Chronic Cough - An Approach to Diagnosis and Management

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ABSTRACT

Cough is a common manifestation of many respiratory conditions and mostly is non-specific on its own as a symptom of underlying disease. Most transient coughing episodes tend to settle within 2-3 weeks. Yet cough can herald more sinister disease such as malignancy or progressive respiratory conditions. In epidemiological surveys, cough persisting more than 8 weeks has been shown to have a significant impact on quality of life and is often difficult to diagnose and treat, taking weeks to months. There is consensus that a logical, evidence based, standardised approach is most likely to lead to an efficient diagnosis and provide the highest chance of effective resolution. This paper describes the current evidence and offers a best practice approach for primary care practitioners and general internists.

Keywords

Chronic cough, upper airway cough syndrome, post-nasal drip, gastro-oesophageal reflux

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Background

Cough is a defensive reflex that protects the airways in response to an inhaled foreign body or noxious and harmful environmental irritants. One of the commonest non-acute conditions presenting to a respiratory physician is a chronic, unexplained cough affecting approximately 12% of the population. It is associated with poor quality of life with psychological, social and physical consequences often leading to feeling fed-up and depressed. Patients typically complain of a dry irritating cough, driven by a strong urge to cough and usually associated with a discomfort located in the throat. [1] The severity and frequency of chronic cough is exceptionally difficult to measure or quantify. Traditionally, there is heterogeneity of chronic cough with the recognition of different types of cough which may be due to a variety of underlying aetiologies and therefore require specific approaches to treatment.

There are various definitions of when a cough requires further evaluation. In primary care, a cough lasting more than 3 weeks usually heralds a chest X-ray, a full blood count and if available, a spirometry. Provided there are no warning signs such as haemoptysis, weight loss or chest pain, most patients may receive a trial with an antibiotic, a bronchodilator, a

short course of inhaled corticosteroids and sometimes a proton-pump inhibitor, before a specialist referral is warranted.

In some cases, investigations may reveal an 'expected cause of cough' such as asthma, gastro-oesophageal reflux, post-nasal drip or rhino-sinusitis but in such cases cough remains refractory to treatment. The American College of Chest Physicians in 2016, published results of a systematic review and guidance where any cough lasting more than 8 weeks without an identifiable cause from systematic investigations was defined by consensus, as '*Unexplained Chronic Cough*' [2].

Definition

Acute Cough (<3w)
Sub-acute cough (3-8w)
Chronic cough (>8w)

In population studies the most common cause of acute cough (< 3 weeks) were respiratory infections, (viral), exacerbations of asthma, chronic obstructive pulmonary disease (COPD) and pneumonia. Subacute cough (duration, 3-8 weeks) was most commonly associated with postinfectious cough, exacerbation of underlying diseases such as asthma, COPD, and upper airway cough syndrome (UACS). For chronic cough (> 8 weeks), common causes were UACS from rhino-sinus conditions, asthma, gastroesophageal reflux disease (GORD), non-asthmatic eosinophilic bronchitis, any combinations of these four conditions, and, less commonly, a variety of miscellaneous conditions including atopic cough. [3]

Aetiology

There are a variety of aetiologies including (i) environmental causes such as cigarette smoke, air pollution (especially particulates), (ii) common respiratory conditions such as asthma, bronchitis and COPD, where the cough is typically related to the pathophysiology of the disease, (eg excessive airway mucus and inhalation of irritants), (iii) other causes include eosinophilic bronchitis, interstitial lung diseases, bronchiectasis, (iv) inadvertent side-effects of drugs (i.e. angiotensin-converting enzyme inhibitors) and (v) extra-pulmonary diseases, such as gastro-oesophageal reflux disease (GORD) and post-nasal drip secondary to rhinosinusitis. Furthermore, up to a quarter of patients may have multiple aetiologies combined.

