

Taming Cough in the Peds World

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Potential Conflicts of Interest

- Consulting: Glaxo, DBV, Kaleo, Teva
- Research: AstraZeneca, Novartis
- Adjudication: Quintiles, PRA, Icon
- Associate editor: Annals of Allergy, Asthma and Immunology and AllergyWatch
- Reviewer: Up to date

Off label discussion

- Gabapentin, narcotics, PPIs, nasal corticosteroids are not FDA approved for the treatment of cough

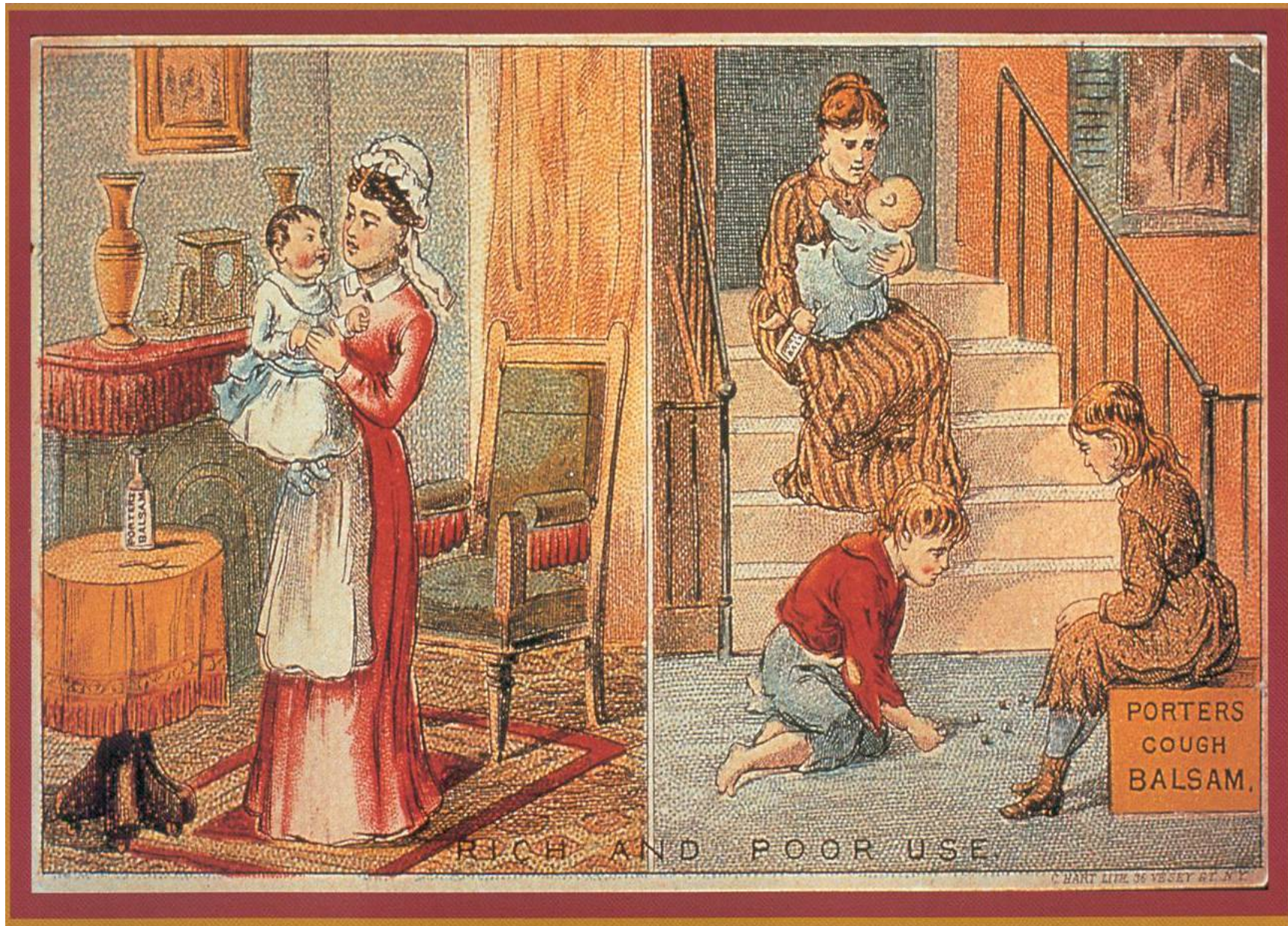
Cough

- defense mechanism
- spread infection
- one of the most common causes to see an MD*
 - *Internist's 3rd most common serious problem generating an office visit (*The Nat Amb Care Survey US 17:975. Wash, DC. Dep HEW Pub PHS 79-1787 . Vital Health Stat Series #36. 1978. Pp.4-29*).

