Arch Bronconeumol. 2015;51(11):579–589

ARCHIVOS DE BRONCONEUMOLOGIA

www.archbronconeumol.org

Recommendations of SEPAR

Chronic Cough☆

Adalberto Pacheco,[a,*] Alfredo de Diego,[b] Christian Domingo,[c] Adelaida Lamas,[d] Raimundo Gutierrez,[e] Karlos Naberan,[f] Vicente Garrigues,[g] Raquel López Vime[h]

[a] Servicio de Neumología, Hospital Ramón y Cajal, Madrid, Spain
[b] Servicio de Neumología, Hospital La Fe, Valencia, Spain
[c] Servicio de Neumología, Hospital Parc Taulí, Sabadell, Barcelona, Spain
[d] Servicio de Pediatría, Hospital Ramón y Cajal, Madrid, Spain
[e] Servicio de Otorrinolaringología, Hospital Rey Juan Carlos, Móstoles, Madrid, Spain
[f] Centro de Salud Belchite, Zaragoza, Spain
[g] Servicio de Gastroenterología, Hospital La Fe, Valencia, Spain
[h] Servicio de Neumología, Hospital Severo Ochoa, Madrid, Spain

ARTICLE INFO

Keywords:
Cough
Antitussive agents
Respiratory aspiration
Gastroesophageal reflux
Vocal cord dysfunction

ABSTRACT

Chronic cough (CC), or cough lasting more than 8 weeks, has attracted increased attention in recent years following advances that have changed opinions on the prevailing diagnostic and therapeutic triad in place since the 1970s. Suboptimal treatment results in two thirds of all cases, together with a new notion of CC as a peripheral and central hypersensitivity syndrome similar to chronic pain, have changed the approach to this common complaint in routine clinical practice. The peripheral receptors involved in CC are still a part of the diagnostic triad. However, both convergence of stimuli and central nervous system hypersensitivity are key factors in treatment success.

Tos crónica

Palabras clave:
Tos
Agentes antitusivos
Aspiración respiratoria
Reflujo gastroesofágico
Disfunción de cuerdas vocales

RESUMEN

La tos crónica (TC), o tos que perdura más de 8 semanas, ha merecido un interés creciente en los últimos años debido a los avances producidos que han motivado un cambio de visión respecto a la clásica tríada diagnóstica y terapéutica en vigor desde la década de los setenta. Unos resultados no óptimos en el tratamiento que alcanza los dos tercios de casos, junto a una nueva concepción de la TC como síndrome de hipersensibilidad con 2 polos, periférico y central, similares al dolor crónico, ocasionan que se contemple este problema tan frecuente en la práctica clínica de una nueva manera. Los receptores periféricos de la TC siguen teniendo vigencia bajo la tríada diagnóstica; sin embargo, tanto la convergencia de estímulos como la hipersensibilidad adquirida a nivel del sistema nervioso central son hechos que tienen una repercusión clave en el éxito del tratamiento.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; BCT, bronchial challenge test; BHR, bronchial hyperreactivity; CC, chronic cough; CNS, central nervous system; CPAP, continuous positive airway pressure; CUACS, chronic upper airway cough syndrome; EB, eosinophilic bronchitis; FeNO, fraction of nitric oxide in exhaled air; GABA, gamma-aminobutyric acid; GER, gastroesophageal reflux; GERD, gastroesophageal reflux disease; LCQ, Leicester Cough Questionnaire; LHS, laryngeal hypersensitivity syndrome; CCHS, chronic cough hypersensitivity syndrome; LPR, laryngopharyngeal reflux; PBI, proton pump inhibitors; PC, primary care; PCR, polymerase chain reaction; RAST, Radio Allergo Sorbent Test; RCT, refractory chronic cough; SAHS, sleep apnea–hypopnea syndrome; TRP, transient receptor potential channel; TRPV1, transient receptor potential vanilloid 1; VCD, vocal cord dysfunction.

☆ Please cite this article as: Pacheco A, de Diego A, Domingo C, Lamas A, Gutierrez R, Naberan K, et al. Tos crónica. Arch Bronconeumol. 2015;51:579–589.

* Corresponding author.
E-mail address: apacheco.hrc@salud.madrid.org (A. Pacheco).

1579-2129/

Introduction

Chronic cough (CC), or cough lasting more than 8 weeks, is the most common symptom encountered in outpatient medical practice. Research into the mechanisms causing chronic pain and CC has detected similar neuronal pathways in both conditions, enabling investigational advances in chronic pain to be used to improve the understanding of CC. These guidelines discuss the medical problems associated with CC, either as an isolated entity or as the major symptom of a syndrome, and make proposals that take into account the level of evidence and grade of recommendations (GRADE system).[1] In this respect, it should be pointed out that in CC, the available evidence is based mainly on observational studies.[2]

These guidelines are presented in 3 sections: (a) description and management of CC; (b) management of CC in the various clinical care scales; and (c) problems and future perspectives in CC.

Each section may contain several subsections.

Description and Management of Chronic Cough

Definition

Cough is an inherent protective respiratory tract symptom. Duration of cough has been defined as acute (lasting up to 4 weeks), subacute (up to 8 weeks), and chronic (more than 8 weeks).[3] In this document, CC will be called specific, if it is associated with a known cause, or non-specific, if not. Finally, we will examine current knowledge and the available guidelines on refractory CC (RCC), i.e., CC that persists despite treatment targeting known associated conditions.

Epidemiology

CC is a very common symptom in clinical practice, and prevalence in the general population ranges from 12% to 3.3%.[4,5] It is closely related with tobacco use, and the prevalence of CC in smokers is 3 times that of never-smokers or former smokers.[6] A higher prevalence of CC has also been associated with environmental pollution.[7]

During the initial contact with the CC patient, the physician should determine the general causes of CC and the associated warning symptoms (Table 1). In all CC guidelines currently in use, if the patient has a normal chest X-ray, does not smoke and is not receiving angiotensin-converting enzyme inhibitors (ACEI), the causes associated with CC that will directly impact on the initial treatment are considered.

Physiopathology of Chronic Cough

CC is reported by patients as either a single isolated symptom or one of several. Neurobiological mechanisms in chronic pain and in CC are similar,[8] so the patient with chronic pain or CC responds more intensely to a painful stimulus or tussigenic stimulus of a specific magnitude than a healthy individual; this effect has been called hypertussia (similar to hyperalgesia). If the patient receives a stimulus that is not at all painful or tussigenic and responds excessively, the condition is called allotussia (or allodynia, in the case of pain).[9] Hypertussia or allotussia are clinical conditions that are now grouped under the heading of "chronic cough hypersensitivity syndrome" (CCHS). The cough circuit is unquestionably complex, and may involve interaction between the different stimuli from the very start[8] (Fig. 1). In short, the possible impact of CC on physiology means that the following must be taken into consideration when treating this condition: (a) cough neural pathways themselves may be affected, or (b) an aggravating factor that alters the cough reflex may need to be treated (Fig. 2).

Table 1
Causes of chronic cough and warning symptoms.

Causes of chronic cough	• Acute tracheobronchial infections including pertussis • Chronic infections: bronchiectasis, tuberculosis, cystic fibrosis • Airway problems: chronic bronchitis, osteoplastic tracheopathy, asthma, post-nasal drip • Pulmonary parenchymal diseases: diffuse interstitial fibrosis, emphysema, sarcoidosis • Tumors: lung cancer, bronchioloalveolar carcinoma, benign airway tumors, mediastinal tumors • Foreign bodies in the airways • Irritation of external auditory meatus • Cardiovascular diseases: left ventricular dysfunction, pulmonary infarction, aortic aneurysm • Other diseases: gastroesophageal reflux or bronchoesophageal reflux, Zenker's diverticulum, achalasia, recurrent aspiration, endobronchial sutures • Drugs: angiotensin-converting enzyme inhibitors, covertine
Warning symptoms	Hemoptysis, snoring, significant production of sputum, systemic symptoms, gastroesophageal reflux complicated with weight loss, anemia, hematemesis, dysphagia, or no response to specific treatment, choking or vomiting, recurrent pneumonia, or abnormal chest X-ray

The neurological mechanism of cough in humans originates from stimulation of 2 types of neuron terminals that converge in the cough center: unmyelinated C fibers and myelinated Aδ fibers.[10,11] Most C fibers respond to a range of irritant stimuli of inflammatory origin, while Aδ fibers respond to mechanical and acid stimuli.[12]

Excitability of the CNS cough center is increased by 3 mechanisms[13]: peripheral, central and secondary hypersensitivities (Fig. 3). In the case of central sensitization, paresthesia is often observed in the area of the larynx, as well as hypertussia or allotussia, indicating a neuropathic response.[14] In the second mechanism, connections with the cough center via the emotional brain lead to participation of consciousness and the emotional status in the control of cough.

