Rouadi et al. World Allergy Organization Journal (2025) 18:101034
http://doi.org/10.1016/j.waojou.2025.101034

WORLD ALLERGY ORGANIZATION JOURNAL

REVIEW

Open Access

WAO - ARIA consensus on chronic cough: Executive summary

Philip W. Rouadi, MD[a], Samar A. Idriss, MD[a]*, Jean Bousquet, MD, PhD[b,c,d], Mario Morais-Almeida, MD[e], Cecilio R. Azar, MD[f,g,h], Mona Sulaiman Al-Ahmad, MD[i], Anahí Yáñez, MD[j], Maryam Ali Y Al-Nesf, MD, MSc[k], Talal M. Nsouli, MD[l], Sami L. Bahna, MD, DrPH[m], Eliane Abou-Jaoude, MD[l], Fares H. Zaitoun, MD[n,o], Usamah M. Hadi, MD[p], Glenis K. Scadding, MD[q], Peter K. Smith, MBBS, PhD[r], René Maximiliano Gómez, MD, PhD[s], Sandra N. González-Díaz, MD, PhD[t,u], Ludger Klimek, MD, PhD[v], Georges S. Juvelekian, MD[w], Moussa A. Riachy, MD[x], Giorgio Walter Canonica, MD[y], David Peden, MD[z], Gary W. K. Wong, MD[aa], James Sublett, MD[ab], Jonathan A. Bernstein, MD[ac], Lianglu Wang, MD[ad], Luciana Kase Tanno, MD, PhD[ae,af,ag], Manana Chikhladze, PhD[ah], Michael Levin, MBChB, MMed(Paeds), PhD[ai], Yoon-Seok Chang, MD, PhD[aj], Bryan L. Martin, DO[ak], Luis Caraballo, MD, PhD[al], Adnan Custovic, MD, PhD[am], José Antonio Ortega-Martell, MD[an], Olivia J. Ly Lesslar, MBBS[ao], Pedro Giavina-Bianchi, MD[ap], Nikolaos Papadopoulos, MD, PhD[aq,ar], Elham Hossny, MD, PhD[as], Motohiro Ebisawa, MD, PhD[at], Alessandro Fiocchi[au] and Ignacio J. Ansotegui, MD, PhD[av]

ABSTRACT

Acute cough is a highly prevalent symptom in clinical practice. Chronic cough is a complex disease with significant impact on quality of life. The mechanistic pathways of chronic cough in cough-comorbid clinical phenotypes are elusive. Mounting evidence suggests presence of a hypersensitive cough reflex and implication of transient receptor potential channels and P2X receptors in cough neuronal pathways. Previously, the World Allergy Organization (WAO)/Allergic Rhinitis and its Impact on Asthma (ARIA) Joint Committee on Chronic Cough published updated experimental and clinical data on chronic cough, in addition to a multidisciplinary care pathway approach to its management. The goal of this manuscript is to provide clinicians with a succinct summary of chronic cough pathophysiology, clinical phenotypes, and management strategies in both primary and cough specialty care. This executive summary is a primer for clinicians on chronic cough. Increasing awareness on the topic among primary care physicians will improve the outcome of management of patients with chronic cough.

Keywords: Chronic cough, Primary care physician, Hypersensitive cough reflex, Upper airway disease, Lower airway disease, Gastroesophageal reflux disease, Refractory chronic cough, Unexplained chronic cough, Neuromodulators, Multifactorial chronic cough

[a]Department of Otolaryngology, Dar Al Shifa Hospital, Hawally, Kuwait
*Corresponding author. E-mail: samar.a.idriss@hotmail.com
Full list of author information is available at the end of the article

http://doi.org/10.1016/j.waojou.2025.101034
Received 29 August 2024; Received in revised from 28 January 2025; Accepted 10 February 2025

Online publication date xxx

INTRODUCTION

The executive summary of chronic cough (CC) is developed as a conspectus of the previous WAO-ARIA joint consensus publications on CC.[1–3] The goal of this manuscript is to provide clinicians, more so primary care physicians (PCPs), with succinct summary of CC epidemiology and pathophysiology, clinical phenotypes, and multidisciplinary management strategies.

DEFINITIONS OF COUGH

Cough is a forced expulsive maneuver against a closed glottis. Arbitrarily, cough persisting for more than 4 or 8 weeks in children and adults, respectively, is termed CC.[4] In normal individuals, up to 15 coughs are recorded per day compared to 794 coughs per day in chronic coughers.[5] If exhaustive clinical investigations fail to determine a cough etiological factor, CC is termed Unexplained Chronic Cough (UCC).[6] Alternatively, if CC fails conventional pharmacotherapy despite extensive exploration of probable etiologies, it is termed Refractory Chronic Cough (RCC) (see Fig. 1).[7] As it will be discussed, CC can be considered as a distinct clinical illness with an underlying pathophysiological hypersensitivity of the cough neural reflex, occasionally linked to environmental triggers, cough-comorbid airway diseases, and/or gastroesophageal reflux disease (GERD).

EPIDEMIOLOGY AND BURDEN OF CHRONIC COUGH

Cough represents one of the most common symptoms encountered in clinical practice.[8,9] CC prevalence ranges between 2.5% and 18% in primary care,[10,11] increases with age, and is predominant in females in their sixth decade of life.[12,13] It is estimated both UCC and RCC comprise 2%–5% of the CC found in the general population.[6] CC poses a detrimental impact on the quality of life (QoL)[14–17] and a significant burden on the health care system.[18]

ANATOMICAL CONSIDERATIONS IN CHRONIC COUGH

The vagus nerve expresses 2 afferent cough neuronal pathways in the airway mucosa. These carry distinctive sensory functions in the cough reflex arc. One mechanosensitive pathway carries A-δ fibers and responds to light touch. Thus, it protects the airways from mucus, inhalation of foreign material, and intrinsic acid. Incorporated mechano-transducers can include

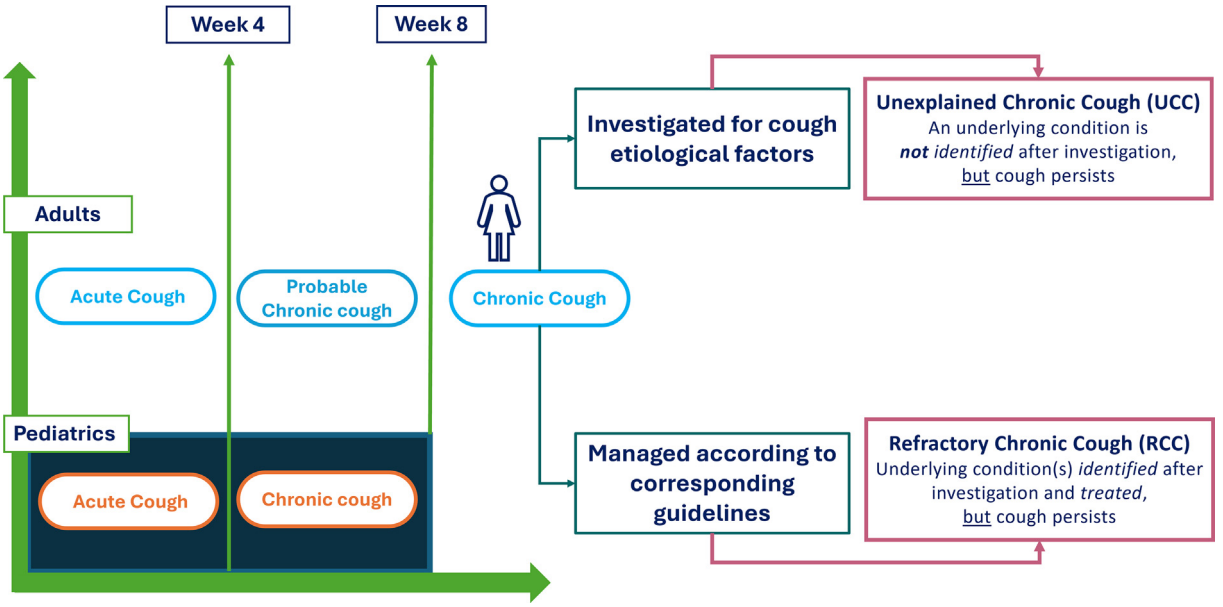

Fig. 1 Cough definition according to chronology of symptom, diagnostic workup, and response to management.

transient receptor potential (TRP) channels, voltage-gated sodium channels subtype, and acid-sensing ion channels. Another chemosensitive pathway carries unmyelinated C fibers and responds to various noxious stimuli. These can include adenosine triphosphate (ATP) released during cell damage in the airways,[19] inflammatory mediators such as prostaglandins,[20,21] irritants, temperature and acidity changes.[21,22] Activation of receptors in different pathways is not mutually exclusive but can occur simultaneously, according to the nature of trigger. Of note, cough can occur by itself, in the absence of triggers, reminiscent of neuropathic pain syndrome.[23]

