Acute and Chronic Cough

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Alyn H. Morice and Helen Fowles

Introduction

A cough is recognised by its characteristic sound, produced by a forced expulsive manoeuvre against a closed glottis. The cough reflex is a protective mechanism in humans and other vertebrates, aimed at protecting the airway from foreign matter and clearing the mucus produced by the airways. It is normal to cough, on average, about 20 times a day. When coughing becomes more frequent than this, patients may seek treatment or advice from their healthcare provider, who is frequently unable to provide any evidence-based management.

Despite sub-specialisation within the respiratory field, chronic cough is one of the most common presentations to general respiratory clinics. This suggests that whilst the pathophysiology and treatment of chronic cough is often poorly understood, the respiratory practitioner needs to have a reliable protocol for managing such patients.

Whilst research in the area of cough and its treatment has greatly increased over the last few decades, there is still a paucity of data from clinical trials. As a result, much of the guidance on the management of chronic cough is dated, based on consensus opinion, and sometimes controversial.

A. H. Morice (✉)
Respiratory Research Group, Hull York Medical School/University of Hull, Castle Hill Hospital, Cottingham, UK
e-mail: A.H.Morice@hull.ac.uk

H. Fowles
Respiratory Research Group, Hull York Medical School, Castle Hill Hospital, Cottingham, UK

Acute Cough

Epidemiology

Acute cough is arbitrarily defined as a cough which lasts less than 2 weeks. It is the commonest new symptom with which patients present to their GP, accounting for approximately 12 million presentations a year in the UK. Clearly this represents only a fraction of the morbidity caused by this condition, since many patients either self-medicate with over-the-counter (OTC) products or use home remedies. The overwhelming majority of cases of an acute cough are due to viral upper respiratory tract infection caused by a myriad of highly adapted pathogens. It is normally benign and self-limiting, but if it lasts longer than 3 weeks it is usually termed "post-viral" cough. In this phase of the illness the afferent sensory nerves remain hypersensitive even though the infection has disappeared. Patients are exquisitely sensitive to external stimuli such as a change in atmosphere, smoke, or strong smells. Why the hypersensitivity persists in some patients is unknown, but may be due to persistent low-grade inflammation.

Upper respiratory tract infections (URTI) are commoner in young children than adults, with

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about five episodes per year, as opposed to one to two episodes in the normal adult population. About 50% of URTI have cough as a symptom, and in the evolution of the illness, cough follows the coryzal symptoms by about 2 days.

Nearly a billion pounds is spent annually in the UK on OTC remedies for acute cough. However, as an estimate of the impact on the economy, this does not include loss of productivity and healthcare utilisation [1].

Clinical Assessment

In acute cough, advice regarding preventing spread of viral infection is recommended and may include avoidance of social contact. Since viral transmission is both by the aerosol route and by hand, handwashing should be encouraged. Simple home remedies such as honey and lemon are sufficient and are thought to have a demulcent effect, reducing cough reflex sensitivity through an as-yet undefined mechanism.

Occasionally acute cough is part of the presentation of a serious condition. Symptoms which indicate the need for further investigation such as a chest radiograph are haemoptysis, breathlessness, fever, chest pain, and weight loss. Pneumonia often presents with cough as a predominant symptom and should be suspected on examination of the chest by localised findings of dullness on percussion, bronchial breathing, and crackles [1].

Many adverts for OTC antitussive medication focus on whether a patient's cough is dry and tickly or "mucous" and chesty. Recently this classification, beloved of pharmacists, has been called into question, and indeed the classification of medicines into expectorants, antitussives and mucolytics is now regarded by many as obsolete. Clinically, in acute cough, there is little evidence that this should alter management.

Treatment

Benefit from OTC medications in acute cough has been questioned. Simple remedies provide much of the antitussive efficacy seen with OTC cough syrups. Over-the-counter medications are often targeted at control of other symptoms of upper respiratory tract infections and may thus contain several active ingredients [1].

The evidence for dextromethorphan as an antitussive is probably the strongest. Dextromethorphan, although derived from opiates, has few, if any, characteristic opiate effects and is thus non-sedating. Recommended doses may be sub-optimal to suppress cough efficiently, and concern exists over its recreational use as a hallucinogen. It is estimated that 60 mg once daily provides additional cough suppressant activity of about 15% over the demulcent effect of the linctus. A number of currently licensed OTC medications in the UK contain dextromethorphan.

When inhaled, menthol has been found to produce a short-lived suppression of cough. This may be of benefit acutely, when administered via menthol crystals dissolved in steam, although many OTC linctuses also contain this as an active ingredient. Recent work has suggested that the antitussive activity is from the vapour acting on nasal afferents rather than within the airways.

First-generation antihistamines such as chlorpheniramine suppress cough but can also cause drowsiness. They may be suitable for a nocturnal cough. Until recently there was no evidence to support the use of second-generation antihistamines in the treatment of acute cough. However, a recent randomised, controlled trial demonstrated significant reduction in cough severity and a more rapid resolution of symptoms using a preparation containing diphenhydramine.

