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Noneosinophilic asthma: A distinct clinical and pathologic phenotype

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The use of induced sputum to assess airway inflammation in large and diverse populations with asthma has led to the recognition that significant numbers of patients do not have evidence of eosinophilic airway inflammation. The absence of a sputum eosinophilia has been noted in patients across the range of asthma severity; it has also been reported in patients presenting with an asthma exacerbation. However, whether noneosinophilic asthma represents a pathologically distinct and clinically important asthma phenotype remains unclear. In this review, we present recent evidence suggesting that noneosinophilic asthma represents a stable phenotype associated with a distinct lower airway pathology and structure. We suggest that this lower airway inflammation develops in response to etiologic factors acting through the innate immune pathway and that elements of this immune response contribute to airway dysfunction. Finally, we argue that noneosinophilic asthma is associated with clinically important differences in natural history and treatment response. We particularly highlight evidence that noneosinophilic asthma is associated with a reduced short-term and long-term response to corticosteroid therapy. (*J Allergy Clin Immunol* 2007;119:1043-52.)

The current Global Initiative for Asthma description of asthma encompasses pathologic, physiological, and clinical aspects of the disease.¹ However, within these confines, clinicians acknowledge that heterogeneity exists in the patterns of disease expression within the asthma population. From a pathophysiological perspective, the 2 hallmarks of the disease are chronic airway inflammation

and airway dysfunction, manifesting as airway hyper-responsiveness and variable airflow obstruction. Until recently, the 2 were considered closely related, with airway inflammation leading directly to structural and functional changes in the airway. The eosinophil has long been credited with a central role in this process, because early necropsy data and later biopsy studies have consistently revealed eosinophilic inflammation within the airway mucosa of patients with asthma.² The functional relevance of these cells has been supported by studies demonstrating an elevated level of eosinophil degranulation products in bronchoalveolar lavage fluid³ and bronchial biopsy specimens of patients with asthma of varying severity⁴ and by the consistent demonstration that factors that improve asthma control, notably inhaled corticosteroids, also improve underlying eosinophilic airway inflammation,⁵ whereas factors associated with a loss of asthma control, such as exposure to environmental allergens, also lead to a worsening of eosinophilic airway inflammation.⁶ Against this background, it could be argued that the term *noneosinophilic asthma* is an oxymoron.

Early postmortem and biopsy studies were limited in their scope, because numbers were small and the populations were not representative of the general asthma population. The development of noninvasive techniques to assess airway inflammation has been an important advance in that it has made it possible to investigate airway inflammation, and its relationship with other features of asthma, in larger and more representative populations of patients with asthma.

Induced sputum has been a particularly valuable research tool for examining airway inflammation in asthma.⁷ Studies in patients with mild to moderate asthma have shown a close correlation between inflammatory cell counts in induced sputum and bronchial wash⁸ and a less close correlation with bronchoalveolar cell counts.^{8,9} The relationship between induced sputum findings and cell counts in bronchial biopsy is more variable,¹⁰ probably because granulocytes are not resident cells and they are not represented well in tissue. Techniques that evaluate bronchial luminal cell counts such as induced sputum may therefore be the best way to evaluate the pattern of granulocytic inflammation in airways disease. In keeping with this,

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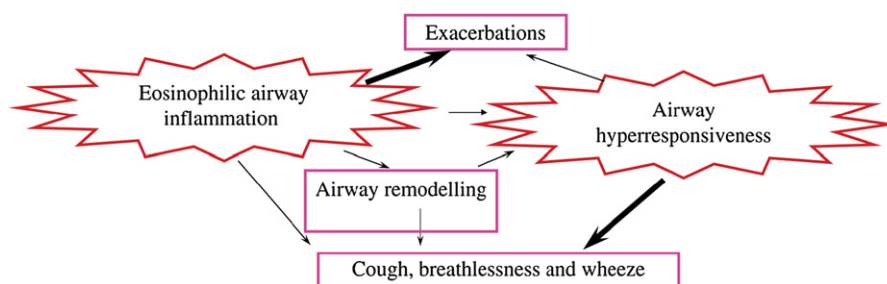


FIG 1. A new model of asthma with eosinophilic airway inflammation and airway hyperresponsiveness viewed as relatively independent features of asthma that contribute to the clinical manifestations of the disease in different ways, airway hyperresponsiveness being particularly associated with day-to-day symptoms and eosinophilic airway inflammation with exacerbations. The thickness of each *arrow* reflects the strength of the association.

the suppressive effect of corticosteroid therapy^{5,11} and anti-IL-5^{12,13} on eosinophilic airway inflammation is more readily apparent in sputum than bronchial biopsies.

