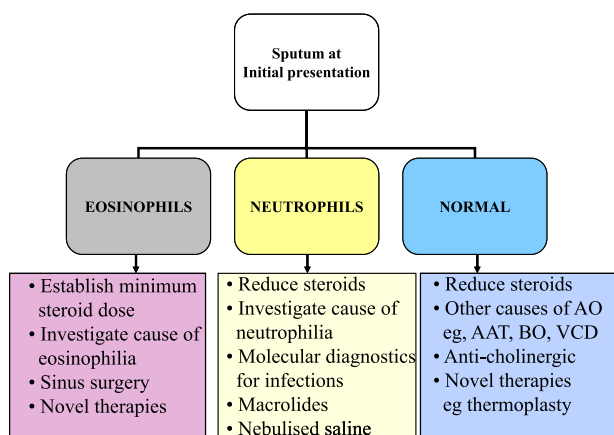


FIGURE 1. Flow chart shows the strategy used to manage asthma based on sputum cell counts. AAT = α antitrypsin deficiency; AO = airflow obstruction; BO = bronchiolitis obliterans; VCD = vocal chord dysfunction.

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Counterpoint: Is Measuring Sputum Eosinophils Useful in the Management of Severe Asthma? No, Not for the Vast Majority of Patients

Quantitating airway inflammation in patients with asthma by noninvasive methods, mainly by enumerating inflammatory cells such as eosinophils in induced sputum, has provided unique information concerning both asthma pathogenesis and the airway response to treatment. Although it is possible for highly specialized centers to reliably induce, process, and quantitate inflammatory cells and markers in sputum,¹ the procedure is time and labor intensive (it takes a skilled coordinator or technician about one-half day), requires meticulous attention to detail, and is expensive (the most expensive procedure done in the Asthma Clinical Research Network of the National Heart, Lung and Blood Institute [NHLBI], except bronchoscopy). Largely for these reasons, a recent meta-analysis concluded that "At present, there is insufficient justification to advocate the routine use of...sputum analysis (due to technical expertise required)...in everyday clinical practice" for tailoring asthma treatment.² Although the data discussed in the meta-analysis that support this conclusion should end this debate, the answers to the following five questions provide an additional perspective on this issue.

QUESTION 1: HOW OFTEN IS SPUTUM EOSINOPHILIA FOUND IN PATIENTS WITH ASTHMA?

In 295 of 377 sputum samples that were acceptable for analysis (those containing <80% squamous cells) from the Wake Forest NHLBI Severe Asthma Research Program site, 35% had $\geq 2\%$ eosinophils (considered to be elevated by most investigators), whereas 65% (192) had <2% eosinophils (Stephen P. Peters, MD, PhD, FCCP, unpublished data, 2011). Of the 58 patients who met the American Thoracic Society definition of severe asthma,³ all of whom were on high-dose or inhaled or oral corticosteroids, 43% (25) had $\geq 2\%$ eosinophils, whereas 33% (78) of the 237 patients with nonsevere asthma (63% on low or medium doses of inhaled corticosteroids) had $\geq 2\%$ eosinophils (Stephen P. Peters, MD, PhD, FCCP, unpublished data, 2011). Therefore, increased sputum eosinophils are found in a minority, but still a considerable number, of patients with severe and nonsevere asthma, including those on corticosteroid therapy. However, I contend that this cross-sectional

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