

# Latest in COUGH

Sidney S. Braman MD Master FCCP

Professor of Medicine, Emeritus

Icahn School of Medicine at Mount Sinai

New York, NY

MOUNT SINAI - NATIONAL JEWISH HEALTH

## Respiratory Institute



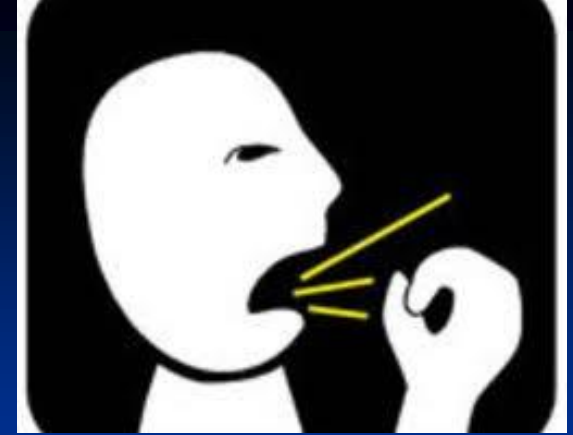
# Objectives

- Explore the components of the cough reflex and common causes of cough
- Define the work up of cough and the value of history/exam/laboratory evaluation
- Use illustrative cases presenting with cough to discuss current approach to diagnosis and treatment.

