Review Article on Novel Insights into Chronic Cough

Is fractional exhaled nitric oxide a treatable trait in chronic cough: a narrative review

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Background and Objective: Current management of chronic cough is largely based on sequential therapeutic trials. The concept of treatable traits was first introduced for individualized treatment of chronic airway diseases; however, it has emerged as a potentially useful strategy in revising the management of chronic cough. This narrative review aimed to analyze the literature to determine if fractional exhaled nitric oxide (FeNO) is a treatable trait in chronic cough, compared to other type 2 biomarkers, and to summarize current knowledge and gaps in the clinical application.

Methods: An online electronic search was performed on PubMed, Web of Science, and Scopus of English-language literature with following keywords: cough, nitric oxide (NO), eosinophils, biomarker, and treatable trait. Relevance and eligibility of each article were assessed by one or more of the authors and a narrative review was composed.

Key Content and Findings: Eosinophilic or type 2 airway inflammation is a major treatable trait in patients with chronic cough. Induced sputum tests are regarded as the gold standard for defining inflammatory phenotype, however, technically demanding and cannot be widely applied in clinical practice. FeNO, a practical biomarker, has emerged as an alternative to induced sputum analyses. Mechanistic and clinical evidence indicated that FeNO had a potential for diagnostic utility and treatment response predictability.

Conclusions: FeNO measurement may help to identify patients with chronic cough that will benefit from corticosteroid treatment. Further studies are warranted to determine the diagnostic roles of FeNO in the management of patients with chronic cough.

Keywords: Chronic cough; asthma; eosinophilic bronchitis; fractional exhaled nitric oxide (FeNO)

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Introduction

Over recent decades, heterogenous clinical characteristics and variable treatment responses have been recognized in patients, including those with a single diagnostic label, such as asthma or chronic obstructive pulmonary disease (COPD). Asthma is now regarded as a clinical syndrome with varying phenotypes and endotypes rather than a single disease entity. COPD is an umbrella term encompassing different respiratory conditions commonly characterized by irreversible airflow obstruction. Thus, a diagnostic label-based approach is no longer much effective in the individualized management of asthma or COPD, and the concept of treatable traits has been introduced (1).

Chronic cough is a clinical syndrome usually defined as a cough lasting more than 8 weeks. It is prevalent and can affect the quality of life in patients (2-4). Anatomic diagnostic protocols, which aim to identify and treat the causes of cough according to the neuroanatomy of relevant reflex pathways, are key principles in managing patients with chronic cough (5-7). However, certain aspects of the approach are lacking. First, diagnostic labels, such as asthma, upper airway diseases, or gastroesophageal reflux disease (GERD), cannot precisely inform treatment. For example, asthma is not always eosinophilic, and GERD is not necessarily acidic. Second, in the absence of biomarkers or controls, any responses to empirical treatments are difficult to interpret. Current cough management is largely based on empirical sequential therapeutic trials; however, such treatments cannot differentiate true therapeutic benefits from spontaneous improvement, often leading to the risk of overuse or misuse of medications (8,9). Thus, chronic cough treatments should ideally be guided by observable or definable traits such as biomarkers.

Eosinophilic or type 2 (T2) airway inflammation is frequently detected in adults with chronic cough (20–40%) (10). Importantly, T2 inflammation is one of the few traits that can be objectively measured. Practical biomarkers, such as the fractional exhaled nitric oxide (FeNO) test or blood eosinophil counts, have emerged as alternatives to sputum eosinophil counts in guiding a diagnosis or corticosteroid treatment decision (11,12). In particular, FeNO is a non-invasive, convenient, and point-of-care test to measure the degree of T2 inflammation in the airways (13). However, there are controversies regarding the use of FeNO in chronic cough practice. Current international guidelines do not endorse the routine use of FeNO in patients with chronic cough (14). The mechanistic pathways regulating eosinophils and nitric oxide (NO) are distinct from each other (15); thus, FeNO is not only a biomarker of T2 inflammation but also it should be considered as a treatable trait on its own. This paper aimed to analyze the literature to determine if FeNO is a treatable trait in chronic cough, in comparison to other T2 biomarkers, and summarized major knowledge gaps in clinical application. We present this article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-135/rc).

