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Chronic cough management: Practical guidelines and PICO-based evidence for treatment

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Abstract

This part reviews the management of chronic cough and proposes a management algorithm. Despite proven improvements in quality of life following chronic cough treatment, a clear understanding of the disease and the evidence for the efficacy of some treatments remain vague. Eight key questions regarding the treatment in the uncertain areas were systematically addressed based on the PICO framework and applying the GRADE system for evidence synthesis to provide the strength of recommendation and quality of evidence for key questions, with narrative components for the description of other chronic cough treatment including non-pharmacological therapy. Practical diagrams were developed to facilitate clinical decision-making on treatment. Our guideline introduces the concept of the cough management process for guiding practitioners to assess chronic cough using a holistic approach.

Keywords: cough, chronic cough, guideline, evidence-based, PICO, treatment

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Introduction

The previous part of this guideline illustrates a practical approach for investigations in patients with chronic cough in adults. This part reviews the management of chronic cough and proposes a management algorithm. Despite proven improvements in quality of life following treatment, a clear understanding of the disease and effective, curative treatments remain elusive for many patients with chronic cough.[1] These patients often receive diagnoses such as upper airway cough syndrome (UACS), allergic rhinitis (AR), asthma, non-asthmatic eosinophilic bronchitis (NAEB), gastroesophageal reflux (GERD), and laryngeal reflux. However, some treatment options are ineffective if used empirically without a specific diagnosis of chronic cough and can lead to poor patient compliance.

This guideline provides evidence-based recommendations for chronic cough management and treatment in adults. It incorporates a comprehensive review of treatments, particularly in patients with nonspecific chronic cough and cough-specific diseases. By translating this evidence into practical, diagnosis-driven clinical approaches, this guideline will serve as a valuable resource to assist clinicians in effectively managing adult patients with chronic cough and improving their quality of life. Initial evaluation aims to identify the specific causes and initiate appropriate treatments.

Methodology

This guideline uses a dual-model approach, combining the scientific rigor of the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework for eight key questions,[2] and a narrative component based on the consensus of the Chronic Cough Guidelines Working Group in areas without supporting evidence (see Supplementary file). The narrative components address clinically important aspects of chronic cough, while the key questions systematically review evidence in the areas of clinically important controversy. The Thai Asthma Council (TAC) Chronic Cough Guidelines Working Group was invited and recruited from the TAC steering committee and experts from other medical societies in Thailand. Evidence synthesis in this part applies the same methodology as the screening and investigation part to evaluate available treatment options and make evidence-based recommendations.

Formulating Clinical Questions

The working group listed key questions related to the management of chronic cough using the Population, Intervention, Comparator, and Outcomes (PICO) format. The PICO questions in this guideline focus on treatment. The number of questions addressed was determined by group consensus. The PICO components are outlined as follows:

1) Population

The guideline focuses on adult patients aged 18 and older with chronic cough lasting at least 8 weeks, which is the criteria for chronicity. Patients with a specifically identified cause of cough with chronic cough as a presenting symptom i.e., cough variant asthma (CVA), NAEB, UACS including AR, and chronic rhinosinusitis. Non-specific chronic cough is referred to as cough with no specific diagnosis identified. Details of chronic cough with specific etiologies and non-specific cough are discussed in each PICO statement and included in the approach scheme diagram.

2) Interventions and Comparators

The working group selected relevant treatment interventions with comparators.

3) Outcomes

Changes in treatment decisions, treatment outcomes such as cough frequency, cough severity, cough score, cough-specific quality-of-life, cough response to cough challenge testing, and adverse events, were included.

Literature Search and Study Selection

Refer to Chronic Cough Management: Practical Guidelines and PICO-Based Evidence for Screening and Investigations

Formulation of strength of recommendation

Refer to Chronic Cough Management: Practical Guidelines and PICO-Based Evidence for Screening and Investigations

