

Cough and Eosinophilia



Sarah Diver, MBChB, Richard J. Russell, MBBS, and Christopher E. Brightling, PhD, FMedSci *Leicester, United Kingdom*

INFORMATION FOR CATEGORY 1 CME CREDIT

Credit can now be obtained, free for a limited time, by reading the review articles in this issue. Please note the following instructions.

Method of Physician Participation in Learning Process: The core material for these activities can be read in this issue of the Journal or online at the *JACI: In Practice* Web site: www.jaci-inpractice.org/. The accompanying tests may only be submitted online at www.jaci-inpractice.org/. Fax or other copies will not be accepted.

Date of Original Release: July 1, 2019. Credit may be obtained for these courses until June 30, 2020.

Copyright Statement: Copyright © 2019-2021. All rights reserved.

Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

Accreditation/Provider Statements and Credit Designation: The American Academy of Allergy, Asthma & Immunology (AAAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The AAAAI designates this journal-based CME activity for 1.00 *AMA PRA Category 1 Credit*[™]. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

List of Design Committee Members: Sarah Diver, MBChB, Richard J. Russell, MBBS, and Christopher E. Brightling, PhD, FMedSci (authors); Robert S. Zeiger, MD, PhD (editor)

Learning objectives:

1. To define how common it is for chronic cough to be associated with eosinophilic inflammation.
2. To describe the conditions associated with chronic cough and eosinophilic inflammation, in particular, asthma, nonasthmatic eosinophilic bronchitis, and upper airway cough syndrome.
3. To understand different approaches to noninvasively measure eosinophilic inflammation as well as to consider their relative strengths and weaknesses.
4. To describe the treatments available and the evidence supporting these approaches for cough and eosinophilia.
5. To understand how new insights of the mechanisms of airway hyperresponsiveness and cough itself have been derived from studies of cough and eosinophilic inflammation.

Recognition of Commercial Support: This CME has not received external commercial support.

Disclosure of Relevant Financial Relationships with Commercial Interests: C. E. Brightling has received grants and personal fees paid to his institution from MedImmune (AstraZeneca), GlaxoSmithKline, Roche/Genentech, Novartis, Chiesi, Pfizer, Teva, Sanofi/Regeneron, Glenmark, Mologic, PreP, and Vectura, outside the submitted work. The rest of the authors declare that they have no relevant conflicts of interest. R. S. Zeiger declares no relevant conflicts of interest.

Eosinophilic airway inflammation is observed in 30% to 50% of chronic cough sufferers. It is a common feature of asthma and upper airway cough syndrome, and it is required in the diagnosis of nonasthmatic eosinophilic bronchitis. Our understanding of the mechanisms underlying allergic and nonallergic eosinophilic inflammation have evolved tremendously in the last 2 decades,

but the cause of this inflammation in any individual is often uncertain. Inhaled corticosteroids are the mainstay therapy for cough due to asthma or nonasthmatic eosinophilic bronchitis, and response is related to the presence of biomarkers of eosinophilic airway inflammation. In upper airway cough syndrome, nasal topical corticosteroids are beneficial in allergic rhinitis and chronic rhinosinusitis with polyposis. This review will describe the diagnosis, current and possible future treatments, and prognosis of chronic cough in adults with eosinophilic inflammation. © 2019 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (*J Allergy Clin Immunol Pract* 2019;7:1740-7)

Key words: *Asthma; Nonasthmatic eosinophilic bronchitis; Upper airway cough syndrome; Rhinitis; Chronic rhinosinusitis; Eosinophil; FENO; Chronic cough; Mast cell*

INTRODUCTION

Cough is an essential protective physiological mechanism that prevents foods, liquids, dust, and chemicals from reaching the lower airways, but it is also a common respiratory symptom.

Institute for Lung Health, NIHR Leicester Biomedical Research Centre, Department of Respiratory Sciences, University of Leicester, Leicester, United Kingdom

Conflicts of interest: C. E. Brightling has received grants and personal fees paid to his institution from MedImmune (AstraZeneca), GlaxoSmithKline, Roche/Genentech, Novartis, Chiesi, Pfizer, Teva, Sanofi/Regeneron, Glenmark, Mologic, PreP, and Vectura, outside the submitted work. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication March 28, 2019; revised manuscript received and accepted for publication April 25, 2019.

Corresponding author: Christopher E. Brightling, PhD, FMedSci, Institute for Lung Health, University Hospital of Leicester, Leicester LE3 9QP, UK. E-mail: ceb17@le.ac.uk.

2213-2198

© 2019 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaip.2019.04.048>

Abbreviations used

AHR- Airway hyperresponsiveness
CRS- Chronic rhinosinusitis
FENO- Fractional exhaled nitric oxide
ICS- Inhaled corticosteroid
LTRA- Leukotriene receptor antagonist
NAEB- Nonasthmatic eosinophilic bronchitis
PGD₂- Prostaglandin D₂
UACS- Upper airway cough syndrome
VAS- Visual analogue scale

Chronic cough in adults is defined as a cough lasting for more than 8 weeks with no overt clinical and radiological evidence of lung disease.^{1,2} It is frequently documented as both a symptom precipitating health care interaction and consequent referral for specialist assessment.³ It most commonly affects middle-aged women and is associated with cough reflex hypersensitivity. Cough-specific measures of health status such as the Leicester Cough Questionnaire, symptom visual analogue scale (VAS) scores, and cough monitors provide patient-centered outcomes of cough frequency and severity.⁴

Approximately 30% to 50% of people with chronic cough have eosinophilic airway inflammation.⁵⁻⁸ In this review, we shall describe (1) the immunopathology and biomarkers of

eosinophilic airway inflammation; (2) the clinical management of the causes of cough in adults commonly associated with eosinophilic airway inflammation, namely, asthma, nonasthmatic eosinophilic bronchitis, and upper airway cough syndrome (UACS); and (3) mechanistic insights derived from studying cough for the role of eosinophilic inflammation in airway hyperresponsiveness (AHR) and cough.