# Disclosures

- Consultant AstraZeneca
- Speaker Genentech

# Cough

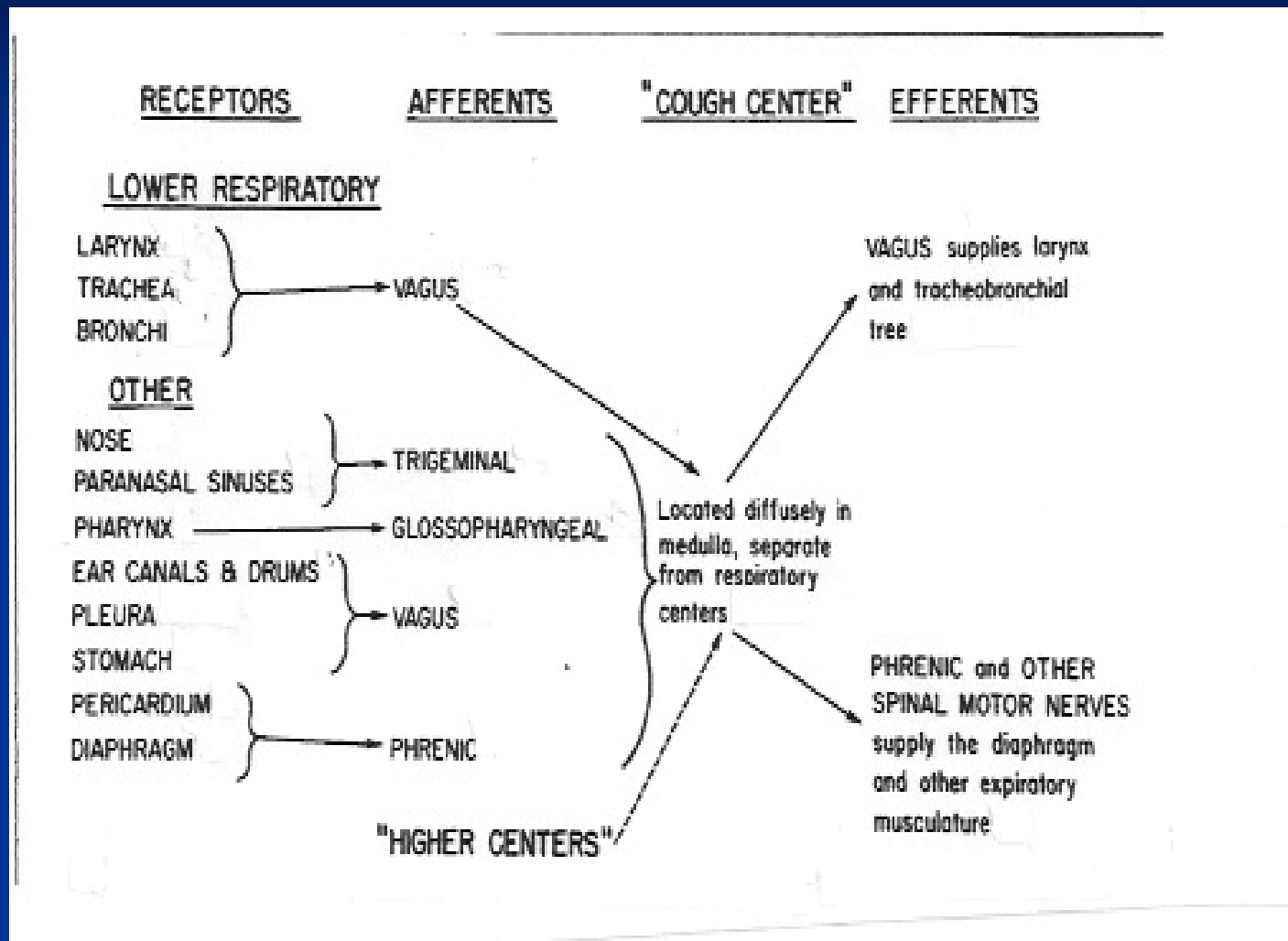


- Cough is protective physiologic reflex
- Defense mechanism for protecting and clearing foreign particles from the airways
- Can be a source of spread of disease
- Can represent serious medical disease or be benign self-limited illness
- 3% of all ambulatory visits; \$3.6 Billion dollars spent in US on OTC cough remedies
- Specific diagnosis and treatment of chronic cough can be made in majority of cases

# Common Causes of Cough

Cough Classification	Most Common Causes
Acute Cough <3 weeks	Viral upper respiratory tract infection (eg, common cold) Exacerbation of underlying lung disorder (eg, asthma) Acute environmental exposure Acute cardiopulmonary disease (eg, pneumonia, pulmonary embolism, congestive heart failure)
Subacute cough 3-8 weeks	Postinfectious cough (eg, viral upper respiratory tract infection, pertussis infection, exacerbation of underlying lung disorder) Non-postinfectious cough (chronic cough)
Chronic Cough > 8 weeks	Active cigarette smoking or other chronic irritant Angiotensin converting enzyme inhibitor use Radiographically apparent disease processes of the lung If normal chest radiograph, most common causes are: <ul style="list-style-type: none"><li>• upper airway cough syndrome</li><li>• asthma</li><li>• nonasthmatic eosinophilic bronchitis</li><li>• gastroesophageal reflux disease</li></ul>

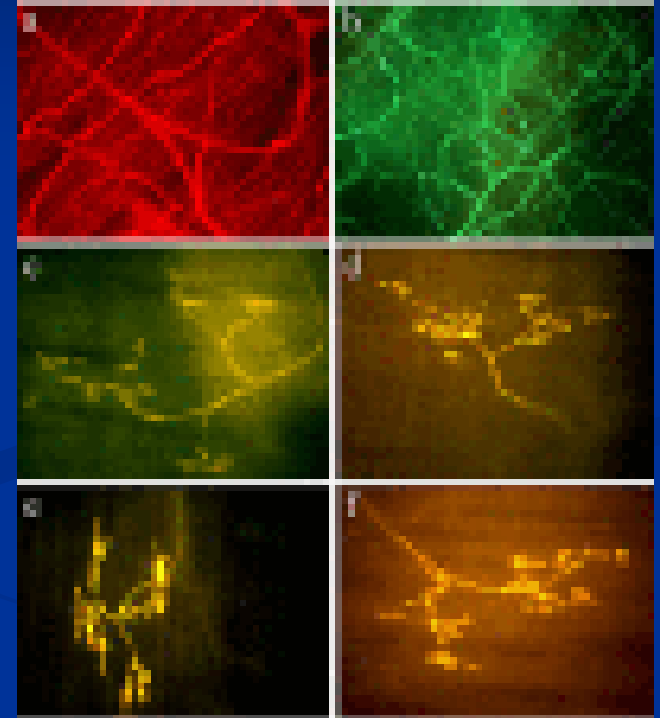
# The Cough Reflex



Irwin RS, Rosen MJ, Braman SS. [Cough. A comprehensive review.](#)  
Arch Intern Med. 1977 Sep;137(9):1186-91.

