

Management of Cough



Peter G. Gibson, MD^{a,b} Newcastle, NSW, Australia

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1. To identify treatment for chronic cough on the basis of results of positive randomized controlled trials.
2. To identify the initial assessment of cough on the basis of symptom duration.

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People with chronic cough can experience significant quality-of-life impairment. New concepts based around cough reflex hypersensitivity are leading to improved management strategies and showing promise in relieving the distress from persistent cough. The clinical cough assessment seeks to classify patients on the basis of symptom duration, and to identify and manage exposures and diseases that activate the afferent limb of the cough reflex. Cough hypersensitivity is also addressed by managing

laryngeal dysfunction with speech pathology therapy and managing central cough reflex sensitization with neuromodulators. There are prospects for novel therapies based around several new treatment targets. Crown Copyright © 2019 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:1724-9)

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^aDepartment of Respiratory and Sleep Medicine, John Hunter Hospital, Newcastle, NSW, Australia

^bPriority Research Centre for Healthy Lungs, The University of Newcastle, Newcastle, NSW, Australia

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Corresponding author: Peter G. Gibson, Department of Respiratory and Sleep Medicine, Hunter Medical Research Institute Building, Locked Bag No. 1, Hunter Region Mail Centre, Newcastle, NSW, Australia, 2310. E-mail: peter.gibson@newcastle.edu.au.

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INTRODUCTION

Cough, a fundamental protective reflex, can become disordered and lead to a persistent symptom complex that limits quality of life. The area of chronic cough is undergoing a fundamental reevaluation that is leading to improved clinical management approaches and novel treatment targets. Underpinning this paradigm shift is recognition of the role of cough hypersensitivity and how this builds on existing clinical approaches, leading to improved patient outcomes. The clinical implications of these advances are detailed in this review article, together with a practical approach to the management of chronic cough that is based around the available evidence.

THE INITIAL ASSESSMENT

The initial assessment of cough seeks to classify the duration and severity of the symptom at the time of presentation, link this

Abbreviations used

ACE-I- Angiotensin-converting enzyme inhibitor
CHS- Cough hypersensitivity syndrome
GORD- Gastroesophageal reflux disease
OSA- Obstructive sleep apnea
PNDS- Postnasal drip syndrome
PPI- Proton pump inhibitor
UACS- Upper airway cough syndrome
VCD- Vocal chord dysfunction

to suggested management algorithms, and also assess the patient for any serious underlying causes by considering whether any alarm symptoms are present^{1,2} or whether the cough may be a manifestation of a significant underlying disease, such as pneumonia, cardiac failure, or an exacerbation of asthma or chronic obstructive pulmonary disease. If alarm symptoms or features suggesting a life-threatening condition are present, then the investigation and management of these underlying possibilities become the priority.

Alarm symptoms

The clinical history and initial evaluation elicits any symptoms or results that suggest a serious underlying disease is present. Recognized alarm symptoms include hemoptysis; a significant tobacco smoking history; a smoker older than 45 years with a new cough, altered cough, or cough with voice disturbance; prominent dyspnea, especially at rest or at night; substantial sputum production; hoarseness; systemic symptoms such as fever or weight loss; recurrent pneumonia; an abnormal clinical respiratory examination; and an abnormal chest x-ray.¹

Cough duration and probable diagnosis

Cough duration is categorized as acute (<3 weeks), subacute (3-8 weeks), or chronic (>8 weeks). After the initial assessment of cough duration and exclusion or management of any alarm symptoms and significant conditions, it is useful to consider the most probable diagnoses based on how long the symptom has been present. This information helps frame the possible diagnoses and prioritizes further investigation and management. This approach is supported by evidence from a systematic review, albeit with low-quality studies,² and represents the most common approach described in the published literature.³

For an acute cough that has been present for less than 3 weeks, the most probable diagnoses are respiratory tract infection, an exacerbation of asthma or chronic obstructive pulmonary disease, and pneumonia.^{2,4,5} Subacute cough is a cough that has been present for 3 to 8 weeks, and the most probable diagnoses are postinfectious cough syndrome, an exacerbation of asthma or chronic obstructive pulmonary disease, eosinophilic bronchitis, and upper airway cough syndrome (UACS).⁶ Postinfectious cough syndrome and UACS describe syndromic presentations that have several underlying causes or associations, as described below. Chronic cough refers to a cough that has been present for more than 8 weeks.⁷ The most probable diagnoses for chronic cough are UACS, asthma, gastroesophageal reflux disease (GORD), and eosinophilic bronchitis.