EOSINOPHILIC AIRWAY INFLAMMATION AND BIOMARKERS

Mechanisms of eosinophilic airway inflammation

Eosinophilic inflammation in chronic cough can occur with or without allergy and can be due to occupational exposures. Another important consideration when evaluating cough with eosinophilia is recent travel or residence in areas where parasite infections are endemic. The cytokine networks underlying eosinophilic, type-2 immunity-mediated airway inflammation with or without allergy are illustrated in Figure 1 (reviewed in references⁹⁻¹¹). Following allergic sensitization and consequent stimulation of adaptive T_H2 cells by dendritic cells in the presence of coactivators such as epithelium-derived thymic stromal lymphopoietin, T_H2 cells produce the characteristic cytokines IL-4, IL-5, and IL-13. IL-5 is an obligate cytokine for eosinophil survival and maturation, whereas IL-4 and IL-13 upregulate the integrin and adhesion molecule P-selectin and vascular adhesion molecule-1, involved in preferential endothelial adhesion of

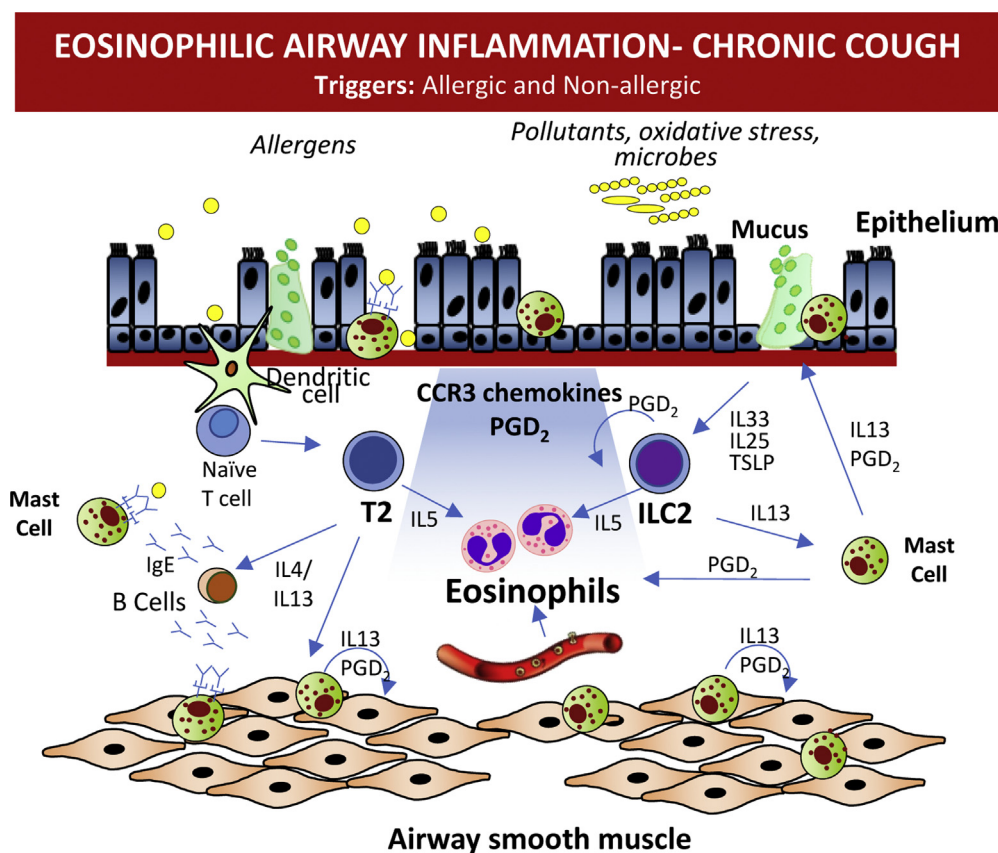


FIGURE 1. Eosinophilic airway inflammation. Illustration of the mechanisms underlying eosinophilic airway inflammation in chronic cough due to allergic and nonallergic pathways. CCR3, C-C chemokine receptor type 3; ILC2, type 2 innate lymphoid cells; TSLP, thymic stromal lymphopoietin.

eosinophils. Eosinophil recruitment to the lung mucosa is mediated via production of predominantly epithelium-derived C-C chemokine receptor type 3 chemokines and other eosinophil chemoattractants, including mast cell–derived prostaglandin D₂ (PGD₂). Eosinophil products directly cause epithelial damage.¹² IL-4 drives B-cell isotype switching and IgE synthesis, which binds to high-affinity IgE receptors predominately expressed by mast cells. Following IgE-dependent and independent activation, mast cells release important effector mediators, such as histamine and tryptase, and synthesize the eicosanoids leukotrienes and prostaglandins, followed by cytokines and chemokines. PGD₂ promotes T₂ immunity via activation of PGD₂ type 2 receptors (formerly chemoattractant receptor homologous molecule expressed on T_H2 cells). Eosinophilic inflammation also occurs in the absence of allergy via activation of type 2 innate lymphoid cells. These cells produce IL-5 and IL-13 in response to PGD₂, and epithelium-derived “alarmins” IL-33, IL-25, and thymic stromal lymphopoietin are released in response to epithelial damage by pollutants and microbes.

Biomarkers of eosinophilic airway inflammation

Eosinophilic inflammation can be measured in peripheral blood and in the airway, invasively by bronchoscopic sampling or noninvasively by sputum induction. The use of sputum cytology to explore airway inflammation was first described by Ernst Leyden and Jean Charcot of Charcot-Leyden crystals, and was implemented clinically in the 1950s by Dr Morrow-Brown, before optimization in the 1980s and 1990s by Freddy Hargreave and colleagues (reviewed in Brightling⁵). It is a safe and well-tolerated procedure in all stages of disease severity. A more than 3% nonsquamous cell sputum eosinophil count is accepted to be indicative of eosinophilic bronchitis, because this is outside the 90th percentile for normal patients (1.1%).¹³ Sputum induction is typically unsuccessful in approximately 20% of patients and requires laboratory support, which has limited its adoption outside of specialist centers. Fractional exhaled nitric oxide (FENO) is highly correlated with eosinophilic airway inflammation in corticosteroid naïve airway disease and moderately correlated in those treated with inhaled corticosteroids (ICSs).¹⁴⁻¹⁶ In chronic cough, FENO value of more than 30 parts per billion indicates eosinophilic airway inflammation. It is a simple and quick near-patient test that does not require laboratory support, and thus has been more widely adopted than sputum analysis. A sputum eosinophilia is associated with a good response to corticosteroids⁵⁻⁸ as described further below. However, in contrast to sputum eosinophilia, FENO does not consistently predict response to corticosteroids in chronic cough.¹⁷⁻¹⁹

