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STATE OF THE ART REVIEW

Management of chronic refractory cough

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ABSTRACT

Chronic refractory cough (CRC) is defined as a cough that persists despite guideline based treatment. It is seen in 20-46% of patients presenting to specialist cough clinics and it has a substantial impact on quality of life and healthcare utilization. Several terms have been used to describe this condition, including the recently introduced term cough hypersensitivity syndrome. Key symptoms include a dry irritated cough localized around the laryngeal region. Symptoms are not restricted to cough and can include globus, dyspnea, and dysphonia. Chronic refractory cough has factors in common with laryngeal hypersensitivity syndromes and chronic pain syndromes, and these similarities help to shed light on the pathophysiology of the condition. Its pathophysiology is complex and includes cough reflex sensitivity, central sensitization, peripheral sensitization, and paradoxical vocal fold movement. Chronic refractory cough often occurs after a viral infection. The diagnosis is made once the main diseases that cause chronic cough have been excluded (or treated) and cough remains refractory to medical treatment. Several treatments have been developed over the past decade. These include speech pathology interventions using techniques adapted from the treatment of hyperfunctional voice disorders, as well as the use of centrally acting neuromodulators such as gabapentin and pregabalin. Potential new treatments in development also show promise.

Introduction

Chronic cough affects 8-10% of the adult population.[1 2] Specialist respiratory physicians, allergists, general physicians, and otolaryngologists often see patients with refractory chronic cough. The management of these patients is difficult and their treatment response often limited. Consequently better approaches to refractory chronic cough are needed. This review outlines several important new developments, including new concepts of its pathogenesis as a neuropathic disorder, the results of several recently published randomized treatment trials, and an evidence based clinical practice guideline for unexplained chronic cough. The review also summarizes current approaches to the management of chronic cough and evidence based guidance for clinicians managing this condition.

Prevalence

The community prevalence of cough is estimated at 2.3-18% of the adult population.[1 2] The prevalence of chronic cough in respiratory outpatient practice ranges from 10% to 38%.[1 2] A meta-analysis found that the prevalence of chronic cough (defined as a cough lasting longer than three months) in the general population was 9.6%.[2] Cough was more common in Europe (12.7%), Oceania (18.1%), and America (11.0%) than in Asia (4.4%) and Africa (2.3%). A limitation of the meta-analysis was that the definition of chronic cough differed between studies.[2]

Other studies reported that the community prevalence of cough was 5.5-13.1% in Europe,[3 4] 7.3-13.6% in Australasia,[3] 2-11% in the United States,[3 5] and 1.6-14.1% in the United Kingdom.[3 6 7] Cough accounts for 10-38% of patients attending specialist cough clinics in the UK and US,[1 8] and it is the most common reason for primary care visits, accounting for 6% of presentations in Australia and the US.[9 10]

Cough is more common in smokers than in non-smokers,[11 12] and the prevalence of cough increases with the mean annual concentration of nitrogen dioxide, total suspended particulates, and particulates less than 10 µm in diameter in the atmosphere.[11 13] A survey of 10 032 patients referred to specialist cough clinics in 11 countries found that cough was most common in the fifth to seventh decades and was more common in women (66%).[14] Another questionnaire survey reported that the mean age of patients with cough was 65 years and 73% of patients were female.[15] The median duration of cough was 6.5 years. Of those who had seen a primary care physician, 85% had been prescribed treatment and 61% were referred to a specialist. Symptoms persisted in 60% of patients despite treatment.

Cough also has a substantial impact on quality of life.[6 16] Patients with chronic cough experience impaired quality of life and interruption of activities of daily living.[17] It can result in depression,[18 19] and it can persist for many months or years, despite systematic investigation and treatment of known causes.

Sources and selection criteria

We searched PubMed from 1960 to July 2015 using the terms chronic cough, chronic refractory cough, chronic idiopathic cough, unexplained chronic cough, and cough hypersensitivity syndrome. Titles and abstracts were reviewed to identify potentially relevant controlled trials of therapy for chronic cough and the full text of these articles was retrieved. Randomized controlled trials, controlled clinical trials, or systematic reviews were included. We excluded case studies and articles that were published in non-peer reviewed journals. The American College of Chest Physicians (ACCP) guidelines on unexplained chronic cough were included.[20]

Definition and terminology of chronic refractory cough

Cough is a reflex activity with elements of voluntary control. It forms part of the somatosensory system that involves visceral sensation, a reflex motor response, and associated behavioral responses. Cough is also a symptom of many common respiratory diseases, where it can be acute (less than three weeks' duration), subacute (three to eight weeks' duration), or chronic (more than eight weeks' duration).[1]

The cough persists in 0-46% of patients who present to specialist cough clinics despite assessment and treatment according to an accepted guideline.[21] This condition is termed chronic refractory cough (CRC), chronic idiopathic cough, or unexplained chronic cough.[20 21] It can be diagnosed when patients have no identified causes of chronic cough (unexplained or idiopathic chronic cough) or when the cough persists after investigation and treatment of cough related conditions (refractory chronic cough). Because patients with unexplained chronic cough often receive specific therapies, such as inhaled corticosteroids or proton pump inhibitors, they can also be classified as having refractory chronic cough.

Cough hypersensitivity syndrome

Recent research has highlighted the similarities between chronic cough and neuropathic disorders, the role of cough reflex hypersensitivity, and hypersensitivity of laryngeal responses (the larynx has the highest concentration of cough receptors) in chronic cough. The recently introduced concept of cough hypersensitivity syndrome groups all patients with chronic cough under a single umbrella with different subtypes.[22]

Cough hypersensitivity syndrome is associated with hypersensitivity of the larynx and upper airway. It is considered to be a disorder of sensory airway nerves caused by hypersensitivity to innocuous irritants,[23] as a result of mucosal upregulation of cough receptors such as transient receptor potential V1 (TRPV1) and TRPA1. Diseases previously evaluated and treated as causes of chronic cough[21]—such as asthma, rhinosinusitis, and gastroesophageal reflux disease (GORD)—are thought to be different phenotypes of the syndrome.[24] CRC is considered to be a phenotype of the cough hypersensitivity syndrome; although the precipitating factor is unknown, it has been hypothesized to be gastroesophageal reflux.[22]

The concept of cough hypersensitivity syndrome has advantages. It may explain why only some people have associated conditions such as asthma, rhinosinusitis, and gastroesophageal reflux and others do not. It explains why cough is often refractory to treatment of associated conditions and why it may occur without an associated condition. It is also consistent with the observation that CRC often starts after an upper respiratory tract infection.

