Biomarkers in cough

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- Cough and airway eosinophilia
- Biomarkers of airway eosinophilia
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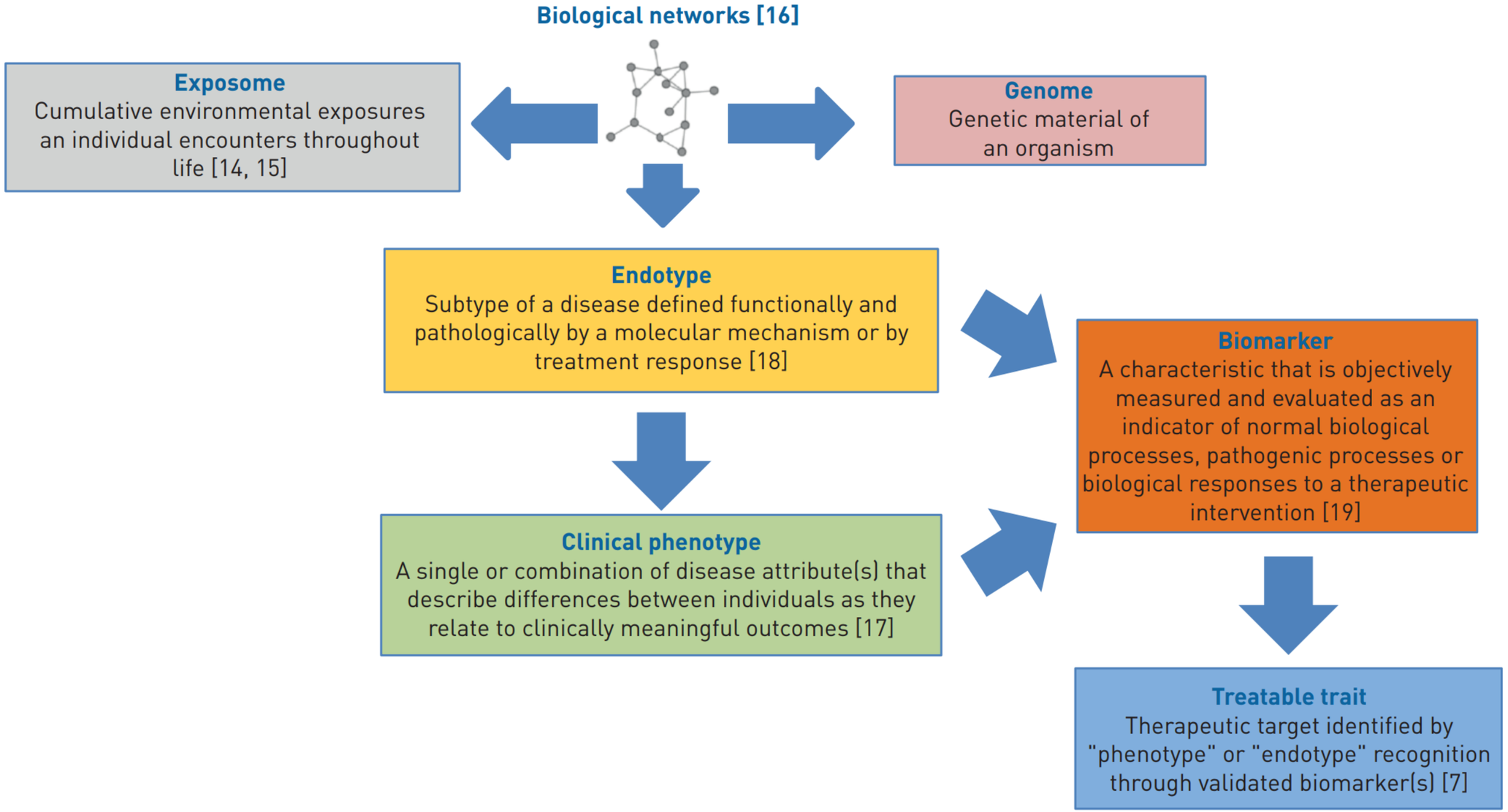
Biomarker



Eur Respir J. 2017;50:1701655.

Treatable trait

TABLE 1 Key components of treatable traits and research opportunities

Domain	Essential	Clinical application
Clinically relevant	Yes	Trait predicts/associates with clinically important outcomes.
Trait identification marker Measurable biomarker	Yes	Identifies the presence of a trait. Appreciation of the measurement characteristics of the test (*i.e.* sensitivity, specificity) is required for optimum use. A test with high specificity is required to "rule in" the presence of a trait. A highly sensitive test can be used to screen, or "rule out" the presence of a trait.
Treatable	Yes	Trait is responsive to a specific targeted therapy. Established *via* randomised controlled trials.

Eur Respir J. 2019;53:1802058.

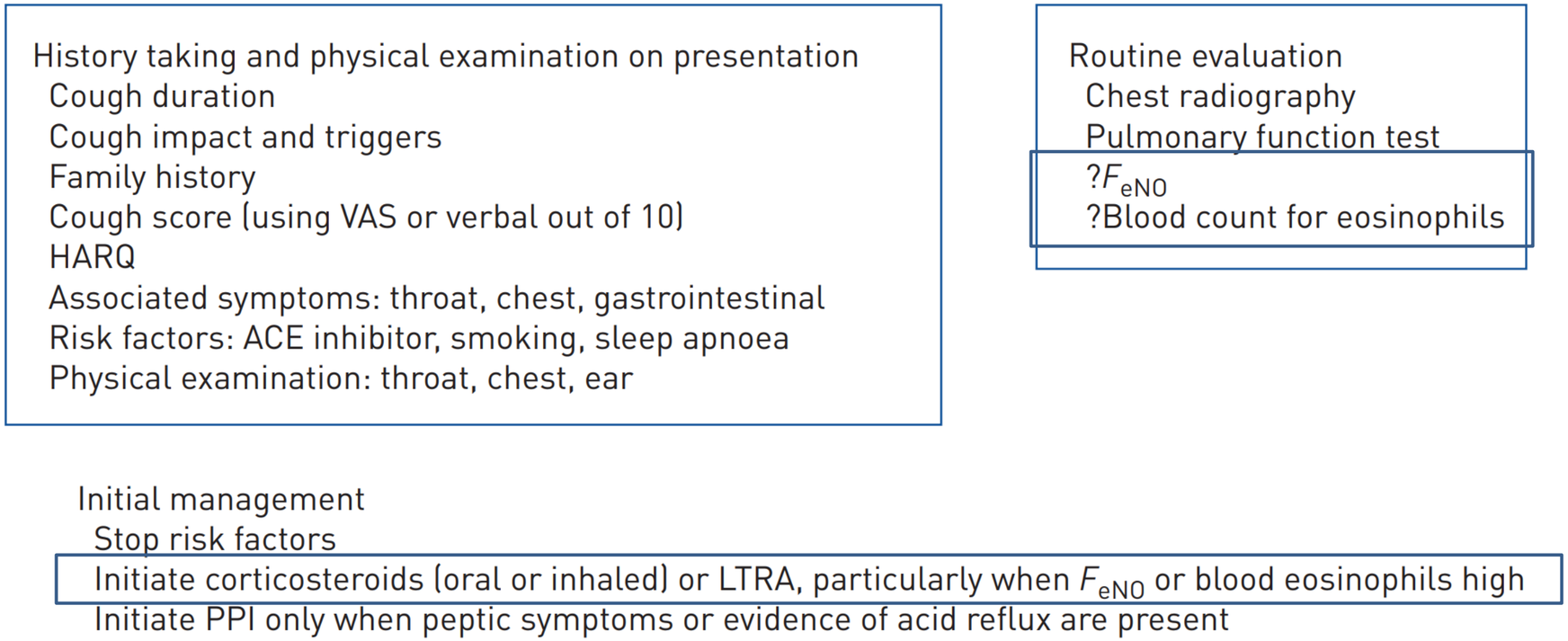
Treatable trait in cough guideline

Phenotypes of chronic cough

- **Asthmatic cough/eosinophilic bronchitis** lies in the therapeutics as it may be considered as a **treatable trait**.

Cough assessment

- The guideline panel placed a higher value on control of any ongoing pathology such as reflux or **airway eosinophilia** before currently available neuromodulatory treatments are considered.



Eur Respir J. 2020;55:1901136.

Asthmatic cough

The New England
Journal of Medicine

Volume 300 MARCH 22, 1979 Number 12

CHRONIC COUGH AS THE SOLE PRESENTING MANIFESTATION OF BRONCHIAL ASTHMA

WILLIAM M. CORRAO, M.D., SIDNEY S. BRAMAN, M.D., AND RICHARD S. IRWIN, M.D.

Abstract Six patients with chronic cough, without history of dyspnea or wheezing, had normal base-line spirometry but hyper-reactive airways, as demonstrated with methacholine. Maintenance therapy with bronchodilators promptly eliminated the cough in all patients. Three to 12 months later therapy was discontinued for three days, cough returned, and detailed pulmonary-function studies were carried out. Again, base-line values were normal, but after methacholine one-second forced expiratory volume decreased an average of 40 per cent in the patients as compared to 3 per cent in normal controls ($P<0.001$). The point of identical flow was increased by methacholine to 43.5 per cent of vital capacity in the patients, as compared to 6 per cent in normal controls ($P<0.001$), and the alveolar plateau was 4.8 ΔN_2 per liter, as compared to 1.4 in normal controls ($P<0.01$). Specific airway conductance was lowered in patients and controls, but the post-methacholine value was significantly lower in the patients.

On the basis of their persistently hyper-reactive airways, inducible diffuse airway bronchoconstriction and excellent response to bronchodilator therapy, these patients appear to have a variant form of asthma in which the only presenting symptom is cough. (N Engl J Med 300:633-637, 1979)

24% - 32% of chronic cough in adult nonsmoker

THE LANCET, JUNE 17, 1989

CHRONIC COUGH: EOSINOPHILIC BRONCHITIS WITHOUT ASTHMA

P. G. GIBSON J. DOLOVICH
J. DENBURG E. H. RAMSDALE
F. E. HARGREAVE

Departments of Medicine and Pediatrics, McMaster University and St Joseph's Hospital, Hamilton, Ontario, Canada

Summary Sputum cell-counts were studied in 7 non-smokers with corticosteroid-responsive chronic cough productive of sputum and 8 smokers with a clinical diagnosis of chronic bronchitis, all of whom had normal lung function tests and methacholine airway responsiveness, and in 10 non-smokers with asthma, examined during an exacerbation. Sputum from asthmatic patients and subjects with corticosteroid-responsive cough contained eosinophils and metachromatic cells. Macrophages were by far the dominant cell type in sputum from subjects with chronic bronchitis. Airway inflammation with eosinophils and metachromatic cells is not always accompanied by increased airway responsiveness, and current definitions of obstructive airways disease may need to be revised.

10% - 30% of cases for special investigation

Asthmatic cough

ASTHMA

Cough, wheeze, SOB

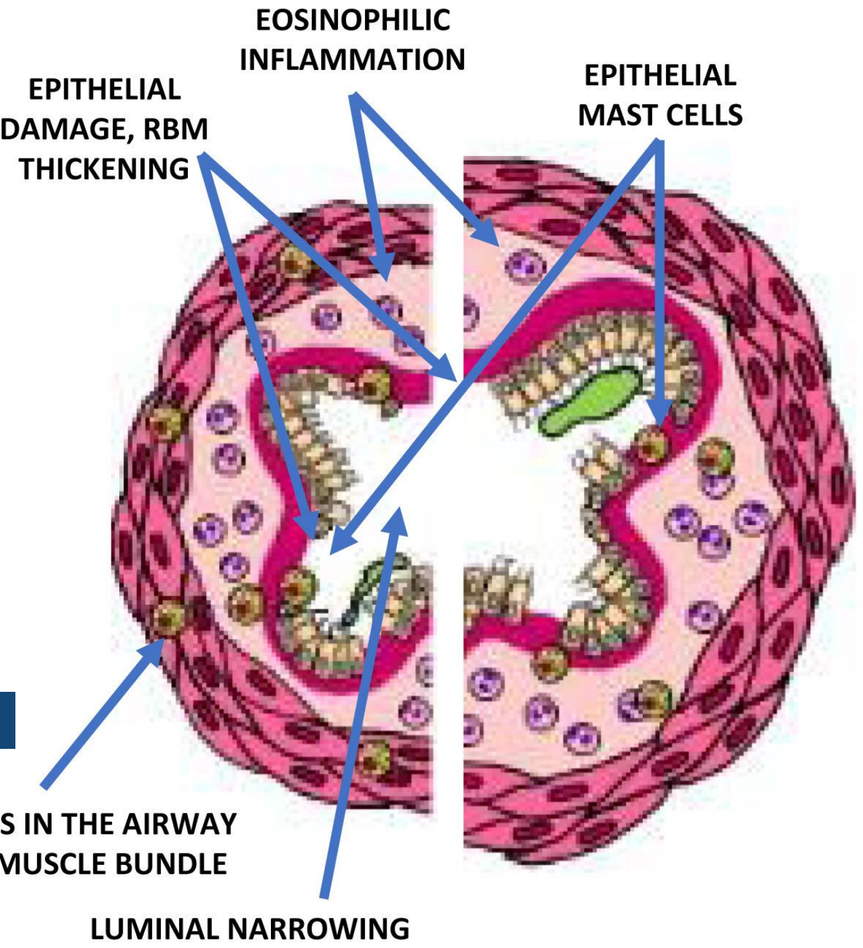
Sputum eosinophilia

Variable airflow obstruction

Lower airway hyper-responsiveness

Luminal narrowing on CT scan

Increased IL-13 expression



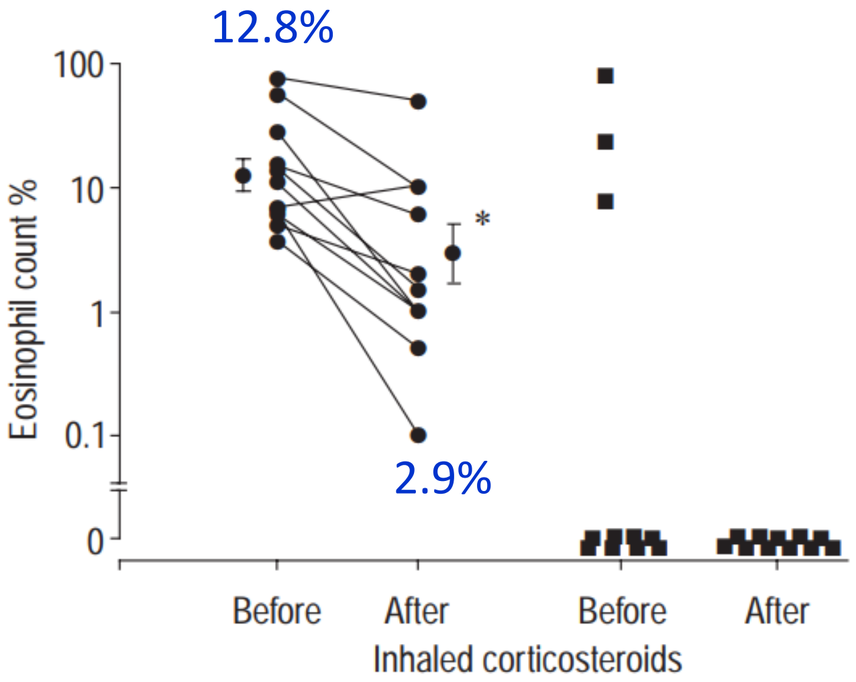
NON-ASTHMATIC EOSINOPHILIC BRONCHITIS

- Chronic cough
- Sputum eosinophilia
- No variable airflow obstruction
- No lower airway hyper-responsiveness
- No luminal narrowing on CT scan

J Allergy Clin Immunol Pract. 2019;7:1740-1747.