Normal sputum cell counts consist of 2/3 macrophages and 1/3 neutrophils; eosinophils and lymphocytes are not usually seen in significant numbers. In patients with symptomatic asthma, 70% to 80% of corticosteroid-naïve patients and 50% of corticosteroid-treated patients have a raised sputum eosinophil count.¹⁴ The absence of sputum evidence of eosinophilic airway inflammation in a significant proportion of patients suggests that factors independent of eosinophilic airway inflammation, and perhaps independent of airway inflammation, make an important contribution to airway dysfunction and symptoms. This view is supported by evidence that eosinophilic airway inflammation and clinical manifestations of asthma can be dissociated¹⁵; by studies showing that effective suppression of eosinophilic airway inflammation with anti-IL-5 treatment does not alter airway responsiveness or symptoms¹³; and by the clear demonstration that the main effect of management strategies that seek to control eosinophilic airway inflammation as well as symptoms is a reduction in the frequency of asthma exacerbations rather than a reduction in symptoms or airway dysfunction.^{16,17} This new understanding of the relationship between eosinophilic airway inflammation and the clinical expression of asthma has led to a new model for asthma in which airway hyperresponsiveness and eosinophilic airway inflammation are viewed as separate, independent domains of the disease (Fig 1).

If this model is correct, then it should be possible to identify patients who exhibit one but not the other cardinal feature of asthma. This has been shown to be the case: a significant number of patients with isolated chronic cough have eosinophilic bronchitis,¹⁸ a condition in which patients have eosinophilic airway inflammation but no airway hyperresponsiveness. The presence of patients with clinical and physiological features of asthma but no sputum evidence of eosinophilic airway inflammation has also been reported.^{11,19} In comparative studies of patients with eosinophilic bronchitis, eosinophilic asthma, and noneosinophilic asthma, it is the presence of mast cells within the airway smooth muscle rather than eosinophilic

mucosal inflammation and basement membrane thickening that is related to the presence of asthma and airway hyperresponsiveness.^{20,21}

As many as 25% of patients with untreated symptomatic asthma¹⁹ and 50% of patients with asthma treated with high doses of inhaled corticosteroids²² have a normal sputum eosinophil count. Noneosinophilic asthma is also commonly seen in patients with occupational asthma,²³ in patients with refractory asthma,²⁴ and in patients presenting with a mild²⁵ or more severe²⁶ exacerbation of their asthma. The consistent finding of a subpopulation of patients without sputum evidence of eosinophilic airway inflammation has led some to suggest that noneosinophilic asthma represents a pathologically distinct and clinically important asthma phenotype. However, before accepting this, it is necessary to consider a number of questions, including the following: how should the condition be defined, does it represent a stable inflammatory phenotype, do the sputum findings reflect important differences in lower airway pathology that might have distinct causes and relationships with airway dysfunction, and does the phenotype differ from eosinophilic asthma in a clinically important way?

DEFINING NONEOSINOPHILIC ASTHMA

There are 4 important elements to this diagnosis: the presence of typical symptoms, objective evidence of variable airflow obstruction and/or airway hyperresponsiveness, the consistent absence of a sputum eosinophil count, and the absence of an alternative explanation for the symptoms and findings on investigation (Table I). Values for the upper limit of the eosinophil count that constitutes noneosinophilic disease have varied between studies. Green et al¹⁹ used <1.9%, the upper limit of the normal range, whereas Gibson et al²² used a cutoff of 2.5%, and Pavord et al¹¹ <3% for classification and analysis of noneosinophilic asthma. The 90th centile for the sputum eosinophil count in normal controls has been reported as 1.8% and 1.9% in 2 large, community-based studies.^{27,28} We suggest a sputum eosinophil count below 1.9% on at least 2 occasions as being a reasonable compromise level

for defining noneosinophilic asthma. The exhaled nitric oxide concentration is reasonably closely related to the sputum eosinophil count in adults with asthma,²⁹ and it is possible that this more noninvasive test could be used to identify patients with noneosinophilic asthma, although this has not been formally evaluated.