Furthermore, it is important to remember that the phenomenon of different converging peripheral stimuli can have a practical application, as suggested by the Australian cough guidelines of 2010, which recommend simultaneous triple therapy, proton pump inhibitors (PPIs), and speech pathology intervention for RCC[15] (*Strong recommendation/very low evidence*). When central hypersensitivity has developed, a mechanism that is much more sensitive to mild peripheral stimuli is established, and this may be the cause of the phenomenon known as visceral hypersensitivity, also called secondary hypersensitivity (Fig. 3). The problem is that central hypersensitivity may decrease clinically, without changes being observed in the CC capsaicin challenge test due to peripheral hypersensitivity.[16]

Cough Study: Clinical Characterization and Laboratory Determinations

Patients' perception of cough may be expressed differently, depending on the causative pathology. In general, cough accompanying upper airway diseases or laryngopharyngeal reflux (LPR) manifests as irritation in the throat. The "urge to cough" has been the subject of recent research which has located the origin of this impulse within the brain.[17,18] Several standardized

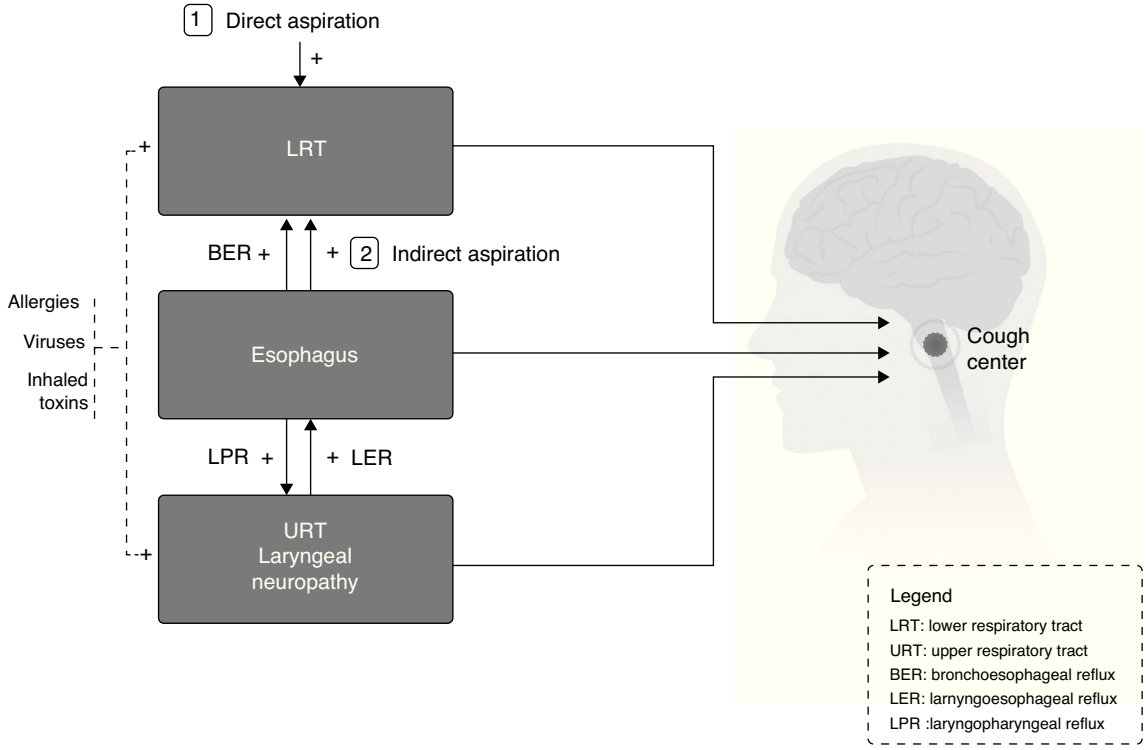

Fig. 1. Interactions among peripheral stimuli of cough reflex.

questionnaires have recently been developed to determine the characteristics of cough. These need further studies before they can be validated,[19] and their utility in practice is still limited (*Weak recommendation/low evidence*). The intensity and frequency of cough have little diagnostic value, and these parameters are of most use when studying the therapeutic effect of antitussive agents. The intensity of cough can be determined with symptom questionnaires or quantified scales, mainly of the visual analog

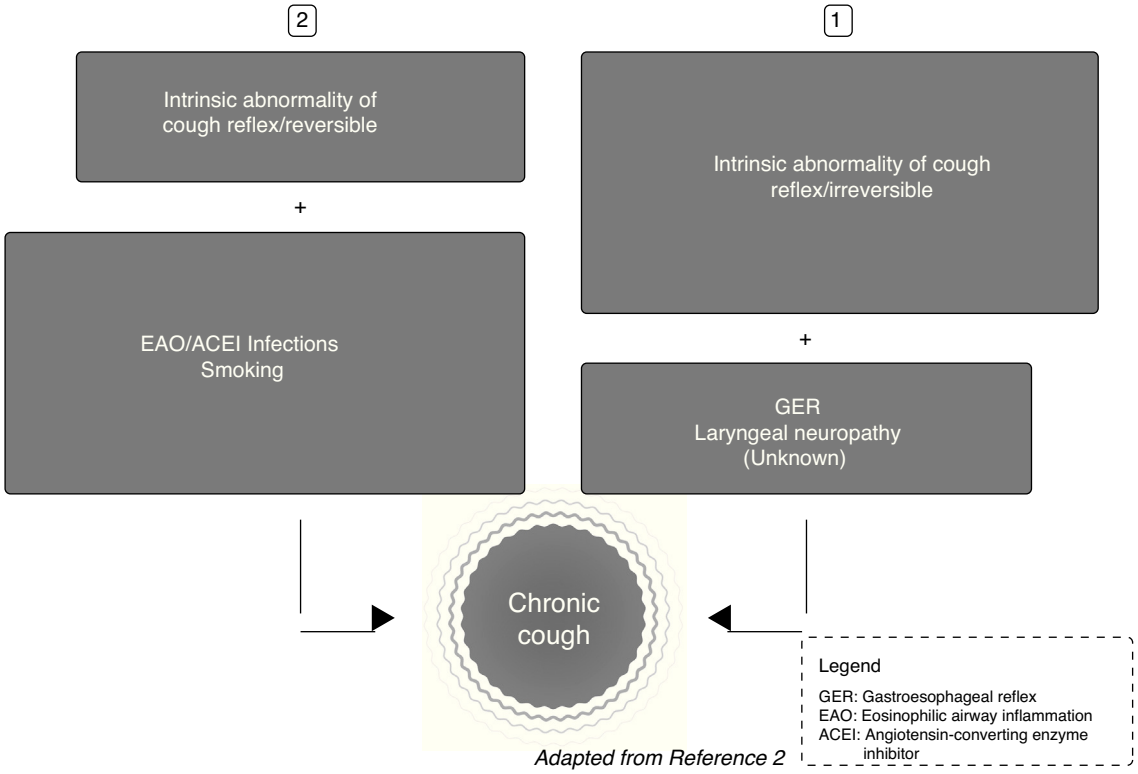

Fig. 2. Two possible access pathways of stimuli of chronic cough.