PATHOPHYSIOLOGY OF CHRONIC COUGH

It is speculated the cough reflex undergoes both neurogenic and inflammatory alterations of its vagal neuronal pathways and thus becomes hypersensitive, the so-called hypersensitive cough reflex (HCR). This neuro-immune modulation of the cough reflex occurs via production of several neuromediators (ie, neurokinin and bradykinin, prostaglandin and calcitonin gene related peptide), in addition to immune cell activation (mast cells, eosinophils, and neutrophils).[24] The TRP channels and P2X receptors play a pivotal role in this neuro-immune cross-talk.[25] Consequently, HCR is a manifestation of a neuronal tussive threshold modulation, resulting in CC.[26]

Clinical cough models use experimental inhaled tussigens such as capsaicin, citric acid, among others, to study cough mechanistic pathways in patients with CC. The resulting dose-response curves are expressed in terms of tussigen concentration which can elicit 2 (C_2) or 5 (C_5) coughs. Chronic coughers can exhibit smaller C_2 or C_5 levels when compared to healthy individuals,[23,27] denoting presence of HCR in the former.[28–34]

PHENOTYPES OF CHRONIC COUGH

CC phenotypes can be broadly divided according to their etiological anatomical origins, namely upper and lower airways, or GERD-related cough. Other important cough-comorbid pathologies include laryngeal hyperresponsiveness (LHR) and obstructive sleep apnea (OSA), drug-induced cough and post-COVID-19 cough, psychological cough, and UCC/RCC, in addition to multifactorial cough.[35] The prevalence of etiologic CC phenotypes are quite variable in epidemiologic studies,[36,37] and can be age-related. For example, rhinitis, adenoiditis, and rhinosinusitis are important etiologies of CC among pre-school and school-aged children.[38,39] This can be related to the poor maturation of the cough reflex in children.[40]

Upper airway cough syndrome (UACS)

UACS is poorly characterized in terms of a universal definition and prevalence rates, likely due to confounding variables in epidemiological studies.[37,41,42] Pathogenesis of cough in UACS can be multifactorial. Mechanical or chemical triggers at peripheral sensory terminals of the trigeminal nerve and superior branches of vagus nerve can elicit cough, reminiscent of central neuronal convergence centers described elsewhere.[43,44] Other mechanistic pathways involve a hematogenous as well as a neural spread of inflammatory mediators between the upper and lower airways, in accordance with the united airway hypothesis.[45,46] Notwithstanding, cough challenge models indicate nasal triggers can potentiate the cough reflex in the lower airways denoting the presence of a HCR in the upper airways.[32,47]

Rhinitis and rhinosinusitis

Epidemiological studies suggest patients with upper respiratory tract infection and post-viral cough,[48] in addition to allergic rhinitis (AR), can manifest CC. A longitudinal cohort study revealed, non-infectious rhinitis is a significant and independent risk factor for development of CC in adults.[49] This is further elucidated by cough challenge data which confirm presence of a decreased cough threshold to inhaled capsaicin (ie, presence of HCR) in patients with upper respiratory tract infection[48] and allergic rhinitis.[31,50] The increased tussive response ($\downarrow C_2$ and/or $\downarrow C_5$) to capsaicin challenge in AR is in accordance with the "priming effect", ie, reduced activation threshold of sensory nerves in response to IgE and non-IgE related stimuli following allergen exposure.[51,52] Non-allergic

rhinopathies involve variable degrees of nasal hyperactivity,[53,54] yet CC is infrequently reported.[55] Clinically, cough is a major feature of chronic rhinosinusitis among pediatric population but not adults.[56] Also, pharmacotherapy of sinusitis improved cough in children, but not in adults.[57–59]

Obstructive sleep apnea syndrome and laryngeal hyperresponsiveness

OSA syndrome can present solely with CC.[60] When compared to the general population, OSA patients have a higher prevalence of cough (33%–39%).[61] This has been linked to increased production of inflammatory mediators, exhaled nitric oxide, sputum neutrophilia, or dysfunctional tussive central inhibition by the obstructive respiratory events.[62,63] Continuous positive airway pressure therapy in patients with OSA and cough improves cough reflex sensitivity, cough related QoL, and cough scores.[60,61,64,65]

Patients with vocal cord dysfunction, muscle tension dysphonia, and globus, collectively called LHR,[66] exhibit paradoxical vocal cord movements in response to noxious stimuli.[67] LHR can be present in up to 50% of CC patient population.[68] Epidemiological studies demonstrate a high association of LHR with cough as expressed in different CC phenotypes, irrespective of presence or absence of asthma. Chemosensitive receptors of the afferent laryngeal branch of vagus nerve and efferent recurrent laryngeal nerve are implicated, however comprehensive immunological and physiological data on neurogenic inflammatory pathways involved in LHR are currently lacking.[69]

Lower airway cough syndrome

CC is a cardinal symptom in chronic inflammatory lower airway diseases, such as classic asthma (CA) and cough variant asthma (CVA), non-asthmatic eosinophilic bronchitis (NAEB) and chronic obstructive pulmonary disease (COPD).[70] The clinical and immunological characteristics of these cough phenotypic traits are complex. They can feature variable airway eosinophilia, airway hyperreactivity (preservation or loss of deep inspiration cough bronchoprotective reflex), prostaglandin E_2 receptor expression (bronchodilation), and hyperresponsiveness to bronchial challenge testing.[2] For example, methacholine-induced bronchial responsiveness can be present in patients with CA and COPD, but can be borderline in patients with CVA and absent in those with NAEB. Notwithstanding, cough challenge studies demonstrate the presence of HCR in all reactive lower airway diseases (vagal C fibers activation), except for NAEB where currently insufficient data exist.[2] The presence of atopy can further complicate the picture. In cough challenge studies, atopic patients with asthma had unexpectedly better cough scores when compared to patients with non-atopic asthma. However, both asthmatic groups in single or combination had worse cough scores when compared to healthy controls.[27] This suggest atopy is not a risk factor for CC in asthma although type 2 inflammation and airway eosinophilia are prominent features of CC phenotypes in the lower airways. Also, neuromechanical modifications of the bronchial tree diameter, its length and pressure, as occurs for example during bronchoconstriction in asthma, can also contribute to CC.[71] How these factors interact collectively to modulate cough threshold is elusive.

CA is one of the most common etiologies of CC.[72] The control of cough predicts the severity and prognosis of asthma.[73] The pathophysiology of cough in asthma is complex and includes a HCR, an increase in inflammatory mediators, abnormal neuromechanical properties, and loss of deep inspiration-broncho protective reflex. These factors can act either in single or in combination, which adds to the complexity of CC.[2] NAEB is an atopic or non-atopic cough phenotype with marked endogenous prostaglandin E_2 receptor expression (bronchodilation) and thus lacks bronchoconstriction and bronchial hyperresponsiveness.[74,75] Also, CVA lacks wheezing or dyspnea[76] and can present solely or predominantly with cough.[77] Patients with CVA demonstrate borderline airway hyperresponsiveness on methacholine challenge[78] and can respond properly to anti-asthma medications.[76] In patients with COPD, sputum production is a frequent cause of chronic cough which is associated with lower FEV1, more severe dyspnea and airflow limitation, and worse clinical outcomes compared to non-coughing COPD patients.[79,80]

Reflux-related cough syndrome

The diagnosis of GERD is complex. The gastroesophageal refluxate can be liquid or gaseous, acidic or non-acidic, and occasionally exaggerated

by esophageal impaired motility. Cough is an extra-esophageal symptom frequently experienced in GERD with high variability in reported prevalence rates.[81-83] The "reflex theory" speculates the presence of central convergence centers linking esophageal afferent and bronchial efferent nerve fibers, which can trigger cough. Alternatively, the "reflux theory" hypothesizes a direct injury to the lower airway mucosa by esophageal refluxate.[84] Clinically, acid and non-acid reflux can be measured using pH and impedance probes, respectively, whereas esophageal motility disorders can be assessed using a pressure probe. Notwithstanding, pathogenic mechanisms linking CC and GERD are inconclusive.[85,86]

Multifactorial cough

Multifactorial cough is poorly defined in terms of prevalence rates, symptomatology, and response to therapy.[70] It should be considered in coughing patients with severe symptoms who do not respond to classical treatment of a single cough-underlying condition. Epidemiological data suggest the most common combinations of cough phenotypes are CVA and UACS in children,[37] and atopic cough with GERD in adults.[36] Also, GERD-related cough in association with either upper or lower airway cough syndrome is reportedly more severe than airway only-related CC.[87] This is expressed in terms of utilization of health care resources (ie, emergency visits, hospitalization), and intake of anti-tussive medications.[87]

MANAGEMENT OF CHRONIC COUGH

Management of CC entails exhaustive diagnostic evaluation and proper control of cough "treatable" traits, thus necessitating an integrated care pathway approach (see Fig. 2). PCPs encounter initially most of CC patients. They can identify risk factors and environmental triggers, such as drug-induced CC, tobacco smoke exposure, and recommend proper avoidance measures.[88,89] PCPs can also administer empirical therapy for common cough etiological diseases, such as upper respiratory tract infection and GERD, AR and asthma, among others.[90] If cough control fails, PCPs can then refer patients to cough specialists in view of a limited access of the formers to advanced cough diagnostic modalities. Multidisciplinary cough specialists hold a wide armamentarium of ancillary testing