Codeine and pholcodine are not recommended in the treatment of acute cough. Their cough suppression effect is no greater than that of morphine, for which they are pro-drugs. A particular problem is their variable metabolism within the liver, giving no effect in some patients, whereas others have a high degree of sedation. Following deaths in children, the regulatory authorities have banned their sale for use in children under age 12. There is no evidence that antibiotics or steroids are effective in acute cough, and their prescription should be avoided [1].

Chronic Cough

A chronic cough is usually defined as a cough that persists for more than 8 weeks. This is, however, an arbitrary definition, which whilst agreed in both the American and European guidelines, does vary somewhat in cough research literature. Most cases of chronic cough referred to secondary care in the UK have persisted for much longer than 8 weeks [1–3].

Epidemiology

The prevalence of chronic cough is difficult to estimate, and suggested figures vary from 3% to 40%. This wide range probably reflects the variation in the specific question asked in different prevalence studies. A recent comprehensive literature review of 90 studies found the overall global prevalence of chronic cough to be 9.6%. The most common time definition used was greater than 3 months, rather than the guideline [1] stated time of more than 8 weeks. There were regional differences in chronic cough, with prevalence being higher in Australasia, Europe, and America, and lower in Asia and Africa. The authors speculate that this may be due to environmental factors or comorbidities, such as obesity, but recognise that the majority of the studies considered were carried out in Europe [4].

Chronic cough seems to be twice as common in women as men, and more prevalent in postmenopausal women. Cough frequency is also higher in female healthy volunteers and respiratory patients. Women have been shown to have increased sensitivity of their cough reflex, and functional MRI studies suggest that their "sensory cough centre" is more pronounced [5].

Tobacco smokers have a higher prevalence of chronic cough than non-smokers, and this effect is dose-related. Smokers, however, seem to be less likely to present to healthcare providers complaining of cough, which may be due to a cultural acceptance that smoking causes cough. Interestingly, nicotine delivered either by cigarette or by e-cigarette has been shown to suppress the cough reflex, and smokers have a lower cough sensitivity than normal subjects. Smoking cessation removes this inhibition and explains the frequent observation of patients complaining of increased cough in the month or two after quitting.

Obesity has been shown to be a risk factor for cough, and the rising prevalence of obesity in the United States and Europe may account for the increased prevalence in these areas. With rising levels of obesity in the United Kingdom, chronic cough is predicted to become an even greater cause of morbidity.

Other risk factors for chronic cough include an underlying diagnosis of asthma, living in an area with higher particulate matter and pollution, symptoms of gastro-oesophageal reflux, and irritable bowel syndrome.

The Cough Reflex

Like any other reflex in the body, the cough reflex is made up of an afferent arc (the vagus nerve) and an efferent arc—the nerves supplying the inspiratory and expiratory respiratory muscles (Fig. 5.1).

The nerves that appear to be implicated in the afferent limb of the cough reflex are myelinated A-delta fibres (sometimes also referred to as rapidly activated receptors or RARs); and myelinated C-fibres of the vagus nerve. The involvement of these nerves in cough is better established in animals than in humans, although recent studies suggest that similar entities do exist in humans [6, 7].

The receptors involved in signalling at these afferent nerve endings are of interest as targets for therapies for cough. The TRPV1 receptors were the first to be described as potential "cough receptors". They respond to heat and irritant substances such as capsaicin and acids. TRPV1 receptors form ion channels which respond to external stimuli and open to cause depolarisation of the cell they are located on.

Inhalation of capsaicin provokes a reliable cough response, which has been utilised experimentally as a cough challenge. Another