# The Cough Reflex

- Cough begins with stimulation of receptors in and under the airway epithelium
- Most abundant in larynx and large airways
- Stimulated by irritants or inflammatory mediators and mechanical stimulation



Subepithelial cough receptors

# The Cough Reflex

- Two types of sensory afferents are thought to mediate cough
  - A $\delta$  fibers originate from nodose ganglia; they are nociceptors sensitive to mechanical stimuli [“irritant receptors”]
  - C-fibers originate mainly from the jugular vagal ganglia and are mostly chemosensitive (respond to noxious chemicals such as bradykinin, ATP, nicotine, and capsaicin)
- Activation of these sensory afferents goes through vagus nerve to synapse in the solitary tract nucleus in the medulla and then to “cough center” via second order neurons
- Efferent neurons activated to produce cough



# Ion Channels and Cough

- **Chemical, mechanical, and thermal stimuli can trigger opening of specific ion channels expressed by the terminals of these vagal nerves**
- **These include several members of the Transient Receptor Potential (TRP) super family of ion channels**
- **TRPA (ankyrin) 1, TRPV (vanilloid) 1 and Purinergic (P2X) receptors. They are implicated in cough; channels open and activate afferent nerves in response to noxious stimuli**
- **In health, cough functions to remove irritants from the airways; in disease states receptors can become sensitized and hyperresponsive.**

# Why Do We Cough?

- 1) Excessive stimulation of the  $A\delta$  cough receptors
  - Too much mucus
  - Foreign body
- 2) Stimulation of the afferent vagus nerve (rare)
  - Mediastinal tumor
  - Aortic aneurysm

# 62 year old man

## Chief Complaint: Cough for 4 years

- His cough was non-productive; mild dyspnea walking up stairs. No wheeze or history of asthma or atopy. Cough started suddenly one day sitting at the edge of the pool after swimming laps as usual
- Past medical history only positive for systemic hypertension well controlled with a beta blocker; recurrent external otitis media corrected by wearing earplugs in the pool
- Social history positive for 30 pack years of smoking. Quit 10 years ago
- Exam & CXR negative. PFT negative- no COPD

Further History needed?

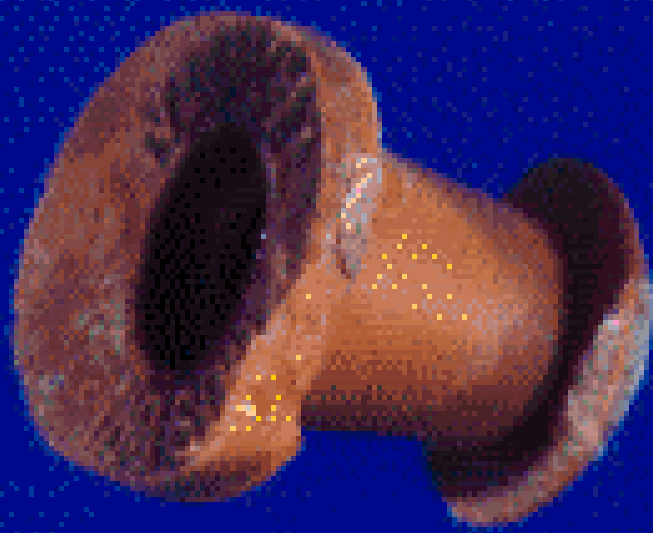
Further studies to be done?

Empiric Treatment?