Another important consideration is that normal eosinophil counts may indicate well controlled asthma, so it is necessary to define a level of symptoms above which this becomes unlikely. We propose that subjects have a normal sputum eosinophil count on at least 2 occasions while symptomatic with a Juniper asthma control score of more than 1.57 points, a level consistent with the Global Initiative for Asthma recommendations for an increase in treatment.^{30,31} Many of the features seen in noneosinophilic asthma could occur in chronic obstructive pulmonary disease or bronchiectasis, and it is necessary for these conditions to be excluded before the diagnosis is made. From a practical point of view, this means that patients with a significant smoking history (ie, >20 pack years) and fixed airflow obstruction (ie, a postbronchodilator FEV₁ <80% predicted and FEV₁/forced vital capacity <0.7) and those with bronchiectasis as demonstrated by high-resolution computed tomography scan should be excluded.

STABILITY OF NONEOSINOPHILIC ASTHMA

There is limited evidence from longitudinal studies to address the question of whether noneosinophilic asthma is a consistent phenotype over time. Simpson et al³² have recently shown that the absence of a sputum eosinophilia is a consistent finding at 4 weeks and 5 years after first sputum induction, and Green et al¹⁶ identified a subgroup of patients with refractory asthma who had predominantly noneosinophilic sputum on repeated observations made over a period of 12 months. However, 70% of these patients had 1 or more episodes of sputum eosinophilia during the period of assessment. Jayaram et al¹⁷ showed that sputum inflammatory patterns were similar at baseline and during exacerbations in patients with asthma studied longitudinally for 2 years, indicating that patients with noneosinophilic asthma are far less likely to have eosinophilic exacerbations.

We have recently recruited a cohort of 11 patients who met these criteria for noneosinophilic asthma and performed bronchoscopy followed by a double-blind, placebo-controlled cross-over study of the effects of 6 weeks of treatment with inhaled mometasone.²¹ Patients had 6 assessments of airway inflammation using sputum and 1 bronchoscopic assessment of airway inflammation over 6 months; the bronchoscopy and 5 of the sputum assessments were done off treatment with inhaled corticosteroids. No patients defined as having noneosinophilic asthma at study entry had evidence of eosinophilic airway inflammation at bronchoscopy or in the sputum tests performed over the course of the study. The bronchial biopsies showed that noneosinophilic asthma was associated with normal basement membrane thickness. Similar

TABLE I. Criteria for diagnosis of noneosinophilic asthma

- Consistent clinical picture
- Evidence of abnormal variable airflow obstruction and/or airway hyperresponsiveness as reflected by 1 or more of the following: a >15% improvement in FEV₁ after treatment with albuterol; a >20% within-day peak expiratory flow variability derived from twice daily readings over a period of 2 weeks; a methacholine PC₂₀ <8 mg/mL
- Sputum eosinophil count <1.9% on 2 or more occasions when symptomatic with a mean Juniper asthma control score >1.57
- Absence of an alternative explanation for the findings, ie, excluding those with a significant smoking history (ie, >20 pack years) and fixed airflow obstruction (ie, a postbronchodilator FEV₁ <80% predicted and FEV₁/forced vital capacity <0.7); and those with bronchiectasis as demonstrated by high-resolution CT scan

findings were reported by Wenzel et al²⁴ in a population of patients with severe asthma. Longitudinal studies have suggested that increased subepithelial layer thickness is a longer-term marker of eosinophilic airway inflammation than bronchial mucosal cell counts,³³ so the observation that subepithelial layer thickness is normal in noneosinophilic asthma supports the view that the absence of eosinophilic airway inflammation is a stable feature.

In summary, the evidence suggests that patients identified as being noneosinophilic at one time point are likely to remain so prospectively for the majority of the time.

