

## Editorial



# New ERS cough guidelines: A clinical framework for refining the patient management strategy

Woo-Jung Song <sup>1</sup>, Eva Millqvist<sup>2</sup>, and Alyn H. Morice<sup>3</sup>

<sup>1</sup>Department of Allergy and Clinical Immunology, Airway Sensation and Cough Research Laboratory, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

<sup>2</sup>Department of Allergology, Institution of Internal Medicine, The Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden

<sup>3</sup>Respiratory Research Group, University of Hull, Hull York Medical School, Castle Hill Hospital, Cottingham, East Yorkshire, United Kingdom



Received: Oct 13, 2019

Accepted: Oct 15, 2019

### \*Correspondence to

#### Woo-Jung Song

Department of Allergy and Clinical Immunology, Airway Sensation and Cough Research Laboratory, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea.

Tel: +82-2-3010-3288

E-mail: swj0126@amc.seoul.kr

Copyright © 2019. Asia Pacific Association of Allergy, Asthma and Clinical Immunology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

### ORCID iDs

Woo-Jung Song

<https://orcid.org/0000-0002-4630-9922>

### Author Contributions

Conceptualization: Woo-Jung Song, Eva Millqvist, Alyn H. Morice. Data curation:

Woo-Jung Song, Eva Millqvist, Alyn H. Morice.

Formal analysis: Woo-Jung Song, Eva Millqvist, Alyn H. Morice. Investigation: Woo-Jung

Song, Eva Millqvist, Alyn H. Morice. Validation:

Woo-Jung Song, Eva Millqvist, Alyn H. Morice.

Writing - original draft: Woo-Jung Song.

Writing - review & editing: Woo-Jung Song, Eva

Millqvist, Alyn H. Morice.

The new European Respiratory Society (ERS) cough guidelines were published this September [1]. These are pragmatic and practical guidelines developed to guide management of chronic cough patients in primary and secondary clinics. The guidelines are based on the recent paradigm shift that represents chronic cough as a disease entity with a common neurophysiological basis of vagal nerve hypersensitivity in the cough reflex pathway [2, 3]. Hypersensitive cough, such as allotussia (cough induced by nontussive stimuli such as cold air, dry air, perfume, talking, or eating) or hypertussia (increased cough sensitivity in response to a known tussigen), is a common feature of most adult patients with chronic cough [4, 5].

In the previous guidelines, chronic cough was considered merely as a symptom, or a consequence, of another disease (or causative) condition [6-8]. However, many disease conditions previously classified as “causes,” such as asthma, rhinitis, reflux or drugs, may not directly cause cough but act as “triggers” and sensitize the cough reflex [9]. It is also apparent that the majority of patients with the disease triad do not complain of troublesome coughs [9]. In addition, systematic reviews of randomized controlled trials (RCTs) have indicated that treatment responses to specific therapies, such as antiacid drugs or inhaled corticosteroids (ICS), are not solely therapeutic benefits but may include considerable placebo effects or self-remission [10, 11]. As the causal determination relies on the treatment response, it is possible that the proportion of cough previously explained by these diseases may have been overestimated. Thus, in the new guidelines, the conditions have been re-defined as “phenotypes” and translated into “treatable traits” of chronic cough [1] (Fig. 1).

Controlling treatable traits is highly important and should be attempted before considering antitussive drugs. A thorough clinical assessment, including a detailed history taking and physical examination, should help to identify which of the treatable traits underlies the patient's chronic cough (Fig. 2). However, the identification is frequently difficult, particularly in primary and secondary clinics, because there is still no test with good validity and practicability for guiding a trait-specific treatment. Induced sputum tests are considered the standard for predicting corticosteroid treatment responses or asthmatic cough [12], but they are not available in most clinics. The utility of methacholine challenge test is unclear in guiding the treatment strategy for cough patients without wheezing or breathlessness. Simple and convenient tests, such as fractional exhaled nitric oxide or blood eosinophil counts, have gained much attention for their predictability of the anti-inflammatory treatment response [13];