Eosinophilic bronchitis

- Open label study in 11 patients with eosinophilic bronchitis
- Cough VAS: 27.2 mm → 12.6 mm ($p<0.01$) after budesonide 400µg for 4weeks



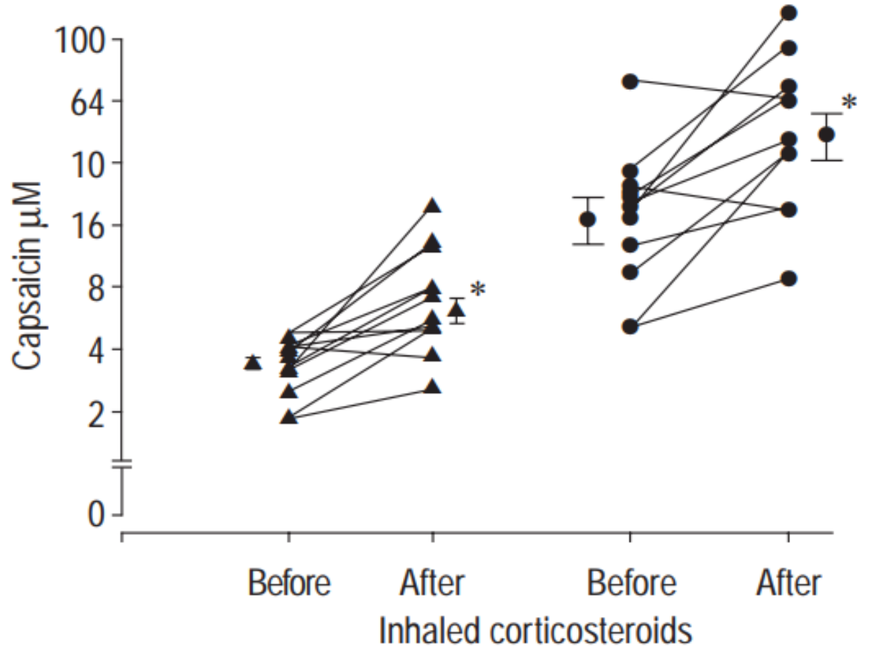


Fig. 2. – Capsaicin concentration causing two coughs (▲) and five coughs (●) before and after inhaled budesonide

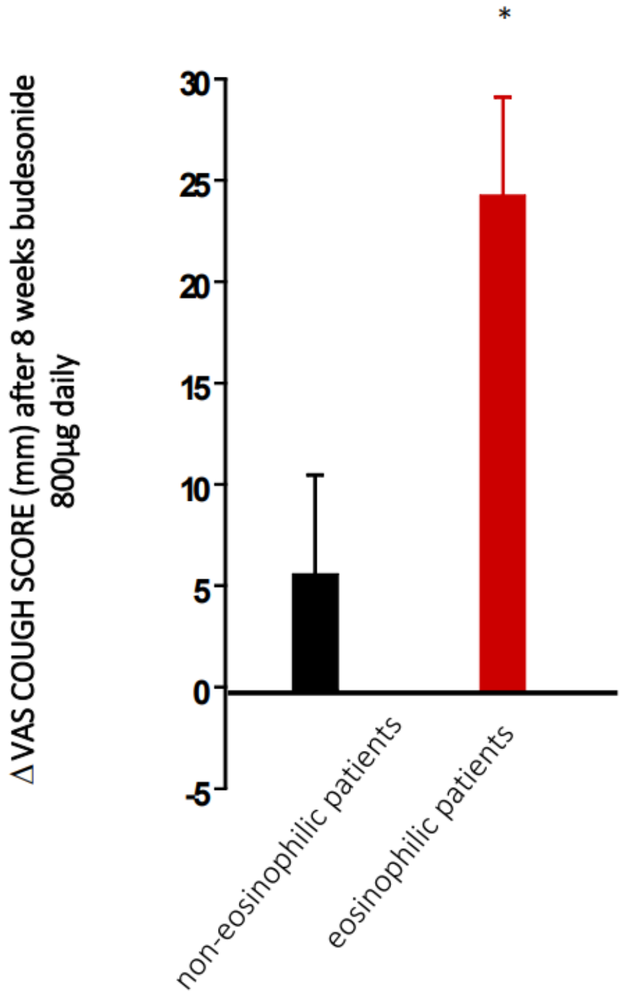
✓ ICS improves cough severity, sputum eosinophilia, and sensitivity, suggesting a causal link between eosinophils and cough.

Eur Respir J. 2000;15:682-686.

Cough response to ICS in asthma

Table 3 Baseline characteristics of patients studied before and after treatment with budesonide 400 µg twice daily for 2 months

	Neutrophilic§ (n=11)	Others¶ (n=38)
Male (%)	27.3	55.3
Age†	57 (21)	45 (22)*
Age at onset†	56 (13)	40 (29)*
VAS (mm)	59 (9)	48 (5)
FEV_1 (% pred)	82 (5.7)	89 (2.4)
FEV_1/FVC ratio (%)	72 (3.2)	74 (0.6)
% atopic	9.1	42.1*
No of current (ex) smokers	2 (5)	3 (10)
PEF (A%M)	22.8 (4)	17.0 (1.5)
Methacholine PC_{20} (mg/ml)‡	1.0 (0.2)	1.3 (0.11)
Sputum eosinophil count (%)†	0.2 (0.9)	6.0 (7.2)*
Sputum neutrophil count (%)	78.5 (2.6)	49.5 (4.1)*

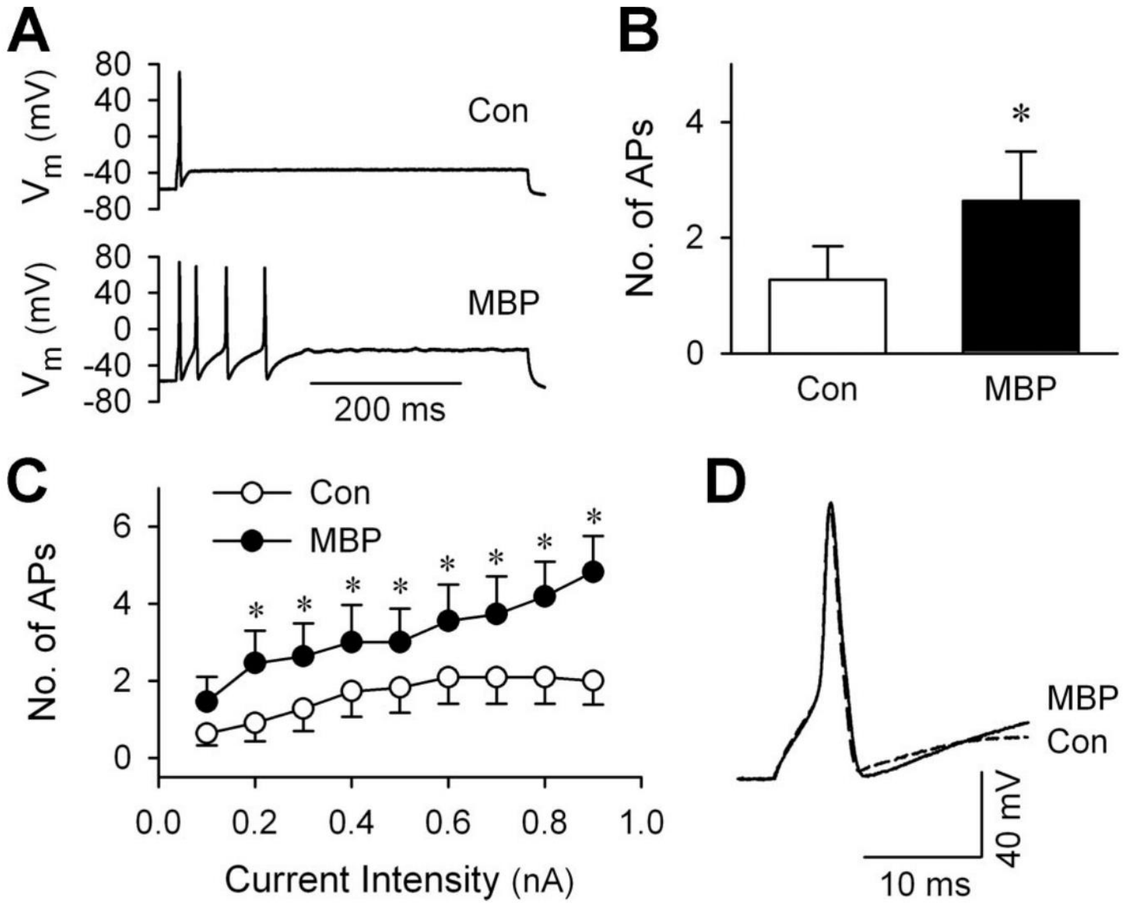


✓ Cough improved in those with eosinophilic inflammation after ICS treatment.

Thorax. 2002;57:875-9.

Cough hypersensitivity and eosinophils

- Effect of major basic protein (MBP) in rat vagal pulmonary chemosensitive neurons

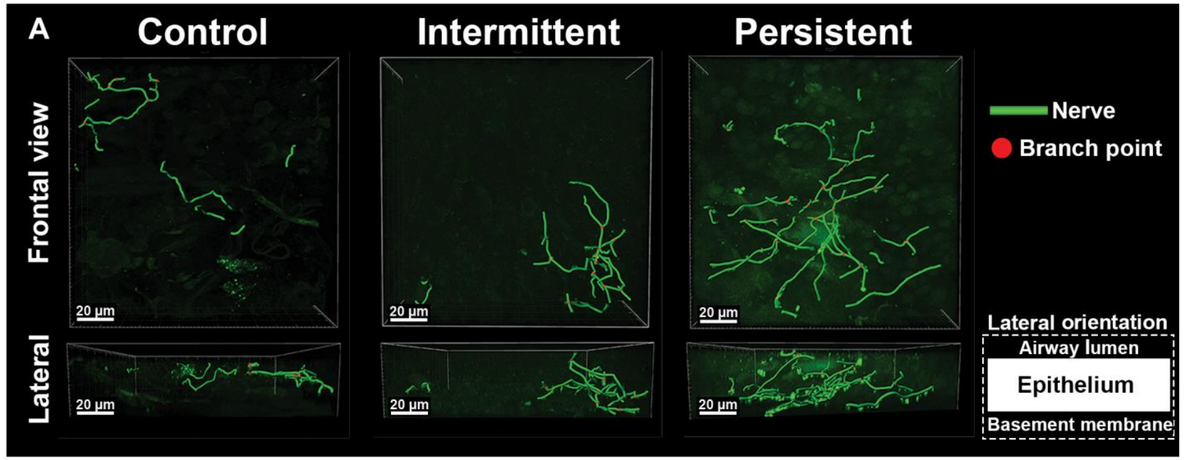


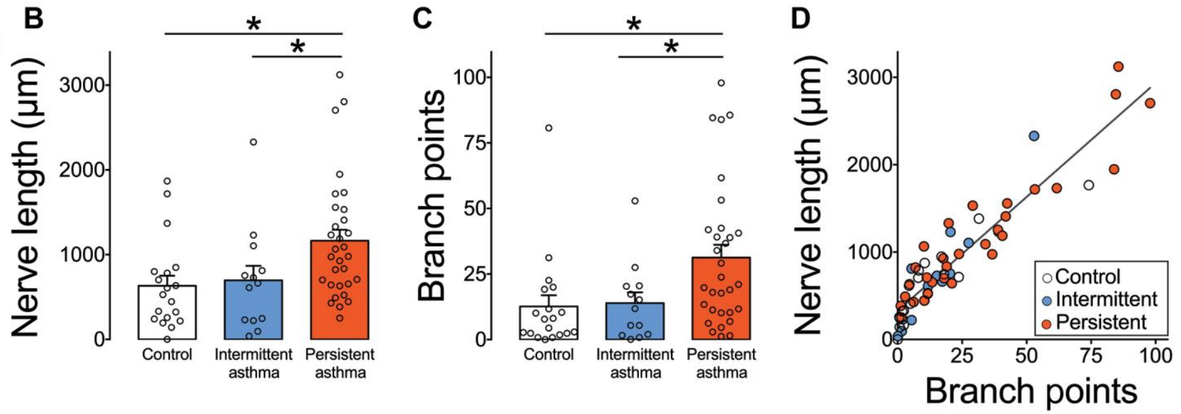
✓ MBP significantly enhanced the excitability of rat vagal pulmonary chemosensitive neurons.

