

Chronic Cough

Alan P. Baptist, MD, MPH, FAAAAI

Professor of Medicine and Division Head
Division of Allergy & Clinical Immunology
Henry Ford Health / Michigan State University
Detroit, MI

 CONTINUING EDUCATION COMPANY

1

Disclosure

Consultant: Astra Zeneca; GSK; Teva

Research Grant: American Lung Association; Astra Zeneca;
GSK; Novartis; Takeda

 CONTINUING EDUCATION COMPANY

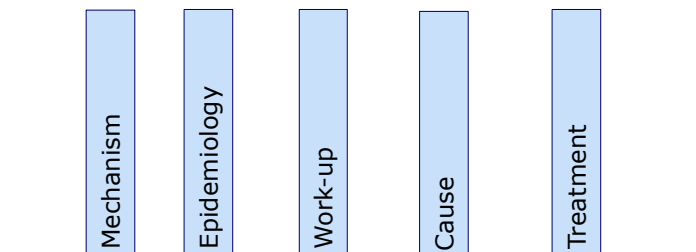
2

Objectives

- To understand the epidemiology and pathophysiology associated with chronic cough
- To describe the common, and uncommon, causes of chronic cough
- To develop an appropriate algorithm for the diagnosis and treatment of chronic cough

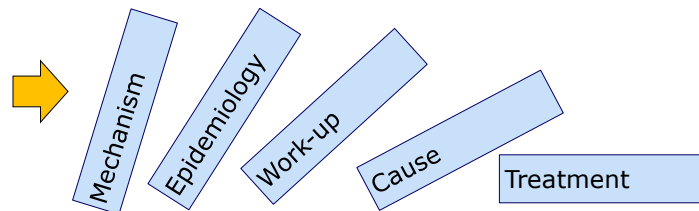
3

I Just Want to Know What to Treat Chronic Cough With!



4

I Just Want to Know What to Treat Chronic Cough With!

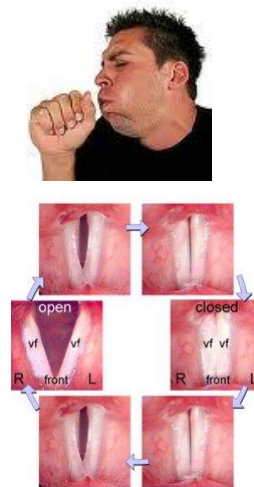


HENRY FORD HEALTH

5

Why Do We Cough?

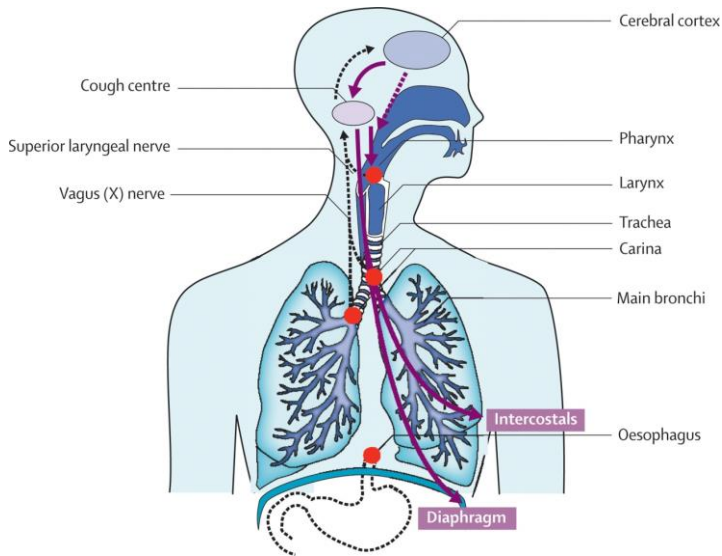
- A defense reflex mechanism
- Three phases:
 - Inspiratory phase
 - Forced expiratory effort against a closed glottis
 - Opening of the glottis with subsequent rapid expiration



