# Nonasthmatic Eosinophilic Bronchitis: A Systematic Review of Current Treatment Options

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## Abstract

Nonasthmatic eosinophilic bronchitis is characterized by persistent dry or barely productive cough and bronchial eosinophilia without airway obstruction or bronchial hyperreactivity. It is primarily a chronic disease, in which some patients have clinical and pathophysiological relapses, while others progress to asthma or chronic obstructive pulmonary disease. It accounts for 5% to 30% of cases referred for chronic cough. Exposure to common inhalants and occupational sensitizers has been proposed as a possible cause of the disease, although the etiology and underlying mechanisms are uncertain. Some features are similar to those of asthma, such as airway eosinophilia, inflammatory mediator levels, and airway remodeling.

Differences in airway pathophysiology, such as the location of airway inflammation and levels of IL-13 and PGE-2, have been reported. Sputum cell count is the gold standard test for diagnosis, and other biomarkers, such as exhaled nitric oxide, could support the diagnosis. A systematic review of treatments for the disease shows that while inhaled corticosteroids are the primary option, the appropriate dose, the type of corticosteroid, and the duration of treatment remain unknown. Treatment duration is inversely correlated with the relapse rate. Increased doses of inhaled corticosteroids, oral corticosteroids, and leukotriene receptor antagonists are recommended in persistent disease. Anti–IL-5 biologics could be promising in this disease. Studies that investigate biomarkers for diagnosis and prognosis are necessary, as are randomized controlled studies for second-line treatments.

**Key words:** Eosinophilic bronchitis. Nonasthmatic eosinophilic bronchitis. Sputum. Chronic cough.

## Resumen

La bronquitis eosinofílica se caracteriza por tos persistente seca o escasamente productiva y eosinofilia en la vía aérea, sin obstrucción ni hiperreactividad bronquial. Generalmente, es una enfermedad crónica en la cual algunos pacientes tienen recaídas clínicas y fisiopatológicas, mientras que otros progresan a asma o enfermedad pulmonar obstructiva. Supone en torno al 5-30% de los casos de tos crónica. La exposición a inhalantes habituales y sensibilizantes ocupacionales ha sido propuesta como posible causa de la enfermedad, pero su etiología y mecanismos subyacentes se mantienen inciertos. Algunas características son similares al asma, como la presencia de eosinofilia en la vía área, niveles de mediadores inflamatorios y remodelado aéreo, pero hay diferencias en la fisiopatología aérea como la localización de la inflamación y los niveles de IL-13 y de PGE-2. La celularidad en esputo es el *gold standard* para el diagnóstico, y otros biomarcadores como el óxido nítrico exhalado pueden apoyar el diagnóstico. Se ha realizado una revisión sistemática sobre tratamientos de la enfermedad. A pesar de que los corticoides inhalados son el principal tratamiento, la dosis adecuada, el tipo de corticoide y la duración del mismo no son conocidas. La duración del tratamiento se correlaciona inversamente con la tasa de recaídas. El aumento de la dosis de corticoide inhalado, corticoide oral y antagonistas de receptor de leucotrienos se recomiendan en caso de persistencia de la enfermedad. Los biológicos anti-IL-5 podrían ser prometedores en esta enfermedad. Se requieren estudios para investigar biomarcadores diagnósticos y pronósticos, y estudios aleatorizados y controlados para tratamientos de segunda línea.

**Palabras clave:** Bronquitis eosinofílica. Bronquitis eosinofílica no asmática. Esputo. Tos crónica.

## 1. Introduction

Nonasthmatic eosinophilic bronchitis (NAEB) is characterized by airway eosinophilia without bronchial hyperreactivity. It is a chronic disease, in which relapses and progression are common. Although etiology-pathogenesis, diagnostic and prognostic biomarkers, and appropriate interventions remain largely unknown, there have been important advances in our understanding of this entity. The first part of this manuscript encompasses a narrative review of pathogenesis, epidemiology, and diagnosis. In the second part, a systematic review of the treatment options is presented.

## 2. Etiology and Pathogenesis

In 1960, Glynn et al [1] observed the presence of eosinophils in the airway mucosa of 5 nonsmokers with chronic bronchitis. However, the diagnosis was made based on symptoms of chronic cough, and neither lung function nor bronchial hyperresponsiveness was evaluated. In 1989, Gibson et al [2] demonstrated higher levels of sputum eosinophilia in 7 nonsmokers presenting with chronic cough, in whom asthma was ruled out. The authors went on to describe eosinophilic bronchitis for the first time and subsequently coined the term NAEB, which manifests as persistent cough responsive to inhaled corticosteroids characterized by bronchial eosinophilia without airway obstruction or bronchial hyperreactivity. Patients with eosinophilic bronchitis typically present in middle age with dry or barely productive cough lasting more than 8 weeks [3,4]. Although the prevalence of NAEB is unknown, it has been estimated to affect 5%-30% of patients with chronic cough [5-7]. See table S1 in the supplementary material.

The degree of eosinophilic inflammation in the airway is independent of the severity of cough and its duration [8]. Nasal symptoms are present in 25%-60% of patients with NAEB [8-10], despite an absence of eosinophilic inflammation in nasal lavage samples [11], and atopy in 40%-60% of cases [9,12-14]. In studies with few patients, the prevalence of atopy ranges from 0% [8] to 90% [15]. Similar rates were observed in asthma patients [13,16], although these were significantly higher than for other causes of chronic cough [15].

Exposure to common inhalants and occupational sensitizers has been proposed as a possible cause of the disease; however, the etiology and underlying mechanisms are unknown [17]. NAEB can occur after exposure to dust mites [18] and fungus [19] and after intake of drugs such as bucillamine [20] and leflunomide [21]. While exposure to dust mites has been demonstrated to be present in about 44% of patients with NAEB, the clinical implications of this finding are uncertain [14].

In 1997, Lemiere et al [22] reported a case of NAEB caused by workplace exposure to acrylates in a female patient who presented with cough at work. Increased sputum eosinophilia was demonstrated during work time (0% to 13%) and in a specific inhalation challenge test (0% to 5.8%), with no bronchial hyperresponsiveness [22]. Since then, occupational NAEB (ONAEB) has been diagnosed after exposure to a wide variety of agents: latex [23], flour [24], egg proteins [25], mushroom spores [26], acrylate [22,27], epoxy resins [28], metal fluids [29], chloramine [30], isocyanate [24], formaldehyde [31], and polymers [32]. Isolated cough is present in about 20% of patients with ONAEB. Thus, the presence of other respiratory symptoms is frequent [33]. The potential for progression of this entity to occupational asthma remains unknown [34].

NAEB shares immunopathologic features with asthma, as follows: increased eosinophilia in sputum, bronchial epithelium, and submucosa [35-38], as well as in the basement membrane, with thickening of the lamina reticularis and vascular remodeling and proliferation [37-39]; eosinophil progenitor cells and $CD34^{+}$-derived hematopoietic progenitor cells in blood and sputum [40]; and similar levels of sputum cytokine and proinflammatory mediators such as IL-5, IL-4, IL-10, IL-2, IL-8, IFN-γ, and eosinophilic cationic protein (ECP) [35-37,41-44]. Eosinophil counts in bronchoalveolar lavage are similar between the 2 diseases according to some authors [42,45] but not to others [37]. The explanation for this difference remains unknown. The presence of some radiological findings, such as bronchiectasis, emphysema, and air trapping, was similar in both diseases [16].