HISTOPATHOLOGIC FEATURES OF NONEOSINOPHILIC ASTHMA

In a study of patients with severe asthma, Wenzel et al²⁴ have shown that noneosinophilic disease defined histologically by the absence of eosinophils in the mucosa was associated with normal thickness of the subepithelial basement membrane and a lower number of CD3⁺ cells and macrophages, compared with severe eosinophilic asthma. These differences were present despite the use of comparable doses of corticosteroid therapy by patients in each group. Berry et al²¹ reported similar differences in cellular and structural components of the inflammatory response in eosinophilic and noneosinophilic asthma in a cohort with mild corticosteroid-naïve disease. There has been less consistent information on the presence of markers of neutrophilic airway inflammation. A sputum neutrophilia and elevated sputum supernatant IL-8 concentration have been found in this phenotype,²² but this is not a consistent finding, and excess neutrophils in bronchial biopsy have not been reported consistently.^{21,24} A potential explanation for the discrepant results is that there are different subgroups of patients with noneosinophilic asthma (Fig 2). The subdivision of noneosinophilic asthma into neutrophilic and paucigranulocytic groups has been suggested on the basis of the presence or absence of a sputum neutrophil count >61%.^{32,34} Whether these subtypes of noneosinophilic asthma can be distinguished reliably and consistently, and to what extent sputum findings reflect stable differences in the underlying lower

	Noneosinophilic asthma	Eosinophilic asthma
	Normal eosinophil count (<1.9%)	Raised eosinophil count
Normal neutrophil count (< 61%)	Paucigranulocytic - Well controlled or intermittent asthma - Consider alternative diagnosis	Eosinophilic - Typical asthma, frequently associated with atopic disease - May indicate inadequate corticosteroid therapy
Raised neutrophil count	Neutrophilic - Acute infection (viral or bacterial) - Chronic infection (chlamydia, adenovirus) - Smoking - Environmental pollutants (ozone, NO₂) - Occupational antigens - Endotoxin exposure - Obesity	Mixed granulocytic - (Severe) asthma exacerbations - Refractory asthma

FIG 2. Classification based on induced sputum patterns of cellular inflammation in asthma.

airway immunopathology or the cause of the pathology, remain to be determined.

There may also be differences in airway wall dimensions between eosinophilic and noneosinophilic asthma, because a spiral CT study has shown significantly greater bronchial wall thickening in patients with eosinophilic asthma and proximal bronchial dilatation with normal wall thickness in the noneosinophilic cohort.³⁵ Further work is required to confirm this finding and to investigate the mechanism and the clinical significance of the difference in airway dimensions.

MECHANISMS OF AIRWAY INFLAMMATORY RESPONSE AND DISORDERED AIRWAY FUNCTION

It has been suggested that the different inflammatory profiles now recognized in asthma populations are a result of different patterns of antigen exposure in the airways.³⁶ Thus, eosinophilic disease is considered a consequence of allergen mediated activation of mast cells and T cells in the airway with release of T_H2 cytokines. In contrast, neutrophilic inflammation is the product of innate and cell mediated immune responses. Numerous etiologic factors are believed to evoke responses along these immune pathways, particularly through the direct activation of macrophages.³⁷ Important examples include endotoxin, viral, and bacterial infection, constituents of cigarette smoke, and many occupational agents.

Endotoxins are soluble fragments of LPS that form a part of the outer membrane of Gram-negative bacteria. These fragments aggregate to form micelles. The polysaccharide portion carries organism-specific antigenic determinants that are processed and presented in conjunction with MHC II molecules by antigen presenting cells. However, the lipid portion binds CD14 and Toll-like

receptors on the surface of macrophages, leading to innate immune activation and LPS toxicity. Toll-like receptors 2 and 4 are the most important molecules binding endotoxins. Their involvement in the pathogenesis of noneosinophilic asthma is supported by a recent study by Simpson et al³⁴ showing increased expression of both of these receptors, together with CD14 and mRNA for the cytokines IL-8, TNF- α , and IL-1 β in sputum from patients who were classified as having noneosinophilic, neutrophilic asthma compared with other asthma subtypes and healthy controls. The inflammatory profile seen in sputum in patients with noneosinophilic, neutrophilic asthma was similar to that seen in patients with bronchiectasis, although the sputum endotoxin concentration tended to be higher and the proportion with bacterial colonization lower. Markers of chronic *Chlamydia pneumoniae* or *Mycoplasma pneumoniae* infection were not evaluated; this is an important area for further study because chronic infection with these agents has been implicated in severe asthma,^{38,39} and it could be responsible for a predominantly neutrophilic airway inflammatory response. Patients classified as having paucigranulocytic asthma did not have sputum features suggesting activation of innate immunity. Indeed, their sputum inflammatory markers did not differ from normal, indicating that other mechanisms, perhaps entirely independent of airway inflammation, are contributing to airway dysfunction.

