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REVIEW ARTICLE

# Eosinophilic bronchitis – Chronic cough with a treatable trait

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## ABSTRACT

Eosinophilia in sputum is an important finding in patients with chronic cough, as it identifies a treatable trait with available therapy that is well tolerated and can be effective. While most patients have airway hyperresponsiveness or airway obstruction which define asthma, an important number of cases lack these features of bronchoconstriction but sputum induction still demonstrates excess eosinophilia, indicating eosinophilic bronchitis without asthma. Unfortunately, this test is largely limited to research centers and speciality cough clinics, but associated measures of allergic airway inflammation can be used to support the diagnosis. While the mechanisms that initiate and drive non-asthmatic eosinophilic bronchitis (NAEB) are not well understood, there is emerging evidence that eosinophils and inflammatory mediators are important contributors of nerve sensitivity, a hallmark of chronic cough. Inhaled steroids form the major treatment used in non-asthmatic eosinophilic bronchitis (NAEB). Novel targeted therapies for asthma known as biologics are likely to be tried in the common and debilitating condition of chronic cough, while their efficacy in NAEB is yet to be seen.

## Introduction

Chronic cough is one of the most common reasons to seek medical care yet remains poorly understood and effective therapies have been challenging to identify[1–3]. Guidelines recommend the identification of treatable traits of underlying conditions such as asthma, non-asthmatic eosinophilic bronchitis, acid reflux and vagus nerve hypersensitivity[3,4]. The clinical hallmark of non-asthmatic eosinophilic bronchitis (NAEB) is sputum eosinophilia without airway hyperresponsiveness, and this condition may be a contributor to cough in 10% of cases. Although it exists on a continuum of allergic and eosinophilic disease, it is not a pre-asthmatic condition. Eosinophils and other inflammatory mediators are present in the mucosa of NAEB patients, but they are not found in associated with airway smooth muscle, which likely explains the absence of airway hyperresponsiveness and wheeze. The diagnosis of eosinophilic bronchitis relies on sputum inflammometry. While relatively simple to perform, sputum analysis for cell differential is not commonly available outside of research centers, and its processing and interpretation are rarely compensated by public payers, which has limited its wider use in airway diseases such as asthma, COPD and chronic cough. Sputum eosinophilia greater than 3% is the standard to identify cases of eosinophilic bronchitis, but other biomarkers including blood eosinophils and FeNO are often used as surrogate markers with inconsistent results. While treatment targeting eosinophilic inflammation can improve cough frequency and severity, many cases are refractory highlighting the importance of nerve hypersensitivity in chronic cough. This review seeks to summarize advances in our understanding of the pathophysiology of NAEB, as well as the tools available to clinicians in all centers to recognize and manage this common condition.

## Immunopathology of Eosinophilic Bronchitis

Eosinophilic bronchitis describes sputum eosinophil count of greater than 3% and is often associated with symptoms of cough. As a clinical phenomenon, non-asthmatic eosinophilic bronchitis (NAEB) describes specifically those patients without airway hyperresponsiveness or variable airflow obstruction characteristic of asthma. The absence of airway hyperresponsive highlights the differences in the immunopathology of NAEB and asthma. Both conditions are marked by increased numbers of eosinophils in the airway wall and submucosa, as well as thickening of the basement membrane[5]. In NAEB, mast cells are found in the superficial airway mucosa but not in the airway smooth muscle, compared to the airway of asthmatic patients[5,6]. In NAEB, there is a higher density of IL-4+ and IL5+ TH2 lymphocytes in bronchial submucosa compared to healthy controls[7]. These superficial airway eosinophils, mast cells and lymphocytes are associated with elevated inflammatory mediators including IL 4, IL 5, cysteinyl leukotrienes and eosinophilic cationic protein as found in bronchoalveolar lavage samples of NAEB patients[8–10]. Although inhaled and oral steroids may deplete airway eosinophils and improve cough severity, persistent airway eosinophilia despite treatment is associated with relapse of cough symptoms[11]. As in asthma, higher blood eosinophils is

associated with higher sputum eosinophil counts in NAEB, although this finding varies across studies[11–13]. In a recent prospective study, researchers found that subjects with NAEB had elevated levels of human progenitor cells and eosinophil progenitor cells in sputum when compared to healthy controls. In addition, IL-5 and GM-CSF were increased, two factors which stimulate eosinophil differentiation. This may suggest the in-situ differentiation of eosinophils from their progenitors in the airway tissue is an important process in NAEB, beyond recruitment from bone marrow or distant lymphoid sites[12]. However, one month of inhaled steroid therapy improved cough symptoms in NAEB patients, but the total numbers of progenitor cells or mature eosinophils did not change.

