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Investigations and management of chronic cough: update from the European Respiratory Society Chronic Cough Taskforce 2020

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ABSTRACT

Chronic cough affects approximately 10% of general population, is highest amongst people aged 50-60, and is twice as common in women than men. It is described to last 8 weeks or longer in adults and not treated effectively with most over-the-counter medications. This is a debilitating condition with physical, social, and psychological consequences. The purpose of this review is to highlight the key messages from the task force commissioned by The European Respiratory Society on the management of chronic cough. The assessment of chronic cough should include a thorough detailed history and examination to identify potential causes. The impact and severity can be assessed in clinic using questionnaires. Potential causes of the condition vary; ACE inhibitor induced, smoking, asthma, non-asthmatic eosinophilic bronchitis, gastroesophageal reflux disease and upper airways cough syndrome. In many patients, coughing is persistent despite optimum medical therapy of the underlying medical condition and is hence referred to as refractory chronic cough. In some cases, no cause is found and is classified as unexplained chronic cough. If treatment of any underlying disease is unsuccessful at controlling cough, then neuromodulatory treatment such as low dose opioid, gabapentin, pregabalin or speech and language therapy may be considered. There is no licensed treatment for chronic cough, but a new class of treatment targeting the purinergic P2X3 receptor are currently in phase 2 and phase 3 development.
Introduction

Chronic cough is a common condition that globally affects 7-11% of adults, and accounts for a major burden of primary care visits in both developed and developing nations [1, 2]. In adults, it is defined as a cough that lasts for 8 weeks or longer, is twice as common in women and peaks in the 50’s-60’s [3]. Refractory symptoms can be distressing, leading to incontinence, dysphonia and social isolation, with resultant detriment in the quality of life [4]. Chronic cough can be challenging to treat, with most over the counter therapies being ineffective [5, 6]. As a result, a comprehensive approach to the diagnosis and management of chronic cough is critical to optimize care towards this condition with a significant clinical burden. The European Respiratory Society (ERS) recently commissioned a task force on the management of chronic cough and the purpose of this review is to highlight the key messages of the most recent guideline [7].

Causes of Chronic Cough

Chronic cough can occur with respiratory conditions such as asthma, chronic obstructive pulmonary disease, bronchiectasis, interstitial lung disease and occasionally with lung cancer. The most common causes of chronic cough in patients with a normal chest x-ray are medications (specifically, ACE-inhibitors, approximately 15% [8]), asthma, non-asthmatic eosinophilic bronchitis, gastroesophageal reflux disease (GERD), and upper airways cough syndrome (UACS) (Table 1). These conditions, either alone, or in combination, account for a large proportion of chronic cough cases [9]. However, there are large variations amongst clinicians in the prevalence of associated conditions due to the availability of testing, for e.g. sputum induction, 24-hr pH impedance/manometry or the expertise of the consulting specialist [10].
There are age-related differences in the prevalence of certain causes for chronic cough, which usually coincides with age-related distribution of the underlying disease. For example, asthma and UACS are more common in younger adults, compared to chronic obstructive pulmonary disease (COPD) and GERD which are more common in older patients [11]. It is unclear why chronic cough is more prevalent in women, although age-related hormonal changes may contribute but yet to be fully elucidated[12, 13]. Patients who have persistent cough despite guideline-based treatment for the above conditions are classified as having refractory chronic cough (RCC). Patients in whom no clear cause of cough is identified are considered to have unexplained chronic cough (UCC) [14].

**Mechanisms of Cough**

Chronic cough has also been described as “cough hypersensitivity syndrome” as many patients have coughing which is triggered by exposure to low levels of thermal, chemical or mechanical stimulation [15, 16]. Patients often describe sensations of ‘itch’, ‘irritation’ and ‘unpleasantness’ in the throat region or even describe it as ‘something physically stuck on the throat’. Cough is often triggered by changes in temperature, perfumes, aerosols, strong smells, talking, laughing and singing [17, 18]. The concept of cough hypersensitivity syndrome has been endorsed as an overarching syndromic diagnosis and can be found concomitant with any of the other above causes of chronic cough. The aetiological mechanisms for cough hypersensitivity syndrome remain controversial, and both central and peripheral sensitization mechanisms have been suggested [15].