DEFINITION, DIAGNOSIS, AND PREVALENCE

Cough due to asthma

Asthma is characterized by variable airflow obstruction with bronchodilator reversibility and AHR.^{9,20} It is consistently reported as a major cause of chronic cough, and multiple prospective studies have shown that between 24% and 32% of chronic cough in adult nonsmokers is related to asthma.^{5-8,21} Typically, cough is associated with other symptoms such as dyspnea and wheeze, but may be present in isolation (ie, “cough-variant asthma”).^{21,22} Asthma is typically, but not exclusively, associated with eosinophilic inflammation (50%-75%), identified by the noninvasive inflammatory markers, that is, blood or sputum eosinophil counts and FENO.^{5,9,23-25}

Cough, as a symptom, is specifically excluded from evaluation in the asthma control questionnaire,²⁶ whereas in the asthma control test²⁷ it is considered as a component of overall symptomatology (alongside wheeze and breathlessness). Because the focus of guideline-based asthma management has been to improve the control score, cough measures have been largely excluded from key studies and hence, the burden of cough in asthma is not fully appreciated. Using the Leicester Cough Questionnaire in severe asthma demonstrates that cough-specific health status is impacted to a similar degree as observed for unexplained chronic cough.²⁸

Cough due to nonasthmatic eosinophilic bronchitis

The wider application of noninvasive assessment of airway inflammation led, in 1989, to the identification of a condition manifesting as a corticosteroid-responsive, chronic cough in nonsmokers, characterized by sputum eosinophilia, but without the variable airway obstruction or AHR typical of asthma. This condition was described as nonasthmatic eosinophilic bronchitis (NAEB).⁶

The prevalence of NAEB is uncertain, because most reports of etiology in chronic cough have not included measures of airway inflammation. In a 2-year prospective study of patients presenting to a single specialist center with chronic cough,⁸ sputum induction was performed in all patients in whom the cause remained unclear after simple clinical assessment and a methacholine inhalation test. Ninety-one patients with chronic cough were identified among 856 referrals, and sputum analysis led to a diagnosis with subsequent successful treatment in 85 (93%) of these cases. NAEB, defined as above, was identified in 12 (13.2%) patients, representing 30% of those who underwent sputum induction. Studies of chronic cough in which assessments of airway inflammation were made indicate that NAEB accounts for 10% to 30% of cases referred for specialist investigation.⁶⁻⁸

The diagnosis of chronic cough due to NAEB is predicated on the assessment of eosinophilic airway inflammation. Thus, measuring inflammation is included in the cough guidelines for the American College of Chest Physicians²⁹ with recommendation to perform a sputum differential cell count or, if unavailable, to consider alternatives such as FENO to confirm a diagnosis of NAEB. A condition analogous to NAEB, atopic cough, was first described in Japan^{30,31} and is characterized by eosinophilic airway inflammation, no variable airflow obstruction, nor airway AHR and presence of atopy. Atopic cough is considered part of the NAEB spectrum because its diagnosis differs from NAEB only by the need for atopy.

The severity of cough, measured by VAS symptom score, is similar in NAEB and asthma, but comparisons of cough monitor–determined cough frequency and impact on health status between the conditions have not been reported.

Cough due to UACS

UACS is a condition associated with a number of diseases involving the upper respiratory tract including allergic and nonallergic rhinitis and chronic rhinosinusitis (CRS) with or without polyps. UACS contributes to 20% to 40% of patients presenting with chronic cough.^{2,8} UACS is diagnosed by the presentation of chronic cough with evidence of rhinitis or CRS confirmed by consistent history, nose and throat examination, allergy tests, laryngoscopy, and paranasal sinus computed

tomography, as per current guidelines.^{2,32-35} Comorbid asthma is very common with allergic rhinitis (odds ratio, ~6) and CRS with nasal polyposis (odds ratio, ~10) but not in those with CRS without nasal polyposis.³⁶ Conversely, these conditions also need to be considered in patients with cough and asthma. These causes of UACS are commonly associated with an elevated blood eosinophil count and eosinophilic inflammation assessed by nasal lavage, nasal scrapes, and histology of nasal polyps. Noninvasive assessment of upper airway eosinophilic inflammation is not routinely performed, and whether inclusion of these measures would inform clinical management requires further study.^{37,38}

CLINICAL MANAGEMENT

Anti-inflammatory treatment with locally delivered corticosteroids or avoidance strategies, when the inflammation is due to an occupational exposure or inhaled allergen, are the mainstay therapies for asthma, NAEB, and UACS^{2,21,29,39} and their response to therapy is used to support the initial diagnosis.

Cough due to asthma

The evidence for the use of ICSs in asthma is overwhelming, and international guidelines recommend titrating the ICS dose to gain asthma control.²⁰ However, as noted above, asthma control using the Asthma Control Questionnaire and Asthma Control Test does not explicitly assess chronic cough and thus findings from these studies are largely extrapolated for the management of chronic cough. Similarly, ICS trials in asthma that have reported symptom VAS scores have typically reported total symptoms, rather than each symptom independently, such that the benefit in the symptom of cough is often overlooked. For example, in a single-center trial of open-labeled, inhaled budesonide for 8 weeks, a retrospective analysis of the response in the subjects with asthma dichotomized on the basis of their baseline sputum eosinophil count found that cough improved in those with eosinophilic inflammation⁴⁰ (Figure 2, A). Notwithstanding these limitations, there are 4 randomized controlled trials of ICS versus placebo, involving a total of 277 participants.⁴¹⁻⁴⁴ All 4 studies showed a reduction in cough score with ICSs. There were 2 studies of leukotriene receptor antagonists (LTRAs) versus placebo with 22 subjects, both showing reduction in cough following treatment with LTRAs.^{45,46} Benefits were also observed in response to inhaled β -agonists in 2 studies with a total of 168 subjects.^{47,48}

Cough due to NAEB

The effects of ICSs on cough were evaluated in 3 trials including 56 patients, and cough outcomes universally improved, although no control groups were studied.⁴⁹⁻⁵¹ Two trials compared LTRAs to ICSs in 91 subjects and cough improved with LTRAs in both trials.^{52,53}

In NAEB, patients improve symptomatically and have a significant fall in their sputum eosinophil count following ICS treatment.^{49,50} In one study, capsaicin cough sensitivity, which was moderately increased before treatment,⁴⁹ improved toward normal after treatment with budesonide (400 μ g inhaled twice daily) for 4 weeks and there was a significant positive correlation between the treatment-induced change in cough sensitivity and sputum eosinophil count (Figure 2, B). These findings suggest that heightened cough sensitivity contributes to the cough in NAEB and that eosinophilic airway inflammation is causally associated with the increased cough sensitivity.

