

Non-asthmatic eosinophilic bronchitis review. A systematic review of current treatment options

Brief running title: review on non-asthmatic eosinophilic bronchitis

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ABSTRACT

Non-asthmatic eosinophilic bronchitis is characterized by persistent dry or less 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, but its etiology and underlying mechanisms are uncertain. Some features were similar to those of asthma, such as airway eosinophilia, level of inflammatory mediators and airway remodeling.

Nevertheless, there are differences in airway pathophysiology, such as the location of airway inflammation and levels of IL-13 and PGE-2. 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 has been done. Although inhaled corticosteroids are the primary treatment, the accurate dose, the kind of corticosteroid, and the treatment time remain unknown. Treatment duration is inversely correlated with relapse rate. Increased doses of inhaled corticosteroids, oral corticosteroids and leukotriene receptor antagonists are recommended in perseverance disease. Anti IL-5 biologic could be promising in this disease. There is a requirement for studies that investigate biomarkers for diagnosis and prognosis and randomized controlled studies for second-line treatments.

Key words: Eosinophilic bronchitis. Non-asthmatic 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. Es generalmente 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 aérea, 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-IL5 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. Espudo. Tos crónica.

INTRODUCTION

Non-asthmatic eosinophilic bronchitis consists on airway eosinophilia without bronchial hyperreactivity. It is a chronic disease in which relapses and progression are common. Although ethio-pathogenesis, diagnostic and pronostic biomarkers and adequate interventions remain largely unknown there has been important advances in our understanding of this entity. The first part of this manuscript encompass a narrative review of its pathogenesis, epidemiology and diagnosis. On the second part of the manuscript a systematic review of the treatment options is presented

ETIOLOGY AND PATHOGENESIS

In 1960, Glynn et al. observed the presence of eosinophils in the airway mucosa of five non-smoking patients with chronic bronchitis [1]. However, the diagnosis was made with symptoms of chronic cough, but lung function or bronchial hyperresponsiveness was not evaluated. In 1989, Gibson et al. demonstrated higher levels of sputum eosinophilia in seven non-smoker patients presenting with chronic cough, in which asthma was ruled out [2]. Then, they described eosinophilic bronchitis for the first time and later named as non-asthmatic eosinophilic bronchitis (NAEB). It is manifested by a 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 little productive cough lasting more than 8 weeks [3,4]. Although its prevalence is unknown, it has been estimated that it affects 5-30% of patients with chronic cough [5-7]. See table S1 in supplementary.

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

Exposure to common inhalants and occupational sensitizers has been proposed as a possible cause of the disease, but its etiology and mechanisms are unknown [17]. Cases of NAEB have been published secondary to dust mites [18] and fungus [19] exposure and after drug- intake as bucillamine [20] and leflunomide [21]. Exposure to dust mites has been demonstrated to be present in about 44% of patients with NAEB, with uncertain clinical implications [14].

In 1997, Lemiére et al. published a workplace acrylates-exposure NAEB in a female patient who presented with cough at work. Increased sputum eosinophilia was demonstrated during work time (0 to 13%) and at specific inhalation challenge test (0 to 5.8%) with no bronchial hyperresponsiveness [22]. Since then, occupational non-asthmatic eosinophilic bronchitis (ONAEB) has been diagnosed after exposure to great 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]. In ONAEB, isolated cough is present in about 20% of the patients. Thus, the presence of other respiratory symptoms is frequent [33]. The possible progression of this entity to occupational asthma remains unknown [34].

NAEB shares immunopathologic features with asthma, such as increased eosinophilia in sputum, and in bronchial epithelium and submucosa [35-38], basement membrane and lamina reticularis thickening and vascular remodeling and proliferation [37-39], levels of eosinophil progenitor cells and CD34+ derived hematopoietic progenitor cells in blood and sputum [40] and similar cytokines and proinflammatory mediators concentration levels in sputum as interleukine (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 two diseases, according to some authors [42,45] but not by others [37]. The explanation for this difference remains unknown. The presence of some radiological findings, such as bronchiectasis, emphysema and air trapping, were similar in both diseases [16].

