Brigham and Women's Hospital
Founding Member, Mass General Brigham

Assessment and Management of the Patient with Chronic Cough

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DISCLOSURES

None

Summary

- Chronic cough lasting more than 8 weeks is most commonly due to upper airway cough syndrome (UACS), type 2 inflammation in the airways (eosinophilic bronchitis or asthma), GERD, or ACEI therapy, and sometimes more than one of these

- Less common causes of chronic cough include chronic bronchitis, tuberculosis, lung cancer, and foreign body aspiration

- Cough that persists despite adequate trials of empiric therapy or remains unexplained is called Refractory Chronic Cough (RCC) or Unexplained Chronic Cough (UCC), which are likely caused by cough reflex hypersensitivity and vagal neuropathy

- Treatment options for RCC/UCC include speech therapy, cough desensitization, anticholinergics, certain neuromodulators, and (occasionally) time-limited opioids. New treatments are under development.

Review question 1

A 45-year-old non-smoking female presents to her primary care physician with a persistent cough of three months duration. She reports no associated fever, shortness of breath, or wheezing. She has a history of hypertension, for which she was started on lisinopril six months ago. Vital signs are within normal limits. Physical examination is unremarkable, and pulmonary auscultation reveals no abnormalities. Chest X-ray shows no infiltrates or masses. Which of the following is the most appropriate next step in evaluation and management?

A) Obtain spirometry
B) Initiate inhaled beta-agonist therapy
C) Start a trial of proton pump inhibitor therapy
D) Discontinue lisinopril

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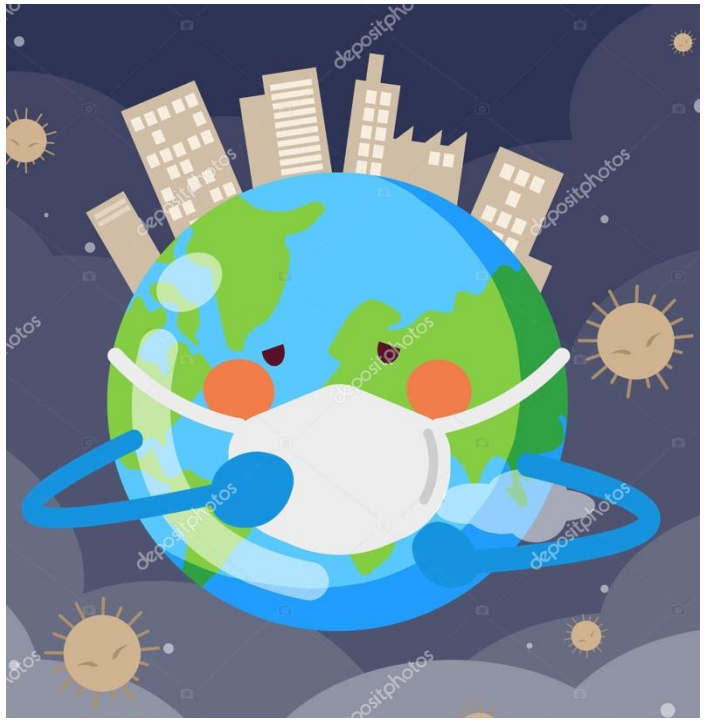
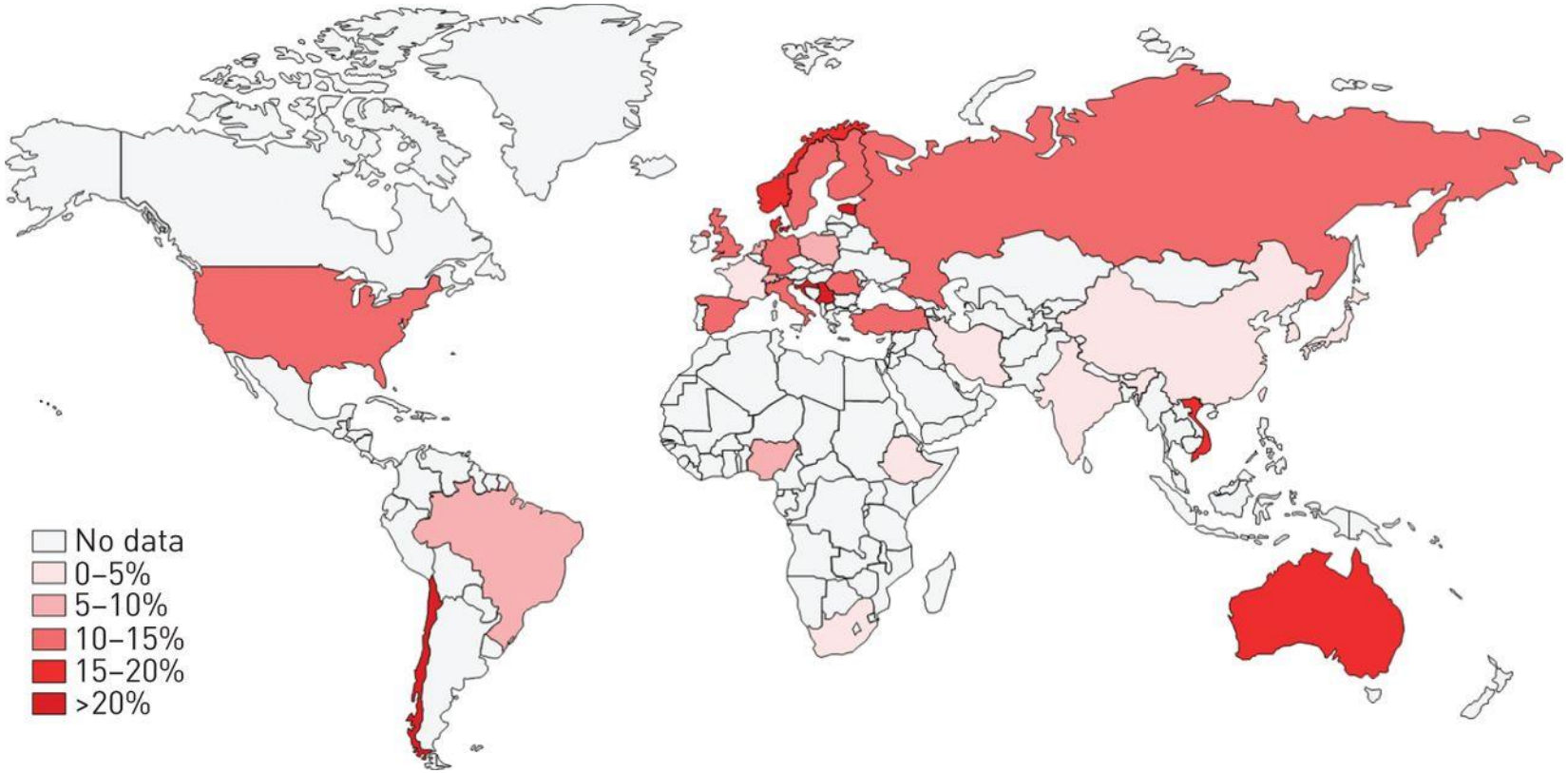
Epidemiology and definition of chronic cough

- Cough represents about 30 million annual clinic visits in the U.S., likely more in the era of CoVID
- Subacute (3-8weeks) and chronic (>8 weeks) cough can make up about 40-50% of a community outpatient pulmonary practice volume
- Women tend to have heightened cough sensitivity and are more likely to seek care for cough symptoms
  - Refractory/unexplained chronic cough shares demographic characteristics with neuropathic disorders (women in 5th-6th decade, concomitant neuropathic problems)
- The actual coughing frequency described by patients with chronic cough is **extraordinarily** variable



Map showing the pooled prevalence of chronic cough by country.



Woo-Jung Song et al. Eur Respir J 2015;45:1479-1481

Consequences of chronic cough

- Comorbidities such as incontinence, cough syncope, vomiting, insomnia, and dysphonia
- Social isolation, social stigma, depression, and difficulties in work and relationships
- Concern about severe underlying illness

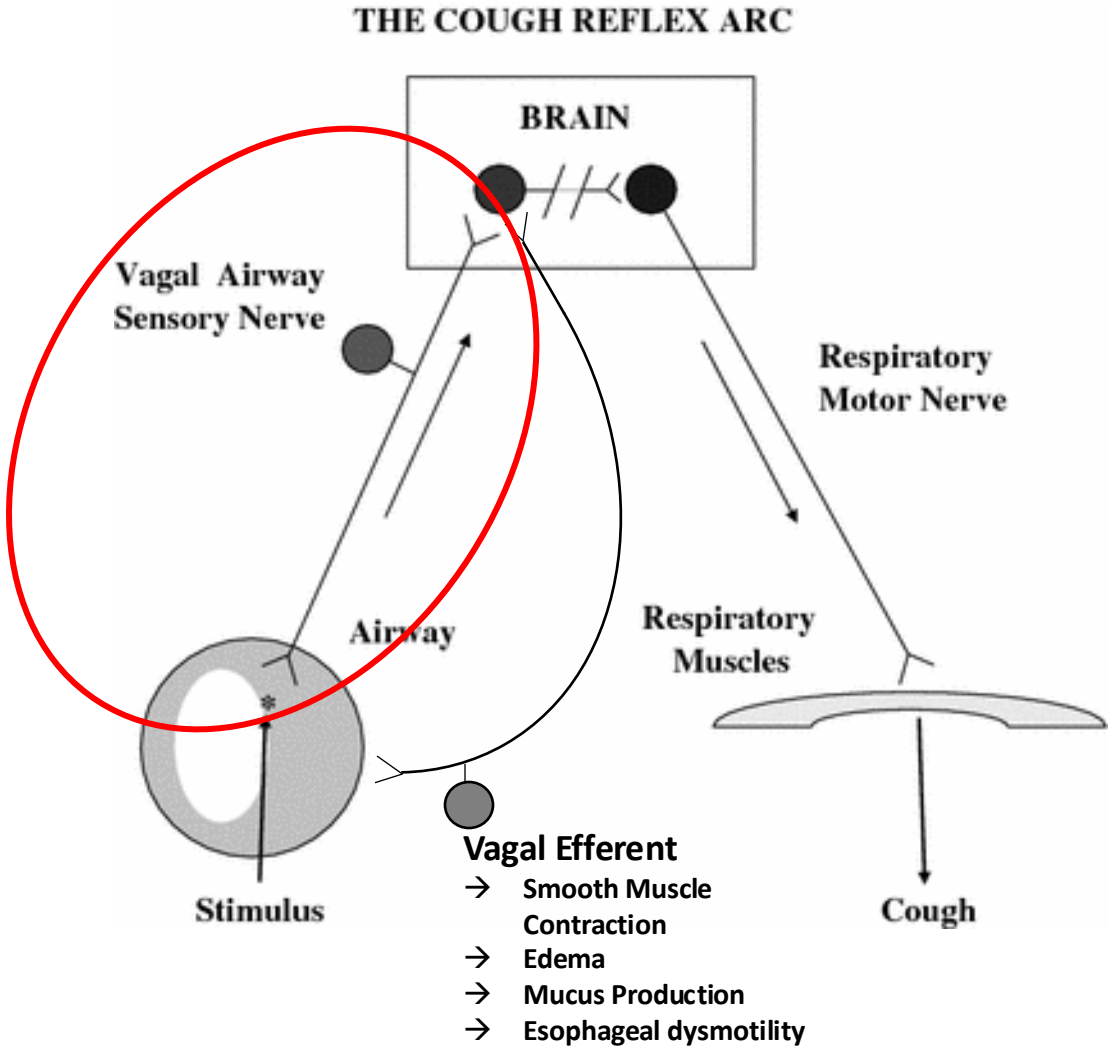
Why we Cough

Cough is a protective reflex to prevent aspiration of infectious and harmful particles into the lung

