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WAO-ARIA consensus on chronic cough - Part III: Management strategies in primary and cough-specialty care. Updates in COVID-19

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ABSTRACT

Background: Chronic cough management necessitates a clear integrated care pathway approach. Primary care physicians initially encounter the majority of chronic cough patients, yet their role in proper management can prove challenging due to limited access to advanced diagnostic testing. A multidisciplinary approach involving otolaryngologists and chest physicians, allergists, and gastroenterologists, among others, is central to the optimal diagnosis and treatment of conditions which underly or worsen cough. These include infectious and inflammatory, upper and lower airway pathologies, or gastro-esophageal reflux. Despite the wide armamentarium of ancillary testing conducted in cough multidisciplinary care, such management can improve cough but seldom resolves it completely. This can be due partly to the limited data on the role of tests (eg, spirometry, exhaled nitric oxide), as well as classical pharmacotherapy conducted in multidisciplinary specialties for chronic cough. Other important factors include presence of multiple concomitant cough trigger mechanisms and the central neuronal complexity of chronic cough.

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Subsequent management conducted by cough specialists aims at control of cough refractory to prior interventions and includes cough-specific behavioral counseling and pharmacotherapy with neuromodulators, among others. Preliminary data on the role of neuromodulators in a proof-of-concept manner are encouraging but lack strong evidence on efficacy and safety.

Objectives: The World Allergy Organization (WAO)/Allergic Rhinitis and its Impact on Asthma (ARIA) Joint Committee on Chronic Cough reviewed the recent literature on management of chronic cough in primary, multidisciplinary, and cough-specialty care. Knowledge gaps in diagnostic testing, classical and neuromodulator pharmacotherapy, in addition to behavioral therapy of chronic cough were also analyzed.

Outcomes: This third part of the WAO/ARIA consensus on chronic cough suggests a management algorithm of chronic cough in an integrated care pathway approach. Insights into the inherent limitations of multidisciplinary cough diagnostic testing, efficacy and safety of currently available antitussive pharmacotherapy, or the recently recognized behavioral therapy, can significantly improve the standards of care in patients with chronic cough.

Keywords: Upper airway cough syndrome, Lower airway disease, Reflux cough, Chronic cough management, Neuromodulators, Speech therapy, Cough primary care, Cough specialty care

INTRODUCTION

Chronic cough is a troublesome and complex condition with significant impact on quality of life (QoL).^{1,2} Various triggers originating from the airways and gastrointestinal tract (GIT), among others, can result in chronic cough. This is mediated by transient receptor potential (TRP) channels and P2X purinergic receptors located on peripheral afferent and central neuronal network of the vagus nerve.³ Data on tussigen challenges and expression of neuromediators and inflammatory biomarkers in animal and human cough models provide insights into the pathogenesis of chronic cough. Accordingly, the cough reflex manifests a neurogenic inflammation and becomes hypersensitive.⁴ Part I of the World Allergy Organization (WAO)/Allergic Rhinitis and its Impact on Asthma (ARIA) consensus (see appendix) on chronic cough described the important role of the hypersensitive cough reflex (HCR) as a trigger mechanism of chronic cough in infectious and inflammatory, respiratory and GIT-related conditions.³ Part II of the consensus examined other pathogenic mechanisms inherent to cough-associated inflammatory conditions which can also modulate HCR. These include Type 2 (Th1 and Th2) inflammation, cough plasticity and tissue remodeling, among others.⁵ Yet, a clear

description of how different cough trigger mechanisms interact with each other to cause persistent coughing is yet unknown.

Chronic cough management necessitates a clear integrated care pathway approach. A proper diagnostic and management protocol consists of a thorough evaluation and control of treatable traits which may underlie or worsen the cough reflex. These include infectious and inflammatory, upper and lower airway pathologies or gastroesophageal reflux, and are conducted in primary and multidisciplinary health care.⁶ Subsequent management conducted by cough specialists aims at control of cough refractory to prior interventions⁷ and includes cough-specific behavioral counseling and pharmacotherapy with neuromodulators, among others. The lack of direct access to cough specialists may result in misdiagnosis of chronic cough or overdiagnosis of idiopathic chronic cough.

EVALUATION AND EMPIRICAL TREATMENT IN PRIMARY CARE

Initially, identification of potential habitual and environmental cough triggers is merited, followed by exposure avoidance, if possible (Fig. 1A). Triggers may include smoking, dust/chemicals/