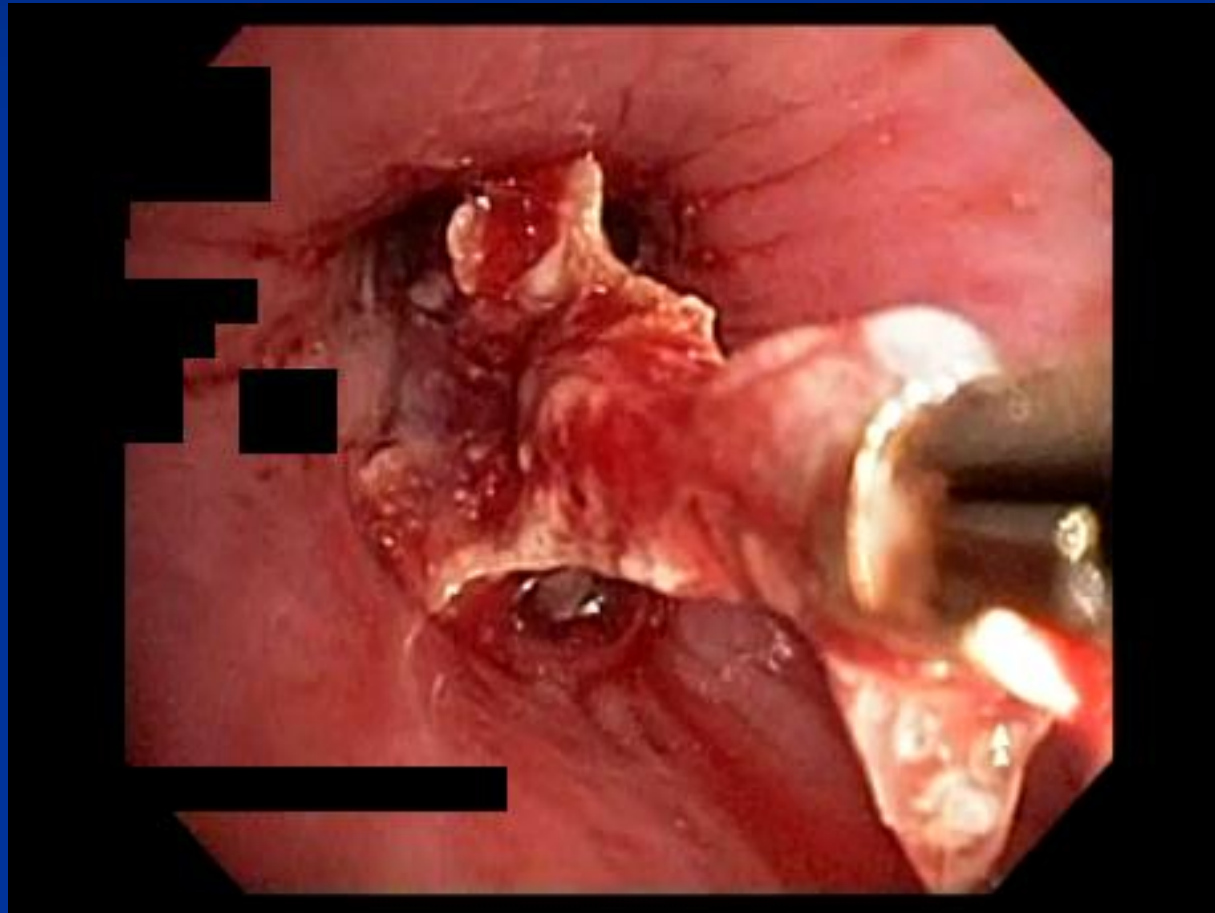
# 62 year old man

Chief Complaint: Cough for 4 years

- On further questioning the cough started after the patient swallowed one of his earplugs. He had a habit of taking them out of his mouth and chewing on them while resting at the side of the pool



# Fish Bone Being Extracted Patient with Chronic Cough



# Why Do We Cough?

- 3) Heightened sensitivity of C-fiber receptors
  - ACE-inhibitor induced cough
  - Airway inflammation/injury/trauma



# Cough Hypersensitivity Syndrome

- **European Respiratory Society Task Force as a “disorder characterized by troublesome coughing often triggered by low levels of thermal, mechanical, or chemical exposure”**
- **The triggering of cough by relatively innocuous stimuli (talking, eating, laughter, perfumes) suggests heightened sensitivity of the sensory nerve pathways considered a disease entity caused by a disordered nervous system.**
- **Hypertussia Similar? to hyperalgesia (abnormally increased sensitivity to pain)**

## **Chief Complaint: Cough**

**HPI: 55 year old woman presents with a non-productive cough for the past 8 weeks. She has been reluctant to go to the doctor because her cousin was just diagnosed with inoperable lung cancer and she thought she might have it too.**

**PMH: positive for migraine headaches and systemic hypertension discovered 6 months ago. Meds: enalapril, estrogen replacement therapy for menopausal symptoms**

**SH: born in Hong Kong and came to this country 20 years ago Lives with her husband. One child. Non-drinker. Smoked 1-2 packs of cigarettes a day and gave it up one year ago when her cousin was diagnoses with lung cancer**