As cough is ubiquitous in any population presenting to primary care or to general internists, it is most efficacious if clinicians work systematically towards a clear diagnosis, considering common before rare illnesses. In the past three decades, the diagnostic triad of asthma, GORD or rhinosinusitis in any combination has been suggested to be the likely cause of chronic cough. However, the vast majority of patients with these common conditions do not complain of persistent coughing or have features suggestive of cough hypersensitivity. Treatment of these conditions in patients with chronic cough may improve cough but rarely stops it completely. In some patients, however no clear cause can be identified, leading to the diagnosis of idiopathic cough.

Cough Hypersensitivity

Chronic cough is often associated with an increased response to tussive agents such as capsaicin, a phenomenon identified as cough hypersensitivity. Plastic changes in intrinsic and synaptic excitability in the brainstem, spine, or airway nerves can enhance the cough reflex, and can persist even after resolution of the initiating cough event. Structural and inflammatory airway mucosal changes in non-asthmatic chronic cough could represent the cause or the traumatic response to repetitive coughing. [4]

Recent unravelling of the neurophysiology of cough, suggests that it is likely that neuronal dysfunction may be the primary cause of chronic cough. Indeed, evidence for such has been demonstrated by heightened cough responses to inhaled capsaicin in patients with chronic cough and asthma. In the presence of airway hyper-responsiveness, cough can be triggered by endogenous factors (asthma, GORD, post-nasal drip, even speaking and laughing) or exogenous factors (eg cold air, passive smoking, deodorants etc).

Neurophysiology

Activated sensory airway nerves transmit information via the vagus nerve to first synapse in the brainstem, which rapidly initiates the motor cough response [1]. The cough reflex is thought to involve two main subtypes of sensory vagal afferent nerves. The first subtype is **c-fibres**; these form networks of unmyelinated nerves throughout the airways and are characteristically sensitive to capsaicin (chilli pepper extract) through activation of the transient receptor potential vanilloid type 1 (TRPV1) receptor and other irritant chemicals. They can also respond to other stimuli such as heat, acidity and inflammatory mediators. The second type, **myelinated sub-epithelial Aδ fibres**, are found in the proximal airways and respond to mechanical stimuli, osmolarity and acidity but do not typically express TRPV1, and are normally insensitive to capsaicin and inflammatory mediators. The morphology of these airway nerves has been delineated in human airway tissue and shows similarity to that seen in animal models (Fig 1).[5]

The transient receptor potential (TRP) ion channels are found abundantly in the airways, present in primary airway sensory neurons, and also in airway smooth muscle and epithelial cells. They have important functions in airway chemo-sensation and reflex control regarding temperature, osmolarity and oxidant stress. Reactive oxygen species that are induced by exposure to air pollutants can activate TRPV1 and TRPA1 to induce cough and could underlie air pollutant-induced cough. Increased expression of TRPV1 ion channels has been reported in airway epithelial nerves of patients with chronic cough.

P2X3 receptor antagonist, AF-219 ATP is known to activate and sensitize signal transmission at sensory sites including primary afferent neurons such as airway vagal afferent nerves via its P2X and P2Y receptors and P2X3-containing trimers. P2X3 antagonists have been shown to be active in many inflammatory and visceral pain models, by inhibiting inappropriate chronic signals and decreasing peripheral and central hypersensitivity.