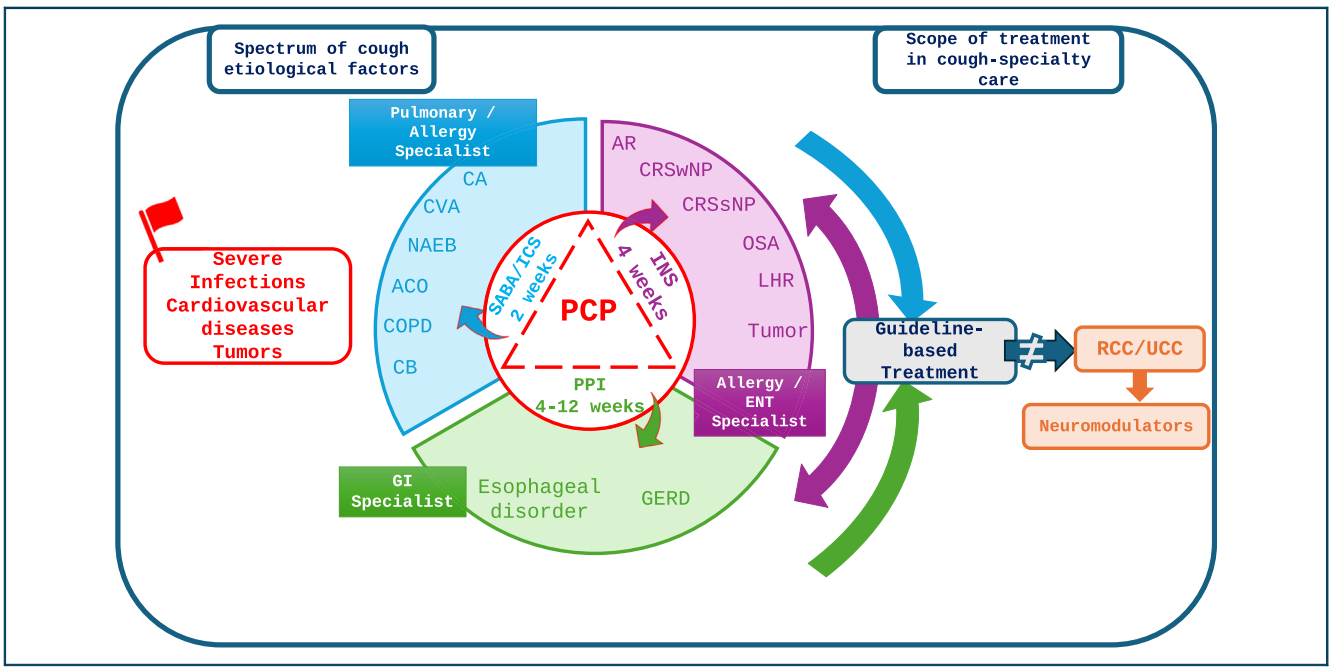

Fig. 2 "Propeller" model for management of chronic cough in primary (central circle) and cough specialty (propeller "blades") care. ACO (asthma COPD overlap), AR (allergic rhinitis), CA (classic asthma), CB (chronic bronchitis), COPD (chronic obstructive pulmonary disease), CRS (chronic rhinosinusitis), CVA (cough variant asthma), GERD (gastroesophageal reflux disease), LHR (laryngeal hyperresponsiveness), NAEB (non-asthmatic eosinophilic bronchitis), NP (nasal polyp), OSA (obstructive sleep apnea), PCPs (primary care physicians), RCC (refractory chronic cough), UCC (unexplained chronic cough).

to improve cough diagnostic accuracy. Cough control using conventional, guideline-based recommendations can then be achieved in most CC patients.[4,91–95] Alternatively, a minority of patients with UCC or RCC necessitates therapy with neuromodulators. Hence, such a multidisciplinary approach enhances overdiagnosis of idiopathic cough and improves outcomes of cough management.[6,96]

SCOPE OF MANAGEMENT IN PRIMARY CARE

Diagnosis

- Risk factors can be habitual, environmental, natural or acquired, ie, smoking (active/passive), occupational or environmental pollutant exposure, travel history, OSA, along with age.
- "Red flag" symptoms should alert the physician to more serious comorbid conditions with CC, eg, tumors, cardiovascular diseases, or severe infections.[97]
- Drug-induced cough encompasses a spectrum of frequently prescribed medications encountered in primary care, ie, angiotensin-converting enzyme inhibitors and opioids, prostanoid eye drops, statins, and non-steroidal anti-inflammatory drugs.[98–100] Cough-induced by non-selective betablockers relates more to a direct bronchospasm effect rather than activation of cough receptors.[101]
- A comprehensive physical examination
- Radiology: a chest X-ray is routinely performed as an informative screening test for lower airway diseases, ie, pneumonia, tuberculosis, or foreign body inhalation; however, it has poor sensitivity for interstitial lung diseases (chronic dry cough) and bronchiectasis (chronic productive cough).[102]
- QoL cough questionnaire or visual analog score are recommended to quantitate the current impact of CC prior to or following therapy,[103] ie, Leicester cough questionnaire.[104]

Pharmacotherapy

Based on the initial evaluation, a PCP can tailor pharmacotherapy according to suspected etiological trigger(s) of cough (ie, atopy, infection).[90] Listed below are recommended empirical therapies for CC, based on their level of evidence and consensus among authors.

1. Upper airways cough syndrome: An initial 4-week course of intranasal corticosteroids is recommended in atopic (ie, AR) and non-atopic (ie, chronic rhinosinusitis) cough-comorbid upper airway diseases, in view of data suggesting efficacy.[105–107] Symptomatic improvement entails continuation of therapy for one additional month and reassessment later on.[108] The expert panel does not recommend use of second generation oral antihistamines and leukotriene receptor antagonists in UACS in absence of evidence suggesting efficacy in reducing cough.[109–111]
2. Lower airways cough syndrome: An initial 2-week course of inhaled beta 2 agonists and corticosteroids combination is recommended. If poorly tolerated, inhaled corticosteroids can be substituted with oral corticosteroids.[112] Symptomatic improvement entails continuation of therapy for one additional month and reassessment later on.[113]
3. Reflux cough syndrome: A 4- to 12-week course of proton pump inhibitors (PPIs) was recommended in the initial manuscript, as an off-label use.[3] In view of recent data promoting a judicious use of PPIs (2023),[114] the expert panel recommends a shorter empirical therapy of 4- to 8-weeks followed by tapering of dosage. Anti-reflux measures also include diet modification, weight loss, and use of antiacids, among others.

SCOPE OF MANAGEMENT IN ADVANCED CARE

Failure to control cough in primary care entails referral to one or multiple cough subspecialties (ie, multifactorial cough). Allergy, Ear-Nose-Throat, Pulmonary, and Gastroenterology specialists can conduct clinical investigations for guideline-based management of cough-comorbid conditions.

- In the upper airways, naso-pharyngo-laryngoscopy[115] and polysomnography[116] are invaluable in diagnosing sinusitis and OSA, respectively. Laryngoscopy, at times coupled with stroboscopy, is helpful in diagnosing laryngeal pathologies

such as LHR and tumors, foreign body inhalation and vocal cord mobility disorders.[117] Evidence-based management of cough-associated upper airway disorders and its impact on CC awaits further investigation.

- In the lower airways, spirometry with bronchodilator reversibility test and bronchial challenge testing (BCT) can be decisive in diagnosing cough-associated lower airway diseases.[2] For example, NAEB is marked by absence of hyperresponsiveness on spirometry and BCT. In CVA, bronchial hyperexcitability is absent (or borderline) on spirometry, but not on BCT. In asthma, both tests can be positive. In addition to asthma, abnormal spirometry is encountered in COPD and asthma-COPD overlap. Additionally, FeNO levels can assist in identifying subgroups with asthma, CVA, and NAEB as potential causes of chronic cough.[2] However, the lack of clear cut-off level of FeNO for the etiological diagnosis of the aforementioned subgroups limits its usefulness as a routine diagnostic and follow-up tool in CC.[118-120] Blood eosinophil counts have a moderate diagnostic value for identifying sputum eosinophilia in patients with chronic cough.[121] Despite its inherent technical difficulties, induced sputum is a proper surrogate marker for airway eosinophilia.[122,123] CT scan of lung is informative in parenchymal lung diseases, such as bronchiectasis. Efficacy data on pharmacotherapy of cough-comorbid diseases of the lower airways is overwhelming. Yet, its efficacy in improving CC is currently unknown.[124,125]
- GERD-related cough which is refractory to PPI therapy can suggest non-acid or gas reflux. The multichannel impedance and pH-metry (MII-pH-metry) is the gold standard diagnostic modality for non-acid reflux, yet it is an invasive 24-hr ambulatory test with limited availability.[126] An EGD is performed concomitantly to rule out other diagnoses which can aggravate cough but are not necessarily related to it, such as eosinophilic esophagitis and Barrett's esophagus, among others.[127,128] Esophageal manometry is reserved for patients with suspected esophageal motility disorders. Patients with non-PPI-responsive cough and negative MII-pH-metry studies are unlikely to have GERD-related cough. Alternately, those with confirmed GERD-related cough can benefit from surgery.[129]