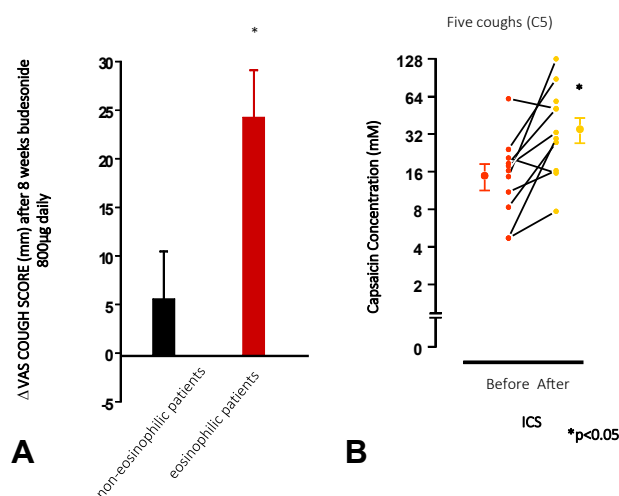


FIGURE 2. ICS response in cough, eosinophilic asthma, and NAEB. **A**, In patients with cough due to asthma, baseline eosinophilic inflammation determined by sputum eosinophil count ($>3\%$) was associated with a greater reduction in cough VAS score in response to 8 weeks of ICS therapy than in those without eosinophilic inflammation. **B**, In NAEB, 6 weeks of ICS treatment led to an improvement in capsaicin cough sensitivity.

Cough due to UACS

Similarly to asthma there are well-established guidelines for the management of rhinitis and CRS.^{2,32-35} Topical nasal corticosteroids are recommended for allergic rhinitis often as second line to antihistamines, with immunotherapy recommended in refractory disease. Nasal corticosteroids are first line for CRS with nasal polyposis. In both conditions, LTRAs are also recommended. For UACS, recommended treatments are the same as for rhinitis and CRS, with the addition of antibiotics only in patients with CRS without nasal polyposis, who are less likely to be eosinophilic and may have other disease drivers including bacterial infection.

Assessing eosinophilic inflammation: A new management paradigm for chronic cough

To date the anatomical-physiological approach to defining the cause of chronic cough has led to successful treatment in most sufferers. Often, chronic cough is multifactorial, with a number of aggravating factors in addition to an underlying heightened cough reflex. Consequently, patients can be required to undertake multiple treatment trials over extended periods, and in combination, before the right treatment is selected. The consistent evidence that eosinophilic airway inflammation identifies people with corticosteroid-responsive cough and, reciprocally, the absence of eosinophilic inflammation confers a poor response to corticosteroids⁵⁴ enables a more targeted precision medicine approach to cough as outlined in Figure 3. This approach means that corticosteroid therapy is introduced early in those most likely to respond and the measurement of inflammation can be used as a diagnostic and theranostic outcome to titrate treatment. Persistent chronic cough with adequately suppressed eosinophilic airway inflammation then warrants further investigation and alternative treatments. Cough suppression training to reduce

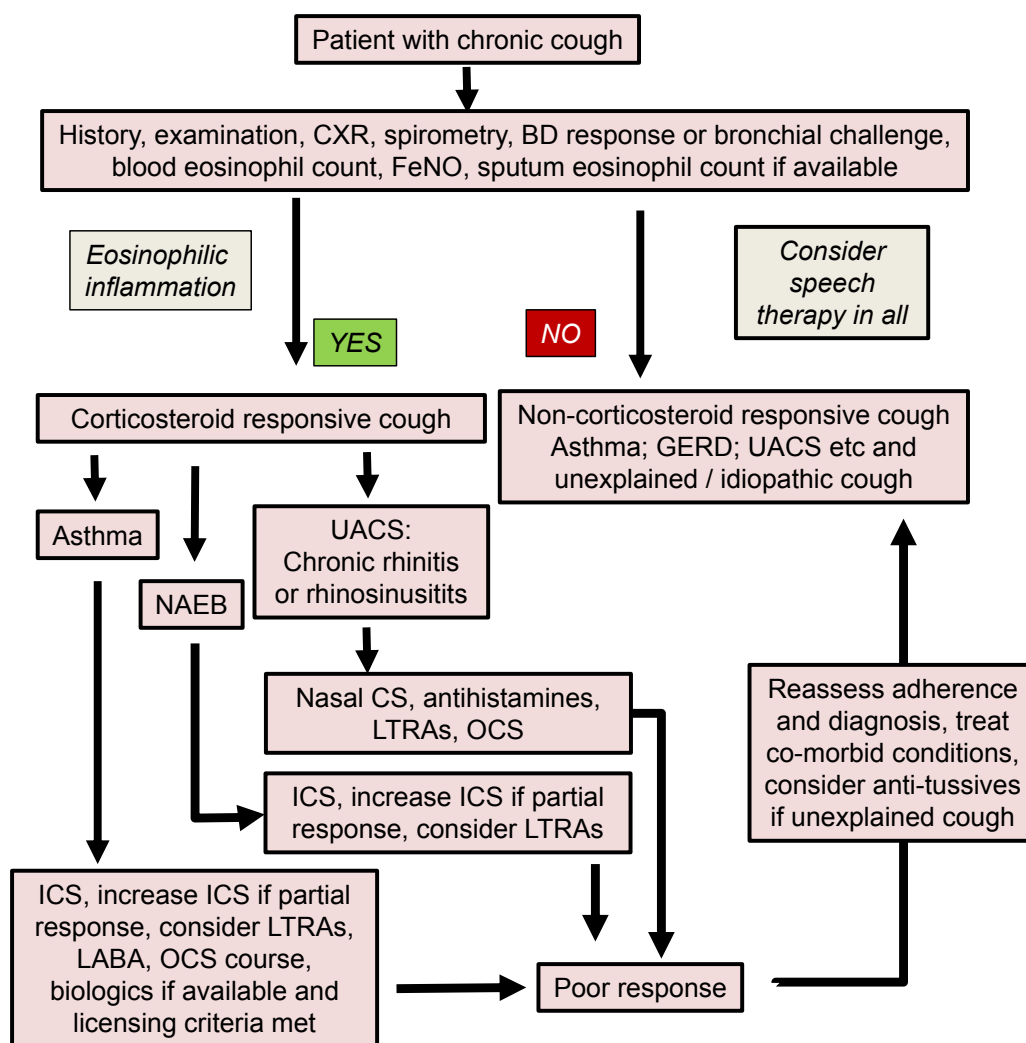


FIGURE 3. Management algorithm. Proposed management algorithm for chronic cough that positions investigation of eosinophilic inflammation as an early and critical part of the patient assessment to determine patients most likely to respond to corticosteroids and LTRAs. *BD*, Bronchodilator; *CS*, corticosteroid; *CXR*, chest X-ray; *GERD*, gastroesophageal reflux disease; *LABA*, long-acting β -agonist; *OCS*, oral corticosteroid.

cough reflex hypersensitivity can be undertaken in concert with treatment of aggravating factors.⁵⁵

Measures of eosinophilic inflammation are not routinely evaluated in UACS and thus the relationship between the intensity of upper airway eosinophilic inflammation and response to corticosteroids is poorly understood.