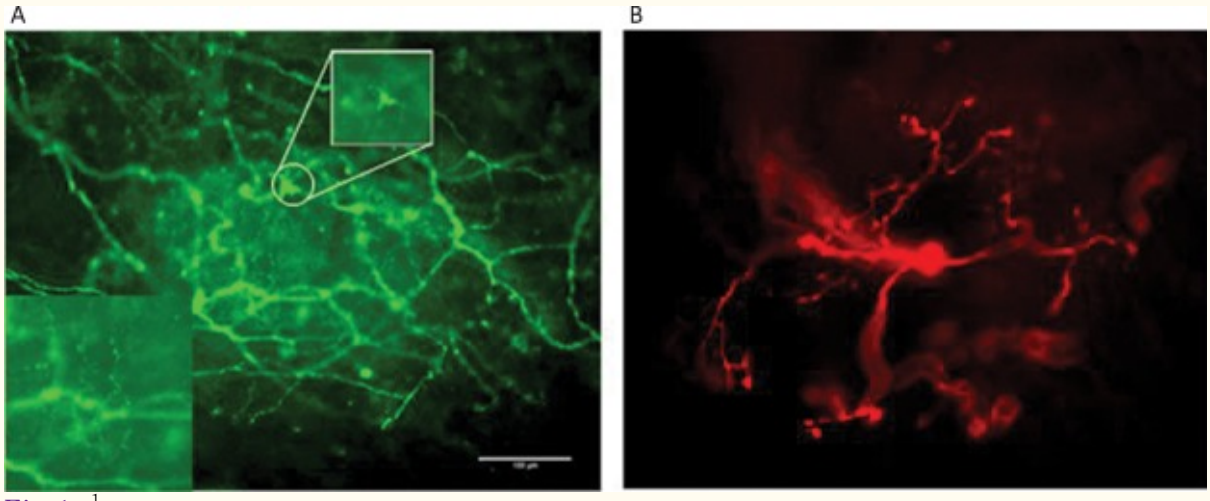

Fig 1. [1]

Structure of human airway nerves. A – thin unmyelinated c-fibres located near the epithelial membrane; B – sub-epithelial myelinated Aδ fibres. Reprinted with permission of the American Thoracic Society. Copyright © 2016 American Thoracic Society.

Stimulating these airway nerves generates action potentials that synapse in the nucleus tractus solitarius (NTS) and paratrigeminal nucleus of the brainstem. These afferent nerves then activate complex neural networks, projecting to cortical and sub-cortical areas responsible for sensations of airway irritation and the urge to cough and ultimately, if the stimulus is sufficient, results in coughing via activation of spinal motor nerves to the diaphragm, intercostal muscles and larynx (Fig 2). Importantly, coughing can also be initiated voluntarily without any peripheral stimulus or precipitating sensations, and in some cases voluntarily supressed.[6] Thus, the potential drivers of excessive cough could originate either in the peripheral nerves or central nervous system, including the brainstem.

