Chronic cough: diagnosis, treatment and psychological consequences

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Educational aims

- To motivate the clinician to see chronic cough as a serious condition with extensive morbidity.
- To arm the clinician with the knowledge of the pathophysiology of chronic cough giving rise to the typical clinical history, enabling a firm diagnosis to be made.
- To suggest successful treatment strategies in patients with chronic cough.

Summary

Chronic cough is a common and disabling symptom leading to a marked decrement in a patient's quality of life. The vast majority of patients with chronic cough can be helped by making an accurate diagnosis, usually of either reflux disease or asthma.

Reflux cough presents in a fashion markedly different from the classic symptoms of gastro-oesophageal reflux, such as heartburn. Indeed, <50% of patients with reflux cough suffer from heartburn. The correct diagnosis and correct treatment modality leads to amelioration of cough in the majority of cases.

Where no diagnosis is obtained or there is a failure of therapy, non-specific cough suppression can dramatically improve the patient's quality of life.

This overview provides information on the pathophysiology of the causes of chronic cough, hence enabling the reader to make an accurate clinical diagnosis and suggest therapy to improve even those with apparently intractable symptoms.

Chronic cough, *i.e.* cough lasting longer than 8 weeks, is a common clinical presentation to the respiratory department, yet it is only in the last 20 years that it has been recognised for what it is: a syndrome with a unique and often baffling presentation, causing what seems like intractable distress to the patient and the clinician alike. Previous surveys have determined the incidence of chronic bronchitis; however, it has become increasing clear that a far more common problem is a chronic disabling cough, productive of none or only small quantities of sputum.

The first hint to the high prevalence of this syndrome was obtained by a survey undertaken by the European Respiratory Society (ERS), which indicated that 30% of subjects reported nocturnal cough and 10% cough during the day. However, questions were not specifically targeted to recurrent episodes of coughing, nor to whether the cough interfered with activities of daily living.

Recently, a survey of representative subjects from general practices in Yorkshire in the UK was conducted. The survey of >4,000 people was conducted during the summer months to minimise the effect of seasonal cough and cold. Some 11% of this population had a cough on a daily or weekly basis in the preceding month, and 7% of the population

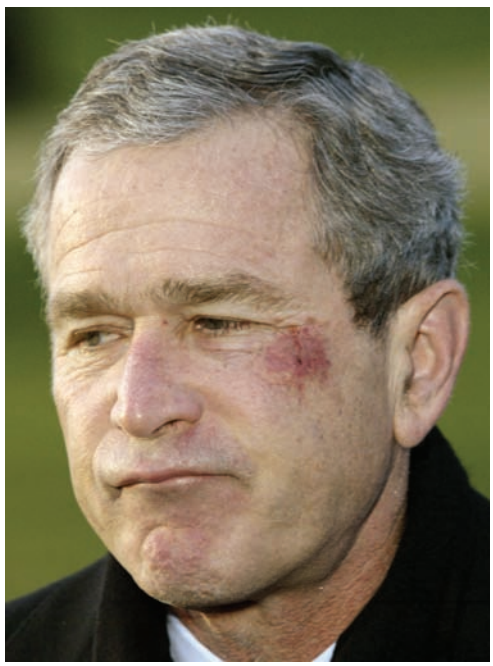
felt that their cough interfered with activities of daily living. Further analysis of the associations with other conditions revealed important clues to the aetiology of the chronic cough syndrome, but this survey demonstrates the astonishingly high morbidity occurring within the general population.

The impact of chronic cough

Those patients attending cough clinics represent the extreme end of the chronic cough spectrum. However, given the high incidence of chronic cough within the general population, there must be considerable morbidity.

A patient with chronic cough suffers numerous physical and psychological consequences from their condition. President Bush famously "choked on a pretzel", which was, in reality, an episode of cough syncope. Cough syncope is perhaps the most dramatic and potentially life-threatening consequence of chronic cough. Indeed, in the UK, a driving licence will be withheld from a patient with cough syncope who has an associated respiratory disorder.

Approximately half of the females who attend a cough clinic have significant episodes of urinary incontinence while coughing. Double incontinence, which can be socially destroying, is also not uncommon. Other psychological consequences include the effect of paroxysms of coughing on other people. In particular, it causes marital disharmony and social exclusion. Frequently, patients are accused of harbouring diseases such as tuberculosis, or are simply embarrassed by coughing episodes occurring, for example, in church or at the opera.



President Bush, who suffered pretzel-induced cough syncope, which can be fatal while driving, but obviously not in this case! Photograph by REUTERS/Kevin Lamarque

For those with reflux cough whose symptoms are brought on by eating or immediately postprandially, eating out may be impossible. Thus, the patient with chronic cough may become increasingly socially isolated.

Not surprisingly, these physical and social consequences of chronic cough may have a devastating psychological effect. In a survey of patients attending the New York (USA) cough clinic, Peter Dicpinigaitis found that half had demonstrable clinical depression. When quality-of-life instruments are used to estimate the impact of chronic cough, the effect is comparable to that of severe chronic obstructive pulmonary disease.