The limitations are that much of the evidence to support cough hypersensitivity syndrome is based on expert opinion and that ways of objectively confirming cough hypersensitivity (such as cough reflex testing) are neither agreed nor recommended. In addition, it is not yet determined how the concept of cough hypersensitivity syndrome explains the origin of other symptoms, such as laryngeal symptoms and fatigue, which often coexist in patients with chronic cough.

The European Respiratory Society task force examined the clinical relevance of the syndrome in a survey of 44 opinion leaders in 14 different countries.[14] Most respondents (89%) agreed that it was a useful concept, that it may mimic other pulmonary or extrapulmonary diseases (82%), and that it was distinct from bronchial hyper-responsiveness (82%). There was less agreement between respondents about the mechanisms involved. For example, although 70% agreed that upregulation of neuronal mechanisms is a key feature of chronic cough, only 41% agreed that airway inflammation is directly responsible for activation of sensory nerves in cough, and only 45% agreed that hypersensitivity of the cough reflex accounts for most symptoms.

Although it is characterized by hypersensitivity of the afferent nerves, because there are no agreed quantitative tests it can currently be diagnosed only by clinical history.[24] A cough inhalation challenge using capsaicin or citric acid is not considered to be useful because of the variability in cough reflex sensitivity in the general population. Further studies are therefore needed to determine the pathophysiology of cough hypersensitivity syndrome.[25]

Laryngeal hypersensitivity

Laryngeal hypersensitivity is another new concept that has been introduced to help understand CRC.[26-29] It is defined as increased sensitivity of the larynx to innocuous stimuli resulting in symptoms of laryngeal paresthesia with cough, dyspnea, dysphonia, or laryngeal spasm. Although some features of CRC are encompassed by the term cough hypersensitivity syndrome, in many patients symptoms are localized to the larynx. The term laryngeal hyper-responsiveness syndrome may therefore be a useful concept that defines a sensory abnormality.[30] This sensation (laryngeal paresthesia) is crucial and perhaps more annoying for patients than the cough itself. The laryngeal hypersensitivity questionnaire can be used to measure laryngeal hypersensitivity.[31] It is a validated, reproducible, and responsive questionnaire that comprises 14 items grouped into subscales of pain/thermal, irritation, and obstruction. The cut-off point for normal function is 17.1 and the minimally important difference is 1.3.

Cough hypersensitivity syndrome may overlap with other laryngeal hypersensitivity syndromes. Cough hypersensitivity can be activated in the lower airways,

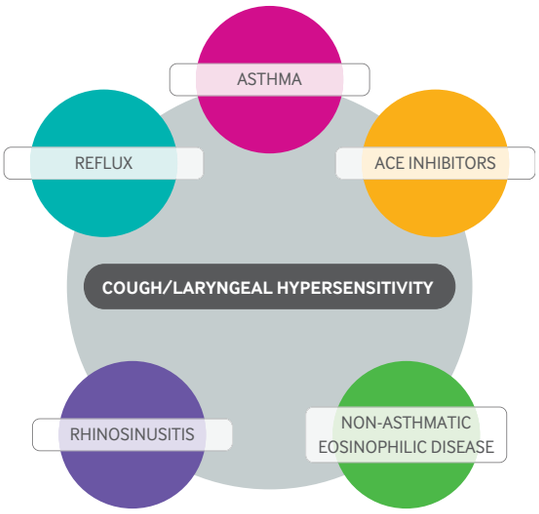

Fig 1 | Proposed association between cough hypersensitivity syndrome, laryngeal hypersensitivity syndrome, and related diseases; ACE=angiotensin converting enzyme

and also in the larynx, as part of laryngeal hypersensitivity.[23] Additional manifestations of laryngeal hypersensitivity syndrome are paradoxical vocal fold movement (PVFM), globus pharyngeus, and muscle tension dysphonia.[32-35] In people with cough hypersensitivity syndrome and laryngeal hypersensitivity syndrome, several related diseases can act as triggers. These conditions are gastroesophageal reflux disease, rhinosinusitis, use of angiotensin converting enzyme 1 inhibitors, asthma, and non-asthmatic eosinophilic disease (fig 1). This is supported by the similar abnormalities seen in quantitative sensory tests, pulmonary function, voice function, and swallowing between patients with a range of laryngeal hypersensitivity syndromes.[34] Further research into the concept of cough hypersensitivity syndrome is therefore needed, including understanding its association with laryngeal hypersensitivity syndromes, its mechanisms, and the use of tools for diagnosis and treatment.

Pathogenesis of chronic refractory cough

Cough reflex hypersensitivity

Cough reflex hypersensitivity is a key feature of CRC that involves both peripheral and central sensitization of the cough reflex.[23 36] It is an afferent response to stimulation that activates sensory neurons with neural transmission by the vagus nerve to the nucleus tractus solitarius in the brainstem. These fibers are integrated into a brainstem circuit that is responsible for generating the basic cough motor pattern, which provides coordinated output through phrenic, intercostal, laryngeal, and abdominal motor neuron pathways to the muscles involved in coughing. Cough often occurs after an upper respiratory tract infection, which can cause damage to the airway mucosa and subsequently cause inflammatory neuropathic changes in the sensory nerves.[23] In addition, the common respiratory viruses, such as human rhinovirus, can upregulate TRP receptors on nerves.[37] Repeated coughing activates the release of chemical mediators that enhance cough through inflammatory mechanisms.[23]

Peripheral sensitization

Peripheral sensitization in chronic cough can occur in areas with sensation mediated by the vagus nerve, such as the larynx, esophagus, pharynx, nasal cavity, and bronchi. Inflammatory mediators, such as histamine and prostaglandins, sensitize cough fiber afferent nerve endings (C fibers), which increases the excitation of afferent nerves,[38] and subsequently reduce the threshold for cough. In CRC this is associated with increased expression of TRPV1 receptors on non-adrenergic-non-cholinergic nerve endings.[39] Hypersensitivity results in cough after exposure to low level tussive stimuli such as smoke (termed hypertussia). Cough reflex hypersensitivity can be measured by graded inhalation of capsaicin, which activates TRPV1 receptors. In chronic refractory cough, there is marked cough reflex hypersensitivity to capsaicin (fig 2); this explains why hypertussia is common in CRC.

Although the role of TRPV1 is recognized in cough, a trial of the TRPV1 antagonist SB-705498 showed equivocal results. SB-705498, produced a significant improvement in cough reflex sensitivity to capsaicin but did not improve cough outcomes, such as objective cough frequency, cough severity, urge to cough, and cough specific quality of life compared with placebo.[40] These results indicate that cough reflex sensitivity can be reduced by targeting peripheral mechanisms but for treatment to modulate cough behavior it may also need to target central mechanisms.