Cough stimulus is carried by vagal afferents in the following locations:

- Larynx and conducting airways
- Lung parenchyma/vasculature (e.g. Pulmonary embolism, heart failure, altitude sickness)
- Pharynx, esophagus, and ear (Arnold's reflex)

Vagal afferents are triggered by a variety of channels (TRPs, ASIC, P2X3), and a variety of stimuli (chemical, ATP, protons, particulates, hyper/hypotonicity)



Adapted from Canning et al, *Lung* 2008: 186 supp 1; 23-8

Why we Cough (2)

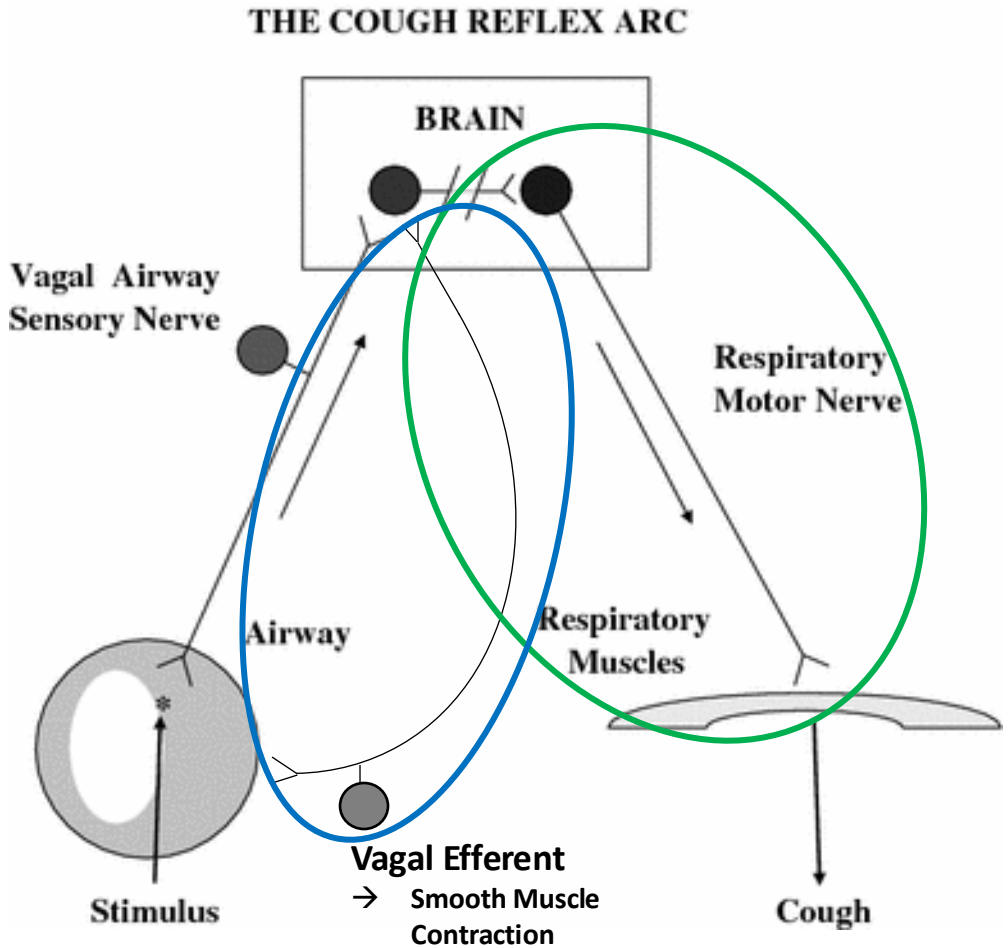
Efferent limb of the normal cough reflex is through motor nerves

Vagal efferents stimulated by persistent afferent stimuli can lead to:

- Bronchoconstriction
- Airway edema
- Mucus production
- Esophageal dysmotility (including reflux)

Many patients with chronic cough have developed cough reflex hypersensitivity, with heightened sensitivity to low level irritants (capsaicin in studies, cold/perfumes etc. upon typical questioning)

- Both central and peripheral mechanisms have been postulated (Mazzone et al., *Lancet resp. Med* 2018: 6(8): 636-646)



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Approach to Chronic Cough

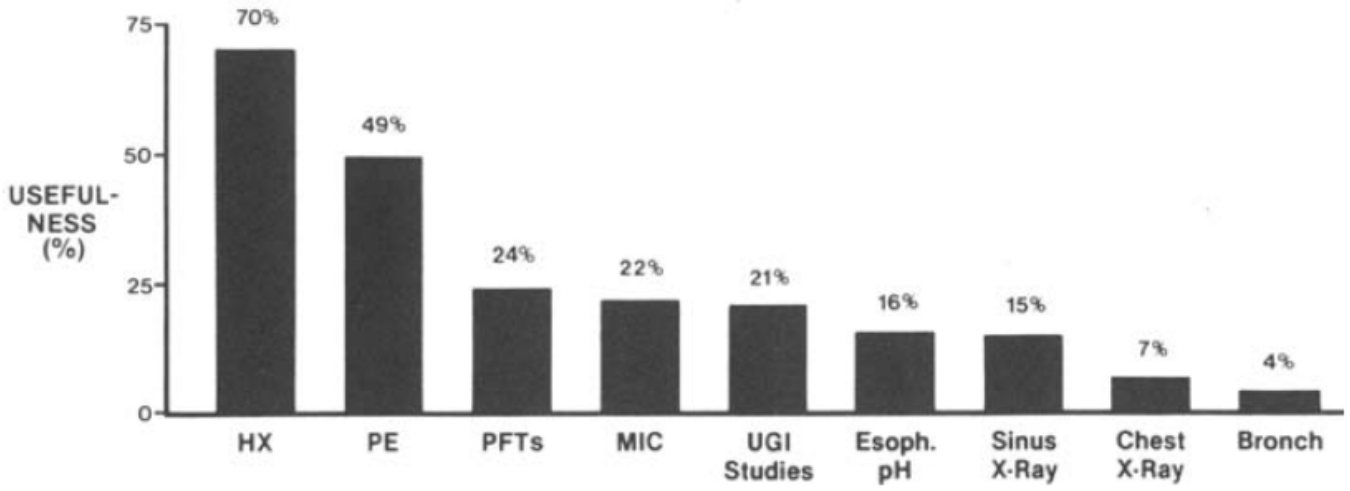


Fig. 2. The relative usefulness (true positive result) of each component of the diagnostic protocol in determining the 131 causes of cough (HX = history; PE = physical examination; PFTs = pulmonary function tests; MIC = methacholine inhalational challenge; UGI = upper gastrointestinal; esoph. pH = prolonged esophageal pH monitoring; bronch = flexible fiberoptic bronchoscopy).

Irwin et al. Am Rev Resp Disease 1990; 141:640-7

A solid history and physical is essential to determining best initial course of diagnostics or therapy

Upper airway cough syndrome, asthma/eosinophilic bronchitis, or reflux/esophagitis are present in >90% of patients with chronic cough (>99% of non-smokers without ACEI and normal CXR) **Mello et al., Arch Int Med. 1996;156(9):997-1003**

The prevalence of all 3 of the above conditions is high, and some patients have multiple etiologies, leading to poor response to empiric therapies

Common pathway of cough reflex hypersensitivity – unhelpful common characteristics

Self-reported nature of the cough (with some small exceptions)

Gravely / raw voice (common after all prolonged cough reflex hypersensitivity)

Paroxysms of coughing, even with vomiting (extreme cough reflex hypersensitivity, more of a severity marker than diagnostic tool)

Excess sensitivity to cold, particulates, perfumes (general to all cough reflex hypersensitivity)

Productivity of the cough (other than completely dry or extremely large volume purulence)

Rib/musculoskeletal pain with cough

Table 4. Descriptive Characteristics of Cough

Character or Timing	No. (%)	Character or Timing	No. (%)
Paroxysmal	69 (78)	Postprandial	15 (17)
Self-propagating	66 (75)	>60 mL/d*	13 (15)
Productive	43 (49)	Barking	12 (14)
Dry cough	43 (49)	With meals	12 (14)
On awakening	29 (33)	With milk products	10 (11)
Nocturnal	26 (30)	30-60 mL/d*	7 (8)
Brassy	26 (30)	Syncope	7 (8)
<30 mL/d*	25 (28)	Hemoptysis	6 (7)
Loose	24 (27)	Honking	3 (3)

*Sputum production.

Table 5. Spectrum and Frequency of Diagnosis by Character and Timing of Cough*

Cough Descriptor	N	Diagnosis, %				
		Asthma	GERD	PNDS	Bronchiectasis	Other
Paroxysmal	69	10	43	37	4	6
Propagating	66	13	41	38	4	4
Productive	43	14	36	37	7	6
Dry cough	43	12	46	38	1	3
Awakening	29	18	37	41	2	2
Nocturnal	26	17	36	43	0	4
Brassy	26	10	46	40	2	2
<30 mL/d†	25	16	36	40	2	6
Loose	24	11	37	35	11	6
Postprandial	15	21	42	34	0	3
>60 mL/d†	13	12	40	32	8	8
Barking	12	0	50	40	10	0
With meals	12	17	48	35	0	0
With milk products	10	15	40	45	0	0
30-60 mL/d†	7	16	23	38	23	0
Honking	3	0	67	33	0	0

Mello et al., Arch Int Med. 1996;156(9):997-1003
98 Prospectively evaluated pts with chronic cough

Red flags in patients with chronic cough

Fevers, night sweats, or weight loss suggest chronic infection (eg, tuberculosis, atypical mycobacterial disease, lung abscess), rheumatic disease, or malignancy.