NEUROMODULATOR PHARMACOTHERAPY

Neuromodulators can be indicated in UCC or RCC patients who fail a significant response to therapy with various medications for a long period, in some cases over a year.[95] In principle, neuromodulators can "attenuate" or "modulate" the HCR, thus improving cough. They can be classified into peripherally acting or centrally acting drugs.[7]

Central neuromodulators, such as morphine and amitriptyline, gabapentin and pregabalin can improve cough severity, frequency, and cough related QoL, albeit to variable degrees.[3] They exhibit significant central side effects (ie, drowsiness, confusion) and low evidence of efficacy (Grade IIC) in reported studies, which precludes their approval for CC management in Europe or in the United States.[7,130,131] Interestingly, overpitant, a neurokinin antagonist, improved cough qualities with an acceptable safety profile in a phase II pilot study, thus awaiting further investigation.[132]

Peripheral neuromodulators, such as P2X3 antagonist (gefapixant), have an anti-tussive effect. ATP, a breakdown product of cellular damage, is a neurotransmitter in the purinergic system and has a high predilection to P2X channels present on peripheral cough neuronal networks. Once depolarized by ATP, P2X3 channels desensitize the cough neuronal pathway, thus suppressing cough.[133] In a proof-of-concept study, gefapixant improved cough qualities in patients with UCC. Though self-limited, dysgeusia was noted in majority of patients.[96] Of note, more recent data suggest consistent efficacy of gefapixant in UCC/RCC.[96] However, this compound has yet been to be approved by the Food and Drug Administration (FDA) in the United States.

SPEECH THERAPY

Speech therapy is a behavioral modification technique for patients with RCC. The cough suppression strategy consists of several training protocols including breathing and swallowing exercises, avoidance of cough-triggering diets, and psychogenic counselling vis-a-vis cough-impacted QoL.[134–136] This strategy can be implemented prior, during, or following medical therapy for CC, with limited benefit noted in some patients.[134,135,137]

CONCLUSION

Chronic cough is a challenging clinical entity characterized by complex neuro-anatomical networks and intricate pathophysiological mechanisms, resulting in hypersensitivity of the cough neural reflex. The management of chronic cough comorbid conditions involves an integrated care pathway approach. Initially, PCPs have a cardinal role in a comprehensive assessment and management of CC patients. Referral to cough specialty care for further investigations is recommended if cough control fails or is partially achieved. In patients with RCC/UCC, neuromodulator pharmacotherapy targeting peripheral cough neuronal receptors (eg, P2X3) is promising, yet further data is needed regarding efficacy and safety.

Abbreviations

ATP, adenosine triphosphate; CA, classic asthma; CC, chronic cough; COPD, chronic obstructive pulmonary disease; CVA, cough variant asthma; GERD, gastroesophageal reflux disease; HCR, hypersensitive cough reflex; LHR, laryngeal hyperresponsiveness; NAEB, non-asthmatic eosinophilic bronchitis; OSA, obstructive sleep apnea; PCPs, primary care physicians; PPI, proton pump inhibitor; QoL, quality of life; RCC, refractory chronic cough; TRP, transient receptor potential; UACS, upper airway cough syndrome; UCC, unexplained chronic cough.

Availability of materials and methods

N/a.

Author consent for publication

All authors reviewed and approved the final version of the work and consented to its publication in WAO Journal and take full responsibility for the content.

Funding

N/a.

Author 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 in the manuscript draft and reviewed the whole article. All other others contributed to the manuscript draft each according to his/her specialty and domain of interest. They reviewed closely the whole article and added their remarks.

Declaration of competing interest

Talal Nsouli: speaker for AstraZeneca.
Jonathan A Bernstein: Merck and GSK related to chronic cough.
Georges S Juvelekian: speaker for AstraZeneca, Abbott, Boehringer Ingelheim, Sanofi Aventis, Organon, Novartis, and Pfizer. Member of the Advisory board of AstraZeneca, Novartis, and Pfizer.
Pete Smith: PI/Consultant GSK, Sanofi Regeneron, Viatris.
Glenis Scadding: Honoraria for articles and speaker for GSK, advisory boards for GSK, ALK, Bayer, Chiesi, GlaxoSmithKline, Haleon, Noucor, Sanofi- Regeneron, and Viatris. Chair of BSACI rhinitis guidelines, Scientific Chief Editor, Rhinology Section of Frontiers in Allergy, Vice President, and AR lead for EUFOREA, and Chair/member Data Monitoring Committees on SLIT for ALK. Scientific Chief Editor, Rhinology Section, Frontiers in Allergy.
L Klimek (LK) has received research grants from Allergy Therapeutics/Bencard, Great Britain/Germany; ALK-Abelló, Denmark; Allergopharma, Germany; Aimmune, USA; ASIT Biotech, Belgium; AstraZeneca, Sweden, Bionorica, Germany; BioNTech, Germany, Biomay, Austria, Boehringer Ingelheim, Germany, Circassia, USA; Chiesi, Italy; Cytos, Switzerland; Curalogic, Denmark; HAL, Netherlands; Lofarma, Italy; Menarini, Italy; MSD, USA, Viatris/Mylan, USA; Novartis, Switzerland, Leti, Spain; ROXALL, Germany; GlaxoSmithKline (GSK), Great Britain; Sanofi, France; Stallergenes, France; Thermofisher, USA and/or has served on the speaker's bureau or was consulting for the above mentioned pharmaceutical companies.
Alessandro Fiocchi: Member of an advisory board: Abbott S.A., Danone, Ferrero SpA,
Sponsored research: Ferrero SpA, Novartis S.A., Astrazeneca S.A, Vertex S.A., GSK S.A., Sanofi S.A., DVB S.A.
Pedro Giavina-Bianchi: speaker and member for advisory board for: AstraZeneca, Abbvie, CSL Behring, GSK, Novartis, Sanofi, Takeda/Shire.

Ethics statement

No patients were involved in the development of this executive summary. No consent was required.

Author details

[a]Department of Otolaryngology, Dar Al Shifa Hospital, Hawally, Kuwait. [b]Institute of Allergology, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany. [c]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology and Immunology, Berlin, Germany. [d]MASK-air, Montpellier, France. [e]Allergy Center, CUF Descobertas Hospital, Lisboa, Portugal. [f]Department of Gastroenterology, American University of Beirut Medical Center (AUBMC), Beirut, Lebanon. [g]Department of Gastroenterology, Middle East Institute of Health (MEIH), Beirut, Lebanon. [h]Department of Gastroenterology, Clemenceau Medical Center (CMC), Beirut, Lebanon. [i]Department of Microbiology, College of Medicine, Kuwait University, Kuwait. [j]INAER - Investigaciones en Alergia y Enfermedades Respiratorias, Buenos Aires, Argentina. [k]Allergy and Immunology Division, Department of Medicine, Hamad Medical Corporation, Doha, Qatar. [l]International Cough Institute,

Washington, DC, USA. [m]Allergy & Immunology Section, Louisiana State University Health Sciences Center, Shreveport, LA, USA. [n]Allergy, Asthma and Immunology Center, Beirut, Lebanon. [o]Clemenceau Medical Center Hospital, Dubai, United Arab Emirates. [p]Clinical Professor Department of Otolaryngology Head and Neck Surgery, American University of Beirut, Lebanon. [q]Department of ENT, RNENT Hospital and Division of Immunity and Infection, University College London, London, UK. [r]Clinical Medicine Griffith University, Southport, Qld, 4215, Australia. [s]Faculty of Health Sciences, Catholic University of Salta, Argentina. [t]Universidad Autónoma de Nuevo León, Hospital Universitario and Facultad de Medicina, Monterrey, Nuevo León, Mexico. [u]Head and Professor Centro Regional de Alergia Asma e Inmunologia, Mexico. [v]Center for Rhinology and Allergology, Wiesbaden, Germany. [w]Visiting Clinical Associate Professor of Medicine, American University of Beirut Medical Center, Beirut, Lebanon. [x]Department of Pulmonary and Critical Care, Hôtel-Dieu de France University Hospital, Beirut, Lebanon. [y]Humanitas University & Personalized Medicine Asthma & Allergy Clinic-Humanitas Research Hospital-IRCCS-Milano, Italy. [z]UNC Center for Environmental Medicine, Asthma, and Lung Biology, Division of Allergy, Immunology and Rheumatology, Department of Pediatrics UNC School of Medicine, USA. [aa]Department of Pediatrics, Chinese University of Hong Kong, Hong Kong, China. [ab]Department of Pediatrics, Section of Allergy and Immunology, University of Louisville School of Medicine, 9800 Shelbyville Rd, Louisville, KY, USA. [ac]University of Cincinnati College of Medicine, Department of Internal Medicine, Division of Rheumatology, Allergy and Immunology, Cincinnati, OH, USA. [ad]Department of Allergy, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Precision Medicine for Diagnosis and Treatment of Allergic Disease, State Key Laboratory of Complex Severe and Rare Diseases, National Clinical Research Center for Dermatologic and Immunologic Diseases (NCRC-DID), Beijing, 100730, China. [ae]Université Montpellier, Montpellier, France. [af]Desbrest Institute of Epidemiology and Public Health, UMR UA-11, INSERM University of Montpellier, Montpellier, France. [ag]WHO Collaborating Centre on Scientific Classification Support, Montpellier, France. [ah]Medical Faculty at Akaki Tsereteli State University, National Institute of Allergy, Asthma & Clinical Immunology, KuTaisi, Tskaltubo, Georgia. [ai]Division of Paediatric Allergology, Department of Paediatrics, University of Cape Town, South Africa. [aj]Division of Allergy and Clinical Immunology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea. [ak]Department of Otolaryngology, Division of Allergy & Immunology, The Ohio State University, Columbus, OH, USA. [al]Institute for Immunological Research, University of Cartagena, Cartagena de Indias, Colombia. [am]National Heart and Lund Institute, Imperial College London, UK. [an]Health Science Institute, Autonomous University of Hidalgo, Mexico. [ao]The National Centre for Neuroimmunology and Emerging Disease, Griffith University, Southport, Qld, 4215, Australia. [ap]Clinical Immunology and Allergy Division, University of Sao Paulo, Brazil. [aq]Allergy Department, 2nd Pediatric Clinic, National and Kapodistrian, University of Athens, Athens, Greece. [ar]Division of Infection, Immunity and Respiratory Medicine, University of Manchester, Manchester, UK. [as]Ain Shams University, Ain Shams University Children's Hospital, Cairo, Egypt. [at]Clinical Research Center for Allergy and Rheumatology, NHO Sagamihara National Hospital, Sagamihara, Japan. [au]Translational Pediatric Research Area, Allergic Diseases Research Unit, Bambino Gesù Children's Hospital IRCCS, Rome, Holy See. [av]Department of Allergy and Immunology, Hospital Quironsalud Bizkaia, Bilbao, Spain.