Differences in airway pathophysiology have been reported. Firstly, in NAEB, the degree of airway inflammation gradually decreases from the main bronchus to the peripheral airway. There is an increase in mast cell infiltration in the central airway compared to asthma and cough-variant asthma (CVA) [37], implying an increased concentration of these cells in bronchial brushing [45]. At the same time, inflammation decreases in the peripheral airway and the airway smooth muscles [37,38]. The quantity of mast cells in airway smooth muscle is inversely correlated with airway hyperresponsiveness, thus explaining the differences between the diseases [38]. Levels of the chemokines CXCL8 and CXCL10 involved in mast cell recruitment to the superficial airway are increased in bronchoalveolar lavage (BAL) fluid and bronchial wash in NAEB compared to asthma [46]. One possible explanation is that inflammatory cell infiltration in NAEB is more localized to the epithelium and bronchial mucosa, with the result that mediators released by mast cells or other inflammatory cells reach airway smooth muscle in lower concentrations than in asthma. Similar findings were demonstrated with lymphocyte count distribution, with significantly higher levels in bronchial biopsies of the central airway [37] and no difference in the peripheral airway with respect to asthma, CVA, and healthy controls [38]. The thickness of the basement membrane has been related to eosinophilic inflammation [37]. In contrast, using high-resolution computed tomography, Park et al [16] showed that in NAEB, the thickness of the large airway is normal, as observed in healthy individuals, but that of the small airways was not. The authors suggested that the thickening of the large airway walls in asthma that may contribute to airway hyperresponsiveness is absent in NAEB.

Secondly, compared with asthma, NAEB is characterized by a significant decrease in IL-13 concentrations and protein expression in sputum and bronchial submucosa, and values are similar to those of healthy individuals [35,36,41,47]. In the bronchial submucosa, eosinophils are one of the cell types that most express IL-13 protein. The number of submucosal eosinophils is similar in NAEB and in asthma, although the

proportion of eosinophils that expressed IL-13 is higher in asthma [35]. IL-13 induces airway hyperresponsiveness, thus revealing pathophysiological differences between these 2 entities that could explain their clinical manifestations [35,36].

Moreover, concentrations of sputum prostaglandin E2 were greater in NAEB [41,43] and in other causes of chronic cough (idiopathic and CVA) [48] than in asthma. This has been shown to protect against bronchoconstriction and to inhibit bronchial smooth muscle cell proliferation [49]. Higher levels of other inflammatory biomarkers, such as histamine, were demonstrated in the sputum of NAEB patients, thus pointing to mast cell activation [43,48]. Sputum cysteinyl-leukotriene levels are higher in NAEB than in asthma according to some authors [48] but not to others [43]. However, the population in the first study [48] comprised both CVA and NAEB patients, thus preventing the role of sputum cysteinyl-leukotriene in NAEB from being elucidated. These findings could explain the characteristic cough observed in NAEB in the absence of bronchial hyperresponsiveness.

## 3. Epidemiology and Natural History

The natural history and clinical course of NAEB remain unknown. A 10-year follow-up evaluation of 12 patients with NAEB demonstrated remission of airway eosinophilia after inhaled corticosteroids, suggesting that this condition is generally benign and self-limiting [50]. However, data from only 8 patients were analyzed, symptoms resolved completely in half of the patients, and the other half continued with cough related to other causes (gastroesophageal reflux and postnasal drip).

All other studies have identified NAEB as a chronic disease with recurrent clinical relapses whose frequency ranges from 20.8% to 60% depending on follow-up time and recurrence criteria [5,10,12,14,35,51]. More information is given in the Table. While patients with no symptoms but persistent sputum eosinophilia were considered a recurrence group according to Berry et al [35], the same characteristic was considered remission of NAEB by Park et al [52]. Similarly, persistent cough despite no sputum eosinophilia was considered recurrence by Berry et al [35] but remission by Hancox et al [50]. Detailed information is given in the Table.

The frequency of remission, defined as absence of symptoms and of sputum airway eosinophilia, varied from 3% in 32 NAEB patients followed up for a mean of 3.1 years [14] to 37.5% in 24 NAEB patients followed up for 2 years [52]. When the absence of cough without treatment was considered a remission criterion alone without considering sputum analysis, the frequency increased to 40.4% in 141 NAEB patients followed up for a median of 4.1 years [51] and 53.6% in 41 NAEB patients followed for a mean of 5.8 years [12]. Asymptomatic persistent sputum eosinophilia was reported by Berry et al [35] and Park et al [52] in 9.4% and 52.6% of patients, respectively. The clinical implication of this finding remains unclear.

Most cases of relapse of NAEB (up to 90%) are reported during the first year of follow-up [10,51,52]. The underlying pathophysiological mechanism of NAEB relapses remains unknown, although the clinical characteristics and inflammatory profiles of these patients have been evaluated. Lai et al [51] demonstrated that allergic rhinitis (OR, 4.37; 95%CI, 1.049-18.203; *P*=.043) was a risk factor for relapse, in contrast to Villalobos-Violan et al [12]. Persistent sputum eosinophilia after treatment was demonstrated to be a risk factor for relapse by Lai et al (OR, 9.5; 95%CI, 2.4-37.8; *P*=.001) and by Zhan et al [10] (OR, 1.2; 95%CI, 1.0-1.4; *P*=.05). Park et al [52] observed a significantly higher age in patients with recurrent NAEB, as well as an increased but nonsignificant frequency of atopy (42.1% vs 20%), nasal symptoms (42.1% vs 20%), and peripheral blood eosinophilia (420 vs 258/μL). Other inflammatory parameters, such as fractional exhaled nitric oxide (FeNO), do not correlate with relapses of NAEB [12]. Treatment time is related to relapses of the disease. Zhan et al [10] demonstrated significantly more relapses in NAEB patients treated for 1 month compared to 4 months (41.9% vs 10.7%).

NAEB has been proposed as the initial stage of asthma. This disease was shown to occur during follow-up in 5%-15% of NAEB patients through the presence of asthma symptoms and a methacholine challenge result of $PC_{20}$ <16 mg/mL and/or postbronchodilator $FEV_1$ >12% in spirometry [12,35,50-52]. Puolijoki and Lahdensuo [53] found that asthma developed in 16% of patients with chronic cough after 4.4 years of follow-up. The diagnosis of NAEB was not confirmed in these patients (Table). The median time for development of asthma was over 24 months [12] and 27.5 months [51]. In order to predict development of asthma, some outcomes, such as higher baseline FeNO (124.3 vs 58.56 ppb), atopy (100% vs 50.0%), and allergic rhinitis (100% vs 50.0%) were identified as predictors of progression in affected patients [12]. Chen et al [54] demonstrated that rhinitis, FeNO, and lung function test values (spirometry or plethysmography) were related to bronchial hyperreactivity in patients with chronic cough [AUC, >0.9]. However, more extensive NAEB patient series demonstrated no significant difference in these clinical characteristics [51].

Some authors have suggested that NAEB could also be an early manifestation of chronic obstructive pulmonary disease (COPD). In 1999, Brightling et al [55] reported the case of a nonsmoking patient with NAEB who presented progressive, irreversible airflow obstruction. Since then, some publications have shown that 12%-16% of patients developed a persistent postbronchodilator $FEV_1/FVC$ <70% [35,50]. However, many patients with NAEB demonstrated no airway obstruction or a decline in lung function volume values [51]. Park et al [52] demonstrated a greater reduction in $FEV_1$ in 60% of patients with recurrent NAEB compared to 0% in patients without recurrence. The authors suggested that recurrent NAEB may be a risk factor for chronic airway obstruction.