**P.E. negative**

**Labs: Blood work negative Chest x-ray negative**

# ACE inhibitor-induced cough

- Important medications for patients with hypertension, heart failure and renal disease
- Cough occurs in 2-33% of ACE-I treated patients
  - Dry cough typically associated with throat tickling or scratching sensation in the throat
  - Usually occurs within 1-2 weeks of starting ACE-I, but lag time may be up to 3 months
- Diagnose by stopping ACE-I – angiotensin receptor blockers (ARBs) can be substituted

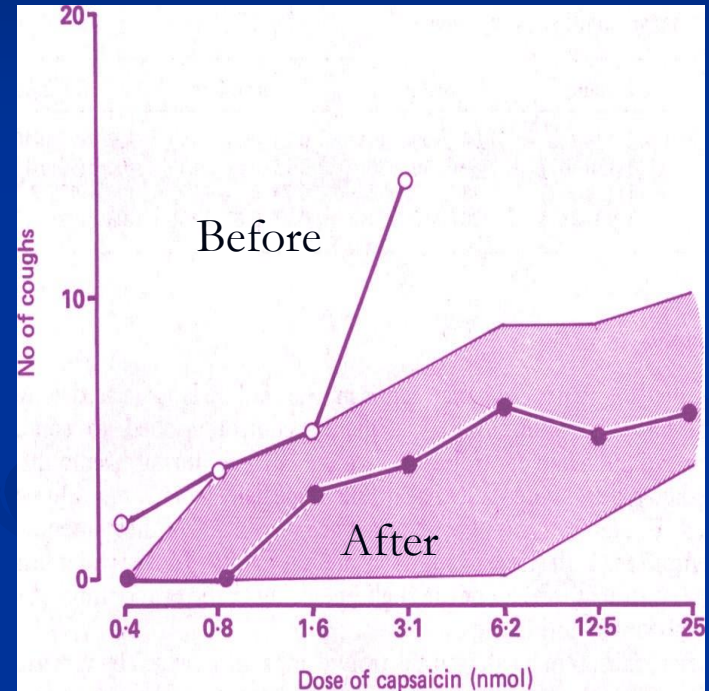
# ACE inhibitor-induced cough

## Mechanisms

- The mechanism of ACE-inhibitor-induced cough is still unclear.
- Proposed mechanism: ACE also metabolizes bradykinin & substance P – these molecules accumulate with ACE inhibitors, producing cough
- A question of why cough does not occur in all ACE-inhibitor users is still unknown; mechanisms that include ACE insertion/deletion polymorphisms have been found
- No effect on bronchial reactivity; It is safe for asthmatics

# Example of Hyperreactivity of Cough Receptor

❖❖ ACE-inhibitors cause increased levels of substance P, bradykinin, and prostaglandin concentrations in airway secretions



Number of coughs during capsaicin cough challenge before and after stopping ACE-inhibitor

# Chief Complaint: Cough

**HPI:** 44-year-old man who had been working in a glass washing factory presented with a non productive cough that is worsened with exertion, laughter and speaking on the phone. The cough began after accidental exposure to hydrofluoric acid (HF) of 50% concentration (used to polish and frost glass) 10 days ago. After opening the cap of the HF bottle for approximately 1–2 min, he experienced a burning sensation in his eyes, nose, and mouth and he noted chest tightness and dyspnea.

**PMH** Negative He was a former 5 pack-year smoker who 10 years ago

**PE:** Negative.

**LABS:** CXR Negative Spirometry normal  
Methacholine positive PC20 0.8 mg/ml

# RADS

## Reactive Airways Dysfunction Syndrome

- **RADS and irritant-induced asthma are closely related forms of asthma. RADS results from**
  - **a single exposure (minutes to hours) to a high concentration of irritant agents; +Bronchial reactivity.**
  - **The initial change is rapid denudation of the mucosa with a fibrinohemorrhagic exudate.**
  - **Treatment with asthma medications**
  - **Repeated exposure to moderate to low doses of irritant agents- irritant induced asthma**

