



Chronic cough in adults: recommendations from an Italian intersociety consensus

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Abstract

Background Chronic cough (CC) is a burdensome health problem in adult and older people, with a major impact on quality of life. Its management is often troublesome, and many guidelines have been released. Notwithstanding, a proportion of cases still do not reach a definite diagnosis and resolute treatment. A coordinated approach between different specialists would be highly recommended, but its implementation in clinical practice suffers from the lack of shared protocols and poor awareness of the problem. The present consensus document has been implemented to address these issues.

Aims To develop evidence-based recommendations for the management of adults with CC.

Methods A 12-member expert task force of general practitioners, geriatricians, pneumologists, allergologists, otorhinolaryngologists and gastroenterologists was established to develop evidence-based recommendations for the diagnostic and therapeutic approach to subjects with CC. A modified Delphi approach was used to achieve consensus, and the US Preventive Services Task Force system was used to rate the strength of recommendations and the quality of evidence.

Results A total of 56 recommendations were proposed, covering 28 topics and concerning definitions and epidemiology, pathogenesis and etiology, diagnostic and therapeutic approach along with the consideration of specific care settings.

Conclusion These recommendations should ease the management of subjects with CC by coordinating the expertise of different specialists. By providing a convenient list of topics of interest, they might assist in identifying unmet needs and research priorities.

Keywords Chronic cough · Unexplained chronic cough · Refractory chronic cough · Adult cough hypersensitivity syndrome · Multidisciplinary care team

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Introduction

Chronic cough (CC) is a burdensome health problem in adults and older people, and one of the most frequent causes of medical consultation, particularly in high-income countries, where its prevalence peaks at 10–20% [1]. The disorder is often reported as being severe and disabling, with a major impact on quality of life (QoL), the latter of which may be further compromised by the onset of sequelae such as urinary incontinence, cough syncope, or visceral organ herniation [2]. Such a circumstance frequently ends in social isolation, depression, and difficulties with relationships. The diagnosis and management of CC are also troublesome, with underlying causes such as respiratory disease (e.g., asthma and upper airway disease) and extra-respiratory disorders (e.g., gastroesophageal (GE) reflux), as well as multifactorial etiologies, frequently remaining uncertain. Finally, the central mechanisms of cough reflex hypersensitization—the so-called ‘cough hypersensitivity syndrome’ [3]—have recently been highlighted, which potentially further complicates the diagnostic and therapeutic pathway of these patients. To overcome these problems, and improve overall health status, several international guidelines [3–7] have been developed. Notwithstanding the availability of such valid assessment tools, a proportion of patients still fail to obtain a definitive diagnosis and receive resolute treatment. Moreover, given the wide spectrum of potential diseases underlying CC, undiagnosed and/or unresponsive patients require an integrated and coordinated multidisciplinary team approach to their care, the implementation of which—in clinical practice—is frequently hampered by local healthcare resourcing. The availability of updated and shared management protocols would potentially assist in the management of these patients. For this reason, the present consensus document has been developed by a multidisciplinary panel comprising geriatricians, general practitioners, internists, pulmonologists, otorhinolaryngologists, allergologists, and gastroenterologists to propose recommendations for the integrated and coordinated management of the adult, and older adult, with CC. This consensus document is designed to help clinicians, patients, researchers, and health policy makers to tailor management strategies to the individual patient.

Materials and methods

The present article is the outcome of a collaborative initiative between the following organizations: Associazione Italiana Pneumologi Ospedalieri (AIPO), Associazione

Italiana Studio Tosse (AIST), Consiglio Nazionale delle Ricerche (CNR), Istituto Superiore Sanità (ISS), Società Italiana di Allergologia, Asma ed Immunologia Clinica (SIAAIC), Società Italiana di Geriatria e Gerontologia (SIGG), Società Italiana di Medicina Generale e delle Cure Primarie (SIMG), and Società Italiana di Pneumologia (SIP). These societies appointed a task force of 12 experts who met on 3 March 2021 to define the scope of the project, identify key issues, and agree consensus methods.

It was decided that the consensus document would focus on the management of adults with CC. The following areas of investigation for CC were identified: (1) definition, epidemiology, and impact on health status; (2) pathogenesis and etiology; (3) diagnostic approach; (4) therapeutic approach; (5) specific settings of care; (6) diagnostic and therapeutic algorithms. Corresponding subcommittees were nominated which compiled a list of relevant topics for each area of focus. For each topic, a review of currently available evidence was carried out by a group of experts. A modified Delphi approach was used to achieve consensus (unlike traditional Delphi method, we began the process with literature review instead of an open-ended survey), and the US Preventive Services Task Force system [8] was used to rate the strength of recommendations (Table 1) and the quality of evidence (Table 2).

Based on the literature review, each subcommittee proposed specific recommendations with supporting evidence for each topic. Key issues were discussed at a subsequent meeting on 3 June 2021, after which a comprehensive document was shared with all task force members and subjected to three rounds of revision. Statements for each consensus (defined as greater than 70% agreement with less than 15% disagreement) were achieved and then resubmitted to the task force at a consensus conference on 30 October 2021, when recommendations and supporting evidence were reviewed and discussed by the entire group. Subsequently, a draft report of the final consensus was prepared and sent to the experts for modification and comment. Each author approved the final version prior to submission.

Definition, epidemiology and impact on health status

Definition

Cough is a physiological reflex, characterized by a sudden explosive expulsion of air from the lungs through the respiratory airways. While the cough reflex usually represents a protective mechanism, clearing the airways from noxious agents and unwarranted secretions, it is occasionally the expression of an underlying pathologic condition, which may frequently be difficult to diagnose. The definition

Table 1 US Preventive Services Task Force (USPSTF) grading of strength of recommendations

Grade	Definition	Suggestion for practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial	Offer or provide this service
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial	Offer or provide this service
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small	Offer or provide this service for selected patients depending on individual circumstances
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits	Discourage the use of this service
I	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined	Read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms

Table 2 Grading of quality of evidence (modified from US Preventive Services Task Force)

Quality of evidence	Description
High (A)	The available evidence usually includes consistent results from a multitude of well-designed, well-conducted studies in representative care populations. These studies assess the effects of the service on the desired health outcomes. Because of the precision of findings, this conclusion is therefore unlikely to be strongly affected by the results of future studies. These recommendations are often based on direct evidence from clinical trials of screening, treatment, or behavioural interventions. High-quality trials designed as ‘pragmatic’ or ‘effectiveness’ trials are often of greater value in understanding external validity
Moderate (B)	The available evidence is sufficient to determine the effects of the service on targeted health outcomes, but confidence in the estimate is constrained by factors such as: <ul style="list-style-type: none"> •the number, size, or quality of individual studies in the evidence pool •some heterogeneity of outcome findings or intervention models across the body of studies •mild to moderate limitations in the general applicability of findings to routine clinical practice As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion
Low (C)	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: <ul style="list-style-type: none"> • the very limited number or size of studies • inconsistency of direction or magnitude of findings across the body of evidence • critical gaps in the chain of evidence • findings are not generalisable to routine clinical practice • a lack of information on prespecified health outcomes • lack of coherence across the linkages in the chain of evidence. More information may allow an estimation of effects on health outcomes

of cough is generally based on features such as duration, underlying causes, associated characteristics, or treatment response.