Methods

We searched PubMed, Web of Science, and Scopus for relevant articles published in peer-reviewed journals until 29 October, 2022. The search terms were “cough”, “nitric oxide”, “eosinophils”, “biomarker” or “treatable trait”. We included studies pertaining to clinical evidence for FeNO regardless of study design, such as observational cohort, retrospective studies, randomized controlled trials (RCTs), meta-analyses, and review articles. Moreover, experimental studies were sought for mechanistic evidence of biomarkers in chronic cough. Manuscripts written only in English language were evaluated. Detailed process of search strategy is described in *Table 1*.

Discussion

Concept of treatable traits

The current consensus proposes that three minimum criteria should be met for a trait to be considered treatable: clinical relevance, trait identifiability/measurability, and treatability (1). First, the trait should be clinically important; for example, it should predict or associate with clinically important outcomes, prognosis, or mortality. Second, it should be measurable using validated objective or subjective tools (with a high specificity to direct a treatment decision or a high sensitivity to rule out such a possibility). Finally, it should be effectively treatable and ideally proven in a RCT. Although treatable traits have not been well established in chronic cough, there is very little doubt that T2 airway inflammation or eosinophilic bronchitis (asthmatic or non-asthmatic) is a major treatable trait (16).

A biomarker is any characteristic objectively measured and evaluated as an indicator of normal biological or pathologic processes, or pharmacologic responses to

Table 1 The search strategy summary

Items	Specification
Date of search	29 October 2022
Database and other sources searched	PubMed, Web of Science, and Scopus
Search terms used	"Cough", "nitric oxide", "eosinophils", "biomarker" or "treatable trait"
Timeframe	1979–2022
Inclusion and exclusion criteria	Inclusion: English language only
Selection process	Lee JH independently reviewed all initial articles and assessed eligibility, with additional review by Song WJ. Final inclusion of relevant articles was determined by all authors

a therapeutic intervention (17). Three biomarkers are frequently used to phenotype or define T2 inflammation in patients with chronic respiratory diseases, including sputum eosinophils, blood eosinophil counts, and FeNO levels.

Sputum eosinophils

Induced sputum has been regarded as the gold standard for defining airway inflammatory phenotypes (18). A sputum eosinophil count of >2–3% is considered sputum eosinophilia (19). Cough variant asthma (CVA) and eosinophilic bronchitis are representative of eosinophil-related conditions in chronic cough (14). In CVA, increased levels of eosinophils in sputum and bronchoalveolar lavage fluid are frequently observed (20,21). Eosinophilic bronchitis was detected by applying induced sputum analysis, a cough responsive to inhaled corticosteroid (ICS) without variable airflow obstruction or airway hyperresponsiveness (AHR), but with eosinophilic airway inflammation (22).

Sputum eosinophil count and subjective cough severity significantly improved after ICS treatment in patients with eosinophilic bronchitis (23,24). In addition, heightened cough sensitivity assessed through the capsaicin cough challenge improved after ICS treatment (23). The degree of improvement in cough sensitivity positively correlated with the change in sputum eosinophil count (23). These findings suggest that sputum eosinophilia determined by induced sputum is a direct noninvasive method with high clinical relevance and treatability to define causal inflammatory phenotype in chronic cough. However, induced sputum analyses are technically demanding, time-consuming, and prone to inter-observer variability. Moreover, their use is restricted to a small number of specialized institutions, mostly for research purposes. Additionally, approximately 10–20% of patients may not produce enough sputum for analysis (10,25). Therefore, the measurability of sputum eosinophils is somewhat limited in clinical applicability despite high sensitivity and diagnostic accuracy.

