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ERS guidelines on the diagnosis and treatment of chronic cough in adults and children

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ABSTRACT These guidelines incorporate the recent advances in chronic cough pathophysiology, diagnosis and treatment. The concept of cough hypersensitivity has allowed an umbrella term that explains the exquisite sensitivity of patients to external stimuli such a cold air, perfumes, smoke and bleach. Thus, adults with chronic cough now have a firm physical explanation for their symptoms based on vagal afferent hypersensitivity. Different treatable traits exist with cough variant asthma (CVA)/eosinophilic bronchitis responding to anti-inflammatory treatment and non-acid reflux being treated with promotility agents rather the anti-acid drugs. An alternative antitussive strategy is to reduce hypersensitivity by neuromodulation. Low-dose morphine is highly effective in a subset of patients with cough resistant to other treatments. Gabapentin and pregabalin are also advocated, but in clinical experience they are limited by adverse events. Perhaps the most promising future developments in pharmacotherapy are drugs which tackle neuronal hypersensitivity by blocking excitability of afferent nerves by inhibiting targets such as the ATP receptor (P2X3). Finally, cough suppression therapy when performed by competent practitioners can be highly effective. Children are not small adults and a pursuit of an underlying cause for cough is advocated. Thus, in toddlers, inhalation of a foreign body is common. Persistent bacterial bronchitis is a common and previously unrecognised cause of wet cough in children. Antibiotics (drug, dose and duration need to be determined) can be curative. A paediatric-specific algorithm should be used.

Introduction

Cough is a vital protective reflex preventing aspiration and enhancing airway clearance. However, pathologically excessive and protracted cough is a common and disabling complaint, affecting perhaps 5–10% of the adult population [1]. When severe, it causes a major decrement in the quality of life, with comorbidities such as incontinence, cough syncope and dysphonia leading to social isolation, depression and difficulties in relationships [2].

While a wide range of diseases may be associated with chronic cough, it has become increasingly clear that the majority of adult patients presenting with chronic cough as the primary complaint have a common clinical presentation [3]. They often complain of exquisite sensitivity to inhalation of environmental irritants such as perfumes, bleaches and cold air which result in sensations of tickling/irritation in the throat and an urge to cough; features suggestive of heightened sensitivity of the neuronal pathways mediating cough [4]. In addition, there is a unique epidemiology with two-thirds of patients being female and the peak prevalence in the fifties and sixties. These observations have led to the concept of cough hypersensitivity syndrome as a diagnosis [5]. In children, chronic cough presents in a markedly different fashion with different aetiology. They are not miniature adults [6].

This guideline aims to improve diagnostic accuracy and promote evidence-based therapy for both paediatric and adult patients in both primary and secondary care. The guideline is intended for use by all healthcare professionals looking after patients with chronic cough. The guideline has been developed by a multidisciplinary international panel of clinicians and scientists with a published record of expertise in the field. Input on patient views and preferences was sought *via* the European Lung Foundation who provided an advisory group of patient representatives who expressed their preferences *via* teleconferences, attendance at the European Respiratory Society (ERS) congress, and in writing. They contributed to formulating and prioritising the key questions.

Guideline scope and structure

This guideline follows the hybrid model of the ERS Guidelines Working Group and Science Council [7], which combines the scientific rigour of the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework for key questions of uncertainty with a narrative component to reflect the expert consensus of the guideline task force. The narrative covers clinically important aspects of chronic cough, while the eight key questions systematically explore the evidence in areas of clinically important controversy.

Full details of the methodological process and the analysis of the individual questions can be found in the supplementary material. Table 1 provides a summary of the eight questions (two diagnostic and six therapeutic questions), the level of evidence and the recommendations arising from the systematic review. All other propositions should be regarded as narrative statements.

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TABLE 1 Table of recommendations, strength and level of evidence, and supporting remarks

	Strength of recommendation	Level of evidence	Values and preferences	Remarks
Question 1: should chest CT scan be routinely performed on chronic cough patients with normal chest radiograph and physician examination?				
Recommendation 1: we suggest that clinicians do not routinely perform a chest CT scan in patients with chronic cough who have a normal chest radiograph and physical examination.	Conditional	Very low	This recommendation places relatively higher value on the impact on patient management and outcomes including adverse events from radiation exposure. Lower value was given to diagnostic sensitivity and specificity.	In chronic cough patients with normal chest radiographs and physical examination, rates of any positive findings on chest CT scan varied widely in the literature. However, the task force members found that these abnormalities were unlikely to explain cough and may not influence management of the patients. For those patients without a clear diagnosis or a chronic cough that is refractory to treatment of associated conditions, a high-resolution CT scan of the chest may identify subtle interstitial lung disease not visible on chest radiographs, *e.g.* pulmonary fibrosis, hypersensitivity pneumonitis and bronchiectasis, or areas of mucus plugging, which may prompt the need for bronchoscopy for clearance, lavage and culture. However, whether these subtle changes are the cause of the cough or a consequence of an underlying condition, such as recurrent aspiration, is unknown. There is a concern about potential cancer risk from CT radiation exposure [89]. According to an estimation study [88], a projected number of future cancers that could be related to chest CT scans performed in the US was 4100 (95% uncertainty limits 1900–8100) cases from 7 100 000 scans, and the estimated rates were higher in children and females.
Question 2: should F_{eNO}/blood eosinophils be used to predict treatment response to corticosteroids/antileukotrienes in chronic cough?				
Recommendation 2: research recommendation.		Very low	This recommendation places a relatively higher value on predictability for the treatment response and the impact on the treatment decision. Lower value was given to diagnostic sensitivity and specificity.	There is a need for convenient, safe, and practical tests for detecting and predicting anti-inflammatory treatment responses in chronic cough. In randomised controlled trials of patients with different respiratory conditions, F_{eNO} or blood eosinophil levels were positively associated with anti-inflammatory treatment responses [133–135]. However, there is no high-quality evidence to guide the use of F_{eNO} or blood eosinophil counts as treatment response predictors in patients with chronic cough. In addition, there are still no optimal cut-off levels determined for the use in chronic cough populations.
Question 3: should anti-asthmatic drugs (anti-inflammatory or bronchodilator drugs) be used to treat patients with chronic cough?				
Recommendation 3a: we suggest a short-term ICS trial (2–4 weeks) in adult patients with chronic cough.	Conditional	Low	This recommendation is based on the higher value of the clinical benefits from ICS in some patients with asthmatic cough (or airway eosinophilic inflammation) and lower value of adverse events.	Asthmatic cough (CVA and eosinophilic bronchitis) is a frequent phenotype of chronic cough. Evidence for ongoing airway eosinophilic inflammation can be collected by performing differential cell counts on samples from sputum induction or bronchoalveolar lavage; however, these tests are not available at most clinics. Moreover, there is no high-quality evidence for the routine use of F_{eNO} or blood eosinophil counts in patients with chronic cough (as recommendation 2). Therefore, empirical therapy for asthmatic cough may be considered. In the literature, there is a heterogeneity in the efficacy of ICS in adult patients with chronic cough. The variability in the treatment response is probably primarily related to patient characteristics, particularly eosinophilic inflammation. Available evidence suggests that a high dose of ICS might be more effective than a low-to-moderate dose regimen, as an empirical trial. A treatment response is usually seen within 2–4 weeks. Thus, the empirical trial should be stopped if there is no response within 2–4 weeks. The task force members were concerned about long-term overuse of ICS in the absence of evidence or treatment response. In addition, they were concerned about pneumonia in relation to fluticasone use in patients comorbid with COPD.