Immunosuppression or substantial sputum warrant evaluation for chronic pulmonary (or sinus) infection or bronchiectasis

Hemoptysis may indicate infection (eg, bronchiectasis), cancer (airway-associated tumor), certain rheumatologic diseases, or foreign body inhalation

Dyspnea leads to a different differential that includes obstructive and parenchymal lung disease

A Word on Sub-Acute vs. Chronic cough

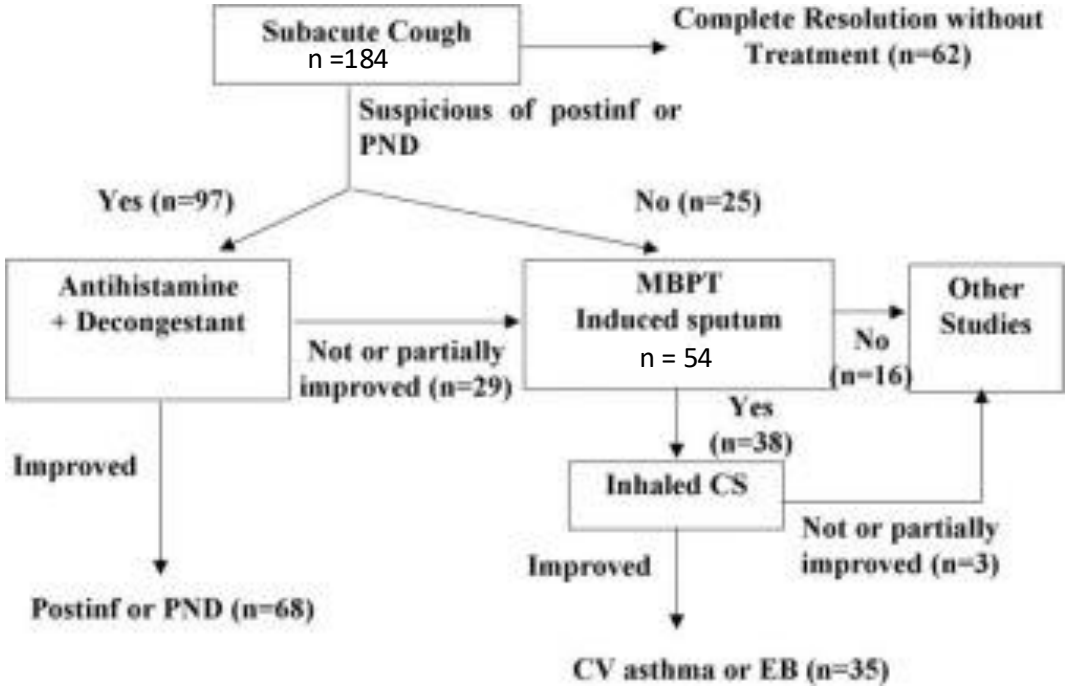
Post-infectious cough is by far the most common reason for subacute cough and should be considered the **most likely** diagnosis for patients who can clearly describe cough onset coincident with other viral symptoms

- It is not abnormal for spontaneous resolution of post-infectious symptoms to take up to 8-12 weeks
- Pertussis is on the differential, but it is too late for treatment
- This will **not** be a cause of **chronic** cough on board examinations

Symptomatic treatment of ongoing sinus or post-nasal drip symptoms may be helpful

Evaluation for airway hyper-responsiveness with spirometry or peak flow testing is reasonable

- In the post-infectious setting, **short-term** treatment with ICS +/- bronchodilator therapy (often LABA/ICS) can be helpful



Treatment algorithm from Kwon et al., CHEST 2006:129(5);1142-7

ACE Inhibitor-induced cough

Extraordinarily common, related to bradykinin activity

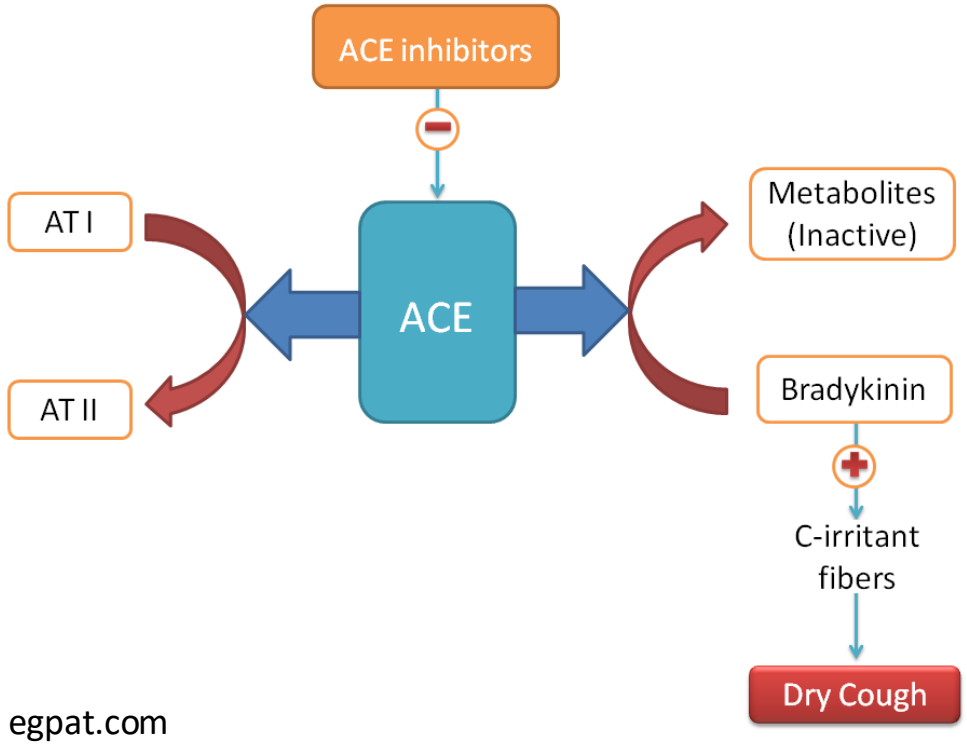
Not seen with ARBs

Usually begins within 6 months of initiation of ACEI

Is not associated with histamine response or asthma exacerbation

Can take up to 4 weeks to resolve, but often does so within days of discontinuation

Occasional other drug-induced cough: CCBs, bisphosphonates, prostanoid eye drops



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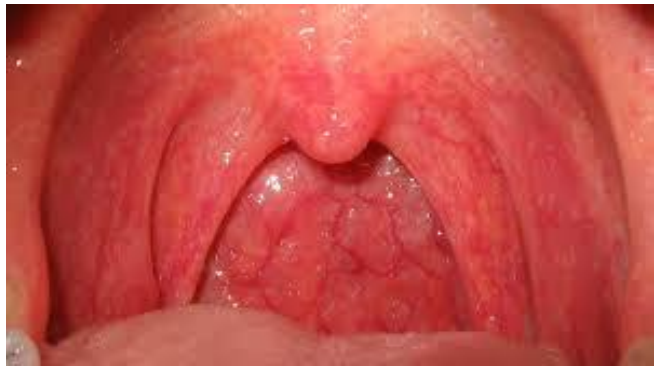
“Upper airway cough syndrome”



A catch-all phrase used to describe cough reflex hypersensitivity initiated by upper airway secretions (post-nasal drip).

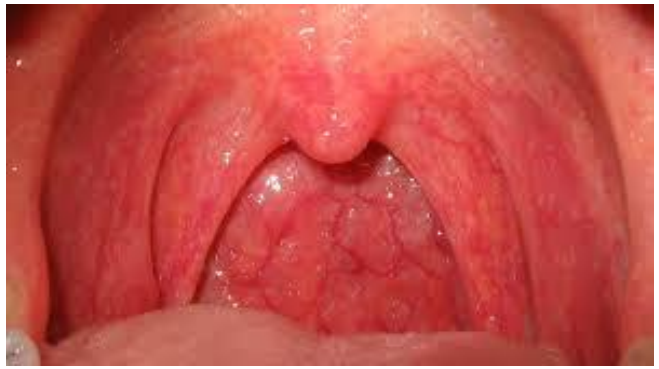
Multiple potential etiologies include post-infectious (for sub-acute cough), allergic rhinitis, non-allergic rhinitis, and chronic sinusitis

The characteristic symptoms include – sensation of post-nasal drip, frequent throat-clearing, and nasal discharge

Physical exam findings supporting the diagnosis – cobblestone appearance of the posterior OP, nasal discharge, inflamed nares and/or nasal polyps

Despite “silent UACS” (asymptomatic pts that nevertheless respond to therapy), ENT work-up of patients without significant nasal/sinus symptoms is discouraged by current guidelines (ERS 2019, CHEST 2006)

“Upper airway cough syndrome”



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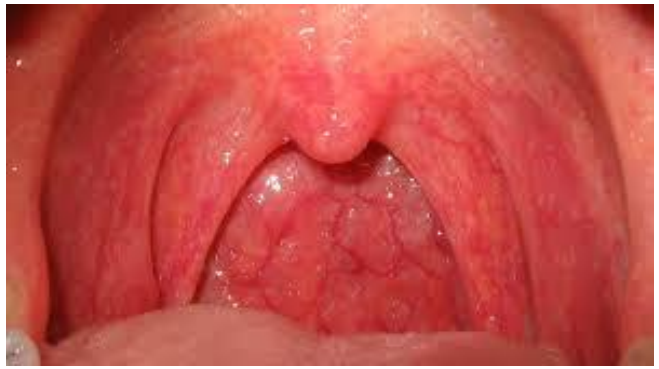
<u>Types of Non-irritant Rhinitis</u>

- Vasomotor rhinitis (direct irritants)
- Gustatory rhinitis
- Oxymetolazine abuse
- Oxygen / CPAP (dryness)
- Medications/Drugs
  - Cocaine, ACEI, alpha blockers,
  - Other antihypertensives
  - PDE5 inhibitors
  - NSAIDs/Aspirin in AERD

“Upper airway cough syndrome” R_x



Intranasal glucocorticoids and nasal irrigation tend to be the mainstay of therapy

Intranasal ipratropium bromide and azelastine are useful adjuncts

Aspirin desensitization for AERD (Asthma symptoms, nasal congestion, nasal polyps, worsening symptoms with aspirin/NSAIDs)

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Review question 2

A 45-year-old non-smoking female presents to the primary care clinic with a persistent cough for the past 6 months. She reports that the cough is non-productive and occurs mostly during the day, with occasional episodes at night. She denies fever, chest pain, shortness of breath, or weight loss. Her vital signs are within normal limits. Physical examination is unremarkable. She has been taking an over-the-counter cough suppressant without any relief. Chest X-ray is normal. Laboratory findings are significant for elevated eosinophil count to 400 cells/microL. In-office peak flow measurement is mildly reduced for the patient's age and height. What is the most likely diagnosis?

A) Asthma
B) Chronic obstructive pulmonary disease (COPD)
C) Gastroesophageal reflux disease (GERD)
D) Upper airway cough syndrome (UACS)

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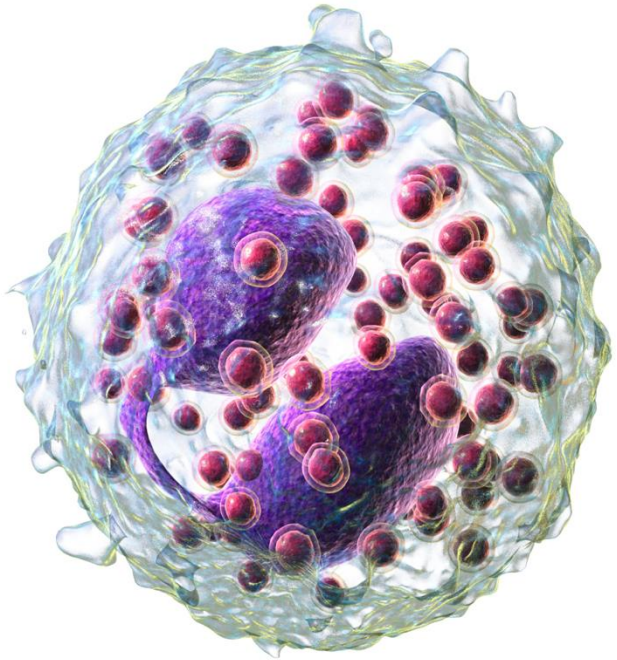
D) Upper airway cough syndrome (UACS)

Eosinophilic Airway Inflammation

Spectrum of T2 inflammation / eosinophilic inflammation in the airways, all of which can lead to cough – classification debates are ongoing

Historical findings supporting this spectrum of diagnoses include:

- Episodic **shortness of breath or wheezing** accompanying the symptoms
- **ATOPY**, childhood asthma, childhood atopy, family history of asthma/atopy
- Seasonal/allergic triggers of symptoms



Physical Exam / laboratory findings include:

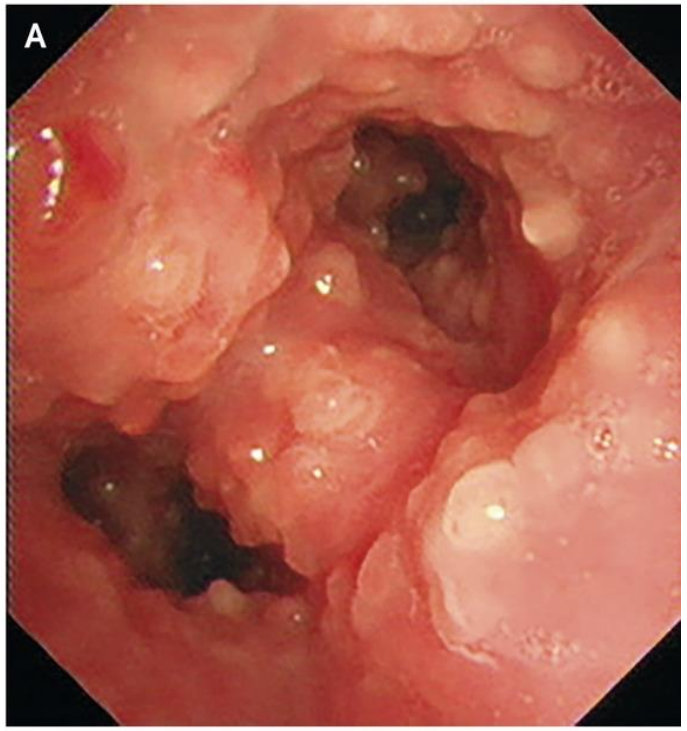
1) non-focal wheezing
2) impaired peak flow or reversible airway obstruction on spirometry
3) evidence of nasal polyps
4) Eosinophilia in the serum or sputum
5) Elevated FeNO

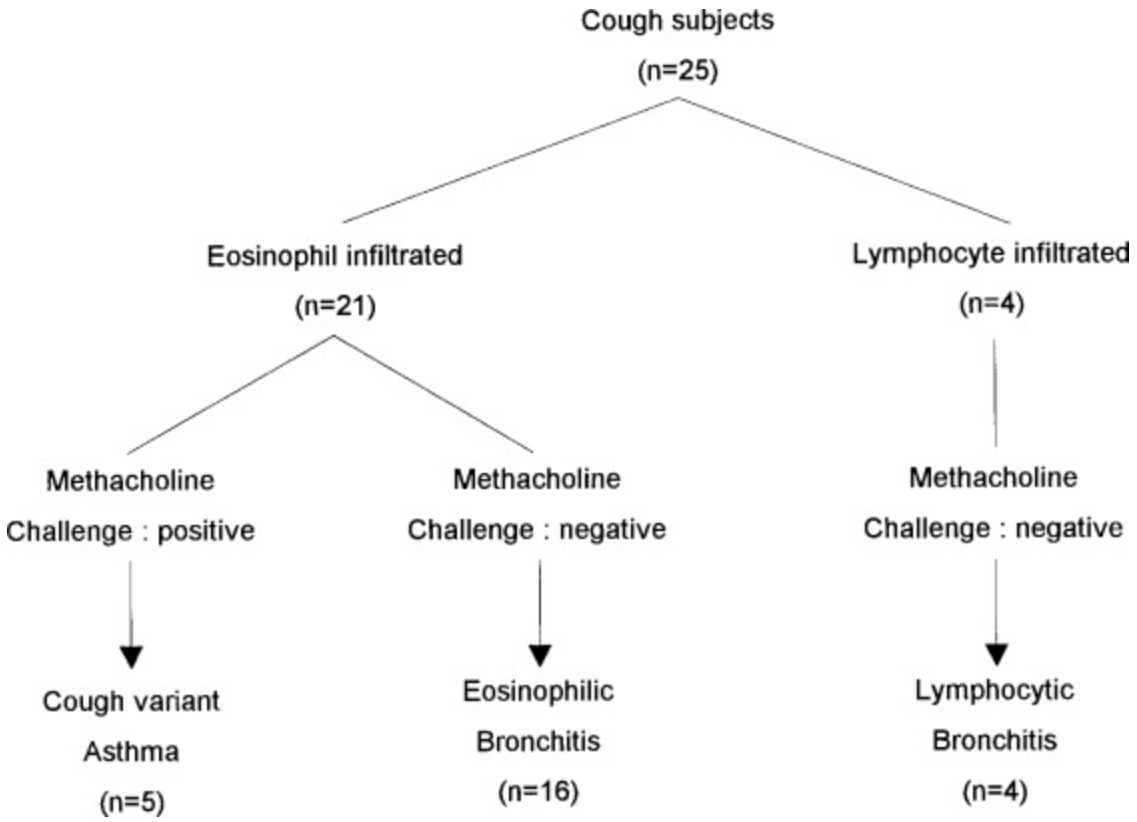
Eosinophilic Bronchitis → Wheezy Bronchitis → Cough-Variant Asthma → Asthma

Non-Asthmatic Eosinophilic Bronchitis

Eosinophilic airway inflammation can be seen in a significant portion of patients with otherwise unexplained cough

- (Negative PND, GERD, ACEI/beta-blocker, chronic bronchitis, other lung disease)





Lee et al., Chest 2001; 120(4):1114-20

Ren and Dai, N Engl J Med 2017; 377:873

SUBJECT DETAILS, SPUTUM CHARACTERISTICS, AND MEAN (SEM) SPUTUM SUPERNATANT MEDIATOR CONCENTRATIONS*

	Eosinophilic Bronchitis	Asthma	Normal
Number	8	17	10
Male	3	9	4
Age, mean (range)	53 (28–70)	42 (15–62)	41 (19–57)
Atopy	3	11	0
On inhaled steroids	0	8	0
% FEV_1†	113 (93, 133)	82 (74, 90)‡	105 (92, 117)
% FEV_1/FVC†	81 (76, 85)	70 (65, 75)‡	85 (79, 90)
Methacholine PC_{20} (mg/ml)§	> 16	1.22 (0.24)	> 16
Total cell count × 10^6/ml‖	2.8 (2.1)	3.4 (3.7)	2.3 (2.0)
Squamous cell contamination, %‖	4.2 (3.3)	3.2 (3.9)	5.1 (4.1)
Viability, %‡	70 (31)	65 (26)	68 (30)
Sputum eosinophils, %§	12.5 (0.14)¶	13.4 (0.11)¶	0.2 (0.11)
Sputum macrophages, %‖	22.5 (18.3)‡	35 (34.4)‡	59 (44.2)
Sputum neutrophils, %‖	64 (39)	41.9 (45.3)	36.7 (47.6)
Sputum lymphocytes (%)‖	0.15 (0.85)	0.6 (1.7)	0.8 (1.2)
Sputum epithelial cells (%)‖	2 (2.8)	1.7 (1.1)	2.9 (6.1)
ECP, ng/ml§	604 (2.2)¶	735 (2.8)¶	95 (1.4)
$LTC_4/D_4/E_4$, ng/ml§	9.27 (0.08)‡	11.1 (0.08)‡	5.86 (0.04)
Histamine, ng/ml§	168 (0.19)¶	25.1 (0.2)	15.5 (0.16)
PGD_2, ng/ml§	0.79 (0.11)‡	0.32 (0.06)	0.15 (0.05)
PGE_2, ng/ml§	1.95 (0.07)	1.36 (0.06)	1.22 (0.10)
$PGF_{2\alpha}$, ng/ml§	0.60 (0.11)	0.53 (0.06)	0.40 (0.07)
TXB_2, ng/ml§	1.58 (0.07)	0.94 (0.10)	0.70 (0.10)

Brightling et al., AJRCCM 2000; 162:878-82.

Utility of Eosinophil Measurement in the work-up of chronic cough

Sputum eosinophilia

- Greatest utility in the literature, but is not routinely available (cutoff >3%)

Serum eosinophilia or FeNO

- More easily obtained surrogates for sputum eosinophils
- Serum eosinophils can be variable, but probably correlate better

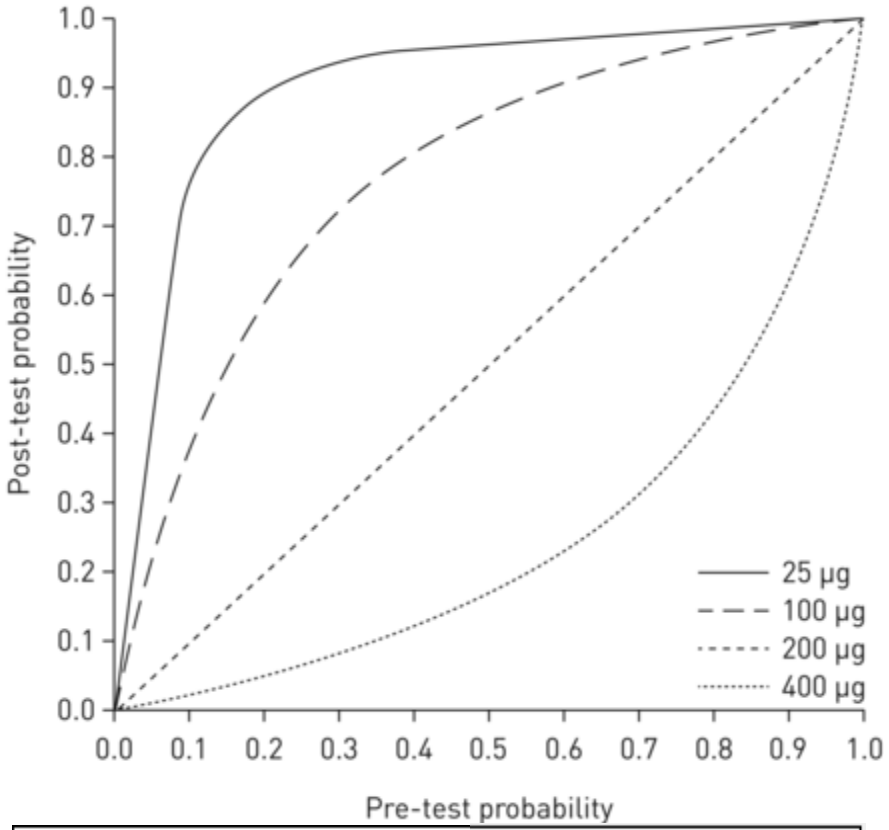
Table 2 Sensitivity, specificity, PPV and NPV of different surrogate markers using alternative cut-points to diagnose eosinophilic airway inflammation (less than, more than or equal to 3% sputum eosinophils)

	Threshold	Sensitivity	Specificity	PPV	NPV
Blood eosinophils	$>0.22\times10^9$/L	86	79	60	93
Blood eosinophils	$\geq0.25\times10^9$/L	79	84	64	91
Blood eosinophils	$\geq0.27\times10^9$/L	78	91	79	91
FE_{NO} level	>20 ppb	74	57	40	87
FE_{NO} level	≥24 ppb	74	63	42	87
FE_{NO} level	≥42 ppb	63	92	74	89
FE_{NO} level	>50 ppb	56	92	67	84
Serum periostin (in-house)	>26 ng/mL	54	57	29	77

NPV, negative predictive value; PPV, positive predictive value.