Based on duration, cough can be defined as acute (lasting for less than 3 weeks), subacute (lasting for 3 to 8 weeks) or chronic (lasting for more than 8 weeks). While such definitions may seem arbitrary, this classification appears to appropriately reflect the different clinical phenotypes and be useful in diagnosing and guiding treatment in patients with cough [9].

In the context of CC, terms such as ‘refractory’, ‘unexplained’ or ‘idiopathic’ are often used to define a cough

that persists despite extensive investigative and therapeutic intervention. However, while all terms refer to a condition of non-responsiveness, each term identifies different types of CC and should not be used interchangeably. Indeed, refractory CC (RCC) relates to a cough that persists despite optimal treatment for the presumed underlying condition which may be common or uncommon—according to published best practice guidelines in an adherent patient [10]. Unexplained CC (UCC) refers to the circumstance in which no cause, common or otherwise, for the cough has been found, despite extensive diagnostic workup [10]. Although the term idiopathic CC is still in current use, UCC is now preferred as the

diagnostic term to describe cough that remains unresolved after thorough diagnostic and treatment intervention [5].

Recent insights into the mechanistic pathways of RCC and UCC have introduced the concept of the ‘cough hypersensitivity syndrome’, defined as a clinical syndrome characterized by troublesome coughing often triggered by low levels of thermal, mechanical or chemical exposure [3].

Statement	Type	Strength of recommendation/quality of evidence
Cough is a physiological protective mechanism of the airways	Statement of fact	
We recommend defining CC as cough persisting for more than 8 weeks	Recommendation	A/low
We recommend defining refractory CC (RCC) as a cough that persists despite optimal treatment for the presumed common and uncommon conditions	Recommendation	A/low
We recommend defining unexplained CC (UCC) in all circumstances when no diagnosable cause for CC has been found, despite extensive assessment for common and uncommon causes	Recommendation	A/low

CC, chronic cough

Epidemiology

Few data are available on the epidemiologic burden of CC. A meta-analysis of 90 studies published between 1980 and 2013 found an overall prevalence of around 10%, which was greater in high-income countries (~18% in Oceania and ~11–12% in Europe and America) than in low-income countries (~2–4% in Africa and Asia) [1]. These differences probably reflect inter-regional variations in air pollution, smoking habit and comorbidities. Regardless of these observations, a significant heterogeneity in reporting was found within the literature; indeed, in 19 studies CC was defined using the cutoff of 3 months, while only 3 studies applied the currently accepted definition of 8 weeks. Moreover, in most studies, the estimation of CC prevalence was not the primary objective, which could have clearly favored a poorly comparable methodology.

A more recent investigation confirmed the CC prevalence of 10% in a general population of 9,824 individuals aged 45 years or more, and prospectively observed an overall incidence rate of around 11 cases every 1000 person-years [11]. As expected, CC was more frequent in women, smokers and in those with chronic obstructive pulmonary disease (COPD) and asthma; CC also increased with age, peaking ~14.5% in the eighth decade.

In Italy, two phone surveys have indicated a slightly greater CC prevalence (~14–18%), with an increasing trend in the last decades [12, 13]. However, the applied methodology negatively affected comparability, which could have been distorted by selection and reporting bias. The epidemiological and clinical characteristics of CC in Italy appeared to be similar to those seen worldwide [14, 15].

Statement	Type	Strength of recommendation/quality of evidence
Prevalence data are uncertain because epidemiological studies on CC demonstrate poor comparison due to heterogeneous study populations, settings, and screening tools	Statement of fact	–

CC, chronic cough

Impact on health status

Chronic cough has a major impact on perceived health status [16, 17] and is associated with many other conditions such as sleep disturbance, depression, headache, dizziness, vomiting, urinary incontinence, costal fractures, herniation or prolapse of abdominal-pelvic organs and syncope [16, 18–21]. If left untreated, patients with CC usually report a mean of eight associated symptoms; they generally seek medical attention for the negative impact of CC on social life and relationships, the impact of which is proportional to the number of related symptoms [16]. After appropriate CC control, the majority of symptoms regress together giving a significant improvement in psychosocial and physical performances [16]. Addressing mood disorders such as anxiety and depression (in addition to CC) is of further importance in optimizing QoL [18].

Statement	Type	Strength of recommendation/quality of evidence
Chronic cough has an important impact on social life and relationships, giving rise to serious psychological consequences for patients and their families	Statement of fact	–
We recommend searching for potential complications of CC (e.g., syncope, GE reflux, mood disturbance, arrhythmias, headache, chronic chest pain, costal fractures, urinary incontinence, herniation or prolapse of abdominal–pelvic organs)	Recommendation	A/Moderate
We suggest exploring the impact of CC on health status via the use of validated questionnaires, either generic (e.g., SF36) or cough specific (e.g., Leicester Cough Questionnaire)	Recommendation	B/moderate

CC, chronic cough; GE, gastroesophageal

Pathogenesis and etiology

Pathogenesis

Cough is controlled by a complex reflex arc, which is subject to partial voluntary control. In summary, the afferent branch consists of a heterogeneous group of vagal afferent sensory fibers originating from the pseudo-unipolar neurons of the nodose and jugular ganglia [22]. Among these fibers, A δ fibers of the nodose ganglion—which are low-threshold and fast-conduction mechanical stretch receptors—form the so-called ‘cough receptor’ [22]. Conversely, C-fibers of the jugular ganglia activate in response to more variegated chemical, inflammatory and noxious stimuli (i.e., chemoreceptors), but with a lower conduction velocity [22]. Additionally, neurons of the jugular and nodose ganglia project ascending sensitive fibers to the nucleus of the solitary tract (i.e., the nodose ganglion) and to the paratrigebral nucleus (i.e., the jugular ganglion), both of which control the effector branch of the cough reflex [22]. However, the cough neural circuitry extends beyond a simple ponto-medullary

reflex arc to incorporate a network of neurons that are also widely distributed throughout the subcortical and cortical brain [23]. Studies have described discrete cortical and subcortical brain responses that account for the sensation of airway irritation, the urge to cough and the voluntary cough [23]. Moreover, two cough inhibitory pathways have been identified [23]. Firstly, the neural pathway of pain modulates the perception of cough; secondly, descending motor inhibitory pathways are responsible for the voluntary inhibition of cough. In this context, CC has been described as being characterized by a cough hypersensitivity syndrome that is underpinned by the dysregulation of neural pathways that control the cough reflex. This can occur following either peripheral or ponto-medullary sensitization or downregulation of the descending inhibitory cough mechanism [24].

Statement	Type	Strength of recommendation/quality of evidence
Individuals with CC have a cough hypersensitivity, which is also evoked by low intensity stimuli	Statement of fact	–
Cough hypersensitivity results from peripheral (vagal afferent receptors) and/or central (hyperactivity of the neural circuits and of the areas that regulate the cough reflex) sensitization	Statement of fact	–
Reduction in the efficacy of the descending inhibitory pathways may contribute to cough hypersensitivity, up to the possible development of a positive modulation similar to that involved in the establishment of chronic pain	Statement of fact	–
Interindividual variability in the mechanisms underlying CC makes the efficacy of central and peripheral pharmacological interventions poorly predictable	Statement of fact	–

CC, chronic cough

Etiology

In most patients with CC, one or more causes are usually identified. Asthma has a heterogeneous presentation and

may express with CC. Cough-variant asthma is a specific asthma phenotype with cough as the sole symptom, which improves with bronchodilator therapy [25]. Conversely, eosinophilic bronchitis manifests with cough but without bronchial hyper-responsiveness [26]. The latter may represent an early stage of occupational asthma with sensitization to high molecular weight compounds, eventually evolving into definite asthma over time [27]. Gastroesophageal reflux disease (GERD), esophageal dysmotility and aspiration may further explain CC (dubbed ‘reflux cough’) [28]. However, some experimental observations, including the inefficacy of proton pump inhibitor (PPI) therapy in the absence of typical reflux symptoms [29], together with the possibility that non-acid esophageal (i.e., non-gastric) fluid reflux could be an etiological factor [30], have shed uncertainties with regard to current theories of the underlying mechanism and therapeutic strategies for these patients.