Coughing, like breathing and swallowing, can be under both voluntary and automatic control at the same time, but it is widely accepted that the cough reflex is the archetypal airway defensive
reflex. Numerous studies have used different inhaled stimuli to evoke coughs to study the mechanisms of coughing [3]. The objective of cough challenge studies is to stimulate the vagal afferent nerves (10th cranial nerve) in the larynx and airways which bind onto ligand gated ion channels and g-protein coupled receptors [19]. Upon activation, sodium and calcium ions flow inside the nerve membrane resulting in depolarization. If sufficient depolarization is achieved, an action potential is generated and transmission to the brainstem occurs via voltage gated ion channels. Once the signal is reached at the first order synapse in the nucleus tractus solitarius (NTS) and paratrigeminal nuclei, second order neurons relay the signal to the thalamus, and third order neurons to the primary somatosensory cortex. This is where patients may feel the unpleasant sensation of urge to cough, which if great enough, will evoke coughing. The most common example of cough challenge agents is capsaicin, the active substance found in hot chili peppers, which specifically binds transient receptor potential vanilloid type-1 (TRPV1). Other challenge agents such as citric acid, are likely to activate multiple ion channels including TRPV1, transient receptor potential ankyrin-1 (TRPA1), and acid sensing ion channels (ASICs) [20, 21]. Challenges of different osmolarities have also been used such as water, normal saline, hypertonic saline, and mannitol [22-24].

Cough challenge studies have revealed that patients with RCC have a more sensitive and hyper-responsive cough reflex in comparison with healthy controls. This has been demonstrated by showing that a lower concentration of substance is required to cause 2 coughs (C2) or 5 coughs (C5) [21]. More recently, other studies have shown that a higher maximum evoked cough is reached (Emax), and the dose evoking half the maximum (ED50), is much lower, i.e. the cough dose response curve reaches a higher plateau and is left shifted [25]. These studies lend support to the concept that the peripheral nerves are sensitized in various associated conditions,
particularly asthma, eosinophilic bronchitis, COPD and GERD [21, 25-31]. However, it must be remembered that these cough challenge studies are testing the entire reflex, and hence the role of the central nervous system, in particular, the brainstem and higher cortical centres, are often ignored and poorly understood. There are currently a small number of studies in healthy controls and chronic cough to have investigated the central cortical pathways in chronic cough using functional magnetic resonance imaging (fMRI) [32, 33].

**Key Questions in History**

A detailed history is integral in the evaluation of chronic cough and involves defining the characteristics of the cough as well as associated features which may point to an underlying trigger. The cough history should focus on identifying the common triggers of cough such as GERD, UACS, asthma, occupational and smoking history, as well as red flags such as hemoptysis, weight loss, fevers, dysphonia, and dysphagia. Interestingly, studies have not shown the characteristics and timing of cough, or presence/absence of sputum production to be of diagnostic value (9, 27). Nevertheless, a history of wheeze, dyspnea, allergies, nocturnal cough or cough triggered by exercise or cold air may be suggestive of asthma. In patients with UACS, there may be a history of post-nasal drip, sinusitis, rhinorrhea, nasal congestion and an examination of the posterior pharynx possibly revealing a “cobblestone” appearance. Patients with GERD may experience heartburn, dyspepsia, dysphonia, or hoarseness, often worse when lying down or bending forwards. A productive cough may prompt consideration of other diagnoses including bronchiectasis, chronic bronchitis, eosinophilic bronchitis or pneumonia, keeping in mind the most common causes of chronic cough in this population remain asthma, eosinophilic bronchitis, GERD, UACS, or a combination of the three [34]. In patients with a smoking history, COPD should be considered as a cause of cough; cough frequency is strongly
associated with cigarette consumption [35]. Cough may be dry or productive, although patients with a productive cough are at an increased risk of exacerbations [36]. Congestive heart failure is an uncommon cause of chronic cough but should be considered in the appropriate clinical context [37].

Severity of cough may be assessed by using a visual analog scale, or cough questionnaires such as the Leicester Cough Questionnaire (LCQ) or Cough Specific Quality of Life Questionnaire (CQLQ), and can be a useful tool in tracking a patient’s response to therapy [38, 39].

The most widely recognized drug causing chronic cough are ACE inhibitors which are associated with a dry cough in up to 15% of patients. The cough occurs days to months after initiation with one population study showing a median duration of onset of 156 days (95% confidence interval 85-242 days) [40]. Other drugs reported to cause cough include calcium channel blockers, and fentanyl when administered as an IV bolus. There are also case reports of topiramate and phenytoin causing cough [41]. There was one case series suggesting sitagliptin may cause cough, however, there was insufficient evidence associated with sitagliptin from the large phase 3 randomised controlled studies [42].