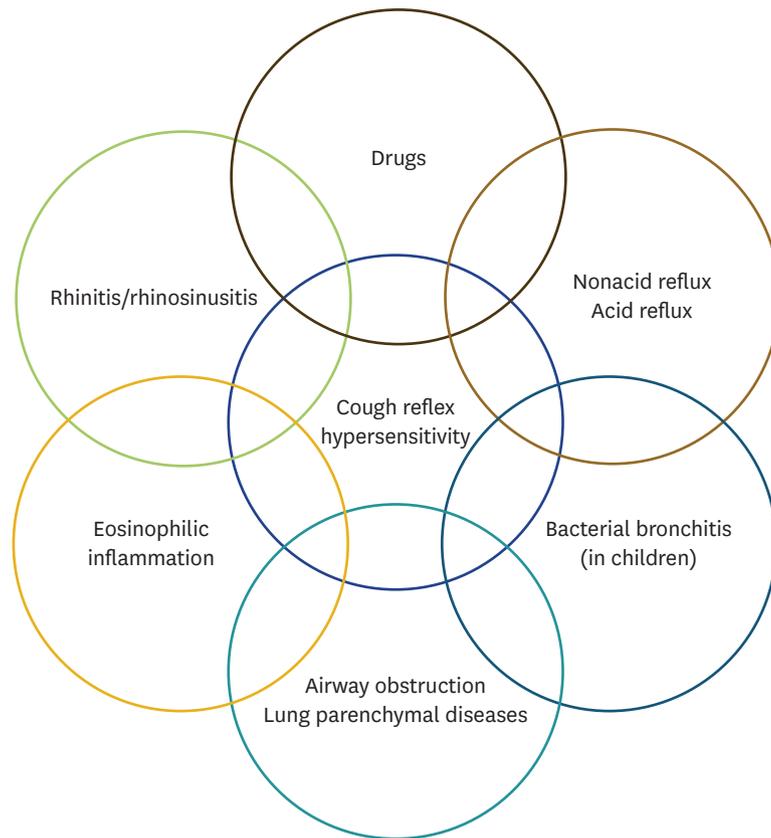


Fig. 1. Treatable traits in patients with chronic cough.

however, there is still no convincing evidence to advocate or refute their use in patients with chronic cough. Thus, sequential trials of each drug in turn are advocated in the new guidelines. However, antacid drugs are not recommended unless patients have peptic symptoms or evidence of acid reflux, since nonacid reflux appears to be a major precipitant of the cough. Patient's clinical information and regional epidemiological data may help to determine the order in sequential drug trials. It is important to withdraw the trial if there is no treatment



Fig. 2. Treatment flow for patients with chronic cough. The guideline panel places higher value on control of any ongoing pathology (or treatable trait), such as reflux or airway eosinophilia, before considering cough neuromodulatory drugs. A detailed history and examination should be directed to exclude malignancy, infection, foreign body inhalation or the use of an angiotensin converting enzyme inhibitor. Further investigations for asthma, eosinophilic bronchitis, reflux and esophageal dysmotility, and rhinosinusitis should be considered depending on the clinical history. If a specific trait is not identifiable, it is preferable to undertake sequential therapeutic trials of each agent in turn; but if no responses were observed, therapy should be stopped. The length of each empirical trial depends on the pharmacology and clinical data reported in previous trials. If the trial is successful, the treatment may be continued for several months to induce resolution of neuronal hypersensitivity [1].

response or if the patient is revealed as not having a trait that responds to the treatment. The length of each drug trial depends on the pharmacology and clinical data reported in RCTs (for example, 1 month for ICS [11]). If the trial is successful, the treatment may be continued for several months to induce resolution of neuronal hypersensitivity.

Emphasis has been put on “cough control” interventions as well. Clinical recommendations have been drawn up for a few drugs, such as opiates, gabapentin or pregabalin; however, as their benefits have been empirically identified (they were not originally developed to treat cough; but they are mostly for pain), response rates are <50% and there are concerns about side effects. Thus, the antitussives should be carefully trialed only in patients with chronic refractory cough. Novel antitussives, such as P2X3 antagonists [14], are expected to be beneficial additions to our treatment strategy soon. Clinical recommendation has been also formulated for non-pharmacological cough control or speech language therapy, which is effective and safe when undertaken by experienced practitioners [15].