PROGNOSIS

Cough due to asthma

The natural history of chronic cough due to asthma has not been comprehensively studied. However, reports suggest that the prognosis is excellent,⁵⁶ with remission in approximately 15% of sufferers⁵⁷ and development of classical asthma in 30% to 47%.^{57,58} Development of classical asthma was associated with presence of eosinophilic airway inflammation at diagnosis, and was less likely with early treatment of cough due to asthma with ICS.^{57,58}

Cough due to NAEB

Similarly, there has been limited study of the natural history of NAEB. A 10-year follow-up evaluation of 12 patients with NAEB suggests that this condition is generally benign and self-limiting,⁵⁹ although this is disputed by a larger series that reported the condition to be self-limiting only rarely.⁶⁰ Fifty-two patients from 1996 to 2003 were identified with NAEB, with follow-up data of more than 1 year available in 32. Three (9%) patients developed asthma with typical symptoms and AHR. Twenty-one (66%) had persistent symptoms and/or ongoing airway inflammation. Only 1 patient with NAEB had complete resolution of symptoms and no evidence of sputum eosinophilia without receiving corticosteroid therapy. In NAEB, only a few studies have explored lung function decline and persistent eosinophilic inflammation.^{51,60,61} These have suggested that a minority develop airflow obstruction. Lai et al⁶¹ undertook the largest observational study of NAEB to date, in terms of length of follow-up and the number of subjects. They found that in most

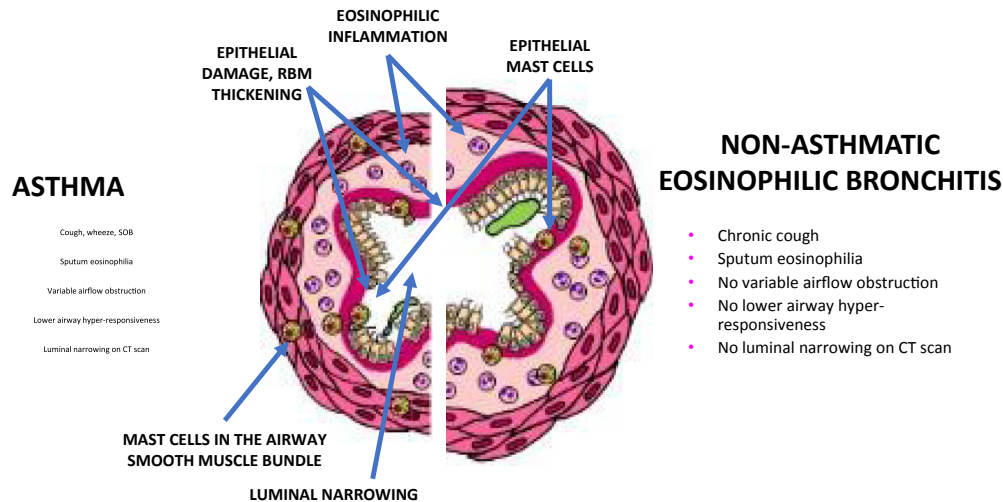


FIGURE 4. Asthma versus NAEB. Comparisons of the clinical and immunopathological features of asthma versus NAEB. *CT*, Computed tomography; *RBM*, reticular basement membrane.

subjects, NAEB had a benign natural history and usually resolved following corticosteroid therapy. In a subgroup, inflammation and symptoms relapsed and in this “relapse” group there was increased development of small airway dysfunction. The magnitude of this decline was small, but does suggest that some subjects are at risk of progressive disease if inflammation is inadequately controlled.

Cough due to UACS

Long-term outcomes of the underlying upper airway conditions leading to UACS and response to therapy are described, but the prognosis of cough due to UACS has not been extensively reported. Whether presence of cough with rhinitis and CRS lead to a different natural history compared with those without cough is unclear. One study found that rhinitis was a risk factor for

persistent cough in a 5-year prospective study,⁶² indicating that further investigation is warranted.

MECHANISTIC INSIGHTS

Cause of AHR

Comparisons between asthma and NAEB have shed light on the mechanisms driving AHR in asthma. Asthma and NAEB share many immunopathological features (summarized in Figure 4) including a similar degree of sputum, bronchoalveolar lavage, and biopsy eosinophilia, and a similar degree of basement membrane thickening.^{5-8,63,64} Similarly, asthma and NAEB were associated with increased sputum concentrations of important effector mediators, cysteinyl-leukotrienes, and eosinophilic cationic protein.^{65,66} Interestingly, histamine and PGD₂ sputum

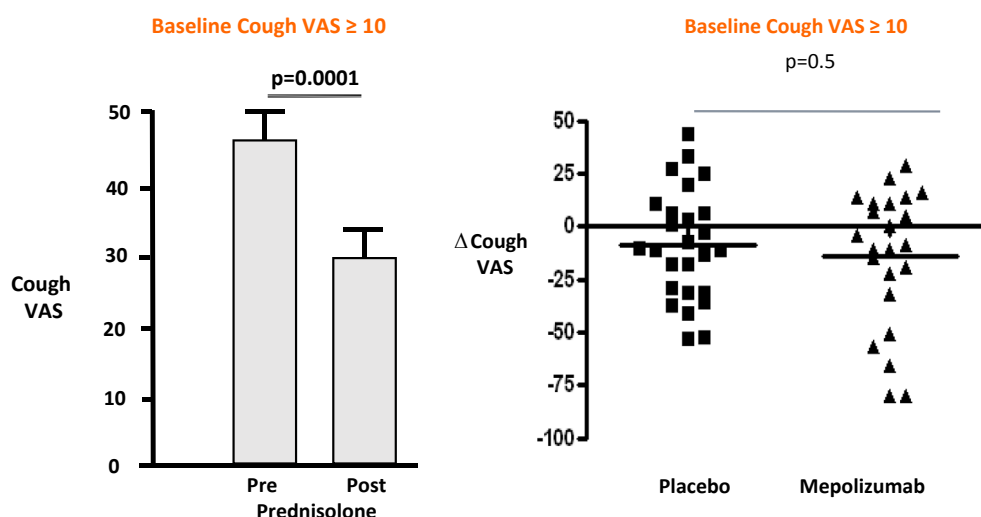


FIGURE 5. Mepolizumab and cough. **A**, In a randomized placebo-controlled trial of mepolizumab, patients received prednisolone for 2 weeks. Those with an elevated cough VAS score at baseline had a reduction in cough following prednisolone. **B**, In the same subjects, there was no reduction in VAS score following mepolizumab versus placebo.