Review of systems should include should enquire about symptoms of aspiration (dysphagia, coughing with liquids/solids), GI symptoms for inflammatory bowel disease, thyroid disease, and an autoimmune screen for connective tissue diseases [43]. A comprehensive review of systems may help detect rare causes of cough such as Holmes Adie syndrome [44, 45]. This is a rare condition presenting with anisocoria, tendon areflexia and autonomic dysfunction, and has been described to be associated with a dry chronic cough.

**Investigations**
A systematic approach to the evaluation of chronic cough is recommended, initially focusing on evaluating for and applying guideline-based management of common causes of chronic cough, specifically asthma, non-asthmatic eosinophilic bronchitis, UACS and GERD (Table 2). Empiric treatment for these conditions may be considered in conjunction with work-up depending on clinical suspicion. Investigations should begin with a chest x-ray to exclude any obvious structural cause of lung disease. If the chest x-ray is normal, then a CT scan of the thorax is not recommended. Spirometry should be considered, with post-bronchodilator measurements in the presence of airflow obstruction to evaluate for asthma and COPD. Bronchoprovocation testing methacholine challenge and sputum induction for airway eosinophilia can be considered based on clinical suspicion for asthma, but they are often not available outside of specialist centers. Sputum eosinophilia can help determine a diagnosis of non-asthmatic eosinophilic bronchitis as well [30]. Blood tests are not usually helpful, although the presence of peripheral eosinophilia may support a diagnosis of asthma and initiation of inhaled corticosteroids. Likewise, exhaled nitric oxide is not currently recommended for routine use in the diagnosis of chronic cough. The ERS task force, however, does recognize that this is due to the lack of quality evidence, and that placebo-controlled trials are needed to assess their utility and optimum cut off values.

Bronchoscopy is also not routinely recommended in the evaluation of chronic cough, unless there are red flag signs (weight loss or haemoptysis) or sputum induction for cell count and differential is needed. A bronchoscopy or laryngoscopy may also aid in the assessment of vocal cord dysfunction, muscle tension dysphonia, inducible laryngeal obstruction [46, 47]. If UACS is being considered, sinus imaging and nasopharyngoscopy may aid with diagnosis, but this is not routinely recommended by the ERS taskforce. For GERD, 24-hour pH impedance monitoring, high-resolution manometry, barium swallow, video fluoroscopic evaluation, and endoscopy are
usually reserved after a trial of empiric therapy has failed in the context of high-suspicion of reflux. These tests are invasive and usually difficult to access [48].

In patients with presyncope or syncope secondary to cough, further assessment for arrhythmias or autonomic dysfunction may be warranted. This may include ECG, 48-72-hour Holter monitoring, echocardiogram and tilt-table testing. If all tests remain negative or inconclusive, patients are considered to have unexplained chronic cough.

**Treatment**

The treatment of chronic cough starts with addressing triggers. Offending medications should be stopped, particularly ACE inhibitors. Patients should be counselled on smoking cessation and any unresolved infections and red flag symptoms should be addressed.

*i) Asthma, non-asthmatic eosinophilic bronchitis, and COPD*

In patients with chronic cough and asthma, a short-term trial of inhaled corticosteroid (ICS) for 2-4 weeks should be attempted [49]. It should be noted that inhalers can sometimes trigger cough which may reduce delivery of the medication to the airways [50]. In patients who do not respond to inhaler therapy, a 1-2 week trial of oral glucocorticoids may be attempted [11]. For patients with non-asthmatic chronic cough, ICS has not been shown to reduce the severity of cough compared to placebo and is not recommended [51, 52]. However, it may be reasonable to trial an ICS in a patient with unknown airway hyperresponsiveness and unknown sputum eosinophilia if testing is unavailable. Patients with non-asthmatic eosinophilic bronchitis should be treated in ICS and/or oral glucocorticoids. Leukotriene receptor antagonists have also shown efficacy in cough variant asthma in two small randomized controlled trials and have been recommended in recent guidelines [53-55]. ICS have not been shown to reduce cough frequency in COPD [56],
but long acting muscarinic antagonists (LAMA) such as aclidinium have been shown to reduce cough and breathlessness in moderate COPD on a symptom severity questionnaire [57]. A randomised placebo-controlled study on codeine in COPD also failed to show improvements in objective cough frequency [58].