Post-nasal drip syndrome (PNDS), often termed ‘upper airways cough syndrome’ (UACS), refers to a group of signs and symptoms such as rhinitis and rhinosinusitis and can cause CC due to chronic irritation and sensitization of the cough receptors by post-nasal mucous drip [31]. More generally, cough can arise from any pathologic condition involving compression, infiltration, obstruction, or distortion of the airways, as often happens in bronchiectasis, lung cancer, pneumonia, COPD, lung fibrosis, cystic fibrosis and sarcoidosis. Lifestyle and medications can also play a role. Smoking is the main remediable cause of CC [32]. Angiotensin converting enzyme inhibitors (ACEIs) increase the sensitivity of the cough reflex and should not be prescribed in individuals with cough or developing cough [33]. Bisphosphonates and calcium channel antagonists may exacerbate pre-existing reflux cough. Prostanoid eye drops (e.g., latanoprost) may drip through the lacrimal duct and irritate the pharynx [34].

As stated previously, however, in 20–30% of cases [6] CC may persist despite optimal treatment for the presumed causal condition or remain unexplained, despite extensive diagnostic workup.

Statement	Type	Strength of recommendation/quality of evidence
Because the diagnostic workup of CC generally allows identification of one or more underlying causes, we recommend focusing the initial assessment (history and clinical examination) on the most common etiologies (e.g., asthma, UACS, reflux cough, lifestyle and medications, and other inflammatory/infiltrative lung diseases)	Recommendation	A/mModerate
If the first-line workup is inconclusive, further diagnostic investigations are needed to exclude a diagnosis of UCC	Recommendation	A/moderate

CC, chronic cough; UACS, uUpper airways cough syndrome; UCC, unexplained chronic cough

Diagnostic approach

The multidisciplinary care team

Given the heterogeneity of potential underlying pathologies, CC should be approached by a multidisciplinary care team (MCT) if first-level investigations fail to reveal the underlying cause. The general practitioner, internist or geriatrician is called to comprehensively evaluate the patient’s medical condition along with the impact of CC on perceived QoL. The initial evaluation should be followed by screening for the most common underlying conditions, such as reflux cough, upper airways cough syndrome (UACS) and asthma, together with an evaluation of medication and lifestyle factors. Based on the outcome of this assessment, the involvement of further specialist physicians should be guided by the most probable underlying cause. Indeed, the otorhinolaryngologist, pulmonologist, allergologist and gastroenterologist can join the MCT to ensure effective diagnosis and therapy. In older patients with more complex requirements, involving multiple co-morbidities, polypharmacy and disability, a multidimensional geriatric assessment can guide the selection of interventions aimed at limiting the impact of CC on QoL.

Statement	Type	Strength of recommendation/quality of evidence
We suggest that patients with CC are initially managed by the general practitioner followed by, should diagnosis/treatment be unsuccessful, a multidisciplinary care team (MCT) comprising different specialists, i.e., geriatricians, pulmonologists, otorhinolaryngologists, allergologists and gastroenterologists.	Recommendation	B/low

CC, chronic cough; MCT, multi-disciplinary care team

History taking, physical examination, chest X-ray and impact on health status

The evaluation of patients with CC begins with careful history taking and accurate physical examination. The former should include any history of smoking, use of medications (e.g., ACEIs) and exposure to environmental and/or occupational pollutants. In addition, some symptoms provide clues to specific etiologies; hemoptysis, dyspnea, dysphagia, weight loss, fever, lower limb edema and change in cough characteristics should always be regarded with concern, because they may indicate more serious pathologies such as cancer and heart failure. Notwithstanding the importance of the initial patient evaluation, it is well documented that history taking alone is insufficient for making a correct diagnosis rendering the need for additional tests [35]. Physical examination should be focused on the upper and lower airways, and directed toward the identification of the typical signs of the most common causes of CC, i.e., reflux disease, UACS and asthma. Some clinical signs have high sensitivity for certain, even severe, pathologies, as in the case of bibasilar Velcro-like crackles for the diagnosis of idiopathic pulmonary fibrosis. Chest X-ray is indicated as the screening examination of choice for lower airway pathologies. Although it is frequently a first-level investigation, taking place at initial patient assessment, chest X-ray is worth performing only in cases of persistent cough after ACEI discontinuation and smoking cessation, whenever the latter is an achievable objective [36]. Finally, the impact of cough on perceived health status should be performed in all patients, applying either generic (Short

Form 36: Health Survey Questionnaire) [37] or cough-specific questionnaires (e.g., Leicester Cough Questionnaire) [38].

Statement	Type	Strength of recommendation/quality of evidence
We recommend directing the initial assessment (history taking and physical examination) towards the search of common conditions potentially causing cough; the assessment must include smoking history, use of medications (e.g., ACEIs) and exposure to environmental and occupational pollutants	Recommendation	A/moderate
We recommend performing chest X-ray as first-choice for screening for lower airway pathologies	Recommendation	A/moderate

ACEI, angiotensin-converting enzyme inhibitor

Respiratory function testing

Respiratory function tests are pivotal for the diagnosis of bronchopulmonary disease and spirometry should be performed in all individuals with CC with inconclusive medical visit and chest X-ray. If bronchial obstruction is documented, spirometry should be complemented by reversibility testing. Patients may sometimes present with cough without dyspnea and normal respiratory function tests; in such cases, cough can represent the sole symptom of asthma (i.e., cough-variant asthma). As such, in the presence of normal spirometry, the bronchoprovocation test with methacholine is indicated when clinical suspicion of asthma is high [39]. It should be noted, however, that, despite its sensitivity, the methacholine test retains poor specificity, frequently turning positive following viral airway infection.

Statement	Type	Strength of recommendation/quality of evidence
We recommend using respiratory function tests (spirometry) in all individuals with CC with inconclusive medical visit and chest X-ray	Recommendation	A/moderate
When lung function tests are normal, we recommend using the bronchoprovocation test with methacholine when the clinical history is suggestive of asthma or eosinophilic bronchitis	Recommendation	A/moderate
The methacholine test has a low specificity, and a positive result does not confirm asthma diagnosis while a negative result excludes it	Statement of fact	

CC, chronic cough

Sputum examination

Sputum analysis is useful in cases of productive cough. The search for common bacteria and acid–alcohol-fast bacilli should be performed by both microscopic analysis and cultures. Molecular tests for mycobacteria are expensive and should be reserved for cases with higher pre-test probability. Studies have shown that the isolation of fungi in patients with allergic bronchitis facilitates the identification of selected clinical phenotypes that may improve following antifungal therapy [40].