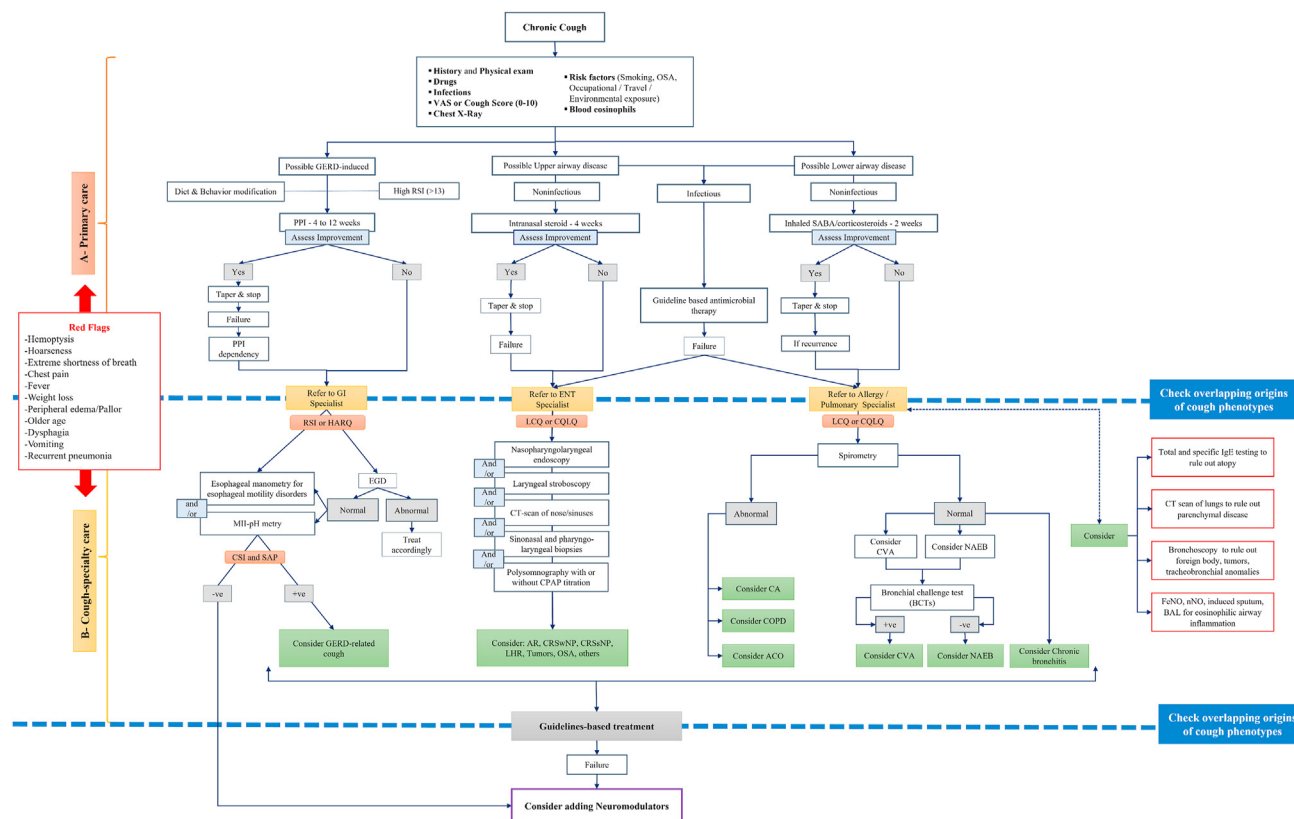


Fig. 1 Suggested algorithm for management of cough phenotypic traits in primary (A) and cough-specialty (B) care. ACO (asthma COPD overlap; AR, allergic rhinitis; BCTs, bronchial challenge tests; CA, classic asthma; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; CQLQ, Cough Quality-of-Life Questionnaire; CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; CSI, cough symptom index; CT, computerized tomography; CVA, cough variant asthma; EGD, esophagogastroduodenoscopy; FeNO, fractional exhaled nitric oxide; GERD, gastroesophageal reflux disease; GI, Gastrointestinal; HARQ, Hull Airway Reflux Questionnaire; LCQ, Leicester Cough Questionnaire; LHR, laryngeal hyperresponsiveness; MII-pH, multichannel intraluminal impedance monitoring combined with pH-metry; NAEB, non-asthmatic eosinophilic bronchitis; OSA, obstructive sleep apnea; PPI, proton-pump inhibitors; RSI, reflux symptom index; SABA, short-acting beta agonist; SAP, symptom association probability)

allergens exposure at home or work, in addition to other factors such as changes in ambient temperature/humidity, scents, sprays, aerosols, and exercise.^{8,9} Diagnosis of infectious etiologies of chronic cough in the upper and lower airways, and their subsequent empirical management, is merited. For example, endobronchial infections manifesting as chronic wet cough such as chronic suppurative lung disease, cystic fibrosis (CF)- and non-CF-related bronchiectasis, among others, can warrant a 3-week empirical antimicrobial treatment and further specialty care referral in case of failed therapy.¹⁰ Reportedly, infrequent but important infectious agents presenting with chronic cough include *Bordetella* (pertussis and paraper-tussis).^{11,12} Inspection of obstructive sleep apnea (OSA) features manifested by snoring, nocturnal apnea/hypopnea, and daytime somnolence concomitantly with cough is essential. Any

concurrent medication that can induce chronic cough¹³ as a side effect should be explored, such as angiotensin-converting enzyme (ACE) inhibitors (5-30%),¹⁴⁻¹⁸ opioids (28-66%),¹⁹ and statins (46%)²⁰ which collectively constitute common causes of drug-induced cough.¹⁸ In asthmatics, the use of nonsteroidal anti-inflammatory drugs²¹ or non-selective beta-blockers, but not cardio-selective beta blockers,²² can induce bronchospasm and cough in subsets of patients and should be ruled out. Other less common causes of chronic cough such as foreign body inhalation and malignancy should be excluded. In primary care, a chest x-ray is an informative screening test in chronic cough despite poor sensitivity to some interstitial lung diseases or mediastinal disorders.²³ Serum eosinophilia as a biomarker of eosinophilic inflammation can be easily measured but its

utility in chronic cough is questionable due to its diurnal and seasonal variability.²⁴ The impact, severity, and treatment response of chronic cough can be assessed by scaled (1-10) cough scores, visual analog scale, and validated cough-related quality of life (QoL) measures²⁵ such as Leicester cough questionnaire.²⁶ Other validated instruments include laryngeal hypersensitivity questionnaire,²⁷ chronic cough impact questionnaire,²⁸ and Hull airway reflux questionnaire.²⁹ Proper chronic cough management in primary care can prove challenging due to limited access to advanced diagnostic testing. Although the efficacy of natural (ie, honey)³⁰ or pharmacologic antitussive agents³¹ in acute cough lacks solid evidence, their role in chronic cough remains to be established. However, a therapeutic/diagnostic pharmacotherapy regimen can be prescribed based on symptom "pointers" (Fig. 1A); its failure in cough improvement entails further referral to multidisciplinary care.

