Chronic Cough Due to Nonasthmatic Eosinophilic Bronchitis

ACCP Evidence-Based Clinical Practice Guidelines

Christopher E. Brightling, MBBS, PhD, FCCP

Objectives: Nonasthmatic eosinophilic bronchitis is a newly recognized cause of chronic cough. Our objective was to review the pathogenesis, natural history, diagnosis, and treatment of this condition.

Methods: The current literature was reviewed using an Ovid MEDLINE and PubMed literature review for all studies published in the English language from 1963 to December 2004 using the medical subject heading term “eosinophilic bronchitis.”

Results: Nonasthmatic eosinophilic bronchitis is a common cause of chronic cough. It is characterized by the presence of eosinophilic airway inflammation, similar to that seen in asthma. However, in contrast to asthma, nonasthmatic eosinophilic bronchitis is not associated with variable airflow limitation or airway hyperresponsiveness. The differences in functional association are related to differences in the localization of mast cells within the airway wall, with airway smooth muscle infiltration occurring in patients with asthma, and epithelial infiltration in patients with nonasthmatic eosinophilic bronchitis. Diagnosis is made by the confirmation of eosinophilic airway inflammation usually with induced sputum analysis after the exclusion of other causes for chronic cough on clinical, radiologic, and lung function assessment. The cough usually responds well to treatment with inhaled corticosteroids. The dose and duration of treatment differ between patients. The condition can be transient, episodic, or persistent unless treated, and occasionally patients may require long-term prednisone treatment.

Conclusions: Further study of this condition may improve our understanding of airway inflammation and airway responsiveness, leading to novel targets for therapeutic agents for the treatment of both asthma and nonasthmatic eosinophilic bronchitis.

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Key words: airway smooth muscle; asthma; cough; eosinophilic bronchitis; eosinophils; mast cells

Gibson et al1 first identified nonasthmatic eosinophilic bronchitis as a cause of chronic cough in 1989. They described a condition that manifests as a corticosteroid-responsive chronic cough in nonsmokers without the abnormalities of airway function that characterize asthma. These patients had evidence of airway inflammation in the form of sputum eosinophilia, hence the term nonasthmatic eosinophilic bronchitis. The development of safe and noninvasive methods of assessing airway inflammation using induced sputum has allowed the further characterization of this condition.

Studies2-4 in which the assessment of airway inflammation has been undertaken in chronic cough patients have shown that nonasthmatic eosinophilic bronchitis accounts for 10 to 30% of cases referred for specialist investigation. However, earlier studies5,6 did not identify patients with nonasthmatic eosinophilic bronchitis as a distinct subgroup among patients with chronic cough. Although we cannot discount the possibility that nonasthmatic eosinophilic bronchitis is a new condition, we feel that the failure to recognize it is more likely to reflect differences in referral pattern. For example many
patients, particularly tertiary referrals, are likely to have received a trial of corticosteroids before referral, and asthma may have been diagnosed in those patients who responded to treatment with corticosteroids as having asthma before further tests were done or irrespective of the results of objective tests of variable airflow obstruction or airway responsiveness.

This section addresses the clinical features and management of nonasthmatic eosinophilic bronchitis as a cause of chronic cough. It also highlights advances in our understanding of the pathogenesis of this disorder, which have particularly improved our understanding of the relationship between eosinophilic airway inflammation and disordered airway function in asthma patients. This section was written following a review of all the studies published in the English language from 1963 to December 2004 using an Ovid MEDLINE and PubMed literature review using the medical subject heading term “eosinophilic bronchitis.”

**Clinical Features and Diagnosis**

Chronic cough, defined as a cough lasting for >8 weeks with no overt clinical and radiologic evidence of lung disease, is a common reason for referral to a specialist. Several series have shown that a cause of persistent cough can be identified relatively simply in 80 to 95% of cases by using an anatomic diagnostic protocol. Nonasthmatic eosinophilic bronchitis is one of the more common causes of chronic cough. Often, there are multiple causes for the chronic cough, and therefore nonasthmatic eosinophilic bronchitis should always be considered even when another cause has been established, or if there is no response or only a partial response to treatment.