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TABLE 1 Continued

	Strength of recommendation	Level of evidence	Values and preferences	Remarks
Recommendation 3b: we suggest a short-term ICS trial (2–4 weeks) in children with chronic dry cough.	Conditional	Low	This recommendation is based on a higher value of the clinical benefits from ICS in some patients with asthmatic cough (or eosinophilic inflammation) and a lower value of adverse events.	Overall remarks are the same as those in adults. The empirical trial should be stopped if there is no response within 2–4 weeks.
Recommendation 3c: we suggest a short-term antileukotriene trial (2–4 weeks) in adults with chronic cough, particularly in those with asthmatic cough.	Conditional	Low	This recommendation is based on a higher value of the clinical benefits from antileukotrienes in some patients with asthmatic cough (or airway eosinophilic inflammation) and a lower value of adverse events.	Overall remarks are similar to those for ICS. Currently, clinical evidence is only available in specific subgroups of patients, such as CVA or atopic cough. Overall efficacy of leukotriene receptor antagonist in nonspecific chronic cough patients is uncertain. The empirical trial should be stopped if there is no response within 2–4 weeks.
Recommendation 3d: we suggest a short-term trial (2–4 weeks) of ICS and long-acting bronchodilator combination in adults with chronic cough and fixed airflow obstruction.	Conditional	Moderate	This recommendation is based on a higher value of the clinical benefits from ICS and long-acting bronchodilator combination in some patients with COPD and a lower value of adverse events.	There is a concern about pneumonia in relation to fluticasone use in patients comorbid with COPD. The empirical trial should be stopped if there is no response within 2–4 weeks.
Question 4: should anti-acid drugs (PPIs and H$_2$-antagonists) be used to treat patients with chronic cough?				
Recommendation 4: we suggest that clinicians do not routinely use anti-acid drugs in adult patients with chronic cough.	Conditional	Low	This recommendation is based on a higher value of the clinical benefits from anti-acid drugs only in some patients with acid reflux and a lower value of adverse events.	Anti-acid drugs are unlikely to be useful in improving cough outcomes, unless patients have peptic symptoms or evidence of acid reflux. Clinical benefits from PPI over placebo on cough outcomes are not significant in patients without acid reflux and only modest in those with acid reflux. These agents effectively block gastric acid production and relieve acid-related symptoms, but have little effect on the number and volume of reflux events. Gastric acid does not appear to play a major role in the aetiology of chronic cough. PPIs are mostly considered to be well tolerated. However, there is a potential concern about increased risks of complications, such as pneumonia, iron deficiency, vitamin B$_2$ deficiency, small intestinal bacterial overgrowth, *Clostridium difficile*-associated diarrhoea or bone fracture [118].
Question 5: should drugs with promotility activity (reflux inhibitors, prokinetics and macrolides with promotility activity) be used to treat patients with chronic cough?				
Recommendation 5: there is currently insufficient evidence to recommend the routine use of macrolide therapy in chronic cough. A 1-month trial of macrolides can be considered in the cough of chronic bronchitis refractory to other therapy, taking into account local guidelines on antimicrobial stewardship.	Conditional	Low	This recommendation is based on a higher value of the clinical benefits from drugs with promotility activity only in some patients with chronic bronchitis and lower value of adverse events.	Current evidence only supports the use of azithromycin in patients with chronic bronchitis phenotype. However, mechanisms of azithromycin in improving cough outcomes are suggested to include prokinetic effects [136]. Since oesophageal dysmotility is a frequent finding in chronic cough patients, promotility agents such as metoclopramide, domperidone and azithromycin might be considered, although the clinical trial evidence in cough is sparse.

TABLE 1 Continued

	Strength of recommendation	Level of evidence	Values and preferences	Remarks
Question 6: Which cough neuromodulatory agents (pregabalin, gabapentin, tricyclics and opiates) should be used to treat patients with chronic cough?				
Recommendation 6a: we recommend a trial of low-dose morphine (5–10 mg twice daily) in adult patients with chronic refractory cough.	Strong	Moderate	This recommendation is based on a higher value of the clinical benefits and adverse events from opiates for chronic refractory cough.	Agents acting directly on cough hypersensitivity rather than the treatable traits causing hypersensitivity is a promising strategy for future developments. Current agents have been shown to be effective, but the side-effect profile is significant and may be mitigated by the use of lower doses than that used to treat pain. Clinical experience suggests that only a proportion of patients (approximately half) respond to opiates. In responders, treatment response is very rapid and clear (usually seen in a week). Thus, discontinuation is recommended if there is no response in 1 or 2 weeks. Codeine is generally not recommended (except where it is the only available opiate) due to interindividual genetic variability in drug metabolism (CYP2D6) and consequent less predictable treatment response and side-effect profile, particularly in children.
Recommendation 6b: we suggest a trial of gabapentin or pregabalin in adult patients with chronic refractory cough.	Conditional	Low	This recommendation is based on a higher value of the clinical benefits and adverse events from gabapentin in chronic refractory cough.	Clinical experience suggests the response rates of gabapentin and pregabalin are lower than that of opiates, and adverse events are more common. Common adverse effects are blurred vision, disorientation, dizziness, dry mouth, fatigue and nausea.
Question 7: should nonpharmacological therapy (cough control therapy) be used to treat patients with chronic cough?				
Recommendation 7: we suggest a trial of cough control therapy in adult patients with chronic cough.	Conditional	Moderate	This recommendation is based on a higher value of the clinical benefits from cough control therapy in chronic refractory cough, but places lower value on adverse events.	Multi-component physiotherapy/speech and language therapy interventions may be considered for short-term improvement of health-related quality of life and cough frequency in patients with refractory chronic cough or who wish an alternative to drug treatment. However, this is a complex intervention that requires further study to determine which components are of value. Thus, experienced practitioners should undertake cough-directed physiotherapy and speech and language therapy intervention. The pool of individuals qualified for cough control therapy is currently lacking in many countries and should be increased.
Question 8: should a trial of antibiotics be used in children with chronic wet cough with normal chest radiography, normal spirometry and no warning signs?				
Recommendation 8: we suggest a trial of antibiotics in children with chronic wet cough with normal chest radiographs, normal spirometry and no warning signs.	Conditional	Low	This recommendation is based on a higher value of the clinical benefit from antibiotics in chronic wet cough, but a lower value of adverse events.	Protracted bacterial bronchitis is a common treatable trait in children. Preferred antibacterial, dose and duration of therapy is unknown. Signs and symptoms suggestive of specific disease should always be investigated.

CT: computed tomography; F_{eNO}: exhaled nitric oxide fraction; ICS: inhaled corticosteroids; PPI: proton-pump inhibitor; H_2: histamine; CVA: cough variant asthma; COPD: chronic obstructive pulmonary disease.

These guidelines were constructed with editorial independence from the ERS. Conflicts of interest were disclosed and statements can be found in the relevant section at the end of this article.

Definition of chronic cough

To define a chronic cough on the basis of longevity is clearly an arbitrary paradigm. Early studies used 3 months based on the Medical Research Council definition of chronic bronchitis [8]. More recent guidelines have adopted 8 weeks in adults [9] and 4 weeks in children [10]. Inclusion criteria for studies of novel antitussives require a cough refractory to treatment to be present for over a year. While some patients cough on a daily basis over many years, for others the disease has a relapsing and remitting course, making a definition based purely on a temporal basis difficult to sustain. The diagnosis of chronic cough should be made on a global clinical assessment taking into account the other features of the phenotypes of cough detailed below. The failure to recognise that the patient is suffering from the syndrome of chronic cough may lead to misdiagnosis with the patient labelled as suffering from recurrent chest infections, treatment resistant asthma or exacerbations of chronic obstructive pulmonary disease (COPD).

The commonly used definition of chronic cough in children is 4 weeks, although cough in children lasting 3–8 weeks has been termed prolonged acute cough [10, 11]. Irrespective of the exact duration, chronic cough in children is different from that in adults due to differences in the airway morphology, a higher degree of vulnerability to noxious insults, reduced control of the cough reflex and differences in maturation of the neurological and immunological system in the different paediatric age groups [6]. Chronic cough in children is best seen as a symptom of an underlying disease.