HENRY FORD HEALTH

6

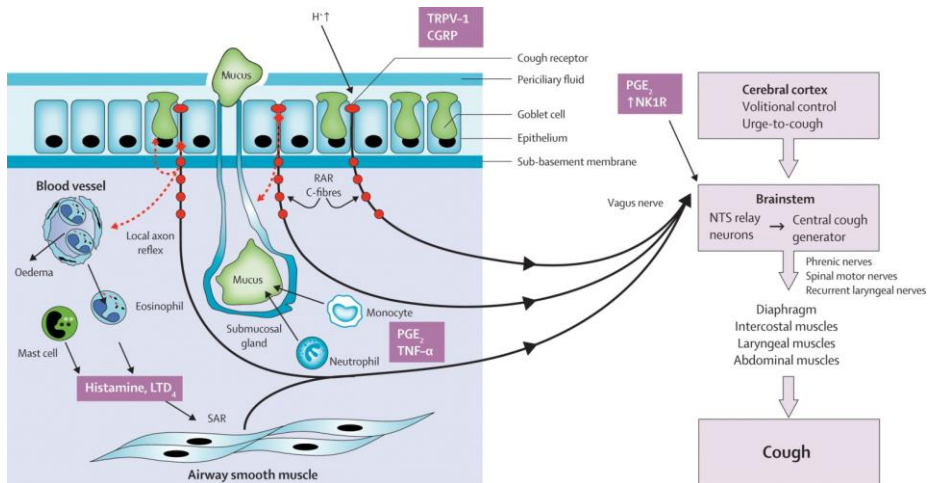
Pathogenesis of Cough



HENRY FORD HEALTH

7

Pathogenesis of Cough



HENRY FORD HEALTH

8

Classification of Cough

- Acute: <3 weeks
- Subacute: 3 – 8 weeks
- Chronic: >8 weeks

HENRY FORD HEALTH

9

In Population Studies, How Common Is Chronic Cough?

- A. 1%
- B. 5%
- C. 10%
- D. 25%

 CONTINUING EDUCATION COMPANY

10

How Common Is Chronic Cough?

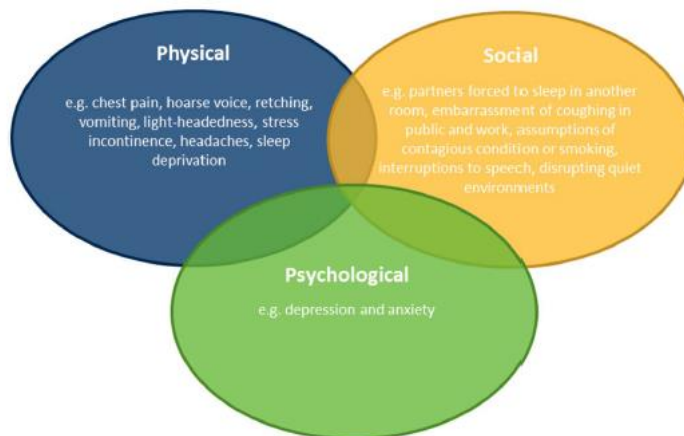
- Affects 10% of the population¹
- Chronic cough accounts for about 20 - 30% of outpatient visits to respiratory specialists
- More common in women than men
- Peak age 50-60s

HENRY FORD HEALTH

*Arinze et al. ERJ Open Res 2020: Apr (6):2
Schellhout J. Chron Respir Dis. 2022;19*

11

Impact of Chronic Cough



HENRY FORD HEALTH

Bali V. Quality of Life Research. 2024:33 - 903

12

Common Causes of Chronic Cough

- Upper airway cough syndrome
- Asthma (and related conditions)
- Gastroesophageal reflux disease (and LPR)

Causes of Chronic Cough

	Number (women)	Diagnosis				
		Asthma/CVA/EB/AC	GORD	PNDS	Idiopathic	Other
USA						
Irwin ⁵⁴	102 (59)	24%	21%	41%	1%	CB (5%)
Irwin ⁵⁵	49 (27)	43%	10%	47%	0	CB (7%)
Poe ⁵⁶	139 (84)	35% (mostly CVA)	5%	26%	12%	CB (7%)
Pratter ⁵⁷	45 (28)	31%	11%	87%	0	Overlap of diagnosis with PNDS
Smyrniotis ⁵⁸	71 (32)	24%	15%	40%	3%	..
Mello ⁵⁹	88 (64)	14%	40%	38%	2%	..
French ⁶⁰	39 (32)	15%	36%	40%	2%	..
Irwin ⁶¹	24 (13)	21%	33% (rhinitis included)	33% (GORD included)	46%	..