Central sensitization

Central sensitization is characterized by increased excitability in the central sensory pathways.[41 42] There are similarities between CRC and other conditions with central sensitization,[43] such as neuropathic pain.[44] Paresthesia (abnormal sensation in the absence of a stimulus), hyperalgesia (pain triggered by low level exposure to a known painful stimulus), and allodynia (pain triggered by a non-painful stimulus) are all features of neuropathic pain.[44] Similar clinical features—such as an abnormal laryngeal sensation or "throat tickle" representing laryngeal paresthesia, increased cough sensitivity in response to known tussigens representing hypertussia, and cough triggered in response to non-tussive stimuli such as talking or cold

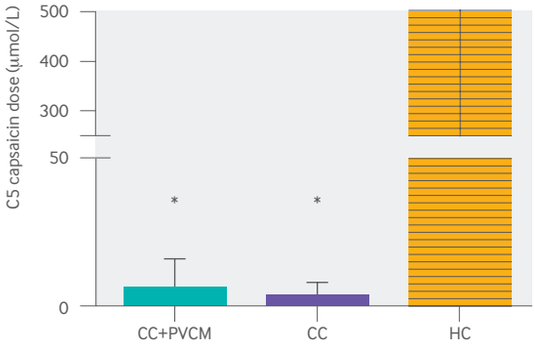

Fig 2 | Cough reflex hypersensitivity in patients with chronic refractory cough (CRC), CRC plus paradoxical vocal cord movement (PVCM), and healthy controls (HC). Median (interquartile range). *P<0.0005 versus healthy controls. C5=capsaicin dose needed to elicit five or more coughs 30 seconds after administration[26]

Table 1 | Comparison of features of chronic pain and chronic refractory cough[46]

Neuropathic pain			Neuropathic cough		
Concept	Definition/description	Example	Concept	Definition/description	Example
Paresthesia	Abnormal sensation	Tingling sensation in the skin	Laryngeal paresthesia or hypersensitivity	Abnormal sensation in the throat	Tickle or itch in throat
Hyperalgesia	Increased response to a stimulus that is normally painful but at a reduced threshold	Increased pain response to a needle prick	Hypertussia	Increased cough response to a tussigenic stimulus	Fumes, smoke, aspirate
Allodynia	Pain in response to a stimulus that does not normally produce pain, such as a mechanical or thermal stimulus	Pain in response to touch	Allotussia	Cough in response to a non-tussigenic stimulus	Thermal, vocalisation, exercise

air (allotussia)—can also be seen in CRC.[43] These features can be elicited by clinical history and confirmed by quantitative sensory testing such as hypertonic saline challenge, cough reflex sensitivity testing, or fiberoptic endoscopic evaluation of swallowing with sensory testing.[34 45] Table 1 shows a comparison of the features of chronic refractory cough and chronic pain.

Several lines of evidence support the involvement of central neural mechanisms in chronic cough (box 1). Allotussia, a symptom of CRC, is a key characteristic of central sensitization that can be confirmed by quantitative sensory testing, and patients with CRC have abnormal results compared with healthy controls.[34] For example, the application of a vocal stimulus in a voice stress test elicits cough in patients with CRC.[34] Furthermore, the symptoms elicited in these patients are not confined to cough but include other domains such as dyspnea, dysphonia, and laryngeal sensations such as a tickle.[28 31] Functional magnetic resonance imaging (MRI) demonstrates cortical activation during cough,[47] and this activation is increased in patients with chronic cough.[14] Cerebral cortex activity has also been identified during successful placebo suppression of the urge to cough.[48] Finally, the response of chronic refractory cough to centrally acting neuromodulators such as gabapentin,[49] pregabalin,[50 51] morphine,[52] and amitriptyline[53] provides further evidence for central sensitization in cough.[23 49]

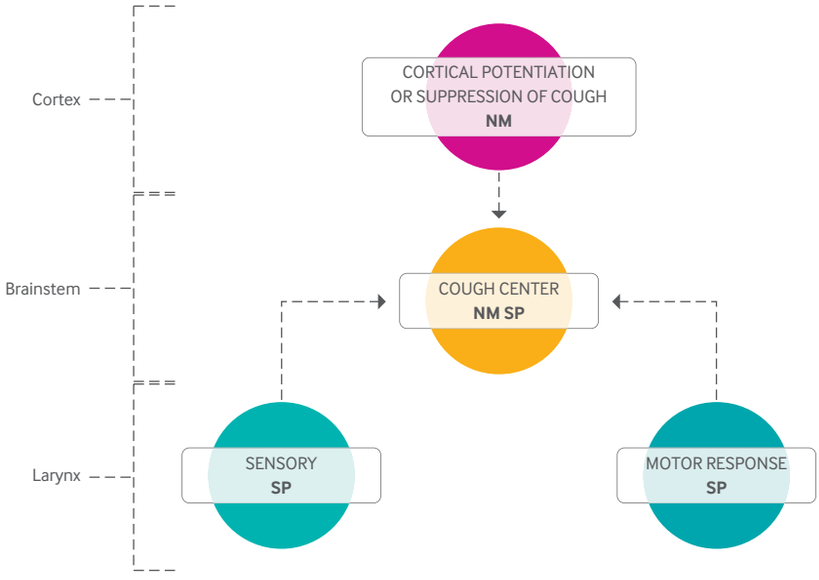

Fig 3 Diagram of key elements in the cough reflex, indicating the association between peripheral and central sensitization, the role of motor responses such as cough and paradoxical vocal fold movement, and the place of convergent stimuli in provoking cough.[56] Proposed sites of action of speech pathology (SP) and neuromodulator (NM) therapy are indicated

Convergence of stimuli that may lead to synergy deserves attention in chronic cough.[55] It has been suggested that multiple sources of stimuli merge to result in CRC and that these multiple sources may need to be treated simultaneously (fig 3).[56]

Paradoxical vocal fold movement

CRC has been associated with PVFM,[26] an abnormal laryngeal motor pattern with adduction of the vocal folds during inspiration after a stimulus. Common symptoms include inspiratory dyspnea, stridor, and throat tightness. This clinical overlap suggests that these symptoms might be features of a single underlying condition.[28] The symptom profile, triggers, voice assessment results, and associated medical conditions do not differ significantly between patients with chronic cough and those with associated PVFM. Although cough was not the primary diagnosis in the patients with PVFM, cough symptoms were prevalent and similar to those with CRC (fig 4).[24 28] The co-occurrence of both conditions can lead to diagnostic confusion because patients may present with severe coughing and severe dyspnea, but with no evidence of lung or lower airway disease to explain the dyspnea. Accurate recognition and diagnosis of PVFM enables the implementation of effective treatment.[57 58]

