The never-ending challenge of chronic cough in adults

A Review for the Clinician

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SUMMARY. Despite progress in the understanding of the mechanisms and aetiology of cough, it remains an alarming and annoying symptom for both patients and physicians. Chronic cough lasting for more than 8 weeks is one of the main reasons for referral in primary or secondary health care and the first symptom of many pulmonary and extra-pulmonary conditions. Its aetiology usually includes environmental causes, including exposure to cigarette smoke and environmental pollution, and several disease entities, both respiratory and non-respiratory. The most common respiratory causes are chronic obstructive pulmonary disease (COPD), bronchiectasis, upper airway cough syndrome (UACS) due to a variety of rhinosinus diseases, asthma and non-asthmatic eosinophilic bronchitis. Non-respiratory causes of cough include the use of angiotensin-converting enzyme (ACE) inhibitor agents and gastro-oesophageal reflux disease. Chronic cough may be multi-factorial and only rarely is its cause not identified, leading to the diagnosis of idiopathic chronic cough. Chronic cough is a disturbing symptom that affects the health-related quality of life of the patients and presents a diagnostic and therapeutic challenge for the clinician. This review summarizes the current evidence on the aetiology and the diagnostic difficulties of chronic cough in adults, and provides an algorithmic approach, along with practical tips, for its management by the busy practicing clinician. *Pneumon 2012, 25(2):164-175.*

INTRODUCTION

Cough is the most common symptom for which individuals seek medical advice and every clinician should be able to manage it[1,2]. Cough is recognized as a reflex defense mechanism, with three phases: an inspiratory phase, a forced expiratory effort against a closed glottis and opening of the glottis with rapid expiration that generates the characteristic sound[3,4].

Cough clears the respiratory tract of secretions, foreign particles, and infectious organisms.I Its protective nature is illustrated by the complications of cough suppression after general anaesthesia, which include retention of airway secretions and infection.

Based on its duration, cough can be divided into: (1) acute cough, which lasts for <3 weeks, (2) subacute cough, lasting between 3 and 8 weeks, and (3) chronic cough, lasting >8 weeks[5]. In epidemiological studies, the prevalence of reported cough ranges from 9-33%, being up to 3 times more prevalent in smokers[4,6]. Most patients present with a dry or minimally productive cough, and the presence of significant sputum production usually indicates primary lung pathology. Chronic cough is the 5th most common problem in the primary health care setting and represents approximately 10% of referrals to a specialist in the UK[7]. The prevalence of nocturnal, non-productive cough is higher in middle-aged women than in men, and this may be related to the increased sensitivity of the cough reflex in women[8,9]. Several sets of guidelines have been developed by the major respiratory societies that provide evidence-based recommendations for the management of cough[4,7,10,11]. This review focuses on chronic cough in adults, its diagnostic difficulties and its management, providing an algorithmic approach, along with practical tips for its management by the busy practicing clinician.

CAUSES OF COUGH

Cough can be the first symptom of many pulmonary and extra-pulmonary disorders, and the differential diagnosis usually includes several conditions summarized in Table 1. In the majority of cases of acute cough (i.e. cough lasting <3 weeks), the aetiology is infectious in origin, but certain life-threatening conditions, including foreign body aspiration and cardiovascular disease, and the exacerbation of pre-existing conditions, must always be considered[10]. Subacute cough, lasting 3-8 weeks, commonly has a post-infectious origin, that may lead to exacerbation of pre-existing conditions, including asthma and chronic obstructive pulmonary disease (COPD), or it may be due to any other cause of chronic cough, in which case its management does not differ from that of chronic cough in general[10]. Chronic cough, lasting >8 weeks, may be caused by several respiratory or non-respiratory conditions, that have been widely documented[6]. It is the primary reason for referral in 38% and the sole complaint in 10% of patients visiting a respiratory physician[12]. Recently, a

TABLE 1. Causes of chronic cough

Common causes of cough[6]

- Acute infections: tracheobronchitis, pneumonia, pertussis
- Chronic infections: bronchiectasis, cystic fibrosis, recurrent aspiration, tuberculosis, non-tuberculous mycobacteria
- Post-infectious cough (e.g., Mycoplasma pneumoniae, Bordetella pertussis)
- Upper airway disease: chronic postnasal drip (chronic upper airway cough syndrome)
- Lower airway disease: asthma, COPD, bronchiectasis, EB
- Parenchymal diseases: chronic interstitial lung disease (e.g., IPF, sarcoidosis)
- Tumours: bronchogenic carcinoma, mediastinal tumours, benign airway tumours
- Foreign bodies (including aspiration and endobronchial sutures)
- Cardiovascular disease: left ventricular failure, pulmonary embolism, aortic aneurysm
- GERD
- Drugs: ACE inhibitors
- Irritation of the external auditory meatus
- Habit and psychogenic cough

Uncommon and recently identified causes of cough[13]

- Obstructive sleep apnoea, snoring
- Tonsillar enlargement
- Autoimmune disease (particularly thyroid disease)
- Hereditary sensory polyneuropathy
- Rare infections (e.g. basidiomycetous fungi)
- Tracheobronchopathia osteochondroplastica
- Premature ventricular complexes

Idiopathic or unexplained chronic cough

ACE: angiotensin-converting enzyme; COPD: chronic obstructive pulmonary disease; EB: eosinophilic bronchitis; IPF: idiopathic pulmonary fibrosis; GERD: gastro-oesophageal reflux disease.

number of conditions associated with unexplained chronic cough have been leading to new therapeutic options for appropriately selected patients[13].

COMPLICATIONS OF CHRONIC COUGH

The complications of cough derive from its physiological course of events. During vigorous coughing, intrathoracic pressures of up to 300 mmHg[14] and expiratory velocities of up to 500 miles per hour (85% of the speed of sound)[15], may be generated. During the expiratory phase of a vigorous cough, the systolic blood pressure approaches 140 mmHg, compared with 75 mmHg during chest compression[16]. While these high pressures and ve-

locities enable coughing to be an efficient reflex defense mechanism, they can at the same time give rise to a variety of adverse events. These may be cardiovascular (e.g., arterial hypotension, arrhythmias, loss of consciousness), respiratory (e.g., pneumothorax, pneumomediastinum and subcutaneous emphysema, laryngeal trauma), gastrointestinal (e.g., gastro-oesophageal reflux events and formation of hernias), genitourinary (e.g., incontinence), musculoskeletal (e.g., rib fractures and muscle ruptures), neurological (e.g., seizures, headache, cough syncope or even stroke), ophthalmological (e.g., intraocular haemorrhage), dermatological (e.g., petechiae and disruption of surgical wounds), or constitutional (e.g., excessive sweating, anorexia, exhaustion)[17]. Cough and its complications may have a significant psychosocial impact on individual patients, who commonly present with fear of serious disease and may adopt lifestyle changes that lead to significant impairment of their quality of life (QoL). The understanding of these complications may help clinicians to appreciate the impact of cough on their patients, and the importance of its successful diagnosis and management[17].