ACEI-angiotensin-converting enzyme inhibitor. AC-atopic cough. CB-chronic bronchitis. CVA-cough-variant asthma. EB-eosinophilic bronchitis. GORD-gastro-oesophageal reflux disease. PNDS-postnasal drip syndrome or rhinosinusitis. ILD-interstitial lung disease. NR-not recorded.

Chung, K., Pavard, I. *Lancet* 2008; 371: 1364 - 74.

Less Common Causes for Chronic Cough

- Chronic Infections or Post-infectious cough
- Airway and Parenchymal disease: (COPD, CF, bronchiectasis, bronchiolitis, ILD, sarcoidosis)
- Tumors
- Cardiovascular disease
- Drugs (ACE-I, B-blocker)
- Other: recurrent aspiration, irritation of external auditory meatus, psychogenic, tracheobronchomalacia, OSA, AV malformations, laryngeal sensory neuropathy, psychogenic cough, disorders of pleura, pericardium, esophagus, stomach, thyroid

HENRY FORD HEALTH

15

Upper Airway Cough Syndrome

- Both post nasal drip and immune factors
- Several studies suggest this is the most common cause
- Mechanisms for UACS:
 - Allergic rhinitis
 - Nonallergic/vasomotor rhinitis
 - Acute nasopharyngitis
 - Sinusitis



HENRY FORD HEALTH

16

Upper Airway Cough Syndrome

- Symptoms: rhinorrhea, throat clearing, sensation of liquid dripping into back of throat
- No definitive criteria for diagnosis

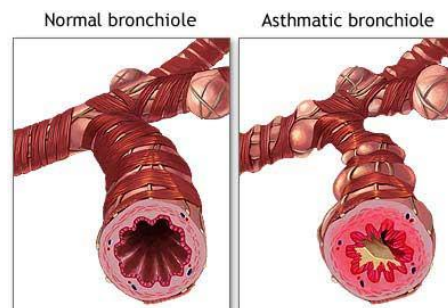


HENRY FORD HEALTH

17

Asthma

- Multiple mechanisms to activate cough reflex
- Can present predominantly with cough
- Very common cause of chronic cough



HENRY FORD HEALTH

18

Asthma

- Diagnosis is suggested by history, especially with typical triggers
- Spirometry and/or methacholine challenge may be helpful
 - However, high false positive rate in chronic cough (20 – 30%)

Asthma – Like Conditions

	Asthma	Cough Variant Asthma	Eosinophilic Bronchitis
Symptoms	Cough, wheeze, SOB	Cough only	Cough +/- sputum
Atopy	common	common	general population
Variable airflow obstruction	+	+	-
Bronchodilator response	+	+	-
Corticosteroid response	+	+	+
Progression to asthma	N/A	30%	10%
Sputum eosinophils	frequent	frequent	always

Asthma-like Conditions: Irritable Larynx Syndrome

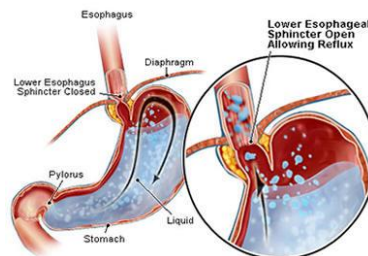
- The vocal cords and surrounding structures adduct with inhalation
- More often found to cause cough than to cause 'wheezing'
- Transient VCD follows an upper respiratory infection with coughing paroxysms due to postnasal drainage inducing VCD

HENRY FORD HEALTH

21

GERD

- Often the 2nd or 3rd most common cause of chronic cough
- Some, but not all, patients complain of typical symptoms