## 4. Diagnosis and Differential Diagnosis

In all patients with chronic cough, it is important to take a full history covering smoking habits, environmental/occupational exposure, and drug treatment. In addition, a physical examination including nasopharyngoscopy should be performed, as should chest radiography, spirometry with bronchodilator reversibility, bronchoprovocation challenge, sputum cell count, and exhaled nitric oxide. A history of reflux

disease should be recorded. Other tests include sinus imaging, endoscopic or 24-hour esophageal pH, chest computed tomography, bronchoscopy, and a cardiac work-up [3].

Sputum analysis is considered the gold standard in diagnosis of NAEB, as it is the most accurate marker of airway eosinophilia [56]. Sputum analysis is a noninvasive, validated, and repeatable test, in which sputum can be collected both spontaneously or through induction [57]. An eosinophil percentage of more than 3% is indicative of eosinophilic bronchitis [56,58]. However, according to some authors, a

**Table.** Studies on the Natural History and Clinical Course of Nonasthmatic Eosinophilic Bronchitis

| | No. of patients | Patients with follow-up data | Period followed up | Recurrence of NAEB | Remission of NAEB | Development of asthma | Airway obstruction[a] |
|---|---|---|---|---|---|---|---|
| Hancox et al, 2001 [50] | 12 | 8 | Not specified. Over 6 y | NP | 8 (100%) considered sputum eosinophilia <2%, of whom 4 were asymptomatic and 4 had persistent cough due to other causes | 1 patient of the total 12 was diagnosed with asthma (8.3%), although no diagnostic tests were shown | 1 (12.5%) |
| Joo et al, 2002 [8] | 11 | 4 | 6 mo | 3 (75%) considered episodes of severe coughing and increased sputum eosinophilia >3% | 1 (25%) considered absence of sputum eosinophilia | NP | NP |
| Park et al, 2004 [52] | 36 | 24 | 2 y | 5 (20.8%) considered persistent cough and sputum eosinophilia >3% | 19 (79.2%) considered asymptomatic, although 10 (52.6%) had persistent sputum eosinophilia >3% | 1 (4.2%) with asthma symptoms and positive spirometry bronchodilator test result | NP |
| Berry et al, 2005 [14] | 52 | 32 | Mean 3.1 y | 23 (72%) patients of whom 13 (40.6%) had persistent cough and eosinophilic sputum, 7 (21.9%) had persistent unexplained cough despite no sputum eosinophilia, and 3 (9.4%) had no symptoms despite sputum eosinophilia | 1 patient (3%) considered by asymptomatic and with no sputum eosinophilia off treatment | 3 patients (9%) demonstrated by symptoms and a methacholine $PC_{20}$<8 mg/mL | 5 (16%) |
| Lai et al, 2015 [51] | 234 | 141 | Median 4.1 y | 84 (59.6%) considered as persistent cough with sputum eosinophilia (≥2.5%) | 57 (40.4%) defined as asymptomatic off treatment | 8 patients (9.5%) with asthma symptoms and BHR[b] or bronchial reversibility[c] | 0 (0%) |
| Zhan et al, 2019 [10] | 101 | 89 | 1 y | 22 (24.7%) considered as persistent cough and sputum eosinophils ≥2.5% | 67 (75%) defined as clinically asymptomatic with no treatment | NP | NP |
| Villalobos-Violan et al, 2022 [12] | 41 | 41 | Mean of 5.8 y | 13 (31.7%) considered as persistent cough | 22 (53.6%) considered asymptomatic | 6 patients (14.6%) defined as having asthma symptoms with BHR[b] or bronchial reversibility[c] | 0% |

Abbreviations: BHR, bronchial hyperresponsiveness; NAEB, nonasthmatic eosinophilic bronchitis; NP, not performed.
[a]Airway obstruction demonstrated by persistent postbronchodilation $FEV_1/FVC$ <70%.
[b]BHR was defined as $PC_{20}$<16 mg/mL in a methacholine challenge test.
[c]Bronchial reversibility was defined as postbronchodilator $FEV_1$>12% in spirometry.

cut-off of 2.5% is considered positive [2,37,51]. There is no significant difference in the level of sputum eosinophil levels between NAEB and asthma [37,42] or between NAEB and CVA [37]. The absence of eosinophilia in a sputum isolate does not rule out the presence of NAEB. DaSilva et al [59] demonstrated that a neutrophilic exacerbation can mask up to 34% of cases of NAEB [59].

FeNO has been validated as a surrogate marker of eosinophilic airway inflammation and, therefore, proposed as a biomarker of NAEB. Elevated FeNO values have been demonstrated in patients with NAEB compared with healthy adults [40], adults with nonasthmatic chronic cough [15,60], and children [61], but not in asthma patients or patients with CVA [15,60,62]. This would not be the case for other measurements of NO, such as the nasal or alveolar concentration [15], which indicates probable inflammation of the central respiratory tract but not of the nasal mucosa or the lung periphery. Yi et al [62], Zhang et al [63], and Sato et al [64] found significantly higher FeNO values in patients with asthma than in those with NAEB, in contrast to the results of other authors [15,42,65].

A meta-analysis published in 2017 found FeNO to be an adequate diagnostic biomarker, with an AUC of 0.81, a sensitivity of 72%, and a specificity of 83% [66]. Among the studies included in the meta-analysis, the cut-off value of FeNO to predict the disease ranges between 22.5 ppb [62] and 31 ppb [14], with sensitivity being similar in both studies (69.8 and 63%, respectively), although significant differences were found for specificity (76.2% and 92%) and positive predictive value (56% and 88%). Oh et al [13] found that FeNO values lower than 31.7 ppb ruled out eosinophilic bronchitis with high sensitivity and specificity (86% and 76%, respectively). However, they could not establish this as a cut-off owing to the low positive predictive value [47%]. The publication by Maniscalco et al [15] established 33 ppb as a cut-off point with a sensitivity of 92% and specificity of 88% for differentiating between CVA and NAEB and other diseases (gastroesophageal reflux and postnasal drip), without evaluating them independently. Studies about NAEB in children are scarce. Kim et al [61] reported 20 ppb as the FeNO cut-off point in the diagnosis of eosinophilic bronchitis when evaluated together with airway resistance after oscillometry. Combined rather than individual evaluation of biomarkers revealed high sensitivity (77.5% and 75%) and moderate specificity (49.6% and 46%, respectively) for a change in X5 of –20% and AX of –30%.

Measurement of FeNO has been demonstrated to be a predictor of response to inhaled corticosteroids. A good correlation between sputum eosinophilia and the FeNO value has been reported in most studies for NAEB [13-15,62], CVA [62], and asthma [67], in contrast with findings reported elsewhere [12]. The various factors that play a key role in FeNO becoming a confounding factor include demographic characteristics (sex, age, race, weight, atopy), clinical conditions (smoking habit, plant-derived food, or beverage intake), and external factors (viral or bacterial infection, corticosteroid treatment, disease exacerbation, exposure to irritants) [68]. Kim et al [61] proposed that atopy was a confounding factor responsible for increased FeNO in patients with NAEB. While some authors supported this finding [4], others rejected it, having demonstrated significantly higher values of FeNO in NAEB in both atopic and nonatopic individuals [13]. The presence of rhinitis as a confounding factor has also been rejected [62]. Wiszniewska et al [69] evaluated the role of FeNO in NAEB and concluded that an increase of more than 4 ppb after the specific bronchial challenge was a predictor of the disease with a high specificity (90%-97%). The sensitivity varied according to the times that FeNO was increased, ranging between values of 8, 14, and 17.5 ppb, which correspond to a sensitivity of 43%, 33%, and 23%, respectively. However, the isolated use of this biomarker in the diagnosis of ONAEB is limited, since it is also elevated in occupational rhinitis and asthma and may lead the frequency of the disease to be overestimated [70].