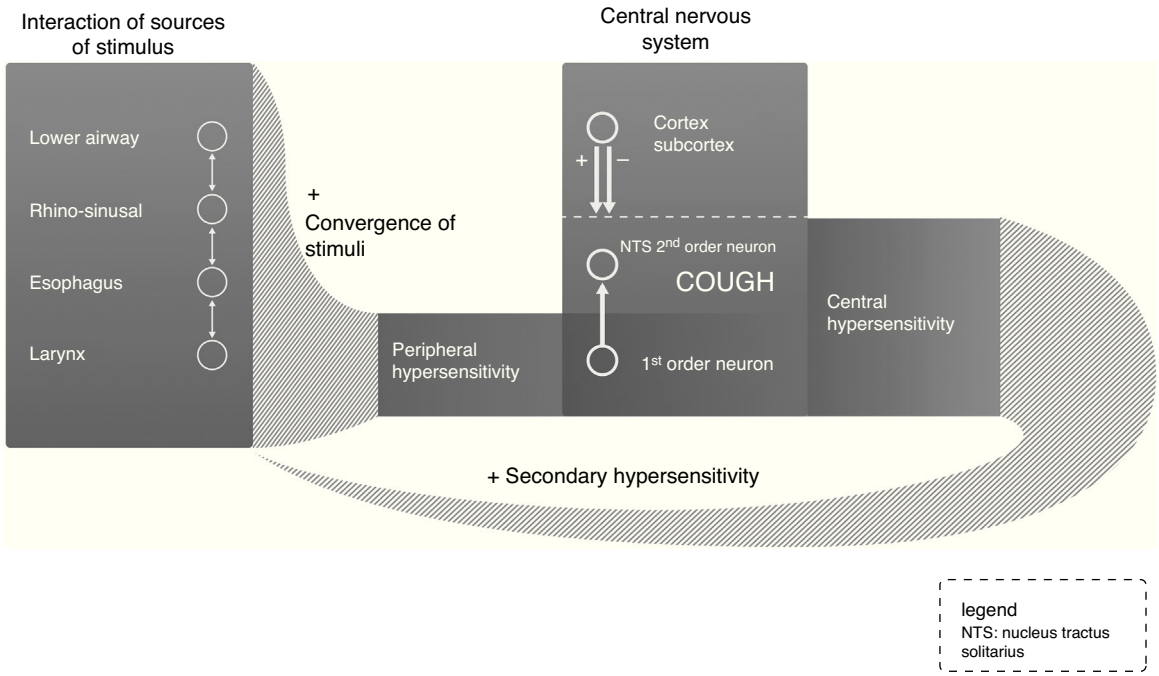

Fig. 3. Neurological feedback circuit of chronic cough.

Adapted from Pacheco.[13]

type (*Weak recommendation/low evidence*). The impact of cough on health-related quality of life is a useful parameter that can be measured objectively. To date, the most widely accepted tool is the Leicester Cough Questionnaire (LCQ).[20] The importance of measuring the impact of cough on quality of life is high (*Strong recommendation/moderate evidence*).

The second aspect to consider is the study of the tussigenic reflex and its sensitivity with objective challenge techniques using inhaled substances. These methods have been described in recent guidelines published by the European Respiratory Society.[21] Capsaicin acts directly on specific TRPV1 receptors. New ways of expressing results have been recently proposed, including the complete analysis of dose–response curve, measuring ED50 and Emax.[22] Sensitivity and specificity of the capsaicin test in the differential diagnosis of CC and in healthy individuals are low.[23,24] It is currently recommended for use in epidemiological studies or for determining the effect of drugs (*Strong recommendation/moderate evidence*). Inhalation of mannitol in dry powder correlates well with the capsaicin test, but the sensitivity and specificity of the technique are similarly low (*Strong recommendation/low evidence*). Quantification of the fraction of nitric oxide in exhaled air (FeNO), when high (>30 or 38 parts per billion [ppb], depending on the author), predicts a favorable response to corticosteroid treatment of CC.[25] Likewise, the quantification of eosinophils in sputum and peripheral blood can characterize a group of CC patients with eosinophilic inflammation of the airways who are potential responders to corticosteroid treatment[26] (*Strong recommendation, low quality of evidence*).

Specific Causes of Chronic Cough

The physiopathological interpretation of CC has changed recently, and it is now understood as a unitary neurological response to stimuli received from distinct but interactive anatomical origins[27,28] (*Strong recommendation/moderate evidence*) (Fig. 1). Current thinking is that (a) CC is partially or totally resistant to specific treatment in up to 2/3 of patients,[29] and (b) most individual carriers of the anatomical-diagnostic triad of conditions do not present CC.

New perspectives in the mechanism of the cough reflex suggest that in these patients, most symptoms are centered in the larynx.[30] This has produced the concept of the "laryngeal hypersensitivity syndrome" (LHS) as a fundamental clinical basis for CC, particularly in its refractory form.[31]

Chronic Cough and Lower Airway Diseases

In prolonged or persistent bacterial bronchitis, extended treatment of over 2 weeks with antibiotics targeting the causative pathogen leads to complete resolution of CC[32] (*Strong recommendation/moderate evidence*). It is now agreed that there are 2 asthma phenotypes: eosinophilic and neutrophilic asthma. It was reported recently that 75% of patients with neutrophilic asthma have moderate to severe CC[33] (*Weak recommendation/low evidence*). Studies of eosinophilic airway inflammation measured by FeNO and eosinophils in sputum are highly specific and sensitive and predict good response to corticosteroids[34] (*Strong recommendation/moderate evidence*). The diagnosis of asthma is defined as reversible bronchial obstruction, variable maximum expiratory flow and bronchial hyperreactivity (BHR), as determined by spirometry with bronchodilator testing, monitoring of maximum expiratory flow, or bronchial challenge testing (BCT) (*Strong recommendation/high evidence*). Asthma can be ruled out by a negative BCT, but if it is positive, the positive predictive value ranges between 60% and 80%[35] (*Strong recommendation/high evidence*). BHR with no evidence of variable flow obstruction associated with CC suggests a diagnosis of cough-equivalent asthma or cough-variant asthma[36]; in this entity, antileukotrienes appear to be more effective than in conventional asthma[37] (*Strong recommendation/low evidence*). A form of CC called eosinophilic bronchitis (EB), characterized by eosinophils in induced sputum, absence of BHR and good response to corticosteroids, was recently defined: prevalence is 7%–33%.[38] Similarities and differences between these entities are summarized in Table 2. With respect to the recently

Table 2
Differential Diagnosis Between Various Diseases With Eosinophilic Inflammation of the Airways Associated With Chronic Cough.

	Eosinophilic Bronchitis	Eosinophilic Asthma	Cough Equivalent Asthma
Symptoms	Cough	Dyspnea, cough and wheezing	Cough
Atopy	No	Yes	Yes
Bronchial hyperreactivity	No	Yes	Yes
FEM viability	No	Yes	No
Eosinophils in sputum	Yes	Yes	Yes
Response to bronchodilators	No	Yes	Yes
Response to corticosteroids	Yes	Yes (if eosinophils in sputum)	Yes (if eosinophils in sputum)

Adapted from Desai and Brightling (Cough: Asthma, eosinophilic diseases. Otorlaryngol Clin North Am. 2010;43:123) and Morice (Epidemiology of cough. Pulm Pharmacol Ther. 2002;15:253–259). Adapted from Desai and Brightling.[86]

described entity of neutrophilic asthma associated with CC and gastroesophageal reflux (GER), treatment with macrolides has been proposed, but the effect on CC has not been specified[39] (*Weak recommendation/low evidence*). Similarly, treatment with the monoclonal antibody mepolizumab has shown success in eosinophilic asthma, although it failed to resolve the accompanying CC,[40] suggesting that the inflammation may be mast cell-mediated.

Chronic Cough and Upper Airway Diseases

Laryngeal conditions have usually been considered in the diagnostic triad as chronic upper airway cough syndrome (CUACS), formerly known as post-nasal drip; nevertheless, in view of the high rate of laryngeal symptoms in CC, LHS has recently been associated with laryngeal neuropathy.

There are 5 upper airway conditions that may present with CC: allergic rhinitis, chronic rhinosinusitis in the adult, obstructive sleep apnea, vocal cord dysfunction (VCD), and extra-esophageal manifestation of ERG or LPR.

Allergic rhinitis: this is diagnosed from signs and symptoms of nasal inflammation and the identification of specific allergens in skin prick testing or RAST. This condition should be managed according to the recommendations of the recent guidelines.[41] *Chronic rhinosinusitis:* treatment consists of irrigation of the nostrils with saline solution, oral corticosteroids for at least 1 month, and oral antibiotics for up to 3 months, in the case of purulent sinusitis (*Strong recommendation/moderate evidence*).