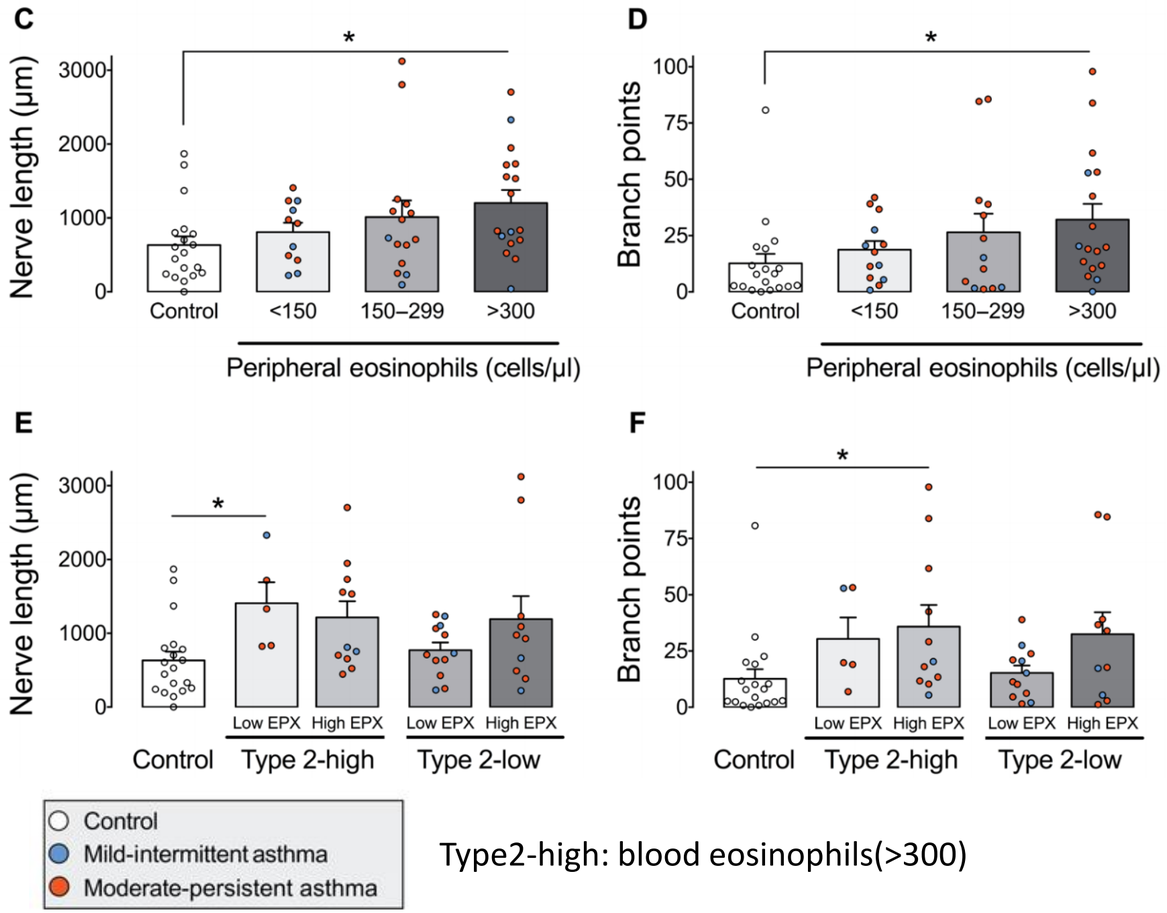
Am J Physiol Lung Cell Mol Physiol. 2009;296:L453-61.

Nerve density and eosinophils

- Human bronchial biopsy in asthma







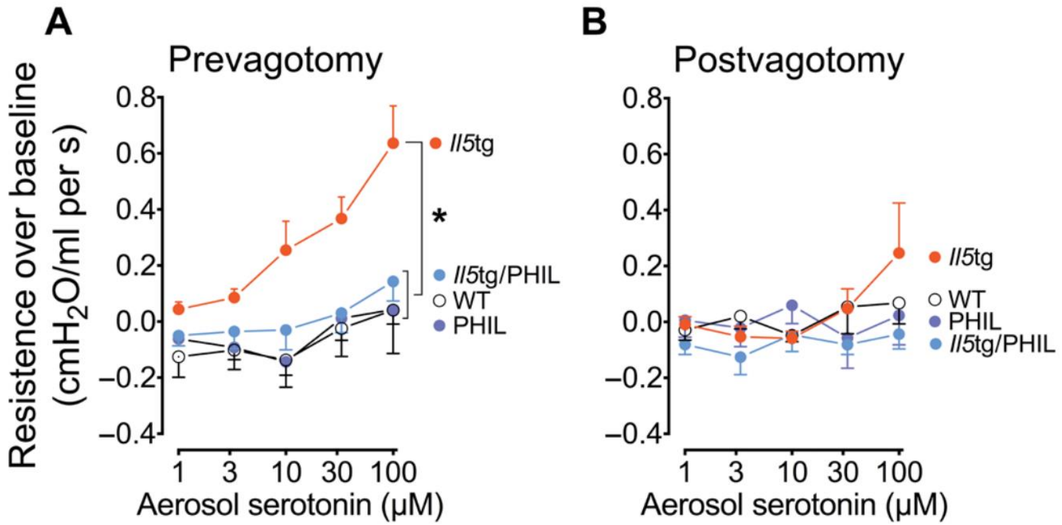
Type2-high: blood eosinophils(>300)

✓ Airway and blood eosinophils are associated with increased airway innervation.

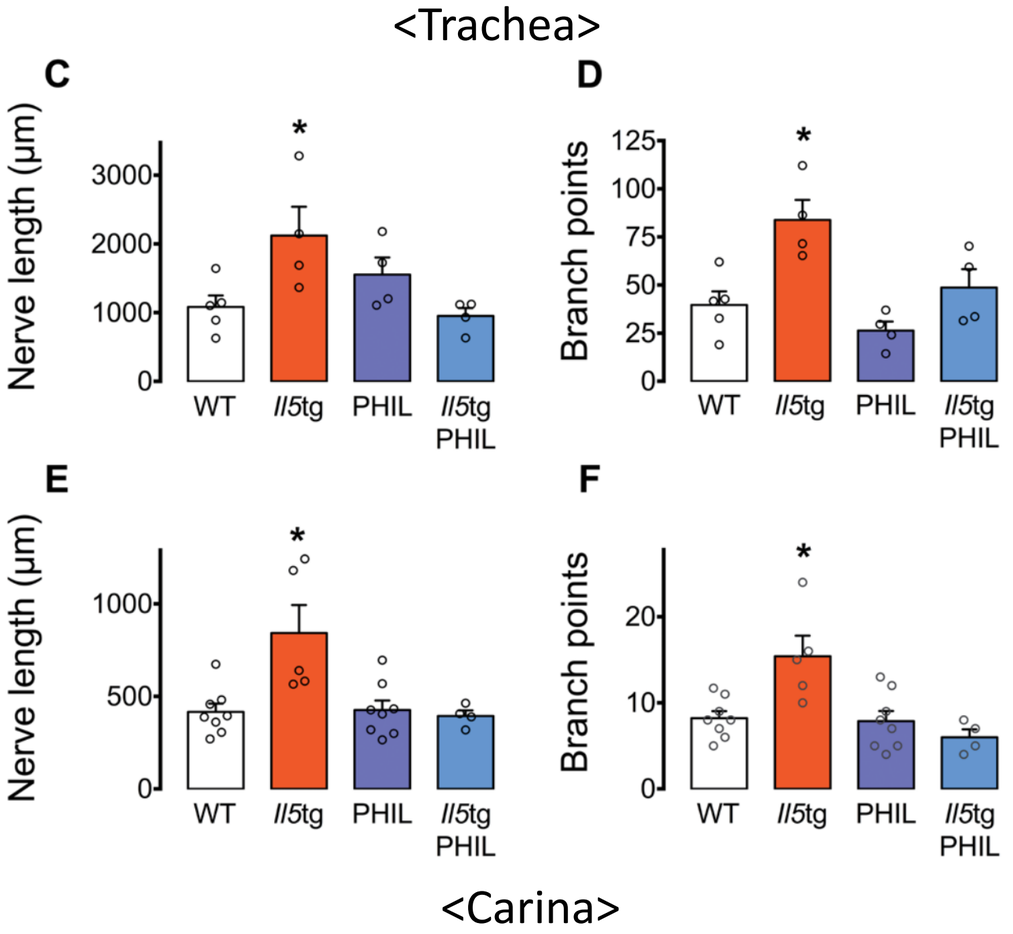
Sci Transl Med. 2018;10:eaar8477.

Nerve density and eosinophils

- Animal study (mouse)



Il5 overproduction (*Il5*tg)
eosinophil-deficient mice (PHIL)

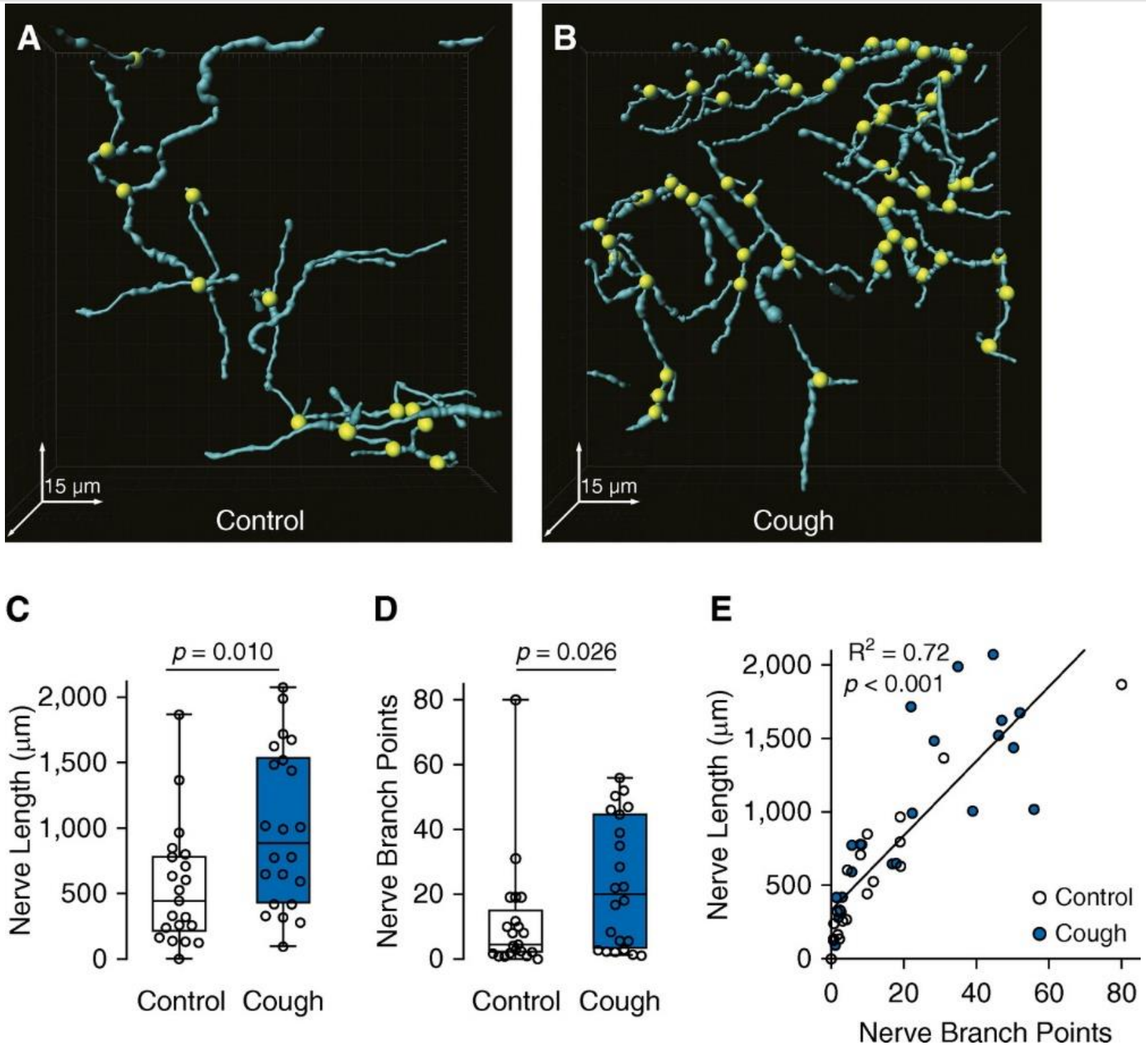


✓ Airway eosinophils increase sensory innervation and cause neuronally mediated airway hyperresponsiveness.

Sci Transl Med. 2018;10:eaar8477.