Blood eosinophils

Accessibility is a relative strength of blood eosinophil counts compared with induced sputum analysis. The threshold of 300 eosinophils/μL in peripheral blood is generally accepted as an airway eosinophilia in asthma (26). However, blood eosinophil counts are highly variable over time (27,28). Thus, a single measurement of blood eosinophils is not sufficient to determine airway eosinophilia. Moreover, the clinical relevance of blood eosinophilia to chronic cough is unclear because most data on the use of blood eosinophil counts have been derived from asthma studies. A recent study by Sadeghi *et al.* examined the correlation of biomarkers in 50 patients with chronic cough (29), in which a strong correlation between FeNO with blood eosinophils was observed ($r=0.79$; $P<0.001$). A modest correlation was noted between blood and sputum eosinophil count ($r=0.59$; $P<0.001$), in contrast to the results of previous asthma studies that reported weak ($r=0.22$; $P<0.001$) or modest correlations ($r=0.51$; $P<0.001$) between FeNO and blood eosinophils (30,31). These findings may indicate diagnostic and therapeutic implications of blood eosinophils in chronic cough. However, increased blood eosinophils were not always found in patients with eosinophilic bronchitis, confirmed by sputum eosinophilia (32). A recent observational study showed the weak power of blood eosinophils as a predictor of treatment response in chronic cough (33). Furthermore, there is no RCT evidence. Further evaluation is warranted to confirm the diagnostic utility of blood eosinophils in chronic cough.

Table 2 Comparison of FeNO with sputum eosinophilia and blood eosinophilia from the perspective of treatable traits

Domain	Sputum eosinophilia	Blood eosinophilia	FeNO
Clinical relevance	+ + +	+	+ +
Trait identifiability/ measurability	+	+	+ +
Treatability	+ + +	+	+ +

Grading was based on the strength of clinical effects or evidence level identified through literature review and was decided by author's discretion: (+) some or limited evidence of effect; (+ +) moderate effect; (+ + +) highly effective/relevant. FeNO, fractional exhaled nitric oxide.

FeNO

Contrary to induced sputum, the measurement of FeNO is not technically challenging, and its levels can be demonstrated promptly (34,35). In addition, FeNO reflects the local level of T2 inflammation, whereas blood eosinophil count does not. Therefore, FeNO test is considered to have better measurability than blood or sputum eosinophil analyses (*Table 2*).

Mechanistic evidence of T2 inflammatory markers

NO and cough reflex

Respiratory epithelium is the primary source of exhaled NO in the airways, and FeNO levels are largely dependent on the activity of interleukin-4 (IL-4) and IL-13 (36). Generation of NO occurs through the conversion of L-arginine to L-citrulline by the action of nitric oxide synthase (NOS) (37). Three NOS isoforms are present in the lungs: neuronal NOS (nNOS or NOS-1), inducible NOS (iNOS or NOS-2), and endothelial NOS (eNOS or NOS-3). nNOS and eNOS isoforms are constitutively expressed, but their contributions to NO levels in exhaled air are minor (38). nNOS is expressed in postganglionic parasympathetic neurons in the airways, wherein NO primarily functions as an inhibitory non-adrenergic, non-cholinergic neurotransmitter exerting bronchodilation effects (39). eNOS is expressed in endothelial cells in the respiratory tract, regulating pulmonary and bronchial circulation, but is rarely expressed in the respiratory epithelium (40).

iNOS can be expressed by various cells, but it is exclusively expressed in the respiratory epithelium in normal human lower airways (40). In a small randomized, double-blind, placebo-controlled trial, administering an oral iNOS-selective inhibitor rapidly reduced FeNO levels to less than 3 ppb in asthmatics and healthy volunteers, supporting the major contribution of iNOS to NO levels in exhaled breath air (41). Endogenous mediators, such as IL-4 and IL-13, can upregulate iNOS expression or activity (38). In addition, exogenous stimuli, such as bacterial toxins, viruses, and allergens, may induce iNOS. In such pathological conditions, NO production increases, and NO has cytotoxic or pro-inflammatory effects, such as AHR, vasodilation, free radical production, mucus hypersecretion, and ciliary motility inhibition at high concentrations (42).

Reactive oxygen and nitrogen species are produced due to airway inflammation, termed oxidative stress. Oxidative stress can activate bronchopulmonary C-fibers, mediated by transient receptor potential ankyrin 1, transient receptor potential vanilloid type 1 (TRPV1), and P2X3, and then stimulate the cough reflex (43). Oxidative stress level, exhaled breath condensate concentration of 8-isoprostane, is increased in patients with chronic cough compared with healthy controls (44). NO is associated with oxidative and nitrosative stress. Nitrosative stress levels in nasal epithelial cells and nasal NO were significantly higher in the cough hypersensitivity group than in the normal cough sensitivity group, which was determined by the capsaicin cough provocation test (45). Substance P, secreted from capsaicin-sensitive C-fibers, was significantly elevated in the cough hypersensitivity group. Expression of substance P was increased in airway epithelial cells treated with NO and suppressed with pretreatment with NO scavenger or NO synthase inhibitor. The consequences of eosinophilic inflammation, such as the oxidative and nitrosative stress, may also explain the association between NO and chronic cough.