However, there are also differences in airway pathophysiology. Firstly, in NAEB, the degree of airway inflammation gradually decreases from the main bronchus to the peripheral airway. There is an increase in mast cells infiltration in the central airway

compared to asthma and cough variant asthma (CVA) [37], which implies an increased concentration of these cells in bronchial brushing [45]. At the same time, it decreases in peripheral airway and the airway smooth muscles [37,38]. The quantity of mast cell in smooth muscle airway is inversely correlated with airway hyperresponsiveness, which can explain the differences between the diseases [38]. Levels of chemokines CXCL8 and CXCL10 involved in mast cell recruitment to the superficial airway are increased in bronchoalveolar lavage (BAL) and bronchial wash of NAEB compared to asthma [46]. One possible explanation is that the inflammatory cell infiltration in NAEB is more localized to the epithelium and bronchial mucosa so 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, significantly higher levels in bronchial biopsies of the central airway [37] compared to no difference in peripheral airway with respect to asthma, CVA and healthy controls [38]. The thickness of the basement membrane has been related to eosinophilic inflammation [37]. Those findings contrast with Park et al. observations [16] that demonstrated using HRCT (high resolution computed tomography) that the thickness of the large airway is normal in NAEB, similar to healthy individuals, but not of the small airways. They suggested that a thickening of the large airway walls in asthma that may contribute to AHR (airway hyperresponsiveness) is absent in NAEB.

Secondly, there was a significant decrease in IL-13 concentration level and protein expression in sputum and bronchial submucosa of NAEB compared to asthma, which level was similar to healthy individuals [35,36,41,41,47]. Eosinophils are one of the bronchial submucosa's main cells expressing IL-13 protein. A similar number of submucosa eosinophils in NAEB and asthma has been shown, but the proportion of eosinophils that expressed IL-13 is higher in asthma [35]. IL-13 induces airway hyperresponsiveness, demonstrating pathophysiological differences between these two entities that could explain their clinical manifestations [35,36].

Moreover, an increase concentration of sputum prostaglandin E2 (PGE-2) was observed in NAEB [41,43] as well as in other causes of chronic cough (idiopathic and CVA) [48] compared to asthma patients, which 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 NAEB patients' sputum, which highly suggests mast cell activation [43,48]. Cysteinyl-leukotrienes sputum levels are increased in NAEB compared to asthma, according to some authors [48] but not by others [43]. However, the first study [48] evaluated CVA and NAEB patients; thus, its role in NAEB could not be elucidated. These findings could explain the disease's characteristic cough in the absence of bronchial hyperresponsiveness.

EPIDEMIOLOGY AND NATURAL HISTORY

The natural history and clinical evolution of this entity 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, only data from 8 patients was analyzed; half had complete symptomatic resolution of the disease, and the other half continued with cough related to other causes (gastro-oesophageal reflux and postnasal drip).

All other studies have identified NAEB as a chronic disease with recurrent clinical relapses that fluctuate from 20.8% to 60% depending on follow-up time and recurrence criteria [10,12,14,35,5,52]. More information is given in Table 1. While patients with no symptoms but persistent sputum eosinophilia were considered a recurrence group according to Berry MA et al. [35], the same characteristic was considered NAEB remission for Park SW et al. [51]. Just like persistent cough despite no sputum eosinophilia that was considered recurrence by Berry MA et al. [35] but remission by Hancox RJ et al. [50]. Detailed information is given in Table 1.

Remission, defined as absence of symptoms and no sputum airway eosinophilia, showed varying rates from 3% in 32 NAEB patients followed by a mean of 3.1 years [14] to 37.5% in 24 NAEBpatient's follow-up for 2 years [51]. When the absence of cough without treatment was considered as remission criteria alone without considering sputum analysis, the rate increased up to 40.4% in 141 NAEB patients, followed by a median 4.1 years [52] and 53.6% in 41 NAEB patients, followed by a mean of 5.8 years [12]. Asymptomatic persistent sputum eosinophilia has been shown by Berry et al. [35]

and Park et al. [51] in 9.4% and 52.6%, respectively, of the patients. The clinical implication of this finding remains unclear.