Epidemiology

Cough is a common medical problem and the socioeconomic burden is substantial [12]. However, there are no precise data on the burden of chronic cough, probably because chronic cough was previously perceived not as a clinical entity but as the consequent symptom from other respiratory conditions. There is no agreed definition of chronic cough for use in epidemiological studies [8].

A meta-analysis estimated the global prevalence of chronic cough in the general adult population as ~10% [1]. It was more prevalent in Europe, America and Oceania than in Asia and Africa. Notably, the prevalence of chronic cough in adults is associated with a number of characteristics [13–16]. In a recent international survey of 10 032 adult patients attending specialist cough clinics, two-thirds were female and the most common age for presentation was in the sixth decade [3]. The distinct demographic pattern is thought to be related to sex differences in central processing of cough sensation. The most commonly associated conditions are irritable bowel syndrome, obesity and a variety of neuropathic syndromes. Iatrogenic chronic cough from drug treatments is frequently unrecognised.

Approximately 35% of preschool children report cough at any given time in a month [17]; however, so far, no studies have systematically compared the prevalence of chronic cough in children worldwide. Reports of chronic cough in populations vary between 1% in India [18], 9% in Eastern Europe [19] and 5–12% in China, with increases in areas with higher air pollution [20]. Subjective perception and parental reporting of symptoms further biases prevalence reports [21]. Studies comparing prevalence rates worldwide are warranted.

Impact on patients

Chronic cough is highly disruptive to the individual affected and those around them. The most common reasons why patients with cough seek medical attention include concern about a serious underlying illness, vomiting, exhaustion, sleep disruption, social embarrassment, difficulty speaking on the telephone, urinary incontinence and annoyance to family, friends and workmates [22].

The consequence of chronic cough is a wide range of complications of coughing [23]. Most impactful on health-related quality of life (HRQoL) are stress urinary incontinence, interference with speech, and depression [24]. However, there are many others that can be equally bothersome, such as syncope. Individuals report, on average, eight adverse symptoms associated with cough [22].

Stress urinary incontinence is particularly impactful, as cough affects females disproportionately compared to males. Female patients with cough and urinary incontinence have worse HRQoL compared to those without incontinence [24]. In a quarter of patients, the incontinence is severe but rarely discussed. Thus incontinence should be enquired about during a consultation.

The impact of cough can be assessed and quantified formally with validated HRQoL tools, such as the Leicester Cough Questionnaire (LCQ) or the Cough-specific Quality of Life Questionnaire (CQLQ) [25, 26]. A strength of cough HRQoL tools is that they can be used to demonstrate the efficacy of antitussive

therapy that is clinically meaningful. In the clinic simply asking "score your cough out of 10" is perhaps the easiest subjective measure of treatment success [27] and should be asked at each consultation.

In children, the caregiver's worries about the underlying reason for the cough are a major driver to seek medical attention [28]. Paediatric cough is best considered as a symptom of an underlying disease. Therefore, the burden of disease is influenced by the quality of the healthcare system as well as healthcare independent factors such as age range [29–31], sex and indoor and outdoor air pollution [32].

Aetiology and mechanisms

Cough is a vital protective reflex preventing aspiration into the lung. Patients with a poor cough reflex such as those who suffer from neurological conditions succumb to recurrent episodes of aspiration [33] frequently misdiagnosed as "chest infections". Cough is a vagal reflex evoked by stimulation of afferents carried by the tenth cranial nerve, with their receptive fields primarily in the larynx and conducting airways, but also potentially in the alveolar septa and parenchyma of the lung (*e.g.* pulmonary embolism, heart failure, altitude sickness), the pharynx and oesophagus, and even the ear, with vagal afferents projecting to the auricular canal from the superior vagal (jugular) ganglia (Arnold's reflex) [34].

Noxious stimuli (*e.g.* gastric fluid, protons, cigarette smoke, particulates, hyper- or hypotonicity) are detected through receptors and ion channels (*e.g.* TRPV1, TRPA1, TRPV4, ASIC, P2X3) localised to vagal afferent nerve terminations in the airways mucosa [35]. The vagal afferent nerves regulating cough are polymodal, *i.e.* responding to a variety of different chemical and mechanical stimuli. Cellular stress releasing ATP appears to be an important stimulus [36]. Afferent neuronal traffic is relayed *via* vagal axons to the brainstem *via* at least two different biochemical pathways [37]. Cortical influences modulate the reflex, with females having a greater area of the somatosensory cortex devoted to cough. The system is characterised by marked redundancy, plasticity and adaption. The neurobiology of cough has recently been reviewed comprehensively [38].

Cough may be caused by excessive stimulation of a normal cough reflex such as occurs following inhalation of a foreign body or noxious vapours. However, most patients presenting with a chronic cough have features of cough reflex hypersensitivity, responding to exposure to low levels of thermal, chemical or mechanical stimulation [5]. The cough hypersensitivity syndrome has been adopted as an overarching diagnosis with the different phenotypes dependent on the type and location of the inflammation seen. Both central and peripheral mechanisms have been postulated for cough reflex hypersensitivity [39].

The aetiological mechanisms for cough hypersensitivity remain controversial and are dealt with in greater depth below. In the airways, T2 inflammation occurs in approximately a quarter of patients, although this may be through stimulation of the innate immune system rather than atopy [40]. This gives rise to the phenotypes of cough-variant asthma and eosinophilic bronchitis [41]. Reflux, particularly non-acid gaseous airway reflux, and oesophageal dysmotility are common features [42]. Central mechanisms for cough hypersensitivity have also been postulated, with circumstantial supportive evidence generated using functional magnetic resonance imaging (fMRI) [43]. It is suggested that there is an underlying neuropathic process responsible for cough hypersensitivity [44], a view that is supported by the development of cough in certain forms of hereditary somatosensory neuropathy [45].

Phenotypes of chronic cough

Asthmatic cough/eosinophilic bronchitis

Asthma is a clinical diagnosis. There is no agreed single diagnostic test to diagnose or exclude asthma, and because of its heterogeneous presentation opinions differ on how to describe the syndrome in patients with chronic cough. Eosinophilic inflammation may be a useful biomarker of asthmatic cough and may have utility in directing therapeutics. All adults and children with chronic cough may be assessed for eosinophilic inflammation. Sputum eosinophilia is perhaps the most accurate indicator, but is not routinely available, is time-consuming and requires expert interpretation. Exhaled nitric oxide can be used as a surrogate marker of eosinophilic airway inflammation and steroid responsiveness in classic asthma, but its role in asthma and chronic cough is questioned (see later). A meta-analysis of observational studies showed exhaled nitric oxide to have a relatively high specificity of 0.85 in predicting asthma among adult patients with chronic cough [46]; however, there is still no consensus on the cut-off level for the diagnosis. Blood eosinophilia is a simple and readily available measure, but is characterised by diurnal and seasonal variability [47], so multiple assessments should be made [48]. An eosinophil count of >0.3 cells·μL^{-1} may be taken to indicate eosinophilic airway inflammation [49, 50].

Three subgroups of asthmatic cough have been recognised. Classic asthma is characterised by airflow variability and bronchial hyperresponsiveness. Spirometry is thus an obligatory investigation. Cough variant asthma was originally described as occurring in patients with asthma and cough as the sole

symptoms and where treatment with bronchodilators improved coughing [51]. Opinions vary as to whether this should be sought by performing a bronchial provocation test. Some centres see this as an important part of the workup, whereas others find it adds little to the patient pathway. The third form of asthmatic cough is eosinophilic bronchitis without bronchoconstriction or hyperresponsiveness. The lack of these latter two features has been suggested to indicate that eosinophilic bronchitis is a separate condition: non-asthmatic eosinophilic bronchitis [52]. However, in chronic cough, communication with patients and other healthcare professionals may be enhanced if it is considered as part of an asthmatic spectrum, particularly as all three subgroups can respond to anti-inflammatory asthma therapy. The vital importance of establishing or refuting the diagnosis of asthmatic cough lies in the therapeutics (discussed in questions later) as it may be considered as a treatable trait.