Clinical features of CRC

Clinical features include a dry cough that occurs in intermittent bouts throughout the day. The cough often originates from the laryngeal region. Triggers include non-tussive stimuli that do not normally trigger cough, such as air conditioning and phonation (allotussia), and very low doses of tussive stimuli (hypertussia). Laryngeal discomfort and paresthesia are also triggers.[43] The cough can persist for months or years.[36] The higher prevalence in women may be explained by a heightened capsaicin cough reflex sensitivity in women compared with men,[14 59] and it correlates with a greater response in the primary somatosensory cortices on functional MRI scanning in women.[14] In some patients the onset of cough may be associated with the menopause, and it is possible that reduced estrogen levels potentiate cough reflex

Box 1 | Evidence for central sensitization in chronic refractory cough

- Abnormalities on quantitative sensory testing[34]
- Overlap in symptoms between chronic refractory cough and related laryngeal conditions[28 43]
- Cortical activation during functional magnetic resonance imaging studies[47 48 54]
- Cross stimulus responses[34]
- Response to centrally acting neuromodulators[20 49 51 52]

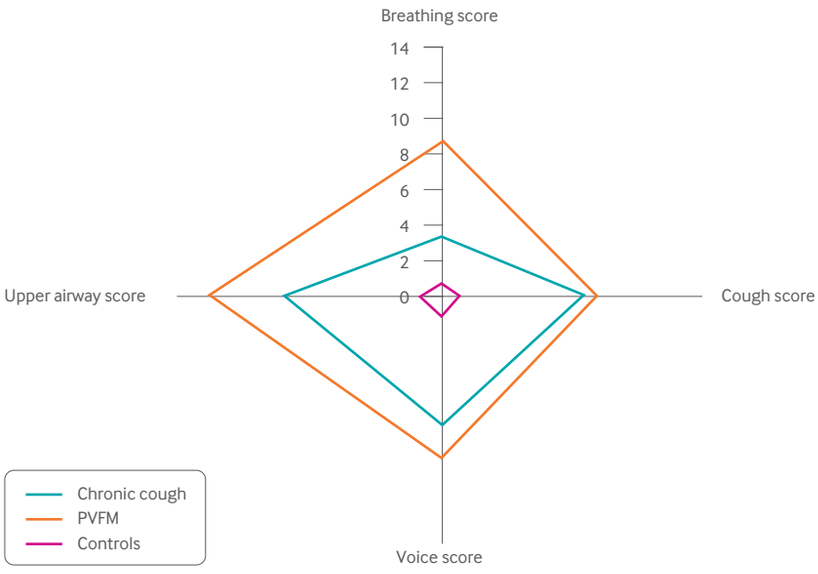

Fig 4| Breathing, cough, voice, and upper airway symptom scores based on the symptom frequency and severity scale for patients with chronic cough (CC), CC plus paradoxical vocal fold movement (PVFM), and healthy controls (HC). All domains were higher in patient groups than in control groups (P<0.05)[34]

sensitivity. Subclinical airway inflammation may also be amplified at the time of the menopause.[59]

Forty two percent of patients report that their cough starts with a viral infection and 36-43% of people with a viral upper respiratory tract infection still have cough three months after the infection.[36 60] Viral infection induces the expression of cough receptors that can be inhibited by tiotropium,[37 49] which may explain this clinical observation and the beneficial effects of anticholinergic agents in chronic cough.[61]

Patients often report laryngeal symptoms in addition to cough (fig 3). Clinically significant dysphonia is seen in 40% of patients with chronic refractory cough and talking is a common trigger for coughing episodes.[43 27] Laryngeal hypersensitivity and cough reflex hypersensitivity are increased compared with healthy controls (fig 2). Reflexive closure of the glottis in response to a laryngeal irritant, termed the glottic stop reflex, is also increased in patients with chronic cough.[62]

Box 2 | Red flags: alarm symptoms and findings in chronic cough[65]

- Hemoptysis
- Smoker with >20 pack year smoking history
- Smoker over 45 years of age with a new cough, altered cough, or cough with voice disturbance
- Prominent dyspnea, especially at rest or at night
- Substantial sputum production: more than one tablespoon a day
- Hoarseness
- Systemic symptoms: fever, weight loss
- Complicated gastroesophageal reflux disease (GORD) symptoms associated with weight loss, anemia, overt gastrointestinal bleeding (hematemesis or melena), severe symptoms, dysphagia, odynophagia, or failure of empiric treatment for GORD
- Recurrent pneumonia
- Abnormal clinical respiratory examination
- Abnormal chest radiograph

Diagnosis of chronic refractory cough

Primary assessment

The condition is diagnosed when the investigation and treatment of known causes of cough have not led to resolution of the cough.[63] The diagnostic approach requires an initial assessment and investigation for alarm symptoms that suggest a serious underlying cause of cough (box 2). Key symptoms such as hemoptysis, a history of heavy smoking, or abnormalities on clinical respiratory examination or chest radiography should prompt investigation for cancer, chronic infection, or serious underlying disease. If no alarm symptoms are identified assessment can focus on diagnoses associated with chronic cough that have specific remediable causes or a usually good treatment response (box 3). This includes assessment for asthma (history, spirometry, airway hyper-responsiveness, exhaled nitric oxide), eosinophilic bronchitis (induced sputum eosinophils, exhaled nitric oxide), rhinitis (history, nasendoscopy), angiotensin converting enzyme inhibitor treatment (history), GORD (history, endoscopy), and obstructive sleep apnea (history, overnight oximetry, polysomnography). At this stage clinicians should also consider the presence of serious conditions that should not be missed (box 3). In clinical practice it is important to distinguish between cough that is truly refractory or unexplained and cough that can be explained and treated effectively.[64] History and physical examination can be used to guide investigation to allow objective confirmation of the conditions listed in box 3.

Because chronic refractory cough is defined as a cough that persists after extensive medical investigation and treatment, it is a diagnosis of exclusion. A guideline based chronic cough assessment is an essential part of the investigation of these patients.[64 66] Once this has been completed and the results reviewed, if the cough persists then the patient can be diagnosed as having chronic refractory cough.

Secondary assessment

A range of second stage investigations can be considered to further characterize the condition. These include nasendoscopy and 24 hour pH monitoring. Laryngeal examination using flexible nasendoscopy will identify the presence of laryngeal lesions or abnormal motor patterns that might be contributing to the cough symptoms and laryngeal discomfort.[59] If present an alternative management approach may be needed. Nasendoscopy with odor or exercise challenge can be used to provoke symptoms of PVFM that can help to confirm the diagnosis.[30 67] Nasendoscopy can identify signs of laryngopharyngeal reflux, particularly if there is edema or erythema in the cricoarytenoid region.