Higher levels of peripheral blood eosinophilia (PBE) were observed in NAEB patients than in healthy individuals, although levels were similar to those found in asthma patients [36,37,40,41]. In asthma, PBE has been proposed as a biomarker of eosinophilic inflammation [67,71], while in NAEB its role is controversial. Villalobos-Violan et al [12] rejected a correlation between PBE and sputum eosinophilia in 41 patients with NAEB (r=–0.17, *P*=.65), ruling out its use as a diagnostic biomarker of NAEB [12]. The usefulness of PBE in the prognosis of NAEB and disease severity has also been evaluated, with no significant findings [12,51,52].

Similarly, IgE level has not proven to be a discriminatory biomarker for NAEB, since similar values have been demonstrated in adults with NAEB, adults with asthma, and healthy controls [40,41]. These results contrast with findings in children reported by Kim et al [61], who demonstrated higher IgE levels for patients with NAEB and asthma than for healthy individuals.

Three other related conditions are also characterized by increased sputum and submucosal eosinophil count and a cough response to corticosteroids as a typical symptom, namely, classic asthma, CVA, and atopic cough. The first 2 diseases are characterized by bronchial hyperresponsiveness. Cough is the sole manifestation of CVA, and wheezing, shortness of breath, and cough are also present in classic asthma.

Atopic cough was first identified in 1992 by Fujimura et al [72]. It is considered an isolated chronic cough with an atopic background, no airway responsiveness, and, potentially, eosinophilia in sputum [73]. Both CVA and NAEB can be precursors of asthma in 20%-33% and in 4%-15% of diagnosed patients, respectively, whilst atopic cough is rare (1.2%) [74,75].

Frequent diseases causing chronic cough that should be part of the differential diagnosis include gastroesophageal reflux disease, postnasal drip syndrome or rhinosinusitis, COPD, pulmonary fibrosis, bronchiectasis, idiopathic cough, and drug-mediated cough (angiotensin-converting enzyme inhibitors). Other less frequent diseases that could cause chronic cough are cancer (bronchogenic carcinoma, alveolar cell carcinoma, benign airway tumors, mediastinal tumors), infections (tuberculosis, cystic fibrosis, sarcoidosis, tracheobronchitis, pneumonia, pertussis), cardiovascular diseases (left ventricular failure, pulmonary embolism, pulmonary infarction), and airway foreign bodies [3,5,6].

## 5. Systematic Review of Treatment

Inhaled corticosteroids (ICS) were proposed as first-line treatment in NAEB owing to their ability to suppress eosinophilic airway inflammation [3,11]. However, the choice of which ICS should be used at which dose and duration of therapy must be based on the available data [58]. Therefore, we performed a systematic review to evaluate appropriate and effective treatments for NAEB. Our findings showed the main goals of disease control to be a reduction in the presence of sputum eosinophils, a subjective and objective decrease in the severity of cough, and the absence of exacerbations. In addition to ICS, avoidance strategies, when inflammation is due to occupational exposure or inhaled allergens, are also considered a concomitant first-line treatment. Randomized controlled studies on treatment of NAEB are scarce.

### *5.1. Objective*

A structured literature review was carried out to identify and synthesize relevant published information on treatment of eosinophilic bronchitis.

### *5.2. Material and Methods*

This systematic review follows the recommendations of the PRISMA guidelines. The search protocol was registered in the international prospective register of systematic reviews, PROSPERO (CRD42023485302). The initial review was completed on October 2, 2023.

#### 5.2.1. Eligibility Criteria

Articles were selected from systematic reviews with or without meta-analyses, randomized controlled trials, post hoc studies of randomized controlled trials, original studies, observational or interventional studies, case reports, and guidelines on the management and treatment of NAEB and nonasthmatic chronic cough. Narrative reviews were excluded. Studies about eosinophilic bronchitis in asthma were excluded.

#### 5.2.2. Search Strategy

The search was carried out in the PubMed database for English language studies published between 1967 and 2023 with the keywords:

((("Eosinophils" [MeSH] AND "Bronchitis" [MeSH]) OR "Eosinophilic Bronchitis"[tw] OR "Eosinophilic Bronchitis"[tiab:~3]) AND (Therapy/Broad[filter]).

#### 5.2.3. Study Selection and Data Collection

The results were screened by 2 independent reviewers. Following the predefined inclusion and exclusion criteria, publications were first selected based on the title/abstract followed by a full-text reading. Data on study design, patient characteristics, main outcomes, and additional findings were extracted from the studies and uploaded by one of the reviewers to a standardized Microsoft Excel template, which was then double-checked and validated by the second reviewer.

#### 5.2.4. Methodological Quality Assessment

We performed a quality assessment of the selected studies using the Critical Appraisal Skills Programme checklists (https://casp-uk.net/casp-tools-checklists/). The quality of evidence of all included studies was evaluated to determine risk of bias. The articles were classified as low-, moderate-, or high-quality evidence according to the type of study/design methodology, outcomes, and results See results in Supplementary material.

## 6. Results

A total of 209 studies were retrieved using the search strategies. Of these, 46 were excluded because they did not evaluate NAEB or chronic cough and 139 because they did not evaluate treatments or interventions after a full-text reading. Out of the 24 papers selected for inclusion, 4 were excluded because they were not in English. A PRISMA diagram showing a detailed workflow of the screening process is presented in the Figure. A total of 7 studies on nonasthmatic chronic cough (3 randomized controlled trials and 4 meta-analyses) and 13 on NAEB (4 randomized controlled trials and 9 prospective/retrospective studies) were included.

Overall, the methodological quality of the studies was poor. Studies including patients with multiple causes of chronic cough in which NAEB is not evaluated in isolation limit the real applicability of the intervention to the disease. The validity of comparisons between studies was limited by the significant heterogeneity resulting from interventions such as doses and type of treatment, variable follow-up time, and variations in outcome measures.