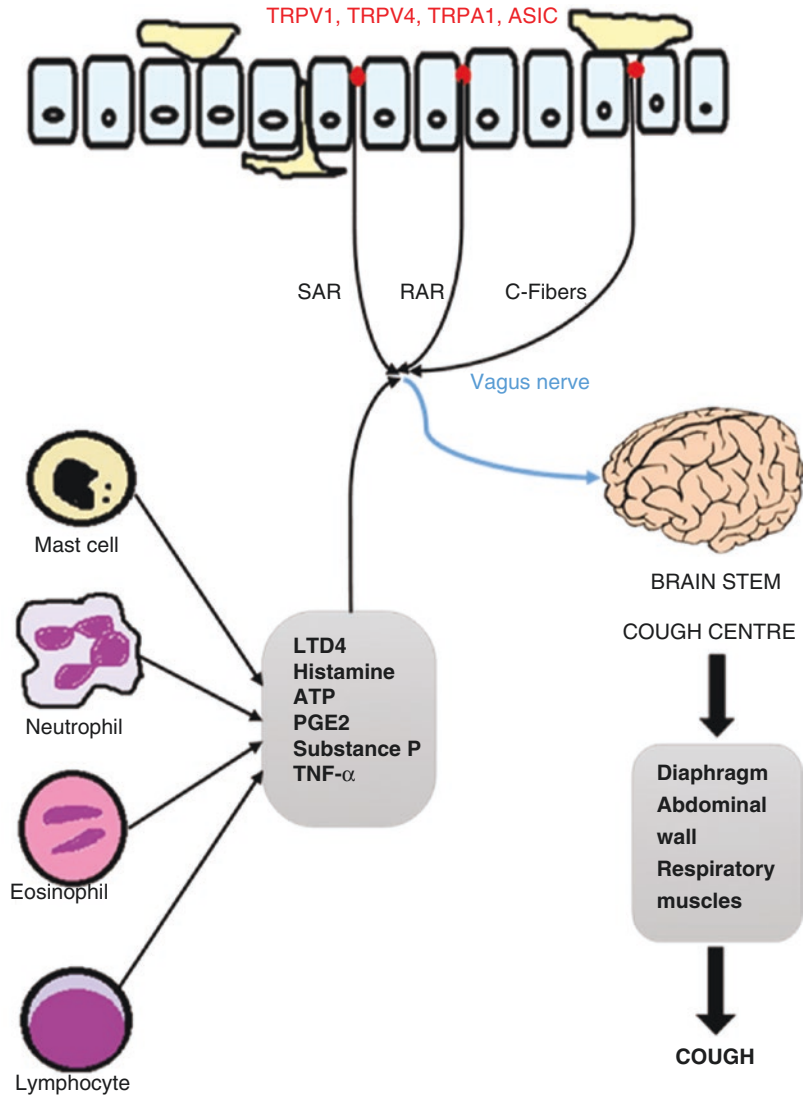

Fig. 5.1 Sensory receptors and inflammatory pathways in chronic cough. Stimulation of sensory pathways, including rapidly adapting receptors (RARs), C-fibres, and slowly adapting stretch receptors (SARs), and cough receptors TRPV1, TRPV4, TRPA1, ASIC, signal via the vagus nerve to the cough centre in the medulla of the brain. Efferent signals are then transmitted to inspiratory and expiratory muscles that mediate cough. Factors that sensitise cough receptors and lead to cough hypersensitivity are shown. *LTD4* leukotriene D4, *ATP* adenosine triphosphate, *PGE2* prostaglandin E2, *TNF* tumour necrosis factor, *TRPV* transient receptor potential vanilloid, *TRPA* transient receptor potential ankyrin, *ASIC* acid sensing ion channel (by kind permission of Mahboobeh H. Sadeghi)

commonly used cough challenge substance is citric acid. Whilst TRPV1 seems to respond to citric acid, there also seems to be a cough response to citric acid even when TRPV1 is blocked, suggesting the presence of other acid-sensing channels.

Experimentation *in vitro* and *in vivo* in humans and guinea pigs has shown that the TRPA1 receptors are involved in the cough reflex and that TRPA1 agonists stimulate vagal nerves; indeed a wide variety of substances are known to stimulate TRPA1 receptors, including the aromatic compounds contained in perfumes, oxidising agents such as bleach, and even tear gas. The TRPA1 agonist cinnamaldehyde provokes a cough response in healthy volunteers and appears to do so independently of other cough challenge stimuli. The many other substances which stimulate TRPA1 receptors *in vitro* have yet to be studied in man. These include a number of substances that patients commonly describe as provoking their cough, such as smoke, perfumes, and other strong smells, indicating that TRPA1 may be the main sensory receptor involved in the cough reflex and its hypersensitivity.

TRPM8 receptors respond to cold temperatures and menthol, and have been implicated in the cough response, perhaps explaining the antitussive effects of menthol. All of the above-

mentioned TRP receptors are also sensitive to change in temperature. The archetypal TRPV1 is a "hot" receptor, explaining why capsaicin-containing chili peppers taste hot and why patients frequently complain of their cough being precipitated by a change in ambient temperature.

Purinergic receptors which respond to adenosine triphosphate (ATP) have more recently become implicated in the physiology of cough, and inhalation of ATP induces cough in healthy volunteers and chronic cough patients.

There are many other receptors which appear to be implicated in the cough response, including voltage-gated sodium channels, acid-sensing receptors, and other TRP classes such as TRPV4.

Whilst coughing is often unavoidable when certain stimuli are introduced, the cough reflex in humans is under a considerable degree of voluntary control. Simply instructing patients with an acute cough not to cough can reduce their coughing levels. This cortical influence leads to a high placebo effect in antitussive trials, making study of antitussives difficult. In addition, it means that some therapies which show good effect in animal studies show very little effect in human trials. It would be incorrect, however, to suggest that chronic cough is "all in the mind," Psychogenic cough (a form of Tourette's syndrome) is very rare in adults.

Whilst chronic cough is a condition often referred to the respiratory physician, it is worth remembering that cough is often caused by, or associated with, pathology throughout the vagal nerve radiation, such as oesophageal dysfunction and irritable bowel syndrome.

Disease Patterns and Subsets

Key to an understanding of both acute and chronic cough is the concept of cough hypersensitivity. Objective testing in a wide range of cough syndromes has demonstrated increased sensitivity when the aforementioned receptors are challenged by inhalation of protussive agents. Thus virtually all patients with excessive cough are provoked by minimal stimulation, which in the normal subject would not lead to the urge to cough. It is clear that this hypersensitivity does not arise purely from the upregulation of cough receptors, since specific drugs blocking these receptors have no important effect in clinical cough. Recently, mediators such as ATP have been suggested to "irritate" the afferent nerves, leading to a syndrome of cough hypersensitivity akin to that of neuropathic pain.