Patients with CRC have a high prevalence of laryngeal dysfunction,[27 34 68] as defined by the high prevalence of voice symptoms and abnormalities in auditory perceptual, acoustic, and electroglottographic assessment. Furthermore, many patients report that talking triggers cough episodes.[43] Therefore, a systematic examination of laryngeal structure and function may be indicated in those with laryngeal symptoms. Co-existing muscle tension dysphonia may be present and may require additional voice therapy techniques. Finally nasendoscopy can identify the

Box 3 | Remediable conditions and conditions not to be missed in patients with chronic cough[65]

Remediable conditions

Asthma

Gastroesophageal reflux disease

Obstructive sleep apnea

Angiotensin converting enzyme inhibitor use

Eosinophilic bronchitis

Rhinosinusitis

Serious cough related conditions

Cancer of the larynx, bronchus, or lung

Parenchymal lung disease: chronic obstructive pulmonary disease, interstitial pulmonary fibrosis, bronchiectasis, sarcoidosis, pneumothorax

Cardiovascular disease: left ventricular failure, pulmonary embolism, aortic aneurysm

Infection: tuberculosis, lung abscess, pertussis

presence of PVFM and motor paresis.[67 69] Access to nasendoscopy will vary between settings. It may be performed by an otolaryngologist as part of the investigation of CRC or as part of the speech pathology evaluation.

The role of esophageal pH and pressure monitoring is controversial. Ambulatory pH monitoring involves insertion of a transnasal catheter with a pH electrode positioned 5 cm above the lower esophageal sphincter.[70] It can enhance the diagnosis of GORD and identify an association between cough and reflux events. Esophageal impedance manometry is usually reserved for research settings. It has the advantage of being able to detect non-acid or weakly acid events that may be temporally associated with cough episodes.[71] However it is expensive and cannot detect a response to anti-reflux treatment.[72] Impedance monitoring has shown a low probability of an objective association between cough and reflux events.[73]

Treatment of chronic refractory cough

Recent ACCP guidelines identified four categories of treatment that were supported by randomized controlled trials (RCTs)—non-pharmacologic therapies, inhaled corticosteroids, neuromodulatory therapies, and other therapies. The two main advances in treatment during the past decade have been non-pharmacologic approaches, such as speech pathology management, and the use of centrally acting neuromodulators.[29 49 51 74] There is not yet evidence to support the use of non-pharmacologic approaches before medical treatment, and thorough medical investigation by a specialist respiratory or general physician or an otolaryngologist is recommended before using non-pharmacologic approaches.

Non-pharmacologic therapies

A systematic review found support for cough suppression strategies based on speech pathology and physiotherapy.[74] The review included one single blinded randomized controlled trial,[29] three prospective non-comparison studies,[75-77] and one retrospective review.[78] Meta-analysis was not possible so the included studies are discussed separately below.

The RCT investigated 87 patients with chronic refractory cough.[29] Participants received either four sessions of speech pathology intervention for chronic refractory cough or an equivalent course of healthy lifestyle education (box 4). The cough score significantly decreased by a mean of 3.9 in the treatment group (95% confidence interval 3.0 to 4.9; P<0.001) and by 0.3 in the placebo group (0.3 to 2.2; P<0.001); the decrease was significantly greater in the treatment group than in the placebo group (mean difference in score 2.8; 1.3 to 4.0; P<0.001). Treatment significantly improved the total symptom score (mean difference before and after treatment 12.7; 9.0 to 16.1; P<0.001) *v* placebo (2.9; −0.7 to 6.5; P=0.170) and daily limitation score (treatment mean difference 0.7; 0.4 to 1.0; P<0.001 *v* placebo mean difference 0.3; 0.0 to 0.6; P=0.038). In addition, the clinical judgment of outcome was positive in 88% of participants in the treatment group versus 14% in the placebo group, although this particular measure has a risk of overestimation of treatment effect.

The first prospective study looked at 24 participants with chronic refractory cough, 14 of whom had coexisting PVFM.[76] Participants underwent four sessions of speech pathology management as described previously.[29 46] Quality of life assessed using the Leicester cough questionnaire (LCQ) improved from 10.5 to 16.2 (P=0.001) in the CRC+PVFM group and from 10.4 to 17.5 (P=0.01) in those with CRC only. Cough reflex sensitivity (capsaicin dose needed to elicit five or more coughs 30 s after administration (C5)) improved from 5.88 µmol/L to 15.7 µmol/L (P=0.008) in the CRC+PVFM group and 2.94 µmol/L to 7.84 µmol/L (P=0.04) in the CRC only group. PVFM resolved in eight of 10 participants.

The effect of a speech pathology intervention on cough reflex sensitivity testing was examined in the second prospective study of 17 participants with CRC.[77] After four sessions of the intervention the LCQ score improved from 13.5 to 16.9 (P=0.002)—twice the minimal important difference of 1.3, the smallest change in quality of life considered to be clinically meaningful.[79] Log CRS C5 improved from 0.88 to 1.65 (P<0.0001). Ambulatory cough monitoring showed that cough frequency dropped from 72.5 to 25.0 coughs/h (P=0.009). Urge to cough reduced significantly from 5 points to 1 point on the urge

Box 4 | Speech pathology treatment for chronic refractory cough[46]

Education

Cough can be triggered by irritation

Cough is not always necessary

Cough has limited physiological benefit in this condition

Cough is under automatic and voluntary control

Symptom control techniques

Cough suppression swallow

Cough control breathing

Paradoxical vocal fold movement release breathing

Release of laryngeal constriction

Reducing laryngeal irritation

Behavioral management of reflux

Reduce phonotraumatic behaviors

Hydration

Minimize exposure to irritating substances

Psychoeducational counseling

Treatment is hard work

Setting realistic goals

to cough scale (P=0.01).[80] Three uncontrolled longitudinal case series have confirmed that speech pathology treatment improves laryngeal hypersensitivity, cough reflex hypersensitivity, and the aberrant laryngeal motor response (PVFM) in CRC (fig 3).[76-78]

The third prospective study assessed a physiotherapy intervention for 23 patients with CRC.[75] The intervention comprised education and lifestyle advice, cough suppression exercises, breathing retraining, and vocal hygiene. LCQ scores improved from 12.4 to 15.1 (P<0.001). Cough frequency measured on a seven point Likert scale improved from 5.4 to 4.3 (P=0.001). Sleep disturbance improved from 4.5 to 3.6 points on a 7 point Likert scale (P=0.02).

The retrospective review looked at 16 patients with CRC who underwent a series of breathing retraining exercises with a speech pathologist including rhythmic breathing, breathing with vocal resistance, pulsed exhalation, and abdominal focus at rest.[78] Fifteen patients reported improved cough symptoms. The reflux symptom index score improved by a mean of 3.74 points and all patients improved (P<0.01). PVFM improved or resolved in 15 patients and laryngeal sensory thresholds improved or resolved in 14 patients (P=0.02).