Reflux cough

The role of reflux, oesophageal dysmotility and aspiration in chronic cough is controversial. Its prevalence has been estimated from 0 to almost 100%. Early studies using the criteria of acid reflux found a low incidence and poor temporal relationship [53]. A systematic review [54] found no significant benefits over placebo of proton-pump inhibitors (PPIs) in patients without acid reflux and only modest benefits even in patients with acid reflux. It was suggested that non-acid reflux, both liquid and gaseous, may be an aetiological factor [55]. However, no technology reliably detects such reflux and the diagnosis relies on the clinical history supported by validated questionnaires such as the Hull Airway Reflux Questionnaire (HARQ) [56] (see www.issc.info for multilingual versions) or reflux symptom index (RSI) [57]. The picture is complicated by the observation that there is a high prevalence of oesophageal dysmotility in patients with chronic cough [42], and thus oesophago-pharyngeal reflux rather than gastro-oesophageal reflux disease may be the problem.

Many of the signs and symptoms associated with chronic cough are explicable by reflux and aspiration. Voice change, nasal symptoms and dysgeusia are common [58]. Frequent "chest infections", bronchitis and even frank bronchiectasis may be the consequence rather than the cause of cough through repeated aspiration. Unsurprisingly, following aspiration of contents from the gastrointestinal tract there is an inflammatory response. This might be neutrophilic or eosinophilic, giving rise to asthmatic cough and mucus hypersecretion [59].

Postnasal drip syndrome/upper airways cough syndrome

The 2006 American College of Chest Physicians cough management guidelines suggested the term upper airways cough syndrome (UACS) to describe the variety of signs and symptoms previously referred to by other synonyms, including postnasal drip syndrome, rhinitis and rhinosinusitis [60]. However, the revised nomenclature did not resolve ongoing controversy regarding the existence of this syndrome and the mechanism(s) by which it may induce chronic cough.

A first-generation antihistamine and decongestant were recommended as the treatment, in the absence of adequate randomised controlled trial (RCT) evidence. However, the first-generation antihistamines are thought to be antitussive through their action as centrally penetrant anticholinergics [61].

However, UACS could be accepted as an aetiology of chronic cough in some patients by acting as a trigger for cough hypersensitivity, although the mechanism remains obscure. The absence of evidence for localised treatment might suggest that upper airway symptoms merely reflect generalised airway inflammation consequent to asthma or airway reflux.

Iatrogenic cough

Chronic cough occurs in ~15% of patients taking angiotensin-converting enzyme (ACE) inhibitors. ACE inhibitors increase the sensitivity of the cough reflex in most subjects [62] and it is probable that additional factors are required to produce clinical impact. Since the reflex is reset there may be no close temporal relationship to drug administration or withdrawal and the cough [63]. No patient with a cough or who develops one should be given an ACE inhibitor. Angiotensin II antagonists do not affect the cough reflex.

Drugs such as bisphosphonates or calcium channel antagonists may worsen pre-existing reflux disease, causing increased cough. Prostanoid eye drops such as latanoprost may descend the lacrimal duct, irritating the pharynx [64].

Chronic cough in children

Chronic cough in children differs from that in adults in terms of common aetiologies and management and is increasingly defined as cough that lasts >4 weeks. Regardless of setting and age, children with chronic cough should be evaluated carefully using child-specific protocols [65].

During childhood, the respiratory tract and nervous system undergo a series of anatomical and physiological maturation processes that influence the cough reflex. Additionally, immunological responses undergo developmental and memorial processes that make infection and congenital abnormalities the predominant causes of cough in children [66]. Thus, tracheomalacia, protracted bacterial bronchitis (PBB) and bronchiectasis occur, in addition to common aetiologies such as asthma and post-infectious cough [67]. PBB is not a new entity, and PBB-like conditions were being reported in the 1980s [68]. An ERS task force has recently advanced a reliable definition of PBB for day-to-day clinical practice when all three of the following criteria are fulfilled. 1) Presence of continuous chronic (>4 weeks' duration) wet or productive cough; 2) absence of symptoms or signs (i.e. specific cough pointers) suggestive of other causes of wet or productive cough; and 3) cough resolved following a 2–4-week course of an appropriate oral antibiotic [69]. PBB may be a precursor of bronchiectasis [70].

Initial assessment for chronic cough in children includes a detailed history and thorough physical examination to identify possible specific causes due to an underlying disease. A sudden onset of cough in an otherwise healthy preschool child may suggest foreign body aspiration and requires bronchoscopy. A chest radiograph as well as spirometry in children who cooperate is essential. If specific cause for the chronic cough is suspected, further investigations are necessary. In case no specific pointers are detected and chest radiograph and spirometry are normal then the guideline panel considered that another period of observation of up to 4 weeks was indicated. In case of persistence of cough, differentiate between dry and wet cough [71]. Exposure to airborne irritants (e.g. tobacco exposure, combustions, traffic-related exposure, etc.), allergen exposure or post-infectious cough may be a reason for dry chronic cough. In case of wet cough, sputum cultures should be attempted.

Habit/tic cough is another aetiology found particularly in children, manifesting the core clinical features of tics including suppressibility, distractibility, suggestibility, variability and the presence of a premonitory sensation whether the cough is single or one of many tic. The cough formerly named psychosomatic should now be labelled somatic cough disorder and this diagnosis should only be made after an extensive evaluation that includes ruling out tic disorders and uncommon causes of chronic cough [72].

Psychomorbidity is present in all patients with chronic cough with a variety of aetiologies, and tends to decrease following successful treatment [73]. There are limited criteria for the diagnosis of psychogenic (or somatic) cough and features of psychogenic cough reported in the literature are not unique to psychogenic cough [72]. Somatic cough disorder has been commonly used to describe cough without obvious aetiology. However, recent research has revealed neurobiological phenomena are responsible for psychogenic cough [43]. The presence of depression and/or anxiety cannot be used to diagnose psychogenic cough because, as in adults, patients with a persistently troublesome chronic cough can develop these psychological symptoms when their coughs remain untreatable. Nonpharmacological trials of hypnosis or suggestion therapy or combinations of reassurance, counselling or referral to a psychologist and/or psychiatrist have been suggested in management, but such strategies lack an evidence base.

Chronic refractory cough

A proportion of patients with chronic cough, particularly among adults, have persistent cough despite thorough investigation and treatment according to published practice guidelines. Terms such as idiopathic chronic cough, unexplained chronic cough and chronic refractory cough have been used to describe this clinical condition [74]. Successful trials of drugs with neuromodulatory effects such as opiates, gabapentin and P2X3 antagonists suggest that aberrant neurophysiology is likely to underlie this condition. Here the term chronic refractory cough is used to indicate that the cough is refractory to conventional treatment of cough-associated conditions or traits.

Chronic cough in other diseases

Most chronic respiratory disease is associated with cough. Physical distortion of the airway such as that which occurs in lung cancer or the bronchorrhea of cystic fibrosis and chronic bronchitis produces cough by mechanical effects. However, cough hypersensitivity through cell damage and inflammation underlies much of the increased cough seen in other pathologies. The different pathological processes in individual conditions contribute to the disease-specific heterogeneous aetiology of cough in other lung disease.

As an example, cough in interstitial lung diseases (ILDs) is common, with a prevalence of 30–90%. Patients with ILD often respond poorly to general antitussive therapy. In an open-label study of idiopathic pulmonary fibrosis (IPF), pirfenidone reduced 24-h objective cough counts and improved cough-related quality of life [75]. Reformulated sodium cromoglicate improved 24-h objective cough by 31% in patients with IPF, whereas there was no effect in chronic idiopathic cough [76]. It seems likely that each individual respiratory condition will have its own profile dependent on the tussigenic factors expressed in that disease.