In those without specialist experience of patients with chronic cough, it may be hard to differentiate which is the psychological chicken and which is the egg. However, when chronic cough is successfully treated, the psychological profile of the population with chronic cough returns to normal.

Understanding chronic cough

If patients with chronic cough are asked what sets them off coughing, an almost invariable response is change in atmospheric conditions, *i.e.* either going from a hot to a cold room or *vice versa*. It is, similarly, almost universal to find that cough is set off by perfumes or other odours. Unlike some of the features in the history of chronic cough, these are non-specific stimuli.

Coughing brought on by change in atmosphere is explained by the fact that one of the chief putative cough receptors is the transient receptor potential vanilloid (TRPV)1 capsaicin receptor. Unsurprisingly, as a receptor responding to the "hot" component of peppers, the TRPV1 is a temperature receptor. Change in temperature will, thus, stimulate this receptor on airway nerves. Perhaps the more interesting question is why normal subjects do not cough as much in response to this stimulus?

In almost all forms of chronic cough, there is upregulation of the various cough receptors. This increased sensitivity can be demonstrated in the clinic using the inhalation cough challenge. In

many respects, it is similar to the bronchial hyperresponsiveness seen in asthma, but is, in fact, an entirely separate reflex pathway. Unfortunately, unlike methacholine bronchial hyperresponsiveness, the normal range for capsaicin or acid sensitivities causing cough is so large that it is of little use clinically in determining the aetiology of the cough reflex (however, cough challenge can be used in drug studies).

What is more important is understanding that when an individual develops a chronic cough, they have heightened cough sensitivity, which leads to cough in circumstances that would not normally lead to paroxysms of coughing. This increased sensitivity has been demonstrated not only with chronic cough, but also in patients with acute cough, which suggests an upregulation of the reflex induced by a respiratory tract virus.

A well-worked-out example of the heightened cough reflex is seen with angiotensin converting enzyme (ACE)-inhibitor cough. In the study illustrated in figure 1, subjects were given cough challenge with capsaicin and responded by increased coughing with increasing concentrations of the tussive agent. After administration of an ACE inhibitor, the cough dose–response curve was shifted to the left, demonstrating hyperresponsiveness of the cough reflex. Therefore, ACE inhibitors do not cause cough themselves, but they heighten an individual's cough reflex, allowing what was previously subclinical disease to become clinically apparent.

The clinical history in chronic cough can be very indicative of a particular aetiology. When taking the history of a patient who is coughing with an ACE inhibitor, one may find all of the classic symptoms associated with reflux cough. However, these symptoms may abate on ceasing the ACE inhibitor (often over a prolonged period of time). This is the cough reflex sensitivity returning to normal. The patient will still experience reflux, but it will not irritate the heightened cough reflex.

Females seem to have a heightened cough reflex when compared with males. Females cough twice as much to any given cough challenge, and start coughing at low doses of any given tussive agent. Twice as many females when compared to males suffer from ACE-inhibitor cough, and females outnumber males in cough clinic referral by 2:1. The cause for this increased cough reflex sensitivity is unknown, but it also occurs in chronic cough patients.

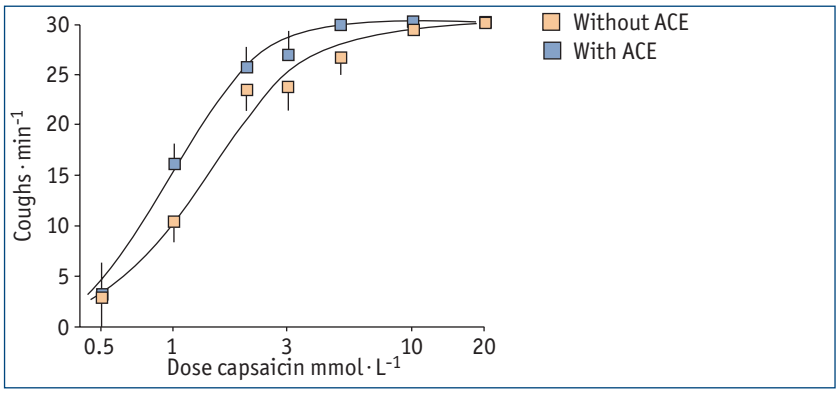


Figure 1
Change in cough reflex sensitivity caused by ACE inhibitors. The leftward shift of the capsaicin dose–response curve indicates increased sensitivity of the TRPV1 cough receptor. Figure reproduced with permission from Morice AH, Lowry R, Brown MJ, Higenbottom T. Angiotensin-converting enzyme and cough reflex. Lancet 1987; 2: 1116–1118.

Diagnosing chronic cough

The patient with chronic cough presents a diagnostic challenge. Indeed, patients often seem quite proud that they have baffled the medical profession and that nobody has been able to get to the bottom of this troublesome symptom: "there is absolutely no pattern to it, doctor". This, however, is rarely true and what the patient really means is that the cough can occur without warning. However, by and large, there is a characteristic pattern that gives the game away.