concentrations are markedly increased in NAEB, suggesting that activation of mast cells in superficial airway structures is a particular feature of this condition, and raising the possibility that localization of activated mast cells might differ in asthma and NAEB. In support of this, mast cell numbers in bronchial brushings were increased in NAEB compared with asthma.⁶⁵ In asthma, mast cell numbers in airway smooth muscle were increased, but not in NAEB,⁶³ and the number of airway smooth muscle mast cells was inversely correlated with AHR.^{63,67} IL-13 expression is increased in asthma compared with NAEB in the bronchial submucosa and sputum.⁶⁸ Although airway remodeling is a feature of both conditions, the consequent effect on airway geometry is distinct, with airway narrowing observed only in asthma.⁶⁹ Thus, localization of mast cells to the airway smooth muscle bundle, increased IL-13 expression, and airway narrowing are likely to be important determinants of AHR and variable airflow obstruction in asthma, whereas epithelial infiltration by mast cells might be more important for cough.

Is eosinophilic inflammation causal of chronic cough?

As described above, the subjective and objective improvement following treatment with corticosteroids in asthma, NAEB, and UACS is associated with the presence of an airway eosinophilia. These data implicate the eosinophil as causal in chronic cough. Biologics that target IL-5 or its receptor would thus be predicted as beneficial for chronic cough with eosinophilia. However, data are lacking because the late-phase biological trials did not assess cough and no trials have specifically studied subjects with chronic cough due to asthma. In a small, single-center, 1-year, randomized controlled study of mepolizumab in severe eosinophilic asthma there was a marked reduction in severe exacerbations in those subjects who received mepolizumab.⁷⁰ In spite of this profound effect on the frequency of severe exacerbations, there was no effect on lung function or symptoms. Interestingly, subjects were treated with 2 weeks of prednisolone 30 mg daily before mepolizumab, which resulted in a reduced cough severity, assessed by VAS score. In contrast, mepolizumab did not affect cough severity compared with placebo over the entire year of therapy.^{70,71} (Figure 5). Thus, eosinophilic airway inflammation is neither sufficient nor necessary for patients with asthma to have chronic cough, and when present, specific attenuation of eosinophilic inflammation does not ameliorate cough. In 2 independent case reports of patients with hypereosinophilic syndrome and chronic cough, the cough improved with imatinib.⁷¹⁻⁷³ Although imatinib is associated with a reduction in eosinophilic inflammation, this benefit may have been due to its attenuation of mast cell activation and survival. Taken together these findings suggest that eosinophilic inflammation might be an epiphenomenon rather than the cause of chronic cough. This apparent lack of a causal relationship between eosinophilic inflammation in asthma and cough raises the importance of other potential mechanisms, such as mast cell interactions with superficial nerves, and warrants further investigation.

CONCLUSIONS

Eosinophilic inflammation is commonly observed in chronic cough, particularly in patients with asthma, NAEB, and UACS. Importantly, the presence of eosinophilic airway inflammation is associated with a favorable response to corticosteroids independent of the underlying diagnosis. Comparisons between asthma

and NAEB have revealed potential mechanisms driving AHR in asthma. Whether the eosinophil is causal in driving chronic cough is uncertain and alternative mechanisms such as mast cell-neuronal interactions might be important in cough associated with eosinophilia. Future trials need to systematically record cough severity and frequency in asthma, NAEB, and UACS to determine natural history and response to therapies including biologics.

REFERENCES

1. Irwin RS, French CL, Chang AB, Altman KW. Classification of cough as a symptom in adults and management algorithms: CHEST Guideline and Expert Panel Report. *Chest* 2018;153:196-209.
2. Irwin RS, Baumann MH, Bolser DC, Boulet LP, Braman SS, Brightling CE, et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. *Chest* 2006;129:1S-23S.
3. Madison JM, Irwin RS. Cough: a worldwide problem. *Otolaryngol Clin North Am* 2010;43:1-13.
4. Boulet LP, Coeytaux RR, McCrory DC, French CT, Chang AB, Birring SS, et al. Tools for assessing outcomes in studies of chronic cough: CHEST guideline and expert panel report. *Chest* 2015;147:804-14.
5. Brightling CE. Clinical applications of induced sputum. *Chest* 2006;129:1344-8.
6. Gibson PG, Dolovich J, Denburg J, Ramsdale EH, Hargreave FE. Chronic cough: eosinophilic bronchitis without asthma. *Lancet* 1989;1:1346-8.
7. Carney IK, Gibson PG, Murree-Allen K, Salties N, Olson LG, Hensley MJ. A systematic evaluation of mechanisms in chronic cough. *Am J Respir Crit Care Med* 1997;156:211-6.
8. Brightling CE, Ward R, Goh KL, Wardlaw AJ, Pavord ID. Eosinophilic bronchitis is an important cause of chronic cough. *Am J Respir Crit Care Med* 1999;160:406-10.
9. Papi A, Brightling C, Pedersen SE, Reddel HK. Asthma. *Lancet* 2018;391:783-800.
10. Lambrecht BN, Hammad H. The immunology of asthma. *Nat Immunol* 2015;16:45-56.
11. Russell RJ, Brightling C. Pathogenesis of asthma: implications for precision medicine. *Clin Sci (Lond)* 2017;131:1723-35.
12. Ayars GH, Altman LC, Gleich GJ, Loegering DA, Baker CB. Eosinophil- and eosinophil granule-mediated pneumocyte injury. *J Allergy Clin Immunol* 1985;76:595-604.
13. Belda J, Leigh R, Parameswaran K, O'Byrne PM, Sears MR, Hargreave FE. Induced sputum cell counts in healthy adults. *Am J Respir Crit Care Med* 2000;161:475-8.
14. Maniscalco M, Fuschillo S, Gaudiosi C, De Felice A, Martucci M, Motta A. Exhaled and nasal nitric oxide measurement in the evaluation of chronic cough. *Nitric Oxide* 2019;83:19-23.
15. Yi F, Chen R, Luo W, Xu D, Han L, Liu B, et al. Validity of fractional exhaled nitric oxide in diagnosis of corticosteroid-responsive cough. *Chest* 2016;149:1042-51.
16. Maniscalco M, Faraone S, Sofia M, Molino A, Vatrella A, Zedda A. Extended analysis of exhaled and nasal nitric oxide for the evaluation of chronic cough. *Respir Med* 2015;109:970-4.
17. Smith AD, Cowan JO, Brassett KP, Filsell S, McLachlan C, Monti-Sheehan G, et al. Exhaled nitric oxide: a predictor of steroid response. *Am J Respir Crit Care Med* 2005;172:453-9.
18. Malinovschi A, Van Muylem A, Michiels S, Michils A. FeNO as a predictor of asthma control improvement after starting inhaled steroid treatment. *Nitric Oxide* 2014;40:110-6.
19. Song WJ, Won HK, Moon SD, Chung SJ, Kang SY, Sohn KH, et al. Could fractional exhaled nitric oxide test be useful in predicting inhaled corticosteroid responsiveness in chronic cough? A systematic review. *J Allergy Clin Immunol Pract* 2017;5:135-143.e1.
20. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2017. Available from: https://ginasthma.org/wp-content/uploads/2019/04/wmsGINA-2017-main-report-final_V2.pdf. Accessed May 30, 2019.
21. Diepinigaitis PV. Chronic cough due to asthma: ACCP evidence-based clinical practice guidelines. *Chest* 2006;129:75S-9S.
22. Corrao WM, Braman SS, Irwin RS. Chronic cough as the sole presenting manifestation of bronchial asthma. *N Engl J Med* 1979;300:633-7.
23. Simpson JL, McElduff P, Gibson PG. Assessment and reproducibility of non-eosinophilic asthma using induced sputum. *Respiration* 2010;79:147-51.