The findings of Simpson et al³⁴ support suggestions⁴⁰ that activation of the innate immune response occurs in noneosinophilic, neutrophilic asthma. The observations are cross-sectional, and it is important to go on to investigate the effect of interventions such as bacterial eradication or removal of sources of inhaled endotoxin on the clinical and inflammatory expression of the disease before we can conclude that there is a direct link between these inflammatory mechanisms and airway dysfunction. The recent demonstration that treatment with telithromycin

improves outcome in patients with exacerbations of asthma⁴¹ is in keeping with a role for bacterial infection, but more studies in both stable and acute asthma are required. Studies are also needed to define whether elements of the innate immune response are capable of altering airway function. TNF- α might be particularly important because treatment with the TNF- α antagonist etanercept has been shown to be associated with a significant improvement in airway responsiveness and airflow obstruction in patients with severe asthma.⁴² The beneficial effects of etanercept are related to overexpression of membrane TNF- α on PBMCs, a feature that was seen in patients with refractory asthma but not healthy controls or patients with mild-moderate asthma. mRNA for TNF- α has been shown to be present in increased amounts in sputum from patients with noneosinophilic, neutrophilic asthma compared with eosinophilic and paucigranulocytic asthma,³⁴ suggesting that activation of the TNF- α axis is a feature of noneosinophilic, neutrophilic asthma as well as refractory asthma. Moreover, mast cells, which represent a potential source of TNF- α ,⁴³ have been shown to be present in abnormal numbers in airway smooth muscle in patients with noneosinophilic asthma,²¹ so there is a local source of this cytokine. Future studies should explore the possibility that TNF- α blockade is associated with beneficial effects in patients with noneosinophilic, neutrophilic asthma.

Studies with endotoxin suggest differences in patterns of airway inflammation under different conditions.⁴⁴ Thus, subjects with ragweed sensitivity that underwent bronchial challenge using ragweed contaminated with endotoxin had a neutrophilic response, whereas endotoxin-free ragweed led to an eosinophilic response.⁴⁵ Endotoxin may also amplify T_H2-mediated responses in susceptible individuals: nasal challenge with endotoxin elicits nasal eosinophilia in atopic subjects⁴⁶ and has been shown to increase skin test reactivity and IgE-mediated histamine release from mast cells and basophils.⁴⁷ Thus, there is the potential for complex, synergistic interactions between elements of the innate immune response and a T_H2-driven immune response, which could lead to the development of a more heterogeneous pattern of airway inflammation and more severe airway disease. Observations made in patients with asthma who smoke suggest that this sort of interaction might be clinically important because, compared with non-smoking patients with asthma, these patients have worse symptoms and lung function, a more neutrophil-dominated lower airway response, physiological evidence of involvement of the small airways, an impaired response to corticosteroids, and a more rapid decline in lung function over time.⁴⁸⁻⁵⁰ It is possible that interaction between different immune responses is an important and potentially modifiable mechanism leading to the development of more severe, corticosteroid-unresponsive airway disease.⁵¹

Airway disease with neutrophilic airway inflammation is also seen in patients with chronic inflammatory conditions elsewhere. The most striking associations are seen with chronic inflammatory conditions involving organs that are embryologically related to the lungs such as

inflammatory bowel disease,^{52,53} chronic hepatitis C infection,⁵⁴ autoimmune thyroid disease,^{53,55} and *Helicobacter pylori*-induced gastritis,⁵⁶ but airway disease is also commonly seen in more generalized inflammatory disorders such as rheumatoid arthritis.^{57,58} The physiological, radiological, and pathologic features of the airway disease seen in association with chronic inflammatory disorders suggest a low-grade obliterative bronchiolitis perhaps involving aberrant homing of alloreactive lymphocytes to the lung in a manner analogous to the small airway disease seen in chronic rejection in lung transplant recipients or chronic graft-versus-host disease in bone marrow transplant recipients.^{57,59} Airway disease associated with chronic inflammatory diseases elsewhere has been strongly linked to chronic cough and chronic obstructive pulmonary disease^{59,60}; there is less evidence of an association with noneosinophilic asthma. Cough associated with chronic inflammatory diseases elsewhere is particularly well recognized in women at around the time of menopause,⁶⁰ perhaps because of menopausal changes in lung immunity.^{61,62} Noneosinophilic asthma has also been associated with onset in females at the time of menopause, and it is possible that there are parallels between these conditions.