Wagener et al., Thorax 2015; 70:115-20

Methacholine Challenge to predict response of chronic cough to Corticosteroids



PD_{20} µmol (µg)	Interpretation
>2 (>400)	Normal
0.5–2.0 (100–400)	Borderline AHR
0.13–0.5 (25–100)	Mild AHR
0.03–0.13 (6–25)	Moderate AHR
<0.03 (<6)	Marked AHR

Coates et al., Eur Resp J 2017 49: 1601526

Chronic cough with normal spirometry but bronchial hyper-reactivity is well-described

Methacholine challenge has a high negative predictive value but relatively low positive predictive value for the diagnosis of asthma

Pts with cough and a positive methacholine challenge who respond to bronchodilator/ICS therapy should be labeled cough-variant asthma

- Asthma has often been worsened by cough reflex hypersensitivity and patients can often be titrated down to intermittent therapy

Pts without positive methacholine challenge may respond to ICS therapy due to non-asthmatic airway eosinophilia

Bottom line – methacholine challenge can help rule out asthma or increase the likelihood of asthma as the most likely diagnosis, but should not be used to avoid an empiric trial of inhaled or oral glucocorticoids

Therapeutic trial for NAEB or Asthma

Inhaled glucocorticoids are the mainstay of treatment

Moderate dose oral glucocorticoids over several days with initiation of inhaled glucocorticoids may prompt a faster response

Lack of response to oral glucocorticoids strongly argues against these diagnoses

Review question 3

A 55-year-old non-smoking male presents to the otolaryngology clinic with a refractory chronic cough persisting for the past 2 years. The cough is dry, non-productive, and often disrupts his sleep. He denies any other respiratory symptoms, such as wheezing or shortness of breath. He has tried over-the-counter cough suppressants and inhalers without significant improvement. Vital signs are normal. Physical examination, including a thorough head and neck examination, is unremarkable. The patient has a history of gastroesophageal reflux disease (GERD) and takes omeprazole daily. Spirometry shows normal lung function. Laboratory findings, including complete blood count and chest X-ray, are within normal limits. What is the most appropriate next step in managing this patient's refractory chronic cough?

A) Begin intranasal glucocorticoid therapy
B) Order a high-resolution computed tomography (HRCT) of the chest
C) Perform 24-hour esophageal pH monitoring
D) Refer the patient for behavioral therapy

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Reflux aspiration - GERD

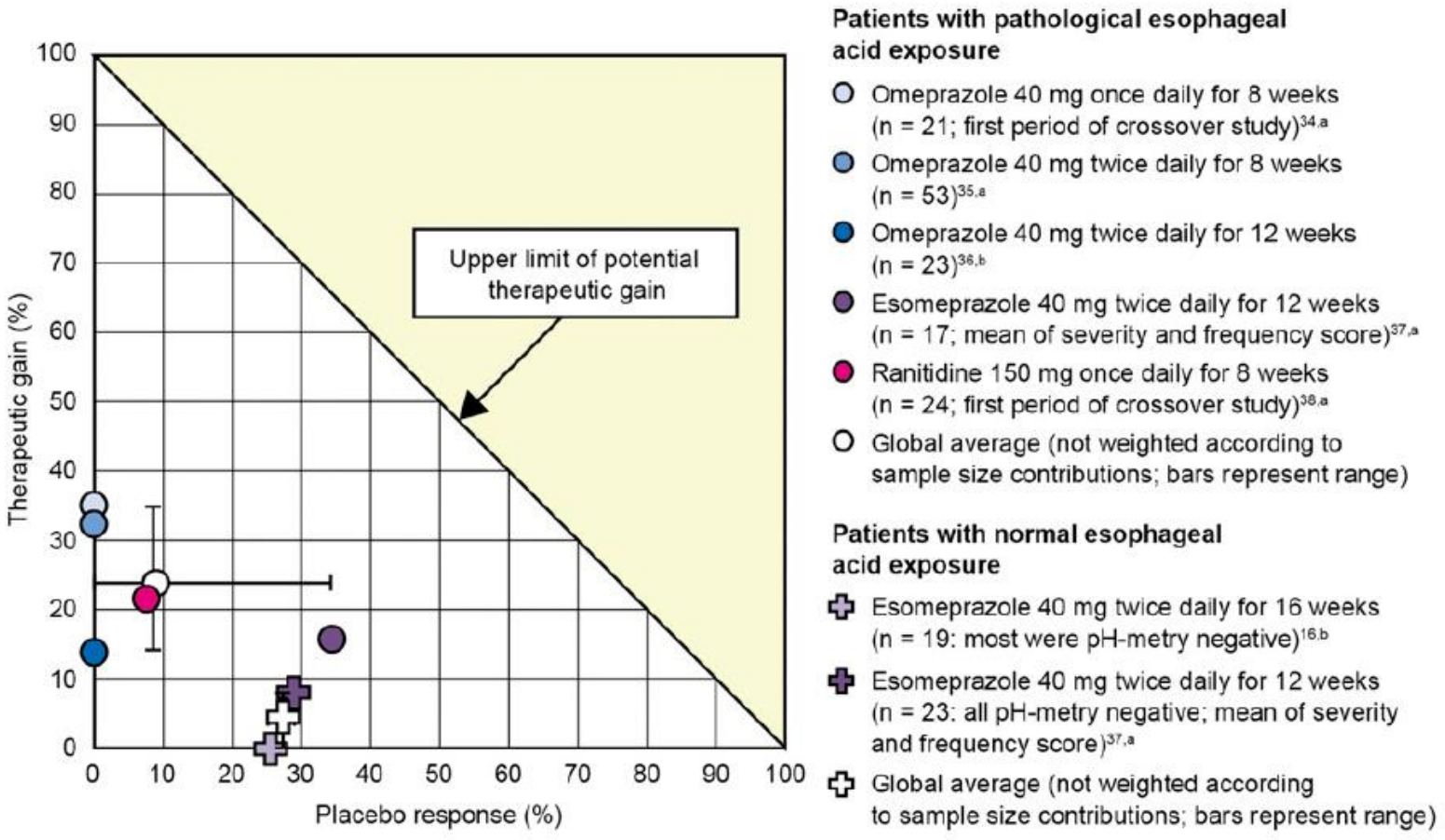


FIGURE 2. Calculated therapeutic gain for datasets derived from patients with pathologic esophageal acid exposure and populations including patients with normal esophageal acid exposure. [a]Percentage change in symptom score; [b]Percentage change in proportion of responders.

Kahrilas et al., *Chest* 2013 Mar; 143(3): 605–612.

Cause or consequence?

Role of self-limited disease and placebo effect

Recurrent weakly-acidic reflux can still result in disease

A high percentage of unselected subjects (56% in one study) show reflux-associated cough, strongly indicating central hypersensitivity

Meta-analysis suggests moderate-high dose PPI therapy outperforms placebo in patients with high exposure to acid (>15%) on testing

PPI therapy is also likely to be helpful in patients with active GERD symptoms

Laryngeal-Pharyngeal Reflux

Cause or consequence?

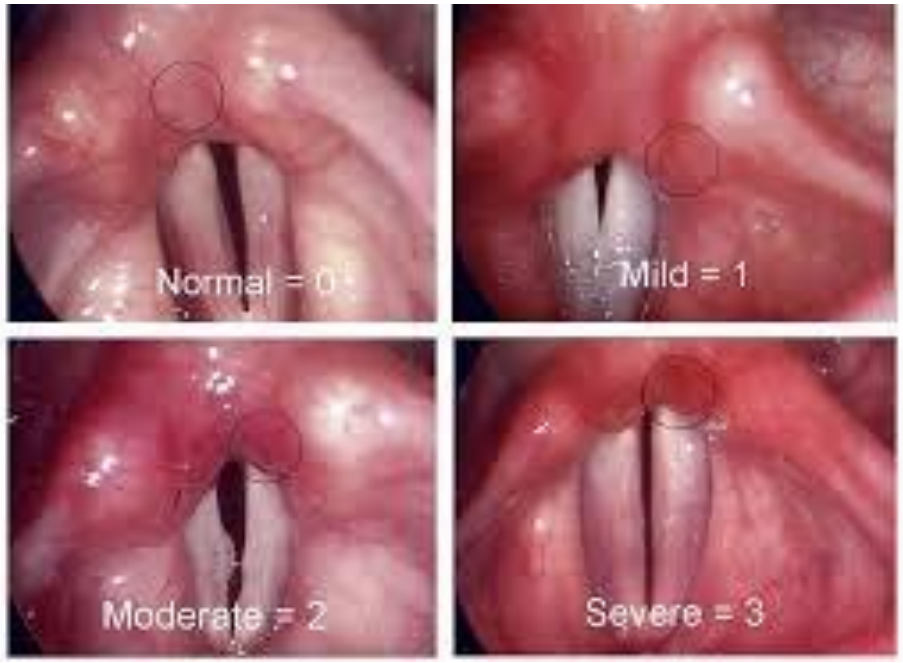
Extremely high prevalence anecdotally

Associated with dysphonia/hoarseness, throat-clearing, dysphagia

Valsalva, bending over, exercise are precipitants of cough (in contrast to GERD)

PPI therapy can be helpful, but will not treat more severe disease (non-acid aspiration)

Esophageal manometry can be helpful in diagnosis



Eller et al., *Journal of Voice 2013*; 23(3): 389-395.

Reflux aspiration in Practice

Patients with symptomatic GERD should be adequately treated w/ PPI +/- H2 blockers

Patients with very prominent voice and upper airway symptoms should be evaluated by ENT

All patients with nocturnal and/or positional cough should be counseled on behavior modification

The literature suggests an appropriate empiric trial length for PPI is 8 weeks; a very short-term trial is not helpful

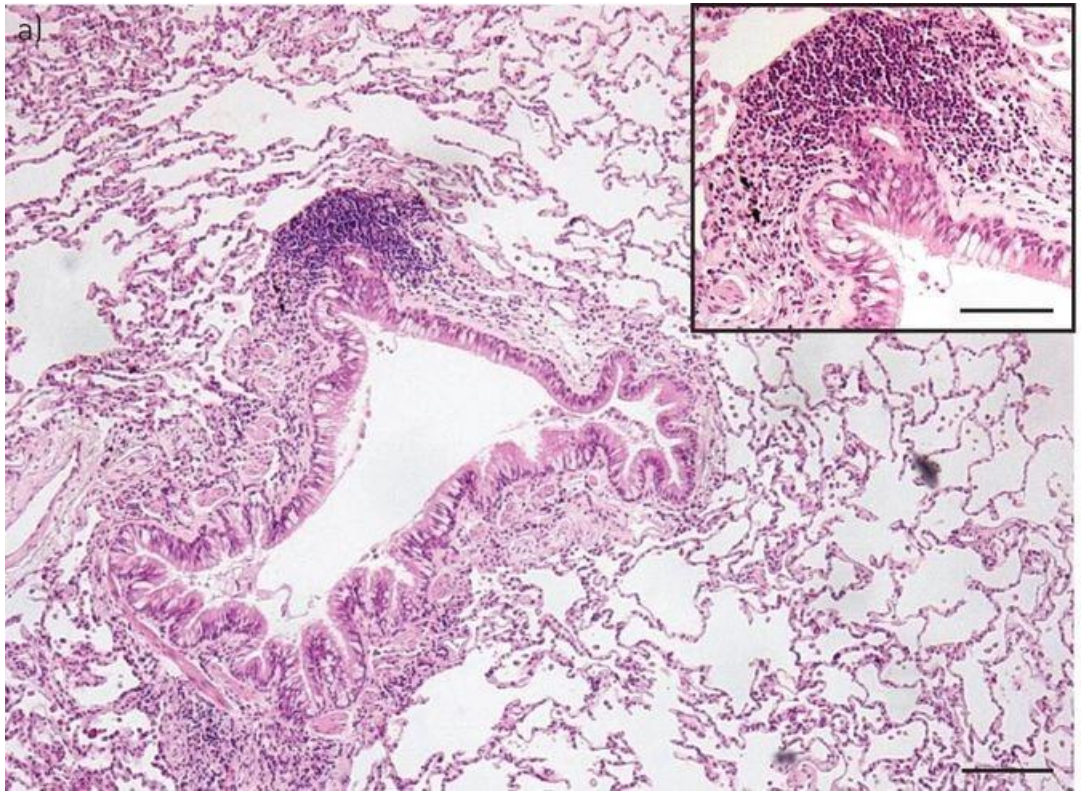
Esophageal Manometry with pH probe is the diagnostic procedure of choice, if needed