24. Pavord ID, Brightling CE, Woltmann G, Wardlaw AJ. Non-eosinophilic corticosteroid unresponsive asthma. *Lancet* 1999;353:2213-4.
25. McGrath KW, Icitovic N, Boushey HA, Lazarus SC, Sutherland ER, Chinchilli VM, et al. A large subgroup of mild-to-moderate asthma is persistently noneosinophilic. *Am J Respir Crit Care Med* 2012;185:612-9.
26. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14:902-7.
27. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol* 2004;113:59-65.
28. Natarajan S, Free RC, Bradding P, McGarvey L, Siddiqui S. The relationship between the Leicester cough questionnaire, eosinophilic airway inflammation and asthma patient related outcomes in severe adult asthma. *Respir Res* 2017;18:44.
29. Brightling CE. Chronic cough due to nonasthmatic eosinophilic bronchitis: ACCP evidence-based clinical practice guidelines. *Chest* 2006;129:116S-21S.
30. Brightling CE, Pavord ID. Eosinophilic bronchitis—what is it and why is it important? *Clin Exp Allergy* 2000;30:4-6.
31. Fujimura M, Ogawa H, Yasui M, Matsuda T. Eosinophilic tracheobronchitis and airway cough hypersensitivity in chronic non-productive cough. *Clin Exp Allergy* 2000;30:41-7.
32. National Institute for Health and Care Excellence. Allergic Rhinitis. 2018. Available from: <https://cks.nice.org.uk/allergic-rhinitis#/topicSummary>. Accessed April 25, 2019.
33. Scadding GK, Kariyawasam HH, Scadding G, Mirakian R, Buckley RJ, Dixon T, et al. BSACI guideline for the diagnosis and management of allergic and non-allergic rhinitis (Revised Edition 2017; First edition 2007). *Clin Exp Allergy* 2017;47:856-89.
34. Fokkens W, Lund V, Bachert C, Clement P, Hellings P, Holmstrom M, et al. EAAACI position paper on rhinosinusitis and nasal polyps executive summary. *Allergy* 2005;60:583-601.
35. Wallace DV, Dykewicz MS, Bernstein DI, Blessing-Moore J, Cox L, Khan DA, et al. The diagnosis and management of rhinitis: an updated practice parameter. *J Allergy Clin Immunol* 2006;117:S1-84.
36. Watelet JB, Van Zele T, Brusselle G. Chronic cough in upper airway diseases. *Respir Med* 2010;104:652-7.
37. Ellis AK, Keith PK. Nonallergic rhinitis with eosinophilia syndrome. *Curr Allergy Asthma Rep* 2008;122:S1-20.
38. Chitsuthipakorn W, Seresirikachorn K, Sommer DD, McHugh T, Snidvongs K. Endotypes of chronic rhinosinusitis across ancestry and geographic regions. *Curr Allergy Asthma Rep* 2018;18:46.
39. Pratter MR, Brightling CE, Boulet LP, Irwin RS. An empiric integrative approach to the management of cough: ACCP evidence-based clinical practice guidelines. *Chest* 2006;129:222S-31.
40. Green RH, Brightling CE, Woltmann G, Parker D, Wardlaw AJ, Pavord ID. Analysis of induced sputum in adults with asthma: identification of subgroup with isolated sputum neutrophilia and poor response to inhaled corticosteroids. *Thorax* 2002;57:875-9.
41. Bergmann KC, Bauer CP, Overlack A. A placebo-controlled, blind comparison of nedocromil sodium and beclomethasone dipropionate in bronchial asthma. *Curr Med Res Opin* 1989;11:533-42.
42. Connolly K, Peake M, Halpin D, Golightly L, Turbitt M, Group oboAPR. Challenging current asthma treatment guidelines: improved control of asthma symptoms with nebulised budesonide in patients with severe asthma receiving continuous oral steroids. *Dis Manage Health Outcomes* 2000;7:217-25.
43. Di Franco A, Dente FL, Giannini D, Vagaggini B, Conti I, Macchioni P, et al. Effects of inhaled corticosteroids on cough threshold in patients with bronchial asthma. *Pulm Pharmacol Ther* 2001;14:35-40.
44. Malo JL, Cartier A, Cote J, Milot J, Leblanc C, Paquette L, et al. Influence of inhaled steroids on recovery from occupational asthma after cessation of exposure: an 18-month double-blind crossover study. *Am J Respir Crit Care Med* 1996;153:953-60.
45. Dipinigit PV, Dobkin JB, Reichel J. Antitussive effect of the leukotriene receptor antagonist zafirlukast in subjects with cough-variant asthma. *J Asthma* 2002;39:291-7.
46. Spector SL, Tan RA. Effectiveness of montelukast in the treatment of cough variant asthma. *Ann Allergy Asthma Immunol* 2004;93:232-6.
47. Bao W, Chen Q, Lin Y, Liu H, Zhao G, Chen Z, et al. Efficacy of procaterol combined with inhaled budesonide for treatment of cough-variant asthma. *Respirology* 2013;18:53-61.
48. Irwin RS, French CT, Smyrniotis NA, Curley FJ. Interpretation of positive results of a methacholine inhalation challenge and 1 week of inhaled bronchodilator use in diagnosing and treating cough-variant asthma. *Arch Intern Med* 1997;157:1981-7.