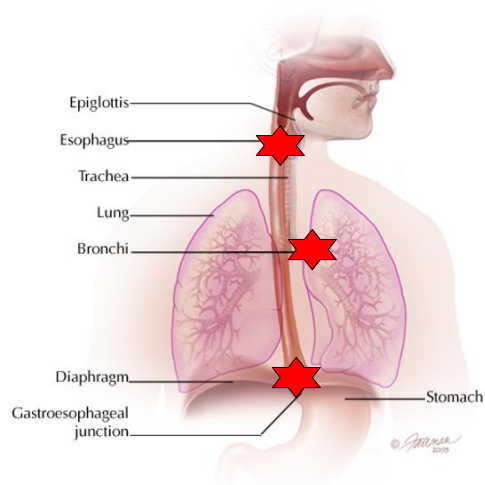


HENRY FORD HEALTH

22

GERD

- Several factors responsible for cough due to GERD



HENRY FORD HEALTH

23

Laryngopharyngeal Reflux (LPR)

- Retrograde movement of gastric contents into the laryngopharynx
- Only 35% report typical GERD symptoms



HENRY FORD HEALTH

24

Post Infectious Cough

- Can last > 8 weeks after an infection – includes post-COVID syndrome

Pneumonias Streptococcus pneumoniae Haemophilus influenzae Moraxella catarrhalis Staphylococcus aureus Pseudomonas aeruginosa Gram-negative bacilli Mycobacteria sp. Mycoplasma pneumoniae	Bronchitis Mycoplasma pneumoniae Chlamydomphila pneumoniae Bordetella pertussis Bordetella parapertussis RSV Influenza Parainfluenza
Fungal infections Blastomyces sp. Cytococcus sp. Histoplasmosis sp. Allergic broncopulmonary mycosis	Parasite infections Paragonimiasis Syngamosis Tropical eosinophilia Wychereria bancrofti Brugia malayi

HENRY FORD HEALTH

25

Airway and Parenchymal Disease

- 70% of patients w/ COPD have a chronic cough
- Bronchiectasis can be from infection, PND, asthma, chronic bronchitis
- Others: CF, sarcoidosis, interstitial lung fibrosis

HENRY FORD HEALTH

26

ACE-I

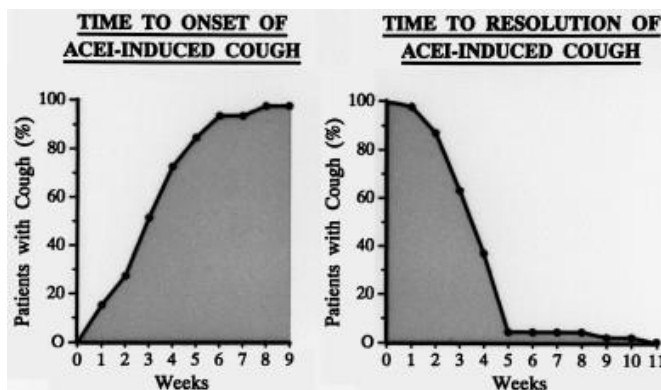
- Cough is seen in about 10 – 20% of patients
- Caused by accumulation of bradykinin and prostaglandins
- ARBs usually OK

HENRY FORD HEALTH

27

ACE-I

- Time course to onset and resolution somewhat variable



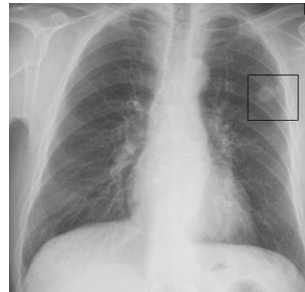
HENRY FORD HEALTH

Lacourciere Y, et al. *J Hypertens.* 1994; 12:169S-73S

28

Lung Cancer

- Less than 2% of cases of chronic cough
- If causing cough, will often originate in the large central airways
- Consider in smoker with change in cough



HENRY FORD HEALTH

29

Causes of Cough in Children

Table 1: Differential diagnoses of chronic cough (in descending order of likelihood).