Chronic cough, tobacco and nicotine

Smoking is the major remediable cause of chronic cough and is inextricably linked to COPD. Epidemiological studies have demonstrated a relationship between cumulative smoking exposure and chronic cough [77]. Furthermore, smoking history and current cigarette consumption are predictors of objectively measured cough frequency [78]. Therefore, a natural inference would be to ascribe a protussive effect to tobacco smoke and its components. However, research in otherwise healthy smokers and nonsmokers has provided additional insights, some of which contradict the general assumption.

Multiple studies of otherwise healthy smokers have demonstrated suppressed cough reflex sensitivity to inhaled capsaicin [79, 80]. The development of electronic cigarettes (e-cigs) provided a mechanism of noncombustible delivery of nicotine to the lungs. One tobacco cigarette equivalent induced significant suppression of cough reflex sensitivity [81]. These data are consistent with previous clinical observations of transient increase in cough within the first month after smoking cessation [82]. All patients should quit smoking and they should be warned that there may be a transient increase in coughing. For those unable to quit because of excessive coughing, e-cigs may be a supportive therapy [83].

Assessing cough in the clinic

Initial assessment

The history, examination and investigations for patients with chronic cough are performed to exclude treatable traits of the disease for which directed therapy can be offered. The guideline panel placed a higher value on control of any ongoing pathology such as reflux or airway eosinophilia before currently available neuromodulatory treatments are considered. A detailed history and examination should be directed to exclude malignancy, infection, foreign body inhalation or the use of an ACE inhibitor. The impact of cough should be assessed either by recording simple measures such a cough score out of 10 or visual analogue scale (VAS) or by more detailed, validated measures of cough quality of life (LCQ or CQLQ). Validated questionnaires may help to detect features of airway reflux (HARQ and RSI) and airway hypersensitivity [84].

Initial evaluation should include spirometry and a recent chest radiograph (good practice statement).

Chest computed tomography

Question 1: should chest computed tomography (CT) scan be performed routinely on chronic cough patients with normal chest radiograph and physical examination?

We suggest that clinicians do not routinely perform a chest CT scan in patients with chronic cough who have normal chest radiograph and physical examination (conditional recommendation, very low-quality evidence).

Some prospective and retrospective cohorts identified CT findings in a range of 6.5–58% of patients with cough and normal chest radiograph; however, the causal relationship was either not specified or considered as unlikely to be related to cough [85–87]. There is a concern about potential cancer risk from CT radiation exposure [88, 89]. Thus, the potential radiation risk needs to be weighed against possible diagnostic yields, particularly in susceptible populations such as children and females.

Further investigations to identify treatable traits in chronic cough

Further investigations for asthma, eosinophilic bronchitis, reflux and oesophageal dysmotility and rhinosinusitis should be considered, depending on the clinical history (figure 1).

Asthma and eosinophilic inflammation

Objective evidence of classic asthmatic cough conventionally requires some evidence of variable airflow obstruction such as peak flow variability, or reversibility to salbutamol of >12–15%. However, these investigations have a very low negative predictive value, particularly in patients with normal lung function [86]. Further investigation of bronchial hyperresponsiveness using either methacholine or histamine inhalational challenge is advocated by some, although its utility in diagnosis is questioned. Evidence for ongoing airway eosinophilic inflammation can be sought by performing differential cell counts on samples from sputum induction or bronchoalveolar lavage. In such cases, elevated eosinophils (>3%) in the airways in the absence of bronchial hyperresponsiveness would suggest eosinophilic bronchitis, which has been reported in up to 13% of patients attending cough clinics [41]. However, most centres do not have such facilities available, hence a non-invasive alternative is the use of exhaled nitric oxide fractional (F_{eNO}) in breath or blood eosinophilia as a surrogate marker to assess airway eosinophilia. The clinical usefulness of F_{eNO} or blood eosinophils in aiding diagnosis or predicting treatment response in patients with chronic cough has not yet been systematically evaluated [90].
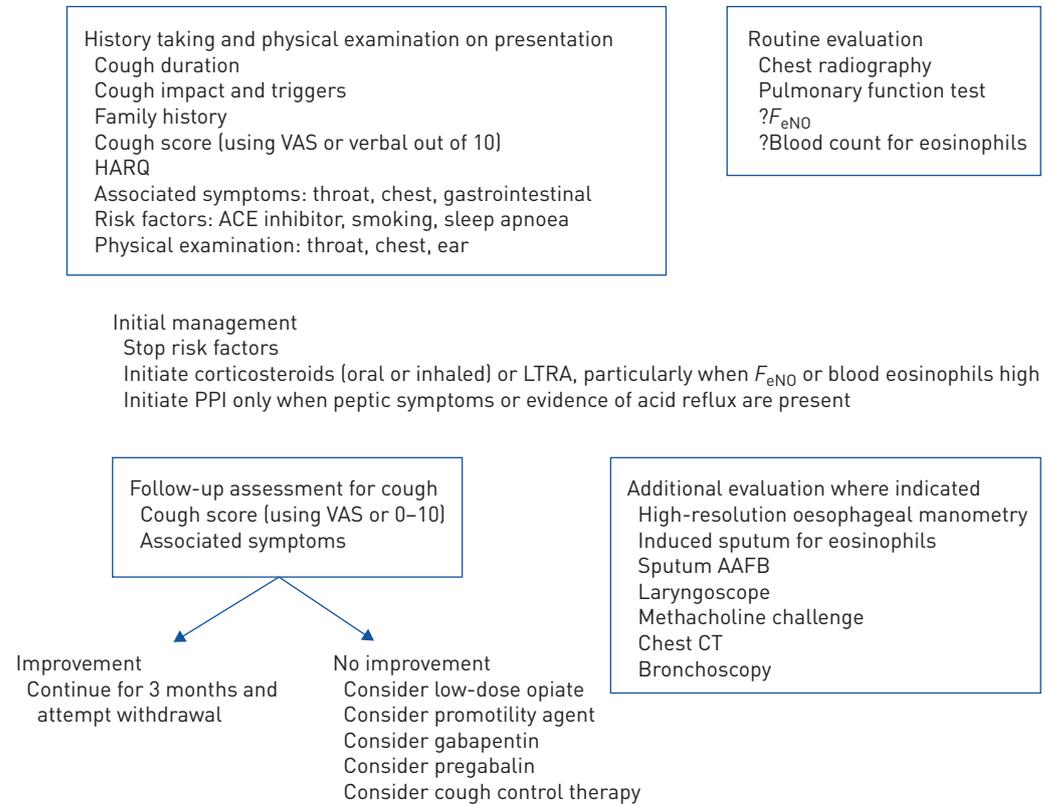
History taking and physical examination on presentation
Cough duration
Cough impact and triggers
Family history
Cough score (using VAS or verbal out of 10)
HARQ
Associated symptoms: throat, chest, gastrointestinal
Risk factors: ACE inhibitor, smoking, sleep apnoea
Physical examination: throat, chest, ear

Routine evaluation
Chest radiography
Pulmonary function test
?F_{eNO}
?Blood count for eosinophils

Initial management
Stop risk factors
Initiate corticosteroids (oral or inhaled) or LTRA, particularly when F_{eNO} or blood eosinophils high
Initiate PPI only when peptic symptoms or evidence of acid reflux are present

Follow-up assessment for cough
Cough score (using VAS or 0–10)
Associated symptoms

Additional evaluation where indicated
High-resolution oesophageal manometry
Induced sputum for eosinophils
Sputum AAFB
Laryngoscope
Methacholine challenge
Chest CT
Bronchoscopy

Improvement
Continue for 3 months and attempt withdrawal

No improvement
Consider low-dose opiate
Consider promotility agent
Consider gabapentin
Consider pregabalin
Consider cough control therapy

FIGURE 1 Cough assessment in adults. VAS: visual analogue scale; HARQ: Hull Airway Reflux Questionnaire; ACE: angiotensin-converting enzyme; F_{eNO}: exhaled nitric oxide fraction; LTRA: leukotriene receptor antagonist; PPI: proton-pump inhibitor; AAFB: alcohol and acid-fast bacilli; CT: computed tomography.