## The impact of eosinophilia on airway nerves

While the hallmark of NAEB is eosinophilic airway inflammation, the pathophysiology may also depend on a hypersensitive cough reflex. Cough is stimulated by vagal afferent fibers in the large and small airways which are triggered by mechanical and chemical stimuli[14]. Patients with chronic cough are more sensitive to chemical stimuli such as capsacin, likely due to increased sensitivity of peripheral nerves[15]. Inflammatory mediators in the airway decrease the threshold required for nerve activation, specifically histamine, ATP, bradykinin and prostaglandins released by mast cells and eosinophils[14–18]. In a study of steroid naïve mild allergic asthma, capsaicin evoked cough was increased by allergen exposure, not only at the time of challenge but also 24hours after allergen exposure, and was associated with an increase in sputum eosinophils[15]. Eosinophils mediated an increase in sensory nerve density in a murine model of allergic airway disease[19], a finding supporting by human studies of severe asthma demonstrating a co-localization of eosinophils and airway nerves. In chronic cough, as in other peripheral nerve phenomenon, excess peripheral sensory activity results in hypersensitivity of the central nervous system and a loss of functional sensory inhibition[16]. Cough patients exposed to capsacin showed increased brainstem activity and reduced activity of anterior insula and dorsomedial pre-frontal cortex on functional MRI associated with higher cough rates, as compared to healthy controls[20]. Capsacin induced coughing could be supressed by progressive pain conditioning and cold water immersion[21]. This suggests patients chronic cough have an impaired inhibition of cough stimuli, which these secondary stimuli can unmask. In summary, as in other chronic cough patients NAEB may have impaired central inhibition of cough stimuli, but the airway eosinophilia characteristic of their disease also potentiates nerve hypersensitivity.

## Diagnosis of Eosinophilic bronchitis

Clinical diagnosis of NAEB is made during the workup of unexplained or refractory chronic cough, defined as a cough lasting >8 weeks. The prevalence of NAEB is challenging to establish, given the limited availability of sputum induction and analysis. In specialty cough clinics, prevalence is estimated to represent at least 10% of referrals overall[22]. Methacholine challenge testing demonstrates no AHR (PC20 >16mg/ml), and there should

be no evidence of variable or fixed airflow obstruction. Sputum eosinophilia has conventionally used an eosinophil count of >3% of measured cells, which is above the 90th percentile for healthy patients[23].

Due to the limited abundance of sputum analysis and its technical expertise, additional testing is used to document allergic inflammation in support of the diagnosis and track treatment response. Serum eosinophilia is more readily available as complete blood counts are part of routine laboratory testing, and when elevated are associated with elevated sputum eosinophilia[22–24]. However, the largest studies of this correlation are drawn from patients with asthma and COPD. Fractional exhaled nitric oxide (FeNO) is non-invasive breath measure used as a marker of allergic inflammation and indicates NO synthesis at the level of the epithelium. Largely driven by IL-4 induced STAT-6 signaling[25], this can also be driven by IL-13 through which STAT6 can drive MUC5 transcription and result in excessive mucous production. However, based on one small study of NAEB, IL-13 expression is not increased in NAEB, which correlates with a lower proportion of patients expressing productive cough[10]. Given the concentration of eosinophils in the superficial layers of the airway and increased levels of IL-4, it would follow that FeNO would be elevated in NAEB, which is largely seen in clinical studies[4,25]. Using at cutoff of 31.7, the sensitivity of FeNO for detecting NAEB in cough patients with a negative methacholine challenge was 86%[26]. While its positive predictive value was only 47%, its negative predictive value was 95%[26]. In a meta analysis of FeNO performance in predicting response to ICS in mixed chronic cough populations, the response to ICS was 87% in those with high FeNO, with a significant difference in FeNO between responders and non-responders, across a variety of FeNO thresholds[27]. Test performance was optimal at a threshold of > 25ppb with a difference of 23ppb between responders and non responders[27]. FENO is elevated in patients with EB regardless of atopic status, a characteristic distinct from studies of asthmatic patients[28]. While many patients with chronic cough are atopic, not all patients with NAEB are sensitive to a seasonal or perennial allergen. Overall, the degree of allergic inflammation when consistently demonstrated across blood, sputum and exhaled NO predicts treatment response with inhaled steroids[28–30].