Infancy	Early childhood	Late childhood
Gastroesophageal reflux	Post-viral airway hyper-responsiveness	Asthma
Infection	Asthma	Post-nasal drip
Congenital malformation	Passive smoking	Smoking
Congenital heart disease	Gastroesophageal reflux	Pulmonary tuberculosis
Passive smoking	Foreign body	Bronchiectasis
Environmental pollution	Bronchiectasis	Psychogenic cough
Asthma		

Acosta R. *Pediatr Ann.* 2014;43(8):e176-e183

HENRY FORD HEALTH

30

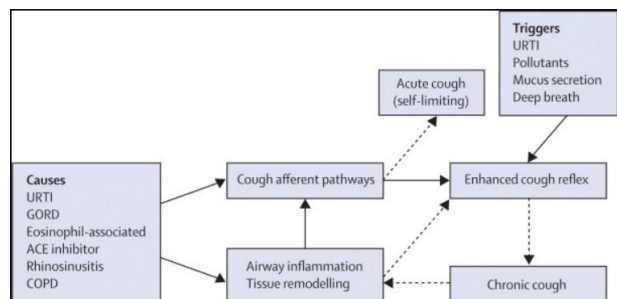
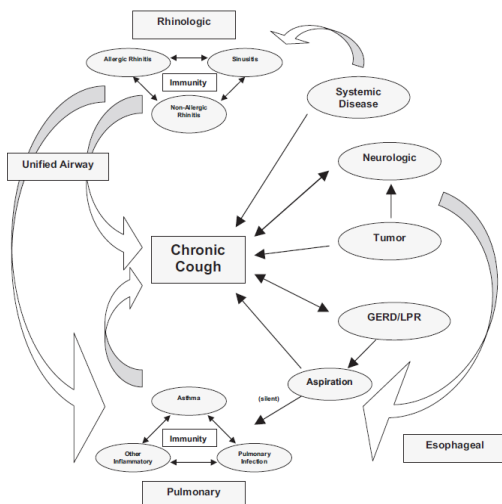
Chronic Cough in Children

•Top 3 causes:

- Asthma
- Protracted bacterial bronchitis (PBB)
- Nonspecific cough

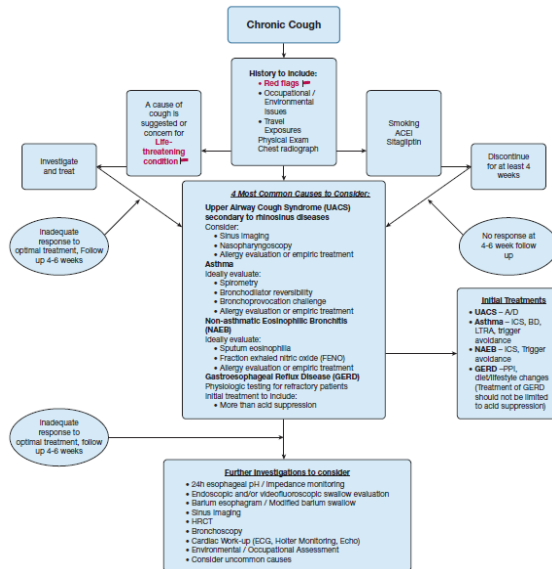
Chang AB, Chest. 2017;152(3):607

Cough Hypersensitivity Syndrome



*Altman KW. JACI In Prac. 2019; 7:1750
Chung KF. Lancet. 2008; 371: 1364*

Work-up



Work-up - History

- Detailed history should include:
 - Time course
 - Aggravating/alleviating factors
 - Occupational and travel history
 - Factors associated when cough began
 - Symptoms of common causes of cough
 - 'Red-flag' signs
 - Character of cough usually not helpful

Which of These Is NOT a 'Red Flag' Sign in Chronic Cough?

- A. Hoarseness
- B. Fever
- C. Smoker over 45 with increased thick sputum
- D. Cough that is worse with eating