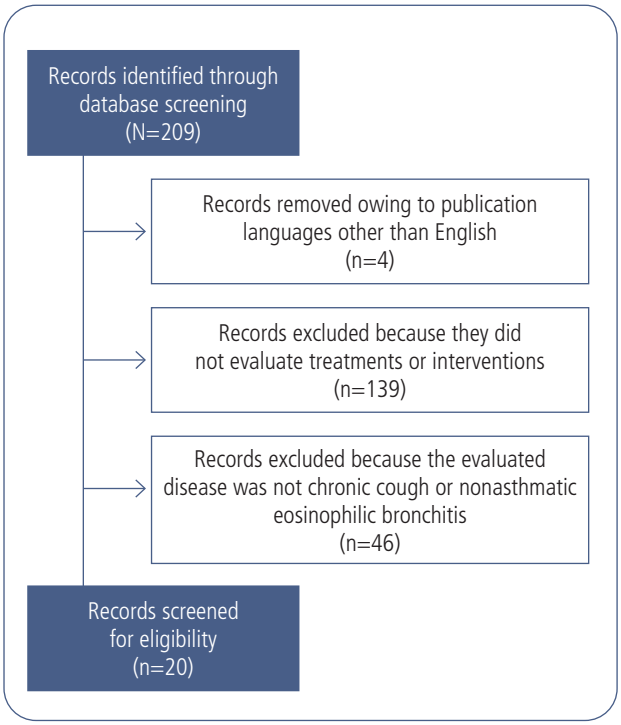


**Figure.** PRISMA diagram showing the workflow of the screening process.

### 6.1. Nonasthmatic Chronic Cough

Two placebo-control longitudinal studies demonstrated an improvement in 88 patients [76] and 44 patients [77] with nonasthmatic chronic cough after 14 days of inhaled corticosteroids (fluticasone 1000 μg/d or beclomethasone 1500 μg/d, respectively) measured based on the symptom diary and visual analog scale (VAS) and the decrease in sputum ECP and FeNO. Three meta-analyses demonstrated an improvement in unspecific subacute/chronic cough after inhaled corticosteroids, 2 in adults (8 studies each) [78,79] and 1 in children (2 articles) [80]. The absence of improvement in cough after bronchodilatation was demonstrated in another meta-analysis [81]. In adults, the mean decrease (standard deviations lower) in the cough score following treatment with ICS compared to placebo was shown to be –0.34 (95%CI, –0.56 to –0.13) by Johnstone et al [78] and –0.38 (95%CI, −0.54 to −0.23) by Lee et al [79], although the quality of the evidence was medium-low. A significant decrease in sputum eosinophils was demonstrated in one of the 3 and 4 studies included in the meta-analysis by Johnstone et al and Lee et al, respectively. However, in all the previous studies, various illnesses causing chronic cough were included, and NAEB was not evaluated in isolation; therefore, extrapolation of the results is limited. Discrepancies in the results were observed for children [80]. While one study demonstrated similar cough frequency following treatment with ICS and with placebo for 4-5 weeks, the other demonstrated an improvement after 15 days' therapy with ICS compared to placebo (OR, 0.28; 95%CI, 0.09-0.92; *P*=.04). As only 2 studies were evaluated in the meta-analysis by Tomerak et al [81] and the results were contradictory, a precise conclusion cannot be drawn. ICS have led to a decrease in sputum eosinophilia in respiratory illnesses other than asthma and NAEB. In one clinical trial, beclomethasone dipropionate 400 μg/d demonstrated a significant improvement in sputum production and sputum eosinophilia in 42 patients diagnosed with eosinophilic bronchitis in silicosis [82].

### 6.2. NAEB

In 1995, Gibson et al [83] demonstrated the usefulness of ICS in NAEB. The authors showed a significant decrease in sputum eosinophilia in 9 patients with NAEB after 1 week of beclomethasone 400 μg twice daily. In their 2000 study of 11 patients with NAEB, Brightling et al [11] found a significant reduction in sputum eosinophilia and the cough VAS score and an increase in cough hypersensitivity based on higher capsaicin sensitivity after budesonide 400 μg once per day for 4 weeks [11]. A significant positive correlation was proven between the change in cough sensitivity induced by treatment and the sputum eosinophil count.

An open-label study of 101 patients treated with budesonide 200 μg twice daily for 1, 2, and 4 months demonstrated a decrease in sputum eosinophilia and an improvement in clinical cough VAS score and the cough symptom score in all groups, with no differences between them [10].

Clinical improvement in cough after ICS treatment was demonstrated in 40.4% of patients by Lai et al [51], 63% by Berry et al [14] measured by VAS, and 75% by Park et al [52], in contrast with the 100% reported by Brightling et al [9]. The first group was treated with oral prednisone 10-15 mg/d for 3 days and budesonide 400 μg/d for at least 4 weeks [51], the second with budesonide 200-400 μg twice daily for a mean of 3.1 years (range, 1-6 years) [14], the third with budesonide or fluticasone 800 μg/d for 2 months [52], and the fourth with budesonide 400 μg twice daily for 6-8 weeks [9]. The impact of the duration of treatment remains unclear.

Recurrences of the disease and incomplete response in some cases [8,12,14,52] highlight the need for other options in patients who are resistant to first-line treatment. In the 2020 CHEST Guideline for chronic cough due to asthma or NAEB, stepping up the dose of ICS and oral corticosteroids and considering a therapeutic trial of a leukotriene inhibitor is suggested as second-line treatment in NAEB patients with incomplete control after ICS [84]. A randomized controlled study compared increased ICS doses with budesonide 400 μg twice daily and budesonide 200 μg twice daily with addition of montelukast 10 mg/d for 4 weeks in 26 NAEB patients and found a similar improvement in the cough VAS and sputum eosinophilia [85]. Another open-label randomized study of 55 patients comparing budesonide 200 μg twice daily with and without montelukast 10 mg/d for 4 weeks supported previous results and added a significantly higher decline in the VAS score and quality of life scores, as well as in eosinophils and sputum ECP in patients also treated with montelukast [86].

Antihistamines improved capsaicin cough sensitivity in 8 of 11 patients with NAEB and upper airway disease [87]. However, this treatment was not able to significantly decrease sputum eosinophilia. The H1 antagonist epinastine at 20 mg significantly improved cough scores and capsaicin cough sensitivity in 10 patients with clinical NAEB [88]. Nevertheless, sputum was not assessed for diagnosis or follow-up. The actual usefulness of antihistamines in isolated NAEB remains doubtful. Other treatments, such as intranasal polymyxin B, demonstrated a decrease in BAL eosinophilia and an increase in capsaicin hypersensitivity in guinea pigs with NAEB. No data were available from humans [89]. Other treatments, such as inhaled lidocaine, were evaluated in randomized clinical trials with NAEB patients several years ago, although the results were poor [90].

## 7. Discussion

The quality of the studies evaluated in this systematic review of treatment of NAEB was medium-low, with high heterogeneity in selection criteria, interventions, and outcome measures. ICS were shown to be efficacious in chronic cough and NAEB, generally through a significant decrease in symptoms and sputum eosinophilia. However, more studies are needed to compare corticosteroids, doses, and treatment periods. Adding oral corticosteroids and antileukotrienes to inhaled treatment has also proven an effective strategy in NAEB. Both the adverse effects of this approach and the potential benefits of each option in monotherapy have yet to be assessed. The efficacy of other treatments, such as antihistamines, intranasal polymyxin B, and inhaled lidocaine, was not successfully demonstrated.

Although beyond the scope of this systematic review, we highlight that a meta-analysis performed in 2014 showed a

significant decrease in sputum eosinophilia and eosinophil mediators with oral prednisone in asthma patients. The authors reported a mean 6-, 5-, and 4-fold reduction in the number of sputum eosinophils, IL-5, and ECP, respectively, after treatment [91]. However, high heterogeneity in dose and duration of treatment with oral prednisone was observed between the studies. Other oral corticosteroids also led to a significant decrease in sputum eosinophilia in animals [92] and in humans [93]. Biological treatments that target IL-5, such as mepolizumab and benralizumab, have demonstrated, both in randomized placebo-controlled trials and in real-life studies, markedly suppressed sputum eosinophilia and PBE both in asthma and in COPD [94-99], together with other eosinophilic diseases such as hypereosinophilic syndrome and eosinophilic granulomatosis and polyangiitis [100]. Unfortunately, none of these studies was performed only in NAEB patients.

## 8. Conclusions

NAEB is a chronic inflammatory disease in which eosinophilic airway infiltration predominates. The presence of different types of inflammatory cells and their location might result in the differences in mechanisms between NAEB and asthma. Assessing the presence of rhinitis and atopy and higher FeNO value is helpful in identifying patients at risk of asthma progression. Sputum eosinophilia should be evaluated before and after treatment to predict relapses. Corticosteroids and antileukotrienes are effective treatments for the disease. The effect of other therapies, such as anti–IL-5 biologics, should be assessed. Studies with large patient populations, more extended follow-up periods, and complete studies, including sputum assessment, are required to evaluate the prognosis and the clinical course of the disease. Placebo-controlled studies are necessary to generate scientific evidence and thus ensure accurate treatment.