Occupational exposures may also be an underappreciated cause of eosinophilic bronchitis related chronic coughing. A retrospective study of 573 patients from multiple referral centers identified that in those investigated for work related asthma, 6% of the cohort had significant sputum eosinophilia and cough to their specific occupational challenge[31]. These individuals would have been considered negative for occupation related disease in the absence of airway hyperresponsiveness and may have continued the same work despite these symptoms or had compensation claims rejected, without the availability of sputum analysis. FeNO was also tested in this cohort and was less sensitive and specific than has been demonstrated in occupational asthma. A post challenge delta of less than 14 ppb had a specificity of 96%, although sensitivity was poor, indicating the absence of significant change may be a helpful tool if when induced sputum cytology is not available[31].

## Emerging therapies for Eosinophilic Bronchitis

Treatment of NAEB aims to reduce intraluminal and submucosal eosinophils and reduce cough frequency and severity. Given the wide availability and limited side effect profile, ICS is often initiated as an empiric trial[3], but one draw back of dry powders inhalers is a tendency to acutely provoke cough. Randomized control trials of small numbers of patients have show improvement in patient reported cough severity with ICS in those with sputum eosinophilia or elevated FeNO, although the visual analogue scale has limitations as a patient reported outcome[30]. A therapeutic trial (when there is evidence of eosinophilic inflammation) should last >2 months, as relapse can be noted with shorter duration of therapy[13]. When escalating doses of ICS has failed to improve cough symptoms, cough frequency or the sputum eosinophil count remains elevated, a short empiric course of oral steroids is often used to confirm the cough is steroid responsive. However, no clinical trial data exists to confirm this treatment, and the long-term use of steroids is associated with significant harm. Steroid sparing therapy for refractory cases of NAEB is currently under investigation[32,33]. Novel biologic therapies targeting eosinophil differentiation, activation, or recruitment may successfully deplete submucosal eosinophils and improve cough frequency, but their cost may prove prohibitive even if effective. When the cough is not steroid responsive, or does not improve with depletion of sputum eosinophils, other causes should be considered - specifically the persistence of nerve hypersensitivity.

## Natural History

Despite the similarities in pathophysiology, studies of the natural history of NAEB have demonstrated that only 5-9% with the condition go on to show asthma over time[34,35], but the majority continue to have bronchitis symptoms. NAEB is not associated with lung function decline[11,34]. However, chronic cough itself can be debilitating and impact patients' quality of life[36–38]. Chronic cough overall results in the highest number of annual ambulatory care visits in the US, and annual costs of over the counter cough medicines are estimated at 1-3 billion dollars[39].

## Conclusion

Eosinophilia in sputum is an important phenotypic characteristic in patients with chronic cough, as it identifies a treatable trait with available therapy that is well tolerated and can be effective. Unfortunately, many patients continue to cough despite empiric inhaled corticosteroid therapy, highlighting the importance of pre-therapy testing with sputum, blood and exhaled nitric oxide where available to confirm cough is associated with eosinophilia. While the mechanisms that initiate and drive NAEB are not well understood, advances in our understanding of eosinophil biology as well as the complex interaction with the protective neurological cough reflex have provided relief and understanding for cough sufferers. Novel therapies for asthma and COPD are likely to be tried in the common and debilitating condition of chronic cough, and their efficacy in NAEB is yet to be seen.

Conflicts of Interest:

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