IS NONEOSINOPHILIC ASTHMA CLINICALLY IMPORTANT?

The view that noneosinophilic asthma represents a clinically important asthma phenotype would be strengthened if there were evidence of differences in epidemiology, natural history, or treatment response. These possibilities have not been explored extensively, and much of the available work is limited by the population size and the uncontrolled, observational nature of the studies. However, there is growing evidence that noneosinophilic asthma is associated with a difference in epidemiology, the nature and severity of exacerbations, and the short-term and long-term response to corticosteroid therapy.

Epidemiology

Many of the case series are limited by the population size, and it is not possible to make any definitive statements on differences in the epidemiology of noneosinophilic asthma. Green et al¹⁹ identified 60 patients with noneosinophilic, neutrophilic asthma among a population of 259 patients referred to secondary care because of asthma. Compared with patients with eosinophilic asthma, those with noneosinophilic, neutrophilic disease were more likely to be female and nonatopic and to report the onset of symptoms in middle age. Subsequently, 2 groups have reported noneosinophilic pathology in elite athletes with asthma,^{63,64} and cross-sectional studies have suggested an association with smoking,⁶⁵ exposure to occupational low-molecular-weight sensitizers,²³ and obesity.⁶⁶ Many of these associations are biologically plausible; however, more work is required before they can be regarded as proven.

TABLE II. Change in inhaled corticosteroid dose in $\mu\text{g}/\text{patient}/\text{d}$ (Δ dose inhaled corticosteroid [ICS]), mean prednisone dose in $\text{mg}/\text{patient}/\text{d}$, frequency of severe exacerbations, and change in methacholine airway responsiveness (Δ PC₂₀) by randomization group according to whether patients had a mean sputum eosinophil count within the normal range (Eos $-$) or above the normal range (Eos $+$) throughout the study*

Category	Traditional protocol		Sputum protocol	
	Eos $-$	Eos $+$	Eos $-$	Eos $+$
No.	11	27	13	23
Δ Dose ICS ($\mu\text{g}/\text{day}$)	464	611	-961	448
Dose predicted (mg/day)	1.2	3.7	0.4	4.0
Exacerbations/patient/yr	0.7	3.9	1.2	0.8
Δ PC ₂₀ (doubling doses)	-1.6	-1.0	0.3	0

*Data obtained from a randomized single-blind trial of sputum eosinophil guided therapy for 12 months in 74 patients with predominantly refractory asthma.¹⁶

The natural history of noneosinophilic asthma

Asthma can be associated with progressive symptoms and the development of irreversible airflow obstruction. There are clear differences in airway remodeling assessed pathologically^{21,24} or radiologically³⁵ in noneosinophilic asthma compared with eosinophilic asthma, so it is possible that noneosinophilic asthma is particularly associated with this outcome. In support of this, cross-sectional and longitudinal studies have shown that elevated sputum neutrophil counts are associated with the presence of fixed airflow obstruction in asthma⁶⁷ and with decline in lung function in smokers.⁶⁸ However, there is currently no comparative longitudinal information on the rate of decline in lung function in different inflammatory phenotypes.

Asthma is also associated with recurrent exacerbations. These episodes of bronchodilator-unresponsive symptoms and bronchoconstriction are typically associated with increased airway inflammation, which develops well before the clinical manifestations of the exacerbation.^{69,70} Sputum studies have shown that most exacerbations are either eosinophilic or neutrophilic with few or no eosinophils. The former are particularly well recognized after corticosteroid withdrawal^{69,70} and allergen exposure in atopic subjects⁷¹; the latter are more closely related to viral and bacterial infections.⁷² Noneosinophilic exacerbations are particularly likely to occur in treated patients who do not have a sputum eosinophilia at baseline,¹⁷ suggesting that the inflammatory phenotype remains stable in many patients. This raises the possibility that there are clinically important differences in the frequency or severity of exacerbations in patients with eosinophilic and noneosinophilic asthma.