Nonasthmatic eosinophilic bronchitis is defined as a chronic cough in patients with no symptoms or objective evidence of variable airflow obstruction, normal airway hyperresponsiveness (ie, a provocative concentration of methacholine producing a 20% decrease in FEV₁ of >16 mg/mL), and sputum eosinophilia. We used a >3% non-squamous cell sputum eosinophil count as being indicative of eosinophilic bronchitis as this is outside the 90th percentile for healthy patients (1.1%), and this level of sputum eosinophilia has been associated with a corticosteroid response in COPD patients and asthma patients.

The etiology of nonasthmatic eosinophilic bronchitis can be uncertain, although like asthma, nonasthmatic eosinophilic bronchitis can be associated with exposure to an occupational sensitizer or to a common inhaled allergen. A similar corticosteroid-responsive cough syndrome has been reported by Fujimura et al and has been given the diagnostic label atopic cough. This condition has been defined as an isolated chronic cough that is associated with no variable airflow obstruction or airway hyperresponsiveness and objective evidence of atopy as defined by one or more of the following: blood or sputum eosinophilia; elevated total or specific IgE levels; or positive skin test results. Whether nonasthmatic eosinophilic bronchitis and atopic cough represent distinct clinical entities is unclear.

The main features and differences among nonasthmatic eosinophilic bronchitis, cough-variant asthma, classic asthma, and atopic cough are summarized in Table 1.

As with other causes of cough, details of the nature and timing of the cough are of limited help in establishing a diagnosis of nonasthmatic eosinophilic bronchitis. Making a positive diagnosis of nonasthmatic eosinophilic bronchitis therefore requires the assessment of lower airway inflammation after other causes of cough have been excluded by clinical, radiologic, and physiologic assessment (ie, spirome-

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**Table 1—Clinical and Pathologic Features of Eosinophilic Bronchitis Compared With Classical Asthma and Cough-Variant Asthma**

<table>
<thead>
<tr>
<th>Features</th>
<th>Eosinophilic Bronchitis</th>
<th>Classic Asthma</th>
<th>Cough-Variant Asthma</th>
<th>Atopic Cough</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Cough, often associated with upper airway symptoms</td>
<td>Dyspnea, cough, wheeze</td>
<td>Isolated cough</td>
<td>Isolated cough</td>
</tr>
<tr>
<td>Atopy</td>
<td>Same as general population</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Airway hyperresponsiveness</td>
<td>Absent</td>
<td>Present</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Cough reflex hypersensitivity</td>
<td>Increased</td>
<td>Normal or increased</td>
<td>Normal or increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Response to bronchodilator</td>
<td>Absent</td>
<td>Good</td>
<td>Good</td>
<td>Absent</td>
</tr>
<tr>
<td>Response to corticosteroids</td>
<td>Good</td>
<td>Good*</td>
<td>Good*</td>
<td>Good*</td>
</tr>
<tr>
<td>Sputum eosinophilia</td>
<td>Always</td>
<td>Usually</td>
<td>Usually</td>
<td>Usually</td>
</tr>
<tr>
<td>Bronchial biopsy eosinophilia</td>
<td>Very common</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Mast cells within airway smooth muscle bundles</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

*When sputum eosinophilia are present.
try and methacholine challenge test). Airway inflammation should ideally be measured by induced sputum analysis, but, if this is unavailable or unsuccessful, bronchial wash fluid obtained at bronchoscopy provides information similar to that obtained from induced sputum. In brief, the procedure of sputum induction involves patients inhaling increasing concentrations of hypertonic saline solution (3%, 4%, and 5%) in sequence for 5 min each via an ultrasonic nebulizer after premedication with a short-acting bronchodilator. Expectorated sputum is dispersed using a mucolytic agent filtered through a 48-μm mesh gauze to remove excess mucus, and then the filtrate is centrifuged to produce a cytospin. A differential cell count can be obtained from the cytospin by counting > 400 nonsquamous cells. Induced sputum cell counts are a safe, valid, and repeatable measure of airway inflammation, but require same-day processing for cell quantification and cell viability, unlike routine cytology. In addition, sputum induction also may identify neutrophilia due to a viral or bacterial infective bronchitis, which are also causes of chronic cough. Measurement of exhaled nitric oxide, which is another noninvasive marker of airway inflammation, has been proposed as an alternative to induced sputum tests. Exhaled nitric oxide levels are usually higher in patients with nonasthmatic eosinophilic bronchitis, but its role in the diagnosis of nonasthmatic eosinophilic bronchitis has not been formally evaluated.