The higher NAEB relapse rate (up to 90%) occurs during the first year of follow-up [10,51,52]. The underlying physiopathological mechanism of NAEB relapses remains unknown, but these patients' clinical characteristics and inflammatory profiles have been evaluated. Lai K et al. [52] demonstrated that allergic rhinitis (OR, 4.37; 95% CI, 1.049-18.203; P=0.043) was a risk factor for relapses in contrast to Villalobos-Violanet al. findings [12]. Persistent sputum eosinophilia after treatment was demonstrated by Lai et al. [52] (OR, 9.5; 95% CI, 2.4-37.8; P=0.001) and by Zhan et al. [10] (OR, 1.2; 95% CI 1.0- 1.4, P=0.05) to be a risk factor for relapses. Park et al. observed significantly higher age in patients with recurrent NAEB as well as an increased but non-significant frequency of atopy (42.1% vs 20%), nasal symptom (42.1% vs 20%) and levels of peripheral blood eosinophilia (420 vs 258/ μ L) [51]. Other inflammatory parameters, such as exhaled nitric oxide (FeNO), do not correlate with NAEB relapses [12]. Treatment time has been demonstrated to be 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 demonstrated to occur during follow-up in 5-15% of NAEB patients demonstrated by asthma symptoms and methacholine challenge $PC_{20}<16$ mg/mL and/or postbronchodilator $FEV_1>12\%$ in spirometry [12,35,50-52]. Puolijoki and Lahdensuo 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 [53] (Table 1). The median time for asthma development was over 24 [12] and 27.5 [52] months. In order to predict asthma development, 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 asthma progression in these patients [12]. Chen et al. [54] demonstrated that rhinitis, FeNO and values from lung function tests (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 [52].

Some authors have suggested that NAEB could also be an early manifestation of COPD. In 1999, a non-smoking patient with NAEB that presented progressive, irreversible airflow obstruction was published [55]. Since then, some publications have shown that 12-16% of patients developed a persistent post-bronchodilator $FEV_1/FVC < 70\%$ [35, 50]. However, many patients with NAEB demonstrated no airway obstruction nor a decline in lung function volume values [52]. Park et al. demonstrated a higher FEV_1 reduction in 60% of patients with recurrent NAEB compared to 0% in patients without recurrence. They suggested that recurrent episodes of NAEB may be a risk factor for developing chronic airway obstruction [51].

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

In all patients with chronic cough, an anamnesis containing smoking habits, environmental/occupational assessment and drug treatment, physical examination including nasopharyngoscopy and history of reflux should be done. Chest radiography, spirometry with bronchodilator reversibility, bronchoprovocation challenge, sputum cell count and exhaled nitric oxide should be measured. Other tests should be done as sinus imaging, endoscopic or 24h esophageal pH, thorax computed tomography, bronchoscopy and cardiac workup [3].

Sputum analysis is considered the gold standard in diagnosing of NAEB as it is the more accurate marker of airway eosinophilia [56]. It is a non-invasive, valid and repeatable test both spontaneous or induced [57]. A more than 3% eosinophil of the cell count is accepted to be indicative of eosinophilic bronchitis [56,58]. However, a cut-off of 2.5% is considered positive as some authors [2,37,52]. There is no significant difference in the level of sputum eosinophilia between patients with NAEB and asthma [37,42] or between CVA [37]. The absence of eosinophilia in one isolated sputum does not dismiss the presence of NAEB. DaSilva et al. demonstrated the neutrophilic exacerbation can mask up to 34% of patients with NAEB [59].

The use of FeNO as a surrogate marker of eosinophilic airway inflammation has been validated and, therefore, proposed as a NAEB biomarker. Elevated FeNO values have

been demonstrated in patients with NAEB, both compared with healthy adults [40], adults with non-asthmatic chronic cough [15,60] and children [61], but not with asthmatic ones or with CVA [15,60,62]. This would not be the case with other measurements of NO, such as the nasal or its alveolar concentration [15], probably related to inflammation of the respiratory tract without the participation of the nasal mucosa or the lung periphery. Authors such as Yi et al. [62], Zhang YM et al. [63] and Sato et al. [64] determined significantly higher FeNO values in patients with asthma than with NAEB, in contrast to the results of other authors [15,42,65].

A meta-analysis published in 2017 determined FeNO as an adequate diagnostic biomarker with AUC 0.81, a sensitivity of 72% and specificity of 83% [66]. Among the studies included in the meta-analysis, the cut-off value of FeNO to predict the disease ranges between 22.5ppb [62] and 31ppb [14], with similar sensitivity between the studies, 69.8 and 63%, respectively, but significant differences in the specificity, 76.2% and 92%, and the positive predictive value, 56% and 88% between them. Oh et al. [13] determined 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 it as a cut-off due to a 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% to discriminate between cough variant asthma and NAEB from other diseases (gastroesophageal reflux and postnasal drip), without evaluating them independently. Studies about NAEB in children are scarce. Kim et al. [61] determined 20 ppb as the FeNO cut-off point in the diagnosis of eosinophilic bronchitis when evaluated together with the resistance of the airways after oscillometry. The biomarker was not evaluated in isolation but jointly obtained high sensitivity 77.5 and 75% and moderate specificity 49.6 and 46%, respectively, for a change of X5 of -20% and AX -30%.