Obstructive sleep apnea (see section on "Chronic cough and sleep apnea–hypopnea syndrome").

Vocal cord dysfunction: VCD is diagnosed from episodic narrowing of the vocal cords during inspiration producing dyspnea on inspiration and CC.[42] CC occurs in more than 50% of adults with this condition. VCD is diagnosed by the observation of glottic narrowing on laryngoscopy or by a fall of more than 25% in inspiratory flow during the serum saline challenge maneuver.[43] Management consists of the treatment of associated comorbidities such as asthma, rhinosinusitis, GER or the use of ACEI (*Weak recommendation/low evidence*), and the application of speech pathology intervention[43] (*Strong recommendation/moderate evidence*).

Laryngopharyngeal reflux (LPR): see below.

Chronic Cough and Gastroesophageal Reflux. Laryngopharyngeal Reflex

Gastroesophageal reflux disease (GERD) has been associated with a variety of extra-esophageal manifestations, including CC.[44]

Relationship Between Chronic Cough and Gastroesophageal Reflux

In a study performed in a series of CC patients exploring the temporal association between episodes of cough, recorded by acoustic analysis, and episodes of GER, recorded by outpatient esophageal pH impedance, Smith et al.[45] found that cough could appear before or after (50% of the time) episodes of GER. Wu et al.[46] showed that distal esophageal acid infusion increases cough reflex sensitivity in asthmatic patients but not in normal subjects. Finally, it has been proposed recently that CC may be caused by the harmful effects of GER products on the larynx, causing laryngeal neuropathy,[47,48] suggesting that CC may be a neuropathic disease caused by GER.

Table 3
Grades of Recommendation/Evidence of Antireflux Treatment in Patients With Chronic Cough.

Treatment	Grade of Recommendation	
General and Dietary Measures	Strong Recommendation	Low Quality of Evidence
H2 antagonists	Strong recommendation	Low quality of evidence
PPIs	Strong recommendation	Moderate quality of evidence
Prokinetics	Weak recommendation	Very low quality of evidence
Antireflux surgery	Weak recommendation	Low quality of evidence

Diagnosis of Chronic Cough Associated With Reflux

The most useful test for corroborating the GER-cough association is 24-h outpatient recording of both pH and esophageal impedances. This technique can detect episodes of both liquid and aerosolized acid (pH<4), mildly acid (pH 4–7) and alkaline (pH>7) GER.[45]

Treatment of Chronic Cough Associated With Gastroesophageal Reflux

Anti-reflux treatment for CT is specified in Table 3. Two systematic reviews have been published on this topic.[49,50] In adults, there is insufficient evidence to conclude definitively that PPIs are beneficial in GER-associated cough. However, the presence of abnormal GER or the temporal association of GER with cough are factors for improved response to treatment.[50] In patients with no signs of GER, a 2-month treatment may be justified if the following criteria are present: non-smoker, no use of ACEI, normal chest X-ray, no asthma, no post-nasal drip, and no non-asthmatic eosinophilic bronchitis.[51]

Laryngopharyngeal reflux: LPR is defined as GER reaching the laryngopharyngeal region. Diagnosis is confirmed by: (a) symptoms of extra-esophageal reflux, or (b) laryngeal endoscopy. Validated indices are available – for the first, the "Reflux Symptoms Index", and for the second, the "Reflux Findings Score"[52]; both have a qualification of *Weak recommendation/moderate evidence* (Tables 4 and 5).

The treatment of GER complicated by LPR is similar to that described for GER associated with CC: high doses of PPIs (20 or 40 mg every 12 h), for at least 2 months. If there is no response after this time, PPIs should be discontinued (*Strong*

Table 4
Laryngeal Reflux Symptom Index.

How Have These Symptoms Affected You in the Last Month?	Not At All					Severely
	0	1	2	3	4	5
Snoring, hoarseness or other problem with your voice						
Clearing your throat, constantly swallowing saliva						
Excessive phlegm in your throat, mucus down the back of your throat						
Cough after going to bed						
Breathing difficulties						
Paroxysmal dry cough (coughing fit)						
Sensation of a foreign body in the throat						
Chest pain, heartburn, dyspepsia						

More than 13 points suggest laryngopharyngeal reflux.

Table 5
Index of Endoscopic Signs of Laryngopharyngeal Reflux.

SUBGLOTTIC edema	2: If present			
Ventricular obliteration	2: Partial			4: Complete
Erythema–hyperemia	2: Only interarytenoidal			4: Complete
Vocal cord edema	1: Moderate	2: Moderate	3: Severe	4: Polypoidal
Diffuse laryngeal edema	1: Moderate	2: Moderate	3: Severe	4: Obstructive
Posterior commissure hypertrophy	1: Moderate	2: Moderate	3: Severe	4: Obstructive
Granuloma. Granulation	2: If present			
Thick endolaryngeal mucus	2: If present			

More than 6 points suggests laryngopharyngeal reflux.

recommendation/moderate evidence), but if the patient shows improvement of CC, administration of PPIs should be reduced to once daily, after which the minimum dose required to maintain sufficient acid suppression should be introduced. If, on the other hand, the patient does not improve and CC due to GER is still suspected, a pH-metry/impedance test with additional manometry should be performed (*Weak recommendation/high evidence*). If suspected LPR is confirmed but treatment with PPIs fails, some authors have reported improvement with GABA inhibitors, such as baclofen, at escalating doses of up to 30 mg/day,[53] or the addition of alginates (e.g., Gaviscon®).[54] Fundoplication for the treatment of LPR with CC would require a major GER complication or risk of massive aspiration (*Weak recommendation/low evidence*) (Table 3). Good outcomes in tussigenic hypersensitivity caused by concomitant laryngeal sensory neuropathy and LPR have been demonstrated with neuromodulating drugs.[55]

If interaction between LPR and laryngeal neuropathy is clinically suspected, there are 2 complementary approaches: changes in patient care and diet, and speech pathology interventions. Raising the head of the bed, adopting a left lateral decubitus position, and weight loss have been shown to improve the total time that esophageal pH is less than 4 (*Strong recommendation/low evidence*).[56] A recent study in GER found that a period of less than 3 h between eating dinner and going to bed was significantly related with GER relapse.[57] Speech pathology intervention reduces response to capsaicin-induced cough reflex.[43]

Chronic Cough and Sleep Apnea–Hypopnea Syndrome

In both healthy individuals and patients with CC, cough is generally more frequent during the day. In some sleep-related diseases, such as sleep apnea–hypopnea syndrome (SAHS), the situation is different.[58] The prevalence of CC in this population can be as high as 33%–39%.[59] In our experience,[60] 42% of patients with SAHS reported CC, of whom 31% had high GER symptom scores. With regard to the effects of CPAP on cough, a significant improvement was found, with resolution of cough in 67%. Similarly, when the prevalence of SAHS was analyzed in patients with CC,[61] 44% were found to have criteria for SAHS. To summarize, CC is frequently associated with SAHS, particularly in patients with associated GER (*Strong recommendation/moderate evidence*). CPAP treatment may be indicated for the treatment of CC (*Weak recommendation/moderate evidence*), although more research is required.