Work-up – History RED FLAGS

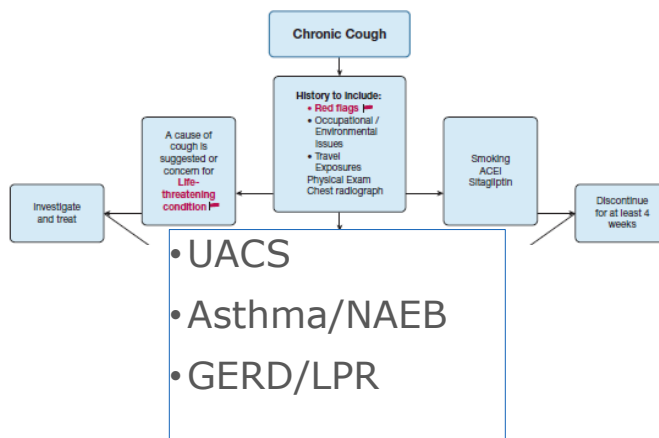
Red Flags

- ▮ Hemoptysis
- ▮ Smoker > 45 years of age with a new cough, change in cough, or coexisting voice disturbance
- ▮ Adults aged 55-80 years who have a 30 pack-year smoking history and currently smoke or who have quit within the past 15 years
- ▮ Prominent dyspnea, especially at rest or at night
- ▮ Hoarseness
- ▮ Systemic symptoms
 - Fever
 - Weight loss
 - Peripheral Edema with weight gain
- ▮ Trouble swallowing when eating or drinking
- ▮ Vomiting
- ▮ Recurrent pneumonia
- ▮ Abnormal respiratory exam and/or abnormal chest radiograph coinciding with duration of cough

Work-up – Physical Exam

- Signs of post-nasal drip or yellow mucus in the posterior oropharynx
- Wheezing
- Clubbing
- Signs of atopy
- Crackles, decreased heart sounds, lower extremity edema

Work-up



Classification of Cough as a Symptom in Adults and Management Algorithms: CHEST Guideline and Expert Panel Report. 2018 Jan

If H&P Suggests UACS:

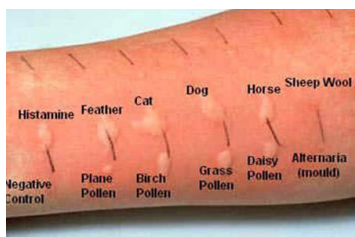
- UACS is a syndrome, so no pathognomonic finding
- Consider an empiric diagnostic and therapeutic trial
- Most effective therapy for allergic rhinitis = intranasal steroids
 - Consider 1st generation antihistamine-decongestant, nasal rinse
- Response seen in about 2 weeks

HENRY FORD HEALTH

39

If H&P Suggests UACS

Response or lack of response – both may need further testing



Skin Allergy Test



HENRY FORD HEALTH

40

If H&P Suggests Asthma

- Ideally evaluate first:
 - Spirometry
 - Bronchodilator reversibility
 - Methacholine challenge
 - FENO test
- Consider empiric therapy

2020 ERS Guidelines on Diagnosis and Treatment of Chronic Cough

HENRY FORD HEALTH

41

If H&P Suggests Asthma



- Medium dose ICS and SABA

CHEST Expert Cough Panel. Managing Chronic Cough Due to Asthma and NAEB in Adults and Adolescents: CHEST Guideline and Expert Panel Report. 2020 Jul.

HENRY FORD HEALTH

42

If H&P Suggests GERD

- If the clinical picture is suggestive, can start therapy without further testing:
 - Lifestyle + dietary changes
 - Acid suppression
 - Consider prokinetic agent

HENRY FORD HEALTH

43

After Treatment for Chronic Cough Due to GERD, How Long Does It Typically Take for the Cough to Improve:

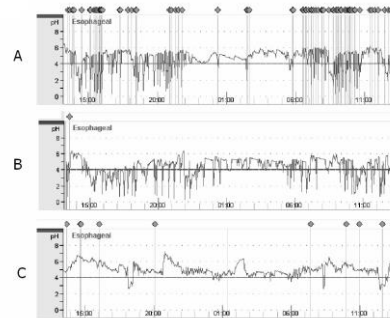
- A. 2 – 3 days
- B. 2 – 3 weeks
- C. 2 – 3 months

 CONTINUING EDUCATION COMPANY

44

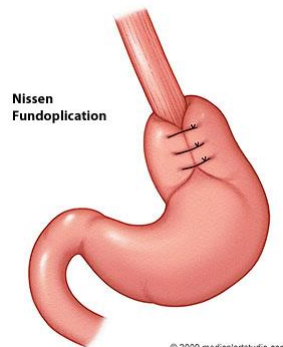
If H&P Suggest GERD

- Often takes 2 – 3 months before cough begins to improve, and 5 – 6 months before it resolves
- Consider 24-hour pH probe if peptic symptoms