COUGH AND QUALITY OF LIFE

The influence of chronic cough on the health-related QoL of patients is a major reason for these patients to seek medical attention[18], as has been shown in several prospective studies[9,19-22]. Various instruments, both specific and non-specific, have been implemented for the quantification of the impact of cough on QoL. French and co-workers developed a self-administered Cough-specific Quality of Life Questionnaire (CQLQ) that consists of 28 items and 6 domains, including physical complaints, psychosocial issues, functional abilities, emotional well-being, extreme physical complaints, and personal safety fears[21]. The CQLQ appears to provide a valid method for assessment of the efficacy of cough therapies, since it is responsive to treatment[22]. Another cough-specific questionnaire is the Leicester Cough Questionnaire (LCQ), which consists of 19 items and three domains, including physical, psychological, and social attributes[19].The LCQ has been shown to be responsive to treatment[19] and to correlate with cough frequency assessed objectively by a sound-based cough monitor.[23] These two questionnaires, along with the Burden of Cough Questionnaire, are currently considered the best validated and most reliable questionnaires for the evaluation of the consequences of cough[24].

One important message derived from studies evaluating QoL in patients with chronic cough is that there are sex-related differences in cough reflex sensitivity in patients with chronic cough[25]. Women with chronic cough seek medical attention more often than men, because their health-related QoL is more adversely affected and they experience more cough-associated physical complaints, and notably, urinary stress incontinence[18].

THE OBJECTIVE ASSESSMENT OF COUGH AND ITS SEVERITY

An important step in the investigation of chronic cough is the objective assessment of cough frequency and severity. Cough visual analogue scores are most commonly used in clinical trials. They are generally responsive to treatment and repeatable in individual patients, but they not very useful for the comparison of cough severity between individuals or populations[19,26], and little is known about the associations of such scores with objective measurements of cough frequency and cough reflex sensitivity[25].

Attempts at quantification of cough have been made by counting individual coughs[23,27], or the number of seconds spent coughing.[28] In small studies, daytime cough frequency was observed to be substantially higher in patients with reported chronic cough than in age-matched and sex-matched controls[27], and a correlation was noted between cough counts and clinical cough scoring systems[11,28]. Ambulatory objective cough monitoring, using specifically designed recording devices[29,30], has shown that effects of sex and age must be taken into account in the study of cough, with one recent study showing that women cough more frequently than men, especially during the night.[31] The availability of commercially available automated cough monitors will represent a major breakthrough in clinical cough research and may be useful in clinical practice in the future[32].

The objective assessment of cough sensitivity has been widely studied by the use of citric acid or capsaicin cough challenge tests[25]. Both techniques have been validated and the methods are well standardized[11]. In both tests, the concentrations causing two (C2) and five coughs (C5) are reported, and their results are highly reproducible in the same individual when performed by an individual investigator or laboratory using appropriate methodology[33-35]. The majority of patients with chronic cough present increased cough sensitivity[36], which decreases after successful cough management[37]. There is

wide inter-individual variation, however, and substantial overlap between healthy volunteers and patients with chronic cough, and between patients with cough of different aetiologies, which limits the role of such tests in the differential diagnosis and quantification of cough[11,25].

ALGORITHMIC ASSESSMENT AND MANAGEMENT OF CHRONIC COUGH

An algorithmic approach to the diagnosis and management of chronic cough, covering the most common causes, is presented in Figure 1[10,25]. The starting point in the evaluation and management of every patient is the elicitation of a careful medical history, including the evaluation of co-morbidities and current medication, fol-lowed by physical examination, spirometry and a chest X-ray. Several studies have shown that serious pulmonary conditions are rare in patients with an isolated chronic dry cough whose physical examination, chest X-ray and spirometry are normal[7,10,11,25], suggesting that these simple tests represent an effective screening strategy[25]. Patients with findings that are indicative of specific respiratory or non-respiratory cause of chronic cough should be managed appropriately.

The onset of cough represents the most significant part of the history and should always be investigated thoroughly by the clinician. An onset of coughing during eating, especially in patients with an impaired swallowing reflex, should raise the possibility of aspiration of a foreign body. The association of cough with the initiation
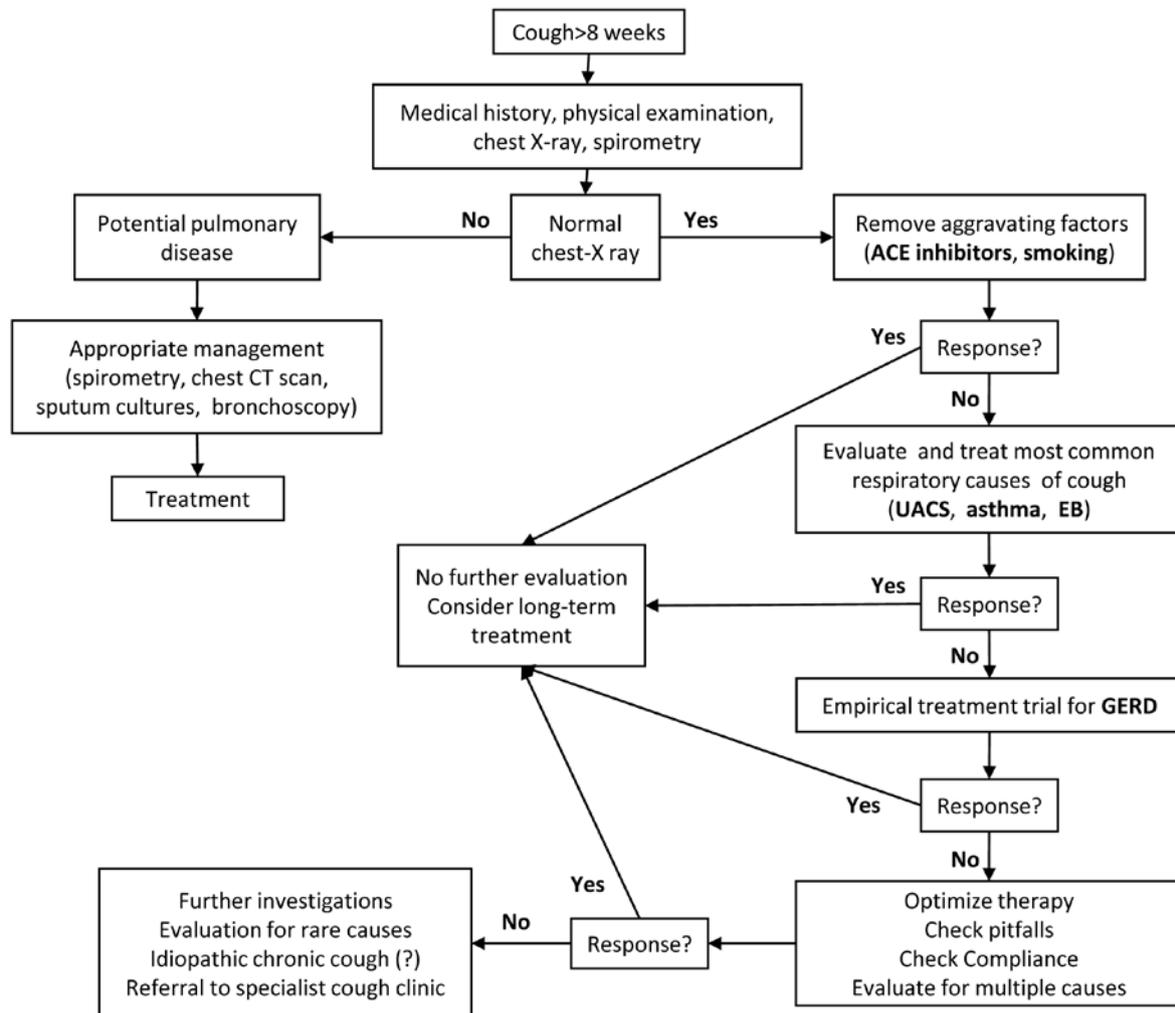
FIGURE 1. A clinical algorithm for the management of chronic cough. Abbreviations: ACE: angiotensin converting enzyme, EB: eosinophilic bronchitis, UACS: upper airway cough syndrome, GERD: gastro-oesophageal reflux disease