Miscellaneous: Post-Infectious Chronic Cough, Psychogenic Chronic Cough. Other Entities Involving Chronic Cough

Post-Infectious Chronic Cough

Numerous publications suggest that most coughs related with upper respiratory tract infections resolve within a period of up to 3 weeks. Nevertheless, cough may persist longer in a small proportion of adult patients. *Bordetella pertussis*, the causative agent of pertussis, is increasingly recognized as the cause of CC. Diagnosis is established from culture and polymerase change reaction (PCR) analysis of upper respiratory tract samples (*Weak recommendation/low evidence*). Antibiotic treatment with azithromycin should be considered in suspected cases, although this will only prevent transmission, rather than improve symptoms (*Strong recommendation/high evidence*).[62]

Psychogenic Chronic Cough

In a recent review of psychogenic cough, 223 patients were identified from a total of 18 uncontrolled studies,[63] 96% of whom were children and teenagers: 95% of patients did not have cough during sleep. Hypnosis is effective in resolving cough in 78% of patients. The large majority of improvements were seen in the pediatric population. To conclude, there is low quality evidence to support a specific strategy that defines and treats psychogenic cough, habit cough and tic cough. In general, the diagnosis of psychogenic cough should be made after ruling out more common causes of CC, and when CC improves with behavioral modification and/or psychiatric therapy.[64]

Other Types of Chronic Cough

CC in occupational exposure has been described in glass workers and in environments with high concentrations of dust and

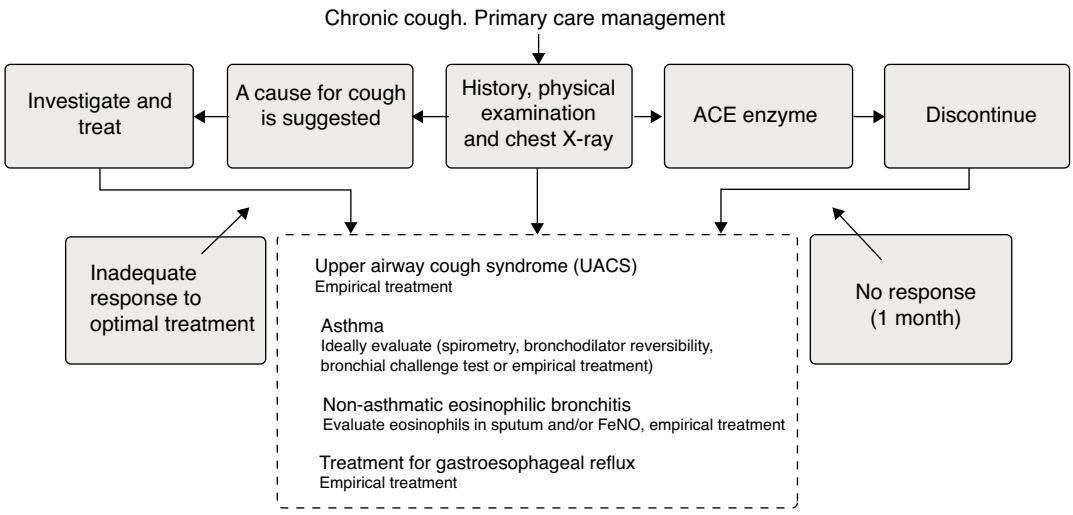

Fig. 4. Algorithm for the management of chronic cough in primary care.

organic material in the air.[65] A sensory neuropathy syndrome with autonomous nervous system dysfunction, cough and GER[66] indicates genetic dysfunction in the neurological network of the digestive tract. CT due to irritation of the auricular branch of the vagus nerve (Arnold's nerve) may occur rarely, as may CC associated with osteoplastic tracheobronchopathy. Other rare cases of CC must be systematically determined according to Table 1.

Management of Chronic Cough in the Different Levels of Medical Care

Chronic Cough in Primary Care

Most patients with CC who present in primary care (PC) can be diagnosed by following the algorithm presented in Fig. 4 (*Strong recommendation/moderate evidence*). In 1 study, only 31% of the patients had any radiological changes that might guide diagnosis.[67] Protocolized empirical and sequential treatment has been shown to be cost-effective.[68,69] In a recent study of 112 patients with CC,[69] sensitivity and specificity of symptoms for 3 of the diseases most frequently associated with CC were determined, as shown in Table 6.

Chronic Cough in Specialized Care

Algorithms for the management of patients with CC referred from PC to a higher level of medical care are given in Figs. 5 and 6. After ruling out neutrophilic asthma in the CC patient, treatment alternatives are neuromodulators, basically gabapentin (300–1800 mg/day) and amitriptyline (10–20 mg/day), and speech pathology intervention. The recommendation for both options is strong, while evidence remains weak (Fig. 7).

Chronic Cough in Pediatric Patients

The American and Australian-New Zealand guidelines define CC as cough lasting more than 4 weeks,[70] while the British guidelines[71] set it at more than 8 weeks. According to several epidemiological studies, causes of CC in the child vary depending on age (*Strong recommendation/high evidence*). In schoolchildren, the most common causes are asthma (27%), cough-equivalent asthma (15.5%) and GER (10%). After adolescence, causes for CT are considered the same as in adults.

Diagnostic Evaluation of Chronic Cough in Children

Clinical history, symptoms and warning signs (Table 7) and the physical examination and initial diagnostic tests are similar to those proposed for adults.

Treatment of Chronic Cough in Children

The aim of CC treatment must be to eliminate the causative agent.[70,71] If non-specific CC is predominantly dry, treatment with medium-dose inhaled corticosteroids for 2–12 weeks should be attempted, but withdrawn in the absence of response.[72] In cases of non-specific productive CC, an initial 2 or 3-week course of antibiotics should be evaluated[73] (*Strong recommendation/high evidence*). Central-acting antitussives are not indicated (*Strong recommendation/high evidence*).

Table 6
Sensitivity and Specificity of Signs and Symptoms of Chronic Cough.

Disease	Symptoms and Parameters	Sensitivity (%)	Specificity (%)	*P*
Asthma	Wheezing	94	66	<.001
	Dyspnea	82	51	.009
	Airway obstruction[a]	35	80	.07
	Bronchial reversibility	11	95	.2
Gastroesophageal reflux	Acid taste in the mouth	50	80	.01
	Retrosternal pyrosis	72	68	.001
Rhinitis	Post-nasal drip	100	67	.002
	Clearing of the throat	100	37	.07

[a] Airway obstruction measured as FEV1/FVC ratio<70%.

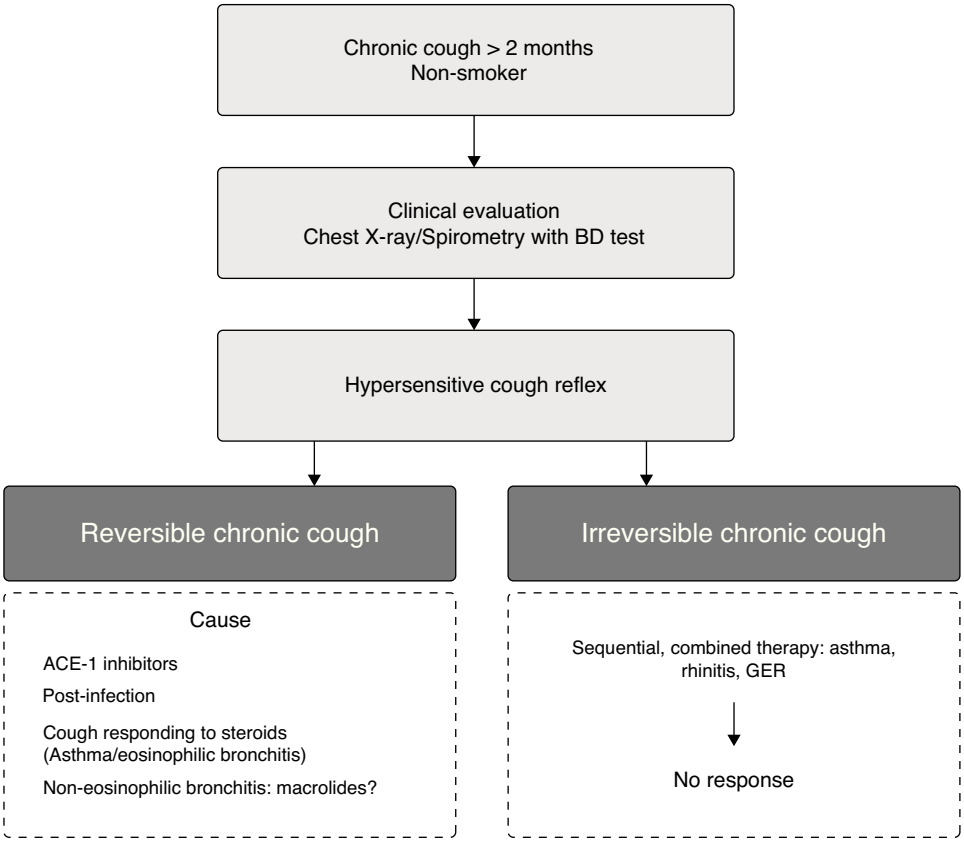

Fig. 5. Practical management of patients with chronic cough.