While surgical therapy for reflux can improve cough in (uncontrolled) studies, other empiric trials including neuromodulatory therapy should be tried before any surgical approach in the absence of other indications

Chronic Bronchitis (in smokers)

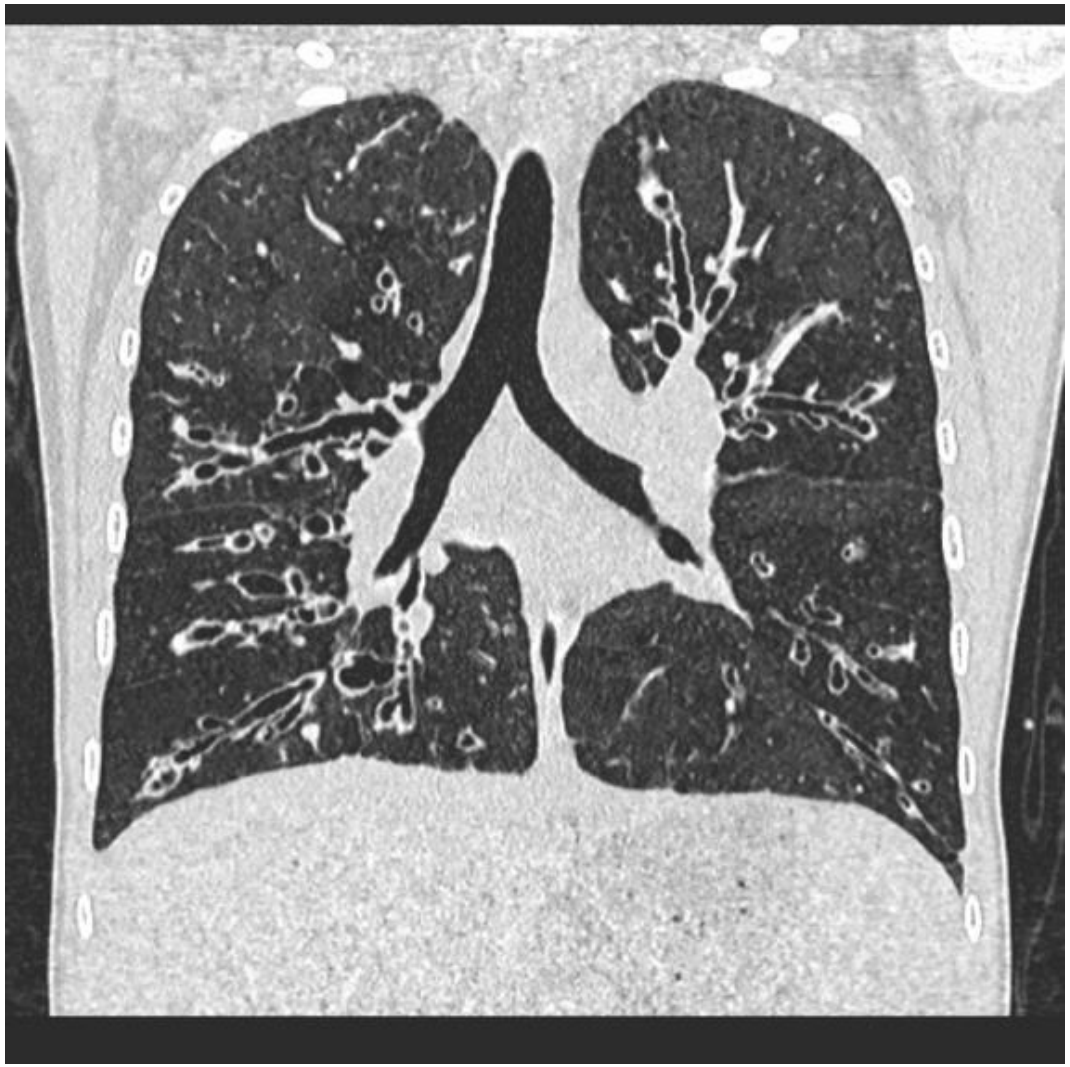
Chronic Bronchitis is defined by the presence of productive cough on most days for at least a 3-month period for two or more consecutive years

- Almost all patients are active smokers or have a very significant smoking history
- Although a reasonable proportion of prevalent chronic cough, the slow onset and well-known features of this disease make it unusual for patients to present to clinic with chronic cough complaints
- For this reason, smokers presenting with this complaint should be carefully screened for bronchiectasis and lung cancer



Brandsma et al., *Eur Resp Rev* 2017 26: 170073

Bronchiectasis



https://bronchiectasis.com.au

Persistent airway inflammation that leads to increased mucous production, airway destruction, and peri-bronchial fibrosis; probably represents **~5%** of chronic cough

Focal bronchiectasis can occur after a severe infection or post-radiation changes

Multi-focal bronchiectasis etiologies include CVID, HIV, severe hypogammaglobulinemia, CF, primary ciliary dyskinesia, and mycobacterial infection

Mild, more focal disease causing dry/small volume cough can be difficult to detect on CXR, but is also difficult to treat

More severe disease will show obstruction on spirometry, crackles/ronchi on PE, and is treatable with mucus clearance devices, bronchodilators, and intermittent or suppressive antibiotic therapy in addition to disease-specific therapies (IVIG, HAART, etc.)

Lung Cancer

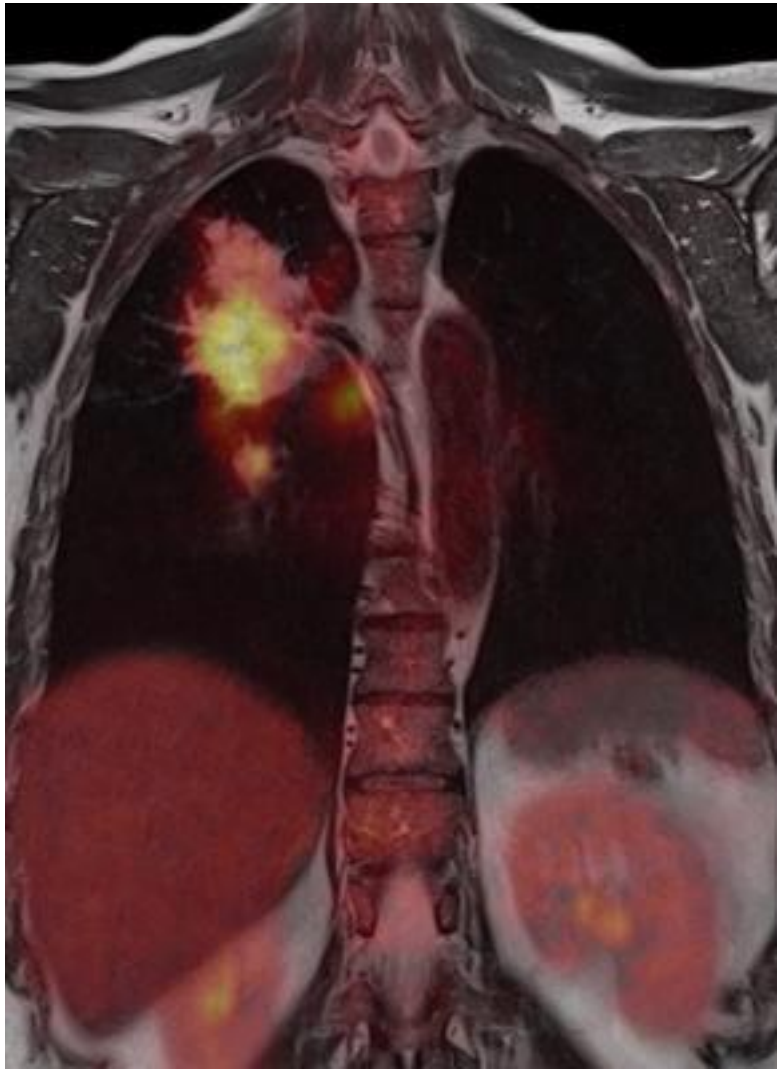
50-75% of persons with lung cancer have cough; cancer represents <2% of patients in chronic cough cohorts

Squamous and small cell central tumors are most likely

Concerning symptoms that should lead to investigation by CXR / CT AND bronchoscopy:

- Focal wheezing or digital clubbing without hypoxemia
- Significant change in smoker's cough that does not return to baseline with infectious bronchitis treatment
- New cough upon smoking cessation that lasts > 1-2months
- Hemoptysis without infection or bronchiectasis
  - ~5% chance of finding a bronchogenic cancer in patients with normal CXR and hemoptysis

Irwin et al. Am Rev Resp Disease 1990; 141:640-7

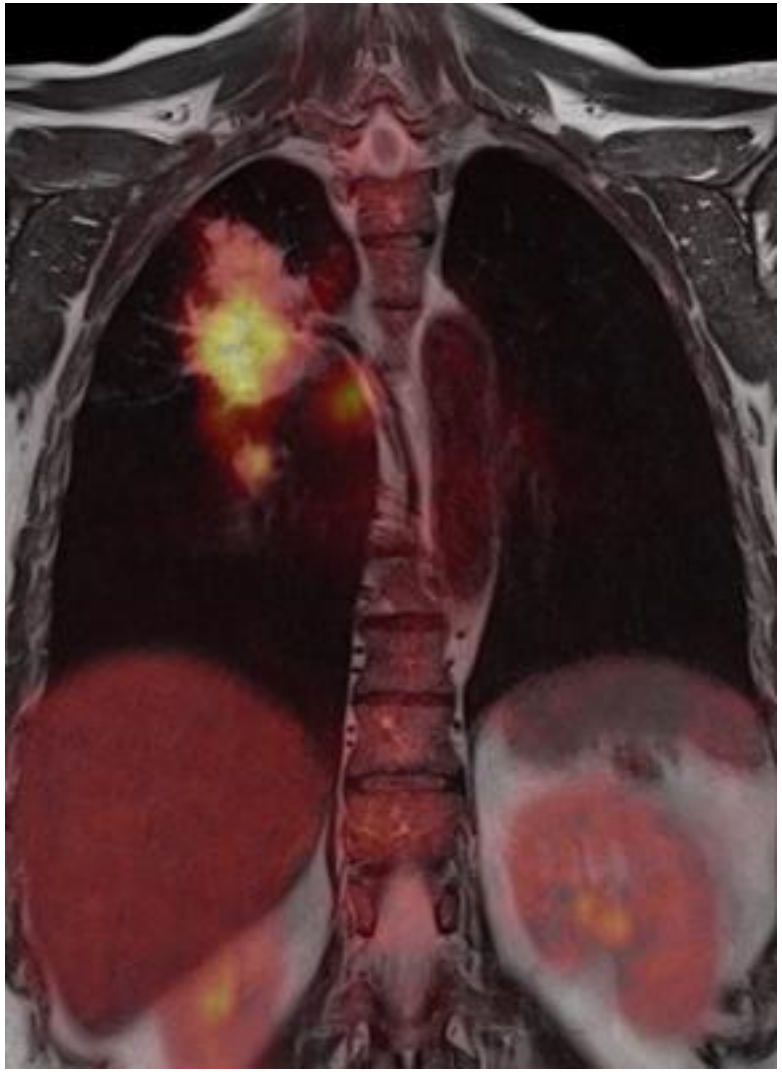


Lung Cancer (2)