of treatment with an angiotensin converting enzyme (ACE) inhibitor strongly supports this as the cause of the cough. Symptoms suggestive of respiratory tract infection at the onset of cough should lead the investigator towards a diagnosis of post-infectious cough, with *Mycoplasma pneumoniae*[38] and *Bordetella pertussis*[39] being increasingly recognized as causes of persistent cough in adults[6]. Specific respiratory symptoms, including dyspnoea, wheezing or haemoptysis, should instigate more specific investigations, including chest computed tomography (CT) scan, sputum culture and/or bronchoscopy. Additional important issues in the medical history include the origin of the patient (e.g., from an area endemic for certain diseases, such as tuberculosis) and the presence of systemic signs of disease, including fever, sweats, or weight loss. A history of cardiovascular disease, cancer or congenital disease is also important in the differential diagnosis, which should generally cover the major causes summarized in Table 1.

In patients with a normal chest X-ray, attempts should be made to remove potential aggravating factors, such as smoking and ACE inhibitors. Every smoker with chronic cough should receive intense consultation for smoking cessation. Cigarette smoking is associated with productive cough that typically meets the definition of chronic bronchitis, and smoking cessation is almost always effective, with significant lessening of the cough within 4 weeks[40]. If the patient is receiving an ACE inhibitor, this should immediately be replaced by some other form of treatment, if possible. The cough is expected to improve within a few days to 2 weeks, but it may take longer to resolve completely[6,41].

Both recent and earlier studies have shown that in patients with a normal chest X-ray, the most common causes of chronic cough are: (1) upper airway cough syndrome (UACS), due to a variety of rhinosinus diseases, also referred to as postnasal drip syndrome (PNDS), (2) asthma, (3) non-asthmatic eosinophilic bronchitis (EB), and (4) gastro-oesophageal reflux disease (GERD)[5-7,12,42-44]. Symptoms such as rhinorrhoea, nasal obstruction, sinus pain, sneezing, PND and nasal or pharyngeal mucosal inflammation are typical indications of rhinosinus pathology. A history of atopy, with seasonal distribution and aggravation of symptoms during the night or with exercise, may be suggestive of cough-variant asthma. A history of heartburn, retrosternal chest pain, a sour taste or regurgitation may support the diagnosis of GERD, although this disorder may present with throat-clearing, hoarseness, or persistent cough, only.

The main strategy in the identification of the cause of chronic cough is to eliminate initially the most common conditions and then to seek alternative diagnoses[10,25]. An important step in the management of chronic cough without any obvious underlying pulmonary disorder is the distinction between cough due to eosinophilic airway disease and non-eosinophilic chronic cough (Table 2)[25]. This distinction is supported by the substantial differences in their epidemiology and pathology, and by the good response of eosinophilic airway disease to corticosteroid treatment[25]. Non-invasive tests, such as induced sputum eosinophilic count[45,46] or exhaled nitric oxide (NO) concentration[47] may be of great value in the identification of eosinophilic airway disease when the values are raised. The greatest difficulties in the management of chronic cough are encountered in those patients whose cough has no obvious major cause and who do not have evidence of eosinophilic airway disease.

An empirical treatment trial for GERD is justified when all the respiratory causes of chronic cough have been

TABLE 2. Differences between the two major types of chronic cough, eosinophilic airway disease and non-eosinophilic chronic cough. (Modified after permission from reference [25]).

	Eosinophilic airway disease	Non-eosinophilic chronic cough
Age	Any	40-60 years
Sex	Equal	Female predominance
Pathology	Eosinophilic	Non-eosinophilic
Sputum cell count	Increased eosinophils	Normal eosinophils
Exhaled nitric oxide (NO)	Raised	Low
Variable airflow obstruction	Present in asthma	Absent
Bronchial hyperresponsiveness (BHR)	Present in asthma but not in EB	Absent
Response to corticosteroids	Good	Poor

EB: eosinophilic bronchitis

ruled out, even in patients with no gastrointestinal symptoms. If this initial clinical and empirical approach does not relieve the cough, a comprehensive evaluation of compliance with optimal treatment should be made, accompanied with a search for pitfalls, following which further investigations for less common causes should be attempted (Figure 1). During this process, the clinician needs to bear in mind that the aetiology may often be multi-factorial and, in such cases, the cough will not resolve until all the various causes have been effectively treated[41]. Absence of improvement after application of this algorithmic approach and extensive investigations constitutes an indication for referral to a specialist cough clinic and are candidates for the diagnosis of "idiopathic chronic cough" (see below).

USEFUL TIPS FOR THE MANAGEMENT OF SPECIFIC CAUSES OF CHRONIC COUGH

The management options for the most common causes of chronic cough are summarized in Table 3.