Assessment tools

Use of a validated cough severity assessment tool, such as the visual analogue scale, a validated numerical tool,⁸ or a validated

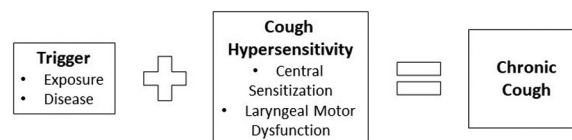


FIGURE 1. Concept of CHS as described by Song et al,¹¹ modified by Vertigan et al,¹² and presented here with permission. Chronic cough is the result of disease or exposure to triggers in an individual with increased hypersensitivity. The components of cough hypersensitivity include central sensitization and laryngeal motor dysfunction.

cough-related health status tool is an important part of cough assessment. These tools allow the assessment of the impact of cough, its severity, and treatment response in cough management. Laryngeal hypersensitivity is a part of cough hypersensitivity and can be identified by the laryngeal hypersensitivity questionnaire.⁹ The high prevalence of laryngeal symptoms in chronic cough and the clinical utility of addressing cough hypersensitivity suggest that screening for laryngeal dysfunction should be part of the chronic cough assessment.

The relevant symptoms include laryngeal paresthesia, allotussia, and hypertussia. Patients with chronic cough frequently complain of a sensation in their throat or upper airway, which can be described as a “tickle,” an itch, pain, or a feeling that “something is stuck in my throat.” When the laryngopharyngeal mucosa is normal and there is no physical agent causing this sensation, these symptoms can be labeled as laryngeal paresthesia. Patients with cough hypersensitivity may report that their cough is triggered by nontussive stimuli, such as cold air, perfume, voice projection, or exercise. This symptom is termed allotussia. Based on research in the chronic pain pathways, it is likely that allotussia and laryngeal paresthesia reflect central sensitization of the cough reflex. The clinical utility of eliciting these symptoms is that they allow a fuller description of the patient’s experience, and in the setting of refractory/idiopathic/unexplained chronic cough they are associated with a response to neuromodulator therapy, as described below.

Cough hypersensitivity syndrome

The cough hypersensitivity syndrome (CHS) concept is a new proposal that offers positive identification of cough syndromes based on a common pathophysiology, a terminology that accommodates newer developments in pathophysiology and therapeutics in chronic cough,¹⁰ as well as addressing the limitations of the anatomic-diagnostic protocol in unexplained chronic cough (Figure 1). CHS was accepted as a useful concept by international experts.^{13,14} The concept is supported by clinical research evidence, such as functional magnetic resonance imaging studies,¹⁵ clinical measurements that suggest central reflex sensitization in patients with cough,^{12,16-22} and positive therapeutic responses from treating cough hypersensitivity.^{23,24}

The practical clinical application of CHS is described in Tables I and II. In this model, chronic cough requires the presence of 2 key components: a cough trigger and cough hypersensitivity (Figure 1). Triggers include exposures and diseases that activate the afferent limb of the cough reflex. The presence of a trigger alone may be insufficient to cause cough, which explains why many patients can have a disease, for example,

TABLE I. Triggers for chronic and subacute cough

Exposures	Diseases
Occupation	Respiratory tract infection
Environment	Rhinosinusitis
Smoking	Asthma
Drug: ACE-I	Eosinophilic bronchitis
“Exercise”	Gastroesophageal reflux disease
Athletes	Obstructive sleep apnea
Voice	Vocal chord dysfunction

asthma or GORD, but not cough. A second component is required to cause the cough, such as CHS. The second component of CHS is a key component of chronic cough. CHS alone can lead to cough, and this explains why patients can present with idiopathic cough, which is cough occurring without an obvious trigger. It also explains why treatment of the trigger alone can be insufficient to resolve the cough, termed refractory cough.

The CHS model has practical treatment applications. Treatment for chronic cough can be targeted at both the triggers and CHS. Triggers include exposures, which are treated by avoidance, and cough-associated diseases, which are managed by specific medical therapy. The components of CHS include laryngeal dysfunction and central sensitization. These can be identified by clinical history and objective testing.¹² Speech pathology is effective for chronic cough with laryngeal dysfunction, and neuromodulators are effective for central cough reflex sensitization.