A 2-year prospective study of chronic cough was reported in which induced sputum was performed in all patients in whom the diagnosis remained unclear after simple clinical assessment and a methacholine inhalation test. Ninety-one patients with chronic cough were identified among 856 referrals. A diagnosis leading to a successful treatment was reached in 85 of cases (93%). Nonasthmatic eosinophilic bronchitis using the above definition was identified in 12 patients (13.2%), representing 30% of those who had undergone sputum induction.

**Recommendations**

1. In patients with chronic cough who have normal chest radiograph findings, normal spirometry findings, and no evidence of variable airflow obstruction or airway hyperresponsiveness, the diagnosis of nonasthmatic eosinophilic bronchitis should be considered. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

2. In patients with chronic cough with normal chest radiograph findings, normal spirometry findings, and no evidence of variable airflow obstruction or airway hyperresponsiveness, the diagnosis of nonasthmatic eosinophilic bronchitis as the cause of the chronic cough is confirmed by the presence of an airway eosinophilia, either by sputum induction or bronchial wash fluid obtained by bronchoscopy, and an improvement in the cough following corticosteroid therapy. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

**Treatment**

Antiinflammatory treatment with inhaled corticosteroids or avoidance strategies, when the inflammation is due to an occupational exposure or inhaled allergen, are the mainstay therapies for the treatment of nonasthmatic eosinophilic bronchitis. Patients improve symptomatically and have a significant fall in their sputum eosinophil count following therapy with inhaled corticosteroids. In one study, capsaicin cough sensitivity, which was moderately increased before treatment, improved toward normal after treatment with budesonide (400 μg inhaled bid) for 4 weeks, and there was a significant positive correlation between the treatment-induced change in cough sensitivity and the sputum eosinophil count. These findings suggest that heightened cough sensitivity contributes to the cough in patients with nonasthmatic eosinophilic bronchitis and that eosinophilic airway inflammation is causally associated with the increased cough sensitivity. In contrast to nonasthmatic eosinophilic bronchitis, patients with chronic cough without sputum eosinophilia did not have an improvement in their cough after 2 weeks of therapy with budesonide (400 μg inhaled bid) in a randomized placebo-controlled study.

There are no data currently available to guide the choice of which inhaled corticosteroid should be used for the treatment of nonasthmatic eosinophilic bronchitis, at which dose, and for how long. The efficacy of inhaled corticosteroids remains to be determined in placebo-controlled randomized trials. Very occasionally, treatment with oral corticosteroids are required to control symptoms and eosinophilic inflammation.

Although there may be thickened basement membrane and other changes to suggest airway remodeling, it remains unclear whether therapy for nonasthmatic eosinophilic bronchitis should be discontinued when symptoms resolve. The role of other potential therapeutic agents such as antihistamines and antileukotrienes needs to be fully explored.
Recommendations

3. In patients with chronic cough due to nonasthmatic eosinophilic bronchitis, the possibility of an occupation-related cause needs to be considered. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

4. For patients with chronic cough due to nonasthmatic eosinophilic bronchitis, the first-line treatment is inhaled corticosteroids (except when a causal allergen or sensitiser is identified [see recommendation 5]). Level of evidence, low; benefit, substantial; grade of recommendation, B

5. For patients with chronic cough due to nonasthmatic eosinophilic bronchitis, when a causal allergen or occupational sensitiser is identified, avoidance is the best treatment. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

6. For patients with chronic cough due to nonasthmatic eosinophilic bronchitis, if symptoms are persistently troublesome and/or the natural history of eosinophilic airway inflammation progresses despite treatment with high-dose inhaled corticosteroids, oral corticosteroids should be given. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

Pathogenesis

An obvious question is why an apparently similar pattern of airway inflammation is associated with different functional abnormalities in patients with nonasthmatic eosinophilic bronchitis and asthma. Conceivably, this might reflect functionally important differences in site, state of activation, or regulation of inflammatory response.