The ERS and British Thoracic Society guidelines on chronic cough both recommend a combined clinical diagnostic approach, consisting of the history, appropriate special investigations and therapeutic trials. These approaches, while logical, do not convey the associated knowledge base required to interpret these types of information. Thus, the patient with reflux cough may well be missed if it is not recognised that cough precipitated by talking on the telephone is a characteristic feature. Conversely, 24-hour pH studies do not rule out a cough due to non-acid reflux. Treatment with high-dose proton pump inhibitors (PPIs) only successfully treats those with cough due to acid reflux and leaves the many patients with non-acid reflux still coughing. The information given by the patients and the diagnostic and therapeutic tests must, therefore, be interpreted by someone who understands the pathophysiology underlying the disease.

Reflux cough

Reflux cough is probably the commonest presentation of chronic cough in secondary care, since other more-easily diagnosed and treated aetiologies have already been excluded. Even in the general population, recent evidence points to a high prevalence of gastroenterological disease in patients with chronic cough. The

survey in Yorkshire, quoted earlier, revealed a very high association of chronic cough with gastrointestinal pathology. Whilst the classic symptoms of reflux, heartburn and regurgitation were associated, it was regurgitation rather than heartburn which had the greatest degree of association. This infers that non-acid reflux is a far more important aetiological factor in chronic cough than acid reflux, which is so important in heartburn. Other associations in the study confirm the importance of gastro-oesophageal disease; in particular, there was a high correlation with irritable bowel syndrome, inferring that patients with chronic cough of an oesophageal origin have a syndrome of gastrointestinal dysmotility from the top to the bottom!

The realisation that chronic cough is frequently a manifestation of reflux that is non-acid requires a paradigm shift away from previous understanding of reflux associated with heartburn. In fact, only half the patients with reflux cough complain of heartburn or indigestion. Similarly, only a proportion (~50%) respond to vigorous acid suppression. The lack of "classic" reflux history, the failure of diagnostic tests, such as 24-hour pH monitoring, and failure of therapeutic trial anti-reflux (in reality anti-acid) medicine often leave the clinician baffled. How can this be reflux in the face of this negative evidence? All of this evidence supports acid reflux but says little or nothing about non-acid reflux, which underlies many of the problems in chronic cough.

Post-prandial coughing

The difference between acid-related symptoms and non-acidic reflux is neatly demonstrated by post-prandial symptoms. The individual with post-prandial coughing typically reports that the cough is maximal at ~10 minutes post-prandially. This is the maximum time for transient opening of the lower oesophageal sphincter (TOLOS). The physiological purpose behind this is to allow the air that we all swallow during eating to be belched out, and the maximum stimulus for TOLOS can be demonstrated physiologically to be ~10 minutes post-prandially. The non-acid reflux associated with these events causes a post-prandial cough at this time in those individuals sensitised to the phenomenon. However, the food has neutralised the gastric acid, so even though this is the peak time for reflux events, heartburn is rare because these reflux events are non-acidic. Post-prandial heartburn typically comes on much later, between 30 minutes and 1 hour after meals. Stomach pH then falls sufficiently to cause painful oesophageal sensation.

Fortunately, the failure of diagnostic strategy aimed at heartburn does not mean that reflux cough cannot be diagnosed. A characteristic history based around the known physiology of the lower oesophageal sphincter, coupled with knowledge of the effect of extra-oesophageal reflux, provides sufficient clues to make a firm clinical diagnosis in the majority of cases.

Humans are highly prone to reflux. This is because we are the only genuinely bi-pedal animal. At first glance, one might think that an upright posture would diminish the tendency for reflux. However, the body plan in all other vertebrates is that the oesophagus runs along the back of the thorax, goes through the diaphragm and the stomach hangs vertically. There is, thus, a right angle between the oesophagus and stomach, helping to prevent any tendency to reflux when the valve opens. In contrast, in humans, the oesophagus descends directly into the stomach, going from a low pressure zone, the thorax, into the higher pressure abdominal cavity. Any opening of the lower oesophageal sphincter immediately predisposes to reflux events. In fact, the body tries to compensate for the lack of the right angle bend by pulling the lower oesophagus into a J shape using the crural diaphragm.

Coughing on phonation

The explanation above helps us understand one of the commonest associations with reflux cough: coughing on phonation. Here, when the patient is laughing or singing, the diaphragm is being used to phonate, allowing the reflux waves to slip past the straightened oesophagogastric junction. This is made worse when talking

on the telephone, since the subject is usually sitting down, increasing intra-abdominal pressure. This history is of cough starting right in the middle of a sentence as the diaphragm relaxes.

Cough during eating

Another stimulus for TOLOS is the so-called pharyngeal lower oesophageal sphincter reflex. Patients may have post-prandial coughing as described above, but perhaps more common is cough during eating. Typically, the history is one of either sharp, *e.g.* citrus or dried foods such as toast or biscuits, causing a cough during the actual act of eating. The patient will swallow the food and, as the bolus hits the pharynx, the pharyngeal reflex opens the lower oesophageal sphincter causing a paroxysm of coughing. In some people, certain foods seem particularly likely to cause TOLOS, including chocolate and various forms of alcohol. It is, in fact, suggested that some of the "food allergies" suffered by some subjects are in fact caused by their propensity to cause reflux episodes.