Question 2: Should F_{eNO}/blood eosinophils be used to predict treatment response to corticosteroids/antileukotrienes in chronic cough?

There is a need for convenient and practical tests for predicting anti-inflammatory treatment responses in patients with chronic cough. However, there is still a lack of quality evidence. Placebo-controlled trials are warranted to assess their utility and also consensus is required on threshold levels in patients with chronic cough.

One RCT [91] in adult non-smoking patients with chronic cough shows that baseline F_{eNO} levels (>30 ppb or <20 ppb) did not predict response to antileukotrienes. Cough frequency and quality of life were similar between high and low F_{eNO} groups at the end of treatment. Observational studies suggested that nonresponders to inhaled corticosteroids (ICS) may have significantly lower levels of F_{eNO} at baseline [92, 93], but the findings were not consistent [94]. Randomised placebo-controlled trials are required to validate the utility or otherwise of F_{eNO} as a predictor of treatment response in chronic cough patients. Currently, there is no study examining the predictive utility of blood eosinophils in patients with chronic cough.

Given the uncertainty of diagnostic testing, a therapeutic trial may be indicated for asthmatic cough. In adults, oral prednisolone for 1 week may cause a dramatic decrease in cough [95]. ICS may be used when oral administration is contraindicated, and they are preferable in children. However, they may be less effective, since inflammation in cough-variant asthma and eosinophilic bronchitis is located in different parts of the airway from that seen in classic asthma [96], and may be driven by other pathways such as the innate immune system [97]. This also may explain the greater efficacy of systemic leukotriene antagonists such as montelukast in asthmatic cough [98].

Reflux and dysmotility
In the absence of peptic symptoms 24-h pH monitoring for the investigation of reflux disease is not helpful. However, abnormal oesophageal physiology is very common in patients with chronic cough and may be detected with poor sensitivity by a barium swallow. More accurately, high-resolution oesophageal manometry provides diagnostic information as to the site and mechanism of dysmotility in the majority of patients [42].

The upper airways

In patients who report upper airway symptoms fibre optic laryngoscopy may be performed. The larynx is commonly found to be red and inflamed. However, the test has poor sensitivity and specificity. In select patients, laryngoscopy may be useful in identifying inducible laryngeal obstruction associated with cough, and this may help plan the need for future cough control therapy [99]. Rhinoscopy may be helpful in identifying polyps and clearing mucus from blocked sinuses in patients with recurrent sinus and nasal inflammation, but routine laryngoscopy, rhinoscopy or sinus CT is not advised as nasal findings are not directly associated with cough [100, 101].

Chronic cough in children

Chronic cough in children should be approached using paediatric-specific cough management protocols or algorithms and basing the management on the aetiology of the cough. The most commonly recognised aetiologies for chronic cough in children are post-infectious or natural resolution, asthma and PBB (figure 2).

Treatment of chronic cough

Even after a thorough clinical assessment, it may be impossible to identify which of the treatable traits is most likely to underlie the patient's chronic cough. Individuals may vary in their response to the different modalities of treatment. The guideline panel considered that it was preferable to undertake sequential therapeutic trials of each agent in turn and if no responses were observed therapy should be stopped. The length of the trial depends on the pharmacology. Response to morphine occurs within 1 week. ICS may take a month to have an effect. If successful, the guideline panel believes that treatment may be continued for several months to allow for resolution of neuronal hypersensitivity. Treatment may then be withdrawn to determine whether remission has occurred. Table 1 provides commentary on the recommendations made.

Anti-asthmatic drugs

Question 3: should anti-asthmatic drugs (anti-inflammatory or bronchodilator drugs) be used to treat patients with chronic cough?

We suggest a short-term ICS trial (2–4 weeks) in adult patients with chronic cough (conditional recommendation, low-quality evidence).

10 RCTs were identified for chronic cough, but with considerable heterogeneity in patient characteristics, intervention, measured outcomes and treatments responses. Two studies of chronic cough patients (unselected by airway hyperresponsiveness or sputum eosinophilia) found significant benefits from a 2-week high-dose ICS treatment over placebo in reducing cough severity [102] and subjective cough frequency. However, in a study of patients with chronic cough and at least one additional respiratory symptom but with normal lung function, an 8-week medium-dose ICS treatment did not produce a significant improvement in cough severity score over placebo. In two studies of patients with nonasthmatic chronic cough (defined by negative methacholine airway hyperresponsiveness), ICS treatment was not superior to placebo in improving cough outcomes [103, 104]. In studies of patients with chronic bronchitis or COPD, ICS treatment did not significantly improve subjective cough scores compared to placebo [105–108].

Although the original definition of CVA demonstrated improvement of coughing in a small number of asthmatic subjects with bronchodilator therapy, we do not recommend the use of a lone bronchodilator therapy as maintenance treatment for cough in asthmatic patients. The current Global Initiative for Asthma 2019 guidelines recommend the use of low-dose ICS–formoterol or low-dose ICS. The effectiveness of these treatment regimes in CVA and asthmatic cough still requires further evaluation.

We suggest a short-term ICS trial in children with chronic dry cough (2–4 weeks) (conditional recommendation, low-quality evidence).

Two RCTs were identified. A trial of 50 children aged 1–10 years with persistent nocturnal cough found that there is a modest but significant benefit in objective cough frequency from a 2-week course of high-dose ICS over placebo [109]. Another study of 43 children aged 6–17 years with recurrent cough (two episodes of cough, each lasting 2 weeks in the past 12 months) found no significant effects of ICS in cough outcomes at 4–5 weeks; there was no association between ICS treatment response and airway hyperresponsiveness with hypertonic saline challenge [110].

We suggest a short-term antileukotriene trial (2–4 weeks) in adult patients with chronic cough, particularly in those with asthmatic cough (conditional recommendation, low-quality evidence).

Three RCTs were identified. Two clinical trials [111, 112] of adults with CVA (defined by clinical history, absence of other common diseases and presence of methacholine hyperresponsiveness) found significant
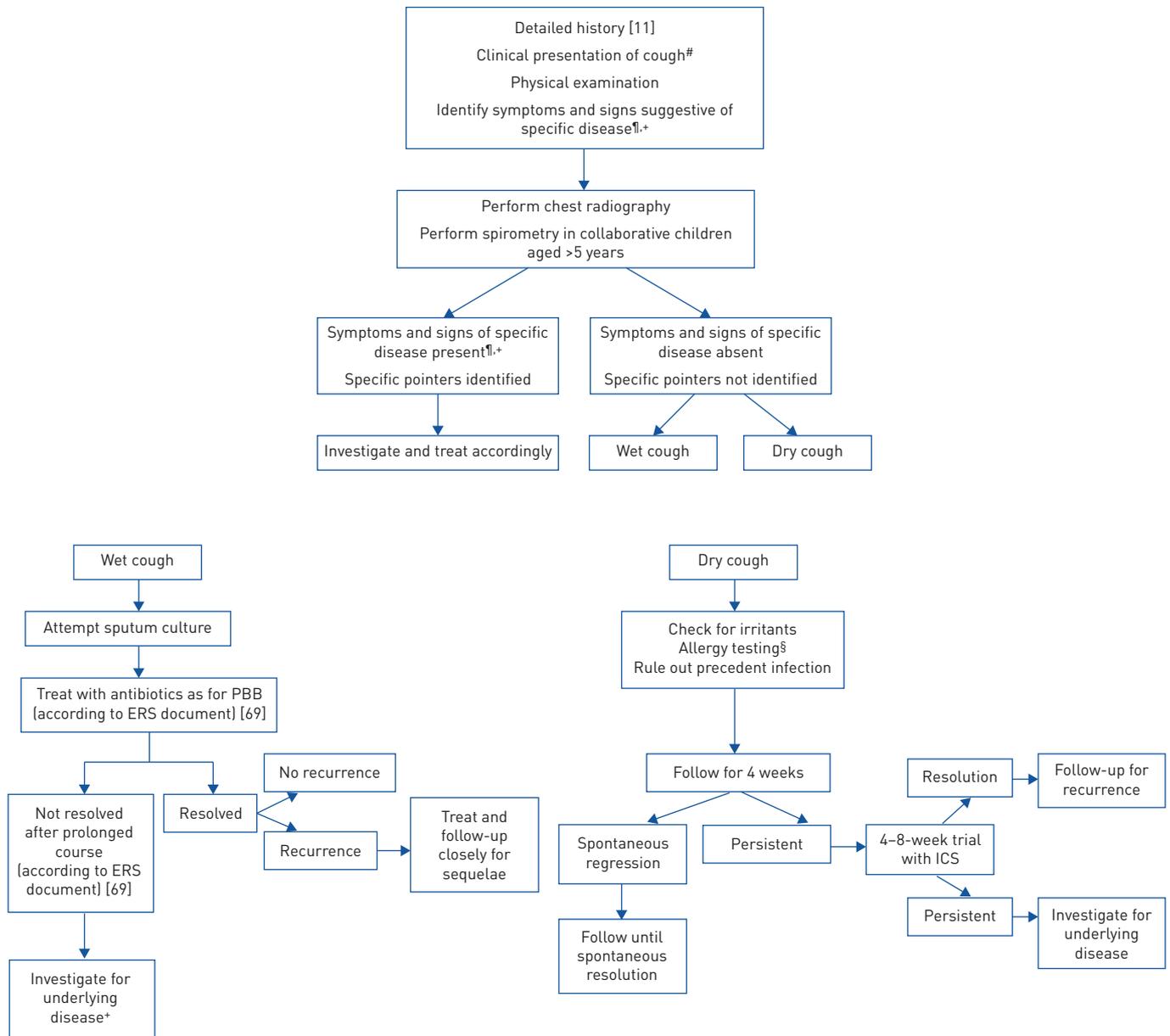
Detailed history [11]