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### *Conflicts of Interest*

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## References

1. Glynn AA, Michaels L. Bronchial biopsy in chronic bronchitis and asthma. Tip Fak Mecmuasi. 1960;23:142-53.
2. Gibson PG, Dolovich J, Denburg J, Ramsdale EH, Hargreave FE. Chronic cough: eosinophilic bronchitis without asthma. Lancet Lond Engl. 1989;17;1(8651):1346-8.
3. Irwin RS, French CL, Chang AB, Altman KW, CHEST Expert Cough Panel*. Classification of Cough as a Symptom in Adults and Management Algorithms: CHEST Guideline and Expert Panel Report. Chest. 2018;153(1):196-209.
4. Wei W, Yu L, Lu H, Wang L, Shi C, Ma W, et al. Comparison of cause distribution between elderly and non-elderly patients with chronic cough. Respir Int Rev Thorac Dis. 2009;77(3):259-64.
5. Lai K, Chen R, Lin J, Huang K, Shen H, Kong L, et al. A prospective, multicenter survey on causes of chronic cough in China. Chest. 2013;143(3):613-20.
6. Carney IK, Gibson PG, Murree-Allen K, Saltos N, Olson LG, Hensley MJ. A systematic evaluation of mechanisms in chronic cough. Am J Respir Crit Care Med. 1997;156(1):211-6.
7. Lai K, Chen R, Peng W, Zhan W. Non-asthmatic eosinophilic bronchitis and its relationship with asthma. Pulm Pharmacol Ther. 2017;47:66-71.
8. Joo JH, Park SJ, Park SW, Lee JH, Kim DJ, Uh ST, et al. Clinical features of eosinophilic bronchitis. Korean J Intern Med. 2002;17(1):31-7.
9. 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(2):406-10.
10. Zhan W, Tang J, Chen X, Yi F, Han L, Liu B, et al. Duration of treatment with inhaled corticosteroids in nonasthmatic eosinophilic bronchitis: a randomized open label trial. Ther Adv Respir Dis. 2019;13:1753466619891520.
11. 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(4):682-6.
12. Villalobos-Violan V, Betancor D, Mahíllo-Fernández I, Sastre J. Nonasthmatic Eosinophilic Bronchitis and Asthma: Analysis of Biomarkers. J Investig Allergol Clin Immunol. 2022;20;32(3):216-7.
13. Oh MJ, Lee JY, Lee BJ, Choi DC. Exhaled nitric oxide measurement is useful for the exclusion of nonasthmatic eosinophilic bronchitis in patients with chronic cough. Chest. 2008;134(5):990-5.
14. 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 J. 2005;35(5):598-601.
15. 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(8):970-4.
16. Park SW, Park JS, Lee YM, Lee JH, Jang AS, Kim DJ, et al. Differences in radiological/HRCT findings in eosinophilic bronchitis and asthma: implication for bronchial responsiveness. Thorax. 2006;61(1):41-7.
17. Quirce S. Eosinophilic bronchitis in the workplace. Curr Opin Allergy Clin Immunol. 2004;4(2):87-91.
18. Pala G, Pignatti P, Perfetti L, Caminati M, Gentile E, Moscato G. Usefulness of basophil activation test in diagnosis of