Upper airways

In the upper airways, rhinitis or rhinosinusitis, whether atopic or nonatopic, is a condition frequently associated with upper airway cough syndrome (UACS). There is clear disparity in the indications of oral antihistamines in children³² and adults³³ with chronic cough in different parts of the world. Treatment of rhinitis patients with oral antihistamines or leukotriene receptor antagonists (LTRAs) does not provide much benefit for cough.³⁴ Also, previous studies reporting efficacy of oral antihistamines used objective cough assessment tools but examined older generation antihistamines marked by their anticholinergic effect and with a short-term duration (<2 weeks) of clinical trials.^{35,36} Other reports^{37,38} recommended (4-6 weeks) empirical therapy of new generation antihistamines in chronic cough patients with rhinitis but with unpredictable response. Taken together, the WAO/ARIA expert panel does not recommend oral antihistamine therapy in patients with rhinitis and cough in view of their low efficacy in reducing cough.

Intranasal corticosteroids improved cough scores in (non-asthmatic) seasonal allergic rhinitis (SAR) patients following 2 weeks of therapy, reportedly linked to a reduction in postnasal

secretions and/or pharyngeal mucosal inflammation.³⁹ Data suggest they can also be effective at reducing daytime cough in patients with chronic rhinosinusitis (CRS), though treatment may require several weeks to achieve maximal effect.⁴⁰ We previously reviewed the capsaicin challenge data indicating allergic rhinitis (AR) is a risk factor for chronic cough.⁵ Taken together, a 4-week therapy with intranasal corticosteroids is warranted (low evidence of efficacy) in AR patients with upper airway disease-related cough. Patients who improve on such therapy can be tapered down gradually, whereas those with partial or no improvement can be referred to cough specialty care. Notwithstanding, controlled trials using validated cough outcome measures are needed to evaluate efficacy of intranasal corticosteroids or combination of intranasal corticosteroids/topical antihistamines in UACS.

Lower airways

In the lower airways, key principles in pharmacotherapy of chronic cough using bronchodilators and inhaled corticosteroids (ICS) are to treat obstructive lung disease (classic asthma [CA]/chronic obstructive pulmonary disease [COPD]) and eosinophilic airway inflammation.⁴¹⁻⁵¹ However, it should be noted that clear data on the role of pharmacotherapy in chronic cough originating from the lower airways are unclear.⁴³ For example, in clinical trials of chronic cough patients with asthma, cough was not studied independently of other asthma symptoms. Also, it is yet unclear how airway eosinophilia impacts cough⁴² although it can identify steroid-responsive patients.⁵² An initial 2-week empirical trial of short-acting bronchodilator supplemented with ICS may be warranted in chronic cough patients. Alternatively, a short course of oral corticosteroids can be prescribed if patient cannot tolerate ICS. The latter has the advantage of causing an earlier response to therapy compared to ICS which may take several weeks to exert an effect. In contradistinction, other expert panels do not advocate an initial empirical trial of ICS not evidenced by airway hyperresponsiveness or eosinophilia.⁵³ Improvement in cough following corticosteroid therapy is inclusive of asthma, cough variant asthma (CVA), or non-asthmatic eosinophilic bronchitis (NAEB).^{54,55}

Gastrointestinal tract

Gastroesophageal reflux disease (GERD)-related cough is ideally a nonproductive postprandial cough often exacerbated in the supine position. Behavioral changes are recommended in all patients with GERD irrespective of concomitant cough. These can include bed head elevation, weight reduction, smoking cessation, and dietary changes.⁵⁶ Initially, a 4-12-week empirical and diagnostic trial of proton pump inhibitors (PPIs) can improve a substantial proportion (up to 79%) of patients, thereby confirming diagnosis of GERD-related cough. Accordingly, PPI therapy can be tapered to the lowest dose for control of cough and the patient should be referred to a GI specialist for further investigation of underlying gastrointestinal disorders, or in case of PPI failure or dependency. Guidelines, consensus, and expert opinions on chronic cough have been well described elsewhere.⁵⁷⁻⁶² Listed below are clinical clues which can improve diagnostic accuracy of chronic cough in multidisciplinary care.

DIAGNOSTIC TESTING IN MULTIDISCIPLINARY CARE BY SPECIALISTS

Upper airways

- Ear exam can trigger cough, a mechanism mediated by Arnold's nerve.⁶³
- Mouth examination can reveal hypertrophied/obstructive tonsils reportedly associated with cough.^{64,65}
- Allergy can be assessed by skin tests or serum specific IgE testing, but tests should be interpreted according to symptoms.
- Endoscopic nasopharyngolaryngoscopy can also be informative (Fig. 1B). Sinonasal polyposis may be associated with asthma as part of the airway eosinophilia syndrome or aspirin exacerbated respiratory disease.^{66,67} CRS without nasal polyps is also associated with airway hyperresponsiveness.⁶⁸ Adenoid hypertrophy/inflammation, frequently diagnosed by X-ray and occasionally by endoscopy (in school-age children), is commonly encountered in pediatric

CRS⁶⁹ which is a major cause of chronic cough in children.⁷⁰

- Pharyngeal endoscopy often supplemented by bronchoscopy is useful in diagnosis of infrequent pharyngolaryngeal^{71,72} and lung tumors which can trigger cough.⁷³
- Laryngoscopy, at times followed by stroboscopy, is helpful in the diagnosis of vocal cord pathologies such as paresis/paralysis, dysphonia, tension voice and tumors.^{71,74,75}
- A split-night polysomnography testing concomitant with a titration cycle using continuous positive airway pressure can assist in the diagnosis and management of patients with OSA and chronic cough, respectively.⁷⁶