Pathophysiological assessment

The first step in speech pathology management of CRC is to evaluate the pathophysiological features of the condition, including cough characteristics, urge to cough, PVFM, and voice symptoms. This assessment is conducted by the speech pathologist and takes 45-60 minutes. The information obtained during the assessment provides baseline measurements and informs the structure and focus of the behavioral management program.

Urge to cough

Urge to cough is an important concept in cough. Patients with chronic cough report a consistent and characteristic sensory experience, which suggests a common somatosensory disturbance associated with the urge to cough and excessive coughing.[81] An assessment of cough triggers and the urge to cough can provide valuable information about the person's cough control. Formal exposure to potential triggers can be trialed in the clinical setting.[82] In such an assessment, the magnitude of the urge to cough[80] and the number of coughs observed are rated at baseline and after exposure to various olfactory, exercise, phonatory, respiratory, and swallowing triggers. The triggers include deep inspiration, reading aloud, exercise, voice assessment tasks, perfume, soap powder, eating, and drinking. Patients can also be coached in strategies to relieve the urge to cough and to implement cough suppression techniques once the urge is recognized, before the cough develops.

Voice assessment

Because dysphonia and laryngeal symptoms are common in CRC,[27 68] voice assessment is part of the speech pathology management of CRC. Voice assessment tasks themselves—particularly ones that extend the voice to the limits of pitch, loudness, and duration—can trigger cough.[43] The extent to which this occurs can be measured during the assessment. Formal voice assessment tasks also provide information about the coordination of respiration and phonation that might not be evident during an informal conversation. We therefore suggest that minimal voice screening is included in the speech pathology assessment of patients with CRC, with more complex acoustic, electroglottographic, and aerodynamic assessment reserved for severe cases or professional voice users.[83]

Laryngeal assessment

Cranial nerve motor deficits have not been reported in CRC. Patients commonly have laryngeal discomfort,[31 43] and oromusculature examination invariably identifies a dry oral cavity. This may be a side effect of drugs or due to dehydration. Poor hydration is common in CRC, and speech pathology treatment programs often target hydration.[43 83] Extrinsic laryngeal muscle tension is often seen around the thyrohyoid and geniohyoid regions. A similar pattern of muscle tension is reported in hyperfunctional voice disorders.[84-86]

This tension might be a result of cough or patients holding their larynx in a tense state in an unconscious attempt to avoid triggering cough. Minor swallowing deficits may also be present.[34] An objective assessment of swallowing in 33 patients with CRC and 28 with combined cough and PVFM found that all patients had significantly lower (worse) timed swallow test results than healthy controls.[34 87] Patients might be over-protecting their airway to reduce uncomfortable laryngeal and pharyngeal sensations.

Speech pathology treatment

Speech pathology treatment for cough has been described in detail previously and is summarized in box 4 and fig 3.[29 46] It consists of four components: education, cough suppression strategies, vocal hygiene training, and psychoeducational counseling. It is typically conducted by speech pathologists with a special interest in the treatment of dysphagia and voice disorders, and training resources are available to ensure the consistency of the treatment program.[46]

The goals of speech pathology interventions are to improve voluntary control over the cough by teaching patients to identify sensations that precipitate the cough and to substitute the cough with another response for example, a breathing or swallowing exercise, and to change behaviors that contribute to laryngeal irritation. It probably acts on both peripheral and central parts of the cough pathway.

Pharmacologic therapy

Neuromodulators

Centrally acting neuromodulators—including gabapentin, pregabalin, morphine, amitriptyline, and baclofen—act on the heightened neural sensitization that is involved in the pathogenesis of CRC.[20] All of these agents have improved cough specific quality of life in patients with CRC (table 2; fig 3). However, although these treatments are promising, adverse effects can be serious and limit the maximum tolerable dose of these agents.[20]

Table 2 | Effects of neuromodulator drugs on cough quality of life*

Study	Tool used	Drug	Change in score from baseline (points)
Jeyakumar et al[53]	CQLQ	Amitriptyline	24.53
		Guaifenesin-codeine	2.92
Morice et al[52]	LCQ†	Morphine	3.2
		Placebo	1.2
Ryan et al[49]	LCQ†	Gabapentin	2.5
		Placebo	1.1
Vertigan et al[51]	LCQ†	Pregabalin‡	6.6
		Placebo‡	3.3

Abbreviations: CQLQ=cough quality of life questionnaire; LCQ=Leicester cough questionnaire.
*Adapted from American College of Chest Physicians guideline.[20]
†Minimally important dose is 2.
‡Treatment given simultaneously with speech pathology treatment.

A systematic review of neuromodulatory therapy for CRC included eight studies[63]—two RCTs that are discussed below,[49 53] and six observational studies.[88-93]

Morphine

A double blind placebo controlled crossover trial of slow release morphine sulfate (5 mg) versus placebo included 27 patients with CRC. The mean LCQ score was 12.3 (standard deviation 2.5) points at baseline, 13.3 (2.7) on placebo, and 15.5 (2.7) on morphine (P<0.01 *v* baseline and P<0.02 *v* placebo).[52] There was no significant difference in geometric mean of citric acid challenge 91 (74) mmol/L at baseline versus 127 (160) mmol/L on placebo and 220 (334) mmol/L on morphine. Morphine was well tolerated and no patient dropped out because of adverse events. The most common side effects noted were constipation (40%) and drowsiness (25%).[52]

Gabapentin

Gabapentin binds to the α2δ subunit of the voltage dependent calcium channel, thereby regulating neurotransmitter release. It was originally developed as an antiepileptic agent but has been more useful in neuropathic pain syndromes. Gabapentin prevents mechanical and thermal allodynia and hyperalgesia in neuropathic pain models. The specific mechanisms of action of gabapentin in the treatment of neuropathic pain and neuropathic cough are yet to be determined.

An RCT of gabapentin randomized 62 non-smokers with refractory cough to treatment with gabapentin 1800 mg/day as the maximum tolerable dose or to a matched placebo dose over 10 weeks.[49] Objective and subjective measures of cough were taken before, during, and after treatment. Gabapentin significantly improved cough specific quality of life (treatment 2.5 *v* placebo 1.1; difference 1.8, 95% confidence interval of the difference 0.56 to 3.04; P=0.004), reduced cough severity (treatment −11.1 *v* placebo 8; −12.23, −23.22 to −2.88; P=0.029), and cough frequency (treatment −22.5 *v* placebo −4.3; −27.31, −51.75 to −2.88; P=0.028). The drug's onset of action was within four weeks and the effect was maintained during maximal dosing at eight weeks. However, the improvement in LCQ was not sustained after treatment withdrawal and the LCQ score returned to baseline. Adverse events, including confusion, dizziness, dry mouth, fatigue, nausea, blurred vision, headache, and memory loss were reported by 31% of the participants taking gabapentin.[49] Adverse events were reported in 10% of the placebo group. The side effects of gabapentin often limit its use, especially at higher doses, but they can diminish with time.