\emph{ii) Gastro-esophageal reflux disease}

The ERS guidelines do not suggest a trial of anti-acid medications for 2 months (proton pump inhibitors [PPI] and H2 antagonists) unless there is objective evidence of reflux or at least symptoms of acid reflux [7]. Randomized controlled trials of PPI in chronic cough are small and systematic reviews of PPI trials have not shown significant benefit in reducing severity of cough in patients without evidence of GERD [59, 60]. In subgroup analyses, patients with symptoms of reflux or objective evidence of reflux on esophageal pH monitoring may have a modest benefit from PPI therapy. The duration of PPI trial is not well defined however a minimum of 8 weeks is likely required to derive benefit [61]. Guidelines also recommend an anti-reflux diet including elimination of coffee, tea, alcohol, chocolate, mints and citrus products based on expert opinion [11].

\emph{iii) Promotility agents}

There are no RCTs for treatment with metoclopramide or domperidone, in patients with chronic cough. There is very limited evidence of the effect of long-term low dose macrolides in chronic cough and hence they are generally not recommended [7]. In patients with features of chronic bronchitis with COPD, one study showed significant benefit of a 12-week low dose of azithromycin [62]. In two other trials of refractory or unexplained chronic cough, low dose
erythromycin or azithromycin did not provide any significant benefits over placebo on cough frequency, cough severity and quality of life [63, 64].

iv) Upper Airway Cough Syndromes

This broadly encompasses allergic and non-allergic rhinitis (most commonly vasomotor), chronic rhinosinusitis and often presents in patients with a sensation of liquid dripping into the posterior naso- and laryngo-pharynx. This is commonly described as post-nasal drip. There is a lack of strong evidence to guide therapy, however, guidelines recommend a trial of antihistamine and decongestant [65].

v) ACE-inhibitor induced cough

The only effective treatment of ACE-inhibitor induced cough is discontinuation of the ACE-inhibitor. Improvement is usually seen in 1-4 weeks, although some cases report to last up to 6 months [66]. Patients are recommended to switch to angiotensin receptor blockers, which are not associated with increased cough [67].

Refractory or Unexplained Chronic Cough

Patients in whom the above therapies do not result in remission of their chronic cough are considered to have refractory or unexplained chronic cough. In these cases, neuromodulatory treatment may be considered in conjunction with speech and language therapy. Neuromodulatory treatment is currently off-label and includes low-dose morphine, typically 5-10mg twice a day [68]; gabapentin titrated up to a maximum of 300mg three times a day [69]; pregabalin up to 150mg twice a day [70]; and amitriptyline 10mg at night [71]. All four therapies have shown
positive results in improving symptoms in randomized controlled trials; however, these trials have been small (all less than 100 patients) and the doses used in the RCTs were associated with high rates of adverse events such as dizziness, drowsiness, unsteadiness, and fatigue. In clinical practice, most patients are unable to tolerate such high dosage use in RCT, hence it is recommended to start at 100mg TID with gabapentin and 50-75 mg BID and to increase slowly on a weekly basis. Speech and language therapy is a safe and effective add-on or alternate therapy in patients who do not wish to take neuromodulatory medications or for those who develop side effects. However, access to therapists adequately trained in the management of chronic refractory cough can be challenging, and patient adherence is necessary to achieve optimal effect, similar to all other therapies.

**Future Treatments**

Blocking airway nerves with TRPV1 antagonist have failed [72, 73], however, there have been encouraging results from recent studies of a new compound called gefapixant (formerly AF-219), a novel oral purinergic antagonist, which blocks the P2X3 receptor. The initial phase 2a proof of concept study using 600mg twice per day demonstrated an unprecedented 75% reduction in objective cough rates compared with placebo [74]. More recently, after completing a dose finding study [75], the 12-week study showed an approximate 37% reduction in cough rates compared with placebo with 50mg twice per day [76]. The full results of the phase 3 studies are eagerly awaited. Other similar P2X3 antagonists are also in development and it is likely the coming years will see a number of compounds available for managing patients with chronic cough [77-79].

**Conclusions**
Chronic cough is a common trouble symptom which is twice as common in women than men and can severely affect the physical, social and psychological well-being of patients.