Diurnal variation

There is usually a diurnal variation in chronic reflux cough. Patients frequently cough severely on going to bed, and this is explicable by the postural component of reflux cough and can also be associated with bending or stooping. However, when the patient finally gets off to sleep, cough waking them from sleep is relatively rare (when it does occur it indicates very poor lower oesophageal sphincter tone). This is because the oesophageal sphincter pressure increases by ~10–15 cmH_2O whilst the patient is asleep. When the patient wakes, they are still recumbent and do not usually cough immediately. The cough typically occurs on rising. This is again a reflex TOLOS, designed to allow the gas accumulated in the stomach overnight to be belched up. So the patient will cough on rising or reaching the bathroom. Even sitting up in bed may precipitate coughing bouts in some patients.

Extra-oesophageal reflux

Another characteristic set of symptoms that occur in patients with chronic cough due to reflux disease are the manifestations of extra-oesophageal reflux. Voice change occurs because reflux hits the vocal cords. Indeed, voice change due to reflux is now recognised as one of the most frequent presentations to otolaryngologists. Patients frequently aspirate and can, on occasions, cough obvious food matter up at a considerable time away from their last meal (figure 2). How the airway reacts to this aspiration is still poorly understood, but clearly bronchial hyperresponsiveness may occur, and, indeed, if a T-helper (Th)2-type reaction is set off within the airways, reflux may actually predispose to an eosinophilic reaction indistinguishable from asthma or eosinophilic bronchitis. Reflux enters the oropharynx and can be tasted; usually this taste is described as metallic. Reflux may go up the nose and give rise to symptoms of rhinitis or post-nasal drip. Reflux has even been reported going up the eustachian canal into the middle ear. Aspiration of fluid from the middle ear of children reveals the presence of pepsin in about half of the cases.

Oesophageal dysmotility

Oesophageal dysmotility is associated with reflux and is described as any refluxate that is poorly cleared, leading to frequent throat clearing. Reverse peristalsis also occurs, leading to vomiting. This disordered contraction of the oesophagus occurs even after anti-reflux procedures, so the patient may not necessarily be helped by fundoplication. Thus, while the gastro-oesophageal reflux may be cured, swallowed food or liquid may be pooling within the oesophagus and then aspirated.

Testing for reflux cough

Unfortunately, most tests used for the diagnosis of gastro-oesophageal reflux associated with heartburn have proven to be, at best, partially helpful in reflux cough. This is because the tests are designed to detect the acid component or the oesophagitis associated with the oesophageal acid, and neither of these may

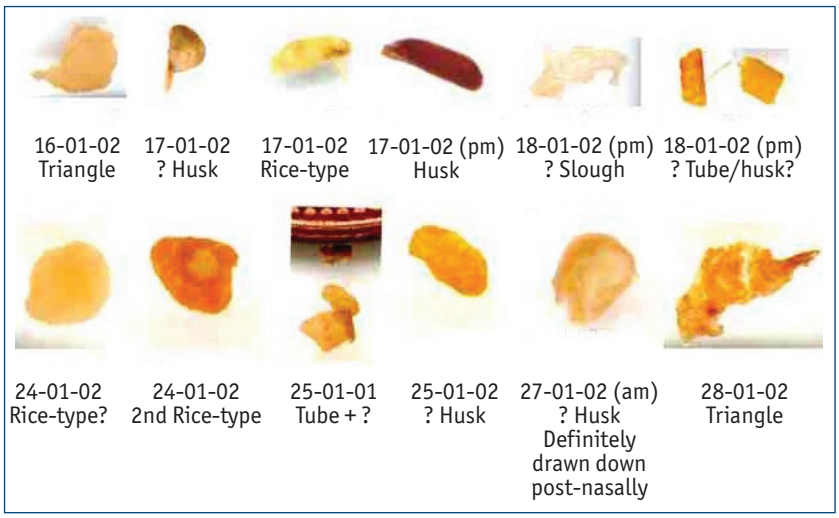


Figure 2
Food debris coughed up following aspiration and scanned into a computer by the patient. Some components are still clearly recognisable as food, despite being several hours post-prandial.