The concept of cough hypersensitivity syndrome helps to explain why some patients with other respiratory conditions present with a cough which is resistant to therapies for that condition. The cough thus represents a separate disease of cough hypersensitivity, which is associated with, rather than directly caused by, for example, asthma.

Patients who are referred to specialist cough clinics with persistent cough are typically middle-aged female non-smokers who have no apparent underlying respiratory disease. In these cases, traditionally the causes of cough considered have been gastro-oesophageal reflux disease (GORD), cough variant asthma, and postnasal drip. However, more recently Cough Hypersensitivity Syndrome (CHS) has been agreed as the unifying concept [8].

Reflux

Gastro-oesophageal reflux disease (GORD) is a widely accepted cause of chronic cough. It accounts for between 5% and 41% of chronic cough. This wide variation in reported incidence is probably due to the lack of recognition of its existence as a cause of cough in non-specialist clinics, highlighting again the importance of thinking "outside the lung" when managing chronic cough.

More recently it has become clear that GORD is merely the tip of the reflux iceberg, and that many patients do not have features such as heartburn and indigestion typical of acid-related liquid reflux. This was first recognised by ear, nose and throat (ENT) specialists where the term *laryngopharyngeal reflux* was coined. Others prefer the term *airway reflux* to describe this phenomenon.

Patients often provide a classical history with coughing occurring at peak times of reflux and

Within the last Month, how did the following problems affect you? **0 = no problem and 5 = severe/frequent problem**						
Hoarseness or a problem with your voice	0	1	2	3	4	5
Clearing your throat	0	1	2	3	4	5
The feeling of something dripping down the back of your nose or throat	0	1	2	3	4	5
Retching or vomiting when you cough	0	1	2	3	4	5
Cough on first lying down or bending over	0	1	2	3	4	5
Chest tightness or wheeze when coughing	0	1	2	3	4	5
Heartburn, indigestion, stomach acid coming up (or do you take medication for this, if yes score 5)	0	1	2	3	4	5
A tickle in your throat, or a lump in your throat	0	1	2	3	4	5
Cough with eating (during or soon after meals)	0	1	2	3	4	5
Cough with certain foods	0	1	2	3	4	5
Cough with you get out of bed in the morning	0	1	2	3	4	5
Cough brought on by singing or speaking (for example, on the telephone)	0	1	2	3	4	5
Coughing more when awake rather than asleep	0	1	2	3	4	5
A strange taste in your mouth	0	1	2	3	4	5

TOTAL SCORE _____ /70

Fig. 5.2 Hull cough hypersensitivity questionnaire. Symptoms are each scored 0–5, and added to provide the total score. Normal people score an average 4/70. The upper limit of normal is 13/70. Higher scores indicate a strong likelihood of Cough Hypersensitivity Syndrome. The most common cause for this is airway reflux

lower oesophageal sphincter relaxation (after meals, on rising from bed, on bending over). A validated questionnaire (Fig. 5.2) is available at: http://www.issc.info in a wide variety of languages.

There are two proposed mechanisms whereby this "non-acid" reflux precipitates coughing. Firstly that micro-aspiration of oesophageal contents into the larynx and lungs occurs, leading to irritation of vagus nerve endings in these areas. Secondly, reflux into the oesophagus itself stimulates a vagal reflex which leads to cough. A further mechanism has been postulated in that, because of the hypersensitivity, spasm or dysmotility of the oesophagus may lead to the urge to cough via an aberrant or "referred" sensation. Thus reflux may not be a prerequisite for production of the symptom by the oesophageal sensory nerves.

Table 5.1 Features of the "Asthma-like" cough syndromes

	Variable airflow obstruction	Airway hyper-responsiveness	Capsaicin cough hyper-responsiveness	Sputum Eosinophilia
Asthma	Yes	Yes	Sometimes	Yes
Cough variant asthma	Sometimes	Yes	Sometimes	Yes
Eosinophilic bronchitis	No	No	Yes	Yes–by definition
Atopic cough	No	No	No	Yes

Eosinophilic Cough Syndromes

A number of patients with chronic cough appear to have cough that is responsive to steroid treatment. The cough shares some features with asthma, namely nocturnal cough, airway hyper-responsiveness on methacholine challenge testing, and positive markers of eosinophilic airways inflammation (blood eosinophilia, sputum eosinophilia or raised exhaled nitric oxide). Patients vary in their degree of airways hyper-responsiveness, leading to a variety of diagnostic labels being applied including cough variant asthma, atopic cough and eosinophilic bronchitis (Table 5.1). More recently it has been posited that these are all variations on a single clinical syndrome, which can be expressed in lay terms as "asthmatic cough." Thus classic asthma includes variable bronchoconstriction, bronchial hyper-responsiveness, and sputum eosinophilia; cough variant asthma does not exhibit bronchoconstriction; and eosinophilic bronchitis is only characterised by sputum eosinophilia. All respond to steroid treatment, although perhaps less well than in classic asthma. The "asthma-like" cough syndromes account for about 20% of referrals to cough clinics.

