

ERS guidelines on the diagnosis and treatment of chronic cough in adults and children

Online-Only Supplement Part 1.

1. Methods

Scope and purpose

The purpose of these guidelines is to provide guidance for the diagnosis and treatment of chronic cough in adults and children. The guidelines aim to improve diagnostic accuracy and promote evidence-based therapy for paediatric and adult patients in primary and secondary care. The guidelines are intended for use by all healthcare professionals treating patients with chronic cough.

Panel composition

The Task Force (TF) chairs (A.H. Morice and E. Millqvist) led all aspects of project management and selected the TF members. The TF consisted of a multidisciplinary international panel of clinicians and scientists with a published record of expertise in the field, a junior member, and methodologists. European Respiratory Society (ERS) methodologists (T. Tonia and D. Rigau) provided expertise in guideline development following the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. The methodologists coordinated and guided TF members throughout the entire process of conducting systematic reviews, generating recommendations, and ensuring methodological robustness, according to the GRADE approach. Input on patient views and preferences was sought via the European Lung Foundation, which provided an advisory group of patient representatives who

expressed their preferences via teleconferences, attendance at the ERS Congress, and in writing. They contributed to formulating and prioritising the key questions.

Formulating clinical questions

The TF members compiled a list of issues that they considered important and relevant to the management of chronic cough. The questions were rephrased by the methodologists using the Population, Intervention, Comparator and Outcomes (PICO) format. Discussion and consensus among the chairs and TF members was used to decide the eight questions of clinical uncertainty that would be addressed in the guidelines.

Outcome importance rating

After choosing the eight PICO questions, the TF identified outcomes that they considered relevant to each question. The following outcomes were considered for the PICO questions on treatment: cough frequency, cough severity, cough-specific quality of life, cough-related complications, specific impact of cough (on self-esteem, sleep, fatigue, depression, social isolation), tussive response to cough challenge, and adverse events. Sensitivity/specificity, association to the treatment response, change in the treatment decision, and adverse events were considered for the PICO questions on diagnostics. Then, all TF members including the patient representatives rated the importance of each outcome using a scale from 1–9: a rating of 1–3 to outcomes of low importance; 4–6 to outcomes important; and 7–9 to outcomes critically important for decision-making. A teleconference was convened during which the ratings were discussed, and some additional outcomes were rated. At the conclusion of the teleconference, all outcomes were categorised as “not important,” “important,” or “critical” for decision-making during development of the guidelines.

Literature search

The methodology group performed a full systematic review of the literature for each PICO question to identify and summarise the current evidence about the effects of diagnostics or therapeutics on cough outcomes. A systematic search was also conducted to collect information about patients' values and preferences. Pubmed MEDLINE, Embase, and Cochrane Central Register of Controlled Trials databases were searched for relevant articles from inception until August 2017, and updated in June 2018. The search strategy was constructed with professional assistance from a methodologist (H.J. Kim, Institute for Evidence-based Medicine and Department of Preventive Medicine, Korea University College of Medicine, Seoul, Korea). Manual searches were performed for cross-referenced articles.

Selection criteria

Study eligibility was assessed using pre-defined criteria for each PICO question. Common eligibility criteria for inclusion were: 1) a population with chronic cough as the main complaint regardless of their underlying conditions (chronic cough defined as cough lasting > 8 weeks in adults and > 4 weeks in children), 2) intervention (or investigation) and/or comparison relevant to each PICO question, and 3) outcomes related to cough. The population criteria were based on the recent ERS Task Force report, which views chronic cough as a clinical syndrome presenting as cough hypersensitivity [1]. Thus, studies of specific chronic cough conditions, such as cough variant asthma, eosinophilic bronchitis, chronic bronchitis in chronic obstructive pulmonary disease, and chronic wet cough, were also considered. Only full-text publications were considered. Only randomised placebo-controlled trials were considered for the treatment efficacy for PICO questions, because placebo or period effects are substantial in cough. Cross-over trials

were considered for inclusion depending on the availability of parallel trials and the pharmacology of drugs. Randomised controlled trials (RCTs) and observational studies were considered for diagnostic questions. There was no language restriction in the selection criteria.

Study selection

The relevancy of the retrieved studies was determined by at least two independent reviewers per PICO questions, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Briefly, the titles and abstracts of initially retrieved studies were screened and the full texts were reviewed for potentially relevant studies. Reasons for full-text exclusion were specified. Disagreements between reviewers were resolved by discussion and consensus within the committee.

Evidence synthesis

Study characteristics, type of participants, interventions (or investigations), the outcomes measured, and results were extracted from each study. If the data were amenable to pooling, effects were estimated via meta-analysis using Review Manager (version 5.3; The Nordic Cochrane Centre, Copenhagen, Denmark). The random effects model was primarily utilised for the meta-analyses, unless otherwise specified. Dichotomous outcomes are reported as odds ratios and continuous outcomes are reported as mean differences or standardised mean differences (SMD), unless otherwise specified. To facilitate understanding of the SMD, we used an interpretation of the effect size following Cohen's criteria [2]: small, SMD = 0.2; moderate, SMD = 0.5; and large, SMD = 0.8.

The methodologists appraised the quality of the evidence using the GRADE approach. The methodologists used the GRADEpro tool (McMaster University, Hamilton, ON, Canada) to

develop evidence profiles that summarised the findings for each outcome and the rationale for the quality of the evidence appraisal. Thresholds for clinically important changes were based on published literature when available, but also relied on the clinical experience of the TF members, as many of the previous outcomes were not validated.

Formulating and grading the recommendations

The evidence profiles were sent to the TF members for review. Using an iterative process conducted face to face, via teleconference, and via email, consensus recommendations were formulated based on the following considerations: the balance of desirable (benefits) and undesirable consequences (burden, adverse effects and cost) of the intervention (or investigation), quality of the evidence, patient values and preferences, and feasibility.

The quality of the evidence was rated for outcomes of interest in each PICO question according to the GRADE approach. Briefly, the evidence supported by RCTs was considered high quality, while that of observational studies was considered low quality. Five factors were considered for possible down-rating of a study (risk of bias, inconsistency, indirectness, imprecision, and publication bias) and three factors for possible up-rating (large effects, dose response, and all plausible residual confounders). Then, the committee members determined the direction and strength of the recommendations based on the following considerations: balance of benefits and undesirable consequences of intervention (or investigation), quality of evidence, patient values and preferences, and feasibility.

Briefly, one of two grades (strong or conditional) was assigned to describe the strength of the recommendations. The criterion for a strong recommendation was evidence that the desirable effects clearly outweighed the undesirable effects (or vice versa). The criterion for a conditional

recommendation was evidence that the desirable effects likely or slightly outweighed the undesirable effects (or vice versa). Two classifications were used to indicate the direction of the recommendations (for or against) of a specific treatment or test.

Reference

- 1 Morice AH, Millqvist E, Belvisi MG, *et al.* Expert opinion on the cough hypersensitivity syndrome in respiratory medicine. *Eur Respir J* 2014; 44: 1132-1148.
- 2 Cohen J. Statistical power analysis for the behavioral sciences. Routledge, 2013.