If H&P Suggest GERD

- May need laparoscopic or open fundoplication



2016 Chronic Cough Due to Gastroesophageal Reflux in Adults: CHEST Guideline and Expert Panel Report

- *Background:* We updated the 2006 ACCP clinical practice guidelines for management of reflux cough syndrome.
- *Methods:* Two PICO questions were addressed by systematic review: 1) can therapy for gastroesophageal reflux improve or eliminate cough in adults with chronic and persistently troublesome cough? and 2) are there minimal clinical criteria to guide practice in determining that chronic cough is likely to respond to therapy for gastroesophageal reflux?
- *Results:* We found no high quality studies pertinent to either question
- *Conclusions:* The panelists: 1) endorsed use of a diagnostic/therapeutic algorithm addressing common cough etiologies including symptomatic reflux, 2) advised that while lifestyle modifications and weight reduction may be beneficial in suspected reflux-cough syndrome, **PPIs demonstrated no benefit when used in isolation**

HENRY FORD HEALTH

47

If H&P Suggest Post-viral Cough

- Keep in mind UACS or asthma
- Sputum cultures usually not recommended
- Remember to consider Bordetella pertussis
- Consider a short course of prednisone, inhaled ipratropium, 1st generation antihistamine, nasal steroids, or a nasal rinse

HENRY FORD HEALTH

48

Chronic Cough in Children

- Empiric therapy not recommended
- Antitussive therapy not recommended
- Protracted bacterial bronchitis: "For children ≤ 14 with chronic wet cough unrelated to an underlying disease and without any specific cough pointers (eg, coughing with feeding, digital clubbing), we recommend that children receive 2 weeks of antibiotics"
 - typically Augmentin

HENRY FORD HEALTH

- Michaudet, C. *Am Fam Phys.* 2017; 96(9):575
- *Management of Children With Chronic Wet Cough and Protracted Bacterial Bronchitis. 2017 CHEST Guideline and Expert Panel Report*

49

If H&P Don't Suggest an Obvious Cause

- Empiric trial of treatment for UACS
- Very careful examination for any of the 'Big 3' causes
- Recognition that chronic cough is often due to multiple causes, and doses of medications may be inadequate

HENRY FORD HEALTH

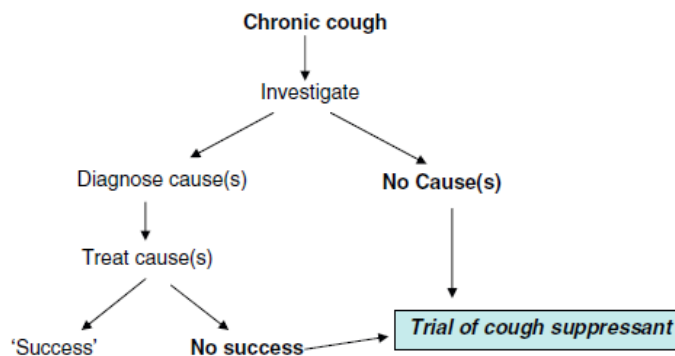
50

If H&P Don't Suggest an Obvious Cause

•Further testing for rare causes:

- HRCT
- Bronchoscopy
- Nasopharyngoscopy
- Echocardiogram
- Swallow study
- Exhaled nitric oxide or sputum eosinophils
- Sweat chloride
- Psychiatric evaluation

Antitussive Therapy



Antitussive Therapy

Very few studies in chronic cough

- Codeine
- Dextromethorphan
- Guaifenesin
- 1st generation antihistamines
- Benzonatate
- Superior laryngeal nerve block
- Inhaled steroids or ipratropium
- Gabapentin, Amitriptyline or Pregabalin

HENRY FORD HEALTH

Bali V. Systematic literature review of treatments used for refractory or unexplained chronic cough in adults. Ann Thorac Med 2024;19:56-73

53

Antitussive Therapy

- Speech pathology:

“In adult patients with unexplained chronic cough, we suggest a therapeutic trial of multimodality speech pathology therapy (Grade 2C).”