Cough and Pediatrics

- Chronic cough is a common reason for presentation of children to their physician with 10 - 20% of pre-school and school-age children presenting with this complaint.

*Thorax 1996;51:630-1.
BMJ 1993;306:1386-90.*

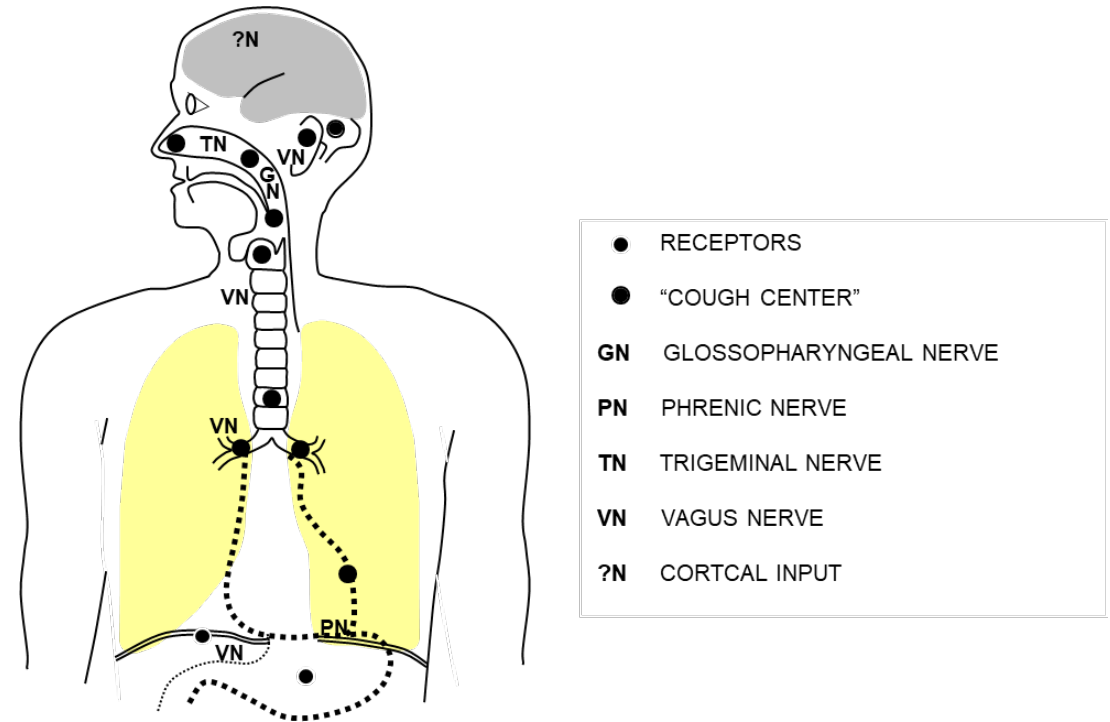


c. 1840

Cough the basics

Involuntary cough appears to be entirely vagally mediated

- stimulation of structures vagally innervated can result in cough.
 - oropharynx
 - larynx
 - respiratory tract
 - tympanic membrane
 - external auditory meatus



Cough the basics

- Most sensitive sites to induce cough: larynx, tracheobronchial tree (esp. corina and bronchial branching points).
 - *Note: experimentally one can't induce cough in smaller airways and the alveoli.*

Cough the basics

- Larynx and pharynx: cough receptors appear to belong to group of rapidly adapting irritant receptors.
 - Usually silent, but when stimulated result in rapid adapting discharge with irregular pattern conducted by fast velocity vagal myelinated fibers.
 - **Triggers:** cigarette smoke, ammonia, ether vapor, alkaline and acid solutions, hypo and hypertonic saline solutions, inflammatory mediators (histamine, bradykinin, PG) and mechanic stimuli (mucus, dust or a foreign body such as a catheter).