REFERENCES

1. Rouadi PW, Idriss SA, Bousquet J, Laidlaw TM, Azar CR, Al-Ahmad MS. WAO-ARIA consensus on chronic cough - Part I: role of TRP channels in neurogenic inflammation of cough neuronal pathways. WAO J. 14(12):100617. doi:10.1016/j.waojou.2021.100617.
2. Rouadi PW, Idriss SA, Bousquet J, Laidlaw TM, Azar CR, Al-Ahmad MS. WAO-ARIA consensus on chronic cough - Part II: phenotypes and mechanisms of abnormal cough presentation - updates in COVID-19. World Allergy Organ J. 14(12):100618. doi:10.1016/j.waojou.2021.100618.
3. Rouadi PW, Idriss SA, Bousquet J, et al. WAO-ARIA consensus on chronic cough – Part III: management strategies in primary and cough-specialty care. Updates in COVID-19. *World Allergy Organ J*. 2022;15(5), 100649. https://doi.org/10.1016/j.waojou.2022.100649.
4. Morice AH, Millqvist E, Bieksiene K, et al. ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. *Eur Respir J*. 2020;55(1). https://doi.org/10.1183/13993003.01136-2019.
5. Hsu JY, Stone RA, Logan-Sinclair RB, Worsdell M, Busst CM, Chung KF. Coughing frequency in patients with persistent cough: assessment using a 24 hour ambulatory recorder. *Eur Respir J*. 1994;7(7):1246–1253. https://doi.org/10.1183/09031936.94.07071246.
6. Gibson P, Wang G, McGarvey L, Vertigan AE, Altman KW, Birring SS. Treatment of unexplained chronic cough chest guideline and expert panel report. *Chest*. 2016;149(1):27–44. https://doi.org/10.1378/chest.15-1496.
7. Gibson PG, Vertigan AE. Management of chronic refractory cough. *Br Med J*. 2015;351. https://doi.org/10.1136/bmj.h5590.
8. Qutub HO. Cough : a practical approach for the primary care physician in Saudi Arabia. *J Fam Community Med*. 2000;7(1):75–79.
9. Marchant JM, Chang AB, Kennedy E, et al. Cough in children and adults: diagnosis, assessment and management (CICADA). Summary of an updated position statement on chronic cough in Australia. *Med J Aust*. 2024;220(1):35–45. https://doi.org/10.5694/mja2.52157.
10. Bergmann M, Haasenritter J, Beidatsch D, et al. Prevalence, aetiologies and prognosis of the symptom cough in primary

care: a systematic review and meta-analysis. *BMC Fam Pract*. 2021;22(1):1–19. https://doi.org/10.1186/s12875-021-01501-0.

11. Song WJ, Chang YS, Faruqi S, et al. The global epidemiology of chronic cough in adults: a systematic review and meta-analysis. *Eur Respir J*. 2015;45(5):1479–1481. https://doi.org/10.1183/09031936.00218714.
12. Morice AH, Jakes AD, Faruqi S, et al. Worldwide survey of chronic cough: a manifestation of enhanced somatosensory response. *Eur Respir J*. 2014;44(5):1149–1155. https://doi.org/10.1183/09031936.00217813.
13. Bai H, Sha B, Xu X, Yu L. Gender difference in chronic cough: are women more likely to cough? *Front Physiol*. 2021;12(May):1–8. https://doi.org/10.3389/fphys.2021.654797.
14. Jin HJ, Kim CW. Understanding the impact of chronic cough on the quality of life in the general population. *Allergy, Asthma Immunol Res*. 2020;12(6):906–909. https://doi.org/10.4168/aair.2020.12.6.906.
15. Kubo T, Tobe K, Okuyama K, et al. Disease burden and quality of life of patients with chronic cough in Japan: a population-based cross-sectional survey. *BMJ Open Respir Res*. 2021;8(1):1–10. https://doi.org/10.1136/bmjresp-2020-000764.
16. Direção Geral de Saúde. Norma Da Direção Geral Da Saúde -Rastreio e Tratamento da Surdez com Implantes Cocleares em Idade Pediátrica. *Norma Da Direção Geral Da Saúde*. 2017;1(1):17. https://www.dgs.pt/upload/membro.id/ficheiros/i018596.pdf.
17. Yu CJ, Song WJ, Kang SH. The disease burden and quality of life of chronic cough patients in South Korea and Taiwan. *World Allergy Organ J*. 2022;15(9), 100681. https://doi.org/10.1016/j.waojou.2022.100681.
18. French CL, Irwin RS, Curley FJ, Krikorian CJ. Impact of chronic cough in quality of life. *Arch Intern Med*. 1998;158(15):1657–1661. https://doi.org/10.1001/archinte.158.15.1657.
19. Birring SS. The search for the hypersensitivity in chronic cough. *Eur Respir J*. 2017;49(2). https://doi.org/10.1183/13993003.00082-2017.
20. Maher SA, Birrell MA, Belvisi MG. Prostaglandin E2 mediates cough via the EP3 receptor: implications for future disease therapy. *Am J Respir Crit Care Med*. 2009;180(10):923–928. https://doi.org/10.1164/rccm.200903-0388OC.
21. Grace MS, Belvisi MG. TRPA1 receptors in cough. *Pulm Pharmacol Ther*. 2011;24(3):286–288. https://doi.org/10.1016/j.pupt.2010.11.002.
22. Adcock JJ. TRPV1 receptors in sensitisation of cough and pain reflexes. *Pulm Pharmacol Ther*. 2009;22(2):65–70. https://doi.org/10.1016/j.pupt.2008.12.014.
23. Morice AH, Kastelik JA, Thompson R. Cough challenge in the assessment of cough reflex. *Br J Clin Pharmacol*. 2001;52(4):365–375. https://doi.org/10.1046/j.0306-5251.2001.01475.x.
24. Chung KF. Approach to chronic cough: the neuropathic basis for cough hypersensitivity syndrome. *J Thorac Dis*. 2014;6(7):S699–S707. https://doi.org/10.3978/j.issn.2072-1439.2014.08.41.
25. Song WJ, Chang YS. Cough hypersensitivity as a neuro-immune interaction. *Clin Transl Allergy*. 2015;5(24):1–10. https://doi.org/10.1186/s13601-015-0069-4.
26. Nasra J, Belvisi MG. Modulation of sensory nerve function and the cough reflex: understanding disease pathogenesis. *Pharmacol Ther*. 2009 Dec;124(3):354–375. https://doi.org/10.1016/j.pharmthera.2009.09.006.
27. Satia I, Tsamandouras N, Holt K, et al. Capsaicin-evoked cough responses in asthmatic patients: evidence for airway neuronal dysfunction. *J Allergy Clin Immunol*. 2017;139(3):771–779.e10. https://doi.org/10.1016/j.jaci.2016.04.045.
28. Brozmanova M, Plevkova J, Tatar M, Kollarik M. Cough reflex sensitivity is increased in the Guinea pig model of allergic rhinitis. *J Physiol Pharmacol*. 2008;59(6):153–161.
29. Brozmanova M, Plevkova J, Bartos V, Plank L, Tatar M. Antileukotriene treatment and allergic rhinitis-related cough in Guinea pigs. *J Physiol Pharmacol*. 2005;56(4):21–30.
30. Plevkova J, Varechova S, Brozmanova M, Tatar M. Testing of cough reflex sensitivity in children suffering from allergic rhinitis and common cold. *J Physiol Pharmacol*. 2006;57(4):289–296.
31. Pecova R, Zucha J, Pec M, Neuschlova M, Hanzel P, Tatar M. Cough reflex sensitivity testing in seasonal allergic rhinitis patients and healthy volunteers. *J Physiol Pharmacol*. 2008;59(6):557–564.
32. Tatar M, Plevkova J, Brozmanova M, Pecova R, Kollarik M. Mechanisms of the cough associated with rhinosinusitis. *Pulm Pharmacol Ther*. 2009;22(2):121–126. https://doi.org/10.1016/j.pupt.2008.11.014.
33. Rybka-Fraczek A, Dabrowska M, Grabczak EM, et al. Does bronchial hyperresponsiveness predict a diagnosis of cough variant asthma in adults with chronic cough: a cohort study. *Respir Res*. 2021;22(1):1–5. https://doi.org/10.1186/s12931-021-01845-2.
34. Xu X, Lv H, Yu L, Chen Q, Liang S, Qiu Z. A stepwise protocol for the treatment of refractory gastroesophageal reflux-induced chronic cough 2016;. 2016;8(6):178–185. https://doi.org/10.3978/j.issn.2072-1439.2016.01.50.
35. Michaudet C, Malaty J. Chronic cough: evaluation and management. *Am Fam Physician*. 2017;96(9):575–580.
36. Ding H, Xu X, Wen S, et al. Changing etiological frequency of chronic cough in a tertiary hospital in Shanghai, China. *J Thorac Dis*. 2019;11(8):3482–3489. https://doi.org/10.21037/jtd.2019.07.86.
37. Yu X, Kong L, Jiang W, et al. Etiologies associated with chronic cough and its clinical characteristics in school-age children. *J Thorac Dis*. 2019;11(7):3093–3102. https://doi.org/10.21037/jtd.2019.07.36.
38. Gao F, Gu QL, Jiang ZD. Upper airway cough syndrome in 103 children. *Chin Med J (Engl)*. 2019;132(6):653–658. https://doi.org/10.1097/CM9.0000000000000118.
39. Wilson NW, Hogan MB, Harper CB, et al. Sinusitis and chronic cough in children. *J Asthma Allergy*. 2012;5:27–32. https://doi.org/10.2147/JAA.S31874.
40. Mazzone SB. Neurobiology of coughing in children. *J Clin Med*. 2023;12(23):7285. https://doi.org/10.3390/jcm12237285.
41. Yu L, Xu X, Lv H, Qiu Z. Advances in upper airway cough syndrome. *Kaohsiung J Med Sci*. 2015;31(5):223–228. https://doi.org/10.1016/j.kjms.2015.01.005.
42. Dąbrowska M, Arcimowicz M, Grabczak EM, et al. Chronic cough related to the upper airway cough syndrome: one entity but not always the same. *Eur Arch Otorhinolaryngol*.