FeNO measurement has been demonstrated to be a predictor of response to inhaled corticosteroids. A good correlation between sputum eosinophilia and the FeNO value was corroborated in the majority of the studies in NAEB [13-15,62], in CVA [62] and asthma [67] in contrast with other author findings [12]. A great variety of demographic characteristics (sex, age, race, weight, atopy), clinical conditions (tobacco habit, plant-

derived food or beverage intake), and external factors (viral or bacterial infection, corticosteroid treatment, disease exacerbation, exposure to irritants) have demonstrated to have a significant effect in FeNO value been a confounding factors [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 non-atopic subjects [13]. The presence of rhinitis was also rejected it as a confounding factor [62]. Wiszniewska et al. [69] evaluated the role of FeNO in NAEB. They concluded that an increase of more than 4 ppb after the specific bronchial challenge was a predictor of the disease with a high specificity of 90-97%. The sensitivity varied according to the times that said biomarker was increased, ranging between values 8, 14 and 17.5 ppb, corresponding to a sensitivity of 43, 33 and 23%, respectively. However, the isolated use of this biomarker in the diagnosis of ONAEB would be limited since it is also elevated in occupational rhinitis and asthma and may overestimate the disease [70].

Higher levels of peripheral blood eosinophilia (PBE) was observed in NAEB patients compared to healthy individuals but similar to asthmatic ones [36,37,40,41]. In asthma, PBE has been proposed as an eosinophilic inflammation biomarker [67,71], while in NAEB it is controversial. Villalobos V et al. refused a correlation between PBE and sputum eosinophilia in 41 patients with NAEB ($r=-0.17$ $P=0.65$, discarding its use as NAEB diagnostic biomarker [12]. Its utility in NAEB prognosis and disease severity has also been evaluate with no significant finding [12,51,52].

Immunoglobulin E (IgE) level was neither not a discriminatory biomarker for NAEB due to similar values has been demonstrated in adults with NAEB, asthma and healthy controls [40,41]. These results contrast with the findings of Kim YH et al. in children that demonstrated higher IgE levels both for NAEB and asthma compared to healthy individuals [61].

Three other related conditions have been described with increased sputum and submucosal eosinophil count and cough corticosteroid response as a typical symptom: classic asthma, CVA and atopic cough. The first two diseases are characterized by

bronchial hyperresponsiveness in which 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 by Fujimura et al. in 1992 [72]. It is considered an isolated chronic cough with an atopic background, no airway responsiveness and eosinophilia in sputum could be involved or could not(73). Both CVA and NAEB can be a precursor of asthma in 20-33% and in 4-15% of the diagnosed patients, respectively, whilst atopic cough is rare (1.2%) [74,75].

Frequent diseases causing chronic cough that should be included in the differential diagnosis as gastro-esophageal reflux disease, postnasal drip syndrome or rhinosinusitis, chronic obstructive pulmonary disease, pulmonary fibrosis, bronchiectasis, idiopathic cough or drug-mediated cough (angiotensin-converting enzyme inhibitors). Other diseases less frequent that could cause chronic cough are tumors (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].

Systematic review of the treatment:

Inhaled corticosteroids (ICS) were proposed as first-line treatment in NAEB due to their eosinophilic airway inflammation suppression [3,11]. However, data must be available to decide which ICS should be used at which dose and for how long [58]. Because of that, a systematic review that evaluates the appropriate and effective treatments for NAEB has been done. Demonstrated reduction in the presence of sputum eosinophils, a subjective and objective decrease in cough severity and the absence of exacerbations are the main goals of controlling the disease. In addition to ICS, avoidance strategies, when the inflammation is due to occupational exposure or inhaled allergen, are also considered a concomitant first-line treatment. Randomized controlled studies about NAEB treatment are scarce.

-Objective:

A structured literature review was carried out to identify and synthesize relevant information published about treating eosinophilic bronchitis.

-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 the 2 of October 2023.

Eligibility Criteria

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

Search Strategy:

The search was carried out in 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])).

Study Selection and Data Collection:

The results were screened by two independent reviewers. Following the pre-defined inclusion and exclusion criteria, publications were first selected based on title/abstract, and then after 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.