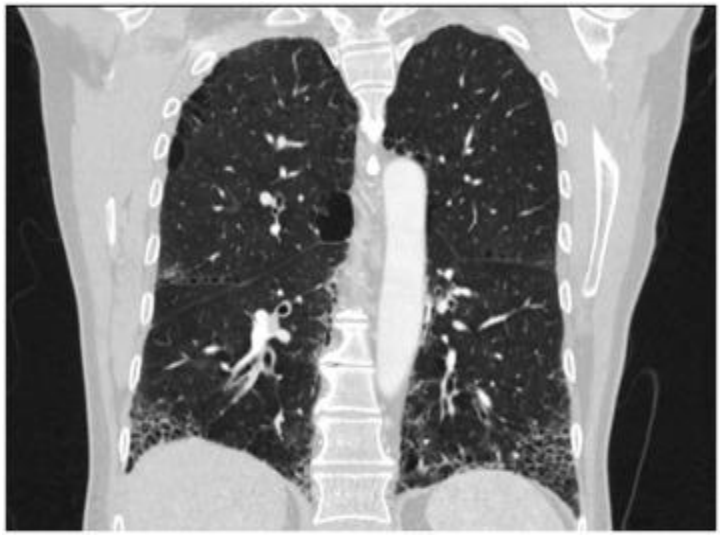
Smokers / former smokers 50-80 with ≥ 20 pack years of smoking and who have quit within the last 15 years merit screening for lung ca regardless of symptoms

Lung cancers of non-smokers rarely present with cough alone – a thin mucoid secretion (bronchorrhea) can occur in advanced mucinous adenoca; this is usually accompanied by dyspnea

Irwin et al. Am Rev Resp Disease 1990; 141:640-7



Occult Interstitial Lung Disease



Brix et al, *Resp Med Case Reports* 2016; 19:61-64

Cough is relatively common in interstitial lung disease, but is frequently accompanied by at least some shortness of breath

Findings: desaturations, crackles on lung exam, and restriction on spirometry (FEV1 and FVC<LLN)

Increased suspicion in the setting of autoimmune diseases (particularly RA, scleroderma)

In the absence of above concerns, CXR and/or spirometry is sufficient screening for these conditions

Appropriate treatment of these conditions can improve cough

Treatment of IPF Improves cough

TABLE 1 Effect of 12 weeks of pirfenidone treatment on objective and subjective cough and health status measures, analysed with a linear mixed model

	Baseline	At 12 weeks	Change# (95% CI)	p-value#
Subjects n	43	31		
24-h cough	520 [91 to 3394]	392 [75 to 1746]	−34% [−48 to −15%]	0.002
Coughs per hour	23 [4 to 141]	17 [3 to 73]	−35% [−49 to −17%]	<0.001
Daytime	28 [5 to 171]	20 [4 to 121]	−33% [−47 to −14%]	0.003
Night-time	7.2 [0.7 to 101]	3.3 [0 to 54]	−34% [−54 to −5%]	0.029
LCQ	12±4	15±4	2.0 [1.0 to 3.0]¶	<0.001
VAS cough	67±15	47±27	−19 [−28 to −10]	<0.0001
VAS urge-to-cough	68±16	49±25	−18 [−26 to −10]	<0.0001
K-BILD total	50±22	55±23	3.4 [−2.3 to 9.1]	0.245
HADS anxiety	8.5±4	8.5±4	0.7 [−0.6 to 1.9]	0.291
HADS depression	4.7±3	6.0±3	1.6 [0.5 to 2.6]	0.004
GAD-7	5.8±6	5.9±6	0.7 [−0.9 to 2.3]	0.396
FVC % pred	78±15	79±17		
T_{LCO} % pred	51±13	51±16		

Van Manen et al., ERJ 2017; 50: 1701157

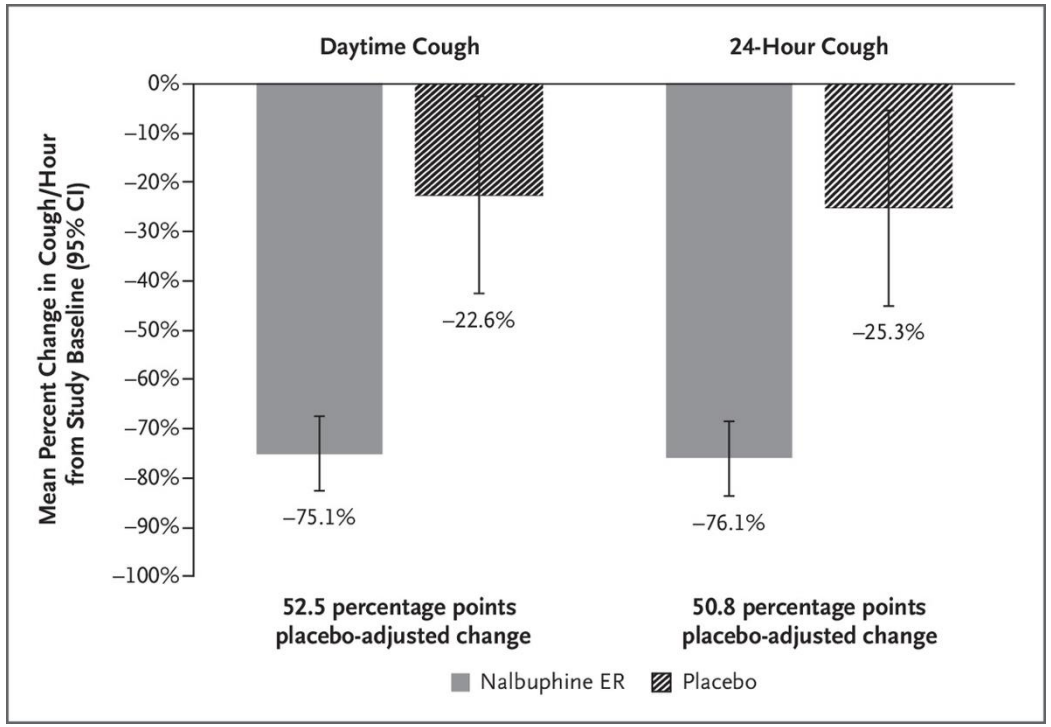
Low-dose opioids for chronic cough associated with IPF

ORIGINAL ARTICLE NEJM Evidence

Nalbuphine Tablets for Cough in Patients with Idiopathic Pulmonary Fibrosis

Authors: Toby M. Maher, M.D., Ph.D., Cristina Avram, M.D., Enoch Bortey, Ph.D., Simon P. Hart, M.D., Ph.D., Nikhil Hirani, M.D., Ph.D., Philip L. Molyneux, M.D., Ph.D., Joanna C. Porter, M.D., Ph.D., Jaclyn A. Smith, M.D., Ph.D., and Thomas Sciascia, M.D. Author Info & Affiliations

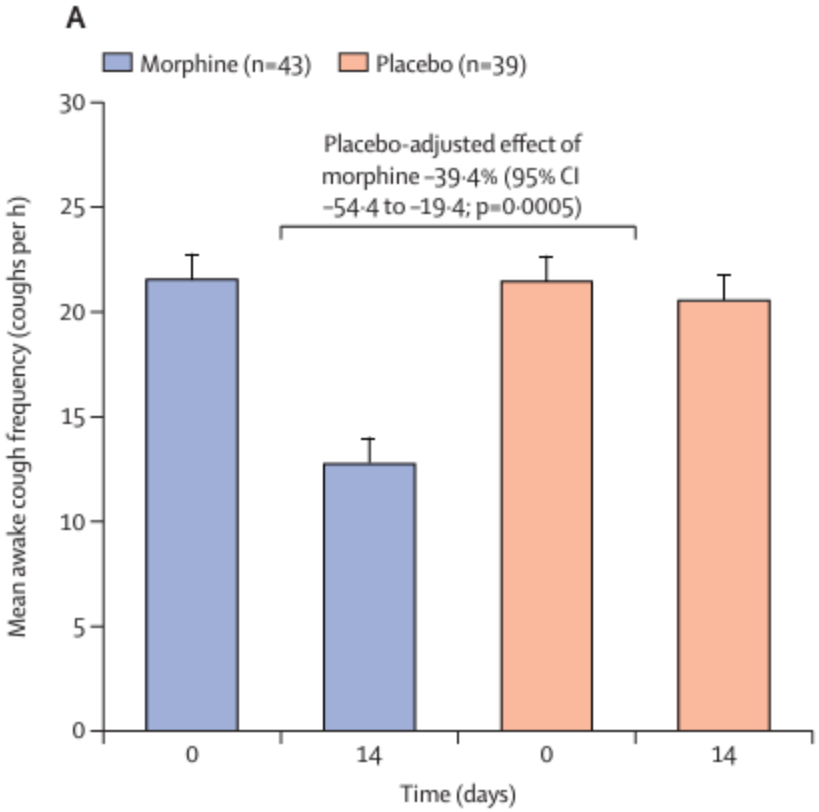
Published May 22, 2023 | NEJM Evid 2023;2(8) | DOI: 10.1056/EVIDoa2300083 | VOL. 2 NO. 8



ARTICLES · Volume 12, Issue 4, P273-280, April 2024 · *Open Access* THE LANCET Respiratory Medicine

Morphine for treatment of cough in idiopathic pulmonary fibrosis (PACIFY COUGH): a prospective, multicentre, randomised, double-blind, placebo-controlled, two-way crossover trial