There is no evidence that atopy is a risk factor for the development of RADS



# Criteria for Diagnosis of RADS

- **No respiratory complaints. The onset of symptoms occurs after a single specific exposure within 24 hours of exposure and should persist for at least three months.**
- **The exposure should be to a gas, smoke, fume, or vapor with irritant qualities in very high concentrations.**
- **The symptoms should simulate asthma with cough, wheezing, and dyspnea.**
- **Pulmonary function tests may or may not show airflow obstruction; Methacholine challenge should be positive. Capsaicin challenge shown to be positive**
- **Other types of pulmonary diseases should be ruled out**

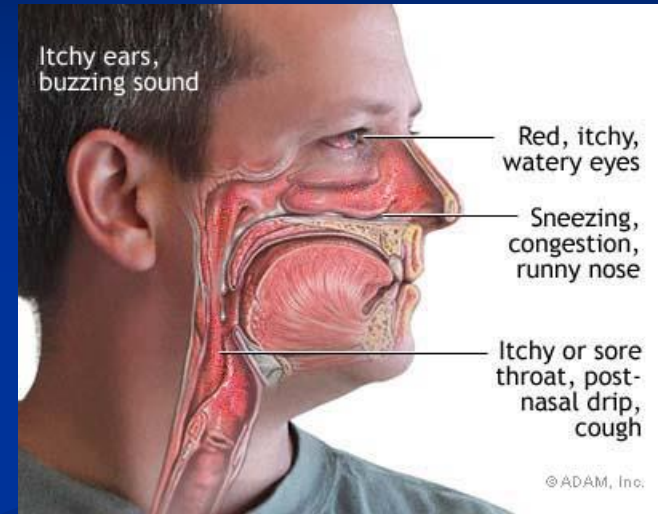


# Upper Airway Cough Syndrome

(post nasal drip associated cough)

## A Cough Hypersensitivity Syndrome?

- ◆ Rhino-sinus secretions drain posteriorly, contacting the vocal cords and producing cough; Allergic rhinosinusitis is most common underlying entity
- ◆ Increased sensitivity to capsaicin found
- ◆ Cough is typically dry and may be associated with tickling sensation and need to clear throat- no diagnostic test
- ◆ Newer generation antihistamines may not work because of significant role of cholinergic receptors
  - Should respond to older generation antihistamines (Dexbromphenamine) with greater anticholinergic activity (also more sedating) and alpha adrenergic constrictors (Neosynephrine,) +/- nasal wash



Visualized drainage with suggestion of cobblestone mucosa

# Obstructive Sleep Apnea and Cough

## A Cough Hypersensitivity Syndrome?

- Prevalence of cough with OSA is high (33-39%)
- May have no daytime sleepiness/normal Epworth score
- OSA patients have a significant lower cough threshold to capsaicin; higher levels of cough neuro-peptides and lymphocytes in sputum
- CPAP improvement 93%; Resolution 67%
- Mechanisms
  - Snoring and upper airway trauma → inflammation
  - GERD

# 31 y.o. male physician with chronic cough for 6 months

- 31 y.o. male physician, a 1st year GI Fellow at Mount Sinai. He began training for a marathon and noted vigorous coughing after his practice runs. The cough worsened and now is more often and occurring at night time. It is non-productive. He is able to run 2-3 miles without dyspnea
- Past medical history of allergic rhinitis; allergic to spring aeroallergens and especially cats. Intranasal Fluticasone did not help the cough. No history of childhood asthma

# 31 y.o. male physician with chronic cough for 6 months

- Physical Exam negative; Lungs Clear; Spirometry nl.

## What is your next step?

FeNO level 225 ppb

A sign of Th2 inflammation

FeNO is IL-13 driven

# COUGH VARIANT ASTHMA

- There is general consensus that asthma is an important cause of cough. The controversies relate largely to its evaluation.
- Although bronchoprovocation challenge tests have high negative predictive value, positive predictive value is poor
- The assessment of airway inflammation by induced sputum eosinophil cell count analysis and exhaled nitric oxide measurement offers high sensitivity and specificity and is predictive of response to corticosteroid therapy
- They also have the potential to guide titration of ICS therapy. No ICS if tests negative.