Eosinophils and cough reflex

Studies suggest that eosinophils are associated with airway sensory nerve innervation and activation. Increased airway innervation was identified in patients with airway and blood eosinophilia (46). Increased nerve density and AHR were observed in IL-5-overexpressed mice, compared with eosinophil-deficient mice and wild-type mice, indicating eosinophils increase neuronally mediated AHR. The mechanism underlying eosinophil-induced sensory nerve hypersensitivity was investigated in animal experiments (47). Vagal pulmonary C-fiber plays a dominant role in sensory nerve hypersensitivity. Activated eosinophils release

cationic proteins such as major basic protein (MBP), eosinophil cationic protein (ECP), EPO, eosinophil-derived neurotoxin, and MBP2 through the process of degranulation. Installation of MBP and ECP enhanced the sensitivity of C-fiber (48). MBP directly interacted with TRPV1 receptor and increased the activity of capsaicin, a selective agonist of TRPV1 (49). When challenged with sulfur dioxide and ammonia inhalation, MBP instillation increased cough response in a dose-dependent manner. These mechanical findings support causal relationships of eosinophilic inflammation with chronic cough or cough hypersensitivity.

FeNO and sputum eosinophil counts both are indicators of T2 airway inflammation, but they have moderate correlations. The discrepancy in their levels is likely attributed to their different regulatory mechanisms and methodological confounders. Mechanistically, IL-5 is directly related to the increase in eosinophils and is not usually involved in the production of FeNO. IL-5 is essential and selective for the maturation, growth, activation, and survival of eosinophils (50). Meanwhile, IL-4 and IL-13 stimulate the expression of integrin, adhesion molecule P-selectin, and vascular adhesion molecule-1, which are required for endothelial adhesion of eosinophils and recruitment to the lungs. Blood and sputum eosinophil counts significantly decrease following treatment with anti-IL-5 (mepolizumab) in patients with severe asthma; however, FeNO levels are not affected (51). In contrast, FeNO levels significantly decrease following anti-IL-13 (lebrikizumab) treatment, whereas blood eosinophil counts are not affected (15).

Considering the mechanistic evidence for eosinophils in chronic cough, it seems plausible that cough would improve following biological treatments targeting eosinophils. In a mepolizumab study for patients with severe asthma, cough severity measured by the visual analogue scale (VAS) did not improve compared with placebo. However, treatment with 2 weeks of prednisolone 30 mg daily led to significant improvement (51,52). The inconsistency of these study findings questions the role of eosinophils in cough for patients with asthma. In addition, other mechanisms responsive to corticosteroids, such as mast cells or NO, may be involved. Another study showed that objective improvement of cough was an early predictive marker of mepolizumab in a small number of patients (n=8) with severe asthma (53). However, this study did not include a placebo group, so the true efficacy for chronic cough could not be determined. The effects of anti-IL-4 and IL-13 (dupilumab), effective drugs for severe asthma with high FeNO, on cough severity were unknown because cough symptoms were included in the composite symptom score, not independently measured.

Therefore, the traits that better reflect the underlying pathophysiology of chronic cough between FeNO and sputum eosinophils remain undetermined. Given that mechanistic evidence in the generation of FeNO mediated by the interaction of T2 cytokines, FeNO could be a relevant surrogate to replace sputum eosinophils in chronic cough management.