Following diagnosis of one or multiple etiological factors of chronic cough originating from the upper airways, corresponding management follows well established guidelines.⁷⁷⁻⁸³

Lower airways

- Spirometry: Patients presenting with chronic cough in primary care frequently have normal lung function. Spirometry, commonly conducted in pulmonary and allergy care, can reveal airflow obstruction,⁸⁴ variability (>20%) in peak expiratory flow measurements,^{60,85} or an improvement in threshold testing (FEV1>12%, improvement from baseline of >200 mL) in response to bronchodilators (β -2 agonists).⁸⁶ An abnormal spirometry can be encountered in patients with CA and COPD, but not in patients with CVA or eosinophilic bronchitis (EB) (Table 1).
- Bronchial challenge testing (BCT) are recommended in the etiological diagnosis of chronic cough in patients with reactive airway diseases (Table 1B).³⁸
- Direct (methacholine/histamine) or indirect (mannitol)⁸⁷ BCT for airway hyperresponsiveness can be helpful in the diagnosis of asthma and NAEB as a primary cause of chronic cough (Table 1). A negative BCT, such as an FEV1 decrease of <20% at the highest methacholine challenge dose (10 mg/mL), has a high negative predictive value of asthma as an etiological

	Spirometry ⁴¹	Bronchial hyperresponsiveness (methacholine) ^{44, 55, 151}	FeNO (ppb) ^{37, 103, 105}	Therapeutic response ^{41, 42, 44-49}			
				Parental steroids	Bronchodilators	ICS	LTRAs
CA	Abnormal	Present	30-40	(+)ve	(+)ve	(+)ve	(+)ve
NAEB ¹¹⁸	Normal	Absent	22.5-31.7	(+)ve	(-)ve	(+)ve	(+)ve
CVA	Normal	Present or Borderline	30-40	(+)ve	(+)ve	(+)ve	(+)ve
COPD	Abnormal	Present	NA	(+)ve	(+)ve	Not fully established	(-)ve

Table 1. Comparative analysis of ancillary testing and pharmacologic response in cough-phenotypic traits originating from the lower airways. CA, classic asthma; COPD, chronic obstructive pulmonary disease; CVA, cough variant asthma; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroids; LTRA, leukotriene receptor antagonist; NAEB, non-asthmatic eosinophilic bronchitis

diagnosis in chronic cough.⁸⁸ In a stepwise diagnostic approach, an initial abnormal lung function testing suggests CA or COPD; normal testing is inclusive of CVA, NAEB, or chronic bronchitis (Fig. 1B). The absence of bronchial hyperreactivity to methacholine or mannitol⁸⁹ challenge in patients with seemingly normal physical examination and spirometry findings raises suspicion of NAEB.⁹⁰ Similarly, a negative airway responsiveness can exclude CVA.⁵⁵ Of importance, a BCT is contra-indicated if immediate spirometry is abnormal.

- Fractional exhaled nitric oxide (FeNO) measurement⁴³ for airway eosinophilia can also be helpful.³⁸ However, its use as a biomarker of eosinophilic airway inflammation and, by inference, steroid responsiveness, requires further elucidation. This is due to variable correlation between FeNO and airway eosinophilia as measured in induced sputum, bronchoalveolar lavage, or bronchial biopsies.⁹¹⁻⁹⁷ Notwithstanding, low FeNO is valuable in determining absence of eosinophilic airway inflammation^{91,98,99} keeping in mind that the test predictive values (positive or negative) are dependent on the prevalence of eosinophilic airway inflammation in the tested population, and hence cannot be generalized. The role of FeNO in chronic cough is less clear. FeNO can generally assist in identifying subgroups with asthma, CVA and NAEB as potential causes of chronic cough^{59,100-103} (Table 1). More precisely, it has been reported FeNO values below 30 ppb can reliably « rule out » asthma as a cause of chronic cough,¹⁰⁴ but higher values do not necessarily « rule it in »¹⁰⁵. Others suggested FeNO can diagnose asthma or CVA as etiological factors in chronic cough with moderate accuracy at optimal cut-off values between 30 and 40 ppb.¹⁰⁵ A meta-analysis revealed a relatively high (0.85) specificity of FeNO in predicting asthma in adults patients with chronic cough despite lack of consensus on cut-off levels for the diagnosis.⁵⁹ In comparison, FeNO diagnostic accuracy in predicting eosinophilic bronchitis (EB) in nonasthmatic chronic cough is lower compared to CVA which questions its utility in the former group.⁵⁹ Notwithstanding, it has been

suggested FeNO can « rule in » NAEB at optimal cut-off values ranging from 22.5 to 31.7 ppb.^{59,103} This lack of clear cut-off levels of FeNO for the etiological diagnosis of asthma, CVA and NAEB in chronic cough¹⁰⁵⁻¹⁰⁷ limits its usefulness as a routine diagnostic modality and follow-up assessment tool for chronic cough and compels its validation in future studies.^{59,62,108,109} In the upper airways, an abnormally low nasal nitric oxide (nNO) is reportedly a predictor of nasal polyposis in severe asthmatic patients even when blood eosinophils are normal or low.¹⁰⁰ Also, primary ciliary dyskinesia can present with chronic cough (sinopulmonary infections) and low nNO^{110,111} which can be supplemented by other testing modalities.¹¹² In conclusion, despite the well-established role of FeNO as an eosinophilic biomarker in asthma, its indication in patients with concomitant chronic cough needs further elucidation.