# Exhaled nitric oxide as a noninvasive assessment of chronic cough.

- FeNO values were significantly higher in patients with chronic cough attributable to non-wheezing asthma as compared with those with chronic cough and no asthma and to healthy volunteers (75.0 ppb; 16.7 ppb; and 28.3 ppb, respectively).
- The sensitivity and specificity detecting asthma, using 30 ppb as the FeNO cutoff point, were 75 and 87%, respectively. The positive and negative predictive values were 60 and 93%



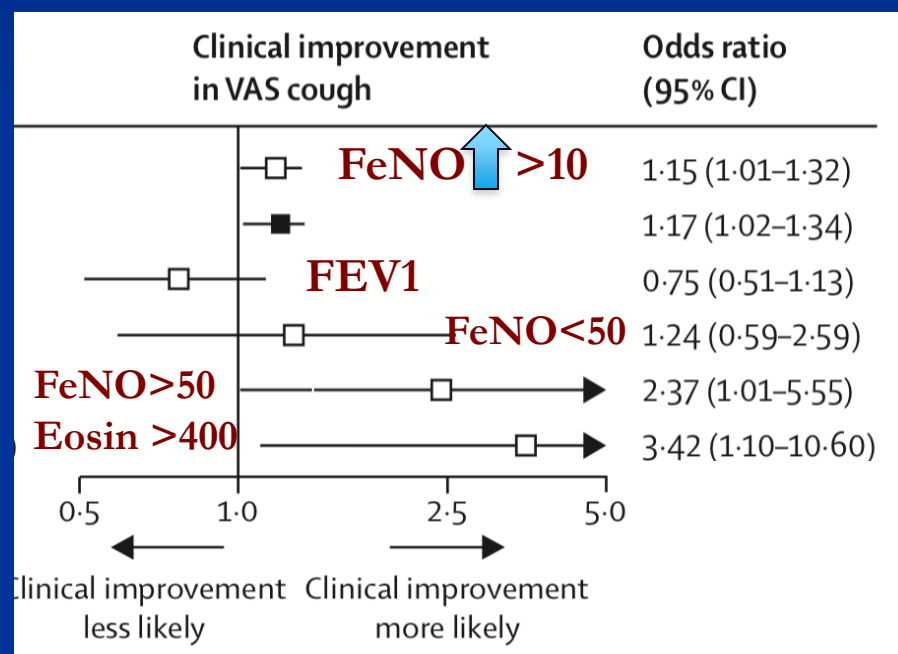
# Exhaled nitric oxide as a noninvasive assessment of chronic cough.

**Table 1. PATIENTS' CHARACTERISTICS AND MEDIAN EXHALED NITRIC OXIDE LEVELS IN THE STUDIED GROUPS**

	Healthy Control Subjects	Chronic Cough		Wheezing Asthmatics
		Nonasthmatics	Asthmatics	
Sex, M/F	8/15	9/21	2/6	13/31
Age, yr <sup>*</sup>	38 ± 8	47 ± 15	41 ± 12	38 ± 14
ENO, ppb	28.3	16.7	75.0	69.0
FEV <sub>1</sub> , % pred <sup>*</sup>	94 ± 6	92 ± 5	93 ± 6	74 ± 8

# FeNO as a predictor of response to inhaled corticosteroids in patients with non-specific respiratory symptoms and insignificant bronchodilator reversibility: a randomized controlled trial

- Strong support for the use of FENO measurement to inform inhaled-corticosteroid prescribing decisions
- FENO levels above 50 ppb strongly associated with improvement in cough severity with ICS





**72 year-old man presented with increasing shortness of breath and nagging non-productive cough**



# Cough and IPF

- Prevalence of cough in IPF has been reported to be 80% with significant impact on QOL; It is predictor of disease severity, time to death, or need for transplant.
- Treatment with conventional antitussive therapies eg. cough syrups, dextromethorphan, codeine not helpful.
- Cause of cough not known: enhanced cough reflex sensitivity by mechanical fibrotic lung distortion destroying either sensory and/or inhibitory cough nerves. Also levels of neurotrophins causing a growth of sensory neurons might play a role
- Mast cells of fibrotic lungs are also sensitive to mechanical stretch. Degranulated mast cells release mediators such as substance P, histamine, serotonin, and proteases that activate sensory nerve C-fibres