Clinical evidence for FeNO in chronic cough

Diagnostic utility

The diagnostic property of the FeNO test has been evaluated in various observational studies of patients with chronic cough, and specificity (to diagnose CVA or eosinophilic bronchitis) has been noted as the major strength. Of the young adults with chronic cough (18–45 years), 33.0% were diagnosed with asthma (54). The median FeNO level in asthma was 86 ppb, which was significantly higher than in rhinitis/sinusitis (37 ppb), GERD (14.8 ppb), and healthy controls (13 ppb). In a study on patients with cough (≥3 weeks), those with cough attributable to asthma had higher FeNO compared with those with a cough that was not or healthy controls (75.0, 16.7, and 28.3 ppb, respectively) (55). Studies have consistently reported a significantly higher FeNO level in asthma and eosinophilic bronchitis compared with other groups, including postinfectious cough, atopic cough, upper airway cough syndrome, and GERD (56-59). Therefore, measurement of FeNO could help identify the underlying inflammatory phenotypes in chronic cough.

In a meta-analysis, the diagnostic accuracy of FeNO for CVA was a sensitivity of 0.72 [95% confidence interval (CI), 0.61–0.81] and a specificity of 0.85 (0.81–0.88), with an area under the curve (AUC) of 0.87 (0.83–0.89). The diagnostic accuracy of FeNO for CVA or eosinophilic bronchitis was a sensitivity of 0.72 (0.61–0.81) and specificity of 0.85 (0.81–0.88) with AUC of 0.89 (0.86–0.92) (60,61). Accordingly, the diagnostic precision of FeNO may be considered moderate.

Sputum eosinophilia is usually accompanied by high FeNO. However, the correlation coefficient between sputum eosinophils (%) and FeNO in chronic cough ranged from 0.576 to 0.666 (57,62,63). A study reported that one-third of patients with sputum eosinophilia (>2.5%) had

low FeNO (<31.5 ppb) (62). Although FeNO of more than 30 ppb is regarded as airway eosinophilia, a decisive cut-off value as an alternative to sputum eosinophilia was not confirmed (10). This moderate correlation between sputum eosinophils and FeNO could be explained by the regulation of different cytokines (64). In addition, the diagnosis of CVA mostly depended on treatment responses in those observational studies, which is likely to be another reason for the variability in the diagnostic property of FeNO.

Treatment response predictability

A systematic review was attempted to define the predictive ability of FeNO for ICS responsiveness (65); however, all included studies were observational in nature and thus could not differentiate true ICS effects from spontaneous improvement. Thus, a major knowledge gap is that no randomized placebo-controlled trial has evaluated the diagnostic utility of FeNO in relation to ICS response in patients with chronic cough. A meta-analysis of RCTs showed that only small to moderate effects of ICS was accompanied by significant placebo effects in patients with cough (66). Most studies did not present eosinophilic biomarkers, which limits the precise evaluation of FeNO (66).

Clinical evidence for FeNO in chronic cough is summarized in *Table 3*. In an RCT of patients with chronic persistent cough, significant improvement in cough severity assessed by VAS after ICS compared with placebo was identified (67). FeNO levels decreased by –2.1 ppb following ICS, whereas sputum eosinophils did not change. FeNO was identified as a better predictive factor of ICS responsiveness (r^2=0.151; P<0.001), than sputum eosinophils (r^2=0.08; P=0.019). However, it was a crossover study and carryover effects could not be excluded. Also, most patients had increased sputum neutrophils rather than eosinophils at baseline. In addition, the degree of VAS improvement was rather small (1.0; 95% CI, 0.4–1.5).

Patients with undiagnosed respiratory symptoms were evaluated to assess the predictability of FeNO in the ICS response (74). After ICS treatment, significant improvements in FEV_1% (forced expiratory volume in one second % predicted), morning peak flow, AHR, and respiratory symptoms were observed in patients with the highest FeNO (>47 ppb). The predictive value of FeNO had a sensitivity of 66.7% and a specificity of 77.5% at 47 ppb (AUC =0.76). Baseline FeNO was a superior predictor compared with other factors. However, no cough-specific analyses were performed.

In RCT recruiting patients with chronic non-specific respiratory symptoms (75), change in cough severity assessed by VAS (0 to 100 mm) from baseline was greater in the ICS group than the placebo group (18.89±30.02 *vs.* 11.83±28.67; P=0.014). FeNO levels were better correlated with improvement of cough severity than blood eosinophil counts. FeNO was retained as a significant predictor for improvement of cough in multivariate regression (odds ratio 1.17; 95% CI 1.02–1.34). Meanwhile, among patients with symptoms suggestive of asthma and low FeNO (≤27 ppb) (76), 45% and 40% had an improvement in cough in the ICS treatment and placebo groups, respectively (P=0.501). Accordingly, RCTs in patients with chronic respiratory symptoms, including cough, suggest that high FeNO may be a predictive factor for the ICS response. However, it should be noted that the predictive utility of FeNO should be validated in patients with isolated chronic cough.