Nerve density in chronic cough

	Control (*n* = 21)	Cough (*n* = 22)
Age, yr, median (range)	57 (21–76)	56 (31–76)
Female, *n* (%)	15 (71)	13 (59)
Body mass index*	27 ± 4.8	27 ± 4.4
Blood eosinophil count, cells/μl	0.159 ± 0.1	0.200 ± 0.1
Prebronchodilator spirometry		
FEV_1, L	2.73 ± 0.6	2.93 ± 0.8
Percent predicted	96.3 ± 12	99.0 ± 12
FVC, L	3.51 ± 0.8	3.84 ± 1.2
Percent predicted	97.8 ± 12	102.4 ± 15
FEV_1/FVC ratio	78 ± 7	77 ± 7
Use of inhaled corticosteroid, *n* (%)	0	3 (14)
Use of systemic corticosteroid, *n* (%)	0	1 (5)
Former smoker, *n* (%)	4 (19)	4 (18)



- ✓ Airway epithelial sensory nerve density is increased in chronic cough.
- ✓ Nerve length and branching were not associated with eosinophil peroxidase.

Am J Respir Crit Care Med. 2021;203:348-355.

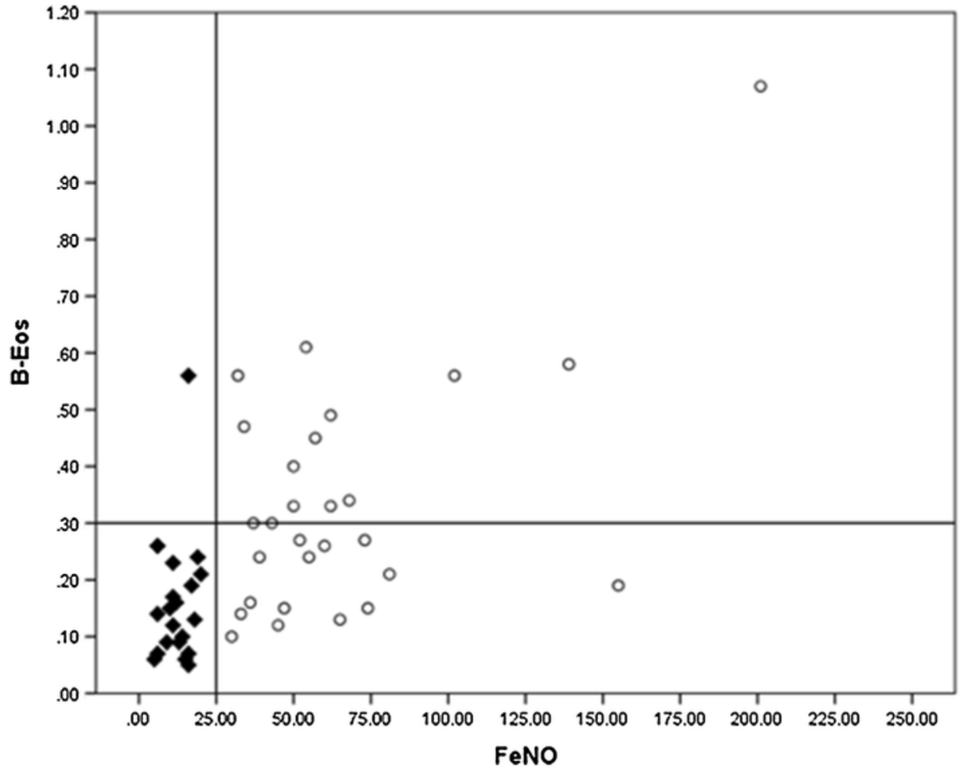
Biomarkers of airway eosinophilia in asthma

Biomarker	Strength	Weakness
Induced sputum	• Correlates with: Airway inflammation Decreased FEV1 Increased bronchial hyperresponsiveness Exacerbation risk • Treatment responses	• Difficult to obtain • Expensive • Technically demanding • Time consuming • Not widely available technique
Blood eosinophils	• Correlates with airway inflammation • Inexpensive • Easy to obtain (in contrast to induced sputum eosinophils) • Predictor of response to type 2 targeting therapies	• Reduced blood eosinophil counts in patients treated with oral corticosteroids • Variable
Exhaled nitric oxide	• Correlates with airway inflammation • Easy to obtain • Noninvasive measurement • Indicator of airway IL-13 activity: strongly correlated with the expression of NOS2 in airway epithelial cells	• Expensive • Not widely available • Influenced by allergy, gender, smoking and inhaled corticosteroids

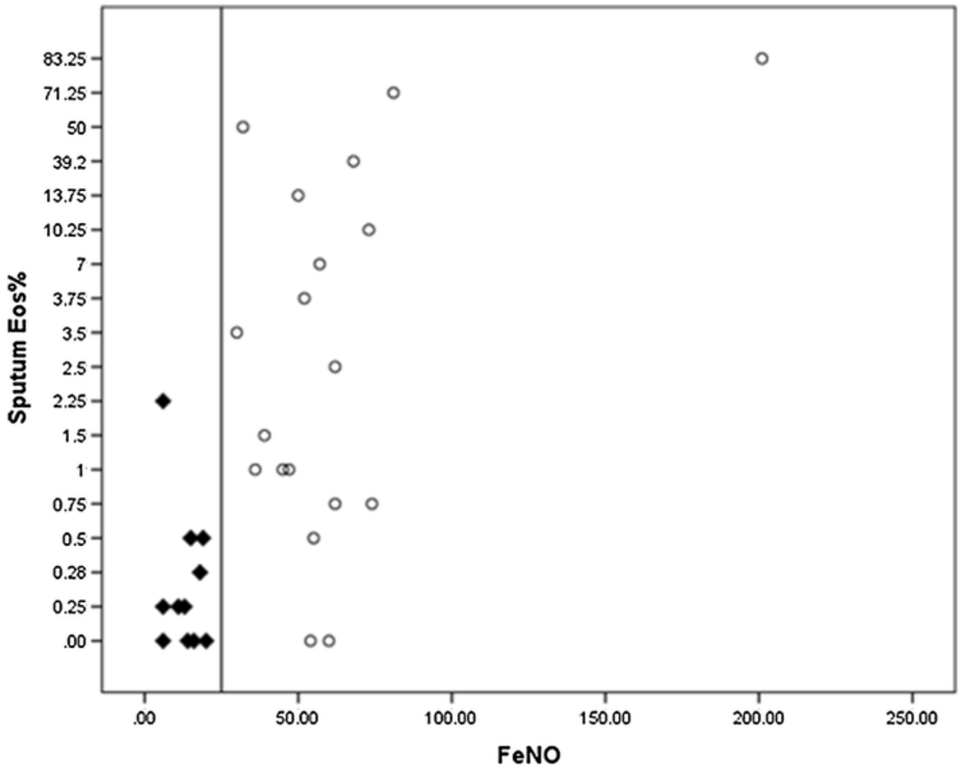
Mabs. 2018;10:34-45.

Correlation of biomarkers in chronic cough

- 30 patients with high FeNO (> 30 ppb) and 20 patients with low FeNO (< 20 ppb)



$r = 0.79$ ($p < 0.001$)



$r = 0.65$ ($p < 0.001$)

✓ The correlation between B-Eos and sputum eosinophil count was more modest ($r = 0.59$, $p < 0.001$).

Lung. 2018;196:59-64.

Correlation of biomarkers in chronic cough

- Duration of treatment with ICS in eosinophilic bronchitis

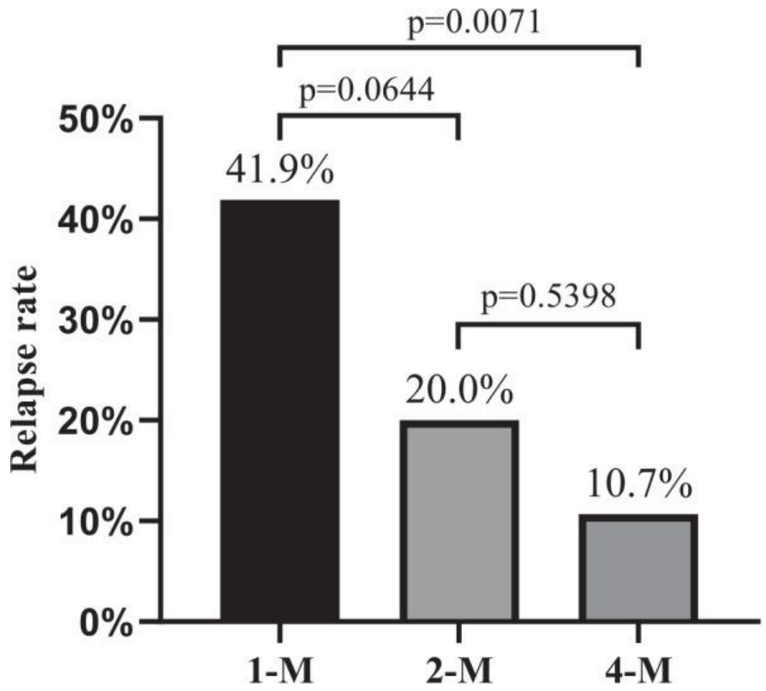


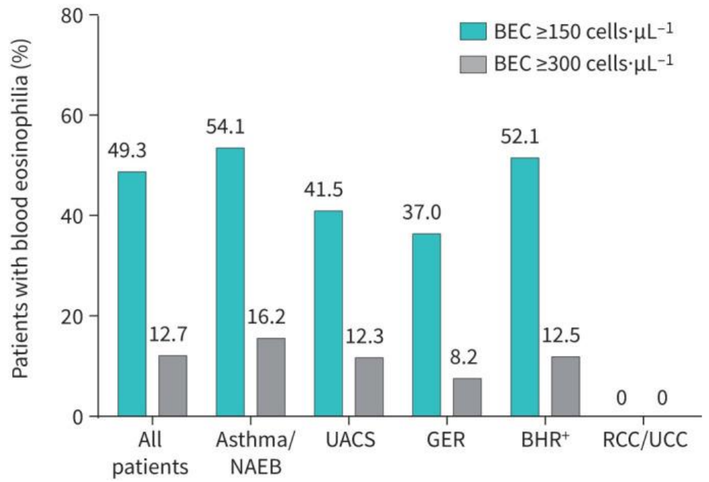
Table 1. Baseline demographic and clinical characteristics.

	1-M group	2-M group	4-M group	*p* value
Case	32	31	31	
Age (years)	43.1 (12.6)	38.1 (13.4)	39.7 (12.5)	0.2928
Sex				
Male	17	14	13	0.6563
Female	15	17	18	
BMI (kg/m²)	22.8 (2.4)	22.7 (2.3)	22.4 (3.2)	0.8614
Smoking history				
Never smoked	29	27	29	N/A
Ex-smoker	3	4	2	N/A
Cough duration (months)[a]	8.0 (2.3–45.0)	3.0 (2.0–12.0)	9.5 (4.0–60.0)	0.0678
Allergic rhinitis	12 (37.5%)	12 (38.7%)	8 (25.8%)	0.4947
Blood eosinophil (10^9/L)[a]	0.15 (0.09–0.20)	0.19 (0.14–0.30)	0.17 (0.06–0.30)	0.6474
Spirometry				
FEV1 (predicted)	102.0% (17.6)	98.6% (13.2)	97.1% (9.0)	0.3707
FVC (predicted)	102.5% (21.6)	104.1% (16.9)	99.3% (12.2)	0.5926
FEV1 / FVC, %	82.9 (10.0)	80.6 (6.9)	83.3 (5.6)	0.3453
Induced sputum				
Eosinophil %[a]	7.6 (4.5–13.0)	8.5 (5.0–26.0)	12.0 (4.0–24.5)	0.5185
Neutrophil %[a]	53.9 (37.9–75.3)	53.0 (22.2–78.7)	55.7 (35.5–72.0)	0.8225
Macrophage %[a]	26.0 (10.4–53.6)	16.0 (6.8–42.5)	21.0 (8.5–46.5)	0.8163
Lymphocyte %[a]	1.0 (0.5–2.9)	1.5 (0.5-3.0)	1.0 (0.5–3.5)	0.9483

Ther Adv Respir Dis. 2019;13:1753466619891520.