- Induced sputum may represent the most accurate surrogate marker of airway eosinophilia¹¹³ despite concerns of its reproducibility¹¹⁴ (Table 1) and inherent technical difficulties. Data suggest that induced sputum eosinophil count is gradually increased in NAEB, CVA, and CA, in sequential order.¹¹⁵ The sensitivity of induced sputum varies widely in the diagnosis of asthma.^{116,117} A sputum eosinophil count of >3% is generally indicative of NAEB in absence of bronchial hyperresponsiveness (BHR) or variability in peak expiratory flow rates^{118,119}; it is also reportedly associated with corticosteroid responsiveness in asthma and COPD.^{120,121} FeNO cannot be substituted for induced sputum in the diagnosis of eosinophilic airway inflammation due to concerns of low sensitivity and specificity of the former in detecting sputum eosinophilia, according to a meta-analysis.¹²² Both induced sputum eosinophilia and FeNO can predict response to ICS in patients with cough.¹²³ In conclusion, spirometry and BCT are powerful tools in the etiological diagnosis of chronic cough in patients with reactive airway diseases. FeNO and induced sputum cells to assess for airway eosinophilia can be helpful and should be considered in patients presenting with chronic

cough but their role in diagnosing etiological factors of the hypersensitive cough reflex needs further elucidation.

- Lung computed tomography (CT) imaging has a low yield in chronic cough in the presence of a normal chest radiography, and clinical examination.¹²⁴ However, a CT is generally indicated to rule out parenchymal lung disease.
- Ancillary procedures in pulmonary care can include bronchoscopy to rule out rare cases of chronic cough such as tracheopathia, tracheomalacia, lung tumors and foreign body aspiration.⁶⁰ Bronchoscopy may also provide bronchoalveolar lavage fluid for eosinophil count examination and biopsies for suspected tumors in chronic cough.

Gastrointestinal tract

Since some degree of reflux is present in healthy people, a self-assessed reflux symptom questionnaire, at a reflux symptom index (RSI) > 13, can assist in identifying subgroups of chronic cough patients with concomitant gastroesophageal and laryngopharyngeal reflux¹²⁵ (Fig. 1B). Reportedly, a high score also suggests presence of proximal rather than distal reflux as well as non-acid and gas reflux in patients with chronic cough.¹²⁶ Interestingly, data suggest the gastric proteolytic enzyme, pepsin, can adhere to laryngopharyngeal epithelium to cause inflammation and hypersensitivity and thus contribute to non-acid gastric reflux.¹²⁷ As stated previously, patients who fail to improve or are dependent on an empirical therapy of PPIs in primary care should be referred to a GI specialist to rule out non-acid/gas reflux. Chronic cough refractory to PPI therapy in patients suspected of having non-acid or gas reflux-related cough can undergo esophagogastroduodenoscopy (EGD) with or without biopsies. EGD can exclude other potential diagnoses which are not necessarily cough-related and include Barrett's esophagus, eosinophilic esophagitis,^{128,129} or its variant, PPI-responsive eosinophilic esophagitis, among others. EGD is also indicated if more serious cough-comorbid signs and symptoms are present, such as older age (>50 years) with weight loss, anemia, and dysphagia. It is generally agreed a normal EGD in patients with chronic cough does

not exclude GERD¹²⁸ and necessitates pH measurement in patients suspected of having GERD-related cough.¹³⁰ Ambulatory multichannel intraluminal impedance monitoring combined with pH-metry (MII-pH) is superior to the standard 24-h esophageal pH monitoring since it can record temporal association of cough with acid as well as non-acid reflux events, as measured by intraluminal pH and impedance probes, respectively.¹³¹ Recently, an ambulatory pH-impedance-pressure monitoring has been introduced to assess concomitantly the impact of esophageal dysmotility in the etiology of GERD-related cough.¹³² Clinically, MII-pH carries the highest sensitivity and specificity for diagnosis of GERD-related cough, yet it is an invasive test with limited availability.¹³¹ It is usually performed off antacid treatment. The temporal association between cough and reflux events is recorded over 24-h using MII-pH probes and assessed by symptom index and symptom-association probability (SAP) index.¹³³⁻¹³⁵ Following this, non-PPI-responsive patients with negative impedance and pH-metry findings are unlikely to have GERD-related cough and can be candidates for neuro-modulator therapy. Patients with confirmed GERD-related cough can be candidates for fundoplication surgery preceded by esophageal manometry to rule out motility disorders.¹³⁶ Recent guidelines suggest fundoplication surgery can be considered in cases of PPI dependency, more so in young patients,^{56,137} but is not advisable with a normal acid exposure time in the distal esophagus as determined by impedance-pH-metry.⁵⁶

COVID-19 cough

- Endoscopic visualization of the respiratory tract can be performed during COVID-19 pandemic if findings may have a significant impact on patient's management or malignancy.^{138,139} Testing for COVID-19 prior to pulmonary function testing (eg, methacholine or exercise challenge), sputum cell examination or bronchoscopy is important since these are aerosol-generating procedures and pose significant risk of spreading infection. Recommendations related to staff personal protective equipment, examination room settings, and instruments disinfection have been described elsewhere¹⁴⁰ and can minimize significantly the

risk of COVID-19 exposure or for that matter, contamination by other microbial agents. In confirmed COVID-19 cases, recommendations on when to perform pulmonary procedures are variable (put the 2 references we discussed yesterday over here) and need be updated according to pandemic status. However, well controlled safety measures (PPE, sterile techniques, etc.) can circumvent a prolonged (ie, 8 weeks) waiting time till full COVID-19 recovery. A mini-broncho-alveolar lavage or tracheal aspirate can be considered before bronchoscopy is performed.¹⁴¹

- Recommendations on intranasal steroids^{142,143} and inhalers^{144,145} use in COVID-19 are summarized elsewhere.

