



WAO-ARIA consensus on chronic cough - Part II: Phenotypes and mechanisms of abnormal cough presentation - Updates in COVID-19

Philip Rouadi, Samar Idriss, Jean Bousquet, Tanya M. Laidlaw, Cecilio R. Azar, Mona S. Al-Ahmad, Anahi Yañez, Maryam Ali Y. Al-Nesf, Talal M. Nsouli, Sami L. Bahna, et al.

► To cite this version:

Philip Rouadi, Samar Idriss, Jean Bousquet, Tanya M. Laidlaw, Cecilio R. Azar, et al.. WAO-ARIA consensus on chronic cough - Part II: Phenotypes and mechanisms of abnormal cough presentation - Updates in COVID-19. World Allergy Organization Journal, 2021, 14 (12), pp.100618. <10.1016/j.waojou.2021.100618>. <hal-03781575>

HAL Id: hal-03781575

<https://hal.science/hal-03781575v1>

Submitted on 20 Sep 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons CC BY-NC-ND 4.0 - Attribution - Non-commercial use - No Derivative Works - International License



WAO-ARIA consensus on chronic cough - Part II: Phenotypes and mechanisms of abnormal cough presentation – Updates in COVID-19

Philip W. Rouadi, MD^{a*}, Samar A. Idriss, MD^{a,b}, Jean Bousquet, MD, PhD^{c,d,e,f}, Tanya M. Laidlaw, MD^g, Cecilio R. Azar, MD^{h,i,j}, Mona S. Al-Ahmad, MD, FRCPCP^k, Anahi Yañez, MD^l, Maryam Ali Y. Al-Nesf, MD, MSc R, CABHS^m, Talal M. Nsouli, MD, FACAAI, FAAAAIⁿ, Sami L. Bahna, MD, DrPH^o, Eliane Abou-Jaoude, MDⁿ, Fares H. Zaitoun, MD, FACAAI^p, Usamah M. Hadi, MD, FACS, ERS, PARS^q, Peter W. Hellings, MD, PhD^{r,s,t,u}, Glenis K. Scadding, MD, FRCP^v, Peter K. Smith, BMedSci, MBBS, FRACP, PhD^w, Mario Morais-Almeida, MD^x, René Maximiliano Gómez, MD, PhD^y, Sandra N. Gonzalez Diaz, MD, PhD^z, Ludger Klimek, MD, PhD^{aa}, Georges S. Juvelekian, MD, FCCP, D'ABSM^{ab}, Moussa A. Riachy, MD, FCCP^{ac}, Giorgio Walter Canonica, MD^{ad}, David Peden, MD^{ae}, Gary W. K. Wong, MD^{af}, James Sublett, MD^{ag}, Jonathan A. Bernstein, MD^{ah}, Lianglu Wang, MD^{ai}, Luciana K. Tanno, MD, PhD^{f,aj,ak}, Manana Chikhladze, PhD^{al}, Michael Levin, MD^{am}, Yoon-Seok Chang, MD, PhD^{an}, Bryan L. Martin, DO^{ao}, Luis Caraballo, MD, PhD^{ap}, Adnan Custovic, MD, PhD^{aq}, Jose Antonio Ortega-Martell, MD^{ar}, Erika Jensen-Jarolim, MD^{as,at}, Motohiro Ebisawa, MD^{au}, Alessandro Fiocchi, MD^{av} and Ignacio J. Ansotegui, MD, PhD^{aw}

ABSTRACT

Background: Chronic cough can be triggered by respiratory and non-respiratory tract illnesses originating mainly from the upper and lower airways, and the GI tract (ie, reflux). Recent findings suggest it can also be a prominent feature in obstructive sleep apnea (OSA), laryngeal hyper-responsiveness, and COVID-19. The classification of chronic cough is constantly updated but lacks clear definition. Epidemiological data on the prevalence of chronic cough are informative but highly variable. The underlying mechanism of chronic cough is a neurogenic inflammation of the cough reflex which becomes hypersensitive, thus the term hypersensitive cough reflex (HCR). A current challenge is to decipher how various infectious and inflammatory airway diseases and esophageal reflux, among others, modulate HCR.

Objectives: The World Allergy Organization/Allergic Rhinitis and its Impact on Asthma (WAO/ARIA) Joint Committee on Chronic Cough reviewed the current literature on classification, epidemiology, presenting features, and mechanistic pathways of chronic cough in airway- and reflux-related cough phenotypes, OSA, and COVID-19. The interplay of cough reflex sensitivity

^aDepartment of Otolaryngology - Head and Neck Surgery, Eye and Ear University Hospital, Beirut, Lebanon

*Corresponding author. E-mail: rouadipws@gmail.com

Full list of author information is available at the end of the article

<http://doi.org/10.1016/j.waojou.2021.100618>

Received 4 September 2021; Received in revised form 30 October 2021;

Accepted 12 November 2021

Online publication date 22 November 2021

1939-4551/© 2021 The Authors. Published by Elsevier Inc. on behalf of World Allergy Organization. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

with other pathogenic mechanisms inherent to airway and reflux-related inflammatory conditions was also analyzed.

Outcomes: Currently, it is difficult to clearly ascertain true prevalence rates in epidemiological studies of chronic cough phenotypes. This is likely due to lack of standardized objective measures needed for cough classification and frequent coexistence of multi-organ cough origins. Notwithstanding, we emphasize the important role of HCR as a mechanistic trigger in airway- and reflux-related cough phenotypes. Other concomitant mechanisms can also modulate HCR, including type2/Th1/Th2 inflammation, presence or absence of deep inspiration-bronchoprotective reflex (lower airways), tissue remodeling, and likely cough plasticity, among others.

Keywords: Multifactorial cough, Cough phenotypes, Type 2 inflammation, COVID 19, Reflux-cough, Upper airway cough syndrome, Lower airway disease, Obstructive sleep apnea

INTRODUCTION

Epidemiological studies suggest the prevalence of cough ranges from 2.5% to 18%¹⁻⁴ with significant impact on quality of life (QoL),^{4,5} especially in the elderly.⁶ Acute cough is defined as lasting up to 3 or 4 weeks in adults,⁷ and is usually self-limited.^{8,9} Cough persisting for ≥ 8 weeks in adults¹⁰ or $4 \geq$ weeks in children^{7,11,12} can be defined as chronic cough. In this arbitrary classification, adult patients presenting for an interim period (ie, 4-8 weeks) may be either recovering from an acute cough-associated illness or in the pre-chronic cough stage and can be labelled as having “probable” chronic cough.¹ Chronic cough affects all ages and genders, although the typical chronic cough patient is a female in her sixth decade.¹³ Chronic cough is more prevalent in western countries compared to Asia and Africa.² A variety of respiratory and non-respiratory tract illnesses can trigger the condition, and the illnesses are listed in Fig. 1. Upper and lower airway etiologies of chronic cough are collectively termed upper airway cough syndrome (UACS) and lower airway cough syndrome (LACS), respectively. Other important etiologies include gastroesophageal reflux disease (GERD)-related cough and laryngeal hyperresponsiveness (LHR), obstructive sleep apnea (OSA), and COVID-19, tumors, and drugs (ie, ACE inhibitors, opioids), among others. However, chronic cough can occur in the absence of known triggers. While cough has been considered traditionally a symptomatic byproduct of these illnesses, the majority of patients do not report

cough, although if asked, most patients describe it to be aggravating. Also, cough severity correlates poorly with severity of cough-associated illnesses.¹⁴ This suggests chronic cough is a distinct clinical entity. Based on clinical models, it is speculated that the underlying mechanism of chronic cough is a neurogenic inflammation of the cough reflex which becomes hypersensitive, thus the term hypersensitive cough reflex (HCR).¹⁵ Still, the physician struggles to decipher how various infectious and inflammatory airway diseases and esophageal reflux, among others, modulate HCR. In a previous part of the consensus (Part I),¹⁵ we reported on the role of transient receptor potential (TRP) ion channels in pathogenesis of chronic cough by mediating a crosstalk between neurogenic and inflammatory pathways in cough associated airways diseases. The current part II of the consensus (see Appendix) examines the presenting features, and mechanistic tussive pathways, in addition to the role of TRP ion channels, in airway- and reflux-related cough phenotypes, OSA, and COVID-19. Cough management in primary and cough specialty care will be further reported in part III of the consensus.

UPPER AIRWAY COUGH SYNDROME

Classification and epidemiology

The term UACS, previously called postnasal drip syndrome (PNDS), is used to describe protracted cough triggered by common infectious, inflammatory, or neurogenic diseases involving the

upper airways (Fig. 1). These can encompass several rhinitis and rhinosinusitis phenotypes, anatomic abnormalities, or chemically induced rhinitis, as well as pharyngeal diseases, among others.^{16–18} Also, diseases of the upper digestive tract can trigger cough. Mechanical manipulation of the external auditory canal can stimulate the auricular branch of the vagus nerve (Arnold's nerve) resulting in chronic dry cough.^{19,20} A uniform definition of UACS/PNDS is lacking across the United States, Europe, and Asia. The discrepancy lies in considering postnasal drip (PND) as a symptom or a separate disease entity.¹⁶ Furthermore, patients with PND do not account for a homogeneous group with respect to etiology. Other considerations, such as lack of standardized objective measures for clinical assessment of chronic cough, co-existence of more than one upper airway cough-associated disease, and absence of a uniform management protocol for chronic cough pose a great challenge to a clear definition of UACS. The characterization of UACS is even more complex in children. Challenges include age-related changes in etiologic frequencies of chronic cough in nursery, pre-school, and school-age children,²¹ possibly related to differential maturation and modulation of cough reflex postnatally.²² Also, inability to perform invasive or noninvasive diagnostic modalities in young children, such as induced sputum analysis, bronchial provocation testing, and computed tomography (CT) scans requiring sedation, poses additional challenges to the classification and consequently to the management of chronic cough in this age group.²³

Epidemiological data on prevalence of upper airway-related cough among chronic cough

patients is highly variable.²⁴ This is partly due to poor awareness amongst physicians of upper airway cough phenotypes leading to chronic cough. Enhanced diagnostic accuracy of cough etiological factors can also affect prevalence data. Other confounding variables can be type of patient population, whether studied in primary or cough-specialty care; this can overestimate or underestimate the true prevalence, respectively. In a 10-year longitudinal study (N = 1311), the reported etiological frequency for chronic cough dramatically changed as UACS and cough variant asthma (CVA) decreased by 50%, while GERD increased by 50%. Moreover, in a series of chronic cough patients, allergic rhinitis (AR), classic asthma (CA), chronic rhinosinusitis (CRS), and nasal polypsis (NP) were found in 46.5%, 31%, 12%, and 8.6% of patients with chronic cough, respectively. The high predictive value for concomitant asthma in UACS warrants a careful search for a lower airway pathology in patients presenting with chronic cough of upper airway origin.²⁵ Cough quality that is either dry or productive cannot predict cough phenotype in adults; however, it can prove useful in determining etiological diagnosis in children.²⁶ For example, in children with bacterial bronchitis a persistent wet cough warrants urgent attention whereas its value in adults remains questionable.²⁷ In conclusion, the characterization of UACS in epidemiological studies lacks objective measures. This is partly due to presence of confounding variables, more so in the pediatric population.

Pathogenesis

It is speculated that upper airway cough-associated diseases can induce mechanical, systemic, or neurogenic stimulation of the afferent limb

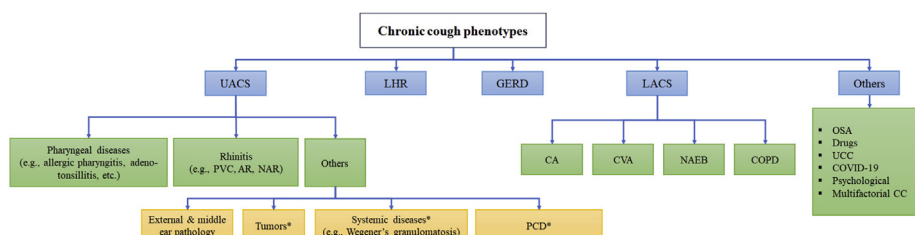


Fig. 1 Classification of chronic cough phenotypes. Abbreviations: AR (Allergic rhinitis), CA (Classic asthma), CC (Chronic cough), CVA (Cough variant asthma), COPD (Chronic obstructive pulmonary disease), GERD (gastroesophageal reflux disease), LACS (Lower airway cough syndrome), LHR (Laryngeal hyperresponsiveness), NAEB (Non-asthmatic eosinophilic bronchitis), NAR (Non allergic rhinitis), OSA (Obstructive sleep apnea), PCD (Primary ciliary dyskinesia), PND (Post-nasal drip), PVC (Post-viral cough), UACS (Upper airway cough syndrome), UCC (Unexplained chronic cough), *disease of rare occurrence.

of cough reflex.²⁸ This includes sensory fibers of the trigeminal nerve^{16,29} and superior laryngeal and pharyngolaryngeal branch of the vagus nerve. Pathogenic mechanisms can be mechanical or chemical stimulation of the vagal afferent nerve by postnasal drip,^{17,30} hematogenous spread of inflammatory mediators,¹⁶ or cough reflex hypersensitivity.¹⁶ As a mechanistic trigger, PND, whether subjectively reported or noted on physical examination, is not a consistent complaint/finding in patients with chronic cough.³¹ Furthermore, the united airway theory speculates a hematogenous or neural spread of inflammatory mediators between upper and lower airways. This is evidenced by bidirectional involvements of both nose/sinuses and lungs in airway inflammatory diseases, such as atopy, and CRS with or without NP.^{32,33} Although evidence of a hypersensitive cough reflex involving vagus central and peripheral neuronal pathways is abundant, data supporting a hypersensitive cough reflex involvement of trigeminal nerve are relatively scarce. Notwithstanding, direct stimulation of trigeminal afferents in the nose can promote the cough reflex. In support of this, mechanical, thermal, and chemo-sensitive polymodal afferent receptors of the trigeminal nerve can be activated by capsaicin through its selective receptor TRPV1.³⁴ Clinical models involving tussigen inhalation and nasal challenges have provided great insight into the mechanism involved in UACS. It is important to note that tussive challenges reflect only a predisposition to cough under controlled conditions since experimental tussigen concentrations demonstrate only a moderate correlation with cough frequency.³⁵ Capsaicin, a TRPV1 agonist, is an important tussigen used in animal and human models of cough inhalation challenges, where capsaicin-mediated activation of TRPV1 results in bronchospasm.³⁶ In healthy subjects, nasal challenge with histamine which lowers activation threshold of TRPV1 triggered sneezing and itching but no cough. One explanation for the absence of cough reflex can be insufficient lowering of the cough receptor threshold by histamine.³⁷ At the peak of nasal itching ensuing from intranasal histamine challenge, subjects who were sequentially challenged with capsaicin inhalation reported more coughs when compared to a concomitant challenge with intranasal saline and

inhaled capsaicin. This suggests nasal triggers can potentiate the cough reflex arc in the lower airways.^{29,38} It also supports existence of a central crossover between trigeminal and vagus neuronal pathways referred to as cough plasticity or the modulation of the cough reflex by other afferent inputs within the vagal neuronal pathway and out of it.³⁹ Hypothetically, "convergence" centers among nasal putative sensory afferents along the paratrigeminal nucleus and afferent cough fibers along the vagal second order neurons in tractus solitarius, can feature interactive activity of both afferent nerves.⁴⁰ This can modulate cough response by increasing cough sensitivity to capsaicin.⁴¹ In support of the convergence theory, capsaicin challenge in guinea pigs increased neuronal activity simultaneously in the brainstem and the trigeminal nerve, as suggested by increased expression of C-fos (proto-oncogene),^{16,38} the gene group of second and higher order neurons.