Cough the basics

- Tracheobronchial tree
 - similar rapid adapting irritant receptors in trachea and large bronchi.
- Receptors within epithelium concentrated at airway branching points
 - enhanced by pulmonary congestion, atelectasis and bronchoconstriction.

Cough the basics

- Central cough receptor:
 - Theoretical has never been established anatomically integrated by medulla oblongata (brainstem)
 - afferent fibers near nucleus of the tractus solitarius
 - motor outputs in ventral receptor group. Nucleus retroambiguoualis sending motoneurons to respiratory muscles
 - nucleus ambiguous to larynx and bronchial tree.
 - *most anti-tussive Rx acts centrally (don't know how)

Cough the basics

- Ineffective cough results in:
 - Atelectasis
 - Pneumonia
 - Gas exchange abnormalities

Cough the basics

- Diagnostic evaluation: in a systematic manner by assessing locations of afferent limb of the cough reflex
= anatomic diagnostic protocol

Acute Cough

- In acute cough recovery seen in 50% of children within 10 days and 90% within 25 days.
- An Australian prospective community study recorded respiratory episodes of 2.2–5.3 per person-year for children aged ≤ 10 years, with mean duration of episodes of 5.5–6.8
- based on current data, many recommend that acute cough be defined as cough of < 14 days duration.

Hay Fam Pac 2003;20:696-705

Aus NZ JI Pub Health 2003;27:3909-404

Acute cough: management issues

- Most children with acute cough are likely to have an acute viral URTI.
- However, key questions to identify a more serious problem should be asked.
- Usually, acute cough is self-limiting and treatment, if any, should be directed at the etiology rather than the symptom of cough.

SUMMARY OF GUIDELINES FOR COUGH IN CHILDREN

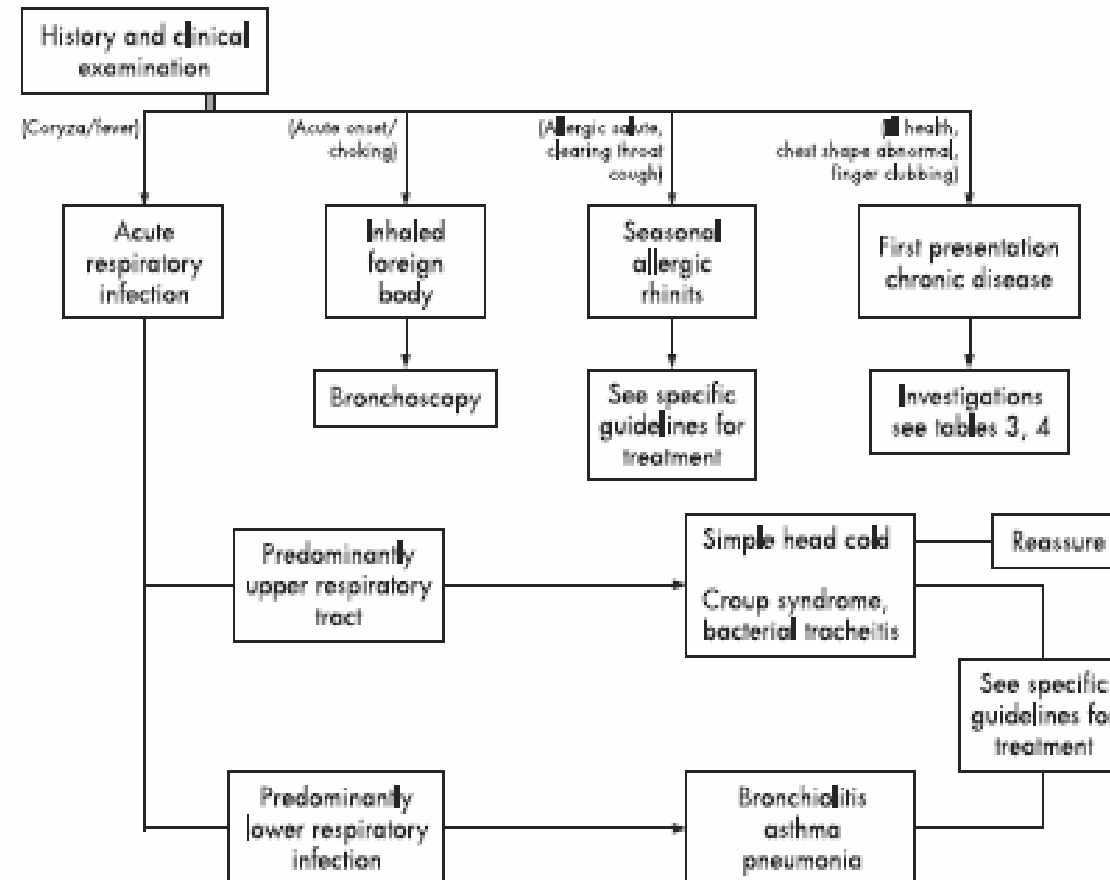
BTS guidelines (all strength C)