# Cough and IPF

- A phase II study analyzing the effect of PA101, an inhaled version of sodium cromoglycate (40 mg tid), had 31% improvement of 24-h objective cough
- Cromoglycate's activity has been attributed to inhibition of mast cell degranulation and the consequential inhibition
- No improvement with chronic idiopathic cough, suggests that cough in IPF might be of a different phenotype

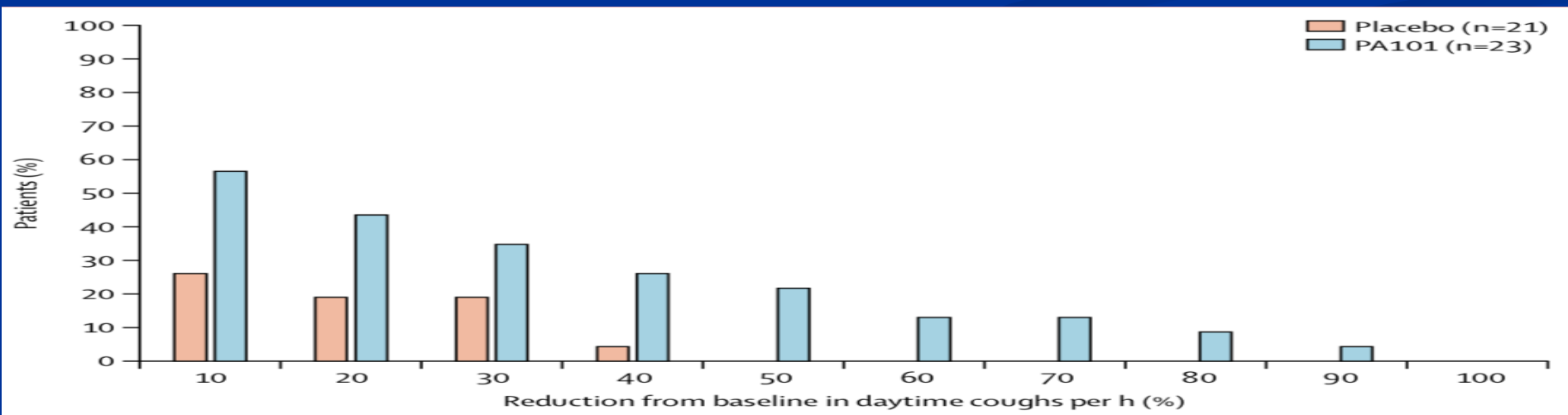


Figure 5: Responder analysis—daytime cough frequency in IPF cohort  
Data are from the efficacy analysis set. IPF=idiopathic pulmonary fibrosis.

# Gastroesophageal Reflux (GER) related Cough A Cough Hypersensitivity Syndrome?

- Laryngopharyngeal Reflux and cough
- A common ENT diagnosis
- Frequent throat clearing & hoarseness
- Laryngoscopy findings of erythema edema and thickening of posterior pharynx. ?? Same findings as trauma
- Only 28% with chronic cough and esophageal pH test have long-term response to PPI



vocal cords showing  
prominent posterior  
inflammation

# Unexplained Chronic Cough

## A Cough Hypersensitivity Syndrome?

**Patients with chronic cough that persists despite optimal treatment of presumed associated common and uncommon conditions**

- **Protective reflex heightened; low level stimuli cause cough; increased sensitivity of cough reflex to Capsaicin**
  - ? Disorder of airway nerves
- **Elevated levels of Histamine and Prostaglandin E<sub>2</sub> and Leukotrienes found**
- **Neutrophils and lymphocytes found ?autoimmune disease**
- **Gabapentin, Pregabalin and Amitriptyline/ Speech therapy**
- **Trials with ion channel inhibitors/receptors (TPRA,TPRV) failed**  
**Future=purinergic receptors? Inhibitors that block sensory nerve activation by ATP (namely antagonists of the P2X3 subunit of the ATP receptor- eg. Gefapixant)**

# Summary

**Cough: the most common symptom world-wide for which patients seek medical attention**

- **Non-specific symptom of respiratory disease with a broad differential diagnosis**
- **Specific diagnosis and treatment of chronic cough can be made in majority of cases**
- **Treatment often unsuccessful, possibly as a result of heightened sensitivity of afferent cough receptors; with better understanding of cough receptor physiology, future approaches are anticipated.**