Exposures

A number of occupational and environmental exposures can trigger cough, especially in a person with cough hypersensitivity (Table I). Occupational and environmental exposures do not appear to be systematically assessed in patients with cough,²⁵ indicating a place for better evaluation of these factors in patients presenting with cough. Guidelines give suggestions for how to do this by eliciting an occupational and exposure history, assessing the relationship of the exposure to the onset or exacerbation of the patient's cough, and assessing the patient's history of smoking and atopic status. If a possible occupational exposure is identified or strongly suspected, then review of Material Safety Data Sheets and/or occupational hygiene reviews of the workplace can be performed.²⁶ Objective tests are needed to confirm asthma or eosinophilic bronchitis.

Exercise is a recognized cough trigger. This can occur with asthma or exercise-induced laryngeal obstruction (Table I). Management of exercise-related cough involves looking for avoidable trigger factors and managing coexisting diseases.²⁷ In asthma, pretreatment with beta-2-agonists or cromoglycate can attenuate exercise-induced asthma. Exercise-induced laryngeal obstruction can be managed by breath retraining, speech pathology interventions, or surgery.

Angiotensin-converting enzyme inhibitor treatment

Chronic cough can occur in up to 20% of patients treated with angiotensin-converting enzyme inhibitors (ACE-Is),²⁸ with up to 5% of treated patients needing to cease ACE-I because of cough. The prevalence may be higher in Asian patients.²⁹ The mechanism involves excessive generation of bradykinin, a potent

TABLE II. Treatment of CHS

Trigger management	CHS Treatment	Outcomes
Avoid exposure	Speech pathology	Reduced cough
Treat disease	Neuromodulators	Improved quality of life
	Gabapentin	
	Pregabalin	
	Amitriptyline, morphine	
	New targets (clinical trials)	

tussive agent, and extrathoracic airway hyperresponsiveness.³⁰ These patients should undergo a careful evaluation for causes of chronic cough, and if ACE-I cough is confirmed, it can be managed by cessation of ACE-I, and/or inhaled cromoglycate.³¹

DISEASES ASSOCIATED WITH CHRONIC AND SUBACUTE COUGH

Chronic and subacute cough can be caused by several associated diseases or exposures (Table I).^{6,32} Identification and treatment of these conditions can improve cough. Postinfectious cough syndrome and UACS are 2 common cough-related clinical syndromes. As described below, they each have subcomponents that require assessment to optimize management.

Postinfectious cough syndrome

Patients with subacute and chronic cough often report that their cough developed following a respiratory tract infection. After resolution of the acute infective symptoms, these patients report the persistence of a dry and irritating cough. The prototype condition causing a postinfectious cough is pertussis.³³ However, many other infective agents also induce postinfectious cough, including influenza.³⁴ The mechanisms of postinfectious cough include heightened cough reflex sensitivity following viral infection³⁵ and transient vocal cord dysfunction induced by the viral infection.^{36,37} The differential diagnosis includes an exacerbation of asthma and eosinophilic bronchitis.⁶

Upper airway cough syndrome

UACS is a cough-related diagnostic label that is specifically used in the context of chronic or subacute cough. It was previously known as postnasal drip syndrome (PNDS); however, this was changed after it was realized that postnasal drip was not the specific mechanism of the cough.³⁸ UACS/PNDS is a common diagnosis for chronic cough in the United States, but it is not often used/accepted as a specific diagnosis in Europe, where rhinosinusitis is the preferred term. In Japan, sinobronchial syndrome and atopic cough are the preferred diagnostic labels. These conditions overlap.³⁹

The initial description of chronic cough with PNDS identified the presence of both postnasal drip and variable extrathoracic airway obstruction.⁴⁰ Although postnasal drip has been discarded as a key pathophysiological mechanism, there is increasing acceptance of the role of extrathoracic airway obstruction in chronic cough syndromes,⁴¹ in particular, as a manifestation of cough hypersensitivity syndrome. This is further supported by observations that chlorpheniramine, which is recommended as an effective treatment for UACS/PNDS, has a positive effect on cough but not on rhinitis/sinusitis in patients with UACS.⁴² This suggests that the beneficial effect of chlorpheniramine on

cough in UACS may be on cough hypersensitivity. Studies of upper airway inflammation support this proposal.⁴³⁻⁴⁵ The CHEST 2006 guidelines⁴⁶ considered that the final common pathway in UACS was not yet resolved, and could represent rhinosinus disease acting via postnasal drip, or these conditions causing irritation of upper airway structures and direct stimulation of cough receptors producing cough independently of PND.