- The majority of children with acute cough have a viral respiratory tract infection.
- An attempt should be made to arrive at a specific clinical diagnosis when possible
- The absence of fever, tachypnoea and chest signs appear to be most useful for ruling out future complications

Investigations

- Most children with cough due to a simple upper respiratory tract infection will not need any investigations.
- Children in whom an inhaled foreign body is a likely cause of cough should undergo urgent bronchoscopy.
- A chest radiograph should be considered in the presence of lower respiratory tract signs, relentlessly progressive cough, haemoptysis or features of an undiagnosed chronic respiratory disorder

Figure 2 A simplified overview of the assessment and management of the common causes of acute cough



Acute cough: management issues

- There are no effective medications for the symptomatic relief of acute cough in children and serious adverse events and accidental poisoning have been reported.

Schroder Cochrane Database Rev 2004
Pediatrics 2001;108:e52

ACCP Pediatric cough guidelines 2006

- OTC Cough Medications Systematic reviews have concluded that OTC cough medications have little, if any, benefit in the symptomatic control of acute cough in children, and the American Academy of Pediatrics has advised against the use of codeine and dextromethorphan for treating any type of cough.
 - Berlin Pediatrics 1997; 99:918–919
- Moreover, the use of OTC cough remedies has been associated with significant morbidity and even with mortality. OTC drugs are common unintentional ingestion medications in children <5 years of age.
 - Gunn Pediatrics 2001; 108:E52

ACCP Pediatric cough guidelines 2006

- For acute cough, a systematic review of antihistamine and nasal decongestion combinations and antihistamines in OTC medication has shown that these pharmaceuticals were no more likely than placebo to reduce acute cough in children.

Cough the basics

- Chronic cough => 8 weeks
 - With use of protocol in studies cause can be determined 88-100% of the time.
 - Resultant therapy with success rate of 84-98%.
 - Single cause 73-82%, multiple causes up to 26% with 3 causes up to 8% of cases.
- In 91-94% of time 4 different causes: PND, Asthma, GER and Chronic Bronchitis.

GERD and Cough

- Utility of prokinetic agents:
 - 56 patients with GERD related cough treated with PPI BID
 - 24 responded
 - 18 others only responded with addition of prokinetic agent
 - Presumed to be a result of nonacid refluxate causing cough*
 - This study also reinforces the utility of empiric Rx as 44 or 56 responded without endoscopy or pH probe

Poe Chest 2003;123:679-84

**Ours Am J Gastro 1999;94:3131-8*

GERD and Cough

- In those that fail PPI and prokinetic agent consider:
 - RLG
 - pH probe
 - Impedance testing via GI consult
- Antireflux surgery should be considered in patients with continued sx and objective evidence of reflux – failing maximal medical Rx
 - *Evidence regarding fundoplication for GERD induced cough is lacking*

Rank Ann All 2007;98:305-13

Chronic Cough - Peds

- Currently, the ACCP and ERS guidelines define a chronic cough in adults as one that persists greater than 8 wks.
- However, ACCP and ERS differ in their definition for children
 - ACCP requiring 4 weeks duration
 - ERS using the same length of 8 weeks as required in the adult criteria.
 - The ACCP chose four weeks as the cut off as URTI, a common cause for a prolonged cough, generally resolve within 1-3 weeks in most children.

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[Evidence-Based Medicine]



Etiologies of Chronic Cough in Pediatric Cohorts

CHEST Guideline and Expert Panel Report

*Anne B. Chang, PhD; John J. Oppenheimer, MD; Miles Weinberger, MD, FCCP; Cameron C. Grant, PhD;
Bruce K. Rubin, MD; and Richard S. Irwin, MD, Master FCCP; on behalf of the CHEST Expert Cough Panel*

The KQs follow: Among children with chronic (>4weeks)cough(KQ1)are the common etiologies different from those in adults?