Upper Airway Cough Syndrome - Post-Nasal Drip Syndrome

Recently, cough specialists in the US have suggested that the term "chronic upper airway cough syndrome" (UACS) should be used to include a variety of upper respiratory conditions, instead of the previously described "post-nasal drip syndrome" (PNDS)[48]. Several studies have shown that UACS is one of most common causes of chronic cough [12,42], being responsible for up to 93% of referrals to specialist respiratory clinics for chronic cough[6,49]. The clinical presentation typically includes complaints of a sensation of drainage to the throat, a need to clear the throat, and/or nasal congestion or discharge. All these symptoms are sensitive but unfortunately not specific, thus the diagnosis of UACS is quite difficult as there is no objective test for it[25]. In patients with an atypical clinical presentation its diagnosis is often established only after the response to empirical treatment, includ-

TABLE 3. Treatment options for the most common causes of chronic cough

Cause of chronic cough	Therapeutic approach
Smoking	• Smoking cessation
ACE inhibitors	• Cessation of drug
Chronic upper airway cough syndrome – Post-nasal drip syndrome	• Avoidance of potential irritants • Oral antihistamines • Nasal corticosteroids • Nasal ipratropium bromide
Asthma	• Avoidance of potential irritants • Inhaled corticosteroids • Inhaled bronchodilators • Leukotriene receptor antagonists • Oral corticosteroids in selected cases
Non-asthmatic eosinophilicbronchitis	• Avoidance of potential irritants • Inhaled corticosteroids • Oral corticosteroids in selected cases
Gastro-oesophageal reflux disease	• Dietary modifications • Weight reduction • Lifestyle changes (smoking, alcohol) • Avoidance of eating within 2 h of bedtime • Proton pump inhibitors • Prokinetics
Postinfectious cough	• It usually is self-limited • When the cough adversely affects the patient's quality of life, inhaled ipratropium or inhaled corticosteroids or antitussive agents may be used • Macrolides in Mycoplasma pneumoniae or Bordetella pertussis infections

ACE=angiotensin converting enzyme

ing oral first-generation antihistamines/decongestants (e.g. dexbrompheniramine)[10], which, however, are not widely available outside the US. For patients with rhinitis the use of intranasal corticosteroids for 2-8 weeks, or oral antihistamines, is also recommended by some specialists, while nasal ipratropium bromide may improve nasal drainage in selected patients[25]. If the empirical treatment trial fails, sinus imaging is indicated, preferably with a CT scan[10]. Common pitfalls in this group of patients are the fact that chronic sinusitis may present with a chronic "dry" cough only, without any other symptoms of acute sinusitis, and that resolution of the cough from sinusitis may need several weeks of treatment.

Asthma and Non-Asthmatic Eosinophilic Bronchitis (EB)

Asthma may present with chronic dry cough as the predominant, or even the only symptom, as in the case of cough-variant asthma. The major characteristic distinguishing asthma from other forms of eosinophilic airway disease, such as atopic cough and non-asthmatic eosinophilic bronchitis (EB), is the presence of variable airflow obstruction and bronchial hyperresponsiveness (BHR)[6,50-54]. All eosinophilic airway diseases are characterized by eosinophilic inflammation in the sputum and in the airways submucosa[55-57], the presence of which predicts a favourable response to corticosteroid treatment. Additional treatment options for patients with cough-variant asthma include long-acting bronchodilators, antileukotrienes[58], and/or low-dose theophylline[59], while a trial of oral corticosteroids (30 mg of prednisolone for 14 days) may be an option for selected patients with severe and/or refractory asthmatic cough[10,25,60].

EB is characterized by a troublesome cough that may sometimes be productive, without any other symptoms of asthma, and in the absence of BHR. It is characterized by a negative response to methacholine challenge testing[61]. Patients with EB have a good response to corticosteroids, but not to bronchodilators[45,62].

Based on the above information, negative bronchial challenge testing (e.g., to histamine or methacholine) may exclude asthma with excellent sensitivity[59,63], but may not rule out the presence of EB, that can respond well to inhaled corticosteroids (ICS). Additionally, a significant proportion of patients with asthma does not present eosinophilic airway inflammation[64]. The establishment of airway eosinophilia with objective tests, such as raised induced sputum eosinophil count[45,46] or increased exhaled NO concentration[47], is important in the management of such patients, since this evidence is a valid predictor of

steroid response[65-67], irrespective of the underlying diagnosis. Exhaled NO measurement has the greatest promise in the evaluation of airway eosiniphilia, since it is easy to perform, and the new portable devices have significantly reduced its cost[68,69]. It is important to stress that, in the absence of objective tests, a trial of ICS in patients with unexplained chronic cough is essential, in order to rule out asthma and EB.

Gastro-oesophageal Reflux Disease (GERD)

In patients with chronic cough who also complain of typical and frequent gastrointestinal symptoms, such as heartburn and regurgitation, the diagnostic evaluation should always include GERD as a possible cause[70]. In patients with GERD, acid and other gastric contents shift from the stomach, via the oesophagus, to the larynx and trachea, because of impaired function of the lower oesophageal sphincter[71]. The term "acid reflux disease" has recently been replaced by the more general term "reflux disease", in order to include all causes of GERD and avoid the misunderstanding that all cases of GERD will respond to acid-suppression therapy[10]. The potential mechanisms of GERD-associated cough include[6]: (a) direct effects of contents (acid or pepsin) or volume of the reflux on the lower oesophageal afferent nerves, (b) direct effects of reflux contents (acid or pepsin) or volume on laryngeal afferents or tracheobronchial afferents, (c) stimulation of oesophageal-bronchial interconnecting neural pathways, (d) increased cough reflex, and (e) increased gastro-oesophageal reflux caused by cough.

Although GERD is among the three most common causes of chronic cough in all age groups, nothing about the character and timing of the cough due to GERD distinguishes it from other causes of cough[72]. It usually occurs during or after a meal, during speaking and after morning awakening, but the association between the reflux and cough is not always consistent. The reflux of gastric contents to the larynx (laryngopharyngeal reflux) may be associated only with frequent throat clearing, voice hoarseness, and globus[73]. It is important to know that patients with GERD-related cough may present no gastrointestinal symptoms in up to 75% of cases[74].