In conclusion, UACS lack a uniform definition of trigger diseases, such as PND, rhinitis, or rhinosinusitis in children or adults. Additionally, mechanistic triggers of chronic cough in UACS can involve a neurogenic or systemic communication between upper and lower airways, and likely cough reflex sensitivity. Because rhinitis or rhinosinusitis are frequent comorbidities of reactive airways and reflux disease, it is sometimes difficult to discern if chronic cough reflects HCR involving the vagus nerve, trigeminal nerve, or both.

Infectious rhinitis

Infectious rhinitis or common cold has been traditionally linked to chronic cough, the so-called post-viral cough (PVC). Mechanical stimulation of the chest by high frequency chest percussion in non-coughing patients with upper respiratory tract infection (URTI) increased cough when compared to healthy volunteers. This suggests airway mechanical and rapidly adapting receptors can trigger cough reflex sensitivity in patients with URTI.⁴² Previous reports demonstrated patients with URTI have increased cough sensitivity to capsaicin but no change in airway responsiveness to methacholine challenge, when compared to healthy volunteers.⁴³ This suggests respiratory infections can induce a hypersensitive cough reflex without airway hyperresponsiveness. Also,

lipopolysaccharide can activate TRPA1, independently of their activation of Toll-like receptor 4 (TLR4),⁴⁴ and viral mRNA is capable of stimulating purinergic receptors via TLR7.⁴⁵

Allergic and non-allergic rhinitis

A longitudinal cohort study demonstrated non-infectious rhinitis is a significant and independent risk factor for development of chronic cough in adults.⁴⁶ In AR, many patients have cough, wheezing, and shortness of breath, and during the pollen season, cough is often severe with no major change in forced expiratory volume during the first second (FEV1), thereby suggesting an upper airway origin.⁴⁷ Bronchial hyperresponsiveness is more frequent in AR patients in cross-sectional studies,⁴⁸⁻⁵⁰ and compared to seasonal rhinitis, perennial rhinitis is much more important as a risk factor for developing nonspecific bronchial hyperresponsiveness.⁵¹ Experimental data suggest that AR is a risk factor for chronic cough. Tussigen challenges in AR indicate that capsaicin-sensitive TRPV1 receptors and capsaicin-insensitive A- δ stretch receptors modulate cough sensitivity.³⁹ Cough reflex sensitivity in the upper airways is heightened in atopic patients^{52,53} when compared to healthy controls. By comparing adults³⁹ or children⁵⁴ with seasonal AR outside their pollen season to healthy controls, a standardized (inhaled) capsaicin challenge model demonstrated significantly increased cough in atopic patients. Using the same model, allergic patients in-season reported significantly more coughs than those out-of-season.⁵² These findings are also in accordance with the "priming effect" reported in the upper airways, that is, reduced activation threshold of sensory nerves in response to IgE and non-IgE related stimuli following allergen exposure.^{55,56} As stated previously, combined challenge with inhaled capsaicin and nasal topical histamine enhanced capsaicin induced cough reflex hypersensitivity in seasonal AR.^{29,41} Conversely, treatment of atopic inflammation with inhaled corticosteroids or antileukotrienes in an animal model of ovalbumin-sensitive guinea pigs restored the cough sensitivity reflex to its pre-treatment values.^{57,58} In conclusion, these results are in line with a speculated increased reactivity

of cough afferent nerve endings in patients with clinical or subclinical AR.

Non-allergic rhinitis is a collective term used to describe non-allergic non-infectious rhinitis phenotypes characterized by nonspecific nasal hyper-reactivity. The latter denotes induction of rhinitis symptoms (rhinorrhea, nasal congestion) in response to nonspecific irritants such as tobacco smoke, changes in temperature and humidity, and air pollutants, among others.^{18,59} Idiopathic (vasomotor) rhinitis constitutes the majority of nonallergic rhinitis⁶⁰ and features many characteristics relevant to UACS. Clinically, this is exemplified by triggering of rhinitis symptoms following nonspecific thermal, mechanical, and endogenous inflammatory triggers. In vasomotor rhinitis there is also over expression of TRPV1 and TRPM8 channels along the C-fiber sensory distribution of the trigeminal nerve endings in the nose.^{61,62} Along the same line, data suggest presence of neuroimmune modulation in vasomotor rhinitis as manifested by neuropeptides (substance P and calcitonin gene-related peptide [CGRP]) mediated-inflammatory response.⁶³ Interestingly allergic, infectious, and nonallergic rhinitis can all have components of nasal hyperactivity, to a varying degree.⁶⁴ Yet, chronic cough is infrequently reported in idiopathic rhinitis,⁵⁹ and to our best knowledge no capsaicin inhaled challenge studies addressing chronic cough have been performed in this rhinitis phenotype.

Chronic rhinosinusitis

Although rhinosinusitis can constitute up to 20% of adult patients with chronic cough,⁴ coughing is not a major feature of chronic rhinosinusitis (CRS),⁶⁵ and cough aggravation has been associated with presence of bacterial biofilms.⁶⁶ In one study of adult patients with rhinosinusitis presenting with chronic cough, pharmacotherapy improved lung function parameters but not subjective cough scores, probably related to the small size of the study.⁶⁷ In contrast to adults, the majority of children with CRS present with chronic cough.⁶⁵ Several studies reported improvement of pediatric CRS-associated (chronic) cough with medical^{68,69} or surgical⁷⁰ treatment modalities. Mechanistic analysis of cough triggers in CRS is hampered by the

frequent coexistence of other cough-associated illnesses such as lower airway pathology⁷¹ or gastroesophageal reflux disease,⁷² which can act as confounding variables.

Obstructive sleep apnea syndrome (OSAS)

OSAS is an increasingly recognized important risk factor for cough in children⁷³ and adults.⁷⁴ OSAS can present solely with cough⁷⁵ and absence of daytime somnolence (normal Epworth sleepiness score).⁷⁶ Other associated symptoms in patients with OSA and cough include rhinitis and GERD.^{75,77,78} The prevalence of chronic cough in OSA patients and general population is estimated at 33–39%^{74,78,79} and 2.5–18%, respectively, which suggests a strong association between cough and OSA. This has been linked to increased production of inflammatory mediators (IL-6, IL-8, INF- γ),⁷⁶ exhaled nitric oxide, and sputum neutrophilia⁸⁰ in OSA. Compared to normal subjects, OSA patients reported a higher incidence of chronic cough, reportedly secondary to nocturnal GERD.⁷⁸ Also, patients with OSA manifest frequent nocturnal arousal and awakening episodes concomitant with the obstructive respiratory events which can cause a dysfunctional central inhibition of cough.⁷⁶ Continuous positive airway pressure (CPAP) therapy in patients with OSA and cough improves cough reflex sensitivity as measured by citric acid challenge,⁸¹ cough-related QoL (Leicester cough questionnaire)^{75,81,82} and cough scores.^{75,78,81} Taken together, these data suggest OSA is implicated in the pathogenesis of chronic cough. The role of CPAP titration in cough improvement requires further elucidation with large scale randomized trials.

LARYNGEAL HYPERRESPONSIVENESS

Anatomical and pathophysiological considerations

Laryngeal hyperresponsiveness (LHR) denotes inspiratory movement of vocal cords towards each other (adduction) in response to noxious chemical stimuli or inhaled histamine challenge.⁸³ LHR encompasses a range of laryngeal pathologies, including vocal cord dysfunction, muscle tension dysphonia, and globus, among others.⁸⁴ LHR is present in up to 50% of patients with chronic

cough.⁸⁵ The laryngo-constriction chemoreflex is mediated by the afferent superior laryngeal branch of the vagus nerve and the efferent recurrent laryngeal nerve. It forms a basic defense mechanism in newborns against aspirated liquids, and is phylogenetically complemented in adults by reflex cough and bronchoconstriction.⁸⁶ LHR can be measured by a decrease in extrathoracic (maximal) mid- inspiratory and expiratory airflow rates and a reduction in the size of the laryngeal inlet, as noted on endoscopic exam. Most patients with upper inflammatory airway diseases and cough displayed LHR as revealed by histamine inhalation protocol.⁸⁷ Using glottic airflow rates as index of extrathoracic hyperresponsiveness and subsequent laryngeal adduction,⁸⁸ LHR was significantly associated with sinusitis, postnasal drip, female gender, and dysphonia.⁸⁷ Also, LHR was prevalent in chronic cough patients with rhinitis/rhinosinusitis (76%), gastroesophageal reflux disease (77%), and asthma (93%); however, it was absent in non-coughing asthmatic patients.⁸³ Taken together, these data suggest LHR is associated with UACS, GERD-associated chronic cough, and cough associated with asthma. However, presence of asthma seems independent of the association of LHR and chronic cough of different etiologies.

Clinical aspects

Cough localized primarily to the larynx, commonly referred to as “throat” cough, is one manifestation of a hyperfunctional larynx along with episodic laryngospasm, muscle tension dysphonia, stridor, wheezes, and globus.⁸⁹ These phenotypes of laryngeal dysfunction have overlapping symptomatology and can be induced by nonspecific triggers such as scents, emotional stress, exertion, and reflux.⁸⁸ The underlying sensory nature of these triggers is suggestive of a neural plasticity of the central laryngeal neuronal pathways,^{89,90} similar to chronic cough and chronic neuropathic pain. Laryngeal provocation models consist of incremental endoscopic insufflation of gases directly into laryngeal inlet and measuring laryngeal adductor reflex as expressed by the air pressure required to achieve glottic closure. A challenge with inhaled air⁹¹ or diluted acid⁹² can reflect mechanical and sensory laryngeal

	Airway eosinophilia ^{113,143,154}	Deep inspiration cough broncho-protective reflex ^{113,143}	PGE2 (bronchodilator) expression ^{98,134,220-222}	Bronchial hyperresponsiveness (methacholine) ^{113,143,152}	HCR mechanism in CC/tussigen challenge studies ^{a,107,108,124,145,161,162}	Innate/adaptive immune system ^{223,224}
CA	Normal or increased	Absent or impaired	Decreased (Vs NAEB)	Present	Confirmed/conclusive data	Innate (ILC ₂) & adaptive (Th ₂) response
NAEB	Increased	Likely preserved	Increased (Vs CA)	Absent	Unconfirmed/Insufficient data	Innate (ILC ₂) response
CVA	Normal or increased	Preserved or impaired	Increased (Vs CA)	Present or Borderline	Confirmed/Preliminary data	Innate (ILC ₂) response
COPD	Normal or increased	Attenuated	Increased (Vs CA)	Present	Confirmed/Preliminary data	Innate (ILC ₁ /ILC ₂) & adaptive (Th ₁) response

Table 1. Comparative analysis of immunological and clinical properties of cough-phenotypic traits originating from lower airways. Abbreviations: CA (classic asthma), CC (Chronic cough), COPD (chronic obstructive pulmonary disease), CVA (cough variant asthma), HCR (hypersensitive cough reflex), ILC (innate lymphoid cell), NAEB (non-asthmatic eosinophilic bronchitis), PGE2 (prostaglandin E2), Th2 (T helper 2). ^aIn comparison with healthy individuals

hypersensitivity, respectively. These models revealed diminished laryngeal sensitivity in patients with chronic cough-associated reflux disease and paradoxical vocal fold motion.⁹³ Therefore, an exaggerated laryngeal adduction reflex was proposed as a compensatory motor response to LHR.⁹³ A recent review on methods of laryngeal sensory provocation confirms that endoscopic visualization of vocal fold motion, in different laryngeal pathologies and during exposure to multiple sensory triggers, is clinically appropriate to objectively assess vocal cord dysfunction;⁸⁸ it can be also assisted by computational algorithms. Comprehensive immunological and physiological data on neurogenic inflammatory pathways involved in LHR are currently lacking. Nevertheless, earlier data suggest efficacy of neuromodulators in treating chronic cough patients with laryngospasm and throat clearing.⁹⁴ Thus, laryngeal cough reflex sensitivity is an evolving concept.

LOWER AIRWAY COUGH SYNDROME

Reactive lower airway diseases can be associated with chronic cough, most commonly classic asthma, cough variant asthma, non-asthmatic eosinophilic bronchitis and chronic obstructive pulmonary disease.¹⁰ Immunological and clinical highlights of these closely related cough phenotypes are shown in Table 1.