Management algorithm

The diagram (**Figure 1**) summarizes evidence on chronic cough from specific diseases (AR, chronic rhinosinusitis, CVA/NEAB, and GERD), incorporating relevant treatment options framed as PICO questions for further detailed management. (**Table 1**, **Figure 2**) Allergic rhinitis and UACS can be managed according to severity score on a visual analog scale (VAS). ARIA guideline recommends using oral antihistamines or intranasal corticosteroids (INCS) in patients with VAS < 5, and INCS or INCS with Azelastine in patients with VAS ≥ 5. In cough variant asthma, severity assessment and spirometry are recommended. Treatment can be managed per GINA or other authorities' guidelines. If GERD is suspected, patients should be referred to a specialist if there are alarming symptoms. Diet, lifestyle modification, and a trial of proton pump inhibitors (PPI) are recommended in patients suspected of GERD who have heartburn or acid regurgitation with no alarming symptoms. Chronic rhinosinusitis is one of the common causes of chronic cough. In chronic rhinosinusitis with red flag symptoms, such as periorbital edema or erythema, change in vision, ophthalmoplegia, severe headache, or signs of meningitis, the patients should be referred to a specialist. In chronic rhinosinusitis patients with no alarming symptoms, INCS and saline nasal irrigation can be used for treatment. Observation for 6-12 weeks after initial treatment is recommended. Patients who partially respond or have no response after initial treatments should be further evaluated and other causes of chronic cough should be considered.

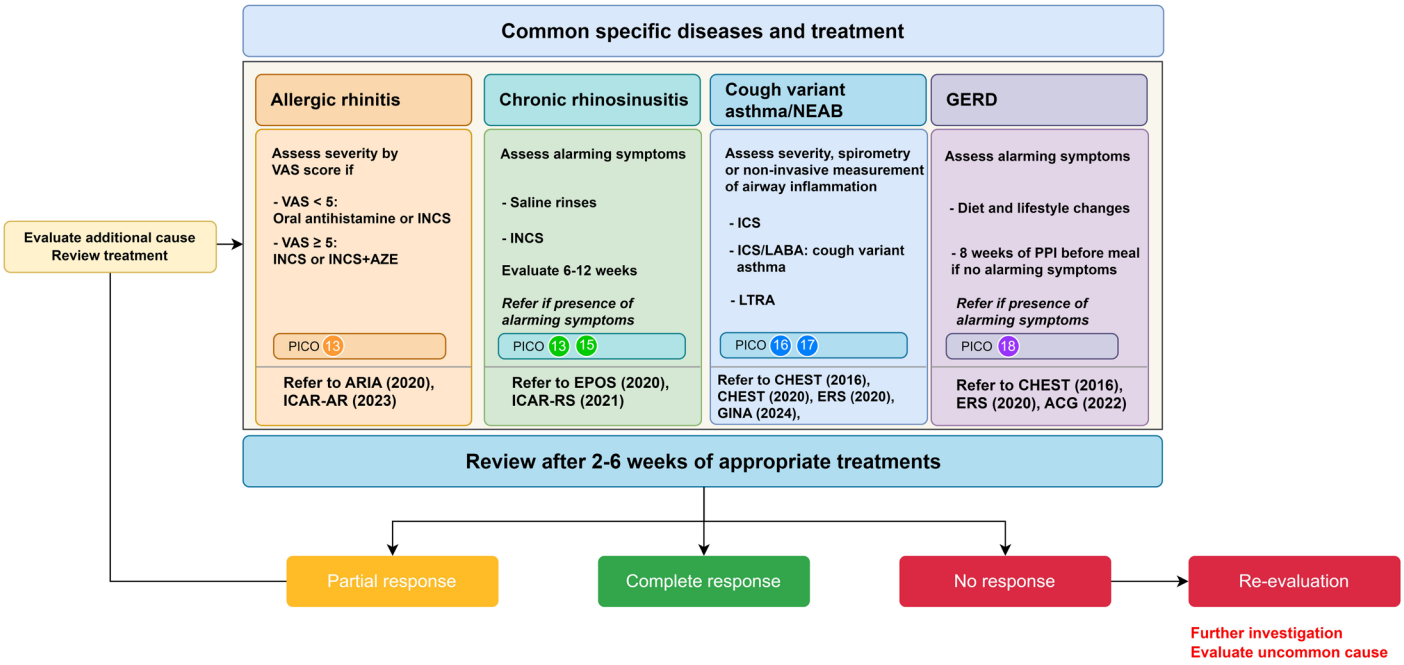

Figure 1. Summarizes the treatment of common specific diseases in chronic cough. The diagram incorporates recommendation guidelines for specific disease management. AZE: Azelastine;

Table 1. Summary of evidence in the treatment of chronic cough.