GUIDELINES AND EXPERT CONSENSUS IN COUGH PHARMACOTHERAPY

Upper airways

Compared to the lower airways, the role of pharmacotherapy in UACS is inconclusive (see Section Lower airways). In one report, improvement of cough in SAR patients was noted using different combinations of intranasal therapy such as azelastine and ipratropium or azelastine and intranasal corticosteroids, although the study lacked objective cough measures.¹⁴⁶ In addition, (non-asthmatic) chronic rhinosinusitis patients with chronic cough reported significant improvement in lung function parameters following long term (3 months) low-dose macrolide therapy. However, cough was not studied independently of other CRS parameters.¹⁴⁷ A metaanalysis suggested oral antibiotics can be beneficial in children with chronic productive cough in terms of clinical cure rates and prevention of illness progression, despite limitations in study designs and quality.¹⁴⁸

Lower airways

If the clinical profile of a chronic cough patient is reminiscent of asthma (typical recurrent symptoms of wheezing, breathlessness, cough, and chest tightness), several drug therapies can be offered. Data suggests a consistent improvement in cough scores with ICS and LTRAs, inhaled beta₂-agonists and muscarinic receptor antagonists (ie,

tiotropium), and to a lesser extent theophylline and mast cell stabilizers, but with variable bias noted in the studies.⁶² Similarly if CVA is suspected, recent guidelines recommend ICS as first line treatment based on strong efficacy data for step-wise therapy of asthma in general rather than distinctively for cough.⁶² Notwithstanding, there is a significant subjective placebo effect of ICS in patients presenting with nonspecific chronic cough albeit a small to moderate therapeutic gain ($\leq +22\%$), according to a metaanalysis.¹⁴⁹ This entails careful interpretation of the therapeutic benefit of ICS in nonspecific cough. In suspected NAEB, a therapeutic/diagnostic trial of ICS followed by LTRAs (if stepping up ICS fails to improve cough) can be suggested despite weak evidence to support efficacy of such a treatment in diagnosing NAEB.⁶² In NAEB, a hypersensitive cough reflex may partly explain clinical resistance to mainstay anti-asthma therapy such as topical bronchodilators or ICS,¹⁵⁰ as revealed by capsaicin challenge models. In COPD, a cough-associated chronic obstructive airway disease, an empirical trial of bronchodilator therapy is often justified but requires more efficacy data.^{50,51} Unlike LTRAs⁴⁹ and contrary to asthma, low dose ICS can only benefit COPD patients experiencing exacerbations with significant BHR.^{151,152} Despite absence of muscarinic receptors on airway afferent nerves, tiotropium, a long-acting muscarinic selective M3 receptor antagonist, can modulate a hypersensitive cough reflex in asthmatic patients refractory to ICS/long-acting β -2 agonist bronchodilators.¹⁵³

Digestive tract

A Cochrane review revealed lack of high-quality evidence to support efficacy of PPIs or histamine H₂-receptor antagonists in treatment of adults and children with chronic cough. The lack of high-quality evidence is partly due to heterogenous trial designs, disparate selection of control and active groups with respect to chronic cough, and indiscriminate testing methods of acid and non-acid reflux events.¹⁵⁴ Along the same line, other reports showed no difference between PPIs and placebo in chronic cough.¹⁵⁵⁻¹⁵⁷ To note, these studies were small in sample size and used non-validated QoL questionnaires.¹⁵⁷ Notwith-

standing, a subgroup of patients with cough reported benefit from PPI therapy in appropriate dosing and duration of treatment with a number needed-to-treat of 5.¹⁵⁸ Presence of acid reflux, either clinically (eg, heartburn, food regurgitation) or confirmed by diagnostic testing, shows modest therapeutic gain in coughing patients on acid suppressive therapy.⁵⁶ Absence of acid reflux contraindicates the routine use of antacid therapy in GERD-related chronic cough patients, according to expert panels.^{56,61} Non-acid or gas reflux, its association with proximal reflux using RSI, and its evaluation by MII-pH monitoring, awaits controlled trials to assess efficacy of antacid therapy in these select patients with cough. As stated earlier, early (within 2 weeks) cough improvement on PPIs can be followed by 4-12 weeks of maintenance therapy before tapering medications. Increasing PPI dose to twice a day confers only marginal benefit which should be weighed against incurred cost and side effects.¹⁵⁶ Cumulative doses of PPI, such as occurs during prolonged drug intake or doubling of PPI dose in partial responders, increases the risk of developing hypomagnesemia, among other side effects, in a dose-dependent manner.¹⁵⁹ Both hypomagnesemia and its consequent decrease in melatonin production can decrease lower esophageal sphincter (LES) tone and instigate a paradoxical iatrogenic cough.¹⁶⁰⁻¹⁶² Night-time magnesium and melatonin supplementation (rather than prescribing an extra dose of PPI) is recommended for partial responders to curtail side effects of long-term PPI intake. Supplementing PPI therapy with prokinetics can enhance gut motility and improve GERD-related cough.³³ Adding H₂-blockers for 2-4 weeks can be beneficial in reducing nocturnal acid breakthrough¹⁶³ in difficult-to-treat cases of GERD but its role in cough has not been investigated. Similarly, neuromodulators such as baclofen or gabapentin in combination with PPI can benefit patients with loose lower esophageal sphincter or high RSI scores. Their use, however, in chronic cough requires further investigation, given the high prevalence of somnolence as a side effect.¹⁶⁴

COVID-19 cough

An open study (N = 14) suggested that ingestion of nuclear factor-erythroid factor 2-related

factor 2 (Nrf2)-interacting foods can modulate COVID-19 symptoms. Broccoli seed capsules (Nrf2 and mild TRPA1),^{165,166} curcumin and black pepper, ginger, and red pepper resulted in immediate (within minutes), significant, and highly reproducible improvement of cough, thereby suggesting TRPA1/TRPV1 desensitization.¹⁶⁷ These effects were relatively short lasting (2–4 h). The duration of efficacy was extended to 6–8 h with broccoli suggesting an Nrf2-TRP crosstalk, and to 12–15 h by low dose paracetamol (some metabolites are Nrf2-TRP agonists).^{168–170} This requires further evaluation in large randomized controlled studies.