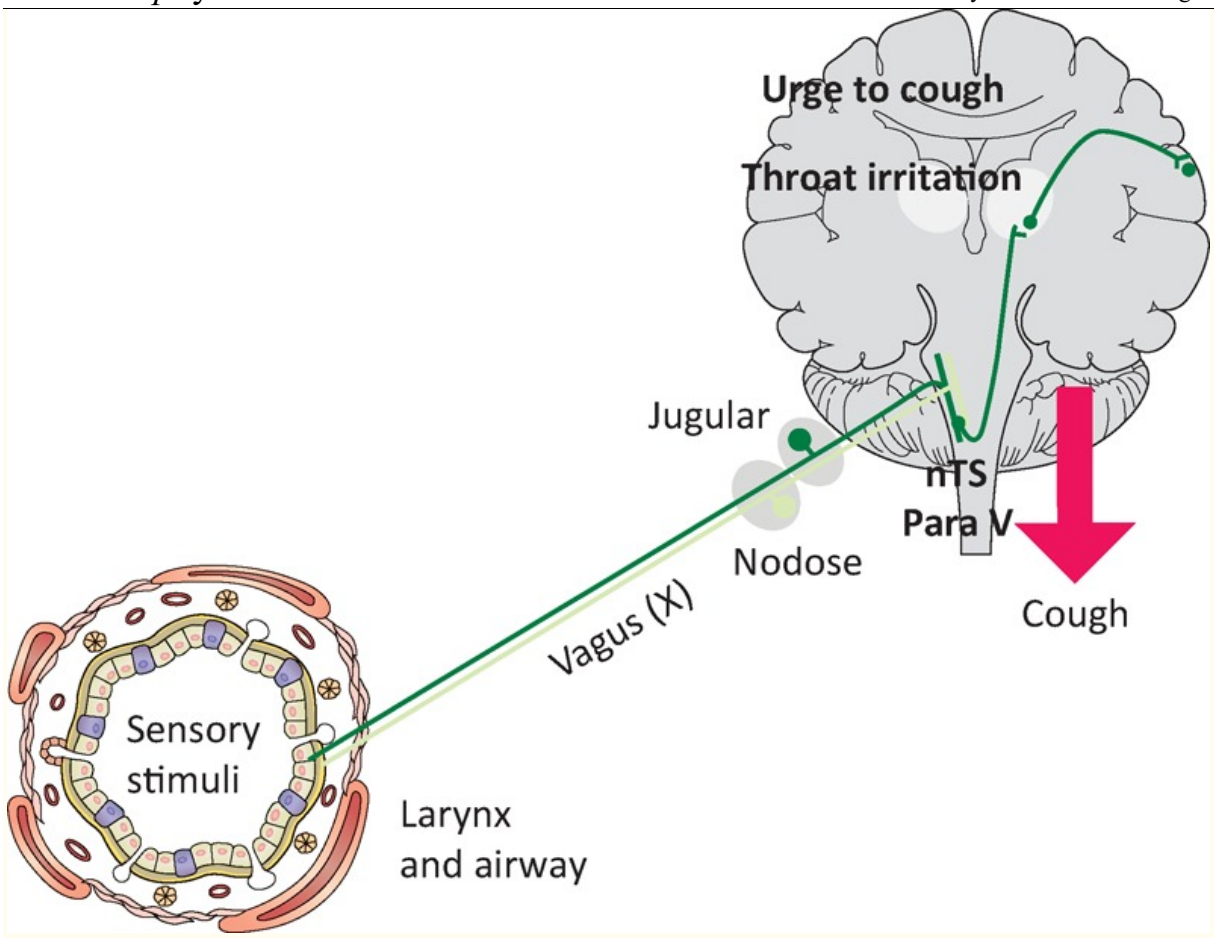

Fig 2. [1]

Schematic diagram representing the cough reflex. Vagal afferents transmit stimuli from the airways to the nucleus tractus solitarius (nTS) and paratrigeminal nucleus (Para V) in the brainstem. Neuronal signals are then transmitted to the somatosensory cortex via the thalamus causing throat irritation and urge to cough. These sensations, if great enough, lead to cough via activation of spinal motor neurons.

Hypersensitive vs hyper-responsive

Recent consensus suggests that '*Cough Hypersensitivity Syndrome*' (CHS) be used to describe patients with chronic cough.[7] However, evidence from experimentally evoked cough suggests that the neuronal pathways exhibit hyper-responsiveness rather than hypersensitivity. Patients complain of an inability to stop coughing and quality of life is most severely impacted by the length and severity of coughing bouts.

The concept of CHS is that there is a stage of peripheral sensitisation induced by inflammatory factors setting up the scene for a central component that can be visualised by functional magnetic resonance imaging (fMRI).[8] One of the potential mechanisms underlying CHS is that this may be triggered by an inflammatory process that impacts on the nerve endings that increases the sensitivity of these nerves leading to peripheral sensitisation. There is already some evidence that in idiopathic cough, there is inflammation measured in terms of inflammatory cells such as mast cells and of

inflammatory cytokines in the upper and lower airways. In addition, in conditions where chronic cough could be a predominant symptom such as asthma, COPD and pulmonary fibrosis, there is a characteristic inflammatory changes for that disease that could interact with cough sensory nerves.

Measuring Cough Hypersensitivity

Measurement of cough hypersensitivity with citric acid or capsaicin indicate that patients with chronic cough usually demonstrate an excessive cough response to inhaled tussigens, with correlation obtained between the level of the neuroinflammatory mediators and the degree of the cough tussive response, supporting the value of cough provocation tests in the diagnosis of CHS. The larynx is an area where the cough hypersensitivity may originate, manifest as inappropriate vocal cord adduction (associated with difficulty in breathing and dyspnoea), globus pharyngeus, impaired phonation (associated with paradoxical vocal fold motion) and muscle tension. This hypersensitivity has been described in athletes who develop cough and dyspnoea during usually with intense exercise.

Imaging of the brain using fMRI physiological sensory circuits, Mazzone et al have shown that sensory hypersensitivity is represented by both an enhanced activity of the brain regions encoding sensation as well as abnormal responses in brain circuits that usually have descending control on primary afferent processing [8]. Patients with chronic cough demonstrating CHS, had increased activity in the midbrain regions that are involved in nociceptive control.