Clinical presentation of cough[#]

Physical examination

Identify symptoms and signs suggestive of specific disease[¶,+]

↓

Perform chest radiography

Perform spirometry in collaborative children aged >5 years

Symptoms and signs of specific disease present[¶,+]

Specific pointers identified

→ Investigate and treat accordingly

Symptoms and signs of specific disease absent

Specific pointers not identified

→ Wet cough | Dry cough

Wet cough

↓

Attempt sputum culture

↓

Treat with antibiotics as for PBB (according to ERS document) [69]

Not resolved after prolonged course (according to ERS document) [69]

Resolved → No recurrence / Recurrence

Treat and follow-up closely for sequelae

Investigate for underlying disease[+]

Dry cough

↓

Check for irritants
Allergy testing[§]
Rule out precedent infection

↓

Follow for 4 weeks

Spontaneous regression

Follow until spontaneous resolution

Persistent → 4–8-week trial with ICS

Resolution → Follow-up for recurrence

Persistent → Investigate for underlying disease

FIGURE 2 Cough assessment flow chart for children. PBB: protracted bacterial bronchitis; ERS: European Respiratory Society; ICS: inhaled corticosteroids. [#]: how and when the cough started, time-course of cough, nature and quality of cough, symptoms associated with cough, triggers of cough, diurnal and nocturnal variations, cough associated with indoor and outdoor irritants; [¶]: chest pain, history suggestive of inhaled foreign body, dyspnoea, exertional dyspnoea, haemoptysis, failure to thrive, feeding difficulties (including choking/vomiting), cardiac or neurodevelopmental abnormalities, recurrent sinopulmonary infections, immunodeficiency, epidemiological risk factors for exposure to tuberculosis, signs of respiratory distress, digital clubbing, chest wall deformity, auscultatory crackles, chest radiographic changes (other than perihilar changes); [+]: cystic fibrosis, primary ciliary dyskinesia, immune deficiency, tuberculosis, aspiration syndromes, tracheobronchomalacia, somatic and tic cough, bronchiectasis, children's interstitial lung disease, upper airway syndrome, asthma, angiotensin-converting enzyme inhibitor-induced cough; [§]: testing for allergy is not to be routinely performed; it should be undertaken in the presence of features and signs of allergy.

benefits of oral antileukotriene (for 2–4 weeks) over placebo in subjective cough frequency or severity scores. However, a single trial of adults with atopic cough (defined as chronic cough with increased capsaicin cough sensitivity and atopic constitution, but without bronchial hyperresponsiveness) did not find any significant benefits of 2 weeks montelukast over placebo in subjective cough score [113]. Adverse drug events were reported in one study, without any significant events related to the treatment [112]. There are no trials conducted in unselected chronic cough patients.

No RCTs are available for children. Mild, transient neuropsychiatric adverse events are common (>10%) in children [114].

We suggest a short-term trial (2–4 weeks) of ICS and long-acting bronchodilator combination in adults with chronic cough and fixed airflow obstruction (conditional recommendation, moderate-quality evidence).

A single RCT [108] of COPD patients with chronic bronchitis, smoking history and at least one episode of COPD symptom exacerbation in the previous year found that the combination of 50 µg salmeterol and 500 µg fluticasone twice daily produced a significant improvement in cough severity score compared to placebo (scale 0–4) (mean difference −0.09, 95% CI −0.17– −0.01), whereas salmeterol or fluticasone monotherapy did not. The treatment was well tolerated, except for an increased incidence of oropharyngeal candidiasis (8% in the combination treatment group *versus* 2% in the placebo group).

Anti-acids

Question 4: Should anti-acid drugs (PPIs and H_2-antagonists) be used to treat patients with chronic cough?

We suggest that clinicians do not routinely prescribe anti-acid drugs in adult patients with chronic cough (conditional recommendation, low-quality evidence).

Anti-acid drugs are unlikely to be useful in improving cough outcomes, unless patients have peptic symptoms or evidence of acid reflux. Systematic reviews have found no significant benefits from PPI over placebo in adult patients without acid reflux and possible modest effect in those with acid reflux [54]. FARUQI *et al.* [115] found no significant benefits of esomeprazole 20 mg twice daily therapy over placebo in subjective cough frequency, cough severity or cough-specific quality-of-life scores at 8 weeks. There was a trend towards greater improvement in the PPI treatment arm in patients with dyspepsia. In a study of chronic cough patients with rare or no heartburn, there were no benefits from a long-term high-dose PPI therapy (esomeprazole 40 mg twice daily for 12 weeks) in cough-specific quality of life or cough scores [116]. While PPI is frequently considered safe, observational studies reported potential risks of iron deficiency, vitamin B12 deficiency, hypomagnesemia, *Clostridium difficile*-associated diarrhoea, osteoporosis-related bone fracture, dementia or pneumonia [117, 118]. However, direct evidence about the safety issues is lacking in the chronic cough population. There is not enough evidence to draw a specific recommendation for PPI use in children.

Drugs with promotility activity

Question 5: should drugs with promotility activity be used to treat patients with chronic cough?

There is currently insufficient evidence to recommend the routine use of macrolide therapy in chronic cough. A 1-month trial of macrolides can be considered in the cough of chronic bronchitis refractory to other therapy, taking into account local guidelines on antimicrobial stewardship (conditional recommendation, low-quality evidence).

No RCTs have been undertaken with promotility agents, such as baclofen, metoclopramide or domperidone, in patients with chronic cough. There are three RCTs with macrolides with promotility activity in adult patients with chronic cough. One study of patients with COPD Global Initiative for Chronic Obstructive Lung Disease stage ≥2 and chronic productive cough demonstrated a significant benefit of a 12-week low-dose azithromycin (250 mg three times a week) over placebo for improving cough-specific quality of life (LCQ; mean difference 1.3, 95% CI 0.3–2.3; p=0.01) [119]. Adverse events were not significantly different. In two other trials of patients with unexplained cough or treatment-resistant cough, low-dose macrolide treatments (erythromycin 250 mg daily for 12 weeks or azithromycin 250 mg three times a week for 8 weeks) did not provide significant benefits over placebo for objective cough frequency, cough severity or cough-specific quality of life [120, 121].