Question	Treatment	Statement	Level of evidence
PICO Question 13: Should oral/intranasal antihistamines be empirically used to treat patients with chronic cough?	Antihistamines	We recommend against the empirical use of antihistamines for chronic cough. However, antihistamines (both oral and intranasal) have shown a benefit in specific cases, such as upper airway cough syndrome (UACS) or cough-associated allergic respiratory conditions.	Weak recommendation, Low quality of evidence
PICO Question 14: Should oral and/or intranasal decongestants be empirically used to treat patients with chronic cough?	Decongestants	There is no evidence supporting the empirical use of oral decongestants in chronic cough. Indirect evidence from a combination of oral antihistamine and decongestant in patients with chronic cough showed a short-term benefit.	Weak recommendation, Low quality of evidence
PICO Question 15: Should saline nasal irrigation be used for upper airway cough syndrome?	Nasal irrigation	No evidence exists for using saline nasal irrigation in chronic non-specific cough. We recommend using saline nasal irrigation in patients with upper airway cough syndrome resulting from allergic rhinitis to improve nasal secretion and postnasal drip symptoms.	Strong recommendation, Moderate quality of evidence

Table 1. (Continued)

Question	Treatment	Statement	Level of evidence
PICO Question 16: Should inhaled corticosteroids (ICS) be used to treat patients with chronic cough?	ICS	We suggest that an empirical trial with ICS can be considered in patients with chronic cough if there is a normal chest radiograph and no clinical suspicion of other conditions such as postnasal drip or gastroesophageal reflux disease.	Weak recommendation, Moderate quality of evidence
PICO Question 17: Should leukotriene receptor antagonists (LTRA) be used to treat patients with chronic cough?	LTRA	A short-term LTRA trial (2-4 weeks) may be considered in adult patients with chronic cough resulting from cough variant asthma	Weak recommendation, Moderate quality of evidence
PICO Question 18: Should anti-reflux medications (proton-pump inhibitors or antacids) be empirically used to treat patients in adult patients with chronic cough suspected of GERD?	Anti-reflux medications	We recommend against the empirical use of PPIs in chronic cough. (Strong recommendation	Against, moderate quality of evidence
PICO Question 19: Should cough suppressants be used to treat patients with chronic cough?	Cough suppressant	We suggest that cough suppressants may be considered for treating persistent cough.	Weak recommendation, Low quality of evidence
PICO Question 20: Should neuromodulating agents be used to treat patients with chronic cough?	Neuromodulating agents	We recommend gabapentin or pregabalin as neuromodulating agents may be used for the treatment of chronic refractory cough in adults. Close monitoring for adverse events is advised.	Weak recommendation, Low quality of evidence