Statement	Type	Strength of recommendation/quality of evidence
We suggest using microscopic and cultural sputum examination in cases of productive cough, to exclude the presence of chronic infection	Recommendation	B / moderate

Statement	Type	Strength of recommendation/quality of evidence
In the absence of sputum, bronchoscopy with broncho-alveolar lavage may be indicated in the presence of high suspicion of infection or interstitial lung disease	Recommendation	C / moderate

Sputum/blood eosinophil evaluation and fractional exhaled nitric oxide

Eosinophilic inflammation can underpin CC and its identification is useful for etiological diagnosis and guidance of subsequent therapy [41]. The sputum eosinophil count (>3%) is the most accurate indicator and can be evaluated via sputum induction or bronchoalveolar lavage; however, it is not routinely available and requires expert interpretation. Evidence of sputum eosinophilia is usually associated with the presence of asthma or cough-variant asthma, although in the absence of bronchial hyper-responsiveness, it is suggestive of eosinophilic bronchitis [42]. The blood eosinophil count is a simple and readily available surrogate for the sputum eosinophil count, but is affected by higher variability [43, 44].

Fractional exhaled nitric oxide (FeNO) has moderate association with blood/sputum eosinophilia [45], and is helpful in both the diagnosis of asthma and useful in monitoring the efficacy of therapy [46]. However, FeNO has been shown to be predictive of positive response to inhaled corticosteroids (ICS) in patients with elevated baseline FeNO values [46, 47].

Statement	Type	Strength of recommendation/quality of evidence
Evidence of eosinophilic inflammation can be determined by induced sputum examination	Statement of fact	
FeNO testing and blood eosinophil count are non-invasive means to determine the presence of airway eosinophilia	Statement of fact	
FeNO levels, if increased, are predictive of a positive response to inhaled corticosteroids	Statement of fact	

FeNO, fractional exhaled nitric oxide

Allergy testing

Many pathologies underlying CC may have an atopic component, e.g., classic bronchial asthma or cough-variant asthma, allergic rhinitis, or atopic cough. If suspicious for such disease activity, allergy testing should be performed, of which the skin prick test is first line [1]. For specific IgE (sIgE) serum measurement, component-resolved diagnostics (CRD) is a novel technique that is used to characterize the molecular components of each allergen involved in an sIgE-mediated response. In clinical practice, CRD can improve diagnostic accuracy and assist the physician in the allergy workup [2]. While evidence of atopy increases the likelihood of allergic asthma, it is not essential for diagnosis. The evolution of CC is highlighted if associated with atopic stigmata (e.g., positive prick test, comorbidities such as rhinitis and eczema, and increase in the peripheral eosinophil count). Preliminary studies highlight interest in considering the continuum of the disease and the usefulness of identifying and monitoring 'respiratory' endotypes from a prevention perspective [3].

Statement	Type	Strength of recommendation/quality of evidence
We recommend performing allergy tests in all patients with CC if atopic sensitization is suspected	Recommendation	A / moderate
We recommend using the prick test as the first-line investigation for allergic respiratory disease	Recommendation	A / moderate
Given its better diagnostic specificity, we suggest searching for specific IgE with CRD	Recommendation	B / moderate

CC, chronic cough; CRD, component resolved diagnosis

Combined multichannel intraluminal impedance and pH-metry

One of the major indications for the use of combined multichannel intraluminal impedance and pH-metry (MII-pH) is the assessment of reflux in patients with extra-esophageal symptoms, for example, gastroesophageal reflux in CC patients without evidence of GERD (i.e., esophagitis or typical reflux symptoms) [48]. In these patients, MII-pH should be undertaken before starting anti-reflux treatment [48]. However, given the high prevalence of both CC and GERD

in the general population, evidence of pathologic reflux does not necessarily imply a cause-effect relationship with CC. Toward this end, an objective assessment of the reflux-cough association should be pursued via a concomitant recording of esophageal pressure to identify episodes of reflux caused by cough (cough-reflux-cough sequences) [49]. In any case, MII-pH should be performed after suspension of antisecretory therapy (e.g., PPIs, H₂ receptor antagonists) for at least 10 days, since discontinuation facilitates the recurrence of both the cough symptoms and acid reflux, thus improving the diagnostic performance, particularly in patients with atypical manifestations [50]. Demonstration of pathological acid reflux in patients with CC, while difficult to achieve, should nevertheless be pursued since it may predict the probability of a positive response to anti-reflux therapy [29].

Statement	Type	Strength of recommendation/quality of evidence
We recommend using MII-pH monitoring in patients with CC who do not have typical GERD signs or symptoms and in whom other more common causes of cough have been ruled out	Recommendation	A / high
We recommend performing MII-pH after suspending antisecretory therapy for at least 10 days; the test must be performed in specialized centers because establishing a causal link between episodes of reflux and cough is crucial and requires technical expertise	Recommendation	A / high

CC, chronic cough; GERD, gastroesophageal reflux disease; MII-pH, esophageal multichannel intraluminal pH-impedance

Proton pump inhibition trials

Due to their highly selective mechanism of action, PPIs have also been used as a diagnostic tool based on the principle that a good clinical response to their administration correlates with the existence of an acid-related disease, particularly GERD [51]. However, the utilization of PPIs as diagnostic tool in patients with atypical symptoms, such as CC, is controversial, since the response to PPIs in these patients is less predictable and can be influenced by several factors such as the coexistence of further pathologies and a significant placebo effect [52]. On the other hand, the

empirical PPI treatment approach has been shown to be cost-effective in comparison with the use of invasive diagnostic tests [53] and has been proposed by international guidelines as first-line approach to the treatment of patients with extra-esophageal symptoms, especially those with concomitant GERD signs or symptoms [48]. To improve the sensitivity of the PPI test, the current recommendation is to use PPIs twice daily for at least 2 months; any lack of response is most likely to be related to an overlap between GERD and other underlying causes [54].

Statement	Type	Strength of recommendation/quality of evidence
A PPI trial is recommended in patients with CC who display concomitant typical reflux symptoms (n.b., the trial should be avoided in patients without typical reflux symptoms). The trial must be undertaken with a twice daily standard dose of PPI for at least 2 months. Lack of response should promote the search for other causes of CC	Recommendation	A / moderate

CC, chronic cough; PPI, proton pump inhibitor

Laryngoscopy

Any suspicion of upper airway disease indicates the need for laryngoscopy. In compliant individuals, traditional laryngoscopy—based on indirect laryngeal view—can effectively provide clues to the etiology of CC. Conversely, in individuals with an accentuated protective reflex or specific anatomical conditions, fiberoptic laryngoscopy or video nasopharyngolaryngoscopy (VNPL) is needed to enable full visualization of the upper airways. In addition, VNPL can provide photos, help monitor patients during therapy and enable collection of data needed for the computation of classification scores of reflux disease or PNDS [55].

Statement	Type	Strength of recommendation/quality of evidence
We recommend performing laryngoscopy on all patients with CC who have suspected upper airway etiology	Recommendation	A / moderate
We suggest performing fiberoptic investigation (e.g., VNPL) when traditional laryngoscopy is not feasible (e.g., due to impeding reflexes or anatomical abnormality) and to objectify clinical signs of potential post-nasal drip or to rate laryngeal clinical signs potentially associated with GE reflux	Recommendation	C /low

CC, chronic cough; GE, gastroesophageal; VNPL, video nasopharyngolaryngoscopy

High-resolution chest computed tomography

The majority of individuals with CC and normal chest X-ray have no abnormal findings upon high-resolution chest computed tomography (HRCT); of those that do, abnormalities are not usually related to the cause of coughing [4]. As such, performing HRCT in patients with normal physical examination and chest X-ray confers no significant diagnostic advantage. Moreover, routine HRCT is associated with increased healthcare costs and not insignificant radiation dosages. Accordingly, the use of HRCT should be restricted to patients with undisclosed CC etiology based on the risk of less common causes being present, i.e., in the presence of occupational or pharmacological risk factors, or when the physical examination suggests a less common etiology (e.g., bibasilar Velcro-like crackles) or in heavy smokers.