Blood eosinophils as a predictor of cough response

- Chronic cough (n = 142)



Correlation

- Blood eosinophils and FeNO: $r = 0.29$ ($p = 0.02$)
- Blood eosinophils and Induced sputum eosinophil percentage: $r = 0.36$ ($p = 0.003$)

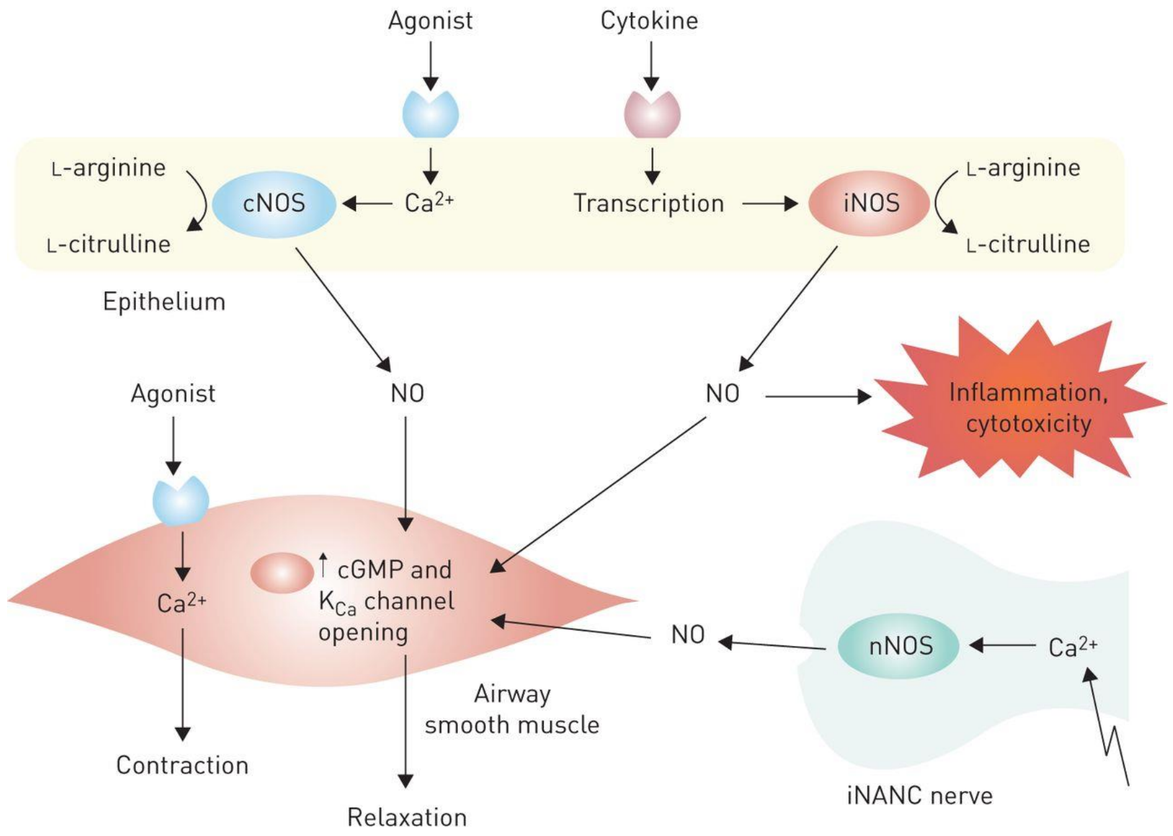
TABLE 3 Diagnostic accuracy of blood eosinophil count in prediction of a good treatment response in patients with chronic cough

	Youden J index	AUC	95% CI	Cut-off BEC threshold cells·µL^{-1}	p-value	Sensitivity	Specificity	PPV	NPV	dACC
All patients	0.23	0.62	0.51–0.72	237	0.026	0.41	0.82	0.50	0.75	0.69
Patients with asthma or NAEB										
Asthma/NAEB	0.34	0.68	0.55–0.81	150	0.005	0.75	0.59	0.53	0.79	0.65
Asthma/NAEB/UACS	0.25	0.63	0.52–0.74	171	0.019	0.58	0.68	0.49	0.75	0.64
ICS/ICS+LABA therapy	0.37	0.69	0.56–0.82	150	0.005	0.74	0.63	0.57	0.78	0.67

✓ Blood eosinophil count is a poor predictor of treatment response in adults with chronic cough.

ERJ Open Res. 2021;7:00432-2021.

Production and function of FeNO

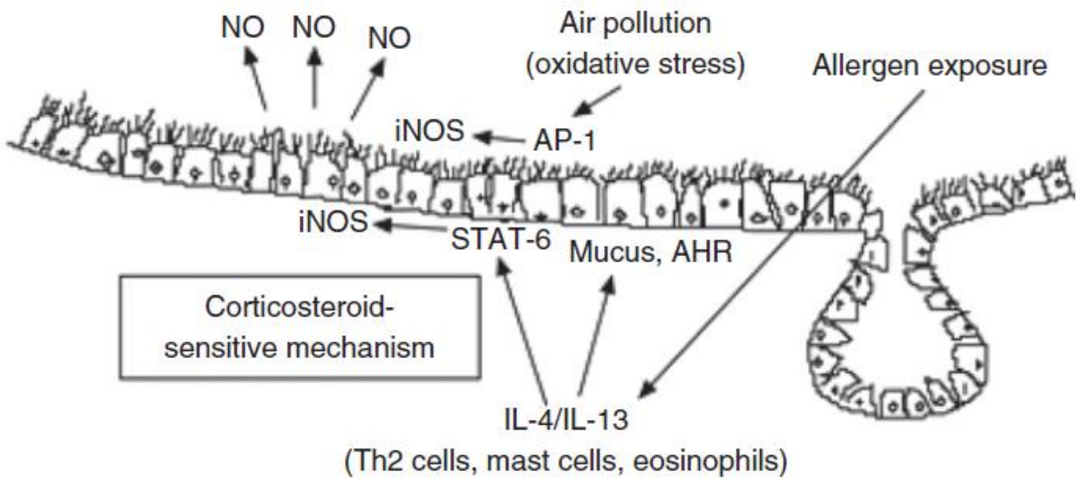


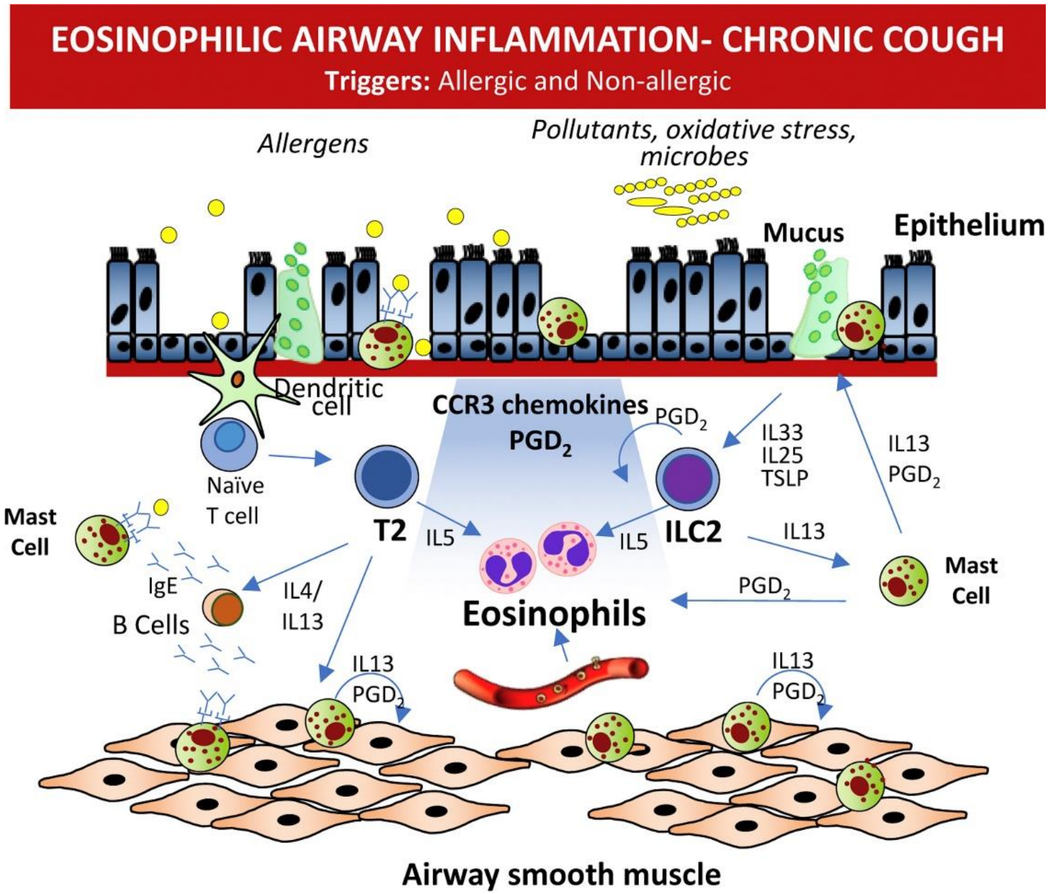
NOS, nitric oxide synthase

Physiology	Pathophysiology
Neurotransmission	Bronchial hyperreactivity
Bronchodilation	Vasodilation
Surfactant production	Free radical production
Mucous secretion	Mucous hypersecretion
Ciliary motility stimulation	Ciliary motility inhibition
Antiinflammatory effect	Proinflammatory effect

Eur Respir J. 2020;55:1901633.

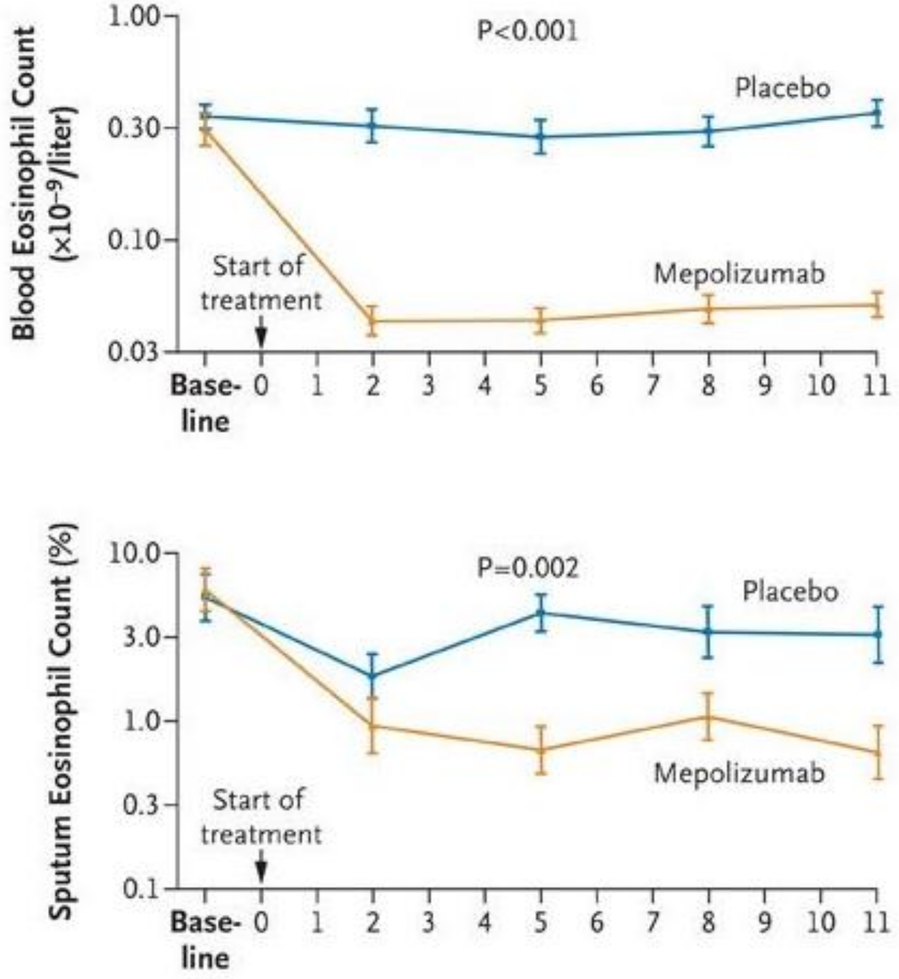
Regulatory mechanism of FeNO

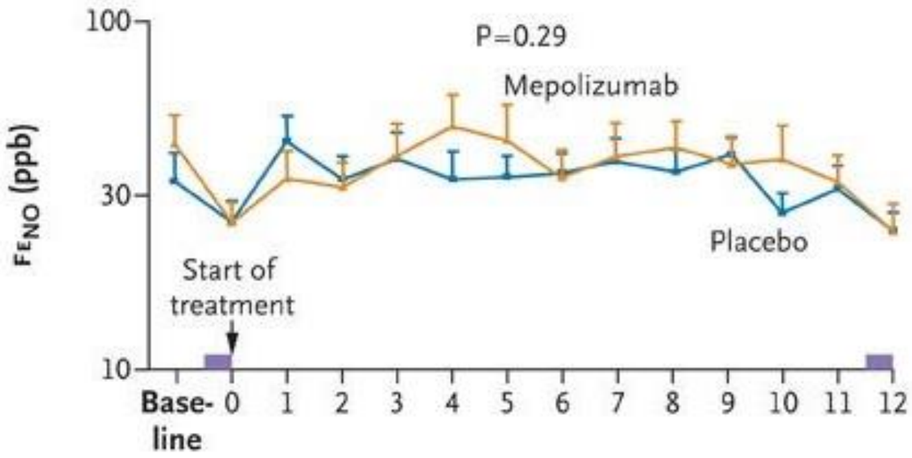




J Allergy Clin Immunol Pract. 2019;7:1740-1747.

Regulatory mechanism of FeNO





N Engl J Med. 2009;360:973-84.

Clinical evidence of FeNO in chronic cough

- Diagnosis of asthmatic cough
- Treatment of chronic cough

Direct evidence	RCT in chronic cough
Indirect evidence	RCT in chronic respiratory symptoms including cough
	Observational study in chronic cough (prospective or retrospective)

Diagnosis of asthmatic cough

- Diagnostic test accuracy of FENO measurement in predicting **CVA**, **EB**, or **both** in adults with chronic cough
- 15 studies involving 2187 adults with chronic cough (10/15 in Asia, 7 in Chinese)

TABLE I. Summary of meta-analyses by RQ

No. of studies	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	Summary AUC (95% CI)	Diagnostic OR (95% CI)	I^2 (95% CI)
RQ1. FENO to predict CVA (in cough ≥8 wk)							
10	0.72 (0.61-0.81)	0.85 (0.81-0.88)	4.7 (3.6-6.2)	0.33 (0.23-0.47)	0.87 (0.83-0.89)	14 (8-26)	94 (89-99)
RQ2. FENO to predict either CVA or EB							
4	0.73 (0.53-0.86)	0.89 (0.84-0.92)	6.5 (4.3-9.8)	0.31 (0.16-0.58)	0.89 (0.86-0.92)	21 (8-54)	44 (0-100)
RQ3. FENO to predict nonasthmatic EB							
4	0.72 (0.62-0.80)	0.83 (0.73-0.90)	4.1 (2.6-6.6)	0.34 (0.25-0.47)	0.81 (0.77-0.84)	12 (6-23)	0 (0-100)

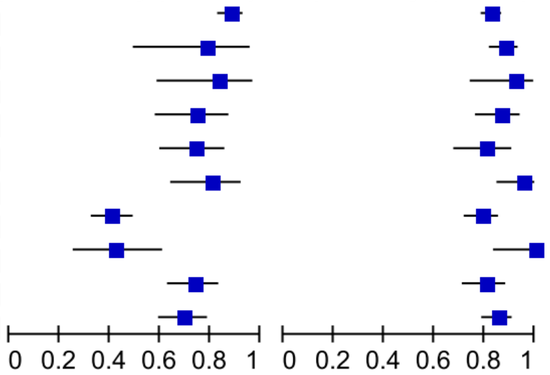
✓ FeNO measurement had a moderate diagnostic accuracy in predicting CVA or EB.