Table 7
Warning Signs and Symptoms in Children With Chronic Cough.

Warning Signs and Symptoms	Comments
Abnormal auscultation	Asthma, bronchitis, foreign body, CF, congenital abnormalities, etc.
Productive cough with mucus	Suppurative diseases (CF, BE, PCD, PBB, etc.), bronchitis
Sudden onset of cough after episode of choking	Foreign body aspiration
Cough associated with food or swallowing	Aspiration syndromes
Chronic dyspnea	Chest disease (airway or parenchymal), heart disease, etc.
Dyspnea with exercise	Asthma, lung disease, etc.
Heart murmur	Heart disease
Neurological disease	Aspiration syndromes, muscle weakness, etc.
Chest wall deformities	Malformations, severe chronic lung disease, etc.
Hemoptysis	Suppurative disease, vascular abnormalities, bronchitis, etc.
Recurrent pneumonia	Asthma, foreign body, malformations, immunodeficiencies, etc.
Failure to thrive	Lung disease, suppurative heart disease
Nail clubbing	Chronic diseases
Comorbidities	PBB

BE: bronchiectasis; CF: cystic fibrosis; PBB: persistent bacterial bronchitis; PCD: primary ciliary dyskinesia.

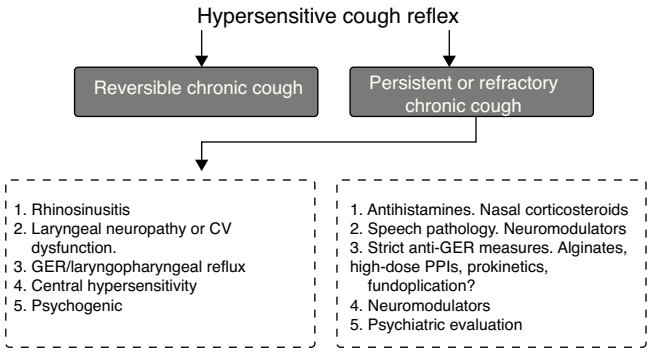

Fig. 6. Algorithm for the management of refractory chronic cough.

Table 8
Causes of Unexplained Cough in Adults.

- The doctor does not follow the treatments recommended in accredited practice guidelines
- The patient does not follow the recommended treatment
- Development of serious comorbidities requiring the patient to discontinue examinations or not follow treatment plans
- Diagnosis is correct, but cough is refractory to prescribed treatment
- A combination of the three above
- The patient was not informed about active participation in cough control
- Cough is truly refractory

Adapted from Irwin.[74]

Problems and Perspectives in Chronic Cough

Chronic Refractory Cough and New Treatments

It is currently assumed that if partial control of cough can be achieved, this may be sufficient, since it is difficult to eradicate completely, except in some cases (Fig. 5). Unsatisfactory treatment in CC may be due to several causes[74] (Table 8). In RCC, treatment possibilities must first be optimized (Fig. 6), and then 2 aspects should be given special attention: (a) LHS, and (b) central

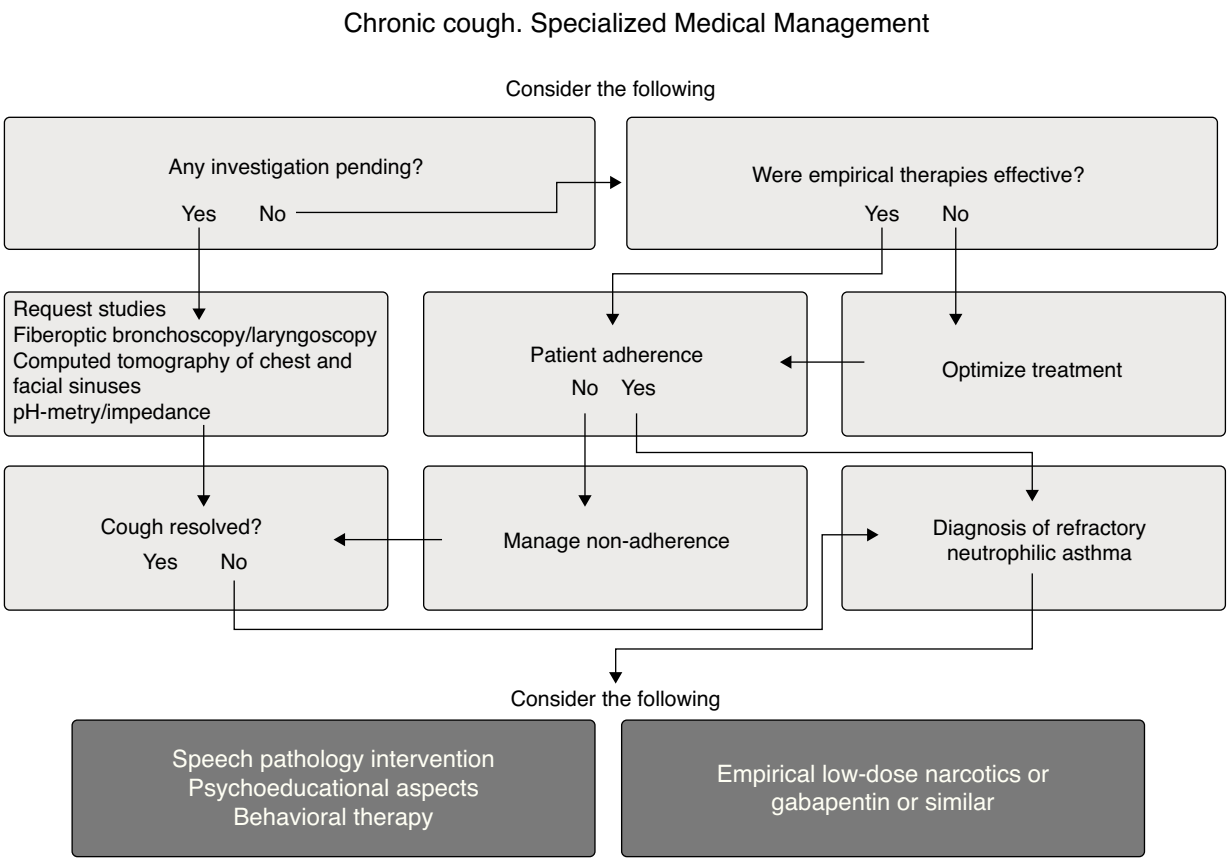

Fig. 7. Management of chronic cough in specialized units.

hypersensitivity[75] (*Strong recommendation/moderate evidence*). Antitussive treatments should be used for "urge-to-cough", but designed to avoid modification of the protective reflex cough. The available evidence suggests that nebulized lidocaine is an option for second-line treatment.[76]

In the second case, central hypersensitivity and treatment in CC, there is growing interest in the use of gabapentin in RCC, with positive responses in around 60% of patients (*Strong recommendation/moderate evidence*).[77] Neuromodulator therapy is being proposed as the future in the treatment of central hypersensitivity.[78] Other similar agents that have been studied in small, observational studies include pregabalin, amitriptyline, and baclofen. Amitriptyline or low-dose morphine have shown subjective improvement in the LCQ (*Weak recommendation/moderate evidence*).[79]

The efficacy of over-the-counter cough suppressants on CC has not been demonstrated.[80] A recent review of dextromethorphan found a modest decrease in cough severity and frequency when compared to placebo.[81] Codeine has shown no improvement in capsaicin-induced cough reflex testing.[82] Its use in CC that does not respond to non-narcotic antitussives is currently recommended (*Weak recommendation/low evidence*).

Drugs for reducing peripheral hypersensitivity focusing on TRP receptor blockade have recently been evaluated.[83] Inhaled tiotropium has recently been seen in laboratory animals to inhibit TRPV1 receptors.[84] Another promising agent in the treatment of CC is AF-219, a receptor antagonist that acts against the purinergic receptor P2X3, and also against peripheral C fibers,[85] and is effective in reducing CC frequency.