Investigations are often all normal, and there are no licensed treatments. Current guideline recommended treatment of any identifiable conditions, but if the cough is refractory or unexplained, then neuromodulatory such as low dose opioids, pregabalin, gabapentin, or speech and language therapy can be trialed. Clinicians are advised to err on the side of caution with the dose and length of treatment with centrally acting neuromodulatory treatment. However, there is potential hope with the ongoing development of novel oral P2X3 antagonists.
References

Table 1: List of Possible Investigations to Perform to Exclude Differential Diagnosis of Chronic Cough. Please note, investigations with an * are those which are not routinely recommended by the ERS Taskforce for evaluating.

<table>
<thead>
<tr>
<th>Differential Diagnosis to exclude</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancy</td>
<td>Chest x-ray</td>
</tr>
<tr>
<td>Parenchymal lung disease</td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>Blood Eosinophil*</td>
</tr>
<tr>
<td></td>
<td>Spirometry with post-bronchodilator measurement if airflow obstruction present</td>
</tr>
<tr>
<td></td>
<td>Bronchoprovocation challenge (methacholine challenge test)</td>
</tr>
<tr>
<td></td>
<td>Exhaled Nitric Oxide*</td>
</tr>
<tr>
<td>Non-asthmatic eosinophilic bronchitis</td>
<td>Induced sputum for cell count and differential*</td>
</tr>
<tr>
<td></td>
<td>(Eosinophil cut off ≥3%)</td>
</tr>
<tr>
<td>Allergy</td>
<td>Skin Prick Testing</td>
</tr>
<tr>
<td>Upper airway cough syndrome</td>
<td>Nasopharyngoscopy*</td>
</tr>
<tr>
<td></td>
<td>Laryngoscopy*</td>
</tr>
<tr>
<td></td>
<td>CT sinuses*</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>24-hour pH impedance monitoring*</td>
</tr>
<tr>
<td></td>
<td>High-resolution manometry*</td>
</tr>
<tr>
<td></td>
<td>Barium swallow*</td>
</tr>
<tr>
<td></td>
<td>Video fluoroscopic evaluation*</td>
</tr>
<tr>
<td></td>
<td>Upper GI endoscopy*</td>
</tr>
<tr>
<td>Interstitial lung disease/Bronchiectasis</td>
<td>High-resolution CT scan*</td>
</tr>
<tr>
<td>Vocal cord dysfunction</td>
<td>Bronchoscopy*</td>
</tr>
<tr>
<td>Central airway lesion</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Summary of Treatments Options

<table>
<thead>
<tr>
<th>Cause</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication related (i.e. ACEi)</td>
<td>Discontinue medication. (If on ACEi can trial ARB).</td>
</tr>
<tr>
<td>Asthma</td>
<td>Inhaled corticosteroid +/- LABA</td>
</tr>
<tr>
<td></td>
<td>Leukotriene Receptor Antagonist</td>
</tr>
<tr>
<td></td>
<td>Systemic glucocorticoids</td>
</tr>
<tr>
<td>COPD</td>
<td>LAMA</td>
</tr>
<tr>
<td>Non-asthmatic eosinophilic bronchitis</td>
<td>Inhaled corticosteroids</td>
</tr>
<tr>
<td></td>
<td>Systemic glucocorticoids</td>
</tr>
<tr>
<td>Gastroesophageal Reflux</td>
<td>Anti-reflux diet</td>
</tr>
<tr>
<td></td>
<td>PPI or H2 antagonist (recommend 8-week trial).</td>
</tr>
<tr>
<td>Nasal disease</td>
<td>Antihistamine</td>
</tr>
<tr>
<td>Condition</td>
<td>Treatment</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Unexplained Chronic Cough</td>
<td>Low dose morphine (5-10mg PO BID)</td>
</tr>
<tr>
<td></td>
<td>Gabapentin (up to 300mg PO TID) – start 100mg TID</td>
</tr>
<tr>
<td></td>
<td>Pregabalin (up to 150mg PO BID) – start 50-75mg BID</td>
</tr>
<tr>
<td></td>
<td>Amitriptyline (10mg PO noche)</td>
</tr>
<tr>
<td></td>
<td>Speech and Language therapy</td>
</tr>
</tbody>
</table>

ACEi (angiotensin converting enzyme inhibitor), ARB (angiotensin receptor blocker), LABA (long acting beta agonist), COPD (chronic obstructive pulmonary disease), LAMA (long acting muscarinic antagonist), PPI (proton pump inhibitor)