An empirical treatment approach to GERD is justified in appropriate patients with chronic cough of no othere apparent cause. Irwin and Madison have proposed a clinical profile of patients with chronic cough that is highly predictive of a response to anti-reflux treatment (over 90%), even in the absence of gastrointestinal complaints[75]. This profile includes non immunocompromised patients,

with a dry or productive cough of at least 2 months dura-tion, with a normal chest X-ray, and without exposure to cigarette smoke or ACE inhibitors, after ruling out PNDS, asthma, and eosinophilic bronchitis. The management of cough due to GERD should include anti-reflux diet and lifestyle changes, a prokinetic agent (e.g., metoclopramide) and an acid suppressant with a proton pump inhibitor (PPI). In the majority of cases of GERD, treatment with a PPI achieves resolution of the cough within weeks, but sometimes it may take 2-3 months of diet, PPI and prokinetic therapy before the cough starts to improve.[42] The effectiveness of PPI treatment has been challenged in a Cochrane meta-analysis[76] and a recent randomized trial of esomeprazole that failed to show significant improvement of chronic cough[77]. However, the relevant studies were underpowered and until results of larger studies are available, an empirical 8-week trial of PPI is still recommended for appropriately selected patients[69,70].

The absence of response to anti-reflux treatment does not exclude GERD as a cause of chronic cough, and objective investigation is recommended in patients with clinical suspicion. Laryngopharyngeal reflux can cause reflux laryngitis with characteristic thickening, redness, and oedema of the posterior larynx that may be evident on laryngoscopy[78]. Oesophagoscopy may provide indirect evidence of GERD (e.g., oesophagitis and oesophageal ulceration and stricture), but normal findings on oesophagoscopy do not rule out GERD as a cause of cough[70]. The most sensitive and specific diagnostic test for the identification of acid reflux is the 24h-oesophageal pH-monitoring test[10,70], but barium oesophagography may be the only available test to reveal non-acid GERD [70,75]. Non-acid GERD has recently been recognized as an important entity in chronic cough due to GERD[69], but cough specialists do not recommend the routine use of objective investigations for GERD[69].

Angiotensin Converting Enzyme (ACE) Inhibitors

ACE inhibitors should be always considered as a pos-sible cause of chronic cough, regardless of the temporal relationship between the initiation of this therapy and the onset of cough. In 2–33% of patients to whom ACE inhibi-tors are administered, a cough, usually dry, is reported[6,79]. The cough can start within a few hours of taking the drug, but can also become apparent only after weeks or even months. It generally improves within 1 to 4 weeks of cessation of ACE medication, but in some cases the resolution may be delayed for up to 3 months[10]. The causal mechanism of the cough of ACE inhibitors is inhibition

of degradation of bradykinin and prostaglandins in the airways, which directly irritates the cough receptors[6]. If treatment with these drugs is necessary for the patient, it can be restarted carefully after resolution of the cough, but generally this is not recommended since cessation of therapy is considered to be the only uniformly effective treatment for ACE inhibitor-induced cough[80].

Post-Infectious Cough

Post-infectious cough represents 11–25% of patients with persistent cough[6,10,81]. It is usually subacute, lasting from 3 to 8 weeks, in patients with a history of respiratory tract infection and a normal chest X-ray. In 25–50% of cases the agent responsible is *Mycoplasma pneumoniae* or *Bordetella pertussis*[38]. A possible mechanism is that the lower respiratory tract infection damages the bronchial epithelial tissue and contributes to inflammation, render-ing the cough receptors more readily exposed to inhaled irritants and leading to a vicious circle. The cough of *B. pertussis* is spasmodic with a typical whoop, usually lasting for 4-6 weeks and sometimes much longer[6]. Macrolides prescribed in the early stages of *B. pertussis* infection is the recommended therapy. Although the optimal treatment for post-infectious cough is not known, antibiotics are not generally recommended, as the cause is not usually bacterial. In contrast, a trial of inhaled ipratropium may be helpful as it may attenuate the cough, or a trial of ICS in the case of cough that persists despite inhaled ipratropium[10]. When all other measures fail, centrally acting antitussive agents, such as codeine and dextromethorphan, should be considered for troublesome cases[10].

UNCOMMON AND RECENTLY IDENTIFIED CAUSES OF CHRONIC COUGH

Recently, a number of uncommon causes of chronic cough have been identified (Table 1)[13].

A recent case series study from the UK showed that chronic cough was the only symptom of obstructive sleep apnoea (OSA) in 4 patients[82], and OSA was present in 44% of patients referred for investigation of chronic cough in a community-based respiratory practice in Utah, USA[83]. The patients with cough due to OSA are more likely to be female, obese, snorers, and with symptoms of GERD[84], but the presence of OSA cannot be detected by the characteristics of the cough alone. Possible mechanisms include the increase in trans-diaphragmatic pressure during episodes of apnoea that may aggravate GERD,

and upper airway inflammation caused by snoring and apnoea. A trial of continuous positive airway pressure (CPAP) in a small number of patients with this problem led to rapid improvement of their cough[82].

Chronic tonsillar enlargement was reported in a small number of adults with otherwise unexplained chronic cough, which improved significantly after tonsillectomy[85]. Chronic upper airway inflammation may be the underlying mechanism, in a way similar to that reported in children [86].

Rare infections may cause unexplained chronic cough, with one study from Japan reporting evidence of environmental basidiomycetous fungi in induced sputum[87]. The cough improved after antifungal treatment with itraconazole, suggesting a pathogenetic role of fungal infections in those patients[88].

IDIOPATHIC OR UNEXPLAINED CHRONIC COUGH

The cause of cough may not be identified and the cough may persist for several reasons, including inadequate investigation, ineffective therapy or poor compliance with treatment[69,89]. Patients with chronic cough that remains unexplained despite specialist investigation and therapeutic trials are considered to be suffering from idiopathic chronic cough, which accounts for up to 42% of patients referred to specialist cough clinics[90]. Specialists suggest that the cough in this case may represent a distinct clinical entity rather than a symptom of other conditions[13,91]. The term "cough hypersensitivity syndrome" has been also proposed to identify patients with an abnormality of the cough reflex[92]. The features of cough hypersensitivity syndrome include: (1) chronic cough (duration >2 months), (2) minimal or no sputum production, (3) one or more cough reflex triggers (i.e., cold air, speech, eating, odours such as certain perfumes), (4) the urge to cough (i.e., a tickle or an itch) located in throat area, (5) an adverse impact of cough on QoL, and (6) a positive cough reflex challenge test (e.g., capsaicin)[13]. Patients with idiopathic chronic cough are predominantly female (up to 80% in some series)[91], with an onset of cough around the menopause[93], and they have high levels of anxiety and depression[94]. Evidence of lymphocytosis in the BAL of patients with idiopathic chronic cough[91,93], and the increased prevalence of autoimmune disease in this group[95], provide evidence for an autoimmune basis in certain patients.