Summary of Recommendations and Suggestions

- There is moderate-quality evidence that common etiologies of chronic cough in children are different from those in adults and are dependent on age and setting.
- The panel recommended that for children aged ≤ 14 years common etiologies of chronic cough in adults should not be presumed to be common causes in children
- The most common ascribed etiologies for chronic cough in the prospective studies varied
 - Common etiologies were asthma or asthma-like conditions, protracted bacterial bronchitis and natural resolution (resolved without a specific diagnosis).
 - Upper airway cough syndrome were common in only two studies
 - Gastroesophageal reflux disease was reported as common in two studies that had substantial limitations in study quality.
 - An etiology consistent with an infection was common in three studies.
 - Asthma (of various different definitions) was a common etiology in three of the retrospective studies.

Cough etiology stratified by cough quality

- Dry
 - Consistent with asthma
- Wet
 - Consistent with protracted bacterial bronchitis

What is PBB

- Protracted or persistent infection of the conducting airways by pathogenic bacteria
 - Non-typable H Influenzae
 - S pneumoniae
 - M catarrhalis
- These bacteria appear to form biofilms which replicate slowly and are difficult to eradicate secondary to biofilms

What is PBB

Symptoms

- Cough is typically worse when changing posture with SOB when coughing
 - Viral infection may exacerbate PBB via release of planktonic forms of bact from biofilms as a response to inflammation
- CXR
 - Usu normal, although may see peribronchial wall thickening
 - No hyperinflation
- Bronchoscopy
 - Definitive investigation
 - Secretions and edematous collapsible bronchi that collapse during suctioning - BAL

What is PBB

- Treatment

- DBPC trial of 50 children with >3 wk of wet cough placed on 2 wk course of Augmentin (40/mg/kg/d) lead to resolution of cough in 48% vs. 16% pbo

- Marchant Thorax 2012;67:689-93

- How long to treat

- 70% of PBB treated with abx for 2wks relapsed

- Kompare J Pediat 2012;160:88-92

- Recent review recommends and empiric 6-8 wks; however admits to lack of consensus

- Pneumococcal conjugate vaccine without reduced incidence

- Craven Arch Dis Child 2013;98:72-6

Unexplained cough

- With use of diagnostic and treatment protocols in cough have led to management in approximately 93% of patients with chronic cough.
- A percentage of patients however continue to suffer from chronic cough with no obvious cause or treatable trigger (+*)
- QOL decrement is similar to severe COPD (^)
- This stresses the need for symptomatic treatment