Pathogenesis

As stated earlier, HCR involves neurogenic and inflammatory dysfunction of vagus nerve cough neuronal pathways. Neurogenic dysfunction involves neuromediators, such as neurokinins (bradykinins) and neuropeptides (substance P), leukotrienes and prostaglandins (PGs) (E2 and D2), nerve growth factor (NGF), and CGRP, among others.^{95,96} These powerful tussigens are associated with TRP channels and can increase cough sensitivity to bronchoconstrictor agents used in human and animal cough models, such as capsaicin, citric acid, and histamine. The inflammatory component of HCR in lower airways is characterized mainly by type 2 inflammation and airway eosinophilia reportedly noted in 50-60% of asthmatics.^{96,97} Type 2

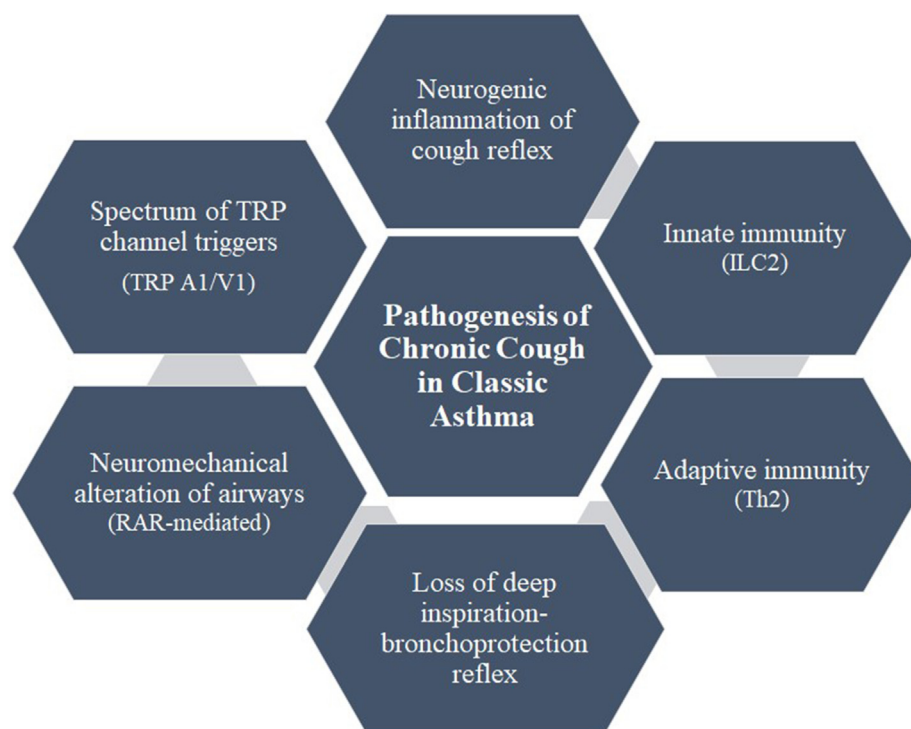


Fig. 2 Classic asthma: suggested mechanisms in pathogenesis of chronic cough, Abbreviations: ILC2 (group 2 innate lymphoid cells), RAR (Rapidly adapting receptors), Th2 (T helper cell type 2), TRPA1 (transient receptor potential ankyrin 1), TRPV1 (transient receptor potential cation channel subfamily V member 1).

cytokines such as IL-4, IL-5, and IL-13 may be expressed following stimulation of the innate immune response orchestrated by mast cells and innate lymphoid cells type 2, among others.^{98,99} The resultant signal cascade can give rise to cough phenotypes such as cough variant asthma (CVA), non-asthmatic eosinophilic bronchitis (NAEB), and nonatopic asthma.^{100,101} Atopic asthma displays activation of innate and adaptive immunity where inflammatory mediators such as histamine, prostaglandins, leukotrienes and platelet activation factor can cause bronchoconstriction and cough secondary to allergen exposure.⁹⁶ Recent evidence supports that neuromechanical properties of the lungs, which are related to a change in airway caliber as occurs during bronchoconstriction, can also contribute to chronic cough in asthmatics¹⁰² (see below). However, the relationship between neurogenic and inflammatory components of cough hypersensitive reflex and their impact on inherent mechanical properties of lower airways through bronchoconstriction is still unclear. Components of neurogenic inflammation are discussed in different cough phenotypic traits of the lower airways highlighting important clinical

symptomatology, tussive challenge testing, and response to medical therapy.

Classic asthma

Asthma is a clinical diagnosis marked by cough, variable airflow obstruction, and airway remodeling. It is one of the most common etiologies of chronic cough and accounts for up to 29% of cases.¹⁰³ Cough is a decisive symptom of asthma. Chronic cough is associated with poor asthma control;^{104,105} conversely, cough control predicts prognosis of asthma.¹⁰⁴ Other factors associated with more severe disease phenotype include objective increase in cough frequency¹⁰⁶ and heightened cough response to tussigen challenges.^{107,108} Cough in asthma is typically dry or minimally productive. Mucus-secreting cough may be potentially associated with steeper decline of pulmonary functions¹⁰⁹ and severe asthma, bronchiectasis, or chronic bronchitis.¹¹⁰ The mechanism of chronic cough in asthma is complex and features intertwined components of a hypersensitive cough reflex, IgE or non-IgE mediated eosinophilic airway inflammation, abnormal neuromechanical properties of the

lungs, and presence or absence of deep inspiration reflex (Fig. 2). In healthy individuals deep-inspiration causes bronchodilation.¹¹¹ During methacholine challenge studies, deep inspiration can also protect against induced bronchoconstriction.¹¹² It is generally agreed that the deep inspiration bronchoprotective reflex is absent or impaired in asthma.¹¹³ Hence, testing airway hyperresponsiveness can assist in the differential diagnosis of asthma (Table 1). Evidence for neuroinflammation of cough-sensitive neurons in asthma is not fully established but supported in several reports. An increased expression of bradykinin and its effector molecules prostaglandin-E2 and leukotrienes can trigger cough in the asthmatic airways¹¹⁴⁻¹¹⁶ by activation of TRP channels (A1 and V1).⁹⁵ Also, compared to healthy subjects or patients with mild intermittent asthma, moderate asthma was associated with increased airway innervation, substance P expression, in addition to airway and serum eosinophilia.⁹⁷ Along the same line, other data suggest asthmatics, compared to healthy subjects, have heightened cough response to capsaicin challenge, independent of inhaled corticosteroids (ICS) dose,¹¹⁷ airway inflammation,¹⁰⁷ FEV1 and airway hyperresponsiveness. Similarly, the observation of a heightened capsaicin-evoked cough response in asthmatics with mild airflow obstruction was independent of fractional exhaled nitric oxide (FeNO), lung function testing or airway hyperresponsiveness.¹⁰⁷ These data suggest presence of a hypersensitive cough reflex in asthmatics independently of airway inflammation or reduction of airway caliber through induced bronchoconstriction. Furthermore, the role of atopy in the etiology of chronic cough in asthma is also revealed from capsaicin challenge models. Patients with mild to moderate stable atopic asthma have unexpectedly lower cough response to capsaicin challenge when compared to nonatopic asthmatics; although both asthmatic groups, in single or combination, had worse cough scores when compared to healthy controls.¹⁰⁷ To note, these observations ensued using a capsaicin challenge which consisted of monitoring maximal cough response following any capsaicin challenge concentration (E_{\max})¹¹⁸ as opposed to a model which determines the lowest capsaicin concentration triggering 2 or 5

coughs (C_2 , C_5).¹¹⁹ Reportedly, the former model (E_{\max}) can discriminate better chronic cough patients from healthy controls compared to the conventional model (C_2 , C_5).¹¹⁸ In addition, the role of airway neuromechanical properties or change in airway caliber, length, and pressure in inducing cough through capsaicin-sensitive nerves is highlighted in both atopic and non-atopic asthmatics. In one report, asthmatics had higher cough response to capsaicin-induced cough (E_{\max}) independently of markers of eosinophilic airway inflammation. More importantly, a decrease in FEV1 resulted in doubling of cough responses in these asthmatics.¹²⁰ This was also confirmed by a recent study involving combined allergen, capsaicin, and methacholine challenges in steroid-naïve stable and atopic asthmatics. These challenges also suggested cough reflex sensitivity is linked to bronchoconstriction and mechanical decrease in airway caliber in addition to type 2 inflammation.¹⁰² In summary, these data highlight the role of altered neurobiology of the afferent cough reflex in addition to atopic or nonatopic inflammatory status as modulators of cough mechanism in asthmatics. Presence of a hypersensitive cough reflex seems independent of airway eosinophilia or hyperresponsiveness. Also, both methacholine and allergen-induced bronchoconstriction or reduction in airway caliber correlates well with capsaicin-provoked cough sensitivity in asthmatics.

Non-asthmatic eosinophilic bronchitis

Epidemiological data suggest that non-asthmatic eosinophilic bronchitis (NAEB) represents up to 35% of chronic cough patients in Asia^{121,122} and can involve children according to a large series.¹²³ Clinically, NAEB is a cough phenotype which lacks bronchoconstriction and bronchial hyperresponsiveness^{124,125} (Table 1). Similar to asthma, it is characterized by airway eosinophilia in induced sputum and responds well to anti-inflammatory therapy.^{126,127} NAEB can include patients with or without atopy. In Japan, atopic patients with a dry cough who lack airway hyperresponsiveness and are resistant to bronchodilator therapy, have been designated to have an atopic cough or eosinophilic tracheobronchitis.¹²⁸⁻¹³⁰

In patients with NAEB, presence of a heightened cough response is studied in relation to anti-asthma medications using capsaicin challenge models. In one report evaluating the cough response in NAEB patients following anti-asthma therapy,¹³¹ an initial increase in HCR at baseline was improved to near normal levels following inhaled corticosteroid therapy. Changes in sputum eosinophil count also correlated with improvement in cough sensitivity following therapy. In NAEB, the role of IL-17A, a Th17-pathway cytokine involved in asthma development, remains obscure.¹³² Comparative analysis of immunopathological profiles of NAEB and asthma has been reviewed elsewhere and highlights mechanisms underlying the absence of airway hyperresponsiveness in NAEB.¹³³ Patients with NAEB have increased mast cells in bronchial brushings, whereas asthmatics have increased mast cells in airway smooth muscle cells, a finding reported to be inversely related to airway hyperresponsiveness in asthma.^{84,134} In addition, patients with NAEB have decreased IL-13 in bronchial submucosa and sputum¹³⁵ and less narrowing of the airway lumen compared to asthma, although both asthma and NAEB express airway remodeling.¹³⁶ Unlike asthma, there is marked expression of the endogenous bronchodilator PGE-2^{134,137} in NAEB, which may account for preservation of deep inspiration-induced bronchoprotective effect from cough,^{113,134} and an antiproliferative effect of bronchial smooth muscle.⁸⁴ In conclusion, NAEB represents a cough trait with distinct immunopathological profile in LACS. Yet, scarcity of tussigen challenge data makes it difficult to ascertain a clear role of HCR as a mechanistic trigger for cough in NAEB.

Cough variant asthma

Cough variant asthma (CVA) is a cough phenotypic trait which lacks wheezing or dyspnea and is associated with airway hyperresponsiveness (Table 1) and a favorable response to anti-asthma medications.¹³⁸ Patients with CVA can account for around 30% of chronic cough referrals¹³⁹ and can present solely or predominantly with cough^{129,140} in response to innocuous triggers such as talking and laughing, allergens and cold air.^{141,142} Currently there is insufficient data to

speculate if CVA is a precursor of classic asthma or a separate cough phenotype.¹²⁹ The discrepancy lies partly in the presence or absence of airway hyperresponsiveness which, as stated earlier, has been linked to the deep inspiration cough bronchoprotective effect.^{113,143} Data suggest the absence of airway hyperresponsiveness in a subset of patients with CVA is due to preservation of cough bronchoprotective reflex.¹⁴³ Conversely methacholine challenge data demonstrated presence of “borderline” airway hyperresponsiveness in patients with CVA compared to moderate-severe airway hyperresponsiveness in asthmatics.¹¹³ This suggests that patients with CVA can manifest mild airway hyperresponsiveness on methacholine challenge with preservation of deep inspiration bronchoprotective reflex.¹⁴³ In support, prospective epidemiological studies demonstrated up to one third of CVA patients can eventually develop wheezing.¹²⁹ Suggested mechanisms of airway hyperresponsiveness in CVA can relate to hypersensitivity of vagal neuronal pathway,¹⁴³ although understanding the nature of the involved mediators requires further evaluation.¹²⁰ Other possible mechanisms to explain CVA airway hyperresponsiveness include variable cough^{144,145} thresholds, or structural changes in respiratory smooth muscle cells secondary to small airway remodeling.^{113,143} The latter has been suggested as a positive feedback mechanism for cough persistence in animal studies.¹⁴⁶

CVA patients can feature an eosinophilic airway inflammation as reflected by increased eosinophil count in induced sputum, biopsied bronchial mucosa, and bronchoalveolar lavage fluid.¹⁴⁷ Eosinophilia in CVA patients has been linked to more severe disease, yet when comparing eosinophilic to non-eosinophilic patients with CVA, no significant difference in spirometry findings was noted and the bronchial hyperresponsiveness (BHR) difference was not dramatic.¹⁴¹ Reportedly, patients with CVA express increased cough sensitivity when compared to healthy controls, but not asthmatics. To note, these observations ensued using a continuous sequential dilutions of capsaicin challenge for 1 min and determining the

concentration at which the total number of coughs per minute was 10 or more (C10min).¹⁴⁵ One explanation for presence of comparable HCR among patients with CVA and asthma can be an insufficient observation period (1 year) of CVA patients prior to their enrollment in the study in order to exclude patients who transitioned to bronchial asthma. In patients with CVA, HCR is also studied in relation to anti-asthma medications using capsaicin challenge models.⁹⁶ Data indicate cough reflex sensitivity measured in terms of the lowest capsaicin concentration triggering 2 or 5 coughs (C₂ or C₅) responds well to leukotriene receptor antagonists (LTRAs) with variable effects on airway hyperresponsiveness.^{148,149} This effect is likely attributed to the anti-inflammatory properties rather than the bronchodilator effects of LTRAs. Conversely, in CVA, bronchodilators or ICS have demonstrated insignificant improvement in capsaicin-induced cough thresholds and variable improvement in airway hyperresponsiveness.¹⁵⁰ Taken together, these data suggest CVA can be a precursor of asthma, and both cough phenotypes can manifest overlapping clinical symptomatology, airway inflammation and hyperresponsiveness. This may act as confounding variable in research studies comparing HCR among both cough phenotypes, despite presence of increased cough sensitivity in both CVA and classic asthma (CA) patients when compared to healthy individuals.