References

1. Schünemann HJ, Jaeschke R, Cook DJ, Bria WF, El-Solh AA, Ernst A, et al. An official ATS statement: grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. Am J Respir Crit Care Med. 2006;174:605–14.
2. Pavord ID, Chung KF. Management of chronic cough. Lancet. 2008;371:1375–84.
3. Irwin RS, Baumann MH, Bolser DC, Boulet LP, Braman SS, Brightling CE, et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. Chest. 2006;129 1 Suppl.:1S–23S.
4. Morice AH. Chronic cough: epidemiology. Chron Respir Dis. 2008;5:43–7.
5. Lai K, Chen R, Lin J, Huang K, Shen H, Kong L, et al. A prospective multicenter on causes of chronic cough in China. Chest. 2013;143:613–20.
6. Zemp E, Elsasser S, Schindler C, Künzli N, Perruchoud AP, Domenighetti G, et al. Long-term ambient air pollution and respiratory symptoms in adults (SAPALDIA study). The SAPALDIA Team. Am J Respir Crit Care Med. 1999;159:1257–66.
7. McCabe D, Altman K. Laryngeal hypersensitivity in the World Trade Center: exposed population. Am J Respir Crit Care Med. 2012;186:402–3.
8. O'Neill J, McMahon SB, Undem BJ. Chronic cough and pain: Janus faces in sensory neurobiology? Pulm Pharmacol Ther. 2013;26:476–85.
9. Bende M, Millqvist E. Prevalence of chronic cough in relation to upper and lower airway symptoms: the Skövde population-based study. Front Physiol. 2012;3:251.
10. Canning BJ, Mazzone SB, Meeker SN, Mori N, Reynolds SM, Undem BJ. Identification of the tracheal and laryngeal afferent neurons mediating cough in anaesthezited guinea-pigs. J Physiol. 2004;557:543–58.
11. Canning BJ. Afferent nerves regulating the cough reflex: mechanisms and mediators of cough in disease. Otolaryngol Clin North Am. 2010;43:15–25.
12. MacAlexander MA, Myers AC, Undem BJ. Adaptation of guinea-pig vagal airway afferent neurons to mechanical stimulation. J Physiol. 1999;521:239–47.
13. Pacheco A. Chronic cough: from a complex dysfunction of the neurological circuit to the production of persistent cough. Thorax. 2014;69:881–3.
14. Chung KF, McGarvey L, Mazzone SB. Chronic cough as a neuropathic disorder. Lancet Respir Med. 2013;3:414–22.
15. Gibson PG, Chang AB, Glasgow NJ, Holmes PW, Katelaris P, Kemp AS, et al. CICADA: cough in children and adults: diagnosis and assessment. Australian cough guidelines summary statement. Med J Aust. 2010;192:265–71.