Neuromodulators

Question 6: which cough neuromodulatory agents (pregabalin, gabapentin, tricyclics and opiates) should be used to treat patients with chronic cough?

We recommend a trial of low-dose slow-release morphine (5–10 mg twice daily) in adult patients with chronic refractory cough (strong recommendation, moderate-quality evidence).

A single RCT of low-dose morphine (5–10 mg twice daily) in adults with chronic refractory cough found significant benefits over placebo in reducing cough severity (self-reported scale 0–9 points) (mean difference −1.96 points, 95% CI −1.09– −2.11 points) and improving cough-specific quality of life (LCQ) (mean difference 2 points, 95% CI 0.93–3.07 points) [27]. Common adverse effects in this clinical trial were constipation and drowsiness in patients receiving morphine.

We suggest a trial of gabapentin or pregabalin in adults with chronic refractory cough (conditional recommendation, low-quality evidence).

A single RCT of gabapentin therapy (maximum tolerable daily dose of 1800 mg) in adults with chronic refractory cough found significant benefits over placebo in improving LCQ (mean difference 1.8 points, 95% CI 0.56–3.04 points) and reducing cough frequency (although only of a single hour of observation) (mean difference −27.31%, 95% CI −2.87– −51.75%) and severity (VAS 0–100 points) (mean difference −12.33 points, 95% CI −1.23– −23.23) [122]. There is one RCT of pregabalin therapy (300 mg daily) in adult patients with chronic refractory cough alongside speech pathology therapy [123]. Pregabalin plus speech pathology therapy significantly improved cough-specific quality of life (LCQ) (mean difference 3.5 points, 95% CI 1.11–5.89; minimal important difference 1.3 points) and cough severity (VAS 0– 100 points) (mean difference −25.1 points, 95% CI −10.6– −39.6 points) over placebo plus speech pathology therapy. There was no significant reduction in cough frequency. There is no comparison between pregabalin and placebo alone. An explanation for a lack of effect on cough frequency is that centrally acting therapies may alter the perception of cough, rather than having truly antitussive effects. In addition, they could affect the intensity of coughing without reducing the frequency. Dizziness, fatigue, cognitive changes, nausea or blurred vision are common side-effects of gabapentin and pregabalin. A systematic review revealed that the risk of withdrawal due to adverse events is 2.3 times higher than placebo [124].

Use of agents acting directly on cough hypersensitivity rather than the treatable traits causing hypersensitivity is a promising strategy for future developments. Current agents have been shown to be effective in adults, but the side-effect profile is significant and may be mitigated by the use of lower doses than those used to treat pain.

Cough neuromodulators, such as opioids, gabapentin or pregabalin, are not used in children, due to reported adverse events, possible toxicity and lack of clinical trials [125].

Nonpharmacological cough control therapy

Question 7: should nonpharmacological therapy (cough control therapy) be used to treat patients with chronic cough?

We suggest a trial of cough control therapy in adult patients with chronic cough (conditional recommendation, moderate quality evidence).

Two RCTs of physiotherapy/speech and language therapy (cough control therapy) in adult patients with chronic refractory cough have been reported. VERTIGAN et al. [126] demonstrated that the 2-month intervention significantly reduced subjective cough score compared to placebo treatment (self-reported scale 2–10 points) (mean difference 2.8 points, 95% CI 1.3–4.0). In a multicentre study by CHAMBERLAIN MITCHELL et al. [127], the weekly intervention for 4 weeks showed benefits over placebo for cough-specific quality of life (LCQ; 1.53 points, 95% CI 0.21–2.85 points) and objective cough frequency (fold change) (0.59, 95% CI 0.36–0.95), but not for VAS severity or other quality-of-life outcomes. The improvements in the intervention group were sustained up to 3 months, but not beyond. No adverse effects were found. There are no RCTs in children. This is a complex intervention that requires further study to determine which components are of value. Experienced practitioners should undertake cough-directed physiotherapy and speech and language therapy interventions.

Antibiotics for chronic wet cough in children

Question 8: in children with chronic wet cough with normal chest radiograph, normal spirometry and no warning signs, should a trial of antibiotics be used?

A trial of antibiotics is suggested in children with chronic wet cough with normal chest radiographs, normal spirometry and no warning signs (conditional recommendation, low-quality evidence).

A single RCT of antibiotics in young children (mean age 1.9 years; interquartile range 0.9–5.1 years) with chronic wet cough (>3 weeks) [128]. A 2-week regimen of twice-daily oral amoxicillin clavulanate treatment (22.5 mg·kg^{-1} per dose) was compared. Cough resolution rates (defined as >75% reduction) were significantly higher in children who received amoxicillin clavulanate compared with those who received placebo (48% versus 16%; p=0.015). Side-effects were not significantly different between two groups; however, mild diarrhoea was found to be slightly greater in the in the amoxicillin clavulanate group than in the placebo group (five out of 25 versus two out of 25) [128].

Future directions and new drugs

As the population ages, the worldwide prevalence of chronic cough increases. This is partially due to an increasing awareness of the problem, changing diagnostic labels, air pollution and increased efforts in educating health professionals. Changes in society, such as the rise in obesity, will also predispose to a greater incidence of causal factors related to chronic cough. Our understanding of the pathophysiological basis of chronic cough has dramatically advanced over the past decade with the realisation that neuronal hypersensitivity underlies the syndrome. Desensitisation through the use of agonists such as capsaicin has recently shown promise as a therapeutic strategy [129]. However, we are still grossly ignorant of the complex interplay in the peripheral and central nervous system. fMRI has given us insights into the central pathways of cough and will continue to do so in the future. However, it is the pharmacology of the peripheral afferent vagus which has given us the most hopeful future therapeutic developments.

Much effort was devoted to the development of blockers of the nociceptors, mainly transient receptor potential receptors, which are responsible for the irritant sensation leading to the tickle that precedes cough. While effective in animal models, these agents have failed in the clinic [130, 131]. The substance P antagonist orvepitant has shown modest efficacy in phase 2 studies. However, one class of drugs has produced a dramatic improvement in chronic cough in phase 2 studies [132]. ATP is released during cell damage and acts on afferent sensory nerves through P2X3 purinergic receptors. The first antagonist, gefapixant, has been studied in several hundred patients with chronic cough with resolution in the majority. Other compounds in this class are in development and we may have the first effective drugs for chronic cough in >40 years.

Research gaps and recommendations for future studies

Because chronic cough has only recently been recognised as a separate entity, a major challenge is the promulgation of the concept of cough hypersensitivity in adults and conditions such as protracted bacterial bronchitis in children. While the aim of these guidelines is to further awareness we recognise the scale of the task and recommend that the ERS should advocate chronic cough as a classification in the World Health Organization International Classification of Diseases.

Very little is known of the natural history of chronic cough. We recommend observational cohort studies to identify the true prevalence of chronic cough in the population; the demographic characteristics of this patient population; the natural history of chronic cough over time; the clinical and psychosocial impact of chronic cough on patients; and the economic burden of chronic cough, both to the individual and society.

The assessment of chronic cough in both the clinical and research settings needs further development. Current instruments to assess quality of life need refinement to be useful in routine clinical practice. Patient reported outcomes need to be developed and validated. There is an urgent need for fully automated cough recording technology that continuously monitors patients in real time. Such devices may help confirm the diagnosis in the clinic, allow for objective assessment of clinical response, and ensure the entry of the correct population into clinical studies. In addition, the current clinical approach is largely based on sequential therapeutic trials; thus, practical biomarkers need to be developed to target treatable traits and guide treatment decisions in the clinic.

There are very few studies of cough in other diseases and currently patients with the syndrome of chronic cough are frequently mislabelled as suffering from other conditions. Studies of the overlap between respiratory disease and chronic cough are urgently needed, particularly in view of the differences in pathophysiology and treatable traits.

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