Amitriptyline

Amitriptyline has been investigated in a randomized controlled trial of 28 patients with CRC.[53] Patients were randomized to receive either amitriptyline or codeine or guaifenesin for 10 days. Amitriptyline showed a greater than 50% response compared with codeine or guaifenesin (P=0.0007).

Baclofen

Baclofen has been investigated as a potential antitussive agent but no randomized trials have been performed. A non-randomized study compared the effect of baclofen 20 mg, baclofen 10 mg, and placebo on cough reflex sensitivity in 41 healthy volunteers.[89] In the patients taking 20 mg baclofen, cough reflex sensitivity decreased after 14 and 28 days compared with baseline, but no significant change was seen with 10 mg baclofen or placebo. Another non-randomized study assessed the effects of baclofen in 16 patients with GORD induced chronic cough.[94] It found improvements in cough, cough reflex sensitivity, and the number of acid reflux episodes. The main adverse events associated with baclofen were somnolence, dizziness, and fatigue.[94]

Although baclofen remains a potential area for development,[95] no conclusions can be drawn about its effectiveness until RCTs are available.

Combined pharmacologic and non-pharmacologic therapy

An RCT examined the effect of combined speech pathology treatment and pregabalin on CRC.[51] Forty patients were randomized to combined speech pathology treatment and pregabalin 300 mg or combined speech pathology treatment and placebo. Cough severity, cough frequency, and cough quality of life improved in both groups. However, the improvement in cough severity and cough quality of life was significantly greater with combined speech pathology and pregabalin than with speech pathology alone. The mean difference in Leicester cough questionnaire scores was 3.5 (1.1 to 5.8) which is greater than the minimally important difference of 2. The mean difference in cough severity visual analog scale scores was 25.1 (10.6 to 39.6). There was no significant difference in improvement in cough frequency between groups. Importantly, and unlike the study of gabapentin,[49] symptoms did not get worse once pregabalin was withdrawn. Capsaicin cough reflex sensitivity (C5) also improved in both treatment groups from 15.7 µmol to 47.5 µmol with combined speech pathology and pregabalin and from 3.92 µmol to 15.7 µmol with speech pathology alone.

At this stage, the choice of intervention may be influenced by patient and physician preference. Although speech pathology and neuromodulators improve cough they have limitations: speech pathology treatment reduces cough but does not eliminate cough, and neuromodulators are limited by side effects and a non-sustained treatment

response. These treatments act on different aspects of the cough pathway and therefore combined treatments might provide more complete resolution of the cough.

Inhaled corticosteroids

Eosinophilic airway inflammation (eosinophilic bronchitis) is an important cause of chronic cough that can occur as a discrete condition or as part of asthma, cough variant asthma, rhinitis, or atopic cough. Inhaled corticosteroids are effective in eosinophilic airway inflammation. Two of three randomized controlled trials of inhaled corticosteroids, including mometasone, budesonide, and beclometasone, showed no significant improvement in cough severity.[96 97] There were no adverse effects.

Optimal assessment of eosinophilic bronchitis requires the measurement of airway eosinophils (from induced sputum or bronchoalveolar lavage) or exhaled nitric oxide. This should be performed as part of the investigation of CRC. A randomized controlled clinical trial found no beneficial effect of inhaled budesonide on cough symptoms in patients with chronic unexplained cough who did not have asthma or eosinophilia.[20 98]

A systematic review to assess whether inhaled corticosteroids could result in cure of chronic unexplained cough in adults identified eight eligible RCTs with 570 participants.[99] The studies were of good quality but were heterogeneous in terms of cough duration (fewer than three weeks to more than eight weeks) and the exclusion of other cough related conditions. Treatment with inhaled corticosteroids significantly reduced cough score but analysis of the primary outcome (cure) was not possible because of study heterogeneity.

Other treatments

GORD is thought to be a contributory factor to chronic cough, with reflux of gastric contents (acid and non-acid) into the esophagus and laryngopharyngeal areas stimulating cough. Symptomatic GORD should be evaluated and treated if present before patients are diagnosed as having CRC.

A trial of high dose esomeprazole, a proton pump inhibitor, in patients with CRC in the absence of symptomatic GORD found no benefit on cough severity or quality of life.[100] This suggests that the cough is not due to acid reflux and does not support the use of empiric antireflux treatment.

The role of the investigation and effective treatment of non-acid reflux in CRC is unclear, as is the place of surgical intervention to prevent reflux of gastric contents into the esophagus and laryngopharyngeal area. An observational study of 67 patients with GORD and cough undergoing fundoplication showed an improvement in cough, as measured on a four point ordinal scale of cough frequency, in 85% of patients. The study was limited by the lack of a standardized measure of cough and the absence of a control group.

Ipratropium bromide, a bronchodilator used in the treatment of asthma, has been investigated in CRC. A randomized controlled trial found a significant reduction in cough severity and a good safety profile.[101] Subsequent work has identified an inhibitory effect of this class of drug on neuronal TRPV1 receptors.[61]

Outcome assessment after treatment

We recommend routine collection of outcome measures after treatment for CRC using validated tools such as the cough severity index,[102] the LCQ,[103] and the laryngeal hypersensitivity questionnaire.[31] These are easily adaptable and do not require additional equipment. Tests such as ambulatory cough frequency monitoring and cough reflex sensitivity testing can be used to provide objective measures.[104] Speech pathologists may also use objective measures of voice, such as maximum phonation time and auditory perceptual voice evaluation, to monitor changes in phonation after treatment.

CRC in comorbid disease

Chronic cough can be a disabling symptom in diseases such as lung cancer, chronic obstructive pulmonary disease (COPD), and interstitial lung diseases. Dry irritated coughing contributes to reduced quality of life and fatigue, thereby exacerbating the symptoms of these conditions. In these situations cough is considered an explained but refractory chronic cough condition.

Cancer

A systematic review of cough treatments in cancer found some effect of morphine, codeine, dihydrocodeine, levodropropizine, sodium cromoglycate, and butamirate citrate linctus (cough syrup), although all of the studies had risk of bias.[105] Speech pathology treatment for cough suppression in cancer has not been studied.