16. Chung KF. Gabapentin: a suppressant for refractory chronic cough. Lancet. 2012;380:1540–1.
17. Davenport PW. Urge-to-cough: what can it teach us about cough? Lung. 2008;186 Suppl. 1:S107–11.
18. Mazzone SB, McLennan L, McGovern AE, Egan GF, Farrell MJ. Representation of capsaicin-evoked urge-to-cough in the human brain using functional magnetic resonance imaging. Am J Respir Crit Care Med. 2007;176:327–32.
19. Dettmar PW, Strugala V, Fathi H, Dettmar HJ, Wright C, Morice AH. The online Cough Clinic: developing guideline-based diagnosis and advice. Eur Respir J. 2009;34:819–24.
20. Birring SS, Prudon B, Carr AJ, Singh SJ, Morgan MD, Pavord ID. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). Thorax. 2003;58:339–43.
21. Morice AH, Fontana GA, Belvisi MG, Birring SS, Chung KF, Dicpinigaitis PV, et al. European Respiratory Society guidelines on the assessment of cough. Eur Respir J. 2007;29:1256–76.
22. Hilton EC, Baverel PG, Woodcock A, van der Graaf PH, Smith JA. Pharmacodynamic modeling of cough responses to capsaicin inhalation calls into question the utility of the C5 end point. J Allergy Clin Immunol. 2013;132:847–55.
23. Couto M, de Diego A, Perpiñá M, Delgado L, Moreira A. Cough reflex testing with inhaled capsaicin and TRPV1 activation in asthma and comorbid conditions. J Investig Allergol Clin Immunol. 2013;23:289–301.
24. Nieto L, de Diego A, Perpiña M, Compte L, Garrigues V, Martínez E, et al. Cough reflex testing with inhaled capsaicin in the study of chronic cough. Respir Med. 2003;97:393–400.
25. Hahn PY, Morgenthaler TY, Lim KG. Use of exhaled nitric oxide in predicting response to inhaled corticosteroids for chronic cough. Mayo Clin Proc. 2007;82:1350–5.
26. Chatkin JM, Ansarin K, Silkoff PE, McLean P, Gutierrez C, Zamel N, et al. Exhaled nitric oxide as noninvasive assessment of chronic cough. Am J Respir Crit Care Med. 1999;159:1810–3.
27. Lavinka PC, Dong X. Molecular signaling and targets from itch: lessons from cough. Cough. 2013;9:8.
28. Mazzone SB, McGovern AE, Yang SK, Woo A, Phipps S, Ando A, et al. Sensorimotor circuitry involved in the higher brain control of coughing. Cough. 2013;9:7.
29. Woodcok A, Young EC, Smith JA. New insights in cough. Br Med Bull. 2010;96:61–73.
30. Sandhu GS. The larynx in cough. Cough. 2013;9:16.
31. Morice AH. Chronic cough hypersensitivity syndrome. Cough. 2013;9:14.
32. Chang AB, Redding GJ, Everard ML. Chronic wet cough: protracted bronchitis, chronic suppurative lung disease and bronchiectasis. Pediatr Pulmonol. 2008;43:519–31.
33. Simpson JL, Baines KJ, Ryan N, Gibson PG. Neutrophilic asthma is characterized by increased rhino-sinusitis with sleep disturbances and GERD. Asian Pac J Allergy Immunol. 2014;32:67–75.
34. Birring S. Controversies in the evaluation and management of chronic cough. Am J Respir Crit Care Med. 2011;183:708–15.
35. De Diego Damiá A, Plaza Moral V, Garrigues Gil V, Izquierdo Alonso JL, López Viña A, Mullol Miret JJ, et al. Tos crónica. Normativa SEPAR. Arch Bronconeumol. 2002;38:236–45.
36. Corrao WM, Braman SS, Irwin RS. Chronic cough as the sole presenting manifestation of bronchial asthma. N Eng J Med. 1979;300:633–7.
37. Dicpinigaitis PV, Dobkin JB, Reichel J. Antitussive effect of the leukotriene receptor antagonist zafirlukast in subjects with cough-variant asthma. J Asthma. 2002;39:291–7.
38. Brightling CE, Ward R, Goh KL, Wardlaw AJ, Pavord ID. Eosinophilic bronchitis is an important cause of chronic cough. Am J Respir Crit Care Med. 1999;160:406–10.
39. Simpson JL, Powell H, Boyle MJ, Scott RJ, Gibson PG. Clarithromycin targets neutrophilic airway inflammation in refractory asthma. Am J Respir Crit Care Med. 2008;177:148–55.
40. Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. N Engl J Med. 2009;360:973–84.
41. Wallace DV, Dykewicz MS, Bernstein DI, Blessing-Moore J, Cox L, Khan DA, et al. The diagnosis and management of rhinitis: an update practice parameter. J Allergy Clin Immunol. 2008;122 2 Suppl.:S1–84.
42. Gibson PG, Vertigan AE. Speech pathology for chronic cough: a new approach. Pulm Pharmacol Ther. 2009;22:159–62.
43. Vertigan AE, Theodoros DG, Gibson PG, Winkworth AL. Efficacy of speech pathology management for chronic cough: a randomised placebo controlled trial of treatment efficacy. Thorax. 2006;61:1065–9.
44. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol. 2006;101:1900–20.
45. Smith JA, Decalmer S, Kelsall A, McGuinness K, Jones H, Galloway S, et al. Acoustic cough-reflux associations in chronic cough: potential triggers and mechanisms. Gastroenterology. 2010;139:754–62.
46. Wu DN, Yamauchi K, Kobayashi H, Tanifugi Y, Kato C, Suzuki K, et al. Effects of esophageal acid perfusion on cough responsiveness in patients with bronchial asthma. Chest. 2002;122:505–9.
47. Gibson PG, Simpson JL, Ryan NM, Vertigan AE. Mechanisms of cough. Curr Opin Allergy Clin Immunol. 2014;14:55–61.
48. Pacheco A, Cobeta I. Refractory chronic cough, or the need to focus on the relationship between the larynx and the esophagus. Cough. 2013;9:10.
49. Chang AB, Lasserson TJ, Gaffney J, Connor FL, Garske LA. Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults. Cochrane Database Syst Rev. 2011:CD004823.
50. Kahrilas PJ, Howden CW, Hughes N, Molloy-Bland M. Response of chronic cough to acid-suppressive therapy in patients with gastroesophageal reflux disease. Chest. 2013;143:605–12.
51. Irwin RS, French CL, Curley FJ, Zawacki JK, Bennett FM. Chronic cough due to gastroesophageal reflux: clinical, diagnostic and pathogenetic aspects. Chest. 2009;104:1511–7.
52. Belafsky PC, Rees CJ. Laryngopharyngeal reflux: the values of otolaryngoloy examination. Curr Gastroenterol Rep. 2008;10:278–82.
53. Koek GH, Sifrim D, Lerut T, Janssens J, Tack J. Effect of the GABA agonist baclofen in patients with symptoms and duodeno-gastro-oesophageal reflux refractory to proton pump inhibitors. Gut. 2003;52:1397–402.
54. Kwiatek MA, Roman S, Fareeduddin A, Pandolfino JE, Kahrilas PJ. An alginate-antacid formulation (Gaviscon Double Action Liquid) can eliminate or displace the postprandial 'acid pocket' in symptomatic GERD patients. Aliment Pharmacol Ther. 2011;34:59–66.
55. Greene SM, Simpson CB. Evidence for sensory neuropathy and pharmacologic management. Otolaryngol Clin North Am. 2010;43:67–72.
56. Kaltenbach T, Crockett S, Lauren B, Gerson LB. Are lifestyle measures effective in patients with gastroesophageal reflux disease? An evidence-based approach. Arch Intern Med. 2006;166:965–71.
57. Yang JH, Kang HS, Lee SY, Kim JH, Sung IK, Park HS, et al. Recurrence of gastroesophageal reflux disease is correlated with a short dinner-to-bedtime interval. J Gastroenterol Hepatol. 2014;29:730–5.
58. Birring SS, Ing AJ, Chan K, Cossa G, Matos S, Morgan MD, et al. Obstructive sleep apnoea: a cause of chronic cough. Cough. 2007;3:7.
59. Chan K, Ing AJ, Laks L, Cossa G, Rogers P, Birring SS. Chronic cough in patients with sleep-disordered breathing. Eur Respir J. 2010;35:368–72.
60. Reig JP, Ballestes M, Leon M, de Diego A, Martinez M, Compte L. Estudio del reflejo tusígeno en pacientes con SAOS. Arch Bronconeumol. 2013;49:6.
61. Sundar KM, Daly SE, Pearce MJ, Alward WT. Chronic cough and obstructive sleep apnea in a community-based pulmonary practice. Cough. 2010;6:2.
62. Kline JM, Lewis WD, Smith EA, Tracy LR, Moerschel SK. Pertussis: a remerging infection. Am Fam Physician. 2013;88:507–14.
63. Haydour Q, Alahdab F, Farah M, Moreno PB, Vertigan AE, Newcombe PA, et al. Management and diagnosis of psychogenic cough, habit cough, and tic cough: a systematic review. Chest. 2014;146:355–72.
64. Irwin RS, Glomb WB, Chang AB. Habit cough, tic cough, and psychogenic cough in adult and pediatric populations. ACCP evidence-based clinical practice guidelines. Chest. 2006;129:174S–9S.
65. Gordon SB, Curran AD, Turley A, Wong CH, Rahman SN, Wiley K, et al. Glass bottle workers exposed to low-dose irritant fumes cough but do not wheeze. Am J Respir Crit Care Med. 1997;156:206–10.
66. Kok C, Kennerson ML, Sprimg PJ, Ing AJ, Pollard JD, Nicholson GA. A locus for hereditary sensory neuropathy with cough and gastroesophageal reflux on chromosome 3p22-p24. Am J Hum Genet. 2003;73:632–7.
67. McGarvey LPA, Heaney LG, MacMahan J. A retrospective survey of diagnosis and management of patients presenting with chronic cough to a general chest clinic. Int J Clin Pract. 1998;52:158–61.
68. Lin L, Poh K, Lim T. Empirical of treatment chronic cough: a cost-effectiveness analysis. Proc AMIA Symp. 2001;2001:383–7.
69. Ojoo JC, Everett CF, Mulrennan SA, Faruqi S, Kastelik J, Morice AH. Management of patients with chronic cough using a clinical protocol: a prospective observational study. Cough. 2013;9:2–7.
70. Chang AB, Landau LI, van Asperen PP, Glasgow NJ, Robertson CF, Marchant JM, et al. Cough in children: definitions and clinical evaluation. Med J Aust. 2006;184:398–403.
71. Shields MD, Bush A, Everard ML, McKenzie S, Primhak R. BTS guidelines: recommendations for the assessment and management of cough in children. Thorax. 2008;63 Suppl. 3:iii1–15.
72. Karabel M, Kelekci S, Karabel D, Gurkan MF. The evaluation of children with prolonged cough accompanied by American College of Chest Physicians guidelines. Clin Respir J. 2014;8:152–9.
73. Marchant J, Masters IB, Champion A, Petsky H, Chang AB. Randomised controlled trial of amoxycillin clavulanate in children with chronic wet cough. Thorax. 2012;67:689–93.
74. Irwin RS. Unexplained cough in the adult. Otolaryngol Clin North Am. 2010;43:167–80.
75. Ryan NM, Vertigan A, Bone S, Gibson P. Cough reflex sensitivity improves with speech language pathology management of refractory chronic persistent cough. Cough. 2010;6:5.
76. Lim KG, Rank MA, Hahn PY, Keogh KA, Morgenthaler TI, Olson EJ. Long-term safety of nebulized lidocaine for adults with difficult-to-control chronic cough: a case series. Chest. 2013;143:1060–5.
77. Ryan NM, Birring SS, Gibson PG. Gabapentin for refractory chronic cough: a randomised, double-blind, placebo-controlled trial. Lancet. 2012;380:1583–9.
78. Lee B, Woo P. Chronic cough as a sign of laryngeal sensory neuropathy: diagnosis and treatment. Ann Otol Rhinol Laryngol. 2005;114:253–7.
79. Morice AH, Menon MS, Mulrennan SA, Everett CF, Wright C, Jackson J, et al. Opiate therapy in chronic cough. Am J Respir Crit Care Med. 2007;175:312–5.
80. Smith SM, Schroeder K, Fahey T. Over-the-counter medications for acute cough in children and adults in ambulatory settings. Cochrane Database Syst Rev. 2008:CD001831.

81. Yanci WS Jr, McCrory DC, Coeytaux RR, Schmit KM, Kemper AR, Goode A, et al. Efficacy and tolerability of treatments for chronic cough: a systematic review and meta-analysis. Chest. 2013;144:1827.
82. Davenport PW, Bolser DC, Vickrov T, Berry RB, Martin AD, Hev JA, et al. The effect of codeine of the urge-to-cough response to inhaled capsaicin. Pulm Pharmacol Ther. 2007;20:338–46.
83. Preti D, Szallasi A, Patacchini R. TRP channels as therapeutic targets in airway disorders: a patient review. Expert Opin Ther Pat. 2012;22:663–95.
84. Birrell MA, Bonvini SJ, Dubuis E, Maher SA, Wortley MA, Grace MS, et al. Tiotropium modulates transient receptor potential V1 (TRPV1) in airway sensory nerves: a beneficial off-target effect? J Allergy Clin Immunol. 2014;133:679–87.
85. Ford AB. In pursuit of P2X3 antagonists: novel therapeutics for chronic pain and afferent sensitization. Purinergic Signal. 2012;8 Suppl. 1:3–26.
86. Desai D, Brightling C. Cough due to asthma, cough-variant asthma and non-asthmatic eosinophilic bronchitis. Otolaryngol Clin North Am. 2010;43:123–30.