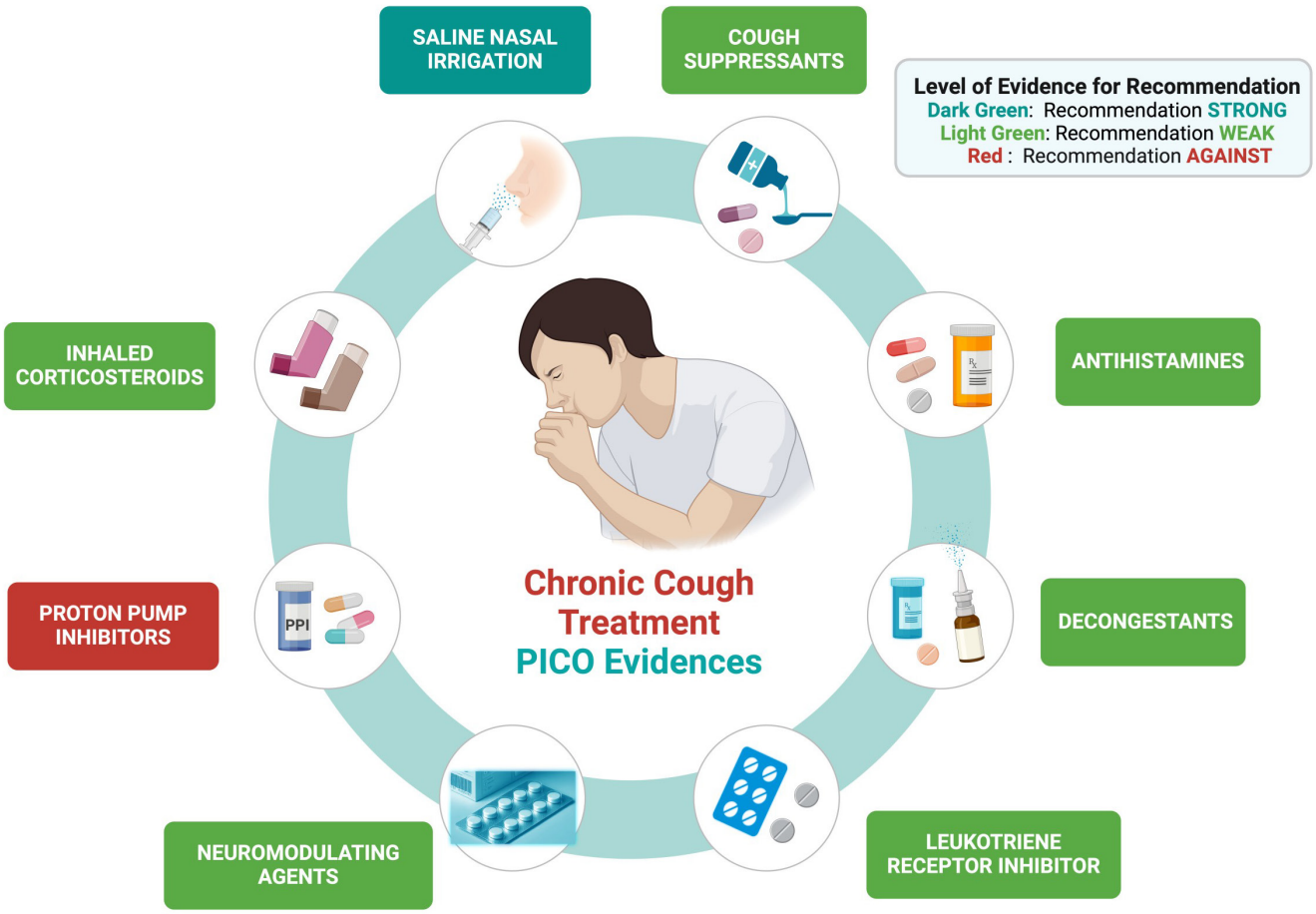

Figure 2. Highlights the PICO-based recommendations of various treatments for chronic cough. (Created in BioRender) The strength of recommendation for treatments with antihistamines, decongestants, saline nasal irrigation, and leukotriene receptor inhibitors is made for chronic cough according to a specific diagnosis. The strength of recommendation for treatment with inhaled corticosteroids, proton pump inhibitors, and cough suppressants is made for non-specific chronic cough.

Evidence for treatments in chronic cough

Antihistamines

Question 13: Should oral/intranasal antihistamines be empirically used to treat patients with chronic cough?

Statement

We recommend against the empirical use of antihistamines for chronic cough. However, antihistamines (both oral and intranasal) have shown a benefit in specific cases, such as UACS or cough-associated allergic respiratory conditions. (Weak recommendation, Low quality of evidence)

Rationale

The empirical use of sedating antihistamines as part of fixed-dose combinations (FDCs) with oral bronchodilators and anti-tussive agents in combination with non-sedating antihistamines in chronic cough patients, as shown in 2 open-label comparative studies, indicated cough symptom alleviation post-treatment compared to pre-treatment but resulted in a considerable number of adverse events (9.8–11.2% for dizziness and fatigue).[3,4] One randomized open-label study followed the same FDCs approach as previous studies. The study compared a modified formulation of the FDCs tablet with its original. The difference between the two formulations was only in their bronchodilator component. Both groups demonstrated improvement in symptoms at around 82% without a difference between the two groups.[5] These studies showed clinical symptom improvement after empirical treatment with FDCs combinations of oral bronchodilators, anti-tussive agents, and non-sedating antihistamines. However, the conclusion regarding the sole benefit of antihistamines was restricted by only indirect evidence and no placebo for comparison.