Chronic obstructive pulmonary disease

The symptom burden from cough is high in COPD—a fifth of patients with moderate airflow limitation report cough as a highly distressing symptom.[106] Patients rank cough as the second most prevalent symptom. Chronic cough with sputum production is common and is often considered to be the first symptom of COPD. Patients with chronic cough have an increased risk of disease progression and exacerbations that might require admission to hospital. There are opportunities to evaluate speech pathology treatment and pharmacologic therapy of cough in COPD.

Cough in idiopathic pulmonary fibrosis

Interstitial lung diseases are a heterogeneous group of diseases that result in progressive functional decline and death. Idiopathic pulmonary fibrosis is the most common of these diseases and cough is a prominent but not universal symptom.[107] Cough is estimated to be present in 84% of patients with idiopathic pulmonary fibrosis and is more prevalent in patients who have never smoked or who have more advanced disease.[108] The cough can be extremely debilitating, with a detrimental effect on quality of life,[109] and it is an independent predictor of disease progression.[108]

The cause of this cough is not clear. Mechanical factors may be at play, including destruction of the cough inhibitory fibers as the lung is distorted by the fibrotic process,[107] leading to increased cough sensitivity.[107 110] Cough reflex sensitivity in this disease responds to prednisolone and corticosteroids,[111] Speech pathology intervention for cough associated with pulmonary fibrosis has not been studied.

Recommendation	ACCP (2015)[20]	CICADA (2010)[65]	ERS (2007)[113]	BTS (2006)[59]	JRS (2006)[114]
CRC is defined as a cough persisting for longer than 8 weeks that remains unexplained after investigation and therapeutic trials conducted according to practice guidelines	√	√	√		
CRC should only be diagnosed after thorough assessment at a cough clinic				√	
Assessment should include the cough severity visual analog scale, cough quality of life questionnaires, and ambulatory cough monitoring			√	√	
Objective testing of bronchial hyper-responsiveness and eosinophilic bronchitis or therapeutic corticosteroid trial	√			√	
Speech pathology	√	√			
Inhaled corticosteroids are not recommended for patients with negative tests for bronchial hyper-responsiveness and eosinophilia	√				
Gabapentin	√				
Deal with patient stress and concern		√			
Treat exacerbating factors		√			
Minimize drugs		√			
Empiric trial of inhaled corticosteroids		√		√	
Empiric trial of proton pump inhibitors/consider reflux as a cause		√			
Antitussive therapy with narcotics		√			

Fig 5| Comparison of cough guidelines in relation to chronic refractory cough (CRC). ACCP=American College of Chest Physicians; CICADA=Cough In Children and Adults: Diagnosis and Assessment; ERS=European Respiratory Society; BTS=British Thoracic Society; JRS=Japanese Respiratory Society

Emerging therapies for CRC

Several novel treatments have been evaluated. A randomized double blind placebo controlled crossover trial assessed an oral purinergic (P2X3) receptor antagonist (AF-219) in CRC.[112] P2X3 receptors in airway vagal afferent nerves contribute to the hypersensitivity of sensory neurons, and treatment with AF-219 was associated with a 75% reduction in cough frequency compared with placebo. Daytime cough frequency fell from a mean 37 coughs per hour to 11 coughs per hour. Dysgeusia occurred in 88% of participants and led to treatment withdrawal in six.

Guidelines

A comparison of cough guidelines from the ACCP,[20] Lung Foundation of Australia (Cough In Children and Adults: Diagnosis and Assessment; CICADA),[65] European Respiratory Society (ERS),[113] British Thoracic Society (BTS),[59] and the Japanese Respiratory Society (JRS)[114] found that recommendations were not consistent across guidelines (fig 5). The ACCP guideline is devoted to CRC, whereas the others cover a broad spectrum of cough disorders. The CICADA guideline has some specific recommendations for CRC. Some recommendations in the BTS and ERS guidelines are assumed to be applicable to CRC. No specific recommendations for CRC were made in the JRS guideline. The range of recommendations may be a result of the timing of publications. New research published since the publication of the ERS, BTS, and JRS guidelines is included in the more recent ones. This supports the need for ongoing review and updating of clinical guidelines. Some recommendations are in conflict. For example, the CICADA guideline recommends an empiric trial of inhaled corticosteroids, whereas the ACCP guideline does not recommend this for patients with negative tests for bronchial hyper-responsiveness and eosinophilia. The ACCP guidelines recommended offering gabapentin for treatment of CRC once the risk-benefit profile has been considered and then reviewing the situation six months later. The ACCP guidelines suggest that the role of neuromodulators in treatment in relation to speech pathology interventions should be defined and that better understanding of the adverse event profile is needed.[20]

Conclusion

Several advances in the theoretical understanding, assessment, and treatment of CRC have been reported in the literature over the past 10 years. CRC is recognized as a clinical entity. The concept of neuronal hypersensitivity in CRC has now been expanded to include laryngeal and central components. Successful treatment programs for CRC use therapies directed at laryngeal and central hypersensitivity, such as speech pathology and neuromodulators. Improvements in clinical practice are needed to ensure that patients who seek help for chronic cough receive a systematic assessment that covers treatable causes of chronic cough as well as assessing laryngeal and central hypersensitivity.

Further research into cough hypersensitivity syndrome is needed to determine its pathophysiology and identify diagnostic criteria and treatment options. Because the clinical features of CRC and laryngeal hypersensitivity syndrome overlap, the association between cough hypersensitivity syndrome and laryngeal hypersensitivity syndrome needs to be determined. The pathophysiology of CRC involves cough reflex hypersensitivity, peripheral and central

sensitization and paradoxical vocal fold movement. Reconceptualizing CRC as a sensory neuropathy and as part of a spectrum of disorders with laryngeal hyper-responsiveness will expand options for treatment and research. Although CRC is a debilitating condition that eludes medical management, there are promising treatments available with speech pathology and neuromodulators. These approaches provide additional options for patients with cough that has failed to respond to medical treatment. Finally, cough can be present in comorbid disease such as cancer, idiopathic pulmonary fibrosis, and chronic obstructive pulmonary disease. These conditions are not typically considered to be CRC. Nevertheless approaches to the assessment and treatment of CRC may have the potential to reduce symptom severity in these conditions.

Questions for future research

- What is the clinical utility of nasendoscopy in chronic refractory cough (CRC)?
- What is the role of laryngeal abnormalities in the pathogenesis of CRC?
- What is the association between cough hypersensitivity syndrome and laryngeal hypersensitivity syndrome?
- Can laryngeal hypersensitivity and its treatment be usefully applied in chronic cough in general and postinfective cough?
- What is the comparative effectiveness of existing and novel therapies in CRC?
- What is the place of combination behavioral and pharmacological approaches in CRC?
- How should we assess and treat chronic cough in comorbid disease?

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