Recent evidence provides an explanation for the diverse nature of these asthmatic cough syndromes. Unlike the classic asthma of childhood, which is mediated through allergic adaptive immunity and IgE, the main trigger in the older coughing patient may be mediated by a non-allergic mechanism involving the innate immune system. This hypothesis proposes epithelial injury (for example, caused by reflux, infection, or air pollution) causes release of interleukin 33, activation of innate lymphocyte type 2 cells, and release of IL-5 and IL-13, leading to eosinophil recruitment.

Postnasal Drip (Upper Airways Cough Syndrome)

Whilst widely described as a cause of cough, postnasal drip has been the subject of some debate. The prevalence of postnasal drip also appears to vary, with much higher incidence in the United States, suggesting a possible cultural aspect. This also means that it features much more heavily in the United States guidelines than the European ones. The U.S. guidelines now refer to the existence of nasal stuffiness, sinusitis, or the sensation of secretions draining into the posterior pharynx from the nose or sinuses in association with cough as the "Upper Airways Cough Syndrome" (UACS). In our opinion whilst rhinitis is associated with chronic cough, there are many patients who have rhinitis, postnasal drip, or sinus disease without cough, and the association remains dubious. Reflux of gaseous non-acid refluxate throughout the airways, including the nose, seems an equally plausible explanation.

ACE-Inhibitor-Induced Cough

The association between ACE-inhibitors and cough is well recognised, as these drugs increase cough sensitivity. In some patients this sensitivity is sufficient to reveal a previously occult cough hypersensitivity syndrome (of diverse cause) to produce a clinically noticeable persistent cough. Stopping the ACE-inhibitor usually leads to

resolution of the cough, although this may require many months for the cough sensitivity to reset.

Auricular Nerve Stimulation

Irritation of the auricular branch of the vagal nerve by a substance in the external acoustic meatus can stimulate cough. Removal of the irritant (cerumen, foreign body, or a hair) should have an effect within a few days.

Other Clinical Conditions Associated with Isolated Chronic Cough

Patients with a congenital tracheo-oesophageal fistula (TOF)/oesophageal atresia with subsequent repair are often left with a dysfunctional oesophagus. These patients often present with a typical cough or bronchiectasis due to recurrent aspiration—the "TOF cough" [9].

Associations between chronic cough and various neurological conditions have been described. These include motor, sensory, and autonomic neuropathies such as Holmes-Adie Syndrome and Hereditary Sensory Neuropathy 1. These associations support the role of an abnormality in the autonomic nervous system as a cause of chronic cough [10].

History

A detailed history of chronic cough is aimed at eliciting risk factors, excluding any differential diagnosis, and determining where to target treatment. It may negate the need for further investigation.

A cough of very sudden onset may be associated with aspiration of a foreign body. Many patients associate the onset of chronic cough with symptoms indicative of an upper respiratory tract infection such as a sore throat. Whilst it is useful to be aware of how long a cough has been present, there is no association between any particular condition and the length of the cough.

Production of excessive amounts of purulent or mucopurulent sputum on a daily basis may point to a diagnosis of bronchiectasis or other underlying pulmonary pathology, which should then be investigated and managed in the usual way. However, patients with CHS may not always describe a dry cough, and many complain of the sensation of persistent mucus at the back of their throat, with difficulty expectorating it from their larynx, often only producing very small quantities of sputum. Patients with reflux may typically describe production of moderate volumes of watery secretions after a coughing bout.

Diurnal variation in cough may prove helpful in determining cause. Using cough-counting technology, the marked reduction of cough seen at night is, however, seen in all forms of cough, including asthmatic cough. It is important to carefully tease out exactly what is meant by reports of "waking with a cough" and "coughing more at night." Patients with reflux-associated cough are rarely woken from sleep by cough, as the lower oesophageal sphincter usually remains closed during sleep. They often report coughing shortly after rising from bed, due to relaxation of the lower oesophageal sphincter at this time to allow release of the stomach gases which have collected overnight. They also frequently cough on first lying down. These symptoms should be carefully distinguished from the classical early morning wakening with breathlessness and wheeze as described by asthmatics.

Some patients describe severe coughing spasms and paroxysms which can lead to retching, vomiting, pre-syncope, or even syncope.

Patients often describe certain triggers and aggravants of their cough—these tend to be common irritants such as scented sprays, and are probably not clinically helpful. Equally, eliciting the location of the irritant sensation within the respiratory tract is unlikely to be of diagnostic value, although some patients can be highly specific about exactly where they feel the tickle in their throat.

A full drug history can sometimes elicit a medication which may be responsible for increased cough sensitivity, in particular ACE-inhibitors. The effect of these medications can take several months to resolve after stopping treatment. It is also useful to know if the patient has already trialled any therapies for their cough and whether they gained any benefit from these.

Other drugs associated with coughing are prostaglandin eye drops, which descend into the throat through the lacrimal duct, and drugs which precipitate reflux through their effect on the lower oesophageal sphincter, such as calcium channel antagonists and high-dose salbutamol.

Certain features in the history may suggest one or other of the three widely accepted causes of cough. Whilst UACS-related cough rarely exists without the presence of one of the classical symptoms suggestive of rhinitis or sinusitis, cough due to reflux or one of the "asthma"- like syndromes often exist without the classically recognised features of these conditions. However, careful history taking and a knowledge of the physiology of the lower oesophageal sphincter often elicit features which suggest reflux-related cough. Some clinical features show a degree of overlap between the different diagnoses, and their presence or absence should not lead to exclusion of the possibility of reflux or eosinophilic airways disease as a cause of the cough.