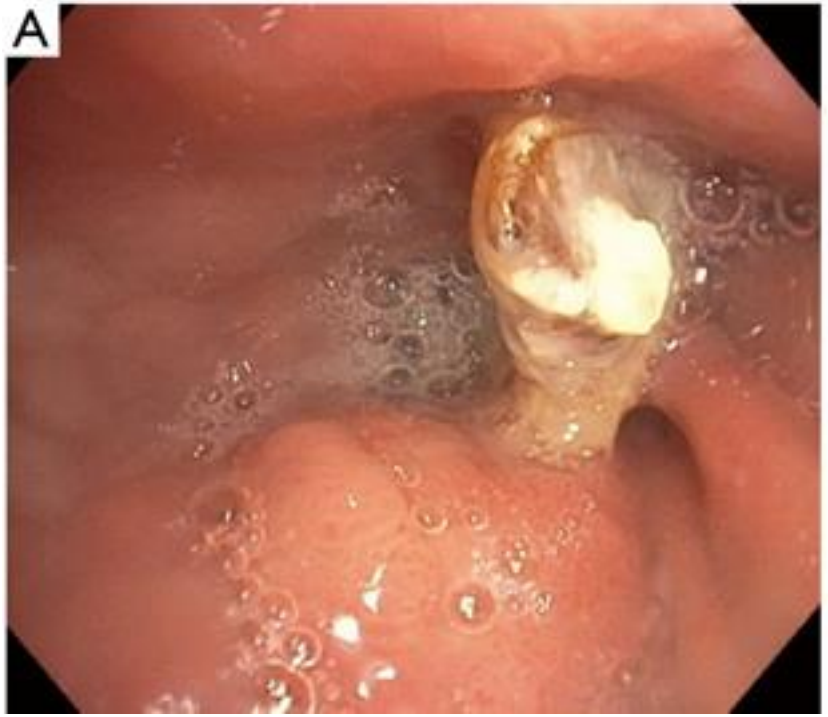
Zhe Wu, MD [a,c] · Lisa G Spencer, MD [e] · Winston Banya [c] · John Westoby [c,†] · Veronica A Tudor, MD [c] · Pilar Rivera-Ortega, MD [f] · et al. Show more



Neither of these very low dose preparations (Nalbuphine ER 27-162mg or morphine CR 5mg BID) is available in the US

A few additional considerations

- CHF
- Foreign body
- Laryngeal disease
- Outer ear blockage / cerumen impaction
- Recurrent aspiration
- Tuberculosis
- Endemic fungal infections
- OSA
- PVCs
- Tracheobronchomalacia



Hewlett et al., *J Thorac Dis* 2017; 9(9):3398-3401

Refractory/unexplained Chronic Cough – Definition and Etiology

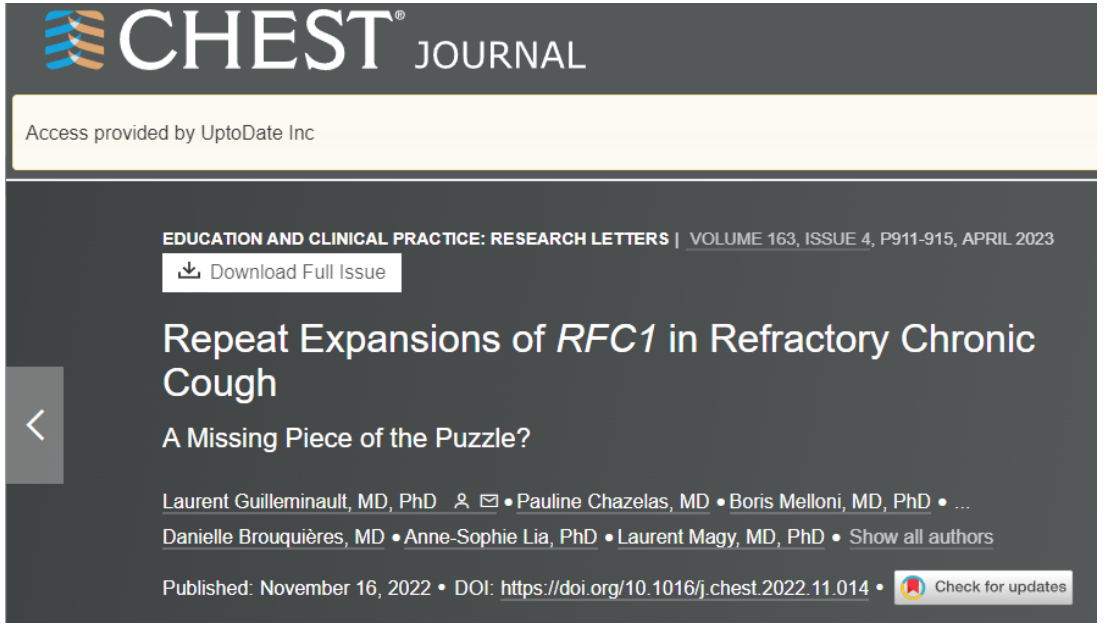
Defined as **failure to improve on empiric therapies** (decongestants/ICS/PPI)

- Negative cross-sectional imaging, no evidence of alternative etiologies

<u>RCC/UCC cough characteristics</u>

- Usually dry, preceded by an urge ("throat tickle"), and comes in bouts and fits
- Triggered by innocuous stimuli (talking, drafts, odor)
- Triggered strongly by noxious stimuli (smoke, irritants)
- Less common in sleep and exercise

25% of patients in one cohort had repeat expansions in the replication factor C subunit 1 (*RFC1*) gene, which in the biallelic form leads to cerebellar ataxia, neuropathy, and vestibular areflexia syndrome (CANVAS). This disorder presents with early chronic cough, likely due to vagal neuropathy.



Refractory/Unexplained Chronic Cough – Treatment

Nonpharmacologic
- Speech therapy
- Cough desensitization therapy
- Breathing exercises

1st line Cough Suppressants
- Dextromethorphan acts centrally, but usually less sedating than opioids at similar strength
- Benzonatate (Tessalon) has a good side effect profile and can be an adjunct
- Topical anesthetic lozenges (sugar, menthol, pectin, benzocaine) can be helpful for intermittent relief

Anticholinergics
- Ipratropium bromide may inhibit efferent receptors, has a drying effect
- Anecdotally most helpful in pts w/ deep & mildly productive cough
- 1st generation antihistamines may work similarly
- Not FDA approved for cough

Gabapentin and Pregabalin
- Not FDA approved for cough
- Trials that have employed them used large doses that are likely significantly sedating (1800mg/day gabapentin 300mg/day pregabalin)
- Modest benefit in single-center trials
- Some support to idea that neuronal hypersensitivity is involved
- Other distantly related neuromodulators (amitryptiline, duloxetine) have not been well-studied

Opioid agents
- Act centrally, likely decrease cough sensitivity
- Codeine and morphine most frequently used
- Some patients respond well to low dose morphine (5-10mg ER BID, where available)
- Time-limited trials can occasionally be helpful, but we usually avoid prolonged therapy outside of the palliative care setting

Experimental Agents – P2x3 Antagonists

	Base	7.5mg	15mg	30mg	50mg	100mg	200mg	Placebo
Awake Cough Freq (c/h)	49.6	39.3	34.8	26.8	27	25.7	28	50.6
Cough Severity (VAS, 0-100mm)	54.5	41.8	37.1	31.2	30.4	33.2	28	50.9
Dysgeusia	0%	6.7%	6.7%	46.7%	53.3%	70.4%	80.8%	0%

Modified from Smith JA, Kitt MM, Butera P, et al., Gefapixant in two randomised, dose-escalation studies in chronic cough. *Eur Respir J* 2020; Mar 20;55(3):1901615

Experimental Agents – P2x3 Antagonists

Original Investigation FREE

September 11, 2023

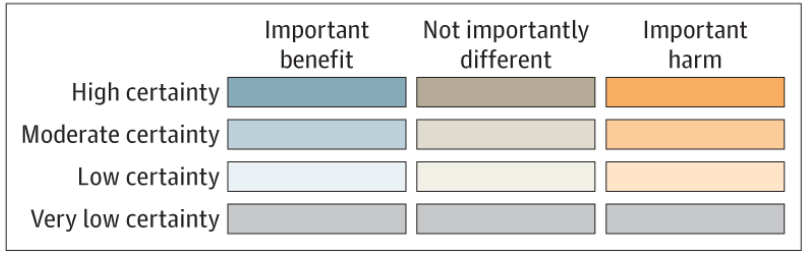
Efficacy and Tolerability of Gefapixant for Treatment of Refractory or Unexplained Chronic Cough

A Systematic Review and Dose-Response Meta-Analysis

Elena Kum, BSc[1,2]; Matthew Patel, MD[3]; Nermin Diab, MD, MPH[3]; et al

	No. of studies	No. of patients	Baseline risk[a]	Gefapixant dosage, mg twice daily			
				15	30	45	60
24-h Cough frequency, % reduction (95% CI)	6	2472	49.7%	5.6 (3.3-8.0)	11.0 (6.4-15.3)	16.0 (9.4-22.0)	20.7 (12.5-28.3)
Awake cough frequency, % reduction (95% CI)	3	2145	54.8%	6.2 (3.7-8.7)	12.1 (7.2-16.7)	17.6 (10.6-24.0)	22.7 (13.9-30.6)
Sleep cough frequency, % reduction (95% CI)	4	541	22.7%	13.1 (-44.8 to 47.8)[b]			
Cough severity on the 100 mm VAS, mean difference (95% CI)[c]	4	2292	-24.2 mm	-2.1 (-1.4 to -2.8)	-4.2 (-2.7 to -5.6)	-6.2 (-4.1 to -8.4)	-8.3 (-5.4 to -11.2)
Cough-specific quality of life on the LCQ, mean difference (95% CI)[d]	8	2651	3.0 points	0.5 (0.3-0.7)	0.8 (0.5-1.2)	1.0 (0.7-1.4)	1.1 (0.7-1.5)
Treatment-related adverse events, absolute risk difference per 100 patients (95% CI)	5	2580	19 per 100	8 more (4-12 more)	18 more (8-32 more)	32 more (13-64 more)	53 more (19-100 more)
Taste-related adverse events, absolute risk difference per 100 patients (95% CI)[e]	9	2974	4 per 100	6 more (5-8 more)	17 more (13-24 more)	32 more (22-46 more)	47 more (31-63 more)
Adverse events leading to discontinuation, absolute risk difference per 100 patients (95% CI)	9	2974	4 per 100	3 more (2-5 more)	8 more (6-12 more)	13 more (9-19 more)	17 more (11-26 more)

- Patients with CANVAS respond well to these agents
- New agents in the same class are being developed



TAKE HOME MESSAGES – KNOWN ETIOLOGIES

- Chronic cough lasting more than 8 weeks is most commonly due to upper airway cough syndrome (UACS), type 2 inflammation in the airways (eosinophilic bronchitis or asthma), GERD, or ACEI therapy, and sometimes more than one of these

- Routine evaluation includes CXR, Spirometry, FeNO, and CBC

- Treatment includes discontinuation of airway irritants (ACEI, smoking) and empiric therapy for the above conditions based on history and comorbidities
  - UACS often has additional accompanying symptoms/signs
  - Glucocorticoid therapy is likely to be effective in type 2 inflammatory conditions
  - PPI is mostly of benefit in patients with symptomatic reflux disease

- Less common causes of chronic cough include chronic bronchitis, tuberculosis, lung cancer, ILD, and foreign body aspiration

TAKE HOME MESSAGES – REFRACTORY CHRONIC COUGH

- Cough that persists despite adequate trials of empiric therapy or remains unexplained is called Refractory Chronic Cough (RCC) or Unexplained Chronic Cough (UCC)

- RCC/UCC are likely caused by cough reflex hypersensitivity and vagal neuropathy

- Treatment options for RCC/UCC include speech therapy, cough desensitization, anticholinergics, certain neuromodulators, and (occasionally) time-limited opioids. New treatments are under development.

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Questions?

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