Methodological Quality Assessment:

We performed a quality assessment of the selected studies using the Critical Appraisal Skills Programme (CASP) 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 and the number of questions in the corresponding See results in Supplementary material.

- Results:

A total of 209 studies were retrieved using the search strategies, of which 46 were excluded based on not evaluating NAEB or chronic cough and 138 for not evaluating treatment neither intervention after full-text reading. Out of the 24 papers selected for inclusion, 4 were excluded due other languages different than english were used. A PRISMA diagram showing in detail the workflow of the screening process is presented in figure 1. A total of 7 studies about non-asthmatic chronic cough (3 RCT and 4 meta-analyses) and 13 about NAEB (4 RCT and 9 prospective/retrospective studies) were included.

The overall 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. Significant heterogeneity resulting from interventions such as doses and kind of treatment, variable follow-up time as well as variation in outcome measures limited the validity of comparisons between studies.

-*Non-asthmatic chronic cough:

Two placebo-control longitudinal studies have demonstrated improvement in 88 [76] and 44 [77] patients with non-asthmatic chronic cough after 14 days of inhaled corticosteroids (fluticasone 1000 µg/d or beclomethasone 1,500 µg/d, respectively) measured by symptom diary and visual analogue scale (VAS) and a decrease in sputum ECP and FeNO. Three meta-analyses demonstrated improvement in unspecific subacute/chronic cough after inhaled corticosteroids, two in adults including 8 studies each one [78,79] and one in children evaluating 2 articles [80]. The absence of cough improvement after bronchodilatation treatment was demonstrated in another meta-analyses [81]. In adults, the mean decrease in cough score following ICS treatment compared to placebo was 0.34 (95% CI -0.56 to -0.13) [78] and 0.38 (95% CI, -0.54, -0.23) [79] standard deviations lower, though the quality of this evidence was

medium/low. A significant decrease in sputum eosinophils was demonstrated in one of the 3 and 4 included studies in the metaanalysis by Johnstone KJ [78] and Lee SE, respectively [79]. However, in all the previous studies, different illnesses causing chronic cough were included, and NAEB was not evaluated isolated, so extrapolation of the results is limited. In children [80], there are discrepancies in results. While one study demonstrated similar cough frequency following ICS treatment and with placebo for 4-5 weeks, the other demonstrated improvement after ICS for 15 days compared to placebo (OR 0.28, 95% CI 0.09 to 0.92; P=0.04). As just two studies were evaluated in the metaanalysis with opposite results, a precise conclusion cannot be achieved. ICS have shown a decrease in sputum eosinophilia in other respiratory illness different from asthma and NAEB. Beclomethasone dipropionate 400 µg/day demonstrated in a clinical trial a significant improvement in sputum production and sputum eosinophilia in 42 patients diagnosed with eosinophilic bronchitis in silicosis [82].

*** NAEB:**

In 1995, Gibson demonstrated the usefulness of ICS in NAEB [83]. They showed a significant decrease in sputum eosinophilia in 9 patients with NAEB after one week of beclomethasone 400 µg twice daily. In 2000, Brightling et al. demonstrated in 11 patients with NAEB a significant reduction in sputum eosinophilia and cough VAS and increased cough hypersensitivity showed by higher capsaicin sensitivity after budesonide 400 µg once per day for 4 weeks [11]. A significant positive correlation between the cough sensitivity change induced by treatment and the sputum eosinophil count was proved.

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

Clinical improvement in cough after ICS treatment was demonstrated in 40.4% of the patients by Lai et al. [52], 63% by Berry et al. measured by VAS [14], and 75% according to Park et al. [51] in contrast with the 100% shown by Brightling et al. [9]. While the first group was treated with oral prednisone 10 to 15 mg/d for three days and

budesonide 400 µg/day for at least four weeks [52], the second was with budesonide 200–400 µg twice daily during a mean of 3.1 years (range 1-6 years) [14], the third with budesonide or fluticasone 800 µg/day after two months [51] and the fourth group was with budesonide 400 µg twice daily after 6-8 weeks [9]. The impact of the dose or the treatment time remains unclear.