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) manifests predominantly as productive cough associated with airflow limitation¹⁵¹ and occasionally bronchial hyperreactivity.¹⁵² Several COPD phenotypes exist, including frequent and non-frequent exacerbators, in addition to the asthma COPD overlap (ACO). The frequent exacerbator phenotype is characterized by airway (and serum) eosinophilia. The ACO phenotype represents asthmatics who later on develop COPD secondary to smoking.¹⁵¹ According to a large Korean survey, COPD constitutes 26.4% of patients with chronic cough.³ Severity of airflow restriction is linked to increased epithelial Th2 signature gene expression¹⁵³ in addition to blood and sputum¹⁵⁴ eosinophilia; the latter

being also a biomarker for frequency of exacerbations¹⁵⁴ and corticosteroid responsiveness.^{155,156} In COPD patients, the presence of chronic cough is associated with lower FEV1,¹⁵⁷ more severe dyspnea, and worse QoL compared to COPD patients without chronic cough. Chronic cough is also associated with more severe airflow limitation and higher levels of inflammatory biomarkers in blood. These include high-sensitivity C-reactive protein, fibrinogen, leukocytes, neutrophils, and eosinophils.¹⁵⁸ Data also suggest chronic cough is an independent risk factor for acute exacerbation of COPD.¹⁵⁷ It is speculated that this property is linked to activation of TRPV1 by oxidative stress, inflammation, hypoxia, and mechanical stress.¹⁵⁹ In fact, TRPV4 may be implicated in the pathogenesis of COPD as revealed by data on genetic polymorphism in TRPV4-encoding genes.¹⁶⁰ Capsaicin challenge data in COPD patients reveal HCR improves in the recovery period (6 weeks) following an acute exacerbation of COPD. This correlated with cough frequency, severity (VAS), but not cough-related QoL questionnaire. Furthermore, improvement of HCR in the recovery period was inversely correlated with frequency of future acute exacerbations monitored over 1 year.¹⁶¹ Despite the small size of the studied patient population, this suggests HCR is heightened in acute exacerbation of COPD and can potentially predict future ones. In another report, chronic cough, or its suppression, was studied in COPD patients and compared to patients with chronic refractory cough (CRC), or to healthy subjects.¹⁶² All subjects with chronic cough, being COPD or CRC patients, had increased HCR when compared to subjects without chronic cough, being COPD patients or healthy individuals. Also, non-coughing COPD patients had comparable cough reflex sensitivity to healthy subjects. This suggests HCR has an important role in COPD patients with cough but is not a general feature of COPD per se. In addition, the ability of all COPD participants, but not those with CRC, to suppress cough suggests different cough mechanisms in both diseases. In conclusion, chronic cough in COPD patients is associated with worse clinical outcomes and manifests as a heightened HCR on tussigen challenge. Yet, underlying cough mechanisms need further elucidation.

REFLUX-RELATED COUGH SYNDROME

Epidemiology

In GERD, gastric regurgitation results in troublesome esophageal and extra-esophageal symptoms, including cough.¹⁶³ Extraesophageal symptoms can manifest in the mouth, lungs, and upper airways, and can lead to asthma (9.3-14%), laryngitis (7-14%), chronic cough (13%), dental erosions, and non-cardiac chest pain (23.1%).¹⁶⁴ Epidemiological data suggest GERD-related cough comprises 7%-85% of chronic cough cases with higher prevalence in western compared to Asian countries.^{10,122,165-167} The high variability in reported prevalence data may be related to different geographical population studies, lack of uniform criteria for diagnosis of chronic cough, and type of patient referral, among other factors.

Pathogenesis

Gastric or esophageal refluxate can be acidic or non-acidic, liquid or gaseous, and proximal or distal in location. Gastric refluxate can trigger cough or be induced by the act of coughing. Cough-induced reflux can be detected by the temporal association of a coughing episode followed by a reflux event on impedance/pH monitoring,^{168,169} which is subsequently computed as a symptom association probability (SAP).¹⁷⁰ The degree and duration of acid or non-acid exposure in esophageal and extraesophageal sites can determine the extent of mucosal injury and the presence or absence of heartburn, ie, silent reflux.¹⁷¹ Reflux events can induce coughing despite natural esophageal and laryngeal mucosal protective structures and mechanisms, such as upper/lower esophageal sphincters and esophago-glottic reflex, respectively.¹⁷² Patients with gastroesophageal and laryngopharyngeal reflux have invariably non-acid and gas reflux which is more likely located in the proximal esophagus as compared to the distal part. This suggests an overlap between laryngopharyngeal and gastroesophageal reflux-related cough.¹⁷³ One mechanism of GERD-related cough speculates a central crosstalk between airway and esophageal afferents (esophageal-bronchial reflex) at their site of convergence in the brainstem, the so-called "reflex theory".¹⁷⁴ Another mechanism of GERD-related cough suggests direct triggering of

the chemo/stretch receptors located on the afferent limb of the laryngopharyngeal reflex by refluxate in the upper esophagus, and/or micro-aspiration into the lungs, the so-called "reflux theory".¹⁷⁴ Several reports investigated the role of HCR and neurogenic inflammation in GERD-related cough.^{175,176} Compared to healthy subjects or patients with GERD but no cough, chronic cough patients with acid or non-acid reflux had lower cough threshold and higher levels of substance P and mast cell tryptase in induced sputum. However, the latter tested parameters were comparable among chronic cough patients with acid and non-acid reflux.¹⁷⁷ This underlines an important role of HCR in coughing patients with GERD but also suggests the acidity of the refluxate may not be of major importance in the mechanistic pathways linking reflux and cough. Discordant data on mechanisms involved in GERD-related cough also exist. Compared to healthy subjects, unselected patients with chronic cough have comparable frequency of proximal esophageal reflux events and extent of acidity. Likewise, the comparison of healthy subjects to chronic cough patients, where extraesophageal causes of chronic cough have been excluded, revealed similar findings.^{169,174} More importantly, no correlation was noted between the number of proximally occurring reflux events and the frequency of coughing. This implies that frequency of proximal reflux events may not be important for provocation of cough.^{174,178} However, in the same studies, a significant temporal association between cough and proximal reflux events (ie, SAP) was observed, reminiscent of hypersensitivity of esophageal-bronchial reflex, ie, reflex theory.¹⁷⁴ Other comorbid conditions need be considered in coughing patients with GERD, such as ineffective esophageal peristalsis.¹⁷⁹ Data revealed that esophageal dysmotility is twice more prevalent in chronic cough compared with heartburn patients, irrespective of the refluxate acidity (ie, acid or non-acid).¹⁷⁹ This adds to the complexity of chronic cough in patients with GERD. In conclusion, pathogenic mechanisms linking chronic cough and GERD are yet unclear. Direct triggering of cough by proximal reflux events (reflux theory) in patients with chronic cough and GERD lacks clear evidence. There is seemingly an

important role of HCR in GERD-related cough (reflex theory) which requires further elucidation.

COVID-19 COUGH

Epidemiology

Three stages of COVID-19 have been described: (i) a viral infection lasting for 1 to 2 weeks; (ii) a second phase characterized by an intertwined cytokine and oxidative stress storm, independent of infection; and (iii) a recovery phase that may last for months during which cough may be persistent.¹⁸⁰⁻¹⁸³ Cough is a major COVID-19 symptom¹⁸⁴ but is not necessarily associated with severity.¹⁸⁵ To date, epidemiological data suggest that prevalence of persistent cough, beyond 2 months from COVID-19 recovery, ranges from 7% to 34%;¹⁸⁶⁻¹⁸⁸ it is infrequently severe or troublesome and associated with symptoms of residual fatigue, breathlessness, and dyspnea, among others.¹⁸⁹ Whether COVID-19 is a risk factor for chronic cough remains to be elucidated. Prevalence data of chronic/persistent cough in general population and in COVID-19, being 2.5-18%¹⁻⁴ and 7-34%¹⁸⁶⁻¹⁸⁸ respectively, are highly variable. Confounding variables may include the spatiotemporal variation in prevalence data of chronic cough in general population studies^{10,190} and likely in COVID-19; also, prevalence data in COVID-19 cough are preliminary¹⁸⁷ and need be constantly updated until after the pandemic is controlled.

Pathogenesis

Mechanistic data on cough in COVID-19 are slowly unveiling and likely involve different immune pathways. TRP channels are involved in lung injury, COVID-19 morbidity, and severity of disease. The underlying pathological events leading also to mortality may be closely linked to the TRPV1-expressing neuronal system (afferent/efferent neurons) in the lungs¹⁹¹ with TRPV1 and TRPV4 also involved in pulmonary chemical injuries.¹⁹² Recent proof-of-concept clinical data in COVID-19 suggest that TRP channels may play a role in cough during all 3 stages of the disease as defined above. Specifically, spices (see below), which are TRPA1 and/or TRPV1 agonists, reduce COVID-19 cough within 1 to 2 min suggesting a channel desensitization. Furthermore, there may be a crosstalk between TRP channels and the

antioxidant transcription nuclear factor erythroid 2-related factor 2 (Nrf2).¹⁹³⁻¹⁹⁷ Activation of TRPA1 and TRPV1 channels augment sensory or vagal nerve discharges to evoke several symptoms of COVID-19, including cough, nasal obstruction, pain, vomiting, diarrhea and, at least partly, sudden and severe loss of smell and taste.¹⁹⁸ Considering another mechanism for cough, the mucosal angiotensin converting enzyme-2 receptor for COVID-19 regulates metabolism of the proinflammatory bradykinin,¹⁹⁹ an important tussigen of the bronchopulmonary C fiber population of the vagus nerve. Increased expression of bradykinin in COVID-19 can induce cough, reminiscent of drug (ACE inhibitors)-induced cough.²⁰⁰ The "two pathways" animal model speculates that chemoreceptors have both a stimulatory and an inhibitory role on cough in proximal and distal airways, respectively.^{201,202} It has been suggested that COVID-19 can curtail cough by stimulating distal cough chemoreceptors and concomitantly induce peripheral lung damage resulting in breathlessness and dyspnea.²⁰³ In summary, clear evidence on immune pathways involved in COVID-19 cough is currently lacking. Current data suggest multiple mechanistic triggers and likely an important role of TRP channels are involved in COVID-19 cough.

Comparison with post-viral cough

COVID-19 cough and post-viral cough (PVC) may have different characteristics in terms of clinical course, immune pathways, and pharmacological response pattern. PVC has a benign clinical symptomatology and frequently manifests solely with cough.²⁰⁴ COVID-19 often requires hospitalization, and residual cough is frequently associated with breathlessness and other symptoms as stated above. Immune pathways in PVC, as inferred from *in vitro* infectious models (human rhinovirus), reveal enhanced expression of TRP channels (A1/V1/M8) mediated by increase in infected cell supernatants of IL-6 and IL-8,²⁰⁵ among others. Similar effects have been described in COVID-19²⁰⁶⁻²¹¹ which, additionally, can also manifest as hemophagocytic lymphohistiocytosis²⁰⁷ and persistent inflammatory interstitial lung disease.²¹² In PVC, a combination of anticholinergic (ipratropium bromide) and a beta-2 agonist (salbutamol) significantly reduced

cough severity,²¹³ but this treatment has not been studied yet in COVID-19.

UNEXPLAINED CHRONIC COUGH

Cough-associated illnesses can frequently point to the origin of cough as upper and lower airway or as reflux-related. In some patients, diagnostic testing and empirical therapies fail to treat cough-associated common and uncommon conditions, hence the name "chronic refractory cough". Its prevalence ranges from 2%²¹⁴ to 42%²¹⁵ of chronic cough patients seen by specialists and reportedly is more prevalent in middle-aged females.

MULTIFACTORIAL CHRONIC COUGH

Chronic cough is multi-morbid with rhinosinusitis, asthma, and GERD and thus can represent a syndrome with multifactorial etiologies. Data on multifactorial chronic cough in terms of prevalence, symptomatology, and response to therapy are being published but they may relate to the most severe patients. A Korean survey revealed that the majority (80%) of chronic cough patients in referral clinics have 1 or multiple etiological diagnoses, including rhinosinusitis, asthma, and bronchitis.²¹⁶ Extracted data from systematic analysis of chronic cough patients revealed prevalence of multifactorial cough is highly variable (7–72%), hence a recommendation to maintain all partially effective treatments during cough management.¹⁰ Reportedly, the most common combinations of cough etiologies are CVA + UACS in school-aged children,²⁴ and atopic cough (atopy and absence of airway hyperresponsiveness) + GERD in adults.¹⁹⁰ Although rarely reported, chronic cough with 3 concomitant etiologies encompassed atopic cough + GERD + UACS.¹⁹⁰ However, these data require careful interpretation due to lack of standardized objective measures for clinical diagnosis of chronic cough (International Classification of Diseases-ICD). In a recent large (N > 11 000) cohort specialty registry, chronic cough patients with both GERD and (upper/lower airway) respiratory diseases were compared to 3 subgroups of chronic cough patients. The comparative subgroups were either GERD (+ve)/Respiratory (-ve), GERD (-ve)/Respiratory (+ve), or GERD (-ve)/Respiratory (-ve) patients, at both

baseline and follow up year.²¹⁷ Specifically, GERD (+ve)/Respiratory (+ve) patients exhibited more cough potential comorbidities, health care resource utilization, use of antitussive medications and psychotherapeutics, when compared to the remaining 3 subgroups, in both baseline and follow up year. Also, the subgroup with GERD (-ve)/Respiratory (-ve) patients scored the lowest frequency of psychological disorders, cough complications and emergency department visits, hospitalizations and use of antitussive medications. In conclusion, multifactorial chronic cough is poorly defined in terms of impact on QoL,²¹⁸ cough severity, and cough control.²¹⁹ This indicates that all causes of cough should be considered in patients who are not responding to classical treatment of asthma or GERD.