NEUROMODULATORS

Unexplained or chronic refractory cough often requiring trials of various medications for over a year can be treated with neuromodulators which target neural hyperresponsiveness of the cough reflex.¹⁷¹ Neuromodulators can encompass centrally acting drugs such as morphine^{172,173} and amitriptyline,^{174,175} pregabalin,¹⁷⁶ and gabapentin,¹⁷⁷ all of which have a negative impact on patient's mood. Novel peripheral-acting antitussive neuromodulators such as P2X3 antagonists may also be beneficial in the management of chronic cough since they lack significant central systemic side effects. Currently, neuromodulators are not approved in the United States or Europe for management of chronic cough due to the low level of evidence with respect to their efficacy (grade II C).^{53,61} An expert panel suggested neuromodulators can improve cough-specific QoL with variable effect on cough frequency and severity despite potential for selection bias in reported studies.⁵³ Metrics are important objective tools to assess antitussive effect of drugs. The vitalograph is a 24-h ambulatory cough monitoring tool approved in the United States for cough assessment.¹⁷⁸

Although central neuromodulators can manifest modest efficacy in protracted cough, they are frequently associated with significant central adverse effects in randomized controlled trials, such as drowsiness and confusion. For example, morphine revealed a 70% reduction in cough frequency versus placebo, but its use is limited by

severe adverse effects.^{179,180} Data suggest amitriptyline at different doses can improve post-viral chronic cough;^{175,181} yet its role in non-viral chronic cough is undefined.⁵³ Randomized controlled trials with gabapentin demonstrated improved cough qualities, namely cough-specific QoL, cough frequency and severity.^{177,182} A review of prospective case-series reported an overall 68% amelioration of cough and sensory neuropathy with gabapentin.¹⁸² Yet, improvement in cough qualities was not sustained upon discontinuation of drug. Reportedly, at an initial dose of 1800 mg and an onset of action at 4 weeks, gabapentin resulted in significant cough improvement with a satisfactory safety profile. Common side effects included confusion and dizziness, nausea, dry mouth, and fatigue.¹⁷⁷ It is recommended the risk-benefit profile of gabapentin be assessed at 6 months before therapy is extended.⁵³ Neurokinin receptor 1 (NK-1) antagonists block substance P tussive effect in the nucleus tractus solitarius mediated by NK-1 receptor.¹⁸³ NK-1 antagonists have been traditionally used for chemotherapy-induced nausea and vomiting.¹⁸⁴ A newer NK-1 antagonist, overpitant, improved cough qualities including frequency, severity and QoL with an acceptable safety profile, and hence warrants further investigation.¹⁸⁵ Similarly, a selective agonist of alpha 7 subtype of acetylcholine receptor, which is under investigation for treatment of schizophrenia,¹⁸⁶ features potential benefit in patients with acute and chronic cough.¹⁸⁷

Peripherally acting neuromodulators include a range of receptor antagonists with variable antitussive effects. Gamma-aminobutyric acid B receptor antagonists, initially used to manage acid reflux by inhibiting the relaxation of the lower esophageal sphincter, improved citric acid-induced cough in animal models.¹⁸⁸ P2X3 purinergic channels are receptors belonging to the P2X family of ion channels, with high predilection to the cellular breakdown product adenosine triphosphate (ATP),¹⁸⁹ and are expressed on both C and A- δ fibers. Upon activation, P2X3 channels quickly depolarize and subsequently desensitize the peripheral cough neuronal pathway. They can also modulate the cough neuronal pathway activity at central synapses in both upper and lower airways, hence the effect of P2X3 antagonists¹⁹⁰ such as gefapixant. It is speculated gefapixant acts

primarily on peripheral sensory neurons and has a significant role in hypersensitive cough reflex.^{43,191} In a proof-of-concept study, gefapixant improved cough-specific QoL, cough frequency (up to 75%), and severity in patients with unexplained chronic cough; however, following 12 weeks therapy and 600 mg twice daily dosing, dysgeusia was noted in most of patients. At lower doses (30–50 mg), gefapixant significantly reduced the awake cough frequency outcome compared to placebo, and taste abnormalities were less reported in a phase IIa study.¹⁹² A large (N > 2000) pooled analysis of three clinical trials using 45 mg gefapixant BID in patients with unexplained chronic cough demonstrated a 17.4% and 18.6% reduction in awake and 24-h cough, respectively.¹⁹³ Cough challenge studies using ATP and capsaicin were examined in patients treated with gefapixant. ATP inhalation studies did not elicit a dramatic decrease in cough sensitivity,¹⁹⁴ nor did gefapixant showed any effect on capsaicin-induced cough,¹⁹⁵ thus denoting complex and heterogenous mechanisms of chronic cough. TRP (A1/V1/M8) antagonists^{196,197} and sodium channel blockers¹⁹⁸ (anesthetic effect) are potential candidates for further investigation in chronic cough.