occupational nonasthmatic eosinophilic bronchitis. Allergy. 2010;65(7):927-9.
19. Ogawa H, Fujimura M, Amaike S, Nishiura Y, Nakagawa-Yoshida K, Suga M, et al. Seasonal chronic cough with sputum eosinophilia caused by Trichosporon cutaneum (Trichosporon asahii). Int Arch Allergy Immunol. 1998;116(2):162-5.
20. Ogawa H, Fujimura M, Heki U, Kitagawa M, Matsuda T. Eosinophilic bronchitis presenting with only severe dry cough due to bucillamine. Respir Med. 1995;89(3):219-21.
21. Butler B, Rubio C, Ie S, Loschner A. Chronic cough and drug-induced eosinophilic bronchitis. Intern Med J. 2022;52(1):150-1.
22. Lemière C, Efthimiadis A, Hargreave FE. Occupational eosinophilic bronchitis without asthma: an unknown occupational airway disease. J Allergy Clin Immunol. 1997;100(6 Pt 1):852-3.
23. Quirce S, Fernández-Nieto M, de Miguel J, Sastre J. Chronic cough due to latex-induced eosinophilic bronchitis. J Allergy Clin Immunol. 2001;108(1):143.
24. Di Stefano F, Di Giampaolo L, Verna N, Di Gioacchino M. Occupational eosinophilic bronchitis in a foundry worker exposed to isocyanate and a baker exposed to flour. Thorax. 2007;62(4):368-70.
25. Escudero C, Quirce S, Fernández-Nieto M, Miguel J, Cuesta J, Sastre J. Egg white proteins as inhalant allergens associated with baker's asthma. Allergy. 2003;58(7):616-20.
26. Tanaka H, Saikai T, Sugawara H, Takeya I, Tsunematsu K, Matsuura A, et al. Workplace-related chronic cough on a mushroom farm. Chest. 2002;122(3):1080-5.
27. Quirce S, Baeza ML, Tornero P, Blasco A, Barranco R, Sastre J. Occupational asthma caused by exposure to cyanoacrylate. Allergy. 2001;56(5):446-9.
28. Kobayashi O. [A case of eosinophilic bronchitis due to epoxy resin system hardener, methle endo methylene tetrahydro phthalic anhydride]. Arerugi Allergy. 1994;43(5):660-2.
29. Wiggans RE, Barber CM. Metalworking fluids: a new cause of occupational non-asthmatic eosinophilic bronchitis. Thorax. 2017;72(6):579-80.
30. Krakowiak AM, Dudek W, Ruta U, Palczynski C. Occupational eosinophilic bronchitis without asthma due to chloramine exposure. Occup Med Oxf Engl. 2005;55(5):396-8.
31. Yacoub MR, Malo JL, Labrecque M, Cartier A, Lemière C. Occupational eosinophilic bronchitis. Allergy. 2005;60(12):1542-4.
32. Arochena L, Fernández-Nieto M, Aguado E, García del Potro M, Sastre J. Eosinophilic bronchitis caused by styrene. J Investig Allergol Clin Immunol. 2014;24(1):68-9.
33. Tarlo SM. Lessons from Occupational Eosinophilic Bronchitis. J Allergy Clin Immunol Pract. 2021;9(2):945-6.
34. Tarlo SM, Altman KW, Oppenheimer J, Lim K, Vertigan A, Prezant D, et al. Occupational and Environmental Contributions to Chronic Cough in Adults: Chest Expert Panel Report. Chest. 2016;150(4):894-907.
35. 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(5):1106-9.
36. Park SW, Jangm HK, An MH, Min JW, Jang AS, Lee JH, et al. Interleukin-13 and interleukin-5 in induced sputum of eosinophilic bronchitis: comparison with asthma. Chest. 2005;128(4):1921-7.
37. Zhang Q, Luo W, Zhan W, Xie J, Wang H, Chung KF, et al. Non-asthmatic eosinophilic bronchitis is characterized by proximal airway eosinophilic inflammation as compared with classic asthma and cough variant asthma. Clin Exp Allergy. 2021;51(12):1637-40.
38. 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 30;346(22):1699-705.
39. Siddiqui S, Sutcliffe A, Shikotra A, Woodman L, Doe C, McKenna S, et al. Vascular remodeling is a feature of asthma and nonasthmatic eosinophilic bronchitis. J Allergy Clin Immunol. 2007;120(4):813-9.
40. Zhan C, Xu R, Li B, Liu J, Liang W, Zhang S, et al. Eosinophil Progenitors in Patients With Non-Asthmatic Eosinophilic Bronchitis, Eosinophilic Asthma, and Normal Controls. Front Immunol. 2022;13:737968.
41. Sastre B, Fernández-Nieto M, Mollá R, López E, Lahoz C, Sastre J, et al. Increased prostaglandin E2 levels in the airway of patients with eosinophilic bronchitis. Allergy. 2008;63(1):58-66.
42. Brightling CE, Symon FA, Birring SS, Bradding P, Wardlaw AJ, Pavord ID. Comparison of airway immunopathology of eosinophilic bronchitis and asthma. Thorax. 2003;58(6):528-32.
43. 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(3 Pt 1):878-82.
44. Brightling CE. Cough due to asthma and nonasthmatic eosinophilic bronchitis. Lung. 2010;188 Suppl 1:S13-17.
45. Gibson PG, Zlatic K, Scott J, Sewell W, Woolley K, Saltos 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(3):320-6.
46. Woodman L, Sutcliffe A, Kaur D, Berry M, Bradding P, Pavord ID, et al. Chemokine concentrations and mast cell chemotactic activity in BAL fluid in patients with eosinophilic bronchitis and asthma, and in normal control subjects. Chest. 2006;130(2):371-8.
47. Siddiqui S, Cruse G, McKenna S, Monteiro W, Mistry V, Wardlaw A, et al. IL-13 expression by blood T cells and not eosinophils is increased in asthma compared to non-asthmatic eosinophilic bronchitis. BMC Pulm Med. 2009;14;9:34.
48. Birring SS, Parker D, Brightling CE, Bradding P, Wardlaw AJ, Pavord ID. Induced sputum inflammatory mediator concentrations in chronic cough. Am J Respir Crit Care Med. 2004;1;169(1):15-9.
49. Sastre B, del Pozo V. Role of PGE2 in Asthma and Nonasthmatic Eosinophilic Bronchitis. Mediators Inflamm. 2012;2012:645383.
50. Hancox RJ, Leigh R, Kelly MM, Hargreave FE. Eosinophilic bronchitis. Lancet Lond Engl. 2001;29;358(9287):1104.
51. 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(4):887-94.
52. 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(6):1998-2004.
53. Puolijoki H, Lahdensuo A. Chronic cough as a risk indicator of broncho-pulmonary disease. Eur J Respir Dis. 1987;71(2):77-85.
54. Chen L, Wu L, Lu D, Zi M, Yu H. The Value of Fractional Exhaled Nitric Oxide and Impulse Oscillometric and Spirometric Parameters for Predicting Bronchial Hyperresponsiveness in Adults with Chronic Cough. J Asthma Allergy. 2021;14:1065-73.
55. Brightling CE, Woltmann G, Wardlaw AJ, Pavord ID. Development of irreversible airflow obstruction in a patient with eosinophilic bronchitis without asthma. Eur Respir J. 1999;14(5):1228-30.
56. 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(2 Pt 1):475-8.
57. Bhowmik A, Seemungal T, Sapsford R, Devalia J, Wedzicha J. Comparison of spontaneous and induced sputum for investigation of airway inflammation in chronic obstructive pulmonary disease. Thorax. 1998;53(11):953-6.
58. Brightling CE. Chronic cough due to nonasthmatic eosinophilic bronchitis: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):116S-121S.
59. D'silva L, Allen CJ, Hargreave FE, Parameswaran K. Sputum neutrophilia can mask eosinophilic bronchitis during exacerbations. Can Respir J. 2007;14(5):281-4.
60. Liu X, Wang X, Yao X, Wang Y, Sun Y, Zhang L. Value of Exhaled Nitric Oxide and FEF25-75 in Identifying Factors Associated With Chronic Cough in Allergic Rhinitis. Allergy Asthma Immunol Res. 2019;11(6):830-45.
61. Kim YH, Kim KW, Baek J, Park HB, Kim H, Song KJ, et al. Usefulness of impulse oscillometry and fractional exhaled nitric oxide in children with Eosinophilic bronchitis. Pediatr Pulmonol. 2013;48(3):221-8.
62. 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(4):1042-51.
63. Zhang YM, Lin JT, Su N, Chen X, Liu GL, Yu HX, et al. [Values of fractional exhaled nitric oxide in the diagnosis of chronic cough]. Zhonghua Yi Xue Za Zhi. 2011;17;91(18):1254-8.
64. Sato S, Saito J, Sato Y, Ishii T, Xintao W, Tanino Y, et al. Clinical usefulness of fractional exhaled nitric oxide for diagnosing prolonged cough. Respir Med. 2008;102(10):1452-9.
65. Berlyne GS, Parameswaran K, Kamada D, Efthimiadis A, Hargreave FE. A comparison of exhaled nitric oxide and induced sputum as markers of airway inflammation. J Allergy Clin Immunol. 2000;106(4):638-44.
66. Song WJ, Kim HJ, Shim JS, Won HK, Kang SY, Sohn KH, et al. Diagnostic accuracy of fractional exhaled nitric oxide measurement in predicting cough-variant asthma and eosinophilic bronchitis in adults with chronic cough: A systematic review and meta-analysis. J Allergy Clin Immunol. 2017;140(3):701-9.
67. Wagener AH, de Nijs SB, Lutter R, Sousa AR, Weersink EJM, Bel EH, et al. External validation of blood eosinophils, FE(NO) and serum periostin as surrogates for sputum eosinophils in asthma. Thorax. 2015;70(2):115-20.
68. Matsunaga K, Kuwahira I, Hanaoka M, Saito J, Tsuburai T, Fukunaga K, et al. An official JRS statement: The principles of fractional exhaled nitric oxide (FeNO) measurement and interpretation of the results in clinical practice. Respir Investig. 2021;59(1):34-52.
69. Wiszniewska M, Dellis P, van Kampen V, Suojalehto H, Munoz X, Walusiak-Skorupa J, et al. Characterization of Occupational Eosinophilic Bronchitis in a Multicenter Cohort of Subjects with Work-Related Asthma Symptoms. J Allergy Clin Immunol Pract. 2021;9(2):937-44.e4.
70. Vandenplas O, Godet J, Hurdubaea L, Rifflart C, Suojalehto H, Wiszniewska M, et al. Are high- and low-molecular-weight sensitizing agents associated with different clinical phenotypes of occupational asthma? Allergy. 2019;74(2):261-72.
71. Korevaar DA, Westerhof GA, Wang J, Cohen JF, Spijker R, Sterk PJ, et al. Diagnostic accuracy of minimally invasive markers for detection of airway eosinophilia in asthma: a systematic review and meta-analysis. Lancet Respir Med. 2015;3(4):290-300.
72. Fujimura M, Sakamoto S, Matsuda T. Bronchodilator-resistive cough in atopic patients: bronchial reversibility and hyperresponsiveness. Intern Med Tokyo Jpn. 1992;31(4):447-52.
73. Fujimura M, Songür N, Kamio Y, Matsuda T. Detection of eosinophils in hypertonic saline-induced sputum in patients with chronic nonproductive cough. J Asthma Off J Assoc Care Asthma. 1997;34(2):119-26.
74. Fujimura M, Ogawa H, Nishizawa Y, Nishi K. Comparison of atopic cough with cough variant asthma: is atopic cough a precursor of asthma? Thorax. 2003;58(1):14-8.
75. Fujimura M, Nishizawa Y, Nishitsuji M, Nomura S, Abo M, Ogawa H. Predictors for typical asthma onset from cough variant asthma. J Asthma Off J Assoc Care Asthma. 2005;42(2):107-11.
76. Chaudhuri R, McMahon AD, Thomson LJ, MacLeod KJ, McSharry CP, Livingston E, et al. Effect of inhaled corticosteroids on symptom severity and sputum mediator levels in chronic persistent cough. J Allergy Clin Immunol. 2004;113(6):1063-70.
77. Ribeiro M, Pereira CA de C, Nery LE, Beppu OS, Silva COS. High-dose inhaled beclomethasone treatment in patients with chronic cough: a randomized placNAEBo-controlled study. Ann Allergy Asthma Immunol. 2007;99(1):61-8.
78. Johnstone KJ, Chang AB, Fong KM, Bowman RV, Yang IA. Inhaled corticosteroids for subacute and chronic cough in adults. Cochrane Database Syst Rev. 2013;28;2013(3):CD009305.
79. Lee SE, Lee JH, Kim HJ, Lee BJ, Cho SH, Price D, et al. Inhaled Corticosteroids and PlacNAEBo Treatment Effects in Adult Patients With Cough: A Systematic Review and Meta-analysis. Allergy Asthma Immunol Res. 2019;11(6):856-70.
80. Tomerak AAT, McGlashan JJM, Vyas HHV, McKean MC. Inhaled corticosteroids for non-specific chronic cough in children. Cochrane Database Syst Rev. 2005;19;2005(4):CD004231.
81. Tomerak AAT, Vyas H, Lakenpaul M, McGlashan JJM, McKean M. Inhaled beta2-agonists for treating non-specific chronic cough in children. Cochrane Database Syst Rev. 2005;20;2005(3):CD005373.
82. Bando T, Fujimura M, Shinagawa S, Mizuhashi K, Noda Y, Ohta G, et al. Effect of beclomethasone dipropionate inhalation on eosinophilic bronchitis in patients with silicosis. Arzneimittelforschung. 1997;47(12):1370-4.