2020;277(10):2753–2759. https://doi.org/10.1007/s00405-020-06071-y.

43. Lucanska M, Hajtman A, Calkovsky V, Kunc P, Pecova R. Upper airway cough syndrome in pathogenesis of chronic cough. *Physiol Res*. 2020;69(1):35–42. https://doi.org/10.33549/physiolres.934400.

44. Plevkova J, Brozmanova M, Pecova R, Tatar M. The effects of nasal histamine challenge on cough reflex in healthy volunteers. *Pulm Pharmacol Ther*. 2006;19(2):120–127. https://doi.org/10.1016/j.pupt.2005.04.004.

45. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic rhinitis and its impact on asthma (ARIA) 2008. *Prim Care*. 2008;63:8–160. https://doi.org/10.1111/j.1398-9995.2007.01620.x.

46. Braunstahl GJ, Overbeek SE, KleinJan A, Prins JB, Hoogsteden HC, Fokkens WJ. Nasal allergen provocation induces adhesion molecule expression and tissue eosinophilia in upper and lower airways. *J Allergy Clin Immunol*. 2001;107(3):469–476. https://doi.org/10.1067/mai.2001.113046.

47. Plevková J, Poliaček I, Adamkov M, Svirlochová K, Varga I. Brainstem neuronal populations activated in the model of ovalbumine induced allergic rhinitis in Guinea pigs - the c-Fos study. *Biologia*. 2011;66(5):922–927. https://doi.org/10.2478/s11756-011-0096-0.

48. O'Connell F, Thomas VE, Studham JM, Pride NB, Fuller RW. Capsaicin cough sensitivity increases during upper respiratory infection. *Respir Med*. 1996;90(5):279–286. https://doi.org/10.1016/S0954-6111(96)90099-2.

49. Guerra S, Sherrill DL, Baldacci S, et al. Rhinitis is an independent risk factor for developing cough apart from colds among adults. *Allergy*. 2005;60(3):343–349. https://doi.org/10.1111/j.1398-9995.2005.00717.x.

50. Pecova R, Vrlik M, Tatar M. Cough sensitivity in allergic rhinitis. *J Physiol Pharmacol*. 2005;56(4):171–178.

51. Jt C. Quantitative intranasal pollen challenges. 3. The priming effect in allergic rhinitis. *J Allergy*. 1969;43:33–44. https://doi.org/10.1016/0021-8707(69)90018-5.

52. Jt C. Quantitative intranasal pollen challenge. II. Effect of daily pollen challenge, environmental pollen exposure, and placebo challenge on the nasal membrane. *J Allergy*. 1968;41:123–139. https://doi.org/10.1016/0021-8707(68)90053-1.

53. Van Gerven L, Steelant B, Hellings PW. Nasal hyperreactivity in rhinitis: a diagnostic and therapeutic challenge. *Allergy*. 2018;73(9):1784–1791. https://doi.org/10.1111/all.13453.

54. Baroody FM, Gevaert P, Smith PK, Ziaie N, Bernstein JA. Nonallergic rhinopathy: a comprehensive review of classification, diagnosis, and treatment. *J Allergy Clin Immunol Pract*. 2024;12(6):1436–1447. https://doi.org/10.1016/j.jaip.2024.03.009.

55. Shusterman D. Nonallergic rhinitis: environmental determinants. *Immunol Allergy Clin*. 2016;36(2):379–399. https://doi.org/10.1016/j.iac.2015.12.013.

56. Fokkens WJ, Lund VJ, Hopkins C, et al. European position paper on rhinosinusitis and nasal polyps. *Rhinology*. 2020;58(S29):1–464. https://doi.org/10.4193/Rhin20.600.

57. Pham V, Sykes K, Wei J. Long-term Outcome of once daily nasal irrigation for the treatment of pediatric chronic rhinosinusitis. *Laryngoscope*. 2015;124:10–16. https://doi.org/10.1002/lary.24224.Long-term.

58. Ozturk F, Bakirtas A, Ileri F, Turktas I. Efficacy and tolerability of systemic methylprednisolone in children and adolescents with chronic rhinosinusitis : a double-blind , placebo-controlled randomized trial. *J Allergy Clin Immunol*. 2011;128(2):348–352. https://doi.org/10.1016/j.jaci.2011.04.045.

59. Chang PH, Lee LA, Huang CC, Lai CH, Lee TJ. Functional endoscopic sinus surgery in children using a limited approach. *Arch Otolaryngol Head Neck Surg*. 2004;130(9):1033–1036. https://doi.org/10.1001/archotol.130.9.1033.

60. Birring SS, Ing AJ, Chan K, et al. Obstructive sleep apnoea: a cause of chronic cough. *Cough*. 2007;3(1):1–5. https://doi.org/10.1186/1745-9974-3-7.

61. Wang TY, Lo YL, Liu W Te, et al. Chronic cough and obstructive sleep apnoea in a sleep laboratory-based pulmonary practice. *Cough*. 2013;9(1):1–5. https://doi.org/10.1186/1745-9974-9-24.

62. Chan K, Ing A, Birring SS. Cough in obstructive sleep apnoea. *Pulm Pharmacol Ther*. 2015;35:129–131. https://doi.org/10.1016/j.pupt.2015.05.008.

63. Fortuna AM, Miralda R, Calaf N, González M, Casan P, Mayos M. Airway and alveolar nitric oxide measurements in obstructive sleep apnea syndrome. *Respir Med*. 2011;105(4):630–636. https://doi.org/10.1016/j.rmed.2010.12.004.

64. Faruqi S, Fahim A, Morice AH. Chronic cough and obstructive sleep apnoea: reflux-associated cough hypersensitivity? *Eur Respir J*. 2012;40(4):1049–1050. https://doi.org/10.1183/09031936.00025012.

65. Sundar KM, Willis AM, Smith S, Hu N, Kitt JP, Birring SS. A randomized, controlled, pilot study of CPAP for patients with chronic cough and obstructive sleep apnea. *Lung*. 2020;198(3):449–457. https://doi.org/10.1007/s00408-020-00354-1.

66. Gibson PG, Simpson JL, Ryan NM, Vertigan AE. Mechanisms of cough. *Curr Opin Allergy Clin Immunol*. 2014;14(1):55–61. https://doi.org/10.1097/ACI.0000000000000027.

67. Bucca CB, Bugiani M, Culla B, et al. Chronic cough and irritable larynx. *J Allergy Clin Immunol*. 2011;127:412–419. https://doi.org/10.1016/j.jaci.2010.10.038.