The guidelines also narratively address clinical questions that may not be easily addressed in RCTs or cannot be formulated as PICO (patient, intervention, comparison, outcomes) questions, including disease pathophysiology, cough assessment tools, diagnostic tests, or smoking cessation. Visual analogue scale (or simply asking “score your cough severity out of 10”) is recommended as the practical tool for cough assessment in daily clinic. Validated questionnaires, such as the Hull Airway Reflux Questionnaire [16] (please see <http://issc.info> for multiple lingual versions) or Reflux Symptom Index [17], are also recommended for the clinical diagnosis of nonacid airway reflux. Clinical pitfall regarding smoking cessation is introduced that the intervention may lead to transient increase in cough within the first month [18, 19]. Hopefully, the information will facilitate clinical decisions and patient consultations.

There are still many knowledge gaps in the guidelines [1]. First, most of clinical recommendations rely on only a few RCTs, thus warranting further clinical trials. Furthermore, the characteristics of cough have been poorly described in most of previous trials. High-quality RCTs are currently being conducted using validated outcomes, which we expect will help in estimating more precisely true treatment effects. Second, there is no practical and valid biomarker in use to guide a trait-specific therapy. Thus, we conclude that sequential therapeutic trials are still inevitable; further efforts should be made to develop and validate biomarkers to target specific traits in patients with chronic cough. Third, diagnostic and therapeutic pathways are not standardized but vary, even among cough specialists. The recently initiated ERS Clinical Research Collaboration, the NEUROCOUGH, will help to standardize patient care [20]. We hope that the new ERS cough guidelines will be a clinical framework to guide clinical thinking, develop further clinical trials and refine treatment strategies for patients with chronic cough in Europe and the Asia-Pacific region. As there will be local issues specific to each Asia-Pacific country [21], development of regional evidence and adaptation to local guidelines are encouraged.

## REFERENCES

1. Morice AH, Millqvist E, Bieksiene K, Birring SS, Diczpinigaitis P, Ribas CD, Boon MH, Kantar A, Lai K, McGarvey L, Rigau D, Satia I, Smith J, Song WJ, Tonia T, van den Berg JWK, van Manen MJG, Zacharasiewicz A. ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. *Eur Respir J* 2019 Sep 12;pii: 1901136 [Epub].  
[PUBMED](#) | [CROSSREF](#)