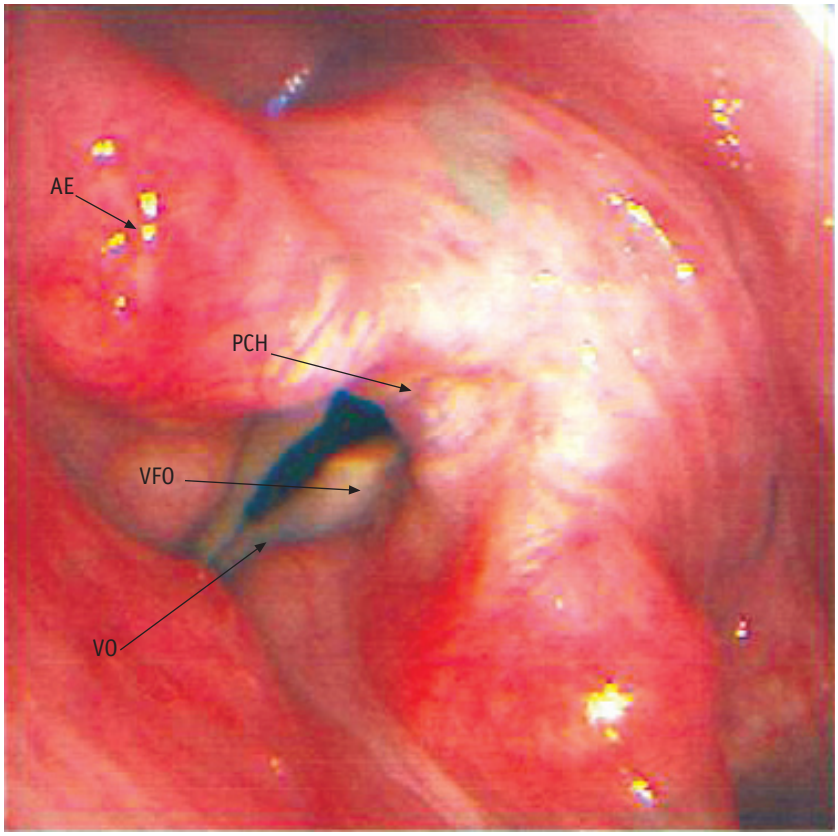


Figure 3
Characteristic features of reflux-induced laryngeal inflammation. There is extensive oedema and hyperaemia. AE: arytenoid erythema; PCH: posterior commisure hypertrophy; VFO: vocal fold oedema; VO: ventricular obliteration.

occur in the patient with reflux cough, where a brief episode of non-acid reflux hitting the vocal cords can precipitate severe coughing but leave no trace with regard to pH monitoring and no inflammation within the oesophagus. Nasal endoscopy may be very helpful in the confirmation of reflux cough. However, the endoscopist needs to understand the characteristic pathological findings. Extra-oesophageal reflux affecting the vocal cords leads to oedema and inflammation (figure 3). The oedema characteristically causes obliteration of the laryngeal ventricle, the space between the true and false cord. The whole laryngeal apparatus may become swollen, leading to subglottic oedema.

Isolated swelling of the posterior cords is claimed to be highly characteristic. Generalised erythema may occur, but is frequently isolated to the arytenoid cartilages. Thick mucous may be seen overlying the entire vocal apparatus. Whilst the global changes illustrated in figure 3 are relatively common, often the signs, particularly of ventricular obliteration, are subtle and require an experienced endoscopist to determine significant changes.

Endoscopy of other areas, such as oesophageal or bronchoscopic evaluation, may occasionally produce evidence of inflammation, but the yield is low. Many centres perform 24-hour pH monitoring with oesophageal manometry. This can be helpful but two-thirds of reflux episodes are non-acidic and are not detected by conventional monitoring. Indeed, the data collection rate advised, which is at 4 Hz, misses many of the brief reflux episodes that occur with reflux cough. Perhaps the greatest utility for oesophageal studies is in determining whether a patient should be offered fundoplication. A successful result seems more likely in patients who are positive on 24-hour pH testing, and it is certainly true that surgeons are more happy to operate in the presence of a positive test.

A number of tests are currently in development. Oesophageal impedance studies detect all forms of reflux and confirm that a considerable proportion of episodes of reflux associated with cough are in fact non-acidic or mildly acidic. High-resolution oesophageal manometry may demonstrate abnormal oesophageal function in the absence of any other positive findings. Finally, the assessment of salivary pepsin or exhaled breath pH may offer important clues to the aetiology of a chronic cough, but, as yet, there is insufficient experience to recommend these are routine clinical tests.

Asthmatic cough

The readers of *Breathe* will require little further information concerning the presence of cough associated with classic atopic asthma. However, very few patients presenting with isolated chronic cough prove to have genuine classic asthma. Most, however, have acquired a diagnosis of asthma (what else could it be!). The ERS guidelines recommend withdrawal of anti-asthma treatment if the major symptom is cough. In many patients, there is no change in cough frequency or severity, demonstrating a mistaken diagnosis of asthmatic cough. In some, there is a worsening of cough symptoms so the patient should be instructed to restart medication should a marked deterioration occur.

Having established that anti-asthma medication does have some effect on cough, it is important to look for additional features pointing to the aetiology. Whilst asthmatic cough may be cough-variant asthma in young people, late-onset cough-variant asthma should prompt the careful evaluation of precipitating factors. A syndrome identical to cough variant asthma occurs in some patients with reflux cough, presumably the aspiration of partially digested protein from the stomach contents sets up a Th2-type reaction within the airways, giving rise to asthmatic inflammation and symptoms. In such patients,

response to inhaled steroids may be virtually complete. However, the characteristic history of reflux cough indicates the origin of the asthmatic reaction. Indeed, treatment with anti-reflux agents may improve bronchial hyperresponsiveness and will reduce symptoms independent of any treatment of the airways.