J Allergy Clin Immunol. 2017;140:701-709.

Diagnosis of asthmatic cough

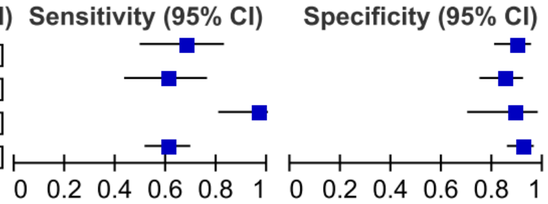
A (CVA)

Study	TP	FP	FN	TN	Cutoff	Sensitivity (95% CI)	Specificity (95% CI)
Kowal 2009	157	63	21	299	40.0	0.88 [0.83, 0.93]	0.83 [0.78, 0.86]
Pizzimenti 2009	11	17	3	125	55.0	0.79 [0.49, 0.95]	0.88 [0.82, 0.93]
Ye 2010	15	2	3	23	15.9	0.83 [0.59, 0.96]	0.92 [0.74, 0.99]
Zhang 2011	29	9	10	58	31.0	0.74 [0.58, 0.87]	0.87 [0.76, 0.94]
Qiu 2012	37	10	13	42	30.0	0.74 [0.60, 0.85]	0.81 [0.67, 0.90]
Lin 2013	29	2	7	42	31.0	0.81 [0.64, 0.92]	0.95 [0.85, 0.99]
Ni 2014	59	32	86	120	36.6	0.41 [0.33, 0.49]	0.79 [0.72, 0.85]
Zhu 2014	14	0	19	20	36.6	0.42 [0.25, 0.61]	1.00 [0.83, 1.00]
Shen 2015	59	18	21	74	33.0	0.74 [0.63, 0.83]	0.80 [0.71, 0.88]
Yi 2016	66	22	29	127	31.5	0.69 [0.59, 0.79]	0.85 [0.79, 0.91]



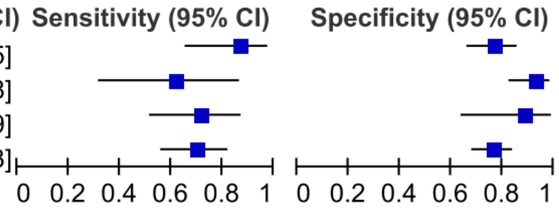
B (CVA or EB)

Study	TP	FP	FN	TN	Cutoff	Sensitivity (95% CI)	Specificity (95% CI)
Oh 2008	23	9	11	74	42.5	0.68 [0.49, 0.83]	0.89 [0.80, 0.95]
Pacheco 2011	23	12	15	66	33.0	0.61 [0.43, 0.76]	0.85 [0.75, 0.92]
Maniscalco 2015	25	3	1	23	33.0	0.96 [0.80, 1.00]	0.88 [0.70, 0.98]
Yi 2016	74	10	48	112	31.5	0.61 [0.51, 0.69]	0.92 [0.85, 0.96]



C (EB)

Study	TP	FP	FN	TN	Cutoff	Sensitivity (95% CI)	Specificity (95% CI)
Oh 2008	19	19	3	62	42.5	0.86 [0.65, 0.97]	0.77 [0.66, 0.85]
Zhang 2011	8	4	5	50	31.0	0.62 [0.32, 0.86]	0.93 [0.82, 0.98]
Lin 2013	20	2	8	15	31.0	0.71 [0.51, 0.87]	0.88 [0.64, 0.99]
Yi 2016	37	29	16	93	31.5	0.70 [0.56, 0.82]	0.76 [0.68, 0.83]



J Allergy Clin Immunol. 2017;140:701-709.

Diagnosis of asthmatic cough

- Diagnostic value of FeNO in cough-variant asthma
- 12 studies involving 1968 participants were selected for the meta-analysis

Table 1. Characteristics of studies included in the Meta-analysis.

Study	Year of Publication	Country	Ethnicity	Age group	Cutoff value (ppb)	CVA of gold standard	FeNO measurement	Expiratory flow rate	Case/Control
Sato et al.	2008	Japan	Asian	Adults	38.8	Blood tests, Pulmonary function tests, Airway hyperresponsiveness testing	Chemiluminescence analyzer	50 mL/s	18/53
Maniscalco et al.	2015	Italy	European	Adults	33.0	ACCP evidence-based clinical practice guidelines [31]	Nasal Nitric Oxide	50,100, and 150 mL/s	26/26
Pizzimenti et al.	2009	Italy	European	Adults	55	NA	NIOX MINO	NA	14/142
Zhang et al.	2011	China	Asian	Adults	40	Chinese Cough Guidelines (version 2009) [33]	NIOX MINO	50 mL/s	39/67
Shimoda et al.	2013	Japan	Asian	Adults	28	European Guidelines [37]	Single breath method	50 mL/s	90/92
Zhu et al.	2015	China	Asian	Children	25.5	Chinese Cough Guidelines for children [36]	Electrochemical method	50 mL/s	38/46
Wang et al.	2015	China	Asian	Children	15.5	Chinese Cough Guidelines for children [36]	Electrochemical method	50 mL/s	120/150
Yi et al.	2016	China	Asian	Adults	33.5	Cough Guidelines [35]	NIOX MINO	50 mL/s	69/175
Asano et al.	2016	Japan	Asian	Adults	58.4	Japanese Cough Guidelines [30]	Chemiluminescence	50 mL/s	40/65
Chen et al.	2017	China	Asian	Adults	25	Chinese Cough Guidelines [32]	NIOX MINO analyzer	50 mL/s	150/300
Kanemitsu et al.	2016	Japan	Asian	Adults	22	Japanese Cough Guidelines [30]	Chemiluminescence analyzer	50 mL/s	104/59
Fang et al.	2017	China	Asian	Adults	24	Chinese Cough Guidelines (version 2010) [34]	NIOX MINO analyzer	50 mL/s	35/50

✓ FeNO test for CVA diagnosis: Sensitivity 0.74, specificity 0.82, and AUC 0.874

J Asthma. 2020;57:335-342.

RCT in chronic cough

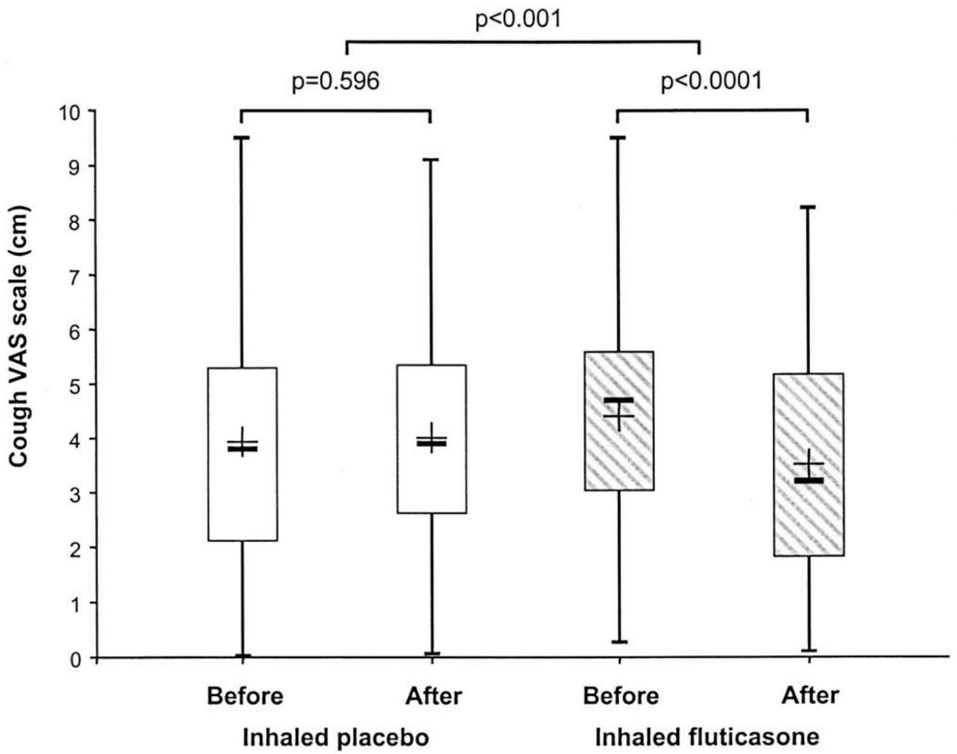
- Double-blind, randomized, placebo-controlled crossover study in Scotland
- Adults with a cough for more than 1 year (n = 88, mean duration of 16.2 years)
- First RCT study to demonstrate an improvement of cough after high dose ICS for 2 weeks

	Normal/ cutoff	All causes	PNDS	GERD	CVA	Bronchiectasis	Idiopathic cough
No.		88	30	18	13	9	10
Exhaled NO, ppb	9	10.4* (5.7)	8.9 (3.5)	10.0 (3.8)	12.6 (7.6)	11.2 (3.7)	8.6 (4.3)
CO, ppm	4	3.7 (1.1)	3.6 (1.0)	3.7 (1.4)	3.4 (0.9)	3.5 (1.2)	4.1 (0.9)
Induced sputum							
Total cell count, × 106	8	10.4* (9.1)	10.1 (7.0)	6.1 (5.6)	7.9 (4.9)	21.3* (12.1)	14.6 (12.9)
Neutrophils, %	53	62 (22.9)†	60.4 (25)	58.1 (20.6)	68.1* (21.2)	81.2 (13)†	62.7 (26.9)
Eosinophils, %	2	1.0 (2.3)	0.3 (0.4)	0.4 (0.5)	2.4 (4.3)	1.4 (3.3)	0.3 (0.8)
Lymphocytes, %	3	0.2 (0.4)	0.3 (0.6)	0.2 (0.4)	0.2 (0.5)	0.1 (0.2)	0.1 (0.2)

✓ Predominant airway neutrophilia rather than eosinophilia

J Allergy Clin Immunol. 2004;113:1063-70.

RCT in chronic cough



Change in cough VAS and noninvasive tests of inflammation

	All causes	PNDS	GERD	CVA	Bronchiectasis	Idiopathic cough
No.	88	30	18	13	9	10
Δ Cough VAS, cm	1.0†	0.9*	1.2	1.4*	0.7	0.5
	(0.4 to 1.5)	(−0.0 to 1.8)	(0.0 to 2.3)	(−0.0 to 2.7)	(−0.9 to 2.4)	(−1.0 to 2.1)
Δ eNO, ppb	−2.1*	0.0	−3.1*	−3.3*	−0.9	−1.4
	(−3.6 to −0.6)	(−2.0 to 2.0)	(−5.8 to −0.5)	(−6.5 to −0.2)	(−4.5 to 2.7)	(−4.8 to 2.1)
Δ Exhaled CO, ppm	−0.3*	−0.1	−0.3	−0.3	−0.7	−0.1
	(−0.6 to −0.0)	(−0.6 to 0.4)	(−1.0 to 0.4)	(−1.1 to 0.5)	(−1.6 to 0.2)	(−1.0 to 0.7)

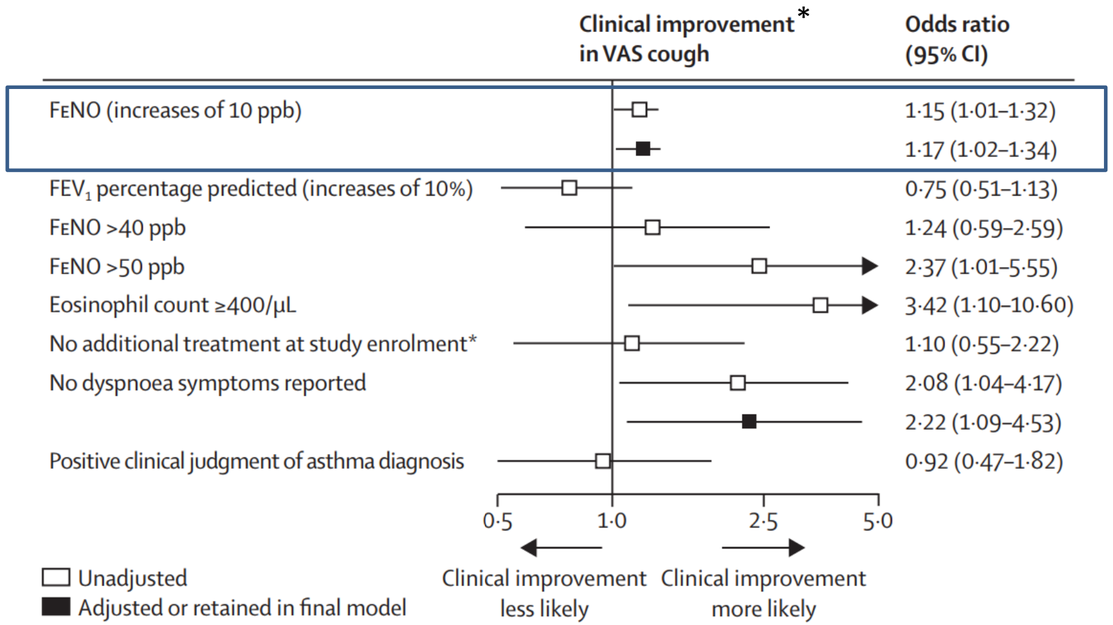
- ✓ Significant improvement in the cough VAS after ICS compared with placebo, accompanied by a decrease in FeNO

J Allergy Clin Immunol. 2004;113:1063-70.