Statement	Type	Strength of recommendation / quality of evidence
We do not recommend the use of HRCT as a first line investigation in patients with CC who display both normal physical examination and chest X-ray	Recommendation	D / moderate

Statement	Type	Strength of recommendation / quality of evidence
We suggest using HRCT only when the common causes of CC have been excluded, or in the presence of bibasilar Velcro-like crackles, or if an occupational or pharmacological risk profile is present	Recommendation	C / moderate

CC, chronic cough; HRCT, high-resolution chest computed tomography

Therapeutic approach

Inhaled corticosteroids

Inhaled corticosteroids offer a well-established therapy for the treatment of asthma [41]. The use of ICS in patients with CC has led to conflicting results, with heterogeneity of data on their efficacy being seen in adults with CC. The variability in response to treatment is mainly related to patient characteristics, in particular, the presence of eosinophilic inflammation. Studies on patients unselected by lung function and airway hyper-responsiveness found some evidence of ICS efficacy in reducing cough severity compared with placebo [56]. However, studies of patients with normal function and non-asthmatic CC failed to confirm these results [57, 58]. Based on this data, a short-term, 2–4 week, ICS trial can be offered to patients with CC, with subsequent discontinuation in the absence of suitable response. Longer-term regimens have not been shown to confer additional clinical advantage. It is noteworthy that the correct choice and use of the ICS delivery device is pivotal for granting any efficacy. The addition of antileukotriene drugs can be considered in patients partially responding to ICS therapy [59].

Statement	Type	Strength of recommendation / quality of evidence
We suggest the use of ICS for 2–4 weeks in cases of cough-variant asthma or eosinophilic bronchitis and, in the absence of a well-established pathogenetic mechanism, in the broader adult population with CC	Recommendation	B / moderate
We do not recommend the use of an ICS trial as a diagnostic <i>ex juvantibus</i> test for bronchial asthma	Recommendation	D / moderate
We suggest ICS as a valid therapeutic choice for the treatment of patients with CC with high suspicion of bronchial asthma	Recommendation	B / low
We suggest considering the addition of an antileukotriene agent (e.g., montelukast), when response to ICS is incomplete	Recommendation	C / Moderate

CC, chronic cough; ICS, inhaled corticosteroids

Neuromodulators

Given the central sensitization underpinning CC, neuromodulating agents—already in use for chronic pain management—can play a role in cough suppression. Within this context, two randomized clinical trials (RCTs) investigated the use of gabapentin and pregabalin in individuals with CC [60, 61]. Both studies disclosed significant benefits on cough severity and related QoL [60, 61]. However, the use of these drugs is hampered by high rates of adverse events (e.g., drowsiness, confusion, blurred vision and fatigue), which frequently lead to discontinuation [62]. Accordingly, patients should undergo close monitoring after prescribing which short start at low dosages, to be progressively increased, as tolerated. Evidence, although sparse, is also available for the use of tricyclic antidepressants (i.e., amitriptyline) [63, 64], but the paucity of available data currently hamper further consideration for routine use in clinical practice.

Statement	Type	Strength of recommendation / quality of evidence	Statement	Type	Strength of recommendation / quality of evidence
We suggest considering the use of neuromodulators (e.g., gabapentin and pregabalin) as an 'off-label' treatment for CC	Recommendation	C / moderate	In adult patients with RCC/UCC, the use of an 'off-label' drug (e.g., low-dose morphine, 5–10 mg twice daily) for the shortest possible time is indicated after careful evaluation of the risk/benefit profile and following patient consent	Recommendation	A / high
We recommend progressive dose titration and close monitoring of patients prescribed with a neuromodulator for CC, since the clinical response can be extremely variable, and the risk of side effects high—especially in older patients with multiple comorbidities	Recommendation	A / hHigh	Codeine might be prescribed in patients with UCC only when other treatments have failed because of the drug's highly variable interindividual metabolism and undesirable side effect profile	Recommendation	C / moderate
We recommend carefully discussing the risk–benefit balance with the patient before starting neuromodulator therapy for CC	Recommendation	A / high	CC, chronic cough; RCC, refractory chronic cough; UCC, unexplained chronic cough		

CC, chronic cough

Opioids

Opioids act by reducing cough hypersensitivity and are known to provide higher response rates (with a safer side effect profile) compared with the other neuromodulating agents. One study reported significant improvement in cough severity and cough-specific QoL with low dose morphine (5–10 mg twice daily) [65]. Response is generally very rapid (usually within a week), and side effects are limited with such low doses. Alternatively, codeine is considered a second-choice opioid given interindividual genetic variability in drug metabolism giving rise to less predictable treatment response and side-effect profile.

Proton pump inhibitors, prokinetics and topical agents

Proton pump inhibitors have been shown to play a pivotal role in the treatment of patients with CC attributed to GE reflux [66]. Unfortunately, the same excellent results have not been obtained in patients with extraesophageal manifestations and results of controlled studies have substantially reduced the use of anti-acid therapy in patients with UCC. In one study carried out on 40 patients with rare or no heartburn, the administration of high-dose esomeprazole for 12 weeks did not improve QoL or cough symptoms [67]. Moreover, a meta-analysis of seven controlled studies involving acid-suppressing therapy showed that the therapeutic gain was greater in patients with pathologic esophageal acid exposure (range, 12.5%–35.8%) than in those without exposure (range, 0.0%–8.6%), with no overlap between groups [29]. Therefore, the efficacy of PPIs in patients with CC substantially depends on appropriate patient selection given the lower, or even absent, efficacy in individuals without typical reflux symptoms.

There are limited data on the benefit of twice daily compared with once daily PPI administration [68] although the former appears preferable since it ensures better reflux control [69]. Similarly, limited data are available for the benefit of prokinetic agents in patients with suspected extraesophageal reflux. These drugs are generally more effective

on gastric motility than on GE reflux. A meta-analysis suggested that the available data does not support the use of these agents in patients with laryngopharyngeal reflux [70]. Finally, no studies are available that specifically address the effect of topical agents, e.g., alginates, on patients with chronic persistent cough.

Statement	Type	Strength of recommendation / quality of evidence
We recommend PPI therapy in patients with CC only in the presence of typical reflux symptoms (e.g., heartburn, regurgitation) and/or objectively documented acid reflux	Recommendation	A / moderate
We do not recommend the use of prokinetics or topical agents (e.g., alginates) as first choice therapy, but rather, as adjunctive treatment	Recommendation	D / moderate

CC, chronic cough; PPI, proton pump inhibitors

Antibiotics

The most consistent evidence for the use of antibiotics in the treatment of CC mainly concerns children [71]; no specific adult trials have been conducted so far. Accordingly, the use of antibiotics is currently restricted to the treatment of bacterial respiratory infection as evidenced by radiology or microbiology. The use of antibiotics in the absence of obvious infection has been shown to have no effect on cough improvement and, conversely, to induce antibiotic resistance.