Recurrences of the disease, as well as incomplete response in some patients [8,12,14,51,51] demonstrated the need for other treatments in first-line resistant patients. In the 2020 CHEST Guideline for chronic cough due to asthma or NAEB, stepping up the ICS dose, oral corticosteroid 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 control study evaluated increased ICS doses to budesonide 400 µg/twice a day, budesonide, 200 µg/twice a day adding montelukast 10 mg/d for four weeks in 26 NAEB patients demonstrating similar improvement in cough visual analogue scale and sputum eosinophilia [85]. Another open-labelled and randomized study in 55 patients comparing budesonide 200 µg/twice a day with and without montelukast 10mg/d for four weeks supported previous results and added a significantly higher decline in VAS and life quality scores as well as in eosinophils and ECP sputum in patients also treated with montelukast [86].

Anti-histaminic agents have improved capsaicin cough sensitivity in 8 of 11 patients with NAEB and upper airway disease [87]. However, this treatment was not able to decrease significantly sputum eosinophilia. Epinastine 20mg, an anti-H1 treatment, significantly improved cough scores and capsaicin cough sensitivity in 10 patients with clinical NAEB [88]. Nevertheless, sputum was not done either for diagnosis or follow-up. The actual usefulness of anti-histaminic treatment 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 was available from humans [89]. Other treatments, such as inhaled lidocaine, have been evaluated in randomized clinical trials with NAEB patients years ago with poor results [90].

-Discussion:

All in all, in this systematic review of NAEB treatments, the quality of studies is medium/low, and there is a higher heterogeneity in selection criteria, intervention and outcome measures. Overall, the efficacy of ICS in chronic cough and NAEB has been demonstrated due to a generally significant decrease in symptoms and sputum eosinophilia. However, more studies need to be designed to compare different kinds of corticosteroids, doses and treatment periods. Adding oral corticosteroids and anti-leukotriene to inhaled treatment has also been demonstrated as an effective strategy in NAEB. Despite side effects need to be evaluated, its potential benefits as isolate treatment are pending to be examined. The efficacy of other treatments, such as anti-histaminic, intranasal polymyxin B and inhaled lidocaine, has not been successfully demonstrated.

Although out of the objectives of this systematic review, we want to highlight that a meta analysis performed in 2014 gave evidence of a significant decrease in sputum eosinophilia and eosinophil-mediators with oral prednisone in asthma patients. They concluded a six, five and four-fold mean reduction in the number of sputum eosinophils IL-5 and ECP, respectively, after treatment [91]. However, a high heterogeneity in dose and time of oral prednisone prescription was observed between the studies. Other oral corticosteroids have also demonstrated a significant decrease in sputum eosinophilia in animals [92] and in humans [93]. Biological treatments that target IL-5 as mepolizumab and benralizumab have demonstrated in randomized placebo-controlled trials as well in real-life studies, markedly suppressed sputum eosinophilia and PBE both in asthma and COPD [94-99] together with other eosinophilic diseases like hypereosinophilic syndrome and eosinophilic granulomatosis and polyangitis [100]. Unfortunately, none of the studies has been done just in NAEB patients.

Conclusions:

In conclusion, NAEB is a chronic inflammatory disease in which eosinophilic airway infiltration predominates. The presence of different inflammatory cells and its location might result in the difference of mechanism between NAEB and asthma. Assessing the presence of rhinitis and atopy and higher FeNO value is helpful in identifying patients with a risk of asthma progression. Sputum eosinophil should be evaluated before and after treatment to predict relapses. Corticosteroids and antileukotriene are effective

treatments for the disease. The effect of other therapies, such as anti-IL5 biologic, 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 for an accurate treatment.

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Conflicts of Interest

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Figure. PRISMA diagram showing in detail the workflow of the screening process.