The presence of wheeze, shortness of breath, and chest tightness may suggest asthma, but are equally as likely with a non-eosinophilic aspiration event and can occur during a bout of coughing from any cause. Their presence is therefore more significant if they are occurring independently of coughing bouts.

Features of "classical" reflux symptoms such as heartburn or indigestion may be present in patients with reflux-related cough, but their absence does not exclude it. Features which point towards a reflux-associated cough include exacerbation of coughing shortly after meal times and association with certain types of food, such as chocolate or curry. Coughing also characteristically occurs during times of diaphragmatic relaxation such as speech, singing, or laughing, particularly when seated such as when driving or talking on the telephone. Movement of the diaphragm disrupts the lower oesophageal sphincter because part of the sphincter is accounted for by the crural diaphragm. Symptoms of airway reflux are also often described and include a hoarse voice, globus (the sensation of a lump in the throat), throat clearing, and an odd taste.

A thorough history of chronic cough should include an occupational history. Occupational sensitizers to cough include hot acid in bottle factories and chili peppers.

Past medical history should include other respiratory conditions, including previous pertussis infection, other atopic disease, and organ-specific auto-immune disease. There is evidence that patients with these conditions are more at risk of developing chronic cough.

Family history may establish a familial tendency to chronic cough, perhaps through the mechanism of atopy. Reflux also seems to have familial tendencies, although this may be more attributable to commonality of diet. An inherited autonomic sensory neuropathy (vagal) associated with chronic cough has been described.

Assessment of patients with chronic cough in clinic should include an assessment of cough severity. Validated tools include the visual analogue score and the Leicester Cough Questionnaire. However, in practice, simply asking the patient to score their cough out of 10 is a simple and accurate measure.

Examination

Examination of the patient with chronic cough should focus on the afferent sites most commonly associated with cough.

A respiratory examination is more useful to exclude respiratory disease such as bronchiectasis and interstitial lung disease (ILD) than providing any specific diagnostic benefit in chronic cough. A chronic cough associated with finger clubbing or signs consistent with a pleural effusion or lobar collapse should be investigated accordingly.

Examination of the nose may reveal nasal polyps or inflamed turbinates. Secretions trickling down the posterior pharynx or tonsillar enlargement may be visible on throat examination. Laryngoscopy can show irritation of the larynx and pharynx consistent with laryngopharyngeal reflux. However, scoring systems have shown this to be inaccurate as a diagnostic test, and we use laryngoscopy only in the presence of stridor.

If a family history of cough is present, neurological examination of the legs may suggest familial neuropathy.

Investigations

A chest radiograph and spirometry are essential in any patient presenting with chronic cough.

Airway reversibility testing is useful to screen for patients with one of the eosinophilic cough syndromes, although the absence of reversibility does not preclude the diagnosis. Other investigations which may aid with the diagnosis include exhaled nitric oxide measurement to detect eosinophilic airways inflammation. The blood eosinophil count is often overlooked but has been shown to correlate with the presence of airways eosinophilia. Identification of sputum eosinophilia is useful but not widely available.

Bronchoscopy is indicated in the initial investigation of chronic cough if the history suggests foreign body inhalation. In the absence of a suggestive history, bronchoscopy in cases of chronic cough rarely provides a diagnosis, although should be considered in treatment-resistant cough. A persistent productive cough should prompt investigations for possible bronchiectasis.

Other investigations should be targeted depending on patient history. It is often appropriate and more cost effective to trial treatment targeted at likely contributors to chronic cough prior to carrying out expensive and invasive testing.

A trial of treatment for GORD is usually suggested prior to further investigation of the upper GI tract. Given the lack of evidence that acid suppression improves cough, and because positive 24-h pH monitoring does not predict treatment response, oesophageal pH monitoring is unlikely to be helpful, particularly if non-acid reflux is causing the cough. As there is no effective test for non-acid reflux currently available, oesophageal function testing in the form of high-resolution oesophageal manometry is probably the most accurate indication of oesophageal disease. However, the interpretation needs to be viewed in the light of cough rather than some other oesophageal pathology. Since therapeutic trials provide a quicker and cheaper relief as well as a diagnosis, manometry is best reserved for patients in whom surgical options such as Nissen's fundoplication are being considered.

Upper airway investigations of the sinuses such as plain radiography or CT imaging may be suggested by ENT examination. The American guidelines suggest a trial of treatment if UACS is suspected before further imaging is carried out.

Cough provocation testing by cough challenges such as citric acid and capsaicin shows a wide variation of cough sensitivity within a normal population. Therefore it has no role in the diagnosis of chronic cough, and its usefulness is confined to clinical research.

The partial correlation between subjective symptom scores and objective measurement (such as cough recording) suggests that objective assessment of cough may be useful in clinical practice. In addition, it is suggested that there is a difference in the cough sound produced by different disease mechanisms. Measurement and monitoring of cough by ambulatory cough monitors would therefore be a viable way of objective cough monitoring. However, currently their use remains essentially limited to clinical trials.