68. Vertigan AE, Theodoros DG, Gibson PG, Winkworth AL. Voice and upper airway symptoms in people with chronic cough and paradoxical vocal fold movement. *Curr Opin Allergy Clin Immunol*. 2007;7(3):361–383. https://doi.org/10.1097/ACI.0b013e328012c587.

69. Canning BJ, Mazzone SB, Meeker SN, Mori N, Reynolds SM, Undem BJ. Identification of the tracheal and laryngeal afferent neurons mediating cough in anaesthetized Guinea-pigs. *J Physiol*. 2004;557(2):543–558. https://doi.org/10.1113/jphysiol.2003.057885.

70. Irwin RS, French CL, Chang AB, Altman KW. Classification of cough as a symptom in adults and management algorithms: CHEST guideline and expert panel report. *Chest*. 2018;153(1):196–209. https://doi.org/10.1016/j.chest.2017.10.016.

71. Satia I, Watson R, Scime T, et al. Allergen challenge increases capsaicin-evoked cough responses in patients with allergic asthma. *J Allergy Clin Immunol*. 2019;144(3):788–795. https://doi.org/10.1016/j.jaci.2018.11.050. e1.

72. Ribeiro M, De Castro Pereira CA, Nery LE, Beppu OS, Silva COS. A prospective longitudinal study of clinical characteristics, laboratory findings, diagnostic spectrum and outcomes of specific therapy in adult patients with chronic cough in a general respiratory clinic. *Int J Clin Pract*. 2006;60(7):799–805. https://doi.org/10.1111/j.1368-5031.2006.00876.x.

73. Çolak Y, Afzal S, Lange P, Laursen LC, Nordestgaard BG, Dahl M. Role and impact of chronic cough in individuals with asthma from the general population. *J Allergy Clin Immunol Pract*. 2019;7(6):1783–1792. https://doi.org/10.1016/j.jaip.2019.02.021. e8.

74. Brightling CE. Chronic cough due to nonasthmatic eosinophilic bronchitis ACCP evidence-based clinical practice guidelines. *Chest*. 2006;129(1):116S–121S. https://doi.org/10.1378/chest.129.1_suppl.116S.

75. Yıldız T, Dülger S. Non-astmatic eosinophilic bronchitis. *Turkish Thorac J*. 2018;19(1):41–45. https://doi.org/10.5152/TurkThoracJ.2017.17017.

76. Vujnović SD, Domuz A, Petrović S. Cough variant asthma as a phenotype of classic asthma. In: Huang KHG, Hsuan C, Tsai S, eds. *Approach Based on Phenotype and Endotype*. IntechOpen; 2018. https://doi.org/10.5772/intechopen.75152.

77. Magni C, Chellini E, Zanasi A. Cough variant asthma and atopic cough. *Multidiscip Respir Med*. 2010;5(2):99–103. https://doi.org/10.1186/2049-6958-5-2-99.

78. Lougheed MD, Turcotte SE, Fisher T. Cough variant asthma: lessons learned from deep inspirations. *Lung*. 2012;190:17–22. https://doi.org/10.1007/s00408-011-9348-6.

79. Cho PSP, Fletcher HV, Patel IS, Turner RD, Jolley CJ, Birring SS. Cough hypersensitivity and suppression in COPD. *Eur Respir J*. 2021;57(5), 2003569. https://doi.org/10.1183/13993003.03569-2020.

80. Cho PSP, Fletcher HV, Turner RD, Patel IS, Jolley CJ, Birring SS. The relationship between cough reflex sensitivity and exacerbation frequency in chronic obstructive pulmonary disease. *Lung*. 2020;198(4):617–628. https://doi.org/10.1007/s00408-020-00366-x.

81. Irwin RS, Mark Madison J. Diagnosis and treatment of chronic cough due to gastro-esophageal reflux disease and postnasal drip syndrome. *Pulm Pharmacol Ther*. 2002;15(3):261–266. https://doi.org/10.1006/pupt.2002.0348.

82. Jaspersen D, Kulig M, Labenz J, et al. Prevalence of extra-oesophageal manifestations in gastro-oesophageal reflux disease: an analysis based on the ProGERD Study. *Aliment Pharmacol Ther*. 2003;17(12):1515–1520. https://doi.org/10.1046/j.1365-2036.2003.01606.x.

83. Kahrilas PJ, Altman KW, Chang AB, et al. Chronic cough due to gastroesophageal reflux in adults: CHEST guideline and expert panel report. *Chest*. 2016;150(6):1341–1360. https://doi.org/10.1016/j.chest.2016.08.1458.

84. Smith JA, Houghton LA. The oesophagus and cough: laryngo-pharyngeal reflux, microaspiration and vagal reflexes. *Cough*. 2013;9:12. https://doi.org/10.1186/1745-9974-9-12.

85. Patterson RN, Johnston BT, Ardill JES, Heaney LG, McGarvey LPA. Increased tachykinin levels in induced sputum from asthmatic and cough patients with acid reflux. *Thorax*. 2007;62(6):491–495. https://doi.org/10.1136/thx.2006.063982.

86. Qiu Z, Yu L, Xu S, et al. Cough reflex sensitivity and airway inflammation in patients with chronic cough due to non-acid gastro-oesophageal reflux. *Respirology*. 2011;16(4):645–652. https://doi.org/10.1111/j.1440-1843.2011.01952.x.

87. Zeiger RS, Schatz M, Butler RK, Weaver JP, Bali V, Chen W. Burden of specialist-diagnosed chronic cough in adults. *J Allergy Clin Immunol Pract*. 2020;8(5):1645–1657. https://doi.org/10.1016/j.jaip.2020.01.054.

88. Shusterman D. Nonallergic rhinitis: environmental determinants. *Immunol Allergy Clin*. 2016 May;36(2):379–399. https://doi.org/10.1016/j.iac.2015.12.013. Epub 2016 Mar 8. PMID: 27083110.

89. Shusterman D. The effects of air pollutants and irritants on the upper airway. *Proc Am Thorac Soc*. 2011 Mar;8(1):101–105. https://doi.org/10.1513/pats.201003-027RN. PMID: 21364227.

90. Qutub HO. Cough: a practical approach for the primary care physician in Saudi Arabia. *J Family Community Med*. 2000 Jan;7(1):75–79.

91. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical practice guideline (update): adult sinusitis. *Otolaryngol Head Neck Surg*. 2015;152(2S):S1–S39. https://doi.org/10.1177/0194599815572097.

92. Seidman MD, Gurgel RK, Lin SY, et al. Clinical practice guideline: allergic rhinitis. *Otolaryngol Neck Surg*. 2015;152(1S):S1–S43. https://doi.org/10.1177/0194599814561600.

93. Song DJ, Song WJ, Kwon JW, et al. KAAACI evidence-based clinical practice guidelines for chronic cough in adults and children in Korea. *Allergy, Asthma Immunol Res*. 2018;10(6):591–613. https://doi.org/10.4168/aair.2018.10.6.591.

94. Irwin RS, Baumann MH, Bolser DC, et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. *Chest*. 2006;129(1):1–23. https://doi.org/10.1378/chest.129.1_suppl.1S.

95. Smith JA, Badri H. Cough: new pharmacology. *J Allergy Clin Immunol Pract*. 2019;7(6):1731–1738. https://doi.org/10.1016/j.jaip.2019.04.027.

96. Smith JA, Birring SS, Dicpinigaitis PV, et al. Improvements in objective and subjective measures of chronic cough with gefapixant: a pooled phase 3 efficacy analysis of predefined subgroups. *Lung*. 2022;200(4):423–429. https://doi.org/10.1007/s00408-022-00553-y.

97. Glashan E, Mahmoud SH. Cough. *Patient Assess Clin Pharm*. 2018;28:67–78. https://doi.org/10.1007/978-3-030-11775-7_5.

98. Sun L, Guo R, Sun L. The impact of prophylactic intravenous lidocaine on opioid-induced cough: a meta-analysis of randomized controlled trials. *J Anesth*. 2014;28(3):325–333. https://doi.org/10.1007/s00540-013-1732-3.

99. Yılmaz İ. Angiotensin-converting enzyme inhibitors induce cough. *Turkish Thorac J*. 2019;20(1):36–42. https://doi.org/10.5152/TurkThoracJ.2018.18014.

100. Laidlaw TM. Clinical updates in aspirin-exacerbated respiratory disease. *Allergy Asthma Proc*. 2019;40(1):4–6. https://doi.org/10.2500/aap.2019.40.4188.

101. Morales DR, Lipworth BJ, Donnan PT, Jackson C, Guthrie B. Respiratory effect of beta-blockers in people with asthma and cardiovascular disease: population-based nested case control study. *BMC Med*. 2017;15(1):18. https://doi.org/10.1186/s12916-017-0781-0.

102. Turner RD, Bothamley GH. Chronic cough and a normal chest X-ray-a simple systematic approach to exclude common causes before referral to secondary care: a retrospective cohort study. *npj Prim Care Respir Med*. 2016;26(June 2015):1–7. https://doi.org/10.1038/npjpcrm.2015.81.