It is usual in everyday practice for patients with unex-

plained/idiopathic chronic cough to be prescribed ICS, which sometimes are effective. A justification for this therapeutic approach is the evidence that idiopathic chronic cough is associated with airway inflammation; specifically, the induced sputum levels of several mediators related to cough, such as cysteinyl leukotrienes, histamine and prostaglandin D2 and E2, have been shown to be elevated in patients with unexplained chronic cough, compared with healthy control subjects[96]. This finding is consistent with the results of a bronchoscopy study that reported increased numbers of mast cells in the BAL fluid of patients with unexplained cough[56]. Despite such evidence, the association between inflammation and unexplained cough is indefinite, as is the potential role of ICS in its management. It is important to remember that the diagnosis of idiopathic cough is a diagnosis of exclusion that should not be reached until a thorough diagnostic evaluation has been performed, including a therapeutic trial of ICS.

The therapeutic options for patients with idiopathic cough are currently limited. Opiates (e.g., morphine sulphate, codeine) may effectively suppress cough with a central mechanism of action[97], but they have adverse sedative effects and introduce a risk of dependence. Novel antitussive drugs are under development, but will not be available in the imminent future[13]. The anti-inflammatory properties of macrolides were recently evaluated in a randomized placebo-controlled 12-week trial of low-dose erythromycin in patients with unexplained chronic cough. Erythromycin reduced the sputum neutrophil count but had no effect on cough frequency or severity[98], limiting its clinical efficacy in idiopathic cough. A randomized trial of a speech therapy programme designed to suppress cough and reduce vocal cord dysfunction improved chronic cough in patients who had not responded to medical therapy[99] and may be an option for selected patients with idiopathic cough, but this is dependant on the availability of appropriately trained health care professionals.

CONCLUSIONS

Despite the indisputable progress in the understanding of chronic cough over the past few years, it remains a troublesome problem for both patients and clinicians. The identification and successful management of the most common causes of chronic cough may prove effective when a stepwise algorithmic approach involving basic medical skills is implemented. Patients who not respond

to this initial approach and empirical treatment should be submitted to extensive and more invasive evaluation that may reveal rarer causes of chronic cough. The diagnosis of idiopathic or unexplained chronic cough may be made in patients with cough that persists despite an extensive work-up and therapeutic trial, but to date the therapeutic options for such patients are limited. Future prospects include the objective assessment of cough and the optimization of treatment of the most common underlying disorders, and the development of effective antitussive medication with limited side effects for patients with idiopathic chronic cough.

REFERENCES

1. Morbidity Statistics from General Practice: 4th National Study 1991– 1992. London: Her Majesty's Stationery Office; 1995.
2. Schappert SM. Ambulatory care visits of physician offices, hospital outpatient departments, and emergency departments: United States, 1995. Vital Health Stat 13 1997:1-38.
3. Korpas J, Tomori Z. Cough and other respiratory reflexes. Basel; London: Karger; [Chichester] : [Distributed by Wiley]; 1979.
4. Morice AH, Fontana GA, Sovijarvi AR, et al. The diagnosis and management of chronic cough. Eur Respir J 2004;24:481-92.
5. Irwin RS, Madison JM. The diagnosis and treatment of cough. N Engl J Med 2000;343:1715-21.
6. Chung KF, Pavord ID. Prevalence, pathogenesis, and causes of chronic cough. Lancet 2008;371:1364-74.
7. Morice AH, McGarvey L, Pavord I. Recommendations for the management of cough in adults. Thorax 2006;61(Suppl 1):i1-24.
8. Fujimura M, Kasahara K, Kamio Y, Naruse M, Hashimoto T, Matsuda T. Female gender as a determinant of cough threshold to inhaled capsaicin. Eur Respir J 1996;9:1624-6.
9. Kastelik JA, Thompson RH, Aziz I, Ojoo JC, Redington AE, Morice AH. Sex-related differences in cough reflex sensitivity in patients with chronic cough. Am J Respir Crit Care Med 2002;166:961-4.
10. 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.
11. Morice AH, Fontana GA, Belvisi MG, et al. ERS guidelines on the assessment of cough. Eur Respir J 2007;29:1256-76.
12. Irwin RS, Curley FJ, French CL. Chronic cough. The spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. Am Rev Respir Dis 1990;141:640-7.
13. Birring SS. New concepts in the management of chronic cough. Pulm Pharmacol Ther 2011;24:334-8.
14. Sharpey-Schafer EP. The mechanism of syncope after coughing. Br Med J 1953;2:860-3.
15. Comroe JH. The physiology of respiration. 2nd ed. ed. [S.l.]: Year Book Medical Pub; 1974.
16. Schultz DD, Olivas GS. The use of cough cardiopulmonary resuscitation in clinical practice. Heart Lung 1986;15:273-82.
17. Irwin RS. Complications of cough: ACCP evidence-based clinical practice guidelines. Chest 2006;129:54S-8S.
18. French CT, Fletcher KE, Irwin RS. Gender differences in health-related quality of life in patients complaining of chronic cough. Chest 2004;125:482-8.
19. Birring SS, Prudon B, Carr AJ, Singh SJ, Morgan MD, Pavord ID. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). Thorax 2003;58:339-43.
20. Curley FJ, Irwin RS, Pratter MR, et al. Cough and the common cold. Am Rev Respir Dis 1988;138:305-11.
21. French CL, Irwin RS, Curley FJ, Krikorian CJ. Impact of chronic cough on quality of life. Arch Intern Med 1998;158:1657-61.
22. French CT, Irwin RS, Fletcher KE, Adams TM. Evaluation of a cough-specific quality-of-life questionnaire. Chest 2002;121:1123-31.
23. Birring SS, Matos S, Patel RB, Prudon B, Evans DH, Pavord ID. Cough frequency, cough sensitivity and health status in patients with chronic cough. Respir Med 2006;100:1105-9.
24. Leconte S, Ferrant D, Dory V, Degryse J. Validated methods of cough assessment: a systematic review of the literature. Respiration 2011;81:161-74.
25. Pavord ID, Chung KF. Management of chronic cough. Lancet 2008;371:1375-84.
26. Brightling CE, Monterio W, Green RH, et al. Induced sputum and other outcome measures in chronic obstructive pulmonary disease: safety and repeatability. Respir Med 2001;95:999-1002.
27. Smith J, Owen E, Earis J, Woodcock A. Cough in COPD: correlation of objective monitoring with cough challenge and subjective assessments. Chest 2006;130:379-85.
28. Hsu JY, Stone RA, Logan-Sinclair RB, Worsdell M, Busst CM, Chung KF. Coughing frequency in patients with persistent cough: assessment using a 24 hour ambulatory recorder. Eur Respir J 1994;7:1246-53.
29. Birring SS, Fleming T, Matos S, Raj AA, Evans DH, Pavord ID. The Leicester Cough Monitor: preliminary validation of an automated cough detection system in chronic cough. Eur Respir J 2008;31:1013-8.
30. Vizel E, Yigla M, Goryachev Y, et al. Validation of an ambulatory cough detection and counting application using voluntary cough under different conditions. Cough 2010;6:3.
31. Kelsall A, Decalmer S, McGuinness K, Woodcock A, Smith JA. Sex differences and predictors of objective cough frequency in chronic cough. Thorax 2009;64:393-8.
32. Dicpinigaitis PV. Sex, cough and (digital) audiotape. Thorax 2009;64:372-3.
33. Bickerman HA, Barach AL. The experimental production of cough in human subjects induced by citric acid aerosols; preliminary studies on the evaluation of antitussive agents. Am J Med Sci 1954;228:156-63.
34. Bickerman HA, German E, Cohen BM, Itkin SE. The cough response of healthy human subjects stimulated by citric acid aerosol. II. Evaluation of antitussive agents. Am J Med Sci 1957;234:191-206.
35. Midgren B, Hansson L, Karlsson JA, Simonsson BG, Persson