2. Morice AH, Millqvist E, Belvisi MG, Bieksiene K, Birring SS, Chung KF, Dal Negro RW, Diczpinigaitis P, Kantar A, McGarvey LP, Pacheco A, Sakalauskas R, Smith JA. Expert opinion on the cough hypersensitivity syndrome in respiratory medicine. *Eur Respir J* 2014;44:1132-48.  
[PUBMED](#) | [CROSSREF](#)
3. Chung KF, McGarvey L, Mazzone SB. Chronic cough as a neuropathic disorder. *Lancet Respir Med* 2013;1:414-22.  
[PUBMED](#) | [CROSSREF](#)
4. Hilton E, Marsden P, Thurston A, Kennedy S, Decalmer S, Smith JA. Clinical features of the urge-to-cough in patients with chronic cough. *Respir Med* 2015;109:701-7.  
[PUBMED](#) | [CROSSREF](#)
5. Won HK, Kang SY, Kang Y, An J, Lee JH, Lee SM, Kwon JW, Kim MH, Jo EJ, Lee SE, Kim SH, Kim SH, Chang YS, Kim SH, Lee BJ, Cho SH, Birring SS, Song WJ. Cough-related laryngeal sensations and triggers in adults with chronic cough: symptom profile and impact. *Allergy Asthma Immunol Res* 2019;11:622-31.  
[PUBMED](#) | [CROSSREF](#)
6. Morice AH, Fontana GA, Sovijarvi AR, Pistolesi M, Chung KF, Widdicombe J, O'Connell F, Geppetti P, Gronke L, De Jongste J, Belvisi M, Diczpinigaitis P, Fischer A, McGarvey L, Fokkens WJ, Kastelik J, Force ERST. The diagnosis and management of chronic cough. *Eur Respir J* 2004;24:481-92.  
[PUBMED](#) | [CROSSREF](#)
7. Irwin RS, Baumann MH, Bolser DC, Boulet LP, Braman SS, Brightling CE, Brown KK, Canning BJ, Chang AB, Diczpinigaitis PV, Eccles R, Glomb WB, Goldstein LB, Graham LM, Hargreave FE, Kvale PA, Lewis SZ, McCool FD, McCrory DC, Prakash UBS, Pratter MR, Rosen MJ, Schulman E, Shannon JJ, Hammond CS, Tarlo SM. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. *Chest* 2006;129:1S-23S.  
[PUBMED](#) | [CROSSREF](#)
8. Morice AH, McGarvey L, Pavord IBritish Thoracic Society Cough Guideline Group. Recommendations for the management of cough in adults. *Thorax* 2006;61 Suppl 1:i1-24.  
[PUBMED](#) | [CROSSREF](#)
9. Song WJ, Morice AH. Cough hypersensitivity syndrome: a few more steps forward. *Allergy Asthma Immunol Res* 2017;9:394-402.  
[PUBMED](#) | [CROSSREF](#)
10. Kahrilas PJ, Howden CW, Hughes N, Molloy-Bland M. Response of chronic cough to acid-suppressive therapy in patients with gastroesophageal reflux disease. *Chest* 2013;143:605-12.  
[PUBMED](#) | [CROSSREF](#)
11. Lee SE, Lee JH, Kim HJ, Lee BJ, Cho SH, Price D, Morice AH, Song WJ. Inhaled corticosteroids and placebo treatment effects in adult patients with cough: a systematic review and meta-analysis. *Allergy Asthma Immunol Res* 2019;11:856-70.  
[PUBMED](#) | [CROSSREF](#)
12. Morice AH, Kastelik JA. Cough. 1: Chronic cough in adults. *Thorax* 2003;58:901-7.  
[PUBMED](#) | [CROSSREF](#)
13. Song WJ, Kim HJ, Shim JS, Won HK, Kang SY, Sohn KH, Kim BK, Jo EJ, Kim MH, Kim SH, Park HW, Kim SS, Chang YS, Morice AH, Lee BJ, Cho SH. Diagnostic accuracy of fractional exhaled nitric oxide measurement in predicting cough-variant asthma and eosinophilic bronchitis in adults with chronic cough: A systematic review and meta-analysis. *J Allergy Clin Immunol* 2017;140:701-9.  
[PUBMED](#) | [CROSSREF](#)
14. Abdulqawi R, Dockry R, Holt K, Layton G, McCarthy BG, Ford AP, Smith JA. P2X3 receptor antagonist (AF-219) in refractory chronic cough: a randomised, double-blind, placebo-controlled phase 2 study. *Lancet* 2015;385:1198-205.  
[PUBMED](#) | [CROSSREF](#)
15. Gibson PG, Vertigan AE. Speech pathology for chronic cough: a new approach. *Pulm Pharmacol Ther* 2009;22:159-62.  
[PUBMED](#) | [CROSSREF](#)
16. Morice AH, Faruqi S, Wright CE, Thompson R, Bland JM. Cough hypersensitivity syndrome: a distinct clinical entity. *Lung* 2011;189:73-9.  
[PUBMED](#) | [CROSSREF](#)
17. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux symptom index (RSI). *J Voice* 2002;16:274-7.  
[PUBMED](#) | [CROSSREF](#)
18. Millqvist E, Bende M. Capsaicin cough sensitivity is decreased in smokers. *Respir Med* 2001;95:19-21.  
[PUBMED](#) | [CROSSREF](#)

19. Dicipinigaitis PV. Cough reflex sensitivity in cigarette smokers. *Chest* 2003;123:685-8.  
[PUBMED](#) | [CROSSREF](#)
20. McGarvey L, Dupont L, Birring SS, Boyd J, Chung KF, Dabrowska M, Domingo C, Fontana G, Guilleminault L, Kardos P, Millqvist E, Morice AH, Smith JA, van den Berg JW, Van de Kerkhove C, Collaboration NCR. New understanding in the treatment of cough (NEUROCOUGH) ERS Clinical Research Collaboration: improving care and treatment for patients with cough. *Eur Respir J* 2019;53:1900787.  
[PUBMED](#) | [CROSSREF](#)
21. Song WJ, Faruqi S, Klaewsongkram J, Lee SE, Chang YS. Chronic cough: an Asian perspective. Part 1: epidemiology. *Asia Pac Allergy* 2015;5:136-44.  
[PUBMED](#) | [CROSSREF](#)