SPEECH THERAPY

Speech pathology treatment for chronic cough (SPTCC), also termed physiotherapy, speech and language therapy intervention (PSALTI), is a non-pharmacological non-invasive therapeutic option¹⁹⁹ to control chronic refractory cough^{199–202} and associated voice disorders¹⁹⁹ that persist despite medical treatment.^{200,203} It is also a reported therapeutic modality for management of habit cough which belongs to the spectrum of functional respiratory symptoms.²⁰⁴ SPTCC consists of multiple modules, namely cough suppression strategies including breathing and swallowing techniques, vocal hygiene such as avoidance of dietary cough-triggers, and psycho-educational counseling to minimize impact of cough on QoL.^{199,200,205} The mechanism of speech therapy in improving cough is yet unknown.²⁰⁵ It is speculated SPTCC can reduce laryngeal irritation responsible for cough, increases cough threshold,²⁰¹ or reduces capsaicin-induced cough reflex hypersensitivity^{201,203,205,206} via cortical

control.²⁰³ Voluntary cough suppression does not appear to be the primary mechanism as the cough suppression component did not decrease cough sensitivity as measured by the C5 endpoint in a tussigen challenge.²⁰⁵ Conversely, vocal hygiene improved C5 and "urge to cough".²⁰⁶ Also, data suggest SPTCC improved short-term, but not long-term, cough associated QoL.^{199,206,207} It also reduced cough frequency,^{201,203,205,207,208} severity,²⁰⁷ and capsaicin-triggered cough reflex sensitivity.^{203,205,207} It is suggested SPTCC can be initiated prior, during, or after²⁰³ medical therapy of refractory cough.⁵³

SUMMARY

In this paper we suggest an algorithm for proper management of patients with chronic cough in an integrated care pathway approach. Management of chronic cough can be diverse depending on cough etiology and is more challenging in patients with multifactorial cough where clinicians often need to add one therapeutic modality to another in an attempt to achieve control. There can be a role for alternative empirical therapies of chronic cough in primary care with limited access to advanced diagnostic modalities for cough etiologies. In cough-specialty care, multiple diagnostic and ancillary tests are available for management of cough-comorbid conditions such as rhinitis/rhinosinusitis, reactive lower airway diseases, and reflux. At best, these modalities can improve diagnostic accuracy of cough etiological factors, albeit to variable degrees due to their inherent limitations. These modalities can also predict cough response to guidelines-based therapy of cough etiological factors but seldom result in overall cough improvement. Safety measures for COVID-19 need to be considered in diagnostic and therapeutic care pathways of chronic cough. Pharmacotherapy with neuromodulators target neural hyper-responsiveness of chronic refractory cough. Preliminary data on neuromodulators suggest overall improvement in cough severity, frequency, and cough specific QoL, albeit to variable degrees. More data are needed regarding proper dosing, duration, and safety of treatment with neuromodulators. Behavioral therapy can be an adjunctive therapeutic modality for chronic cough and associated voice disorders, although mechanisms of cough improvement are yet unknown. In

COVID-19 cough, TRP desensitization with ingestion of Nrf2-interacting foods requires more research in improving post COVID-19 persistent cough.

Abbreviations

ACE, Angiotensin-converting enzyme; AR, allergic rhinitis; ATP, Adenosine triphosphate; BCT, Bronchial challenge testing; BHR, Bronchial hyperresponsiveness; CA, Classic asthma; COPD, Chronic obstructive pulmonary disease; CRS, Chronic rhinosinusitis; CT, Computed tomography; CVA, Cough variant asthma; EB, Eosinophilic bronchitis; EGD, Esophago-gastroduodenoscopy; FeNO, Fractional exhaled nitric oxide; FEV1, Forced expiratory volume during the first second; GI, gastrointestinal; GIT, gastrointestinal tract; GERD, Gastro-esophageal reflux disease; H2-Blockers, Histamine H2-receptor blockers; HCR, hypersensitivity cough reflex; ICS, Inhaled corticosteroids; LES, Lower esophageal sphincter; LTRA, Leukotriene receptor antagonist; MII-pH, Multichannel intraluminal impedance monitoring combined with pH-metry; NAEB, Non-asthmatic eosinophilic bronchitis; NK-1, Neurokinin receptor 1; Nrf2, Nuclear factor erythroid 2-related factor 2; OSA, Obstructive sleep apnea; PPI, Proton pump inhibitor; PSALT1, Physiotherapy, speech and language therapy intervention; QoL, Quality of life; RSI, Reflux symptom index; SAP, Symptom association probability; SAR, seasonal allergic rhinitis; SPTCC, Speech pathology treatment for chronic cough; TRP, Transient receptor potential; UACS, Upper airway cough syndrome.

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Authors' contributions

Philip Rouadi (PR) designed the plan of the article, contributed to the data collection. He wrote the manuscript draft, conceived and designed the tables/figures, and reviewed all parts of the article. Samar Idriss contributed to data collection, tables/figures, and manuscript draft. Jean Bousquet participated to the manuscript draft and reviewed the whole article. Tanya Laidlaw, Cecilio Azar, Mona Al-Ahmad, Anahi Yanez, Maryam Al-Nesf, Talal Nsouli, Sami Bahna, Eliane Abou Jaoude, Fares Zaitoun, Usamah Hadi, Georges Juvelekian and Moussa Riachy contributed to the manuscript draft each according to his/her specialty and domain of interest. The rest of authors reviewed closely the whole article and added their remarks.

Ethical statement

The manuscript entitled "WAO-ARIA CONSENSUS ON CHRONIC COUGH - PART III: MANAGEMENT STRATEGIES

IN PRIMARY AND COUGH-SPECIALTY CARE. *Updates in COVID-19.*" is the authors' own original work, which has not been previously published elsewhere. The paper is not currently being considered for publication elsewhere.

All authors have been personally and actively involved in substantial work leading to the paper and will take public responsibility for its content.

Authors' consent for publication

All authors have approved the manuscript and agree with its submission and final publication to the *World Allergy Organization Journal*.

Competing interests

No competing interests to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.waojou.2022.100649>.

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