83. 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(2):127-32.
84. Côté A, Russell RJ, Boulet LP, Gibson PG, Lai K, Irwin RS, et al. Managing Chronic Cough Due to Asthma and NANAEB in Adults and Adolescents: CHEST Guideline and Expert Panel Report. Chest. 2020;158(1):68-96.
85. Cai C, He M-Z, Zhong S-Q, Tang Y, Sun B-Q, Chen Q-L et al. Add-on montelukast vs double-dose budesonide in nonasthmatic eosinophilic bronchitis: a pilot study. Respir Med. 2012;106(10):1369-75.
86. 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;5;128(1):39-45.
87. Yu L, Wei W, Wang L, Huang Y, Shi C, Lü H, et al. Upper-airway cough syndrome with latent eosinophilic bronchitis. Lung. 2010;188(1):71-6.
88. Shioya T, Satake M, Kagaya M, Sano M, Watanabe A, Fukui S, et al. Antitussive effects of the H1-receptor antagonist epinastine in patients with atopic cough (eosinophilic bronchitis). Arzneimittelforschung. 2004;54(4):207-12.
89. Ogawa H, Fujimura M, Saito M, Matsuda T, Akao N, Kondo K. The effect of the neurokinin antagonist FK-224 on the cough response to inhaled capsaicin in a new model of guinea-pig eosinophilic bronchitis induced by intranasal polymyxin B. Clin Auton Res. 1994;4(1-2):19-28.
90. Duong M, Wilson AM, Jayaram L, Dolovich M, Hargreave F. The effect of inhaled lidocaine-hydrofluoroalkane 134a in prednisone-dependent eosinophilic bronchitis. Eur Respir J. 2008;32(4):1119-22.
91. Sakae TM, Maurici R, Trevisol DJ, Pizzichini MMM, Pizzichini E. Effects of prednisone on eosinophilic bronchitis in asthma: a systematic review and meta-analysis. J Bras Pneumol. 2014;40(5):552-63.
92. Chen L, Li C, Peng M, Xie J, Lai K, Zhong N. Establishment of a mouse model with all four clinical features of eosinophilic bronchitis. Sci Rep. 2020;29;10(1):10557.
93. ten Brinke A, Zwinderman AH, Sterk PJ, Rabe KF, Bel EH. 'Refractory' eosinophilic airway inflammation in severe asthma: effect of parenteral corticosteroids. Am J Respir Crit Care Med. 2004;15;170(6):601-5.
94. Dasgupta A, Kjarsgaard M, Capaldi D, Radford K, Aleman F, Boylan C, et al. A pilot randomised clinical trial of mepolizumab in COPD with eosinophilic bronchitis. Eur Respir J. 2017;49(3):1602486.
95. Brightling CE, Bleecker ER, Panettieri RA, Bafadhel M, She D, Ward CK, et al. Benralizumab for chronic obstructive pulmonary disease and sputum eosinophilia: a randomised, double-blind, placNAEBo-controlled, phase 2a study. Lancet Respir Med. 2014;2(11):891-901.
96. Nagase H, Suzukawa M, Oishi K, Matsunaga K. Biologics for severe asthma: The real-world evidence, effectiveness of switching, and prediction factors for the efficacy. Allergol Int. 2023;72(1):11-23.
97. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. 2014;25;371(13):1198-207.
98. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet Lond Engl. 2012;18;380(9842):651-9.
99. FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet Lond Engl. 2016; 29;388(10056):2128-41.
100. Nolasco S, Portacci A, Campisi R, Buonamico E, Pelaia C, Benfante A, et al. Effectiveness and safety of anti-IL-5/Rα biologics in eosinophilic granulomatosis with polyangiitis: a two-year multicenter observational study. Front Immunol. 2023;14:1204444.
101. Kwon NH, Oh MJ, Min TH, Lee BJ, Choi DC. Causes and clinical features of subacute cough. Chest. 2006;129(5):1142-7.
102. Yu L, Qiu ZH, Wei WL, Liu B, Xu XH, Lü HJ, et al. Discrepancy between presumptive and definite causes of chronic cough. Chin Med J (Engl). 2011;124(24):4138-43.
103. Ayik SO, Başoğlu OK, Erdínç M, Bor S, Veral A, Bílgen C. Eosinophilic bronchitis as a cause of chronic cough. Respir Med. 2003;97(6):695-701.
104. Dąbrowska M, Grabczak EM, Arcimowicz M, Domeracka-Kołodziej A, Domagała-Kulawik J, Krenke R, et al. Chronic cough - assessment of treatment efficacy based on two questionnaires. Arch Med Sci AMS. 2014;27;10(5):962-9.
105. Dąbrowska M, Grabczak EM, Arcimowicz M, Domeracka-Kołodziej A, Domagała-Kulawik J, Krenke R, et al. Causes of Chronic Cough in Non-smoking Patients. Adv Exp Med Biol. 2015;873:25-33.
106. Ribeiro M, De Castro Pereira CA, Nery LE, Beppu OS, Silva COS. A prospective longitudinal study of clinical characteristics, laboratory findings, diagnostic spectrum and outcomes of specific therapy in adult patients with chronic cough in a general respiratory clinic. Int J Clin Pract. 2006;60(7):799-805.

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