Whilst the categorisation of asthmatic cough generates much debate, one view is that all chronic cough associated with Th2 mast cells/eosinophil-type inflammation should be regarded as asthmatic cough and, within this broad grouping, various syndromes overlap with each other. Thus, in classic cough-variant asthma, the patient has little or no variable airflow obstruction and no response to inhaled salbutamol. However, on methacholine challenge testing, bronchial hyperresponsiveness will be present and induced sputum will reveal the presence of eosinophils. Eosinophilic bronchitis is a similar condition characterised by no airflow obstruction, no bronchial hyperresponsiveness, but eosinophils present within the sputum. The literature contains various other forms of asthmatic cough, such as atopic cough. However, in practical terms, none of these subgroups are important in the differential of asthmatic cough, since the prognosis, apart from the morbidity associated with coughing, is relatively benign and the response to anti-asthmatic medication good.

Cough and rhinitis

There is no doubt that rhinitis can be associated with chronic cough, and is classically seen in productive cough associated with bronchiectasis and cilial dyskinesia. These conditions are at the extreme end of the current concept of "one airway". This paradigm suggests that inflammation within the nose, which can give rise to the main morbidity, is merely part of an inflammation affecting the whole of the airway. Biopsy studies have demonstrated that inflammation is even present in the lower airways in seasonal rhinitis outside the pollen season. Thus, the cough probably arises from inflammation around the larynx (since cough is a vagal reflex), but relief of cough can occur if the major burden of inflammation within the nose is treated. The most likely explanation is an alteration in the cough reflex sensitivity, as outlined at the beginning of this article.

Other causes of cough

Unsurprisingly, there are many other causes of cough reported within the literature. In general, they involve some form of irritation within the territory of the vagus nerve.

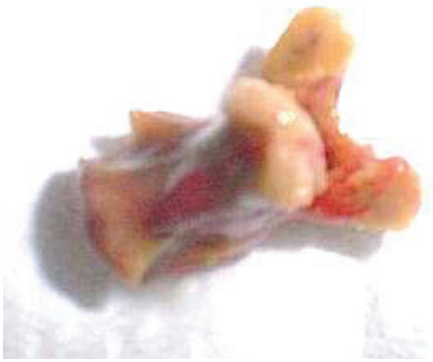


Figure 4
Inhaled foreign bodies can be radiolucent. In this patient, a chicken vertebra produced no distal collapse because of the patent vertebral canal and, even in retrospect, the poorly calcified bird bone was not visible on plain radiograph.

The nerve of Arnold supplying the ear is a branch of the vagus, and impacted ear wax has been described as a cause of chronic cough. Otolaryngologists will confirm that many patients cough when their ears are being instrumented upon, but this is a rare cause of chronic cough in the cough clinic.

Habit or honk cough is a type of chronic cough seen in adolescents, particularly boys. The cough can be diminished by psychological interventions. However, it is now considered to be part of Tourette's syndrome and specific anti-Tourette's treatment may have a dramatic effect on abolishing the cough.

Inhaled foreign bodies may be a potent cause of chronic cough. Chest radiography is usually abnormal. However, radiolucent objects, particularly hollow objects such as ball-point pen tops and chicken vertebrae, may give rise to cough (and wheeze) but can only be detected by bronchoscopy (figure 4). In adults, there is usually a history of aspiration, although in young children this may be unobtainable. Young males aged 2–3 years are at particular risk, as they are then first able to explore the environment and put things into their mouths.

Treatment of chronic cough

The treatment of chronic cough can be looked at in two ways. First, there are measures designed to tackle specific causes of cough. Secondly, there are treatments which are independent of the cause of cough that commonly involve cough suppression. Specific treatments are applied depending on the diagnosis. However, sometimes a diagnosis is not clear or is only suspected. The ERS guidelines on chronic cough endorse therapeutic trials in such cases.

The current author has looked at this method of diagnosis in the form of a probability-