49. Brightling CE, Ward R, Wardlaw AJ, Pavord ID. Airway inflammation, airway responsiveness and cough before and after inhaled budesonide in patients with eosinophilic bronchitis. *Eur Respir J* 2000;15:682-6.
50. Gibson PG, Hargreave FE, Girgis-Gabardo A, Morris M, Denburg JA, Dolovich J. Chronic cough with eosinophilic bronchitis: examination for variable airflow obstruction and response to corticosteroid. *Clin Exp Allergy* 1995;25:127-32.
51. Park SW, Lee YM, Jang AS, Lee JH, Hwangbo Y, Kim DJ, et al. Development of chronic airway obstruction in patients with eosinophilic bronchitis: a prospective follow-up study. *Chest* 2004;125:1998-2004.
52. Bao W, Liu P, Qiu Z, Yu L, Hang J, Gao X, et al. Efficacy of add-on montelukast in nonasthmatic eosinophilic bronchitis: the additive effect on airway inflammation, cough and life quality. *Chin Med J (Engl)* 2015;128:39-45.
53. Cai C, He MZ, Zhong SQ, Tang Y, Sun BQ, Chen QL, et al. Add-on montelukast vs double-dose budesonide in nonasthmatic eosinophilic bronchitis: a pilot study. *Respir Med* 2012;106:1369-75.
54. Pizzichini MM, Pizzichini E, Parameswaran K, Clelland L, Efthimiadis A, Dolovich J, et al. Nonasthmatic chronic cough: no effect of treatment with an inhaled corticosteroid in patients without sputum eosinophilia. *Can Respir J* 1999;6:323-30.
55. Chamberlain Mitchell SA, Garrod R, Clark L, Douiri A, Parker SM, Ellis J, et al. Physiotherapy, and speech and language therapy intervention for patients with refractory chronic cough: a multicentre randomised control trial. *Thorax* 2017;72:129-36.
56. Corrao WM. Pearls and pitfalls in the diagnosis of cough variant asthma. *Allergy Asthma Proc* 2018;39:466-7.
57. Matsumoto H, Niimi A, Takemura M, Ueda T, Tabuena R, Yamaguchi M, et al. Prognosis of cough variant asthma: a retrospective analysis. *J Asthma* 2006;43:131-5.
58. Kim CK, Kim JT, Kang H, Yoo Y, Koh YY. Sputum eosinophilia in cough-variant asthma as a predictor of the subsequent development of classic asthma. *Clin Exp Allergy* 2003;33:1409-14.
59. Hancox RJ, Leigh R, Kelly MM, Hargreave FE. Eosinophilic bronchitis. *Lancet* 2001;358:1104.
60. Berry MA, Hargadon B, McKenna S, Shaw D, Green RH, Brightling CE, et al. Observational study of the natural history of eosinophilic bronchitis. *Clin Exp Allergy* 2005;35:598-601.
61. Lai K, Liu B, Xu D, Han L, Lin L, Xi Y, et al. Will nonasthmatic eosinophilic bronchitis develop into chronic airway obstruction? A prospective, observational study. *Chest* 2015;148:887-94.
62. Koskela HO, Latti AM, Purokivi MK. Long-term prognosis of chronic cough: a prospective, observational cohort study. *BMC Pulm Med* 2017;17:146.
63. Brightling CE, Bradding P, Symon FA, Holgate ST, Wardlaw AJ, Pavord ID. Mast-cell infiltration of airway smooth muscle in asthma. *N Engl J Med* 2002;346:1699-705.
64. Brightling CE, Symon FA, Birring SS, Bradding P, Wardlaw AJ, Pavord ID. Comparison of airway immunopathology of eosinophilic bronchitis and asthma. *Thorax* 2003;58:528-32.
65. Gibson PG, Zlatich K, Scott J, Sewell W, Woolley K, Salto N. Chronic cough resembles asthma with IL-5 and granulocyte-macrophage colony-stimulating factor gene expression in bronchoalveolar cells. *J Allergy Clin Immunol* 1998;101:320-6.
66. Brightling CE, Ward R, Woltmann G, Bradding P, Sheller JR, Dworski R, et al. Induced sputum inflammatory mediator concentrations in eosinophilic bronchitis and asthma. *Am J Respir Crit Care Med* 2000;162:878-82.
67. Siddiqui S, Mistry V, Doe C, Roach K, Morgan A, Wardlaw A, et al. Airway hyperresponsiveness is dissociated from airway wall structural remodeling. *J Allergy Clin Immunol* 2008;122:335-341.e3.
68. Berry MA, Parker D, Neale N, Woodman L, Morgan A, Monk P, et al. Sputum and bronchial submucosal IL-13 expression in asthma and eosinophilic bronchitis. *J Allergy Clin Immunol* 2004;114:1106-9.
69. Siddiqui S, Gupta S, Cruse G, Haldar P, Entwistle J, McDonald S, et al. Airway wall geometry in asthma and nonasthmatic eosinophilic bronchitis. *Allergy* 2009;64:951-8.
70. Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009;360:973-84.
71. Brightling CE. Eosinophils, bronchitis and asthma: pathogenesis of cough and airflow obstruction. *Pulm Pharmacol Ther* 2011;24:324-7.
72. Barker B, Moudgil H, Slocombe G, Srinivasan K. Persistent cough: an unusual cause. Idiopathic hypereosinophilic syndrome (HES). *Thorax* 2010;65:1009, 1024.
73. Chung KF, Hew M, Score J, Jones AV, Reiter A, Cross NC, et al. Cough and hypereosinophilia due to FIP1L1-PDGFR α fusion gene with tyrosine kinase activity. *Eur Respir J* 2006;27:230-2.