Statement	Type	Strength of recommendation / quality of evidence
We suggest using antibiotic therapy only in the presence of bacterial infection, as documented by microbiologic or radiologic findings	Recommendation	B / moderate

New pharmacological agents for chronic cough

New insights into the pathophysiology of CC and its neurobiological correlates have prompted the identification of new therapeutic agents. These agents generally target

specific receptors/transporters on the synaptic terminals of sensitive vagal fibers, which have been recently highlighted to play a role in the mechanisms of cough hypersensitivity. Indeed, new agents targeting TRPV1 (SB-705498 and XEN-D0501) and TRPA1 (GRC 17536) have been studied, but showed suboptimal results [72–74]. Gefapixant is a new selective P2X3 antagonist which has been shown in two recent phase III RCTs to be effective in reducing cough frequency at the dose of 45 mg twice daily in patients with refractory or unexplained CC [75]. The only evident side effect was dose-dependent dysgeusia. The other three P2X3 antagonists (BAY1817080, BLU-5937 and S-600918) are currently in phase of study.

Statement	Type	Strength of recommendation / quality of evidence
The new anti-cough agents, which target specific channel receptors, have shown some effectiveness in reducing the frequency and intensity of cough, improving QoL in patients suffering from RCC and UCC	Statement of fact	
The first of these agents (i.e., gefapixant) demonstrates a good tolerability profile, except for dose-dependent dysgeusia	Statement of fact	

QoL, quality of life; RCC, refractory chronic cough; UCC, unexplained chronic cough

Non-pharmacological therapy

Non-pharmacological therapy includes a variety of strategies based on speech and behavioural training that are directed towards improvement of voluntary cough control. These strategies should be always driven by the clinicopathological evaluation of the treating physician and involve specialists in speech pathology and speech therapy. Available evidence seems to support the standardization of logopedic treatment, based on the following steps: 1) education; 2) strategies to reduce cough; 3) reduce laryngeal irritation; and 4) psycho-educational counseling [76]. Despite many studies evidencing the efficacy of non-pharmacological therapies, their wide application in clinical practice remains hampered by the absence of standardized outcome measures, and of well-designed and larger-powered controlled studies [77].

Statement	Type	Strength of recommendation / quality of evidence	Statement	Type	Strength of recommendation / quality of evidence
We suggest the use of logopedic treatment as a valid and safe non-pharmacological intervention for patients with CC	Recommendation	B / low	We recommend that the general practitioner plays a central role in the management of CC via comprehensive history taking and physical examination, together with the use of first-line diagnostic tests. Referral to the most appropriate specialist physician should be undertaken, as needed	Recommendation	A / moderate
We recommend that logopedic treatment is guided by otorhinolaryngologist assessment	Recommendation	A / low	CC, chronic cough		

Specific settings of care

Primary care setting

Cough is one of the most common symptoms in patients seeking advice from primary care physicians [78], accounting for approximately 8% of all consultations [79]. General practitioners can generally diagnose patients accurately based on their symptom pattern, response to medication, and family history [80]. The medical history often provides important initial clues regarding the underlying cause of CC. All patients should be questioned about the use of ACEIs and the presence of an upper respiratory tract infection at the onset of coughing. Further investigations, such as chest X-ray and spirometry, can be performed as part of a systematic approach to exclude common causes prior to referral. There is evidence that referral to secondary care for CC occurs prematurely. In the UK, a survey reported that only 31% of general practitioners were aware of published guidelines for CC, and less than 75% of patients had undergone chest X-ray and less than 40% underwent spirometry or a trial of corticosteroid treatment to exclude asthma prior to referral [81]. Despite this, even if detailed history-taking and first level examination will provide a diagnosis in most cases, some patients still require specialist referral.

Geriatric setting

Chronic cough is more frequent in older people, reaching a prevalence of nearly 20% compared with 10–12% in the general adult population [82]. Indeed, individuals aged 65 years or more represent around one third of all patients coming to medical attention for CC, a proportion expected to rise with progressive population aging [82]. Moreover, CC exerts a more serious impact on overall health status in this patient group, members of which have been shown to experience high rates of secondary depression and urinary incontinence [17, 83]. The underlying etiologies are also generally different from those observed in the wider adult population, with higher prevalence of congestive heart failure, laryngeal dysfunction, pulmonary disease or cancer, in addition to pharmacological causes [82]. The clinical profile is consequently much more heterogenous and includes the interaction between reported symptoms, multiple coexisting pathologies and prescribed medications. Accordingly, an adequate comprehensive geriatric assessment is necessary to guide diagnostic and therapeutic decision-making to prioritize care offering the most convenient risk–benefit balance. Furthermore, within the context of older people, many commonly used therapies for CC—including antihistamines, morphine, and neuromodulators—are known to potentially induce severe adverse events and, as such, should be prescribed with particular caution. Finally, the ‘double-sided’ nature of cough management in older individuals should be noted. While ongoing cough may indeed be underpinned by hypersensitization, hyposensitization of the cough reflex (with consequent aspiration due to dysphagia) may occur, particularly in patients who are cognitively impaired [84]. Hence, particular attention should be paid to coughing

during and after meals in older patients with dementia or other neurological comorbidities.

Statement	Type	Strength of recommendation / quality of evidence
In older patients with CC, we recommend undertaking a comprehensive geriatric assessment to better evaluate competing causes of cough, the impact on health status, and plan the therapeutic strategy offering the most appropriate risk–benefit balance	Recommendation	A / moderate

CC, chronic cough

Pulmonology setting

The pulmonologist is generally the leading specialist physician for patients with CC, because lung diseases commonly underlie the disorder. The diagnostic workup starts from careful history taking and physical examination directed toward identification of the most common respiratory causes, e.g., bronchial asthma, which can sometimes manifest only with cough (i.e., cough-variant asthma). In the latter case, the diagnosis must be confirmed by appropriate tests because CC remission after ICS trial cannot be regarded as diagnostically conclusive. Conversely, individuals with confirmed bronchial asthma may not fully respond to ICS because of the presence of underlying competing causes. The pulmonologist may also be required to investigate the presence of less common etiologies, such as interstitial lung diseases or bronchiectasis. In this case, HRCT is the radiological examination of choice. Bronchoscopy is also useful in specific circumstances [85]; broncho-alveolar lavage is helpful in the detection of eosinophilic bronchitis or occult infection [86]. Should pulmonary causes of CC be excluded, a wider search should then be pursued via the MCT.

Statement	Type	Strength of recommendation / quality of evidence
We recommend that the pulmonologist fully considers and address any extrapulmonary causes of CC	Recommendation	A / moderate

Statement	Type	Strength of recommendation / quality of evidence
We also recommend considering less common causes of CC, such as interstitial lung disease and bronchiectasis; in such cases, HRTC is the diagnostic examination of choice.	Recommendation	A / moderate

CC, chronic cough; HRCT, high-resolution chest computed tomography

Otorhinolaryngology setting

The clinicofunctional evaluation of the ear, nose and throat region is essential for the correct diagnosis, classification, and treatment of individuals with CC[87]. Indeed, laryngeal and pharyngeal receptors play a central role in the cough mechanism, and many pathologies inducing CC are characterized by alteration in the upper airways (e.g., post-nasal drip) or the swallowing mechanism attributable to presbyphagia.

Statement	Type	Strength of recommendation / quality of evidence
We recommend the clinicofunctional evaluation of the ear, nose and throat region as an essential part of diagnosis, classification and treatment of individuals with CC	Recommendation	A / best practice

CC, chronic cough

Gastroenterology setting

The gastroenterologist is often called to manage patients with CC because GERD is among its potential underlying causes. However, such involvement should be seen in the context of multidisciplinary collaboration and should generally be preceded by pulmonary and otorhinolaryngology evaluation.