Cough associated with respiratory conditions

Cough is often dissociated from other symptoms usually attributable to asthma such as wheeze and shortness of breath. In COPD, cough is reported in 70% of patients, and many consider it to be extremely severe contributing to impaired quality of life. Current smokers with COPD tend to have the highest cough rates, almost double that of COPD + ex-smokers or healthy smokers.

Investigations

Assessment of cough may include a simple visual analogue scale (VAS), cough symptom score, quality of life questionnaire, cough frequency monitoring, and cough provocation test. These tests are used to monitor disease status and treatment efficacy.

In the **VAS scoring system**, patients mark a point on a straight line corresponding to their perception of the severity of cough. The score ranges from 0–10 cm (0–100 mm), with 0 representing minimal severity and 10 representing extreme severity. Compared with the cough symptoms score, the intervals between grades with the VAS are smaller, which is helpful for longitudinal comparison before and after treatment.

The Coughing Score is a quantitative scoring system used to assess the severity of cough and efficacy of treatment. Daytime and night-time scoring is done, however it may be difficult to discriminate between grades [9]. Appreciation of the impact of cough on health-related quality of life has led to the development of three validated, cough-specific, health-related quality-of-life questionnaires that assess cough severity: Leicester Cough Questionnaire (LCQ)[10], Cough-specific Quality of Life Questionnaire (CQLQ)[11], and Chronic Cough Impact Questionnaire (CCIQ)[12]. These tools capture additional information not measured with objective tools and can be used to assess

therapy. They should be used in conjunction with other cough severity measures such as cough frequency monitors to obtain a more complete assessment of cough severity.[13] Investigation for causes of chronic cough are commonly chest radiography, bronchial hyperresponsiveness (BHR) and sinus imaging. Specialized investigations of GORD by using oesophageal pH probe monitoring, a chest CT scan or induced sputum (for eosinophilic bronchitis) are uncommon. Fractional exhaled nitric oxide (FeNO) and maximum mid-expiratory flow (MMEF) might have value as negative parameters for differentiating cough variant asthma (CVA) from chronic cough. [14]

Differential Diagnosis

The common causes of chronic cough are as follows:

- Cough variant asthma (46%)
- Upper airway cough syndrome/postnasal drip syndrome (32%)
- Eosinophilic bronchitis (9%
- Gastroesophageal reflux-related chronic cough (9%)
- Postinfectious cough (6%)
- Angiotensin-converting enzyme inhibitors-induced cough (5%)

In addition to respiratory disease, cough may be a manifestation of cardiovascular, autonomic or neurological disease.

Chronic cough is difficult to manage, and many patients self-medicate with 'over the counter' cough therapies despite lack of evidence supporting their efficacy. A survey of of chronic cough in general practice estimated that 87% of patients could have been managed solely in primary care using a simple guide and that most cases of chronic cough referred to secondary care could be managed with a simple systematic approach. This indicates that efforts need to be made to improve the management of such patients in general practice.

Stage I

Most patients who develop a cough will see their general practitioner first, who will exclude any obvious cause of cough and will most likely order a chest radiograph to exclude any gross pathology in the airways. Asthma and GORD are usually considered and may be excluded with a trial of inhaled corticosteroid therapy and proton pump inhibitor.

Stage II

The next stage is a referral to the hospital respiratory clinic, usually to a chest specialist, although referrals can be made to an otorhinolaryngologist for exclusion of upper airway nasal/laryngeal causes, or to a gastroenterology specialist for exclusion of GORD. Under hospital care, certain additional investigations are usually organised including a lung function test, bronchial hyperresponsiveness, a CT scan of sinuses and thorax and a bronchoscopy may be available.