Gibson PG, et al. Chest 2016;149:27 – 44

HENRY FORD HEALTH

54

Antitussive Therapy

Pregabalin and Speech Pathology Combination Therapy for Refractory Chronic Cough

A Randomized Controlled Trial



*Anne E. Vertigan, PhD; Sarah L. Kapela, BSpPath; Nicole M. Ryan, PhD; Surinder S. Biring, MB, ChB (Hons), MD;
Patrick McElduff, PhD; and Peter G. Gibson, MBBS (Hons)*

CONCLUSIONS: Combined SPT and pregabalin reduces symptoms and improves QOL compared with SPT alone in patients with CRC. CHEST 2016; 149(3):639-648

HENRY FORD HEALTH

55

2016 ACCP Cough Guidelines

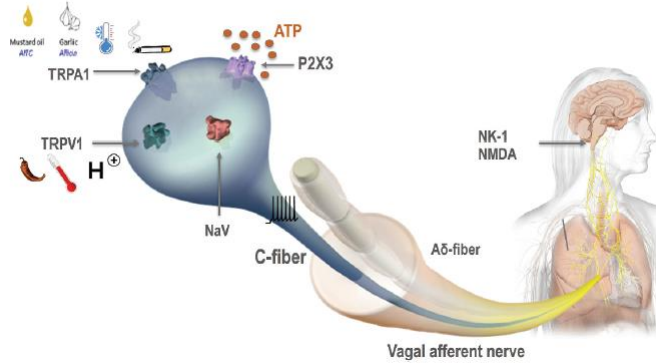
- Don't use inhaled steroids if tests for bronchial hyperresponsiveness and sputum eos are negative
- Don't use PPI if tests for acid GERD are negative
- Careful assessment of adherence
- Consideration of gabapentin – but not morphine
- Consideration of speech pathology

HENRY FORD HEALTH

56

Emerging Options for Chronic Cough

Receptors and Ion Channels Involved in Cough



HENRY FORD HEALTH

57

Emerging Options for Chronic Cough

Table 1. Drugs in active human trials in chronic cough.

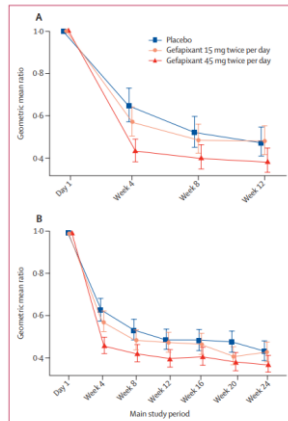
Site of Action	Target	Compound	Company	Stage of Development
Peripheral	P2×3 Receptor	Gefipixant	Merck	Phase 3 complete, under FDA review
		Camlixant (BLU-5937)	Bellus	Phase 2b
		Sivopixant	Shionogi	Phase 2b
Central	TRPA1 TRPM8	GDC-6599	Genentech, Inc	Proof of concept
		AX-8	Axalbia	Phase 2b
	Voltage gated Sodium Channel Neurokinin-1 receptor	NTX-1175	Nocion Therapeutics	Phase 1
		Orvepitant	NeRRe Therapeutics	Phase 2b
		Serlopitant	Menlo Therapeutics	Phase 2b
Non-Neuronal	N-methyl-d-aspartate receptors Kappa opioid receptor (agonist) mu opioid receptors (antagonist) Mast cell	Aprepitant	NeRRe Therapeutics	Off label study
		Ifenprodil	Algermon Pharmaceuticals	Off label study
		Nalbuphine	Trevi Therapeutics	Phase 2
		High-dose Nebulized Sodium Cromoglycate	Patara Pharma	Pilot study

HENRY FORD HEALTH

Brister, D (2023), Expert Opinion on Emerging Drugs, 28:2, 67-77

58

Gefapixant



Interpretation Gefapixant 45 mg twice per day is the first treatment to show efficacy with an acceptable safety profile in phase 3 clinical trials for refractory chronic cough or unexplained chronic cough.

HENRY FORD HEALTH *McGarvey LP. Lancet. 2022 Mar 5; 399(10328): 909-923.*

Not So Fast...

January 24, 2022 | 1 min read

SAVE

FDA declines approval of gefapixant for chronic cough

HENRY FORD HEALTH

Conclusion

- Chronic cough is usually (but not always) caused by one of 3 conditions
- A detailed H&P, along with a CXR, are usually all that are needed
- The first step in management is establishing the etiology

HENRY FORD HEALTH