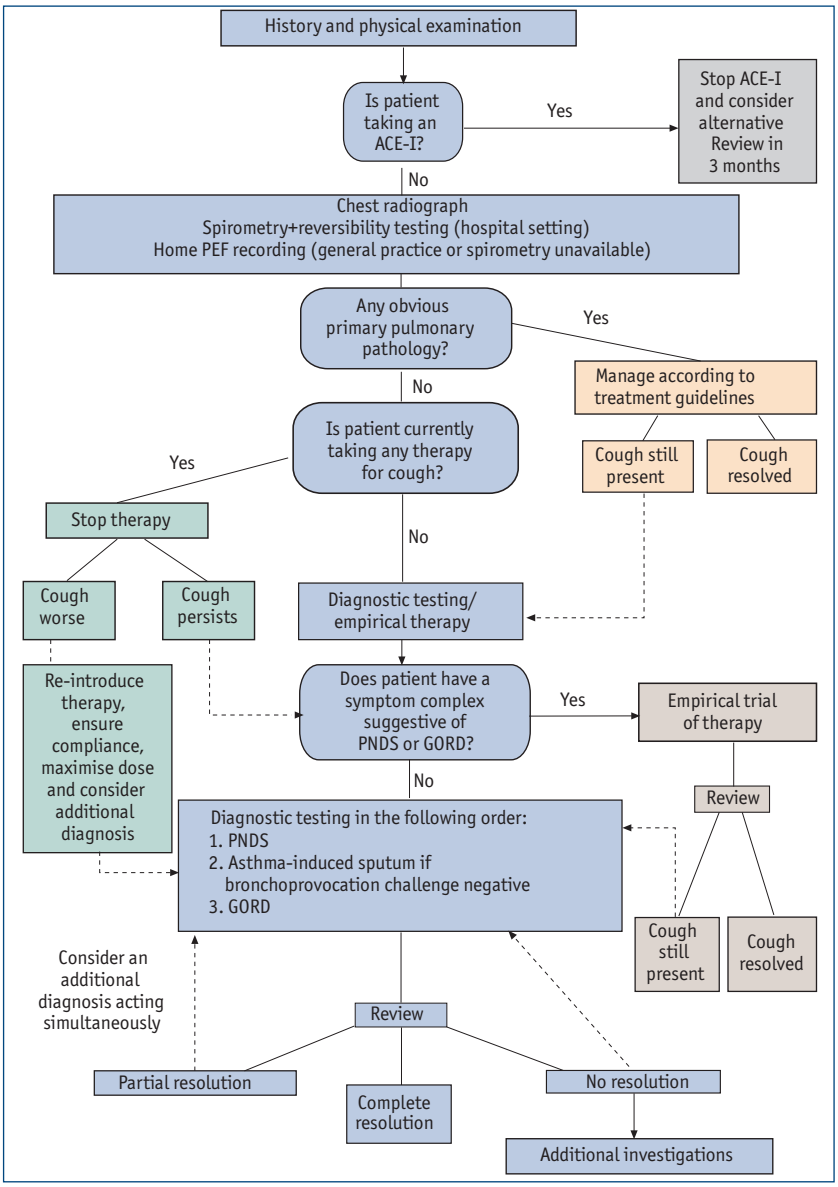


Figure 5
Overview of the evaluation of chronic cough in an adult. Figure modified with permission from Morice AH, Fontana GA, Sovijarvi AR, et al. The diagnosis and management of chronic cough. Eur Respir J 2004; 24: 481–492.

based algorithm (figure 5). One takes an individual with a chronic cough, makes a clinical and basic investigational assessment, and, then, depending on how strong the probability of a particular diagnosis, embarks on therapeutic trials aimed at confirming or refuting the diagnosis. However, care should be taken when using (for example) inhaled steroids, since whilst asthmatic cough will respond to inhaled steroids, any disease process giving rise to Th2 inflammation will also be helped. Thus, some therapeutic trials are not specific. In contrast, a trial of PPIs, which only work on the stomach, can be safely used to conclude that a major component of the cough is due to reflux disease.

Reflux cough

Despite the clear differences between acid reflux causing heartburn and reflux cough, which is far less dependent on acid, the usual treatment strategy is to initiate antacid treatment. There have been few good randomised controlled trials in this area. However, in open-labelled studies, ~50% of patients thought to have reflux cough responded to acid suppression. Since even small quantities of weakly acidic reflux can precipitate coughing paroxysms, acid suppression needs to be much more vigorous than that used in the treatment of heartburn. All PPIs have a relatively short half-life in the body of 1–2 hours. During this time, they irreversibly bind and inhibit active proton pumps. However, after a few hours, the body starts to rebuild proton pumps and, by 24 hours, significant acid-producing capacity has been regenerated. It is, therefore, not crucial what dose of PPI is given, but, more importantly, the frequency with which it is given. Thus, to achieve full acid suppression, PPIs need to be given twice a day. They should be administered in association with food, since active proton pumps are required for the inhibition and food stimulates the activation of the quiescent pump. PPIs given at breakfast and at teatime still result in 50% of patients having a stomach pH <4 first thing in a morning, when most patients with reflux cough start coughing on rising. Therefore, since most nocturnal acid secretion is histaminergic, it is logical to give ranitidine 300 mg at night. This combination of twice-daily PPIs with meals and ranitidine at night is termed full acid suppression. Full acid suppression should be tried for 2 months, since response can be delayed. Experience has shown that persevering beyond this point is unhelpful and may actually make things worse, since the hypergastrinaemia associated with acid suppression may make oesophageal dysmotility worse. Having failed acid suppression, the next two agents to try in sequence are the pro-motility agents metoclopramide and domperidone. If a 1-month trial is unsuccessful, baclofen is the next drug of choice.

The main inhibitory neurotransmitter preventing TOLOS is gamma aminobutyric acid (GABA), and, as a GABA agonist, baclofen replaces this neurotransmitter preventing reflex TOLOS from occurring. There are other specific therapies that can be tried for reflux, such as magnesium glycophosphate, which seems to improve gut motility and oesophageal transit. In addition, some patients respond to anti-spasmodic agents such as hyoscine.