Stage III

When all known causes of chronic cough have been excluded, and cough is still persistent, the skills of a highly specialised chronic cough may be required. These clinics should provide a multidisciplinary approach to diagnosis and management, and should have access to various facilities for assessment of oesophageal function, nasal and laryngeal hypersensitivity measurements, sleep studies, computed tomography of upper airways and lungs, and have access to otorhinolaryngology facilities such as the visualisation and assessment of the postnasal space and larynx and nasal passages. A speech and language

therapist should be part of the team. An important role for specialist cough centres is in educating and training primary and secondary care in the management of chronic cough.

Management of Chronic Cough

Non-pharmacological Measures

This non-pharmacological approach consists of education, cough suppression strategies, vocal hygiene training, and psychoeducational counselling. This has the goal of improving voluntary control over the cough, by teaching patients to identify the causes and sensations that precipitate the cough and to replace the cough response with another response such as a breathing or swallowing exercise, and to alter behaviour that contribute to laryngeal irritation. This method likely acts on both peripheral and central parts of the cough pathway.

(a) Cough control measures such as **Buteyko breathing** control techniques [14] have been shown to improve quality of life and inhaled corticosteroid use by reducing the perception of breathlessness. Although the 'physiology' suggested is of reducing shear stress that leads to mast cell activation [15], several studies have failed to show any change in physiological measures of asthma. [16]

(b) **Yoga- Tai Chi** [17 18] have been found to be more effective than usual care in COPD with clinically meaningful improvements in 6-min walk distance, lung function and health-related quality of life. They have also been found to be comparable to pulmonary rehabilitation interventions in improving breathing control, reduced perception of breathlessness and cough. Mindfulness techniques have been shown to improve perceptions of breathlessness and symptoms in patients with chronic lung disease and may have a role in the management of cough. [19]

(c) **Behavioural - Speech therapy** may be underutilized in practice and could lead to improvement of otherwise recalcitrant cough.[20] A multi-dimensional speech pathology treatment programme (used to treat hyper-functional voice disorders and paradoxical vocal fold movement) included education, vocal hygiene training, cough suppression strategies and psychoeducational counselling. Participants demonstrated a significant reduction in cough, breathing, voice and upper airway symptoms following intervention. [21 22]. However the availability of specialist behavioural-speech therapy services is usually restricted to tertiary units and the usual waiting time is over 2 years in the UK.

Pharmacological Measures

(a) *Macrolide antibiotic* treatment has beneficial effects on lung function in non-asthmatic, productive, chronic cough patients with normal chest X-ray findings. The improvement of chronic rhinosinusitis may have some role in the lung condition.[23] Patients demonstrated neutrophilic or pauci-granulocytic airway inflammation, whereas subjects with eosinophilic airways inflammation do not appear to respond symptomatically.[24] The agreed consensus suggests at least a prolonged therapy of up to 3 months to assess benefit.

(b) *Proton-pump inhibitors* (PPI) – PPIs are ineffective as single agents in the absence of significant acid GORD. A cohort of GORD patients may present with more proximal reflux, non-acid reflux, and gas reflux, and get better efficacy with neuromodulators (gabapentin or baclofen) used as an add-on therapy with a proton-pump inhibitor. [25] Although gabapentin and morphine exhibit positive

effects on cough-related quality of life, only gabapentin is currently supported as a treatment recommendation.

(c) *Inhaled corticosteroids* (ICS) were found to be ineffective for chronic cough except in the presence of asthma or eosinophilic bronchitis. [2]

(d) *Neuromodulatory therapies* are believed to act on the enhanced neural sensitization that is a key component of unexplained cough. Each of the centrally acting neuromodulators (amitriptyline, pregabalin and gabapentin) have been shown to have positive effects on cough-specific quality of life. Adverse effects can be significant and limit the maximum tolerable dose of these agents. Recommendations suggest that reassessment of the risk-benefit profile be performed at 6 months.

(e) *Codeine & Morphine* could be used when all other therapeutic options have failed to improve cough and there was close follow-up at 1 week and then monthly.

New targets for chronic cough

(i) *Transient Receptor Potential ion channel antagonists* - There are TRPV1 and TRPA1 channel blockers in development but it is currently unclear whether they are of benefit in management of chronic cough.