SUMMARY

Epidemiological studies in conjunction with tus-sigen challenge protocols and expression studies of neuroinflammatory biomarkers are helpful in assessing the impact of HCR on the clinical presentation and severity of cough-associated illnesses. These tools also enable us to better understand how inflammation in various cough phenotypic traits can modulate the HCR. Type 2/Th1/Th2 inflammation, tissue remodeling, and cough plasticity, among others, can modulate HCR in cough-related phenotypes, yet exact mechanisms of such interaction need further elucidation. Exploring the mechanistic pathways involved in various chronic cough phenotypes is helpful in designing a better-targeted anti-tussive pharmacotherapy including anti-inflammatory agents, antibiotics, proton pump inhibitors (PPIs), or neuromodulators, among others.

In UACS, HCR is heightened in AR and nasal triggers can potentiate the cough reflex in the lower airways. HCR involving the trigeminal nerve afferents and/or their speculated central convergence centers with vagal neuronal pathway remains to be elucidated. Histamine inhalation protocols reveal laryngeal hyperresponsiveness is a multi-morbid condition with chronic cough irrespective of cough etiology and independently of asthma. Yet, evidence of HCR involving the laryngo-constrictive reflex in LHR is currently lacking. In the lower airways, cough phenotypic traits express considerable

similarity in biocellular profile marked by an important role of mast cells and innate immune system. In asthma, current data suggest chronic cough is a complex interplay between a hypersensitive cough reflex, an IgE or non-IgE mediated airway inflammation, absence of deep inspiration cough bronchoprotective reflex, and the recently recognized abnormal neuromechanical properties of the lungs. HCR in asthma seems independent of airway eosinophilia or hyperresponsiveness and preliminary data suggest atopy in asthma is not a risk factor for chronic cough. In NAEB, the role of HCR as a mechanistic trigger of cough is not clearly evidenced due to scarcity of tussigen challenge data. In CVA and COPD, preliminary data suggest HCR is important in the pathogenesis of chronic cough. The role of esophageal-bronchial reflex hyperreactivity as a mechanism of GERD-related cough awaits further research. Notwithstanding, impedance and pH monitoring can assist in diagnosis of GERD-related cough. TRP channels are involved in COVID-19 cough, but clear description of mechanistic pathways is currently lacking. Prospectively, cough-related QoL questionnaires need be standardized for a better definition and classification of chronic cough in epidemiology surveys. Cough challenge tests are difficult to perform in daily practice, lack a uniform administration protocol and assessment methods, and cannot reliably differentiate patients with HCR from healthy subjects. They also need be validated for reproducibility and correlation with other cough assessment tools.

Abbreviations

ACO: (Asthma COPD overlap), AR: (Allergic rhinitis), CA: (Classic asthma), CGRP: (Calcitonin gene-related peptide), COPD: (Chronic obstructive pulmonary disease), CPAP: (Continuous positive airway pressure), CRS: (Chronic rhinosinusitis), CVA: (Cough variant asthma), FeNO: (Fractional exhaled nitric oxide), FEV1: (Forced expiratory volume during the first second), GERD: (Gastro-esophageal reflux disease), ICS: (Inhaled corticosteroids), HCR: (Hypersensitivity cough reflex), LACS: (Lower airway cough syndrome), LHR: (Laryngeal hyperresponsiveness), LTRA: (Leukotriene receptor antagonist), NAEB: (Non-asthmatic eosinophilic bronchitis), NGF: (Nerve growth factor), NP: (Nasal polyps), Nrf2: (Nuclear factor erythroid 2-related factor 2), OSA: (Obstructive sleep apnea), OSAS: (Obstructive sleep apnea syndrome), PG: (Prostaglandin), PND: (Postnasal drip), PNDS: (Postnasal drip syndrome), PVC: (Post-viral cough), P2X: (Purinoreceptor), QoL: (Quality of life), SAP: (Symptom association probability), TLR: (Toll like receptor), TRP: (Transient receptor potential),

UACS: (Upper airway cough syndrome), URTI: (Upper respiratory tract infection).

Authors' consent

All authors reviewed the final version and agreed to publication of the work.

Authors' contributions

Philip Rouadi designed the plan of the article and 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 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.

Funding

Not applicable.

Ethics statement

Not applicable.

Availability of data and materials

Not applicable.

Declaration of competing interest

- Jean Bousquet discloses financial relationships with the following entities: Purina, Chiesi, Cipla, Hikma, Menarini, Mundipharma, Mylan, Novartis, Sanofi-Aventis, Takeda, Teva, Uriach, KyoMed, MASK-air.
- Glenis Scadding discloses payment for talks from ALK, Bayer, GSK and Viartis. She is also chair/member of 3 Data Monitoring Committees for ALK.
- Jonathan A. Bernstein discloses he is PI and consultant and speaker for Merck.
- Erika Jensen-Jarolim discloses honoraria and support to attend meetings from Bencard Allergie, Germany, and Allergy Therapeutics Ltd, UK; a pending patent and stock or stock options with Biomedical Int. R + D GmbH, Vienna; participation on data monitoring or advisory boards with Allergy Therapeutics Ltd, UK; and receipt of equipment, materials, drugs, medical writing, gifts or other services from Bencard Allergie, Germany.
- Giorgio Walter Canonica discloses speaker or advisory board roles with Menarini, Chiesi, Sanofi, GSK, AstraZeneca, Novartis, Stallergenes, Hall, Allergy Therapeutics.

- All other authors indicated they have nothing to disclose related to the submitted work.

Acknowledgements

Not applicable.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.waojou.2021.100618>.

Author details

^aDepartment of Otolaryngology - Head and Neck Surgery, Eye and Ear University Hospital, Beirut, Lebanon.
^bDepartment of Audiology and Otoneurological Evaluation, Edouard Herriot Hospital, Lyon, France.
^cHospital Charité, Universitätsmedizin Berlin, Humboldt-Universität zu Berlin, Berlin, Germany. ^dDepartment of Dermatology and Allergy, Comprehensive Allergy Center, Berlin Institute of Health, Berlin, Germany. ^eMacvia France, Montpellier France. ^fUniversité Montpellier, France, Montpellier, France. ^gDepartment of Medicine, Harvard Medical School, Division of Allergy and Clinical Immunology, Brigham and Women's Hospital Boston, MA, USA. ^hDepartment of Gastroenterology, American University of Beirut Medical Center (AUBMC), Beirut, Lebanon. ⁱDepartment of Gastroenterology, Middle East Institute of Health (MEIH), Beirut, Lebanon. ^jDepartment of Gastroenterology, Clemenceau Medical Center (CMC), Beirut, Lebanon. ^kDepartment of Microbiology, Faculty of Medicine, Kuwait University, Kuwait. ^lINAER - Investigaciones en Alergia y Enfermedades Respiratorias, Buenos Aires, Argentina. ^mAllergy and Immunology Section, Department of Medicine, Hamad Medical Corporation, P.O. Box 3050, Doha, Qatar. ⁿInternational Cough Institute, Washington D.C, USA. ^oAllergy & Immunology Section, Louisiana State University Health Sciences Center, Shreveport, LA, USA. ^pDepartment of Allergy Otolaryngology, LAU-RIZK Medical Center, Beirut, Lebanon. ^qClinical Professor Department of Otolaryngology Head and Neck Surgery, American University of Beirut, Lebanon. ^rKU Leuven Department of Microbiology, Immunology and Transplantation, Laboratory of Allergy and Clinical Immunology, Leuven, Belgium. ^sUniversity Hospitals Leuven, Department of Otorhinolaryngology, Leuven, Belgium. ^tUniversity Hospital Ghent, Department of Otorhinolaryngology, Laboratory of Upper Airways Research, Ghent, Belgium. ^uAcademic Medical Center, University of Amsterdam, Department of Otorhinolaryngology, Amsterdam, the Netherlands. ^vDepartment of ENT, RNENT Hospital, London, UK. ^wClinical Medicine Griffith University, Southport Qld, 4215, Australia. ^xAllergy Center, CUF Descobertas Hospital, Lisboa, Portugal. ^ySchool of Health Sciences, Catholic University of Salta, Argentina. ^zUniversidad Autónoma de Nuevo León, Hospital Universitario and Facultad de Medicina, Monterrey, NL, Mexico. ^{aa}Center for Rhinology and Allergology, Wiesbaden, Germany. ^{ab}Department of Pulmonary, Critical Care and Sleep Medicine at Saint George Hospital University Medical Center, Beirut, Lebanon. ^{ac}Department of Pulmonary and Critical Care,

Hôtel-Dieu de France University Hospital, Beirut, Lebanon. ^{ad}Humanitas University & Personalized Medicine Asthma & Allergy Clinic-Humanitas Research Hospital-IRCCS-Milano Italy. ^{ae}UNC Center for Environmental Medicine, Asthma, and Lung Biology, Division of Allergy, Immunology and Rheumatology, Department of Pediatrics UNS School of Medicine, USA. ^{af}Department of Pediatrics, Chinese University of Hong Kong, Hong Kong, China. ^{ag}Department of Pediatrics, Section of Allergy and Immunology, University of Louisville School of Medicine, Shelbyville Rd, Louisville, KY, 9800, USA. ^{ah}University of Cincinnati College of Medicine, Department of Internal Medicine, Division of Immunology/Allergy Section, Cincinnati, USA. ^{ai}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. ^{aj}Desbrest Institute of Epidemiology and Public Health, UMR UA-11, INSERM University of Montpellier, Montpellier, France. ^{ak}WHO Collaborating Centre on Scientific Classification Support, Montpellier, France. ^{al}Medical Faculty at Akaki Tsereteli State University, National Institute of Allergy, Asthma & Clinical Immunology, KuTaisi, Tskaltubo, Georgia. ^{am}Division of Paediatric Allergology, Department of Paediatrics, University of Cape Town, South Africa. ^{an}Division of Allergy and Clinical Immunology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea. ^{ao}Department of Otolaryngology, Division of Allergy & Immunology, The Ohio State University, Columbus, OH, USA. ^{ap}Institute for Immunological Research, University of Cartagena. Cartagena de Indias, Colombia. ^{aq}National Heart and Lung Institute, Imperial College London, UK. ^{ar}Health Science Institute, Autonomous University of Hidalgo, Mexico. ^{as}Institute of Pathophysiology and Allergy Research, Center of Pathophysiology, Infectiology and Immunology, Medical University Vienna, Austria. ^{at}The interuniversity Messerli Research Institute, Medical University Vienna and Univ, of Veterinary Medicine Vienna, Austria. ^{au}Clinical Research Center for Allergy and Rheumatology, National Hospital Organization Sagami-hara National Hospital, Sagami-hara, Japan. ^{av}Translational Pediatric Research Area, Allergic Diseases Research Unit, Bambino Gesù Children's Hospital IRCCS, Rome, Holy See. ^{aw}Department of Allergy and Immunology, Hospital Quironsalud Bizkaia, Bilbao, Spain.

REFERENCES

- Holden SE, Morice A, Birring SS, et al. Cough presentation in primary care and the identification of chronic cough: a need for diagnostic clarity? *Curr Med Res Opin.* 2019;36(1):139-150. <https://doi.org/10.1080/03007995.2019.1673716>.
- 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>.
3. Koo HK, Jeong I, Lee SW, et al. Prevalence of chronic cough and possible causes in the general population based on the Korean National Health and Nutrition Examination Survey. *Med*. 2016;95(37):e4595. <https://doi.org/10.1097/MD.0000000000004595>.
 4. Arinze JT, de Roos EW, Karimi L, Verhamme KMC, Stricker BH, Brusselle GG. Prevalence and incidence of, and risk factors for chronic cough in the adult population: the Rotterdam Study. *ERJ Open Res*. 2020;6(2). <https://doi.org/10.1183/23120541.00300-2019>, 00300-02019.
 5. 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>.
 6. Song WJ, Morice AH, Kim MH, et al. Cough in the elderly population: relationships with multiple comorbidity. *PLoS One*. 2013;8(10), e78081. <https://doi.org/10.1371/journal.pone.0078081>.
 7. Chang AB, Robertson CF, Van Asperen PP, et al. A cough algorithm for chronic cough in children: a multicenter, randomized controlled study. *Pediatrics*. 2013;131(5):e1576-e1583. <https://doi.org/10.1542/peds.2012-3318>.
 8. Morice AH, McGarvey L, Pavord I. Recommendations for the management of cough in adults. *Thorax*. 2006;61(1):1-24. <https://doi.org/10.1136/thx.2006.065144>.
 9. Shields MD, Bush A, Everard ML, McKenzie S, Primhak R. Recommendations for the assessment and management of cough in children. *Thorax*. 2008;63:1-15. <https://doi.org/10.1136/thx.2007.077370>.
 10. 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>.
 11. Chang AB, Anderson-James S, Marchant JM. Chronic cough in children. *Clin Pulm Med*. 2014;21(3):138-144. <https://doi.org/10.1097/CPM.0000000000000037>.
 12. Weinberger M, Fischer A. Differential diagnosis of chronic cough in children. *Allergy Asthma Proc*. 2014;35(2):95-103. <https://doi.org/10.2500/aap.2014.35.3711>.
 13. 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>.
 14. Song WJ, Morice AH. Cough hypersensitivity syndrome: a few more steps forward. *Allergy, Asthma Immunol Res*. 2017;9:394-402. <https://doi.org/10.4168/air.2017.9.5.394>.
 15. 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*. Published online. 2021.
 16. 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>.
 17. Pratter MR. Chronic upper airway cough syndrome secondary to rhinosinus diseases (previously referred to as postnasal drip syndrome). *Chest*. 2006;129(1):63-71. <https://doi.org/10.1378/chest.129.1>.
 18. Papadopoulos NG, Guibas GV. Rhinitis subtypes, endotypes and definitions. *Immunol Allergy Clin N Am*. 2016;36(2):215-233. <https://doi.org/10.1016/j.iac.2015.12.001>.
 19. Bloustine S, Langston L, Miller T. Ear-cough (arnold 's) reflex. *Ann Otol*. 2015;85:406-407. <https://doi.org/10.1177/000348947608500315>.
 20. Ryan NM, Gibson PG, Birring SS. Arnold's nerve cough reflex: evidence for chronic cough as a sensory vagal neuropathy. *J Thorac Dis*. 2014;6(7):S748-S752. <https://doi.org/10.3978/j.issn.2072-1439.2014.04.22>.
 21. 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>.
 22. Ioan I, Poussel M, Coutier L, et al. What is chronic cough in children? *Front Physiol*. 2014;28(5):322. <https://doi.org/10.3389/fphys.2014.00322>.
 23. 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>.
 24. 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>.
 25. Watelet JB, Van Zele T, Brusselle G. Chronic cough in upper airway diseases. *Respir Med*. 2010;104(5):652-657. <https://doi.org/10.1016/j.rmed.2009.11.020>.
 26. Chang AB, Oppenheimer JJ, Weinberger MM, et al. Management of children with chronic wet cough and protracted bacterial bronchitis: CHEST guideline and expert panel report. *Chest*. 2017;151(4):884-890. <https://doi.org/10.1016/j.chest.2017.01.025>.
 27. Mello CJ, Irwin RS, Curley FJ. Predictive values of the character, timing, and complications of chronic cough in diagnosing its cause. *Arch Intern Med*. 1996;156:997-1003. <https://doi.org/10.1001/archinte.1996.00440090103010>.
 28. Polverino M, Polverino F, Fasolino M, Andò F, Alfieri A, De Blasio F. Anatomy and neuro-pathophysiology of the cough reflex arc. *Multidiscip Respir Med*. 2012;7(1):1-5. <https://doi.org/10.1186/2049-6958-7-5>.
 29. 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>.
 30. Yu JL, Becker SS. Postnasal drip and postnasal drip-related cough. *Curr Opin Otolaryngol Head Neck Surg*. 2016;24:15-19. <https://doi.org/10.1097/MOO.0000000000000226>.
 31. Morice AH. Post-nasal drip syndrome – a symptom to be sniffed at. *Pulm Pharmacol Ther*. 2004;17(6):343-345. <https://doi.org/10.1016/j.pupt.2004.09.005>.
 32. 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>.