Eosinophilic bronchitis

Eosinophilic bronchitis can occur as part of asthma, or as a separate condition causing chronic cough without asthma.⁴⁷⁻⁴⁹ It is a common cause of chronic cough.⁶ This condition can be confirmed by demonstrating airway eosinophilic inflammation, by induced sputum, by bronchoalveolar lavage, or by finding an elevated fractional exhaled nitric oxide in a breath test. Fractional exhaled nitric oxide can be useful to “rule-in” eosinophilic bronchitis,^{11,50} and indicate a need for corticosteroid therapy. Eosinophilic bronchitis responds well to corticosteroid therapy, which often completely resolves the cough.⁵¹⁻⁵⁴

Obstructive sleep apnea

Chronic cough can occur in patients with obstructive sleep apnea (OSA) and be significantly improved by nasal continuous positive airway pressure therapy. This association was reported in 2007.⁵⁵ In these patients, cough was the sole presenting symptom. Since then, many other reports have confirmed this association. The prevalence of OSA in patients with chronic cough is between 33% and 68%, in part explained by the underlying body mass index of the population studied.⁵⁶ These patients may have nocturnal cough as a feature of their presentation, which is uncommon in a chronic cough population in general. Excessive daytime sleepiness is not a constant finding in patients with cough-OSA. The diagnosis is confirmed by polysomnography. In an uncontrolled case series, continuous positive airway pressure therapy was effective for the cough in most patients, with an effect seen after 1 month-treatment in between 66% and 93% of patients.⁵⁷ The mechanism of OSA-cough is not known, but may involve cough reflex hypersensitivity,⁵⁸ laryngopharyngeal reflux,⁵⁹ or airway inflammation.

Asthma

Asthma is one of the most common diseases associated with chronic cough. Typical asthma presents with variable symptoms involving cough, wheeze, chest tightness, and dyspnea that respond to inhaled beta2-agonist therapy. However, some patients present with cough as the dominant symptom, termed cough-variant asthma, or cough-predominant asthma. In these patients, asthma can be diagnosed by demonstration of variable expiratory airflow limitation, from acute bronchodilator response, a test of airway hyperresponsiveness, or day-to-day variability in lung function, which is demonstrated using a peak expiratory flow diary. Cough due to asthma responds well to inhaled beta2-agonist and corticosteroid therapy.

Gastroesophageal reflux disease

There is a complex relationship between chronic cough and gastroesophageal reflux, and it is difficult to make clear, positive, therapeutic recommendations in this area. This is despite clinicians frequently recalling positive effects on cough when treating gastroesophageal reflux in patients with chronic cough.

There are several mechanisms by which gastroesophageal reflux can cause cough: stomach acid can activate lower esophageal sensory nerves in the distal esophagus; irritation and inflammation of the larynx from acid or nonacid refluxate can occur as part of proximal gastroesophageal reflux; and pulmonary aspiration of gastric contents. In addition, the act of persisting and recurrent coughing leads to increased intraabdominal pressure as well as relaxation of the lower esophageal sphincter, and can therefore induce gastroesophageal reflux, raising the possibility of a vicious cough-reflux cycle developing. Furthermore, gastroesophageal reflux disease is prevalent in many of the diseases that are associated with chronic cough such as asthma and obstructive sleep apnea.

A systematic review of randomized controlled trials⁶⁰ that sought to determine whether therapy for gastroesophageal reflux could improve or eliminate cough in adults with chronic and persistently troublesome cough concluded that proton pump inhibitors (PPIs) demonstrated no benefit when used in isolation, that there was a strong placebo effect for cough improvement in the trials, and that studies including diet modification and weight loss led to better improvement in cough outcomes.