RCT in chronic respiratory symptom

- RCT (ICS or placebo for 4weeks)
- Nonspecific respiratory symptoms
  : cough (85%), only cough (20%), wheeze, or dyspnea and bronchodilator reversibility (<20%)

	Change in outcome		Difference in treatment effect for every 10 ppb increase in baseline FeNO	p value
	Intervention	Placebo		
VAS cough, mm	18·69 (30·02)	11·83 (28·67)	3·406 (0·707 to 6·105)	0·014
VAS symptom, mm	22·04 (30·21)	15·05 (29·09)	2·125 (−0·644 to 4·895)	0·132
FEV_1, L	0·05 (0·18)	0·03 (0·16)	0·021 (0·005 to 0·036)	0·010
FEV_1 percent predicted	1·93% (7·50)	0·73% (5·83)	0·552 (−0·035 to 1·139)	0·065
FVC, L	0·05 (0·23)	0·06 (0·21)	0·013 (−0·008 to 0·034)	0·229
FVC percent predicted	1·76% (8·20)	1·82% (7·90)	0·177 (−0·540 to 0·893)	0·627
FEV_1:FVC	0·00 (0·04)	−0·01 (0·04)	0·002 (−0·002 to 0·006)	0·273
Peak expiratory flow percent predicted	4·05% (12·90)	2·43% (10·76)	0·571 (−0·482 to 1·624)	0·286



*Decrease of at least 20 mm for VAS cough

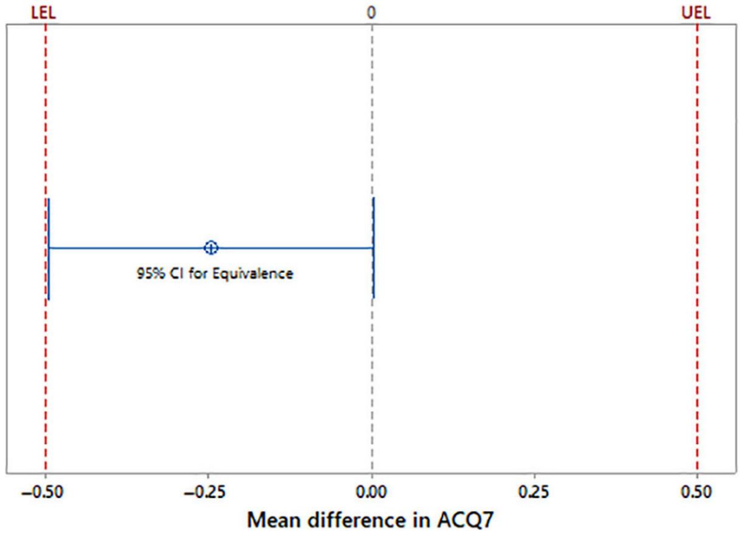
✓ Higher FeNO had a strong association with improvement in cough severity.
✓ FeNO was a better predictor of improvement in cough compared with blood eosinophils

Lancet Respir Med. 2018;6:29-39.

RCT in chronic respiratory symptom

- Suspected asthma and FeNO (≤27) (ICS or placebo for 3months)

Variable	Budesonide *n* = 91	Placebo *n* = 89
Age (years), mean (SD)	42.40 (17.82)	45.80 (18.20)
BMI, kg/m^2, median (IQR)	28.20 (23.53–33.80)	26.67 (23.32–31.60)
Sex – female, *n* (%)	64.00 (70)	66.00 (74)
Presenting symptoms, *n* (%)		
Cough	74.00 (83)	69.00 (80)
Wheeze	58.00 (65)	62.00 (69)
SOB	65.00 (73)	69.00 (80)
Questionnaires, median (IQR)		
ACQ7	1.28 (0.85–2.00)	1.28 (0.57–1.86)
LCQ	17.46 (12.93–20.07)	17.36 (13.43–19.96)
MRC	2.00 (1.00–2.00)	2.00 (1.00–2.00)
Lung function		
FEV_1 (L), mean (SD)	3.02 (0.78)	2.73 (0.72)
FEV_1 % predicted, mean (SD)	95.00 (13.79)	93.11 (14.74)
FVC (L), mean (SD)	3.81 (20.91)	3.52 (0.87)
FEV_1/FVC, mean (SD)	79.24 (8.20)	77.41 (8.50)
FeNO (ppb), mean (SD)	16.31 (6.24)	16.46 (6.75)
Blood eosinophils (cells × 10^9/L),	*N* = 59 0.16 (0.10–0.24)	*N* = 56 0.20 (0.10–0.30)



LCQ increased by 1.85 in ICS and 1.97 in placebo.
: Mean difference in LCQ was −0.12 (−1.06 to 1.31)

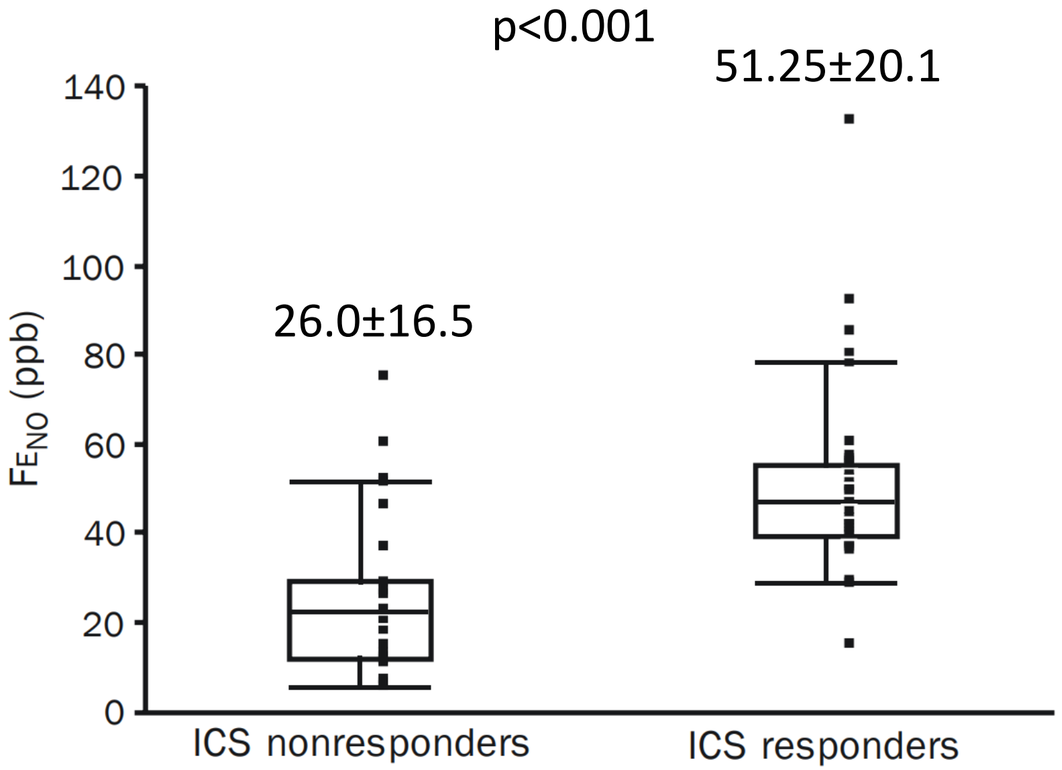
✓ Patients with FeNO ≤ 27 ppb are unlikely to benefit from treatment with an ICS.

Respirology. 2021;26:666-672.

Observational study

- Retrospective observational study of 114 patients evaluated for chronic cough
- 64 patients were prescribed ICS.

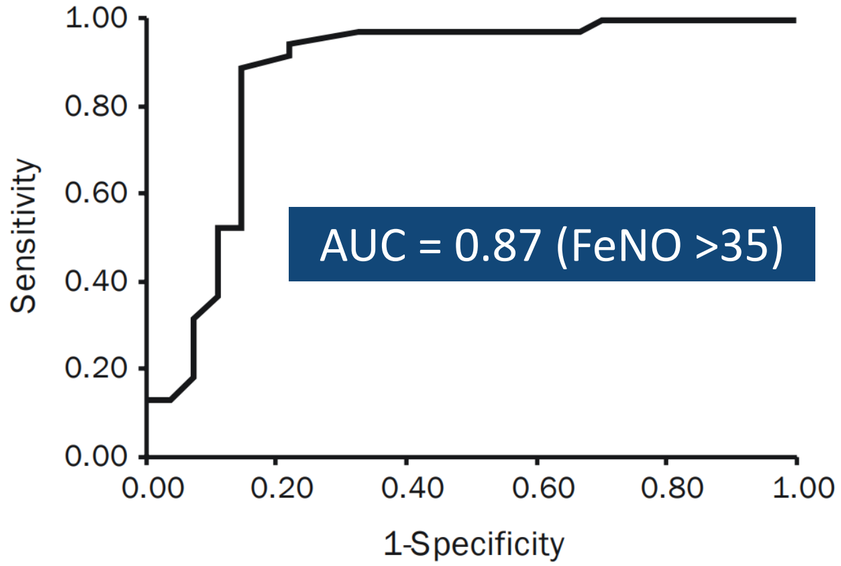
Variable	ICS		*P* value
	Unresponsive (n=26)	Responsive (n=38)	
Age, y	48 ±17	46±13	.43
Female, No. (%)	15 (58)	23 (61)	.82
BMI	28.7±6.7	29.1±10.1	.42
Smoking history, No. (%)	4 (15)	6 (16)	.96
Cough duration, mo	43 (22-63)	40 (18-58)	.36
FEV_1, % predicted	98 ±10	94±8	.43
Current ICS use, No. (%)	3 (12)	6 (16)	.63
Final ICS dose, µg/d†	419±120	445±85	.495
Albuterol or LABA, No. (%)	12 (46)	21 (55)	.32
Follow-up, mo	6 (1-10)	5 (1-9)	.32
Final diagnoses, No. (%)			
Asthma	5 (19)	26 (68)	<.001
GERD	12 (46)	3 (8)	<.001
PNDS	15 (58)	2 (5)	<.001
EB	0 (0)	8 (21)	.01
Other	5 (18)	3 (5)	.18
>1 Diagnosis	10 (36)	4 (11)	.008



Mayo Clin Proc. 2007;82:1350-5.

Observational study

Variable	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
FE_{NO} >35 ppb	95 (83-99)	80 (62-92)	88	91
FE_{NO} >38 ppb	90 (76-96)	85 (76-96)	90	85
MCT	66 (50-79)	46 (29-65)	64	48



- ✓ FeNO accurately predicted response to ICS therapy for chronic cough.
- ✓ The accuracy of FeNO in predicting response to ICS appears to be <u>better than MCT</u>

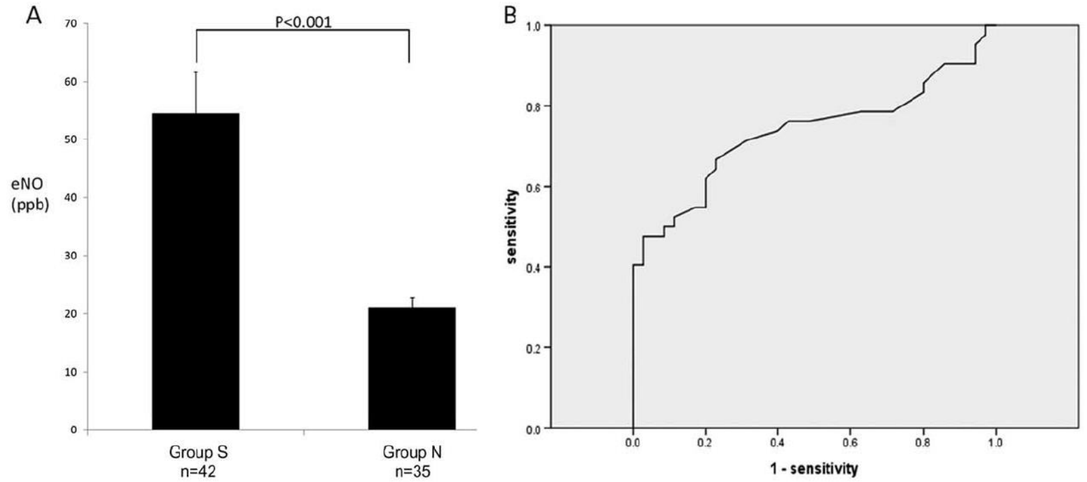
Limitation

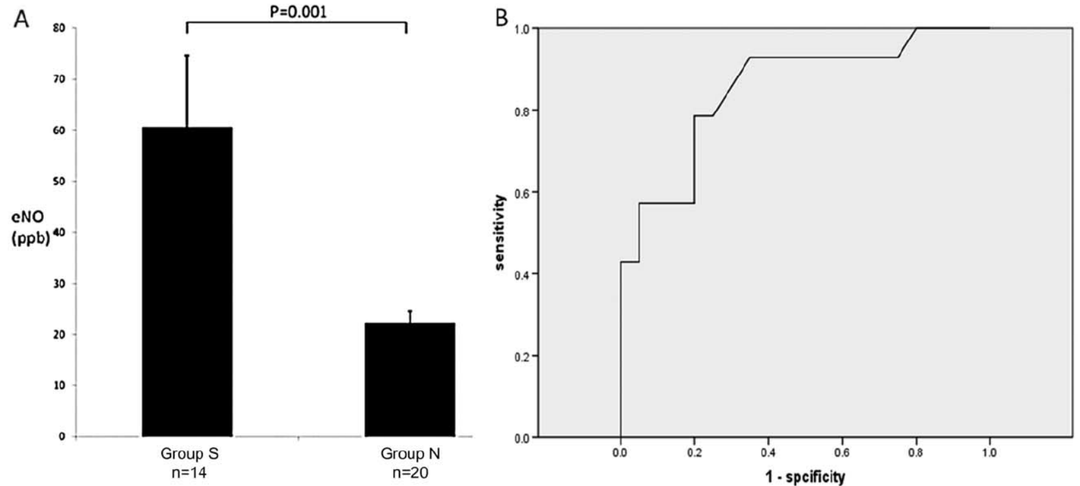
- ✓ Selection bias: patient selection to institute ICS therapy (64/111)
- ✓ No cough specific quality-of-life measurement
  : Response to ICS was determined with clinical documentation

Mayo Clin Proc. 2007;82:1350-5.