33. 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>.
34. Mandadi S, Roufogalis BD. ThermoTRP channels in nociceptors: taking a lead from capsaicin receptor TRPV1. *Curr Neuropharmacol*. 2008;6(1):21-38. <https://doi.org/10.2174/157015908783769680>.
35. Cho PSP, Birring SS, Fletcher HV, Turner RD. Methods of cough assessment. *J Allergy Clin Immunol Pract*. 2019;7(6):1715-1723. <https://doi.org/10.1016/j.jaip.2019.01.049>.
36. Yamasaki M, Ebihara S, Ebihara T, et al. Cough reflex and oral chemesthesis induced by capsaicin and capsiate in healthy never-smokers. *Cough*. 2007;3(9). <https://doi.org/10.1186/1745-9974-3-9>.
37. Bessac BF, Jordt SE. Breathtaking TRP channels: TRPA1 and TRPV1 in airway chemosensation and reflex control. *Physiol*. 2008;23:360-370. <https://doi.org/10.1152/physiol.00026.2008>.
38. 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 (Bratisl)*. 2011;66(5):922-927. <https://doi.org/10.2478/s11756-011-0096-0>.
39. Plevkova J, Song WJ. Chronic cough in subjects with upper airway diseases - analysis of mechanisms and clinical applications. *Asia Pac Allergy*. 2013;3(2):127-135. <https://doi.org/10.5415/apallergy.2013.3.2.127>.
40. 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>.
41. 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>.
42. Lee PCL, Eccles R. Cough induction by high-frequency chest percussion in healthy volunteers and patients with common cold. *Respir Med*. 2004;98(8):771-776. <https://doi.org/10.1016/j.rmed.2004.01.006>.
43. 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](https://doi.org/10.1016/S0954-6111(96)90099-2).
44. Meseguer V, Alpizar YA, Luis E, et al. TRPA1 channels mediate acute neurogenic inflammation and pain produced by bacterial endotoxins. *Nat Commun*. 2014;5:1-14. <https://doi.org/10.1038/ncomms4125>.
45. Park CK, Xu ZZ, Berta T, et al. Extracellular microRNAs activate nociceptor neurons to elicit pain via TLR7 and TRPA1. *Neuron*. 2014;82(1):47-54. <https://doi.org/10.1016/j.neuron.2014.02.011>.
46. 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>.
47. Bousquet J, Boushey HA, Busse WW, et al. Characteristics of patients with seasonal allergic rhinitis and concomitant asthma. *Clin Exp Allergy*. 2004;34(6):897-903. <https://doi.org/10.1111/j.1365-2222.2004.01969.x>.
48. Kim SW, Han DH, Lee SJ, Lee CH, Rhee CS. Bronchial hyperresponsiveness in pediatric rhinitis patients: the difference between allergic and nonallergic rhinitis. *Am J Rhinol Allergy*. 2013;27(3):63-68. <https://doi.org/10.2500/ajra.2013.27.3877>.
49. Shaaban R, Zureik M, Soussan D, et al. Allergic rhinitis and onset of bronchial hyperresponsiveness: a population-based study. *Am J Respir Crit Care Med*. 2007;176(7):659-666. <https://doi.org/10.1164/rccm.200703-427OC>.
50. Suh DI, Koh YY. Relationship between atopy and bronchial hyperresponsiveness. *Allergy, Asthma Immunol Res*. 2013;5(4):181-188. <https://doi.org/10.4168/aair.2013.5.4.181>.
51. Verdiani P, Di Carlo S, Baronti A. Different prevalence and degree of nonspecific bronchial hyperreactivity between seasonal and perennial rhinitis. *J Allergy Clin Immunol*. 1990;86:576-582. [https://doi.org/10.1016/S0091-6749\(05\)80215-5](https://doi.org/10.1016/S0091-6749(05)80215-5).
52. Pecova R, Vrlik M, Tatar M. Cough sensitivity in allergic rhinitis. *J Physiol Pharmacol*. 2005;56(4):171-178.
53. 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.
54. 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.
55. Connell JT. 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](https://doi.org/10.1016/0021-8707(68)90053-1).
56. Connell JT. 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](https://doi.org/10.1016/0021-8707(69)90018-5).
57. 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.
58. Brozmanova M, Calkovsky V, Plevkova J, Tatar M. Effects of inhaled corticosteroids on cough in awake Guinea pigs with experimental allergic rhinitis-the first experience. *J Physiol Pharmacol*. 2004;55(3):23-30.
59. Shusterman D. Nonallergic rhinitis: environmental determinants. *Immunol Allergy Clin*. 2016;36(2):379-399. <https://doi.org/10.1016/j.jiac.2015.12.013>.
60. Scarupa MD, Kaliner MA. Nonallergic rhinitis, with a focus on vasomotor rhinitis. *World Allergy Organ J*. 2009;2(3):20-25. <https://doi.org/10.1097/wox.0b013e3181990aac>.
61. Van Gerven L, Alpizar YA, Steelant B, et al. Enhanced chemosensory sensitivity in patients with idiopathic rhinitis and its reversal by nasal capsaicin treatment. *J Allergy Clin Immunol*. 2017;140(2):437-446. <https://doi.org/10.1016/j.jaci.2017.03.014>.
62. Bernstein JA, Singh U. Neural abnormalities in nonallergic rhinitis. *Curr Allergy Asthma Rep*. 2015;15(4):18. <https://doi.org/10.1007/s11882-015-0511-7>.
63. Van Gerven L, Alpizar YA, Wouters MM, et al. Capsaicin treatment reduces nasal hyperreactivity and transient receptor potential cation channel subfamily V, receptor 1 (TRPV1) overexpression in patients with idiopathic rhinitis.

- J Allergy Clin Immunol.* 2014;133(5):1332-1339. <https://doi.org/10.1016/j.jaci.2013.08.026>.
64. 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>.
 65. Fokkens WJ, Lund VJ, Hopkins C, et al. European position paper on rhinosinusitis and nasal polyps 2020. *Rhinology.* 2020;58(29):1-464. <https://doi.org/10.4193/Rhin20.600>.
 66. Li H, Wang D, Sun X, Hu L, Yu H, Wang J. Relationship between bacterial biofilm and clinical features of patients with chronic rhinosinusitis. *Eur Arch Oto-Rhino-Laryngol.* 2012;269(1):155-163. <https://doi.org/10.1007/s00405-011-1683-y>.
 67. Kariya S, Okano M, Higaki T, Makiyama S, Tachibana T, Nishizaki K. Long-term treatment with clarithromycin and carbocysteine improves lung function in chronic cough patients with chronic rhinosinusitis. *Am J Otolaryngol.* 2020;41(1):102315. <https://doi.org/10.1016/j.amjoto.2019.102315>.
 68. 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>.
 69. Ozturk F, Bakirtas A, Ileri F, Turkas 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>.
 70. 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>.
 71. Ryu G, Min C, Park B, Choi HG, Mo JH. Bidirectional association between asthma and chronic rhinosinusitis: two longitudinal follow-up studies using a national sample cohort. *Sci Rep.* 2020;10:9589. <https://doi.org/10.1038/s41598-020-66479-8>.
 72. Poelmans J, Tack J. Extraesophageal manifestations of gastro-oesophageal reflux. *Gut.* 2005;54:1492-1499. <https://doi.org/10.1136/gut.2004.053025>.
 73. Chang AB, Oppenheimer JJ, Weinberger M, Grant CC, Rubin BK, Irwin RS. Etiologies of chronic cough in pediatric cohorts: CHEST guideline and expert panel report. *Chest.* 2017;152(3):607-617. <https://doi.org/10.1016/j.chest.2017.06.006>.
 74. Sundar KM, Daly SE. Chronic cough and OSA: a new association? *J Clin Sleep Med.* 2011;7(6):669-677. <https://doi.org/10.5664/jcsm.1482>.
 75. 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>.
 76. 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>.
 77. Chan KKY, Ing AJ, Laks L, Cossa G, Rogers P, Birring SS. Chronic cough in patients with sleep-disordered breathing. *Eur Respir J.* 2010;35(2):368-372. <https://doi.org/10.1183/09031936.00110409>.
 78. Wang TY, Lo YL, Liu WT, 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>.
 79. Sundar KM, Daly SE, Pearce MJ, Alward WT. Chronic cough and obstructive sleep apnea in a community-based pulmonary practice. *Cough.* 2010;6:2. <https://doi.org/10.1186/1745-9974-6-2>.
 80. 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>.
 81. 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>.
 82. 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>.
 83. 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>.
 84. 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>.
 85. 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>.
 86. Thach BT. Maturation of cough and other reflexes that protect the fetal and neonatal airway. *Pulm Pharmacol Ther.* 2007;20(4):365-370. <https://doi.org/10.1016/j.pupt.2006.11.011>.
 87. Bucca C, Rolla G, Scappaticci E, Baldi S, Caria E, Oliva A. Histamine hyperresponsiveness of the extrathoracic airway in patients with asthmatic symptoms. *Allergy.* 1991;46:147-153. <https://doi.org/10.1111/j.1398-9995.1991.tb00559.x>.
 88. Famokunwa B, Walsted ES, Hull JH. Assessing laryngeal function and hypersensitivity. *Pulm Pharmacol Ther.* 2019;56:108-115. <https://doi.org/10.1016/j.pupt.2019.04.003>.
 89. Morrison M, Rammage L, Emami AJ. The irritable larynx syndrome. *J Voice.* 1999;13(3):447-455. [https://doi.org/10.1016/S0892-1997\(99\)80049-6](https://doi.org/10.1016/S0892-1997(99)80049-6).
 90. Andrianopoulos MV, Gallivan GJ, Gallivan KH. PVCM, PVCD, EPL, and irritable larynx syndrome: what are we talking about and how do we treat it? *J Voice.* 2000;14(4):607-618. [https://doi.org/10.1016/S0892-1997\(00\)80016-8](https://doi.org/10.1016/S0892-1997(00)80016-8).
 91. Aviv JE, Martin JH, Kim T, et al. Laryngopharyngeal sensory discrimination testing and the laryngeal adductor reflex. *Ann Otol Rhinol Laryngol.* 1999;108(8):725-730. <https://doi.org/10.1177/000348949910800802>.
 92. Phua SY, McGarvey L, Ngu M, Ing A. The differential effect of gastroesophageal reflux disease on mechanostimulation and chemostimulation of the laryngopharynx. *Chest.* 2010;138(5):1180-1185. <https://doi.org/10.1378/chest.09-2387>.