Finally, fundoplication may be dramatically successful, but a significant failure rate of 30% means careful patient selection is required.

Asthmatic cough

In general, the treatment of asthmatic cough follows a very similar pattern to that of classic asthma. However, there is little bronchoconstriction in these patients and the use of long-acting β-agonists appears to be less efficacious. Leukotriene antagonists have been used in patients with asthmatic cough, and a reduction in cough threshold and a clinical improvement in cough have been demonstrated. The major putative cough receptor, the capsaicin receptor TRPV1, is modulated by the lipoxygenase pathway and it is possible that leukotriene antagonists have a specific role in modulating cough in asthma.

Cough suppression

Many of the traditionally used cough suppressants are poorly effective in chronic cough. Two that have been demonstrated to have efficacy are the opiates and a form of antihistamine.

Morphine

Codeine is considered to be as being the archetypal opiate cough suppressant. In fact, this opiate is a poor choice of drug pharmacologically, as it is variably metabolised *via* cytochrome P4502D6. It is, thus, a pro-drug with a variable conversion to the active, morphine. Much more reliable dosing is obtained by giving lose-dose morphine. In a randomised double-blind controlled study, slow-release morphine 5 mg twice a day successfully inhibited cough in one-third of patients with otherwise intractable symptoms. An increase to 10 mg *b.i.d*. helped a further one-third of patients. At this dosage, morphine is relatively free of side-effects, apart from constipation, which responds to laxatives. There appears to be a little tendency to dose escalation. Having suppressed cough for a number of months, some patients are able to withdraw treatment without their cough returning. Presumably the cough reflex has reset itself back to a normal level.

Dexbrompheniramine

The American guidelines on cough recommend dexbrompheniramine in the treatment of post-nasal drip syndrome cough. Most European centres view post-nasal drip as a symptom (secondary to rhinitis or reflux). Conventional antihistamines were, however, tried in European practice and found to be ineffective. When the specific antihistamine recommended in the American literature was used, a high degree of cough suppression was seen. Subsequent work has shown that it blocks the capsaicin TRPV cough receptor in a specific manner unlike other drugs of this class. It appears, therefore, that dexbrompheniramine works as a specific cough suppressant, and clinical studies have demonstrated its utility in a wide range of chronic cough. Unfortunately, the only commercial preparation available is disofrol, which is a combination product with pseudoephedrine. The latter drug prevents dose titration in patients with chronic cough, and indeed the side-effect profile of disofrol including tachycardia and restlessness is presumably due to this component. Ironically, while being unlicensed in Europe, disofrol is obtainable over the counter in pharmacies in the USA. Hopefully, it will become available to the European market shortly.

Useful weblinks

British Thoracic Society Cough Guidelines
www.brit-thoracic.org.uk/guidelinescough
European Respiratory Society: the diagnosis and management of chronic cough
www.ersnet.org/ers/lr/browse/default.aspx?id_dossier=27516
Cough Online Diagnosis
www.coughclinic.org.uk/homepage.php
International Society for the Study of Cough
www.issc.info

Educational questions

1. Which of the following are features of reflux cough? True or false.
   a) Worse at night. b) Exacerbated by laughter. c) A metallic taste. d) Increased by a change in atmosphere.
2. In chronic cough therapy, which of the following apply? True or false.
   a) Initially asthma treatment should be withdrawn. b) Long-acting β-agonists are step 3. c) Leukotriene antagonists are ineffective. d) Second-generation antihistamines should be used in rhinitis.
3. Which of the following statements about the investigation of cough are true?
   a) Should include oesophageal pH monitoring. b) Should be performed before therapeutic trials. c) Nasal endoscopy has a poor yield. d) Bronchoscopy is rarely indicated in children.
4. In the therapy of chronic cough, which of the following are true?
   a) Codeine is the opiate of choice. b) Baclofen decreases cough centrally. c) Twice-daily PPIs are required. d) Treating oesophageal motility is ineffective.

Suggested answers

1. a) False
   b) True
   c) True
   d) False
2. a) True
   b) False
   c) False
   d) False
3. a) False
   b) False
   c) False
   d) False
4. a) False
   b) False
   c) True
   d) False

Suggested further reading

Morice AH, McGarvey LP, Pavord ID, et al. BTS guidelines: recommendations for the management of cough in adults. Thorax 2006; 61: i1–i24.
Comprehensive guidelines on acute and chronic cough. There is an excellent section on how to set up a cough clinic for those wanting to treat this deserving group of patients in a more formal manner.

Morice AH, Fontana GA, Sovijarvi ARA, et al. The diagnosis and management of chronic cough. Eur Respir J 2004; 24: 481–492.
A European view of chronic cough with greater details on investigations of the troublesome patient.

Irwin RS, Baumann MH, Bolser DC, et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. Chest 2006; 129: 1S–23S.
Very comprehensive literature review, but guidelines written very much from an American standpoint. Difficult to use as a practical guideline but an excellent source of the literature.