103. Wang Z, Wang M, Wen S, Yu L, Xu X. Types and applications of cough-related questionnaires. *J Thorac Dis*. 2019;11(10):4379–4388. https://doi.org/10.21037/jtd.2019.09.62.

104. Birring SS, Prudon B, Carr AJ, Singh SJ, Morgan L, Pavord ID. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). *Thorax*. 2003;58(4):339–343. https://doi.org/10.1136/thorax.58.4.339.

105. Gawchik S, Goldstein S, Prenner B, John A. Relief of cough and nasal symptoms associated with allergic rhinitis by mometasone furoate nasal spray. *Ann Allergy Asthma Immunol*. 2003;90(4):416–421. https://doi.org/10.1016/S1081-1206(10)61826-1.

106. Passali D, Spinosi MC, Crisanti A, Bellussi LM. Mometasone furoate nasal spray: a systematic review. *Multidiscip Respir Med*. 2016;11(1):1–5. https://doi.org/10.1186/s40248-016-0054-3.

107. Na GW, Lee DG, Kim JY, et al. Effect of intranasal steroids on chronic cough caused by upper airway cough syndrome. *Allergy Asthma Respir Dis*. 2014;2(November):362–369.

108. Brożek JL, Bousquet J, Agache I, Agarwal A, Bachert C, Bosnic-Anticevich S, Brignardello-Petersen R, Canonica GW, Casale T, Chavannes NH, Correia de Sousa J, Cruz AA, Cuello-Garcia CA, Demoly P, Dykewicz M, Etxeandia-Ikobaltzeta I, Florez ID, Fokkens W, F.

109. Kim JE, Song JH, Kang KW. Rhinitis, sinusitis and ocular disease – 2039. Effect of intranasal steroid on cough symptom in patients with upper airway couth syndrome. *World Allergy Organ J*. 2013;6(suppl 1), P171. https://doi.org/10.1186/1939-4551-6-s1-p171.

110. Wang K, Birring SS, Taylor K, et al. Montelukast for postinfectious cough in adults: a double-blind randomised placebo-controlled trial. *Lancet Respir Med*. 2014 Jan;2(1):35–43. https://doi.org/10.1016/S2213-2600(13)70245-5.

111. Lee JH, Lee JW, An J, et al. Efficacy of non-sedating H1-receptor antihistamines in adults and adolescents with chronic cough: a systematic review. *World Allergy Organ J*. 2021;14(8), 100568. https://doi.org/10.1016/j.waojou.2021.100568.

112. Johnstone KJ, Chang AB, Fong KM, Bowman RV, Yang IA. Inhaled corticosteroids for subacute and chronic cough in adults. *Cochrane Database Syst Rev*. 2013 Mar 28;2013(3), CD009305. https://doi.org/10.1002/14651858.CD009305.pub2.

113. Rajvanshi N, Kumar P, Goyal JP. Global initiative for asthma guidelines 2024: an update. *Indian Pediatr*. 2024 Aug 15;61(8):781–786.

114. Dutta AK, Jain A, Jearth V, et al. Guidelines on optimizing the use of proton pump inhibitors: PPI stewardship. *Indian J Gastroenterol*. 2023 Oct;42(5):601–628. https://doi.org/10.1007/s12664-023-01428-7.

115. Czachor A, Diaz JD, Cho SH, Lockey RF. The use of flexible rhinolaryngoscopy for allergy-immunology practice. *J Allergy Clin Immunol Pract*. 2023 Jan;11(1):149–157.e1. https://doi.org/10.1016/j.jaip.2022.04.045. Epub 2022 Sep 22. Erratum in: J Allergy Clin Immunol Pr.

116. Medical Advisory Secretariat. Polysomnography in patients with obstructive sleep apnea: an evidence-based analysis. *Ont Health Technol Assess Ser*. 2006;6(13):1–38. Epub 2006 Jun 1.

117. Famokunwa B, Walsted ES, Hull JH. Assessing laryngeal function and hypersensitivity. *Pulm Pharmacol Ther*. 2019 Jun;56:108–115. https://doi.org/10.1016/j.pupt.2019.04.003.

118. Maniscalco M, Fuschillo S, Gaudiosi C, De Felice A, Martucci M, Motta A. Exhaled and nasal nitric oxide measurement in the evaluation of chronic cough. *Nitric Oxide*. 2019;83:19–23. https://doi.org/10.1016/j.niox.2018.12.005.

119. Matsunaga K, Hirano T, Akamatsu K, et al. Exhaled nitric oxide cutoff values for asthma diagnosis according to rhinitis and smoking status in Japanese subjects. *Allergol Int*. 2011;60(3):331–336. https://doi.org/10.2332/allergolint.10-OA-0277.

120. Dweik RA, Boggs PB, Erzurum SC, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med*. 2011;184(5):602–615. https://doi.org/10.1164/rccm.9120-11ST.

121. Yi F, Fang Z, Liang H, et al. Diagnostic accuracy of blood eosinophils in comparison to other common biomarkers for identifying sputum eosinophilia in patients with chronic cough. *World Allergy Organ J*. 2023;16(9), 100819. https://doi.org/10.1016/j.waojou.2023.100819.

122. Fleming L, Tsartsali L, Wilson N, Regamey N, Bush A. Longitudinal relationship between sputum eosinophils and exhaled nitric oxide in children with asthma. *Am J Respir Crit Care Med*. 2013;188(3):400–402. https://doi.org/10.1164/rccm.201212-2156LE.

123. Beghè B, Spanevello A, Fabbri LM. Eosinophilia in asthma: the easy way is not always the best. *Lancet Respir Med*. 2015;3(4):260–261. https://doi.org/10.1016/S2213-2600(15)00108-3.

124. Mauer Y, Do RMT. Managing adult asthma: the 2019 GINA guidelines. *Cleve Clin J Med*. 2020;87(9):569–575. https://doi.org/10.3949/CCJM.87A.19136.

125. Levy ML, Bacharier LB, Bateman E, et al. Key recommendations for primary care from the 2022 Global Initiative for Asthma (GINA) update. *npj Prim Care Respir Med*. 2023;33(1). https://doi.org/10.1038/s41533-023-00330-1.

126. Xu X, Chen Q, Liang S, Lv H, Qiu Z. Comparison of gastroesophageal reflux disease questionnaire and multichannel intraluminal impedance pH monitoring in identifying patients with chronic cough responsive to antireflux therapy. *Chest*. 2014;145(6):1264–1270. https://doi.org/10.1378/chest.13-1634.

127. Durazzo M, Lupi G, Cicerchia F, et al. Extra-esophageal presentation of gastroesophageal reflux disease: 2020 update. *J Clin Med*. 2020;9(8):2559. https://doi.org/10.3390/jcm9082559.

128. Eluri S, Dellon ES. Proton pump inhibitor-responsive oesophageal eosinophilia and eosinophilic oesophagitis: more similarities than differences. *Curr Opin Gastroenterol*. 2015;31(4):309–315. https://doi.org/10.1097/MOG.0000000000000185.

129. Gockel I, Rabe SM, Niebisch S. Before and after esophageal surgery: which information is needed from the functional laboratory? *Visc Med*. 2018;34(2):116–121. https://doi.org/10.1159/000486556.

130. Lai K, Satia I, Song WJ, et al. Cough and cough hypersensitivity as treatable traits of asthma. *Lancet Respir Med*. 2023;11(7):650–662. https://doi.org/10.1016/S2213-2600(23)00187-X.

131. Cohen SM, Misono S. Use of specific neuromodulators in the treatment of chronic, idiopathic cough: a systematic review. *Otolaryngol Head Neck Surg*. 2013 Mar;148(3):374–382. https://doi.org/10.1177/0194599812471817.

132. Smith J, Allman D, Badri H, et al. The neurokinin-1 receptor antagonist orvepitant is a novel antitussive therapy for chronic refractory cough: results from a phase 2 pilot study (VOLCANO-1). *Chest*. 2020;157(1):111–118. https://doi.org/10.1016/j.chest.2019.08.001.

133. Burnstock G, Verkhratsky A. Long-term (trophic) purinergic signalling: purinoceptors control cell proliferation, differentiation and death. *Cell Death Dis*. 2010;1(1):e9. https://doi.org/10.1038/cddis.2009.11.

134. Slinger C, Mehdi SB, Milan SJ, et al. Speech and language therapy for management of chronic cough. *Cochrane Database Syst Rev*. 2019;(7). https://doi.org/10.1002/14651858.CD013067.pub2.

135. Gibson PG, Vertigan AE. Speech pathology for chronic cough: a new approach. *Pulm Pharmacol Ther*. 2009;22(2):159–162. https://doi.org/10.1016/j.pupt.2008.11.005.

136. Ryan NM, Vertigan AE, Bone S, Gibson PG. Cough reflex sensitivity improves with speech language pathology management of refractory chronic cough. *Cough*. 2010;6(5):1–8. https://doi.org/10.1186/1745-9974-6-5.

137. Vertigan AE, Kapela SL, Ryan NM, Birring SS, McElduff P, Gibson PG. Pregabalin and speech pathology combination therapy for refractory chronic cough a randomized controlled trial. *Chest*. 2016;149(3):639–648. https://doi.org/10.1378/chest.15-1271.