(ii) *AF-219 is a P2X3 receptor antagonist* - holds promise as a potentially new neuromodulator drug for chronic idiopathic cough, and also for chronic cough associated with chronic respiratory diseases such as asthma, COPD and pulmonary fibrosis. [26] However all patients had taste disturbances (hypogeusia or dysgeusia)

(iii) *Central neuromodulators* - Central targets that selectively disrupt specific encoding mechanisms of cough may present new therapeutic approaches such as the acid-sensing Ion channels (ASIC). N-methyl-d-aspartate (NMDA) receptors are involved in these acid-evoked reflexes. Memantine, an NMDA channel blocker, has been shown to suppress citric-acid induced cough. [8]

Conclusion

Cough is a common presentation to primary care and to internists and may have a significant impact on quality of life and often lead to social and psychological consequences. Once, acute or sinister causes of cough have been excluded in primary or secondary care, a systematic approach is warranted. Even in chronic cough (>8 weeks), the triad of cough variant asthma, rhinosinusitis – postnasal drip and GORD may be the cause of majority of presentations and often in combination. Therefore, a combined therapeutic approach with objective cough intensity and impact measures (Leicester Cough Questionnaire + cough counters) are beneficial. If these commoner conditions have been excluded, a specialist multi-disciplinary approach is recommended. This will involve specialised investigations, provocation testing, and a comprehensive approach with education, physiotherapy, cough suppression and neuro-modulators. Careful and close monitoring of the benefits of this treatment is essential with objective measures and psychological support may also be needed. There are newer agents being tested approaching the cough reflex from a neuro-biology and inflammatory aspects.

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Approach to Management

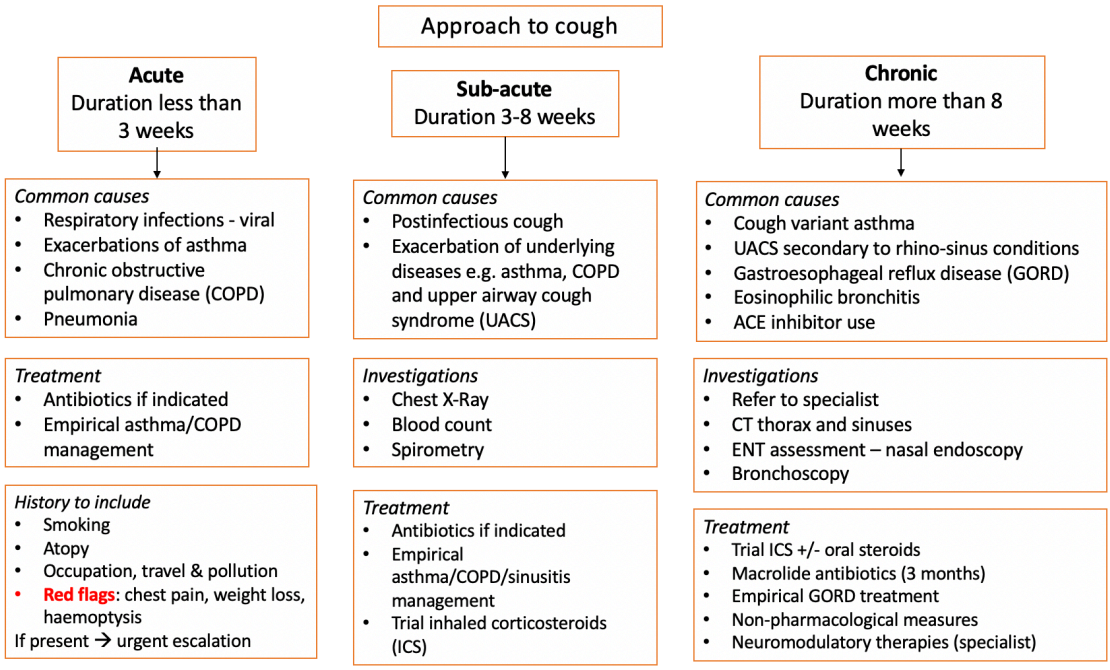

Figure 3: schematic showing approach to cough in primary care