We have recently performed a *post hoc* analysis of exacerbation frequency in patients with severe noneosinophilic and eosinophilic asthma who were randomized to sputum eosinophil-directed therapy or standard monitoring and monitored for 12 months.¹⁶ We found that, with

standard management, exacerbation frequency was substantially lower in patients with noneosinophilic asthma compared with those with eosinophilic asthma (Table II). In contrast, there was no difference in exacerbation frequency between the inflammatory subtypes in the patients randomized to sputum eosinophil-directed therapy. The implication of this finding is that eosinophilic asthma is associated with an increased frequency of exacerbations compared with noneosinophilic asthma unless steps are taken to monitor and control eosinophilic airway inflammation.

There is also evidence that exacerbations are less severe in patients with noneosinophilic asthma. Wenzel et al²⁴ noted a strikingly lower frequency of severe exacerbations resulting in intubation and ventilation in patients with severe asthma and noneosinophilic airway pathology, and Jayaram et al¹⁷ reported that noneosinophilic exacerbations were associated with significantly smaller reductions in FEV₁ than those associated with eosinophilic airway inflammation. Thus, there is a suggestion that noneosinophilic asthma represents a more benign asthma phenotype in terms of exacerbation frequency and severity. This is in keeping with evidence that more severe exacerbations of COPD tend to be eosinophilic and corticosteroid-responsive.^{73,74}

Noneosinophilic asthma and the response to treatment

Corticosteroids have been the mainstay of asthma therapy for 50 years. A large number of studies have demonstrated improvement in symptoms, lung function, airway hyperresponsiveness, and exacerbation frequency with treatment. Heterogeneity in treatment response has been recognized since the early days of corticosteroid treatment for asthma, and in 1958, Brown⁷⁵ showed that the absence of eosinophils in a sputum smear was associated with a poor clinical response.

The possibility that there might be pathologic determinants of the response to corticosteroid therapy in asthma has been rediscovered over the last 10 years. We reported that the short-term improvement in airway responsiveness, symptoms, peak expiratory flow variability, and FEV₁ in response to inhaled budesonide was significantly less in adults with asthma and a sputum eosinophil count $<3\%$.¹¹ This observation has been replicated in most but not all other studies involving mild, steroid-naïve patients with asthma.^{19,76-79} The results of these studies are summarized in Table III. A limitation of most of the studies investigating the effect of inhaled corticosteroids in noneosinophilic asthma is that the condition has not been rigorously defined and the intervention has been uncontrolled and unblinded. However, a recent double-blind, placebo-controlled study of patients meeting the criteria for noneosinophilic asthma set out in Table I has shown clear evidence of a difference in the response to inhaled mometasone²¹ (Table III). Further support for a relationship between noneosinophilic asthma and a diminished response to corticosteroids is provided by evidence that conditions potentially associated with noneosinophilic asthma such

TABLE III. Summary of published clinical trials investigating the effect of inhaled corticosteroids in noneosinophilic asthma