A detailed comparative immunopathologic study of nonasthmatic eosinophilic bronchitis and asthma has been reported. Both conditions were associated with a similar degree of sputum, BAL fluid, and biopsy eosinophilia, and a similar degree of basement membrane thickening in bronchial biopsy specimens, suggesting that the sites within the bronchial tree were similar. Similarly, asthma and nonasthmatic eosinophilic bronchitis were associated with increased sputum concentrations of the important effector mediators cysteinyl-leukotrienes and eosinophilic cationic protein. Interestingly, histamine and prostaglandin D2 sputum concentrations are only increased in patients with nonasthmatic eosinophilic bronchitis, suggesting that the activation of mast cells in superficial airway structures is a particular feature of this condition and raising the possibility that the localization of activated mast cells might differ in patients with asthma and nonasthmatic eosinophilic bronchitis. In support of this, mast cell numbers in bronchial brushing samples were increased in patients with nonasthmatic eosinophilic bronchitis compared to those with asthma, and mast cell numbers in airway smooth muscle were increased in patients with asthma but not in those with nonasthmatic eosinophilic bronchitis. Furthermore, airway smooth muscle mast cell numbers inversely correlated with airway hyperresponsiveness. Thus, a key factor determining the different functional association of airway inflammation in patients with nonasthmatic eosinophilic bronchitis and asthma might be the microlocalization of mast cells with a predominant airway smooth muscle infiltration (Fig 1), resulting in airway hyperresponsiveness and variable airflow obstruction, and an epithelial infiltration producing bronchitis and cough. The...
specific role of the mast cell in the bronchial epithelium of patients with nonasthmatic eosinophilic bronchitis and its interactions with cough sensory afferents needs further study.

**Natural History**

The natural history of nonasthmatic eosinophilic bronchitis has had limited study. A 10-year follow-up evaluation of 27 of the 12 patients from the original reports of nonasthmatic eosinophilic bronchitis suggests that this condition is generally benign and self-limiting. A larger series of patients has been recently reported suggesting that this condition is rarely self-limiting. Fifty-two patients from 1996 to 2003 were identified with nonasthmatic eosinophilic bronchitis, and follow-up data of > 1 year were available from 32 of these patients. Asthma, with typical symptoms and airway hyperresponsiveness, developed in three patients (9%). Twenty-one patients (66%) had persistent symptoms and/or ongoing airway inflammation. Only one patient with nonasthmatic eosinophilic bronchitis had complete resolution of symptoms and no sputum eosinophilia while not receiving corticosteroid therapy. Five patients (16%) developed fixed airflow obstruction, although the decline in FEV1 in the whole group of patients with nonasthmatic eosinophilic bronchitis was not greater than that in healthy control subjects. These findings are similar to those reported for atopic cough in which there was no increased decline in lung function and progression to asthma was rare.

A case has been reported of a patient in whom, over a 2-year period, fixed airflow obstruction developed. The patient's cough improved with inhaled corticosteroid therapy, but the sputum eosinophilia persisted. Several studies have observed that 30 to 40% of patients with COPD without a history of asthma and no bronchodilator reversibility have sputum evidence of an airway eosinophilia. This observation provides one possible explanation for the presence of eosinophilic airway inflammation in some patients with COPD without apparent preexisting asthma in that nonasthmatic eosinophilic bronchitis may in some circumstances be a prelude to COPD. Progressive irreversible airflow obstruction may occur due to remodeling of the airway secondary to persistent eosinophilic airway inflammation in the presence of inadequate corticosteroid therapy. If this is true, it has important implications in the early diagnosis and successful treatment of nonasthmatic eosinophilic bronchitis. Subsequent studies should be able to further define the natural history of this easily treatable condition.

**Conclusions**

Nonasthmatic eosinophilic bronchitis is a common and treatable cause of chronic cough. The airway inflammation is similar to that seen in patients with asthma, although nonasthmatic eosinophilic bronchitis is associated with quite different abnormalities of airway function. These differences might be related to the site of mast cell infiltration of the airways. Future studies should look at the role of other noninvasive markers of airway inflammation in the chronic cough clinic, should define the natural history of nonasthmatic eosinophilic bronchitis, and should investigate the effects of other therapies.

**Summary of Recommendations**

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REFERENCES