Differential Diagnosis

In a patient who presents with a chronic cough, a careful history, examination, and initial investigations, particularly a chest X-ray, are usually sufficient to exclude other respiratory conditions such as lung cancer, bronchiectasis, ILD, COPD, and tuberculosis.

Course, Prognosis, and Outcome

Cough hypersensitivity has considerable impact on quality of life. Patients with a persistent cough have been shown to have worse levels of depression than those with other chronic conditions such as COPD. Some patients may have to cease employment due to their cough, particularly those who rely on talking. Many patients will report that they avoid public gatherings such as concerts and the theatre for fear of having a coughing attack. The fact that coughing is culturally associated with a risk of infection also tends to limit patients' activities.

With targeted treatment, many patients see improvement in their cough. However, in a small group of patients, no treatment appears to be successful, and the cough may be lifelong.

Cough Syncope

Syncopal episodes precipitated by coughing are likely to be due to the elevated intrathoracic pressures caused by a coughing bout. Typical patients who report episodes of cough syncope are males in their middle ages who are overweight, with obstructive airways disease. Elimination of cough will resolve the syncopal episodes. Patients should be made aware of the DVLA guidelines on cough syncope. These state that with a Group 1 car or motorcycle license, driving must cease for 6 months after a single episode of cough syncope. This cessation is increased to 12 months if multiple attacks have occurred. Group 2 license holders who drive lorries or buses must cease driving for 5 years from the last attack. Reapplication may be considered at an earlier time for both types of license if certain criteria are confirmed by a specialist. These are that any underlying chronic respiratory condition is well controlled, the driver has stopped smoking, has achieved a BMI of under 30, and any GORD is treated.

Other Complications of Chronic Cough

Urinary incontinence amongst patients with chronic cough is frequent, particularly in women. Uterine prolapse is also seen in chronic cough patients. Severe coughing bouts often lead to musculoskeletal chest wall pain, or even rib fractures.

Assessment of Chronic Cough

A recommended pathway for assessment in the cough clinic is shown in Fig. 5.3.

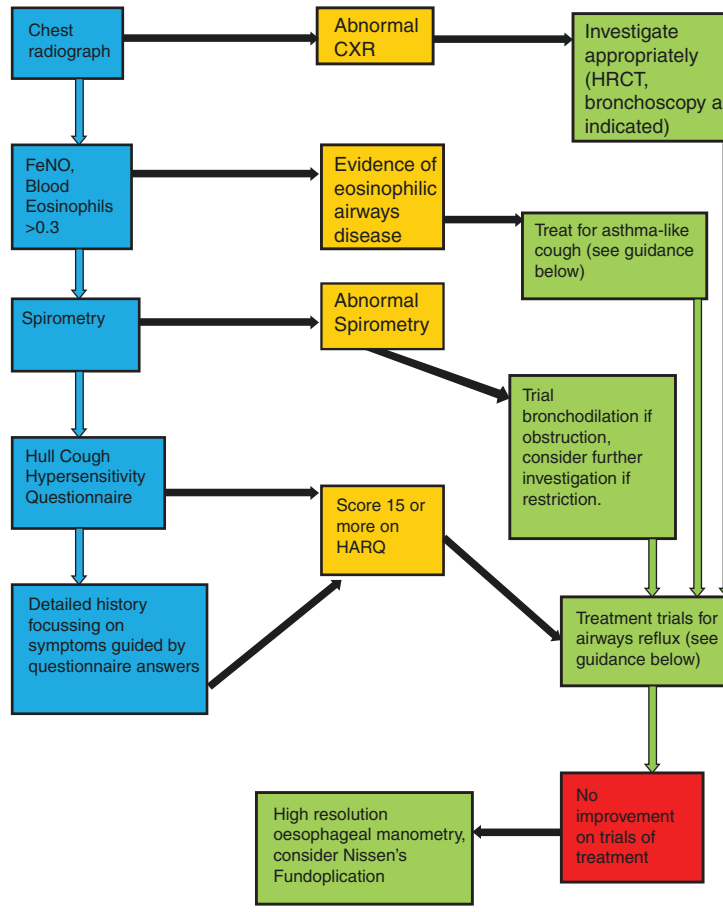

Fig. 5.3 Recommended pathway for assessment in the cough clinic

Treatment

Randomised clinical trials of treatments for isolated chronic cough are limited. The choice of treatment should be guided by the history. Any underlying respiratory pathology should be treated according to treatment guidelines for that condition. Despite these measures, chronic cough often persists and is dismissed as idiopathic. In reality it is often the failure to appreciate the true diagnosis, particularly non-acid reflux, or a failure to understand the differences in treatment required for cough arising from the diagnosis. Treatment specifically targeted at the cough reflex may be required when specific therapy has been ineffective.

Most guidelines recommend establishing a diagnosis by therapeutic trials. Some guidelines suggest that prolonged therapeutic trials are required. Given the relapsing remitting course of some patients with cough, then it is likely that any therapeutic success from such prolonged treatment is more likely to be due to spontaneous remission. We suggest that a month is sufficient to decide whether a particular drug is effective or not.