Among three prospective observational studies, ICS responder was identified in 44% (68). However, the baseline FeNO level did not differ from 23.2 and 18.6 ppb in the responder and non-responder groups, respectively (P=0.25). A low predictive value of FeNO was noted, with a sensitivity of 53% and specificity of 63% at FeNO of 20 ppb. In another study, a responder was identified in 77% of patients (69). FeNO levels were 19.7 ppb in the ICS responder group and 9.8 ppb in the non-responder group. Predictive accuracy in discriminating ICS responsiveness had a sensitivity of 47% and specificity of 89% (AUC =0.74) at a cutoff of 16.3 ppb (69). However, in a study by Shebl *et al.* (63), the ICS responder following high-dose ICS was 64.3% (45/70). The best cutoff value of FeNO to identify the ICS responder was 34.5 ppb with a sensitivity of 85% and specificity of 63% (AUC =0.84).

Several retrospective observational studies investigated the predictive response of FeNO to ICS. Hahn *et al.* reported that ICS responder was 59.4% (38/64) among all patients and 88% (36/41) in patients with high FeNO (>35 ppb) (70). Other studies also reported a greater predictive value of FeNO (AUC >0.8) compared with prospective studies at cut-off levels of ≥25 or 30 ppb (71-73).

In prospective studies, most study participants had low FeNO levels (68,69), attributed to the low sensitivity of FeNO. In retrospective studies, a relatively larger proportion of patients had asthma or eosinophilic bronchitis (70-73). Although we highlighted the importance of RCTs from the perspective of treatable traits, a lack of direct evidence may not conclude that FeNO is not useful. Considering the overall results through indirect evidence,

Table 3 Summary of studies reporting a role of FeNO in predicting ICS response

Study	Study subjects	Intervention	Measurement of ICS response	Cut-off value	Sensitivity	Specificity	Other outcomes
Direct evidence (RCT in chronic cough)							
Chaudhuri, 2004, (67)	Chronic cough (n=88): PNDS (n=30), GERD (n=18), CVA (n=13), bronchiectasis (n=9), and idiopathic cough (n=10)	Fluticasone 1,000 μg or placebo (2 weeks)	Difference in VAS	NA	NA	NA	• FeNO was significantly decreased by –2.1 • Difference in VAS after ICS compared with placebo was 1.0 (–22.3%) • FeNO was identified as a predictive factor of the ICS response
Indirect evidence (observational studies in chronic cough)							
Prieto, 2009, (68)	Chronic cough (n=43)	Fluticasone 200 μg (4 weeks)	VAS (≥50% reduction)	20 ppb	66.7%	77.5%	• Baseline FeNO did not differ: 23.2 ppb in ICS responder and 18.6 ppb in ICS non-responder (P=0.25)
Koskela 2013, (69)	Chronic cough (n=43): UACS (n=22), GERD (n=14), and asthma (n=9)	Budesonide 800 μg (12 weeks)	LCQ (≥1.3)	16.3 ppb	47%	89%	• FeNO levels were 19.7 ppb in ICS responder and 9.8 ppb in ICS non-responder
Shebl, 2020, (63)	Chronic cough (n=70) and Healthy control (n=20)	High-dose ICS (4 weeks)	VAS (≥1 reduction)	34.5 ppb	85%	90%	• Significant correlation between FeNO and sputum eosinophils (r=0.666)
Hahn, 2007, (70)	Chronic cough (n=64): asthma (n=31), GERD (n=15), PNDS (n=17), EB (n=8)	No definition of ICS	Subjective measurement	38 ppb	90%	85%	• FeNO was 51.3±20.1 ppb in ICS responder and in 26.0±16.5 ppb in ICS nonresponder (P<0.001)
Hsu, 2013, (71)	Chronic cough (n=44): UACS (n=31), EB (n=27), and CVA/borderline AHR (n=14)	Fluticasone 500 μg (at least 2 weeks)	Subjective measurement	33.9 ppb	94.7%	76.3%	NA
Watanabe, 2016, (72)	Chronic cough (n=77): CVA (n=39), postinfectious cough (n=10), and atopic cough (n=4)	No definition of ICS	Subjective measurement	44.5 ppb	47.6%	97.1%	• FeNO was 54.5±7.1 ppb in ICS required group and 21.1±1.6 ppb in ICS non-required group (P<0.001).
Lamon, 2019, (73)	Chronic cough (n=100)	Medium dose ICS (at least 3 months)	Subjective measurement	25 ppb	86.4%	53.7%	• Proportion of ICS responders was greater in the high FeNO group (≥25 ppb) than the normal FeNO group (<25 ppb) (86.4% *vs.* 46.3%, P<0.05).

FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid; RCT, randomized controlled trial; PNDS, postnasal drip syndrome; GERD, gastroesophageal reflux disease; CVA, cough variant asthma; VAS, visual analogue scale; NA, not applicable; UACS, upper airway cough syndrome; LCQ, Leicester Cough Questionnaire; EB, eosinophilic bronchitis; AHR, airway hyperresponsiveness.

Table 4 Knowledge gaps and research questions for future study in the application of FeNO for the treatment of chronic cough

Knowledge gaps	Research questions
Lack of strong clinical evidence of FeNO as a predictor of the ICS response	• Is FeNO precise enough for predicting the ICS response of chronic cough in RCTs? • What is the optimal value of FeNO associated with ICS response? • Are patients with chronic cough and high FeNO exclusively efficacious when treated with ICS?
Comparative study of biomarkers	• Which biomarkers could better predict the response of ICS among FeNO, blood eosinophils, and sputum eosinophils?
Stability of clinical and biologic characteristics	• Is treatable trait determined by FeNO static or variable in a longitudinal study? • Is FeNO related to the longitudinal outcomes (persistence or relapse)?
Mechanistic evidence of FeNO	• Is high FeNO causally linked to the development of chronic cough or an ancillary finding secondary to eosinophilic inflammation? • What is the optimal biomarker related to the pathogenesis of chronic cough?

FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid.

high FeNO is closely associated with the ICS response (77). Accordingly, patients with chronic cough and high FeNO could be initially or sequentially treated with ICS. FeNO of more than 30 ppb is generally accepted as a cut-off value for high FeNO, although a few studies indicate that >25 ppb is associated with the ICS response (72,73).

Knowledge gaps

A key knowledge gap in applying FeNO measurement is that there is no high-quality placebo RCT testing FeNO as a guidance for ICS treatment in patients with chronic cough. FeNO level-based stratification may be useful in patient recruitment, particularly for including a group of patients with elevated FeNO levels. The discriminating value (of treatment responsiveness) might be underestimated if most participants have low FeNO levels, due to regression to the mean effects of cough. Placebo controls should be included to differentiate placebo effects from true ICS responses. A comparative study of FeNO with blood eosinophils or sputum eosinophils, or a composite score, would be also helpful to identify the best biomarker(s) in treatment decision.

T2 phenotype of chronic cough may not be a fixed trait, as similarly shown in a longitudinal study using sputum eosinophil counts in asthmatics (78). There is no specific guidance on the use of T2 biomarkers in follow-up evaluation of patients with chronic cough. To date, no studies evaluated longitudinal changes of FeNO levels or FeNO-defined T2 phenotype in patients with chronic cough. Such studies would also help elucidate the relationships between FeNO with longitudinal clinical outcomes of cough, such as persistence or relapse. Finally, further study is warranted to understand the mechanistic relevance of NO to cough reflex sensitivity (*Table 4*).

Conclusions

T2 inflammation has emerged as an important inflammatory phenotype in chronic airway diseases and chronic cough. FeNO is clinically relevant as it has diagnostic utility and treatment response predictability in identifying patients with CVA or eosinophilic bronchitis that will benefit from corticosteroid treatment. Therefore, FeNO should be considered a treatable trait in chronic cough. However, strong mechanistic and clinical evidence for the diagnostic roles of FeNO are still lacking. Further studies are warranted to determine the diagnostic roles of FeNO in the management of patients with chronic cough.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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