Reference	Study population and design	Definition of noneosinophilic asthma	Asthma outcomes measured	Steroid response and study conclusions
76	Steroid-naïve asthma (N = 67) given 0.5 mg inhaled beclomethasone twice a day for 2-4 wk. Comparison of eosinophilic and noneosinophilic groups.	<3% Sputum eosinophils at study entry (N = 17).	Change in FEV ₁ .	Low sputum eosinophil count associated with lack of improvement in FEV ₁ .
21	Steroid-naïve asthma (N = 18) given 0.4 mg inhaled mometasone once a day for 8 wk. Placebo-controlled, double-blind, cross-over study.	<1.9% Sputum eosinophils on at least 2 occasions (N = 12).	Change in methacholine PC ₂₀ and asthma quality of life score compared between treatment and placebo in each group.	No improvement in outcome measures for noneosinophilic group. Significantly greater improvement in eosinophilic asthma.
78	Steroid-naïve asthma (N = 51) given 0.25 mg inhaled fluticasone twice a day for 1 mo. Comparison of eosinophilic and noneosinophilic groups.	≤1% Sputum eosinophils at study entry (N = 15).	Change in FEV ₁ , methacholine PC ₂₀ , and symptom scores.	Improvement in both groups. No significant difference between groups.
19	Steroid-naïve asthma (N = 49) given 0.4 mg inhaled budesonide bid for 2 mo. Comparison of eosinophilic and noneosinophilic groups.	<1.9% Sputum eosinophils at study entry (N = 11).	Change in FEV ₁ , methacholine PC ₂₀ , and symptom scores.	Significantly less improvement in outcome measures in noneosinophilic group.
77	Chronic stable asthma (N = 120) on lowest inhaled corticosteroid dose after phase of downtitration. Given either oral prednisolone 30 mg od or inhaled fluticasone at 0.25 mg bid or 1 mg bid. Double-blind, double-dummy, randomized study.	<3% Sputum eosinophils at study entry.	Change in FEV ₁ , methacholine PC ₂₀ , and quality of life scores.	Blood and sputum eosinophil counts positively predict an improvement in outcome measures.
79	Stable chronic asthma (N = 37) on regular inhaled corticosteroids (median 0.8 mg beclomethasone/d). Response to oral prednisolone 30 mg od for 14 d. Comparison of eosinophilic and noneosinophilic groups.	<4% Sputum eosinophils at study entry (N = 19 of 30).	Change in FEV ₁ >15%.	Sputum eosinophilia had a positive predictive value of 68%. Exhaled NO also predictive.
11	Steroid-naïve asthma (N = 23) given inhaled 0.4 mg budesonide bid for 2 mo. Comparison of eosinophilic and noneosinophilic groups.	<3% Sputum eosinophils at study entry (N = 9).	Change in FEV ₁ , methacholine PC ₂₀ , and symptom scores.	Significantly greater improvement in most outcome measures in eosinophilic asthma.

as smoking,⁴⁸ obesity,⁸⁰ and the presence of chronic inflammatory disease elsewhere⁸¹ tend to be associated with a poor response to corticosteroids.

In addition to their effects on markers of day-to-day asthma control, corticosteroid treatment has been shown to reduce the frequency of asthma exacerbations.^{82,83} No study has evaluated the effect of corticosteroid therapy on exacerbation frequency in noneosinophilic asthma. However, there is some evidence that it is diminished, because a longitudinal study of sputum directed treatment in asthma showed that patients with persistently noneosinophilic

sputum were able to reduce corticosteroid treatment substantially without any obvious increase in the frequency of asthma exacerbations over a period of 12 months¹⁶ (Table II). Moreover, there is no evidence that sputum eosinophil-guided corticosteroid therapy reduces the frequency of noneosinophilic exacerbations.¹⁷ A lot more work needs to be done before we can conclude that noneosinophilic asthma does not respond to corticosteroid therapy. However, the possibility that corticosteroid therapy can be withheld safely or that alternative therapies are a better option should be actively investigated.

Alternative strategies for the management of non-eosinophilic asthma are disappointingly limited. Attempts should be made to identify and remove potential causal factors; experience with smoking cessation in asthma suggests that this might be a particularly fruitful strategy.⁸⁴ Blocking the TNF- α axis might also be worthwhile.⁴² Experience with combination inhalers⁸⁵ and long-term low-dose macrolide antibiotics⁸⁶ in other neutrophilic airway diseases suggests that the effects of these treatments should be investigated. Therapy with long-acting β_2 -agonists has been associated with a modest reduction in the frequency of noneosinophilic exacerbations in patients with noneosinophilic asthma¹⁷; this unexpected observation needs to be confirmed in an appropriately powered double-blind, placebo-controlled study before monotherapy with long-acting β_2 -agonists can be considered, given the recent concerns about excess mortality.⁸⁷

CONCLUSION

There does seem to be sufficient evidence to support the existence of a subgroup of patients with asthma who have stable noneosinophilic and often neutrophilic disease. In comparison with eosinophilic asthma, patients with non-eosinophilic asthma have differences in airway histopathology, airway structure, mechanisms of airway dysfunction, potential etiologic factors, response to treatment, and perhaps prognosis. The identification of this phenotype at the time of diagnosis is important, because present clinical strategies are inadequate. In particular, current prescribing practice with inhaled corticosteroids is unlikely to be as efficacious or cost-effective for this group, and there is a potential for overtreatment with these agents. Further work is needed to establish the role of neutrophilic inflammation in noneosinophilic asthma and identify factors associated with its pathogenesis.

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