Observational study

- Retrospective observational study (n = 77)
- Requirement of ICS: Significant improvement of cough with ICS & ICS therapy more than 3 months
- No requirement of ICS: Improvement of cough without ICS or not improved with ICS





Predicting the requirement of ICS

All

Cut-off	AUC	Sensitivity	Specificity
≥ 44.5	0.735	47.6	97.1

Steroid-naïve & without current

Cut-off	AUC	Sensitivity	Specificity
≥ 26.5	0.852	78.6	80.0

Clin Respir J. 2016;10:380-8.

Observational study

- Retrospective observational study (n = 100)
- High FeNO levels (≥ 25 ppb) were found in 25 patients (25%).
- The proportion of ICS responder was 86.4% in high FeNO and 46.3% in normal FeNO ($p < 0.05$).

	Response to inhaled steroids $n = 38$	No response to inhaled steroids $n = 25$	P
Age	58.1 ± 11.7	60.9 ± 14.3	NS
Female	23 (60.5)	16 (64.0)	NS
BMI (kg/m^2)	26.5 ± 4.1	24.5 ± 4.7	NS
Former or current smoker	10 (26.3)	9 (36.0)	NS
History of asthma	3 (7.9)	3 (12.0)	NS
Time between symptom onset and first visit (months)	48.4 ± 46.9	35 ± 40.4	NS
Age at cough onset (years)	48.9 ± 15.8	55.5 ± 14.3	NS
Rhinitis/sinusitis	15 (39.5)	8 (32.0)	NS
Sensitisation	6 (15.8)	2 (8.0)	NS
FEV1 (L)	2.55 ± 0.89	2.42 ± 1.05	NS
FEV1 (% predicted value)	97.3 ± 25.5	93.3 ± 23.9	NS
FVC (L)	3.87 ±1.08	3.51 ± 1.02	NS
FVC (% predicted value)	110.1 ± 16.8	109.5 ± 18.5	NS
FEV1/FVC (%)	73.7 ± 6.6	71.4 ± 11.5	NS
Blood eosinophils (G/l)	0.14 ± 0.10	0.13 ± 0.07	NS
Steroid dose (µg/day)	1038 ± 563	992 ± 502	NS
FENO (ppb)	45.0 ± 40.2	18.9 ± 3.0	< 0.05

✓ Sensitivity and specificity of FeNO > 25 ppb to predict the ICS response was 86.4% and 53.7%.

Respir Med Res. 2019;76:4-9.

Observational study

- Prospective observational study (n = 43)

Variables	Responders (44%)	Nonresponders	p Value
Age, yr	47 (40–55)	48 (42–54)	0.93
Gender			0.99
Male	8	10	
Female	11	14	
Skin test result positive	9	8	0.53
FEV_1, % predicted	106.7 (100.5–113.0)	118.3 (110.7–125.8)	0.02
FVC, % predicted	107.7 (100.9–114–4)	121.8 (113.9–129.8)	0.01
FEV_1/FVC, %	82.7 (80.6–84.8)	81.3 (79.0–83.5)	0.36
Δ FEV_1 after bronchodilator therapy, %	1.3 (−0.96 to 3.4)	3.9 (2.3 to 5.7)	0.04
PEF variation (amplitude % mean)	6.6 (3.5–9.7)	6.7 (4.6–8.8)	0.96
Increased responsiveness, yes/no			
Methacholine	1/18	3/21	0.42
AMP	1/18	1/23	0.98
BRI, %/log mg/dL			
Methacholine	3.04 (1.58–4.51)	3.78 (2.58–4.98)	0.42
AMP	3.25 (0.96–3.54)	2.29 (1.21–3–38)	0.96
ENO, ppb*	23.2 (17.5–30.7)	18.6 (14.7–24.0)	0.25

- ✓ Sensitivity and specificity of FeNO > 20 ppb to predict the ICS response was 53% and 63%.
- ✓ FeNO level at baseline could not predict the response to ICS therapy in patients with chronic cough.

Chest. 2009;136:816-822.

Observational study

- Prospective observational study (n = 43)
- The response was defined as a ≥ 1.3 points from baseline in Leicester Cough Questionnaire
- FeNO in ICS responder: 19.7 ⇔ FeNO in non-ICS responder: 9.8

Cut-off	Sensitivity	Specificity
≥ 16.3	47	89

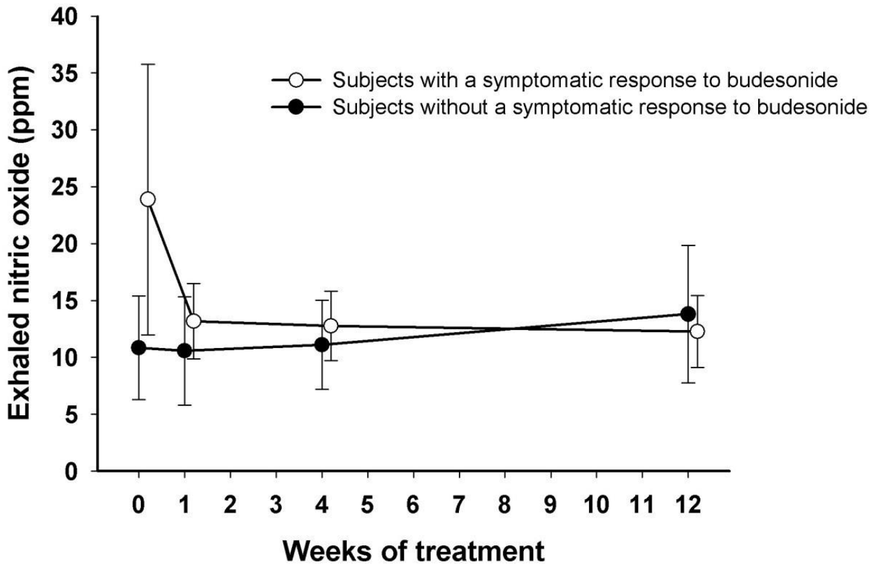


Table 4 Associations of the change in LCQ total score with the changes in exhaled NO concentration and saline CDR at various stages of budesonide treatment

Duration of treatment	Change in NO	Change in saline CDR
1 week	Rs = -0.47, p = 0.038	Rs = 0.37, p = 0.11
4 weeks	Rs = -0.40, p = 0.084	Rs = -0.27, p = 0.26
12 weeks	Rs = -0.39, p = 0.11	Rs = -0.45, p = 0.059

Rs Spearman rank correlation coefficient.

✓ FeNO showed weak predictive value of ICS response.
✓ There was a significant association between the drop in NO and a rise in LCQ.

Cough. 2013;9:15.

Observational study

- Prospective observational study (n = 70)
- The response was defined as a ≥ 1 points from baseline in Cough Symptom Score (0 – 10)

Parameter	Steroid responders *N* = 45(64.3%)	Steroid non-responders *N* = 25(35.7%)	*p*
Age(years) (means ± SD)	47.711 ± 11.885	45.04 ± 9.104	0.333
Male gender *n* (%)	20 (44.4%)	9 (36%)	0.492
BMI(kg/m^2) (means ± SD)	30.044 ± 3.275	30.36 ± 2.856	0.688
CSS	8.3 ± 1.4	7.9 ± 1.6	0.394
FVC % pred. (means ± SD)	96.295 ± 2.12	94.80 ± 3.149	0.06
FEV1, % pred. (means ± SD)	83.533 ± 2.801	91.00 ± 3.606	< 0.001
FEV1/FVC (means ± SD)	85.556 ± 2.312	95.00 ± 1.607	< 0.001
FeNO (ppb) (means ± SD)	48.333 ± 11.576	20.16 ± 8.452	< 0.001
Sputum eosinophils % (means ± SD)	9.062 ± 4.496	1.780 ± 0.847	< 0.001

	FeNO level (ppb) before treatment	FeNO level (ppb) after treatment	*p*
Steroid responsive cough	48.33 ± 11.57	20.16 ± 12.45	0.018
Steroid non-responsive cough	20.16 ± 12.45	19.8 ± 12.36	0.13

Sputum eosinophilia (≥ 3%)

Cut-off	AUC	Sensitivity	Specificity
≥ 33	0.757	65	80

ICS response

Cut-off	AUC	Sensitivity	Specificity
≥ 34.5	0.835	85	90

✓ FeNO can be used as a diagnostic tool of airway eosinophilia and as a predictor for steroid responsiveness in chronic cough

Egypt J Bronchol. 2020;14:15.

Performance of FeNO in predicting response to ICS

- Meta-analysis

Study	Study design	Definition of chronic cough	Cough duration	ICS type/dose	Follow-up	Definition of ICS response
Hahn 2007	Retrospective	≥8 weeks	40.3 months	Fluticasone propionate 434 μg/day	5.3 months	Physician-documented significant improvement in cough, no further diagnostic study ordered for assessment of cough, and no alteration in ICS dose
Hsu 2013	Retrospective	≥8 weeks	15.3 months	Fluticasone propionate 250 μg twice/day	≥2 weeks	Complete control of cough determined by physician
Koskela 2013	Prospective	≥8 weeks	8.5 years	Budesonide 400 μg twice/day	12 weeks	Improvement of > 1.3 points in the Leicester Cough Questionnaire score
Lamon 2019	Retrospective	≥8 weeks	43.1 months	Unspecified ICS 1,020 μg/day	≥3 months	Self-reported reduction of cough frequency
Price 2018	Double-blind randomised placebo-controlled trial	≥6 weeks	–	Beclomethasone dipropionate 800 μg/day	4 weeks	Improvement of ≥ 20 mm in the VAS cough score
Prieto 2009	Prospective	≥8 weeks	–	Fluticasone propionate 100 μg twice/day	4 weeks	Reduction of > 50% in the mean daily cough symptom scores
Shebl 2020	Prospective	≥8 weeks	–	–	4 weeks	Complete cough disappearance according to a cough symptom score[a]
Watanabe 2016	Retrospective	≥3 weeks	15.4 months	–	3 months	Significant improvement in cough with ICS declared by the patient and confirmed by the physician
Yi 2016	Prospective	≥8 weeks	–	–	–	Complete control of cough determined by physician[b]

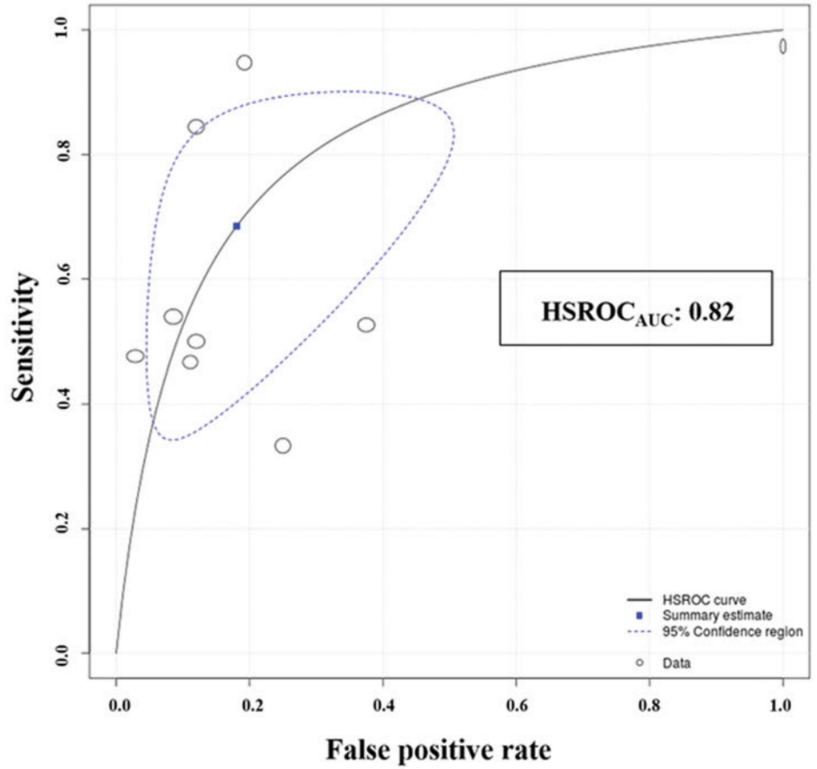
Ann Med. 2021;53:1659-1672.

Performance of FeNO in predicting response to ICS

- 9 studies (n = 740) showed that the response rate to ICS was

  87.4% (83.8–91.0) in 317 patients with a high FeNO and **46.3%** (41.6–51.0) in 423 controls.

AUC	Sensitivity	Specificity
0.82	68.5	81.9



- ✓ High FeNO may help identify chronic cough patients responding to ICS treatment.
- ✓ Suggested cut-off value of FeNO is ≥ 25 ppb

Ann Med. 2021;53:1659-1672.

Summary

- Asthmatic cough is suggested as a treatable trait of chronic cough.
- Biomarkers of airway eosinophilia were used to identify asthmatic cough.
- Blood eosinophils have limited evidence in chronic cough.
- FeNO has been identified as moderate degree of diagnostic utility.
- High FeNO may have the potential to be used as a predictor of the response to ICS.
- More clinical studies and experience on the diagnosis and treatment of chronic cough with FeNO in Korean patients are urgently needed.

경청해 주셔서 감사합니다