Patients with evidence of one of the "asthma-like" cough syndromes typically respond to a course of oral steroids. A trial of treatment of 20 mg prednisolone usually produces a response within a few days. Cessation of treatment leads to relapse, also within a few days. Clearly prolonged oral corticosteroids are inadvisable, and inhaled corticosteroids (ICS) should be substituted. There is no specific evidence regarding doses of ICS in cough, and it is recommended that the asthma guidelines are utilised. ICS may be less effective than they are in classic asthma because inflammation appears to be more deep-rooted, with mast cells having been located near airway nerves. Since most asthmatic cough patients do not have prominent bronchoconstriction, there is little point in adding long-acting beta agonists. Treatment with leukotriene receptor antagonists such as montelukast may be highly effective due to the presence of high levels of leukotriene receptors on the innate lymphoid cells controlling the eosinophilic inflammation.

For the large numbers of patients in whom reflux is the precipitant, the first thing to consider is the deleterious effects of concomitant medication. Many patients are on therapies which can worsen reflux, and eliminating these can lead to significant improvement in cough. These include bisphosphonates, nitrates, calcium channel blockers, theophylline, and progesterones.

Reflux leading to cough tends to be predominantly non-acid and often does not respond to gastric acid-suppressing therapies such as proton pump inhibitors or H2 receptor antagonists such as ranitidine. However, a therapeutic trial of these agents remains recommended by most cough guidelines, and they may be of clinical benefit in patients who do have co-existing symptoms of typical acid reflux. Pro-motility agents such as metoclopramide or domperidone seem to be more effective in treating the cough, presumably by reducing non-acid reflux and improving oesophageal motility. Macrolides such as azithromycin or erythromycin also act as pro-motility agents through their action as motilin agonists and are well established in paediatric practice for treatment of reflux in children. Baclofen may also be useful through its role in increasing tone of the lower oesophageal sphincter as well as having a non-specific effect on the cough reflex through the $GABA_B$ receptor. None of these medications seem to have a universal effect in all patients with GORD-related cough, and a sequential trial is recommended.

There is some evidence to suggest that weight loss in those who are overweight will reduce cough severity scores [11]. Treating co-existing sleep apnoea is also advised [12]. There is little evidence supporting other lifestyle measures aimed at reducing GORD lead to improvement in chronic cough, but some experts suggest that they may be of benefit. Advice includes adapting diet to include no more than 45 g of fat in 24 h and excluding coffee, tea, fizzy drinks, chocolate, mints, citrus products (including tomatoes), and alcohol. Other suggested lifestyle measures include smoking cessation and limiting vigorous exercise that increases abdominal pressure. Elevation of the head end of the bed again has little supporting evidence, but patients at high

risk of aspiration, such as those with co-existent COPD, may do this automatically.

Speech and language therapy has been shown in randomised controlled trials to reduce cough both objectively and subjectively. The technique is a very specific, however, and the protocol developed by Anne Vertigan and colleagues from Newcastle Australia requires experience and skill. Recently it has been combined with pregabalin in a multidisciplinary approach to chronic cough.

Surgical intervention for reflux may be considered, however, its success rates in controlling chronic cough appear to be less than in controlling symptoms such as heartburn or indigestion. There are no specific identifying markers for those who are more likely to benefit. However, it may be a more acceptable treatment option to both the patient and the surgeon if there is clear evidence of reflux on investigations, particularly if there are indications of recurrent aspiration. If abnormal oesophageal motility is identified, there may be less satisfactory surgical outcomes. Careful discussion with the patient regarding risks and benefits needs to be undertaken before pursuing surgical treatment.

Given the concept that chronic cough caused by all of these mechanisms is due to a hypersensitivity of vagal afferent neural pathways, the ideal treatment would appear to be one which reduces this hypersensitivity. Current therapies are likely to have a more centrally acting effect, and therefore can have an unacceptable side effect profile. A recent trial of gabapentin suggested some benefit to patients with chronic cough [13]. Side effects were prominent, and in our experience, outweigh any beneficial effects seen. In some patients there appears to be an initial effect, with this ceasing to be of benefit after a few weeks, suggesting perhaps an initial down regulation in the hypersensitivity but followed by reversion to hypersensitivity.

Low doses of morphine sulphate (5–10 mg) have been shown to be of benefit. In about a third of patients it appears to act like a switch to turn off their cough. There is no evidence that higher doses are of added benefit, and at these low doses the only significant side effect appears to be constipation [14]. Dexbrompheniramine and other first-generation antihistamines also seem to reduce cough hypersensitivity in some patients. However, its lack of availability in the UK limits use, and other first-generation antihistamines such as chlorpheniramine may be tried. The efficacy of these drugs has led to the recommendation of treatment of UACS in the U.S. guidelines, however, efficacy does not seem to be limited to this syndrome and may represent a central cough-suppressing activity.

The paucity of available treatments and clinical trial data for existing treatments in chronic cough make it a viable target for future research. As better understanding is gained of the mechanisms involved in the cough reflex, future targets for therapies are identified. Clinical trials with TRP agonists have so far proved unfruitful, however current work suggests that purinergic receptor antagonists such as AF 219 hold promise.

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