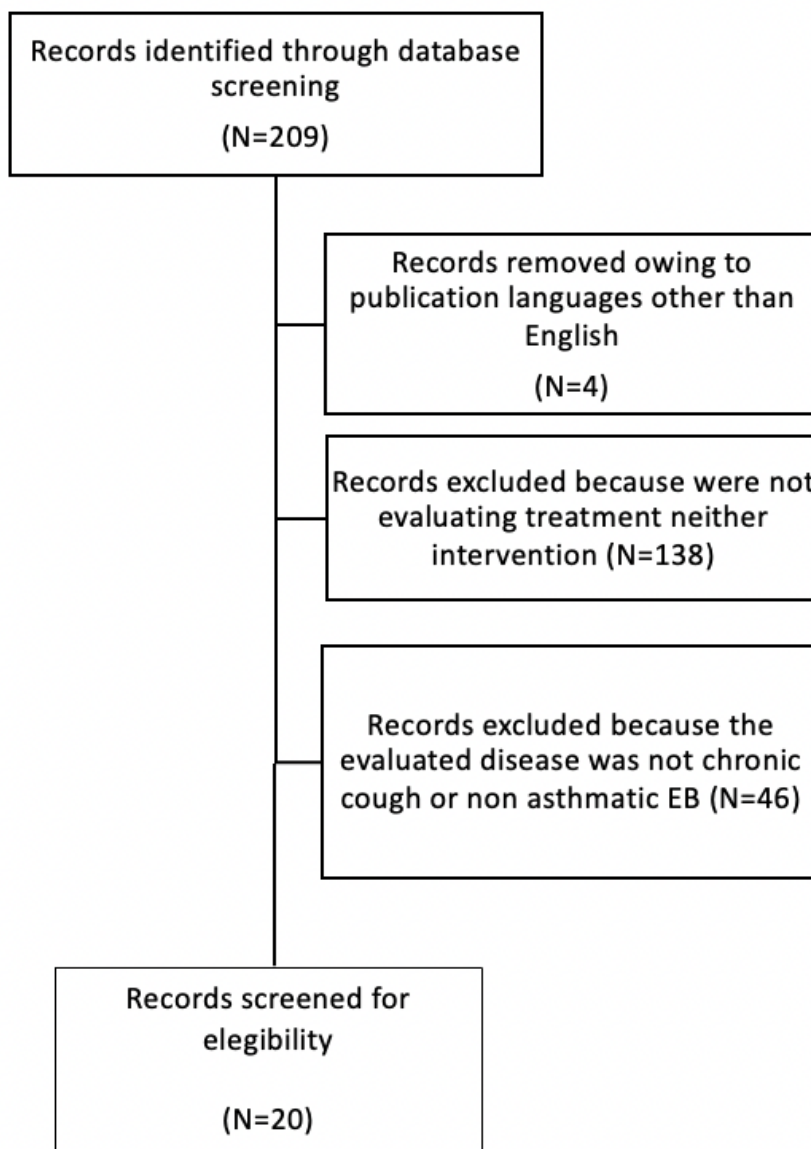


Table 1. Studies about the natural history and clinical course of non-asthmatic eosinophilic bronchitis disease

	Number of patients	Patients with follow-up data	Followed period	NAEB recurrence	NAEB remission	Asthma development	Airway obstruction*
Hancox RJ et al. 2001 (50)	12	8	Not specified. Over 6 years.	NP	8 (100%) considered as sputum eosinophilia <2% of whom 4 were asymptomatic and 4 had persistent cough due to other causes	1 patient of the total 12 had asthma diagnosis (8.3%) but diagnostic tests were not shown	1 (12.5%)
Joo JH et al. 2002 (8)	11	4	6 months	3 (75%) considered as lapses of worse coughing and increased sputum eosinophilia >3%	1 (25%) considered as absence of sputum eosinophilia	NP	NP
Park SW et al. 2004 (51)	36	24	2 years	5 (20.8%) considered as persistent cough and sputum eosinophilia > 3%	19 (79.2%) considered as asymptomatic but 10 (52.6%) of them had persistent sputum eosinophilia >3%	1 (4.2%) asthma symptoms and positive spirometry bronchodilator test	NP
Berry MA et al. 2005 (14)	52	32	Mean 3.1 years	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 no sputum eosinophilia off treatment	3 patients (9%) demonstrated by symptoms and a methacholine PC ₂₀ <8 mg/mL	5 (16%)
Lai K et al. 2015 (52)	234	141	Median 4.1 years	84 (59.6%) considered as persistent cough with sputum eosinophilia (≥ 2.5%)	57 (40.4%) defined as asymptomatic off treatment	8 (9.5%) asthma symptoms and BHR or bronchial reversibility	0 (0%)
Zhan W et al. 2019 (10)	101	89	1 year	22 (24.7%) considered as persistent cough and sputum eosinophil count ≥ 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 years	13 (31.7%) considered as persistent cough	22 (53.6%) considered as asymptomatic	6 (14.6%) defined as asthma symptoms with BHR or bronchial reversibility	0%

* Airway obstruction demonstrated by persistent FEV₁/FVC postBD <70%.

Footnote: BHR was considered when methacholine challenge PC₂₀<16mg/mL. Bronchial reversibility was considered when postbronchodilator FEV₁>12% in spirometry. NP= not permormed.