93. Cukier-Blaj S, Bewley A, Aviv JE, Murry T. Paradoxical vocal fold motion: a sensory-motor laryngeal disorder. *Laryngoscope*. 2008;118(2):367–370. <https://doi.org/10.1097/MLG.0b013e31815988b0>.
94. Lee B, Woo P. Chronic cough as a sign of laryngeal sensory neuropathy: diagnosis and treatment. *Ann Otol Rhinol Laryngol*. 2005;114(4):253–257. <https://doi.org/10.1177/000348940511400401>.
95. Turcotte SE, Loughheed MD. Cough in asthma. *Curr Opin Pharmacol*. 2011;11(3):231–237. <https://doi.org/10.1016/j.coph.2011.04.008>.
96. Niimi A, Fukumitsu K, Takeda N, Kanemitsu Y. Interfering with airway nerves in cough associated with asthma. *Pulm Pharmacol Ther*. 2019;59:101854. <https://doi.org/10.1016/j.pupt.2019.101854>.
97. Drake MG, Scott GD, Blum ED, et al. Eosinophils increase airway sensory nerve density in mice and in human asthma. *Sci Transl Med*. 2018;10(457). <https://doi.org/10.1126/scitranslmed.aar8477>.
98. Sastre B, Fernández-Nieto M, Mollá R, et al. Increased prostaglandin E2 levels in the airway of patients with eosinophilic bronchitis. *Allergy Eur J Allergy Clin Immunol*. 2008;63(1):58–66. <https://doi.org/10.1111/j.1398-9995.2007.01515.x>.
99. Wang JL, Ren ZY, Xia JB, et al. The mechanism of airway inflammation in eosinophilic bronchitis and cough variant asthma. *Zhonghua Jie He He Hu Xi Za Zhi*. 2011;34(6):433–437.
100. Brightling CE, Ward R, Goh KL, Wardlaw AJ, Pavord ID. Eosinophilic bronchitis is an important cause of cough. *Am J Respir Crit Care Med*. 1999;160(2):406–410. <https://doi.org/10.1164/ajrccm.160.2.9810100>.
101. Lund S, Walford H, Doherty T. Type 2 innate lymphoid cells in allergic disease. *Curr Immunol Rev*. 2013;9(4):214–221. <https://doi.org/10.2174/1573395510666140304235916>.
102. 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.
103. 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>.
104. 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.
105. De Marco R, Marcon A, Jarvis D, et al. Prognostic factors of asthma severity: a 9-year international prospective cohort study. *J Allergy Clin Immunol*. 2006;117(6):1249–1256. <https://doi.org/10.1016/j.jaci.2006.03.019>.
106. Marsden PA, Satia I, Ibrahim B, et al. Objective cough frequency, airway inflammation, and disease control in asthma. *Chest*. 2016;149(6):1460–1466. <https://doi.org/10.1016/j.chest.2016.02.676>.
107. 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. <https://doi.org/10.1016/j.jaci.2016.04.045>. e10.
108. Kanemitsu Y, Fukumitsu K, Kurokawa R, et al. Increased capsaicin sensitivity in patients with severe asthma is associated with worse clinical outcome. *Am J Respir Crit Care Med*. 2020;201(9):1068–1077. <https://doi.org/10.1164/RCCM.201911-2263OC>.
109. Ulrik CS. Outcome of asthma: longitudinal changes in lung function. *Eur Respir J*. 1999;13(4):904–918. <https://doi.org/10.1034/j.1399-3003.1999.13d35.x>.
110. Martin MJ, Harrison TW. Causes of chronic productive cough: an approach to management. *Respir Med*. 2015;109(9):1105–1113. <https://doi.org/10.1016/j.rmed.2015.05.020>.
111. Crimi E, Saporiti R, Bartolini S, Baroffio M, Pellegrino R, Brusasco V. Airway responsiveness to methacholine and deep inhalations in subjects with rhinitis without asthma. *J Allergy Clin Immunol*. 2008;121(2):403–407. <https://doi.org/10.1016/j.jaci.2007.09.009>.
112. Scichilone N, Kapsali T, Permutt S, Togias A. Deep inspiration-induced bronchoprotection is stronger than bronchodilation. *Am J Respir Crit Care Med*. 2000;162(3):910–916. <https://doi.org/10.1164/ajrccm.162.3.9907048>.
113. Loughheed 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>.
114. Choudry NB, Fuller RW, Pride NB. Effect of inflammatory mediators prostaglandin E2, bradykinin, and histamine. *Am Rev Respir Dis*. 1989;140:137–141.
115. Maher SA, Birrell MA, Adcock JJ, et al. Prostaglandin D2 and the role of the DP1, DP2 and TP receptors in the control of airway reflex events. *Eur Respir J*. 2015;45(4):1108–1118. <https://doi.org/10.1183/09031936.00061614>.
116. Grace MS, Baxter M, Dubuis E, Birrell MA, Belvisi MG. Transient receptor potential (TRP) channels in the airway: role in airway disease. *Br J Pharmacol*. 2014;171(10):2593–2607. <https://doi.org/10.1111/bph.12538>.
117. Fujimura M, Sakamoto S, Kamio T, Bando T, Kurashima K, Matsuda T. Effect of inhaled procaterol on cough receptor sensitivity to capsaicin in patients with asthma or chronic bronchitis and in normal subjects. *Thorax*. 1993;48(6):615–618. <https://doi.org/10.1136/thx.48.6.615>.
118. Hilton ECY, Baverel PG, Woodcock A, Van Der Graaf PH, Smith JA. Pharmacodynamic modeling of cough responses to capsaicin inhalation calls into question the utility of the C5 end point. *J Allergy Clin Immunol*. 2013;132(4):847–855. <https://doi.org/10.1016/j.jaci.2013.04.042>. e5.
119. Dicipinigaitis PV. Short- and long-term reproducibility of capsaicin cough challenge testing. *Pulm Pharmacol Ther*. 2003;16(1):61–65. [https://doi.org/10.1016/S1094-5539\(02\)00149-9](https://doi.org/10.1016/S1094-5539(02)00149-9).
120. Satia I, Badri H, Woodhead M, O'Byrne PM, Fowler SJ, Smith JA. The interaction between bronchoconstriction and cough in asthma. *Thorax*. 2017;72(12):1144–1146. <https://doi.org/10.1136/thoraxjnl-2016-209625>.
121. Lai K, Chen R, Lin J, et al. A prospective, multicenter survey on causes of chronic cough in China. *Chest*. 2013;143(3):613–620. <https://doi.org/10.1378/chest.12-0441>.

122. Lai K, Pan J, Chen R, Liu B, Luo W, Zhong N. Epidemiology of cough in relation to China. *Cough*. 2013;9:18. <https://doi.org/10.1186/1745-9974-9-18>.
123. Kim YH, Kim KW, Baek J, et al. Usefulness of impulse oscillometry and fractional exhaled nitric oxide in children with Eosinophilic bronchitis. *Pediatr Pulmonol*. 2012;48(3): 221-228. <https://doi.org/10.1002/ppul.22631>.
124. 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.
125. Yıldız T, Dülger S. Non-asthmatic eosinophilic bronchitis. *Turkish Thorac J*. 2018;19(1):41-45. <https://doi.org/10.5152/TurkThoracJ.2017.17017>.
126. Chen L, Lai K, Xie J. Establishment of airway eosinophilic bronchitis mouse model without hyperresponsiveness by ovalbumin. *Clin Exp Med*. 2011;11(1):19-24. <https://doi.org/10.1007/s10238-010-0106-5>.
127. Niimi A, Matsumoto H, Mishima M. Eosinophilic airway disorders associated with chronic cough. *Pulm Pharmacol Ther*. 2009;22(2): 114-120. <https://doi.org/10.1016/j.pupt.2008.12.001>.
128. Fujimura M, Ogawa H, Yasui M, Matsuda T. Eosinophilic tracheobronchitis and airway cough hypersensitivity in chronic non-productive cough. *Clin Exp Allergy*. 2000;30(1): 41-47. <https://doi.org/10.1046/j.1365-2222.2000.00698.x>.
129. Fujimura M, Ogawa H, Nishizawa Y, Nishi K. Comparison of atopic cough with cough variant asthma: is atopic cough a precursor of asthma? *Thorax*. 2003;58(1):14-18. <https://doi.org/10.1136/thorax.58.1.14>.
130. Fujimura M, Sakamoto S, Matsuda T, Fujimura M. Bronchodilator-resistant cough in atopic patients: bronchial reversibility and hyperresponsiveness. *Intern Med*. 1992;31(4):447-452. <https://doi.org/10.2169/internalmedicine.31.447>.
131. Brightling CE, Ward R, Wardlaw AJ, Pavord ID. Airway inflammation, airway responsiveness and cough before and after inhaled budesonide in patients with eosinophilic bronchitis. *Eur Respir J*. 2000;15(4):682-686. <https://doi.org/10.1034/j.1399-3003.2000.15d10.x>.
132. Zhan C, Xu R, Liu J, et al. Increased sputum IL-17a level in non-asthmatic eosinophilic bronchitis. *Lung*. 2018;196(6): 699-705. <https://doi.org/10.1007/s00408-018-0166-y>.
133. Diver S, Russell RJ, Brightling CE. Cough and eosinophilia. *J Allergy Clin Immunol*. 2019;7(6):1740-1747. <https://doi.org/10.1016/j.jaip.2019.04.048>.
134. Sastre B, Del Pozo V. Role of PGE 2 in asthma and nonasthmatic eosinophilic bronchitis. *Mediat Inflamm*. 2012;2012:645383. <https://doi.org/10.1155/2012/645383>.
135. Berry MA, Parker D, Neale N, et al. Sputum and bronchial submucosal IL-13 expression in asthma and eosinophilic bronchitis. *J Allergy Clin Immunol*. 2004;114:1106-1109. <https://doi.org/10.1016/j.jaci.2004.08.032>.
136. Siddiqui S, Gupta S, Cruse G, et al. Airway wall geometry in asthma and nonasthmatic eosinophilic bronchitis. *Allergy*. 2009;64(6):951-958. <https://doi.org/10.1111/j.1398-9995.2009.01951.x>.
137. Sastre B, Fernández-Nieto M, López E, et al. PGE2 decreases muscle cell proliferation in patients with non-asthmatic eosinophilic bronchitis. *Prostag Other Lipid Mediat*. 2011;95(1-4):11-18. <https://doi.org/10.1016/j.prostaglandins.2011.03.002>.
138. Vujnović SD, Domuz A, Petrović S. Cough variant asthma as a phenotype of classic asthma. In: Huang K-HG, Hsuan C, Tsai S, eds. *Approach Based on Phenotype and Endotype*. IntechOpen; 2018. <https://doi.org/10.5772/intechopen.75152>.
139. Pavord ID. Cough and asthma. *Pulm Pharmacol Ther*. 2004;17(6 SPEC.ISS.):399-402. <https://doi.org/10.1016/j.pupt.2004.09.009>.
140. 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>.
141. Gao J, Wu F, Wu S, Yang X. Inflammatory subtypes in classic asthma and cough variant asthma. *J Inflamm Res*. 2020;13: 1167-1173. <https://doi.org/10.2147/JIR.S269795>.
142. Kanemitsu Y, Matsumoto H, Osman N, et al. "Cold air" and/or "talking" as cough triggers, a sign for the diagnosis of cough variant asthma. *Respir Investig*. 2016;54(6):413-418. <https://doi.org/10.1016/j.resinv.2016.07.002>.
143. Wasilewski NV, Fisher T, Turcotte SE, Fisher JT, Lougheed MD. Bronchoprotective effect of deep inspirations in cough variant asthma: a distinguishing feature in the spectrum of airway disease? *Respir Physiol Neurobiol*. 2018;257:55-64. <https://doi.org/10.1016/j.resp.2017.09.004>.
144. Koh YY, Jeong JH, Park Y, Kim CK. Development of wheezing in patients with cough variant asthma during an increase in airway responsiveness. *Eur Respir J*. 1999;14(2):302-308. <https://doi.org/10.1034/j.1399-3003.1999.14b11.x>.
145. Nakajima T, Nishimura Y, Nishiuma T, Kotani Y, Nakata H, Yokoyama M. Cough sensitivity in pure cough variant asthma elicited using continuous capsaicin inhalation. *Allergol Int*. 2006;55(2):149-155. <https://doi.org/10.2332/allergolint.55.149>.
146. Nakaji H, Niimi A, Matsuoka H, et al. Airway remodeling associated with cough hypersensitivity as a consequence of persistent cough: an experimental study. *Respir Investig*. 2016;54(6):419-427. <https://doi.org/10.1016/j.resinv.2016.06.005>.
147. Fujimura M. Pathophysiology, diagnosis and treatment of cough variant asthma. *Rinsho Byori*. 2014;62(5):464-470.
148. Dipinigitis PV, Dobkin JB, Reichel J. Antitussive effect of the leukotriene receptor antagonist zafirlukast in subjects with cough-variant asthma. *J Asthma*. 2002;39(4):291-297. <https://doi.org/10.1081/JAS-120002285>.
149. Takemura M, Niimi A, Matsumoto H, et al. Clinical, physiological and anti-inflammatory effect of montelukast in patients with cough variant asthma. *Respiration*. 2012;83(4): 308-315. <https://doi.org/10.1159/000332835>.
150. Fujimura M, Hara J, Myou S. Change in bronchial responsiveness and cough reflex sensitivity in patients with cough variant asthma: effect of inhaled corticosteroids. *Cough*. 2005;1(3):1-8. <https://doi.org/10.1186/1745-9974-1-5>.
151. Gold. Pocket guide to copd diagnosis, management, and prevention. *Handout*. 2020:1-48. Published online.
152. Hantera M, Abdel-Hafiz H. Methacholine challenge test as indicator for add on inhaled corticosteroids in COPD