The presence of typical symptoms of GERD in the patient with CC may justify the prescription of empiric PPI therapy, because its efficacy is known to be higher in these patients. [29] Diagnostic tests may also be useful in some patients without typical GERD symptoms, both to confirm

the diagnosis and to disclose cases in which reflux and CC coexist but are not causally linked.

Statement	Type	Strength of recommendation / quality of evidence
We recommend gastroenterology consultation in cases of suspected GERD. A confirmed diagnosis of GERD increases the probability of CC remission after acid-suppressive therapy. Conversely, the exclusion of GERD allows avoid unnecessary and potentially harmful therapies and diagnostic tests	Recommendation	B / moderate

CC, chronic cough; GERD, gastroesophageal reflux disease

Allergology setting

The etiology of asthma is multifactorial, and its clinical picture varies greatly among patients. Asthma is characterized by chronic airway inflammation, clinically presenting as variable airway narrowing (i.e., wheezes and dyspnea) and cough [41]. Patients with cough-variant asthma can account for around 30% of CC referrals; these patients manifest mild airway hyper-responsiveness on methacholine challenge with preservation of deep inspiration bronchoprotective reflex. [88] The presence of an allergic component to cough-variant asthma has been identified in most cases, in addition to concomitant atopic pathologies such as allergic rhinitis and eczema. In these cases, the presence of associated cough indicates more severe forms of bronchial asthma [89]. Pathological analyses in asthma demonstrate chronic airway inflammation accompanied by the infiltration of proinflammatory cells—including eosinophils, lymphocytes, mast cells, and others—and detachment of the airway epithelial cells [41, 88]. While many patients are atopic (i.e., positive for IgE antibodies against environmental allergens), airway inflammation and lymphocyte activation are present even in patients without allergen-specific IgE antibodies. Patients with cough-variant asthma can exhibit eosinophilic airway inflammation, a feature that has been linked to more severe disease, when comparing eosinophilic to non-eosinophilic patients with CVA [89]. Asthma symptoms often occur at night and in the early morning. Repeated exacerbations occur amid symptom-free intervals and develop even at rest. Patients with asthma may experience dyspnea during exercise and while performing laborious work. A comprehensive diagnostic workup should be made if asthma-like

symptoms are borderline (and which may relate to other cardiopulmonary disease) or if upper respiratory tract disorders (such as laryngitis, epiglottitis, or vocal cord dysfunction) or eosinophilic bronchitis are considered. The differential diagnosis of COPD should be made carefully, as this may overlap with asthma [41].

Hypersensitivity pneumonitis (HP) can also cause CC, and the identification of potential exposures is an important aspect of its diagnosis. Specific IgG tests can be valuable in identifying suspicious exposures or pointing towards an, as yet, unidentified exposure. However, there is a lack of well-defined predicted values for specific IgGs and the tests cannot differentiate between sensitization and disease. Exposure tests such as the specific inhalation challenge are highly sensitive and specific for HP but can only be performed at specialist centres [90]. Finally, it is important not to forget that cough induced by medicines, such as ACEIs, has an incidence between 3.9 to 35% [91]. In consideration of the evidence, the role of the allergologist is crucial in the diagnosis of CC and in the execution of immunological and allergological tests for etiological and differential diagnosis purposes. The presence or not of an allergic component to CC will then assist the allergologist in making the most appropriate choice of targeted therapy.

Statement	Type	Strength of recommendation / quality of evidence
The role of the allergologist in the diagnostic and therapeutic workup of the patient with CC is essential in all cases when an atopic component and underlying sensitization is suspected	Recommendation	A / low

CC, chronic cough

Diagnostic and therapeutic algorithms

Chronic cough is a common symptom potentially caused by a variety of different, often undetected, pathologies. A carefully reasoned and stepwise approach to diagnosis (Figure 1) is pivotal to optimize the chances of correct diagnosis, and to save healthcare resources. Initial investigations can be undertaken by the general practitioner and are widely available at the level of primary care. A careful history – which should include the comprehensive assessment of CC in terms of duration, ‘triggers’ and pattern of presentation, along with any history of smoking, medications (e.g., ACEIs), and the possible exposure to environmental and



Fig. 1 Suggested diagnostic algorithm for chronic cough (CC). ACEI, angiotensin-converting enzyme inhibitors; COPD, chronic obstructive airways disease; FeNO, fractional exhaled nitric oxide; HRCT, high-resolution chest computed tomography; ICS, inhaled corticosteroids;

LCQ, Leicester Cough Questionnaire; PPI, proton pump inhibitors; QoL, quality of life; Sf-36, Short Form 36: Health Survey Questionnaire; UACS, upper airways cough syndrome

occupational pollutants – together with an accurate physical examination can together provide clues as to the most probable underlying cause. In addition, ‘red flags’ such as the presence of hemoptysis, dyspnea, dysphagia, dysphonia, weight loss, fever, lower limb oedema or change in cough characteristics should be regarded with caution, because they are indicative of pathologies associated with a more severe prognosis (e.g., heart failure or cancer).

Similarly, some physical signs are highly specific for certain diseases, some of which may be severe—as in the case of bibasilar Velcro-like crackles for idiopathic pulmonary fibrosis. The impact on QoL should be also investigated, via the use of validated scales, as well as any onset of potential complications. In older individuals, the geriatrician can help correctly weigh the impact of CC in the context of coexisting pathologies, and tailor an effective diagnostic and therapeutic pathway. Finally, chest X-ray and spirometry are indicated to determine the presence of both structural and functional lung disease. When all these investigations remain inconclusive, referral to other

specialist physicians is indicated, and a multidisciplinary integrated approach (the so called ‘cough clinic’) is the primary choice. The MCT is called to take overall charge of the patient, with each specialist acting in the context of his or her specific competence. Close interaction and case discussion between the MCT members is necessary for the correct interpretation of test results. At the end of the MCT evaluation process, a diagnosis of ‘explained’ or ‘unexplained’ CC is collegially formulated, and the therapeutic management tailored to the individual patient. In this regard, disease-specific guidelines are useful for guiding the treatment of specific CC, while more challenging is the management of unspecific CC (i.e., UCC). Lifestyle changes, control of risk factors, and cessation of smoking, are pivotal to effective management alongside comprehensive logopedic assessment and treatment. A short-duration ICS trial is generally recommended; if ineffective, other therapeutic strategies can be adopted under close monitoring, according to available recommendations (*see Therapeutic Approach and Fig. 2*). Frequent evaluation