In addition, there is now recognition that concomitant treatment of laryngeal hypersensitivity may also be necessary in cough associated with GORD. Extrathoracic airway hypersensitivity is a common mechanism of cough in cough with GORD.⁶¹ PPIs alone do not improve laryngeal symptoms in laryngopharyngeal reflux,⁶² whereas adding treatment for laryngeal hypersensitivity can be beneficial.⁶³ Murry et al⁶⁴ concluded that respiratory retraining therapy combined with management of laryngopharyngeal reflux was an effective treatment for patients with cough and vocal cord dysfunction (VCD) when a single-modality treatment was not sufficient. This is also supported by another trial of PPI combined with voice therapy for GORD and associated dysphonia.⁶⁵

A clinically practical approach at present is to identify and treat the components of the cough syndrome that are present. This means offering effective antireflux treatment with PPIs and lifestyle/diet measures in patients with cough and symptoms of GORD, and treating laryngeal hypersensitivity when this is present. There are specific symptoms suggesting laryngeal hypersensitivity, and the Newcastle Laryngeal Hypersensitivity Questionnaire can be used to assess this. In addition, it is prudent to assess for any symptoms that may suggest complicated GORD, such as weight loss, anemia, overt gastrointestinal bleeding (hematemesis or melena), dysphagia, odynophagia, or empirical treatment failure for GORD symptoms.

Vocal cord dysfunction

VCD occurs when there is paradoxical movement of the vocal folds with adduction during inspiration. Chronic cough occurs in up to 50% of patients with VCD.⁶⁶ There is frequently associated dysphonia and symptoms can be triggered by voice projection, scents, and exercise. VCD is diagnosed by demonstrating variable extrathoracic airflow limitation, a flow-volume curve,⁶⁷ fiberoptic laryngoscopy, or dynamic 320-slice computed tomographic scan of the larynx.⁶⁸ Because of the variability in VCD, provocation is typically required, with either an inhaled irritant (eg, perfume)¹² or exercise. VCD responds well to speech

pathology therapy, with a reduction in cough and a reduction in cough reflex hypersensitivity.⁶⁹

Cough hypersensitivity and management: Unexplained and persistent chronic cough

After triggers have been assessed and managed, the cough may persist. This problem can be common in a specialist cough clinic, occurring in as many as 40% of patients. The underlying mechanisms can include central sensitization of the cough reflex¹⁵ and laryngeal dysfunction.^{12,16,17,63,64} A number of treatment options are available for these patients,⁷⁰ including speech pathology treatment,^{71,72} neuromodulators such as gabapentin,²³ pregabalin,²⁴ amitriptyline, and morphine, and participation in a clinical trial (Table II) (www.centerwatch.com; www.clinicaltrials.gov).⁷³ Current clinical trials targeting the P2X3 pathway are showing promise in the management of refractory chronic cough.

Speech pathology therapy is described by Vertigan et al⁷⁴ in this issue of the journal. This intervention involves 2 to 4 sessions of education, cough suppression techniques, breathing exercises, and counseling. The positive outcomes of speech pathology treatment of unexplained chronic cough include a reduction in cough frequency, an improvement in cough severity, and a beneficial effect on cough-related quality of life. Speech pathology can also be combined with a neuromodulator to give an enhanced treatment response of longer duration.²⁴

Neuromodulatory therapy in unexplained chronic cough targets central cough reflex sensitization with agents such as gabapentin, pregabalin, amitriptyline, and morphine. The rationale for neuromodulatory therapy in unexplained chronic cough relates to the evidence of central neural sensitization as part of persistent cough,¹⁵ the similarities between these changes in chronic cough and chronic pain syndromes, and the success of neuromodulators in these conditions. These agents significantly improve quality of life of patients with cough. Cough frequency and laryngeal hypersensitivity are reduced by gabapentin and pregabalin. Adverse effects are common with neuromodulatory therapy for chronic cough and may limit dose escalation. In the study by Ryan et al,²³ adverse events were reported in 31% of the gabapentin group and included confusion, dizziness, dry mouth, fatigue, and/or nausea; blurred vision, headache, and memory loss was reported in only 1 patient each. For this reason, clinicians slowly escalate doses of neuromodulators, titrating dose to treatment effect and allowing time for accommodation of adverse sensations.

Cough and special diseases

Cough may also be a troublesome symptom in several comorbid diseases, such as interstitial lung disease²⁰ and lung cancer,²¹ and require specific treatment in its own right.

CONCLUSIONS

The assessment and management of cough requires a systematic approach based around cough duration and likely causes. New concepts regarding chronic and subacute cough have reframed this clinical problem as a 2-component process, involving a cough trigger or stimulus, and coexisting cough hypersensitivity. This approach has practical management and research implications, and may explain some of the discrepant findings in the literature. Clinical management is directed at identifying and treating cough stimuli (exposures, diseases) and

managing the components of cough hypersensitivity (laryngeal dysfunction, central cough reflex sensitization). This approach leads to a reduction in cough and improved quality of life for people with persistent cough.

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