+ Kastclic ERJ 2005;25:235-43

*Pratter Chest 2006;129:s222-31

^French Arch Int Med 158;1657-61

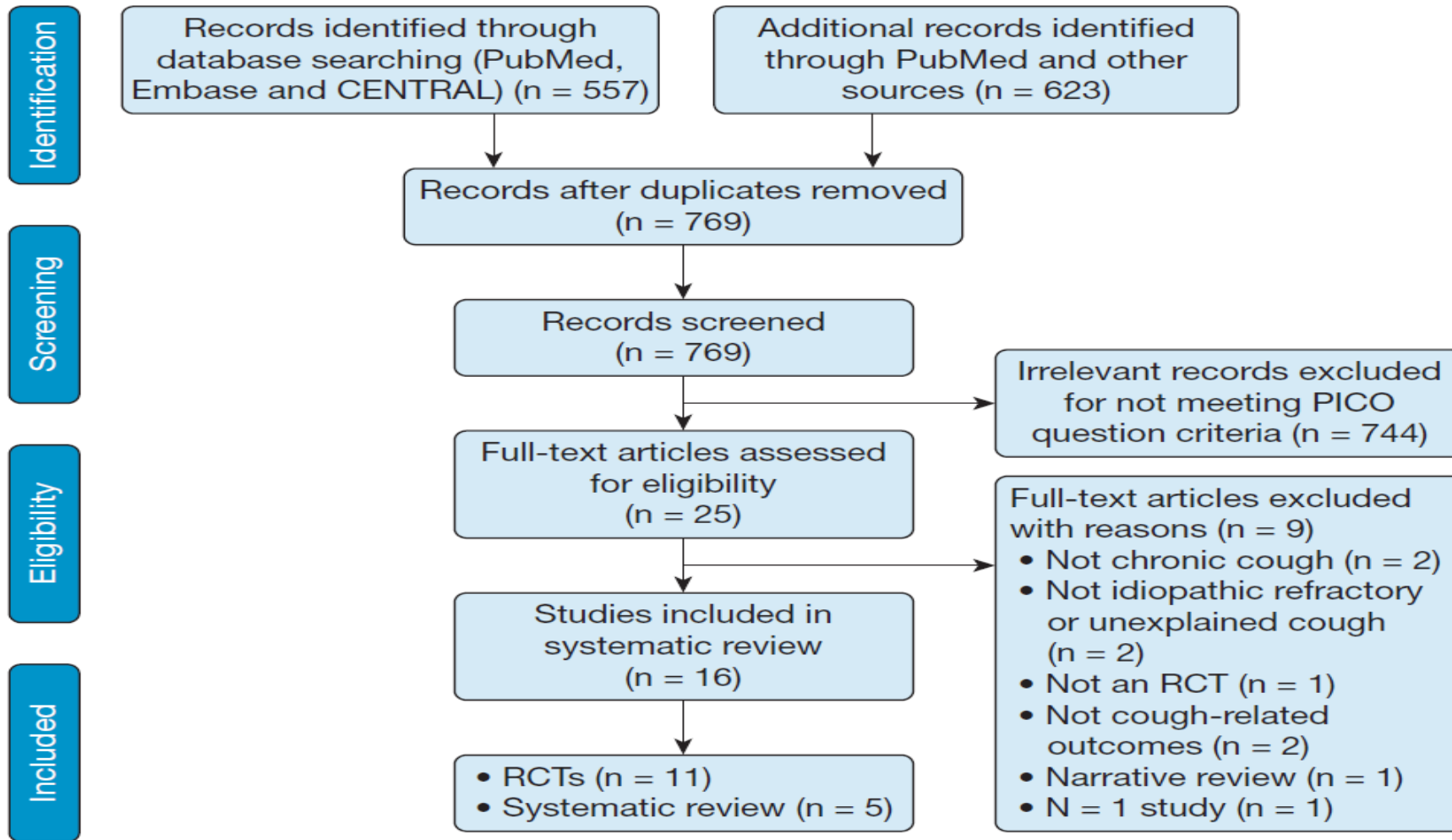
Treatment of Unexplained Chronic Cough

CHEST Guideline and Expert Panel Report

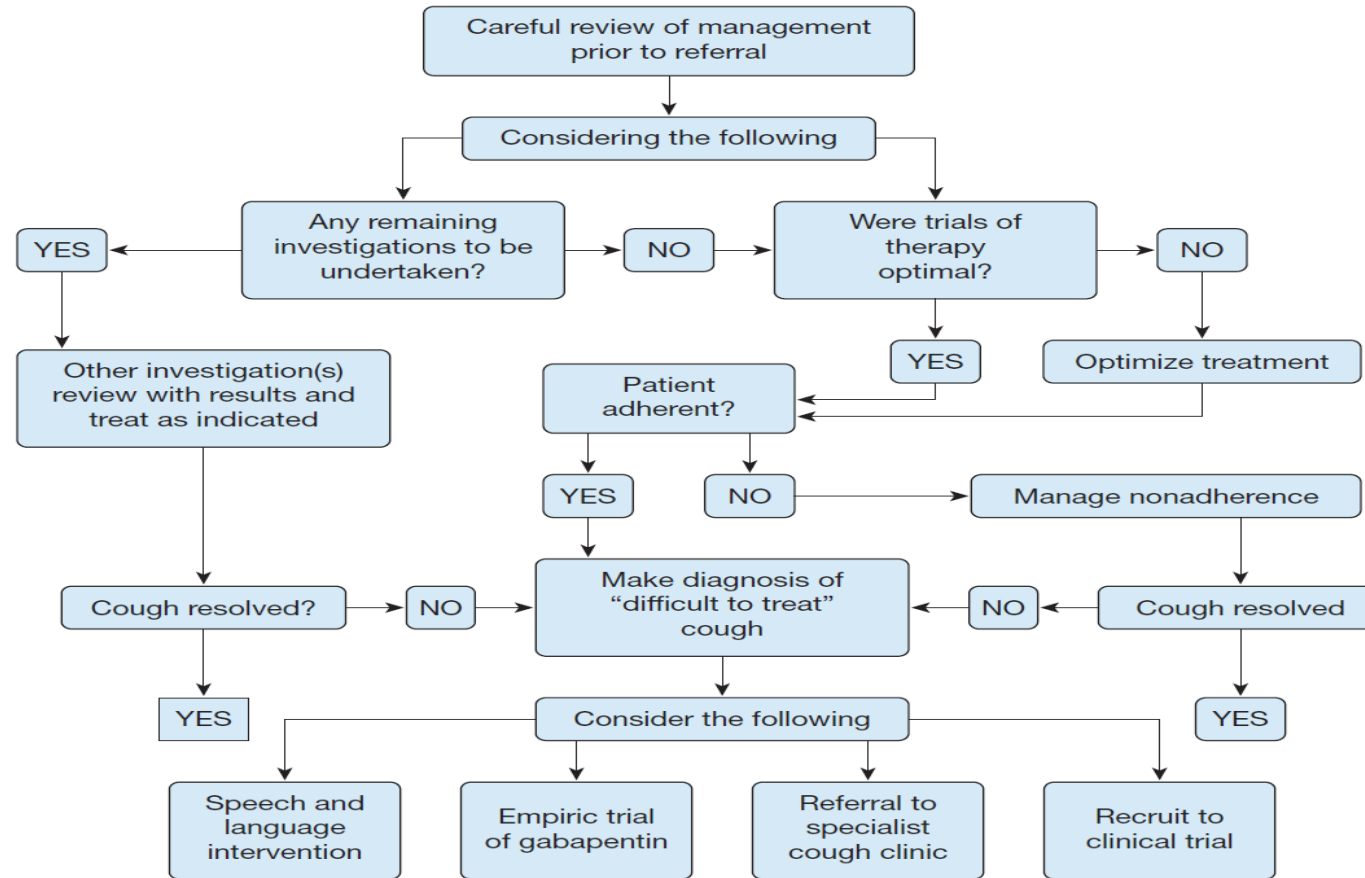
TABLE 1] Eligibility Criteria

Criteria	Study Requirements
Inclusion	English-language publication
	Population
	a. Chronic cough: duration > 8 wk
	b. Age > 12 y
	c. Unexplained or refractory or idiopathic or intractable. Patients were required to have an assessment for associated diseases that could cause chronic cough (eg, chronic lung disease) and diseases commonly associated with cough (eg, asthma, rhinosinusitis, GERD, ACEI use). The assessment could involve physician assessment; relevant investigations that were negative, leading to a diagnosis of unexplained or idiopathic cough; or relevant treatment trials that were negative or the cough was refractory to the treatment trial, leading to a diagnosis of refractory cough or intractable cough
Intervention	Treatment: any pharmacologic or nonpharmacologic intervention
Comparison/control	Randomized controlled trial or controlled clinical trial or a systematic review
Outcome	Cough severity or frequency or quality of life

Treatment of Unexplained Chronic Cough CHEST Guideline and Expert Panel Report



Proposed algorithm for managing “difficult to treat cough”



Neuromodulatory agents

- Initial panel vote 75% in favor of weak recommendation for gabapentin and morphine(80% approval score needed to pass).
- Voting panelists suggesting split into two separate recommendations
- Gabapentin recommendation passed -90%
- Morphine failed
 - initial 71% with revote
 - change in wording of close follow up failed 75%

Gibson Chest 2016;149:27-44

Neuromodulatory agents

- Believed to act on enhanced neural sensitization
 - Key component of unexplained cough
- Gabapentin side effects no statistical difference from Pbo
- Morphine – patients dropped out due to side effects
 - Constipation – 40%
 - Drowsiness – 25%

Gibson Chest 2016;149:27-44

ACCP Remarks:

- Because health-related quality of life of some patients can be so adversely impacted by their unexplained chronic cough, and because gabapentin has been associated with improvement in quality of life in a randomized controlled clinical trial, the CHEST Cough Expert Panel believes that the potential benefits in some patients outweigh the potential side effects.
- With respect to dosing, patients who have no contraindications to gabapentin can be prescribed a dose escalation schedule beginning at 300 mg once a day; additional doses can be added each day as tolerated up to a maximum tolerable daily dose of 1,800 mg a day in two divided doses.