- patients. *Egypt J Chest Dis Tuberc.* 2014;63(2):351-354. <https://doi.org/10.1016/j.ejcdt.2014.01.006>.
153. Christenson SA, Steiling K, Van Den Berge M, et al. Asthma-COPD overlap: clinical relevance of genomic signatures of type 2 inflammation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2015;191(7):758-766. <https://doi.org/10.1164/rccm.201408-1458OC>.
154. Hastie AT, Martinez FJ, Curtis JL, et al. Association of sputum and blood eosinophil concentrations with clinical measures of COPD severity: an analysis of the SPIROMICS cohort. *Lancet Respir Med.* 2017;5(12):956-967. [https://doi.org/10.1016/S2213-2600\(17\)30432-0](https://doi.org/10.1016/S2213-2600(17)30432-0).
155. Brightling CE, Monteiro W, Ward R, et al. Sputum eosinophilia and short-term response to prednisolone in chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet.* 2000;356(9240):1480-1485. [https://doi.org/10.1016/S0140-6736\(00\)02872-5](https://doi.org/10.1016/S0140-6736(00)02872-5).
156. Bafadhel M, McKenna S, Terry S, et al. Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease: a randomized placebo-controlled trial. *Am J Respir Crit Care Med.* 2012;186(1):48-55. <https://doi.org/10.1164/rccm.201108-1553OC>.
157. Koo HK, Park SW, Park JW, et al. Chronic cough as a novel phenotype of chronic obstructive pulmonary disease. *Int J COPD.* 2018;13:1793-1801. <https://doi.org/10.2147/COPD.S153821>.
158. Landt E, Çolak Y, Lange P, Laursen LC, Nordestgaard BG, Dahl M. Chronic cough in individuals with COPD: a population-based cohort study. *Chest.* 2020;157(6):1446-1454. <https://doi.org/10.1016/j.chest.2019.12.038>.
159. Abbott-Banner K, Poll C, Verkuyt JM. Targeting TRP channels in airway disorders. *Curr Top Med Chem.* 2013;13(3):310-321. <https://doi.org/10.2174/1568026611313030008>.
160. Zhu G, Gulsvik A, Bakke P, et al. Association of TRPV4 gene polymorphisms with chronic obstructive pulmonary disease. *Hum Mol Genet.* 2009;18(11):2053-2062. <https://doi.org/10.1093/hmg/ddp111>.
161. 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>.
162. 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>.
163. Vakli N, Van Zanten SV, Kahrilas P, Dent J, Jones R, Global Consensus group. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol.* 2006;101(8):1900-1921. <https://doi.org/10.1111/j.1572-0241.2006.00630.x>.
164. 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>.
165. 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>.
166. 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>.
167. 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>.
168. Herregods TVK, Pauwels A, Tack J, Smout AJPM, Bredenoord AJ. Reflux-cough syndrome: assessment of temporal association between reflux episodes and cough bursts. *Neuro Gastroenterol Motil.* 2017;29(12). <https://doi.org/10.1111/nmo.13129>.
169. Sifrim D, Dupont L, Blondeau K, Zhang X, Tack J, Janssens J. Weakly acidic reflux in patients with chronic unexplained cough during 24 hour pressure, pH, and impedance monitoring. *Gut.* 2005;54(4):449-454. <https://doi.org/10.1136/gut.2004.055418>.
170. Weusten BLAM, Roelofs JMM, Akkermans LMA, Van Berge-Henegouwen GP, Smout AJPM. The symptom-association probability: an improved method for symptom analysis of 24-hour esophageal pH data. *Gastroenterology.* 1994;107(6):1741-1745. [https://doi.org/10.1016/0016-5085\(94\)90815-X](https://doi.org/10.1016/0016-5085(94)90815-X).
171. De Giorgi F, Palmiero M, Esposito I, Mosca F, Cuomo R. Pathophysiology of gastro-oesophageal reflux disease. *Acta Otorhinolaryngol Ital.* 2006;26(5):241-246. <https://doi.org/10.1097/00020840-199402000-00016>.
172. Ates F, Vaezi MF. Approach to the patient with presumed extraesophageal GERD. *Best Pract Res Clin Gastroenterol.* 2013;27(3):415-431. <https://doi.org/10.1016/j.bpg.2013.06.009>.
173. Yu Y, Wen S, Wang S, et al. Reflux characteristics in patients with gastroesophageal reflux-related chronic cough complicated by laryngopharyngeal reflux. *Ann Transl Med.* 2019;7(20). <https://doi.org/10.21037/atm.2019.09.162>, 529-529.
174. 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>.
175. 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>.
176. Chang AB, Gibson PG, Ardill J, McGarvey LPA. Calcitonin gene-related peptide relates to cough sensitivity in children with chronic cough. *Eur Respir J.* 2007;30(1):66-72. <https://doi.org/10.1183/09031936.00150006>.
177. 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>.
178. Decalmer S, Stovold R, Houghton LA, et al. Chronic cough: relationship between microaspiration, gastroesophageal reflux, and cough frequency. *Chest.* 2012;142(4):958-964. <https://doi.org/10.1378/chest.12-0044>.
179. Kastelik JA, Redington AE, Aziz I, et al. Abnormal oesophageal motility in patients with chronic cough. *Thorax.*

- 2003;58(8):699-702. <https://doi.org/10.1136/thorax.58.8.699>.
180. Halpin S, O'Connor R, Sivan M. Long COVID and chronic COVID syndromes. *J Med Virol*. 2021;93(3):1242-1243. <https://doi.org/10.1002/jmv.26587>.
 181. Cortinovis M, Perico N, Remuzzi G. Long-term follow-up of recovered patients with COVID-19. *Lancet*. 2021;397(10270):173-175. [https://doi.org/10.1016/S0140-6736\(21\)00039-8](https://doi.org/10.1016/S0140-6736(21)00039-8).
 182. Gorna R, MacDermott N, Rayner C, et al. Long COVID guidelines need to reflect lived experience. *Lancet*. Published online. 2020. [https://doi.org/10.1016/S0140-6736\(20\)32705-7](https://doi.org/10.1016/S0140-6736(20)32705-7).
 183. Venkatesan P. NICE guideline on long COVID. *Lancet Respir Med*. 2021. [https://doi.org/10.1016/S2213-2600\(21\)00031-X](https://doi.org/10.1016/S2213-2600(21)00031-X). Published online.
 184. Hu Y, Sun J, Dai Z, et al. Prevalence and severity of corona virus disease 2019 (COVID-19): a systematic review and meta-analysis. *J Clin Virol*. Published online. 2020:104371. <https://doi.org/10.1016/j.jcv.2020.104371>.
 185. Blain H, Gamon L, Tuaillon E, et al. Atypical Symptoms, SARS-CoV-2 Test Results, and Immunization Rates in 456 Residents from Eight Nursing Homes Facing a COVID-19 Outbreak. Age Ageing. Published online 2021. doi:10.1093/ageing/afab050.
 186. D'Cruz RF, Waller MD, Perrin F, et al. Chest radiography is a poor predictor of respiratory symptoms and functional impairment in survivors of severe COVID-19 pneumonia. *ERJ Open Res*. 2021;7(1). <https://doi.org/10.1183/23120541.00655-2020>, 00655-02020.
 187. Carfi A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19. *J Am Med Assoc*. 2020;324:603-605. <https://doi.org/10.1001/jama.2020.12603>.
 188. Mandal S, Barnett J, Brill SE, et al. Long-COVID": a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. *Thorax*. 2020;1-3. <https://doi.org/10.1136/thoraxjnl-2020-215818>. Published online.
 189. Arnold DT, Hamilton FW, Milne A, et al. Patient outcomes after hospitalisation with COVID-19 and implications for follow-up: results from a prospective UK cohort. *Thorax*. 2020;1-4. <https://doi.org/10.1136/thoraxjnl-2020-216086>. Published online.
 190. 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>.
 191. Nahama A, Ramachandran R, Cisternas AF, Ji H. The role of afferent pulmonary innervation in ARDS associated with COVID-19 and potential use of resiniferatoxin to improve prognosis : a review. *Med Drug Discov*. Published online. 2020:100033. <https://doi.org/10.1016/j.medidd.2020.100033>.
 192. Achanta S, Jordt SE. Transient receptor potential channels in pulmonary chemical injuries and as countermeasure targets. *Ann N Y Acad Sci*. 2020;1480(1):73-103. <https://doi.org/10.1111/nyas.14472>.
 193. Bousquet J, Anto JM, Czarlewski W, et al. Cabbage and fermented vegetables: from death rate heterogeneity in countries to candidates for mitigation strategies of severe COVID-19. *Allergy*. 2020;6. <https://doi.org/10.1111/all.14549>.
 194. Bousquet J, Cristol JP, Czarlewski W, et al. Nrf2-interacting nutrients and COVID-19: time for research to develop adaptation strategies. *Clin Transl Allergy*. 2020;10(1):58. <https://doi.org/10.1186/s13601-020-00362-7>.
 195. Bousquet J, Wienczyslawa C, Zuberbier T, De-la-Torre R, Anto JM. *Induced Cough Challenges in a Single Patient with COVID-19 Showing an Interplay between Nrf2, TRPA1 and TRPV1 Agonists*. 2020.
 196. Bousquet J, Le V, Blain H, Czarlewski W. Efficacy of broccoli and glucoraphanin in COVID-19 : from hypothesis to proof-of- concept with three experimental clinical cases. *World Allergy Organ J*. 2020;14(1):100498. <https://doi.org/10.1016/j.waojou.2020.100498>.
 197. Bousquet J, Czarlewski W, Zuberbier T, Mullol J, Blain H, Cristol JP, et al. Spices to control COVID-19 symptoms: yes, but not only.... *Int Arch Allergy Immunol*. 2021;182(6):489-495. <https://doi.org/10.1159/000513538>.
 198. Talavera K, Startek JB, Alvarez-Collazo J, et al. Mammalian transient receptor potential TRPA1 channels: from structure to disease. *Physiol Rev*. 2020;100(2):725-803, 1152/physrev.00005.2019.
 199. Colarusso C, Terlizzi M, Pinto A, Sorrentino R. A lesson from a saboteur: high-MW kininogen impact in coronavirus-induced disease 2019. *Br J Pharmacol*. 2020;177(21):4866-4872. <https://doi.org/10.1111/bph.15154>.
 200. Kickbusch I, Leung G. Response to the emerging novel coronavirus outbreak. *BMJ*. 2020;368(January):1-2. <https://doi.org/10.1136/bmj.m406>.
 201. Canning BJ, Mazzone SB, Meeker SN, Mori N, Reynolds SM, Udem 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>.
 202. Chou YL, Mori N, Canning BJ. Opposing effects of bronchopulmonary C-fiber subtypes on cough in Guinea pigs. *Am J Physiol Regul Integr Comp Physiol*. 2018;314(3):489-498. <https://doi.org/10.1152/ajpregu.00313.2017>.
 203. Dicpinigaitis PV, Canning BJ. Is there (will there Be) a post-COVID-19 chronic cough? *Lung*. 2020;198(6):863-865. <https://doi.org/10.1007/s00408-020-00406-6>.
 204. Braman SS. Postinfectious cough: ACCP evidence-based clinical practice guidelines. *Chest*. 2006;129(1 SUPPL):138S-146S. https://doi.org/10.1378/chest.129.1_suppl.138S.
 205. Abdullah H, Heaney LG, Cosby SL, McGarvey LPA. Rhinovirus upregulates transient receptor potential channels in a human neuronal cell line: implications for respiratory virus-induced cough reflex sensitivity. *Thorax*. 2014;69(1):46-54. <https://doi.org/10.1136/thoraxjnl-2013-203894>.
 206. Paces J, Strizova Z, Smrz D, Cerny J. COVID-19 and the immune system. *Physiol Res*. 2020;16(69):379-388. <https://doi.org/10.33549/physiolres.934492>.
 207. Chowdhury MA, Hossain N, Abul M, Shahid MA, Alam A. Immune response in COVID-19 : a review. *J Infect Public Health*. 2020;13:1619-1629. <https://doi.org/10.1016/j.jiph.2020.07.001>.
 208. Del Valle DM, Kim-Schulze S, Huang HH, et al. An inflammatory cytokine signature predicts COVID-19 severity

- and survival. *Nat Med*. 2020;26(10):1636–1643. <https://doi.org/10.1038/s41591-020-1051-9>.
209. Li L, Li J, Gao M, et al. Interleukin-8 as a biomarker for disease prognosis of coronavirus disease-2019 patients. *Front Immunol*. 2021;11(January):1–10. <https://doi.org/10.3389/fimmu.2020.602395>.
210. Bousquet J, Czarlewski W, Zuberbier T, et al. Potential interplay between Nrf2, TRPA1, and TRPV1 in nutrients for the control of COVID-19. *Int Arch Allergy Immunol*. 2021;182:324–338. <https://doi.org/10.1159/000514204>.
211. Bousquet J, Czarlewski W, Zuberbier T. Potential control of COVID-19 symptoms by Nrf2-interacting nutrients with TRPA1 (transient receptor potential ankyrin 1) agonist activity. *Clin Transl Allergy*. 2020;58.
212. Myall KJ, Mukherjee B, Castanheira AM, et al. Persistent post-COVID-19 inflammatory interstitial lung disease: an observational study of corticosteroid treatment. *Ann Am Thorac Soc*. 2021;1–26. <https://doi.org/10.1513/annalsats.202008-1002oc>, 0(Md).
213. Zanasi A, Lecchi M, Del Forno M, et al. A randomized, placebo-controlled, double-blind trial on the management of post-infective cough by inhaled ipratropium and salbutamol administered in combination. *Pulm Pharmacol Ther*. 2014;29(2):224–232. <https://doi.org/10.1016/j.pupt.2014.07.008>.
214. Irwin RS, Curley FJ, French CL. Chronic cough. The spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. *Am Rev Respir Dis*. 1990;141(3 Pt 1):640–647. <https://doi.org/10.1164/ajrccm/141.3.640>.
215. McGarvey LPA. Does idiopathic cough exist? *Lung*. 2008;186(SUPPL. 1):78–81. <https://doi.org/10.1007/s00408-007-9048-4>.
216. Kang SY, Won HK, Lee SM, et al. Impact of cough and unmet needs in chronic cough: a survey of patients in Korea. *Lung*. 2019;197(5):635–639. <https://doi.org/10.1007/s00408-019-00258-9>.
217. 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>.
218. Brignall K, Jayaraman B, Birring SS. Quality of life and psychosocial aspects of cough. *Lung*. 2008;186(SUPPL. 1):55–58. <https://doi.org/10.1007/s00408-007-9034-x>.
219. Chamberlain S, Birring SS, Garrod R. Nonpharmacological interventions for refractory chronic cough patients: systematic review. *Lung*. 2014;192(1):75–85. <https://doi.org/10.1007/s00408-013-9508-y>.
220. Lai K, Luo W, Zeng G, Zhong N. Diagnosis and treatment of chronic cough in China: an insight into the status quo. *Cough*. 2012;8(1):4. <https://doi.org/10.1186/1745-9974-8-4>.
221. Dagouassat M, Gagliolo JM, Chrusciel S, et al. The cyclooxygenase-2-prostaglandin e2 pathway maintains senescence of chronic obstructive pulmonary disease fibroblasts. *Am J Respir Crit Care Med*. 2013;187(7):703–714. <https://doi.org/10.1164/rccm.201208-1361OC>.
222. Zaslona Z, Peters-Golden M. Prostanoids in asthma and COPD actions, dysregulation, and therapeutic opportunities. *Chest*. 2015;148(5):1300–1306. <https://doi.org/10.1378/chest.15-1029>.
223. Sadeghi MH, Morice AH. The emerging role of the eosinophil and its measurement in. *Open Respir Med J*. 2017;11:17–30. <https://doi.org/10.2174/1874306401711010017>.
224. Schleimer RP. Innate immune responses and chronic obstructive pulmonary disease: “Terminator” or “terminator 2”. *Proc Am Thorac Soc*. 2005;2(4):342–346. <https://doi.org/10.1513/pats.200504-030SR>.