CG. Capsaicin-induced cough in humans. Am Rev Respir Dis 1992;146:347-51.

36. Prudon B, Birring SS, Vara DD, Hall AP, Thompson JP, Pavord ID. Cough and glottic-stop reflex sensitivity in health and disease. Chest 2005;127:550-7.

37. O'Connell F, Thomas VE, Pride NB, Fuller RW. Capsaicin cough sensitivity decreases with successful treatment of chronic cough. Am J Respir Crit Care Med 1994;150:374-80.

38. Davis SF, Sutter RW, Strebel PM, et al. Concurrent outbreaks of pertussis and Mycoplasma pneumoniae infection: clinical and epidemiological characteristics of illnesses manifested by cough. Clin Infect Dis 1995;20:621-8.

39. Gilberg S, Njamkepo E, Du Chatelet IP, et al. Evidence of Bordetella pertussis infection in adults presenting with persistent cough in a french area with very high whole-cell vaccine coverage. J Infect Dis 2002;186:415-8.

40. Buist AS, Nagy JM, Sexton GJ. The effect of smoking cessation on pulmonary function: a 30-month follow-up of two smoking cessation clinics. Am Rev Respir Dis 1979;120:953-7.

41. Israili ZH, Hall WD. Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy. A review of the literature and pathophysiology. Ann Intern Med 1992;117:234-42.

42. Irwin RS, Corrao WM, Pratter MR. Chronic persistent cough in the adult: the spectrum and frequency of causes and successful outcome of specific therapy. Am Rev Respir Dis 1981;123:413-7.

43. Pratter MR. Overview of common causes of chronic cough: ACCP evidence-based clinical practice guidelines. Chest 2006;129:59S-62S.

44. Pratter MR, Brightling CE, Boulet LP, Irwin RS. An empiric integrative approach to the management of cough: ACCP evidence-based clinical practice guidelines. Chest 2006;129:222S-31S.

45. Brightling CE, Pavord ID. Eosinophilic bronchitis: an important cause of prolonged cough. Ann Med 2000;32:446-51.

46. Brightling CE, Ward R, Wardlaw AJ, Pavord ID. Airway inflammation, airway responsiveness and cough before and after inhaled budesonide in patients with eosinophilic bronchitis. Eur Respir J 2000;15:682-6.

47. Chatkin JM, Ansarin K, Silkoff PE, et al. Exhaled nitric oxide as a noninvasive assessment of chronic cough. Am J Respir Crit Care Med 1999;159:1810-3.

48. Pratter MR. Chronic upper airway cough syndrome secondary to rhinosinus diseases (previously referred to as postnasal drip syndrome): ACCP evidence-based clinical practice guidelines. Chest 2006;129:63S-71S.

49. Carney IK, Gibson PG, Murree-Allen K, Saltos N, Olson LG, Hensley MJ. A systematic evaluation of mechanisms in chronic cough. Am J Respir Crit Care Med 1997;156:211-6.

50. Corrao WM, Braman SS, Irwin RS. Chronic cough as the sole presenting manifestation of bronchial asthma. N Engl J Med 1979;300:633-7.

51. Pratter MR, Bartter T, Akers S, DuBois J. An algorithmic approach to chronic cough. Ann Intern Med 1993;119:977-83.

52. Wongtim S, Mogmeud S, Limthongkul S, Chareonlap P, Udompanich V, Nuchprayoon C, et al. The role of the methacholine inhalation challenge in adult patients presenting with chronic cough. Asian Pac J Allergy Immunol 1997;15:9-14.

53. Anthrakopoulos MV. Chronic or recurrent cough in children. Is it asthma? Pneumon 2003;16:271-84.

54. Bitsakou C. Cough in Asthma. Pneumon 1999;13:57-63.

55. Gibson PG, Fujimura M, Niimi A. Eosinophilic bronchitis: clinical manifestations and implications for treatment. Thorax 2002;57:178-82.

56. McGarvey LP, Forsythe P, Heaney LG, MacMahon J, Ennis M. Bronchoalveolar lavage findings in patients with chronic nonproductive cough. Eur Respir J 1999;13:59-65.

57. Niimi A, Amitani R, Suzuki K, Tanaka E, Murayama T, Kuze F. Eosinophilic inflammation in cough variant asthma. Eur Respir J 1998;11:1064-9.

58. Dicpinigaitis PV, Dobkin JB, Reichel J. Antitussive effect of the leukotriene receptor antagonist zafirlukast in subjects with cough-variant asthma. J Asthma 2002;39:291-7.

59. Bateman ED, Hurd SS, Barnes PJ, et al. Global strategy for asthma management and prevention: GINA executive summary. Eur Respir J 2008;31:143-78.

60. Moraitaki P, Papamichail D, Georgatou N. Severe Asthma: Definitions, risk factors and phenotype characterization. Pneumon 2010;23:276-92.

61. Gibson PG, Dolovich J, Denburg J, Ramsdale EH, Hargreave FE. Chronic cough: eosinophilic bronchitis without asthma. Lancet 1989;1:1346-8.

62. Gibson PG, Hargreave FE, Girgis-Gabardo A, Morris M, Denburg JA, Dolovich J. Chronic cough with eosinophilic bronchitis: examination for variable airflow obstruction and response to corticosteroid. Clin Exp Allergy 1995;25:127-32.

63. Cockcroft DW, Murdock KY, Berscheid BA, Gore BP. Sensitivity and specificity of histamine PC20 determination in a random selection of young college students. J Allergy Clin Immunol 1992;89:23-30.