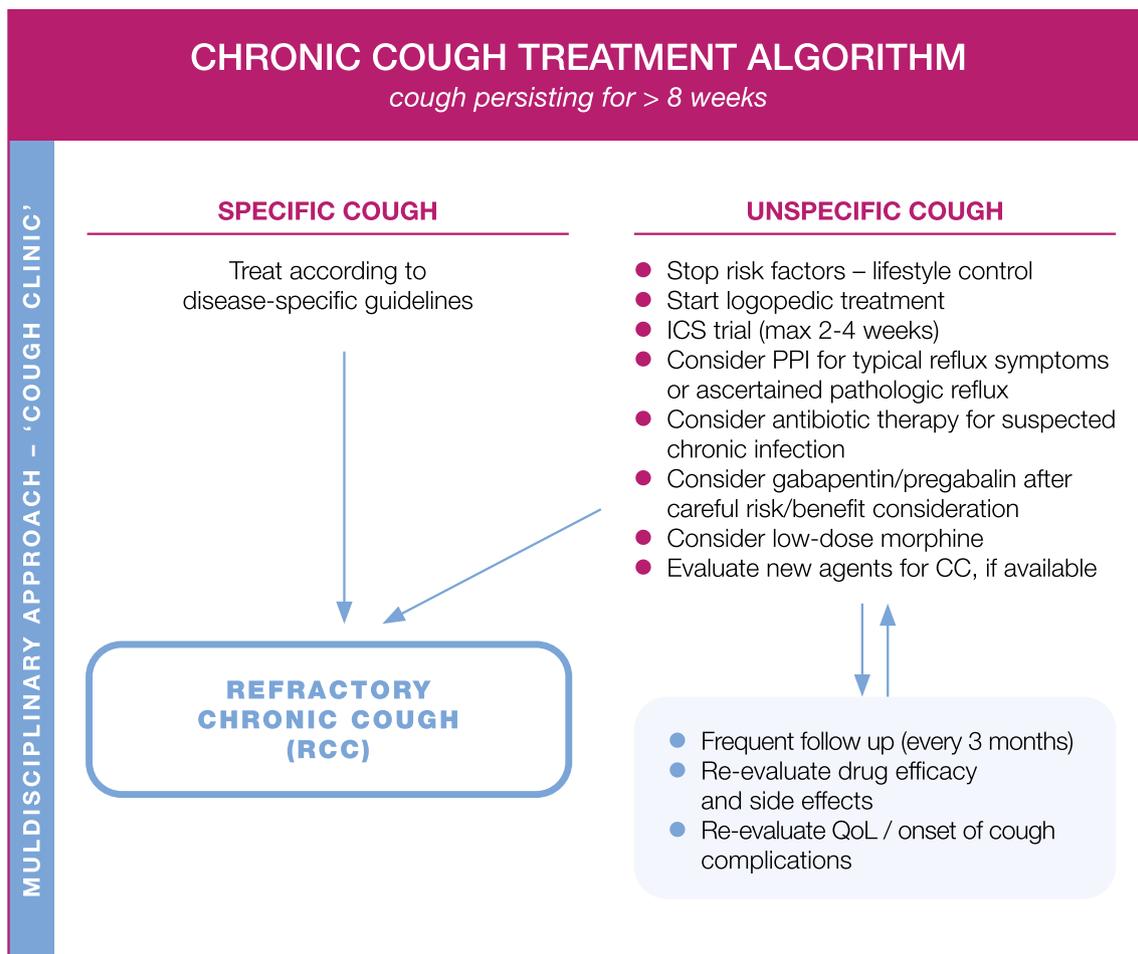


Fig. 2 Suggested therapeutic algorithm for chronic cough (CC); ICS, inhaled corticosteroids; PPI, proton pump inhibitors; QoL, quality of life

of drug side effects, QoL and onset of complications are also important, particularly when patients do not respond, or only partially respond, to the prescribed therapies (i.e., subjects with RCC).

Gaps in knowledge and indications for future research

There are still many gaps in our knowledge about CC, starting from definition and pathophysiology through to diagnostic and therapeutic management. Based on the gaps identified in the available literature, the panel of experts discussed and proposed a research agenda with prioritized tasks for the proposed topics. Evidence on the impact and pathogenesis of CC emerged as an important area for further research.

Research agenda

Definition

CC, UCC and RCC may have significant clinical impact. Research is needed to improve their respective classifications and thus tailor therapeutic approach

To overcome the current 'convenient' classification of cough, studies are needed to clarify the pathophysiological mechanisms underlying cough

Epidemiology

CC has only recently been recognized as a discrete entity; in future, CC might be further characterized as cough hypersensitivity syndrome in adults

Observational cohort studies, based on the use of standardized tools and shared diagnostic criteria, are needed to estimate the true prevalence and incidence of CC; understand its natural history; evaluate its physical, psychological and social impact; and estimate its economic burden

The possibility of including CC among the ICD should be investigated

Impact on QoL

Current tools for assessing QoL should be optimized to provide a validated, standardized and multidimensional view of the impact of CC on overall health status

The prevalence and prognostic implications of the complications of CC are not fully understood

Pathogenesis

It is worth investigating:

1. To what extent the affective status impacts on CC, a prerequisite for potential targeted therapy
2. To what extent RCC/UCC share underlying pathogenetic mechanisms
3. Whether the frequent secondary failure of therapy corresponds to a real change in the pathogenetic mechanisms of cough

Etiology

It is worth investigating:

1. Whether clusters of symptoms, signs and patient history data exist that may suggest the most probable etiology
2. What mechanisms, or supervening contributing causes, account for secondary failure of therapy in CC of known etiology

Diagnostic approach

Research agenda

Studies are needed to evaluate to what extent a multidisciplinary approach involving different medical specialists (i.e., the 'cough clinic') could improve diagnostic and therapeutic outcomes

It would be useful to verify if the diagnostic approach should vary according to age

Studies are needed to validate the use of FeNO as a predictor of treatment response in patients with CC

Therapeutic approach

Controlled studies should be carried out to evaluate the efficacy of topical antacids in patients with CC related to GE reflux

Further pathophysiological studies are needed to investigate the relationship between cough hypersensitivity and new therapeutic targets for CC

Simplified speech therapy treatment techniques should be developed and widely disseminated to ensure access to this type of therapy for every patient with CC regardless of etiology

CC, chronic cough; GE, gastroesophageal; FeNO, fractional exhaled nitric oxide; ICD, International Classification of Diseases; QoL, quality of life; UACS, upper airways cough syndrome; UCC, unexplained chronic cough

Conclusions

These recommendations should support the diagnostic and therapeutic pathway of patients with CC by promoting an evidence-based, multidisciplinary approach to care that integrates the expertise of general practitioners, geriatricians, pulmonologists, allergologists, otorhinolaryngologists and gastroenterologists. Specific contributions of individual team members may vary according to the patient's clinical characteristics, results of baseline examinations and response to therapies. In general, the general practitioner takes responsibility for the initial management of the patient with CC. In cases of undisclosed etiology, or persisting CC despite pharmacologic (trial) intervention, the MCT is called upon to assist with diagnosis and further therapeutic strategies. Even in cases of UCC or RCC, maximum effort should be made to comprehensively assess and monitor patients, particularly with regards to the impact on QoL and the onset of complications. Toward this end, effective and tailored patient communication remains the hallmark of good compliance with clinical management. While this article is designed to promote evidence-based and integrated management of patients with CC by senior clinicians, the findings are also suitable for residents in the specialties commonly involved in the management of these patients as well as medical students. Finally, by providing a convenient list of topics of interest, this article might also assist with the identification of unmet needs, research priorities and the performance of cost-efficacy analyses.

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Declarations

Conflict of interest AZ has received grants from Menarini outside of the submitted work; SM has received grants from Sanofi Pasteur, MSD, GSK, Pfizer and Takeda outside of the submitted work; FL has received grants from MSD, Menarini, Chiesi, GSK and Boehringer Ingelheim outside of the submitted work; FB received grants for scientific consulting of Alfasigma; ADV, RAI, GG, MC, GO, FFL and AV report no conflict of interest.

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Informed consent Not applicable.

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