64. Bakakos P, Schleich F, Alchanatis M, Louis R. Induced sputum in asthma: from bench to bedside. Curr Med Chem 2011;18:1415-22.

65. Smith AD, Cowan JO, Brassett KP, et al. Exhaled nitric oxide: a predictor of steroid response. Am J Respir Crit Care Med 2005;172:453-9.

66. Oh MJ, Lee JY, Lee BJ, Choi DC. Exhaled nitric oxide measurement is useful for the exclusion of nonasthmatic eosinophilic bronchitis in patients with chronic cough. Chest 2008;134:990-5.

67. Prieto L, Ferrer A, Ponce S, Palop J, Marin J. Exhaled nitric oxide measurement is not useful for predicting the response to inhaled corticosteroids in subjects with chronic cough. Chest 2009;136:816-22.

68. Kostikas K, Minas M, Papaioannou AI, Papiris S, Dweik RA. Exhaled nitric oxide in asthma in adults: the end is the beginning? Curr Med Chem 2011;18:1423-31.

69. Birring SS. Controversies in the evaluation and management of chronic cough. Am J Respir Crit Care Med 2011;183:708-15.

70. Irwin RS. Chronic cough due to gastroesophageal reflux disease: ACCP evidence-based clinical practice guidelines. Chest 2006;129:80S-94S.

71. Moayyedi P, Talley NJ. Gastro-oesophageal reflux disease. Lancet 2006;367:2086-100.

72. Mello CJ, Irwin RS, Curley FJ. Predictive values of the character, timing, and complications of chronic cough in diagnosing its cause. Arch Intern Med 1996;156:997-1003.

73. Remacle M, Lawson G. Diagnosis and management of laryngopharyngeal reflux disease. Curr Opin Otolaryngol Head Neck Surg 2006;14:143-9.

74. Irwin RS, French CL, Curley FJ, Zawacki JK, Bennett FM. Chronic cough due to gastroesophageal reflux. Clinical, diagnostic, and pathogenetic aspects. Chest 1993;104:1511-7.

75. Irwin RS, Madison JM. The persistently troublesome cough. Am J Respir Crit Care Med 2002;165:1469-74.

76. Chang AB, Lasserson TJ, Gaffney J, Connor FL, Garske LA. Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults. Cochrane Database Syst Rev 2006:CD004823.

77. Faruqi S, Molyneux ID, Fathi H, Wright C, Thompson R, Morice AH. Chronic cough and esomeprazole: a double-blind placebo-controlled parallel study. Respirology 2011.

78. Ford CN. Evaluation and management of laryngopharyngeal reflux. JAMA 2005;294:1534-40.

79. Berkin KE, Ball SG. Cough and angiotensin converting enzyme inhibition. Br Med J (Clin Res Ed) 1988;296:1279.

80. Dicpinigaitis PV. Angiotensin-converting enzyme inhibitor-induced cough: ACCP evidence-based clinical practice guidelines. Chest 2006;129:169S-73S.

81. Kwon NH, Oh MJ, Min TH, Lee BJ, Choi DC. Causes and clinical features of subacute cough. Chest 2006;129:1142-7.

82. Birring SS, Ing AJ, Chan K, et al. Obstructive sleep apnoea: a cause of chronic cough. Cough 2007;3:7.

83. Sundar KM, Daly SE, Pearce MJ, Alward WT. Chronic cough and obstructive sleep apnea in a community-based pulmonary practice. Cough 2010;6:2.

84. Chan KK, Ing AJ, Laks L, Cossa G, Rogers P, Birring SS. Chronic cough in patients with sleep-disordered breathing. Eur Respir J 2010;35:368-72.

85. Birring SS, Passant C, Patel RB, Prudon B, Murty GE, Pavord ID. Chronic tonsillar enlargement and cough: preliminary evidence of a novel and treatable cause of chronic cough. Eur Respir J 2004;23:199-201.

86. Lewis M, McClay JE, Schochet P. Lingual tonsillectomy for refractory paroxysmal cough. Int J Pediatr Otorhinolaryngol 2000;53:63-6.

87. Ogawa H, Fujimura M, Takeuchi Y, Makimura K. The importance of basidiomycetous fungi cultured from the sputum of chronic idiopathic cough: a study to determine the existence of recognizable clinical patterns to distinguish CIC from non-CIC. Respir Med 2009;103:1492-7.

88. Ogawa H, Fujimura M, Takeuchi Y, Makimura K. Efficacy of itraconazole in the treatment of patients with chronic cough whose sputa yield basidiomycetous fungi-fungus-associated chronic cough (FACC). J Asthma 2009;46:407-12.

89. Irwin RS. Unexplained cough in the adult. Otolaryngol Clin North Am 2010;43:167-80, xi-xii.

90. Haque RA, Usmani OS, Barnes PJ. Chronic idiopathic cough: a discrete clinical entity? Chest 2005;127:1710-3.

91. Birring SS, Brightling CE, Symon FA, Barlow SG, Wardlaw AJ, Pavord ID. Idiopathic chronic cough: association with organ specific autoimmune disease and bronchoalveolar lymphocytosis. Thorax 2003;58:1066-70.

92. Morice AH. The cough hypersensitivity syndrome: a novel paradigm for understanding cough. Lung 2010;188 Suppl 1:S87-90.

93. Mund E, Christensson B, Gronneberg R, Larsson K. Noneosinophilic CD4 lymphocytic airway inflammation in menopausal women with chronic dry cough. Chest 2005;127:1714-21.

94. McGarvey LP, Carton C, Gamble LA, et al. Prevalence of psychomorbidity among patients with chronic cough. Cough 2006;2:4.

95. Birring SS, Murphy AC, Scullion JE, Brightling CE, Browning M, Pavord ID. Idiopathic chronic cough and organ-specific autoimmune diseases: a case-control study. Respir Med 2004;98:242-6.

96. Birring SS, Parker D, Brightling CE, Bradding P, Wardlaw AJ, Pavord ID. Induced sputum inflammatory mediator concentrations in chronic cough. Am J Respir Crit Care Med 2004;169:15-9.

97. Morice AH, Menon MS, Mulrennan SA, et al. Opiate therapy in chronic cough. Am J Respir Crit Care Med 2007;175:312-5.

98. Yousaf N, Monteiro W, Parker D, Matos S, Birring S, Paord ID. Long-term low-dose erythromycin in patients with unexplained chronic cough: a double-blind placebo controlled trial. Thorax 2010;65:1107-10.

99. Vertigan AE, Theodoros DG, Gibson PG, Winkworth AL. Efficacy of speech pathology management for chronic cough: a randomised placebo controlled trial of treatment efficacy. Thorax 2006;61:1065-9.