Additionally, oral H1-antihistamines might benefit certain subgroups of chronic cough due to seasonal AR and atopic cough. One meta-analysis of non-sedating H1-receptor antihistamines found some clues to the therapeutic benefits for improving cough scores, but only in a small subgroup of patients with pollen allergy.[6] However, a recent placebo-controlled trial of bepotastine, a non-sedating H1-antihistamine, found no significant benefit over placebo on cough outcomes in patients with persistent cough and allergic rhinitis.[7] For intranasal antihistamines, the available evidence is primarily from an open-label comparative study that focused on chronic cough patients presenting with postnasal drip and assessed the efficacy of a combination of intranasal antihistamines combined with INCS and ipratropium.[8] This study demonstrated an improvement in cough severity. However, the generalizability of this finding to all chronic cough patients is limited due to the specific focus on postnasal drip symptoms and its indirectness of evidence. Therefore, the routine empirical use of intranasal antihistamines for chronic cough is not recommended.

Of note, UACS resulting from chronic rhinitis may require additional therapeutic interventions if symptoms persist despite empirical treatment. Various professional organizations offer diverse recommendations for managing chronic cough attributable to UACS.[9]

Despite the demonstrated effectiveness of first-generation antihistamines on the upper airway and central nervous system in some studies, the underlying cause of cough cannot be definitively identified based on symptom resolution following empirical treatment. The adverse effects of these medications should be considered in the risk-benefit analysis.

In summary, we recommend starting with a confirmed diagnosis of the chronic cough's etiology. Oral non-sedating H1-antihistamines/ intranasal antihistamines could be considered as monotherapy or in combination with other therapies for chronic cough in patients with UACS, as this condition is prevalent in many adult cohorts.[10,11]

Decongestants

Question 14: Should oral/intranasal decongestants be empirically used to treat patients with chronic cough?

Statement

No evidence supports the empirical use of oral decongestants in chronic cough. Indirect evidence from a combination of oral antihistamines and decongestants in patients with chronic cough showed a short-term benefit. (Weak recommendation, Low quality of evidence)

There is no evidence for the empirical use of topical decongestants in chronic cough patients. There is an optional recommendation of decongestants for treating nasal congestion related to allergic rhinitis or rhinosinusitis. (Weak recommendation, Low quality of evidence)

Rationale

Two prospective cohort studies evaluated the empirical use of oral antihistamines and decongestants in patients presenting with chronic cough. In the first cohort, one week of a combination of antihistamine and decongestant in 45 patients showed symptom resolution in 6 patients (13%). 32 (71%) reported improvement in cough, with 19 (42%) markedly improved, 6 (13%) moderately improved, and 7 (16%) mildly improved. 4 patients (9%) reported unchanged, and 3 (6%) reported worsening.[12] In the second cohort, 3 weeks of antihistamine-decongestant in 97 patients demonstrated a significant improvement in 68 patients (70%).[13]

Because these studies utilized a combination of antihistamine and decongestant, the true effect of decongestant alone cannot be determined.

There is a lack of evidence supporting the use of topical decongestants in chronic cough. However, oral or topical decongestants in AR and acute rhinosinusitis are optional in chronic cough due to sinonasal diseases. Despite showing no demonstrated benefit in symptom improvement and mucociliary clearance, topical decongestants can be an option in acute rhinosinusitis. In chronic rhinosinusitis, there is limited evidence for the use of decongestants. Topical decongestants, in addition to INCS, showed symptom improvement in patients with nasal polyps.[14-16]

Overall, evidence has demonstrated the beneficial use of empirical oral antihistamine-decongestants in chronic cough. However, no definitive conclusion can be drawn regarding the sole benefit of oral decongestants for chronic cough, thus the recommendation is weak due to the indirectness of evidence. Alternatively, topical decongestants can be used as an option in cough associated with acute rhinosinusitis, while evidence is lacking in chronic rhinosinusitis.

Nasal irrigation

Question 15: Should saline nasal irrigation be used for upper airway cough syndrome?

Statement

No evidence exists for using saline nasal irrigation in chronic non-specific cough. We recommend using saline nasal irrigation in patients with upper airway cough syndrome resulting from allergic rhinitis to improve nasal secretion and postnasal drip symptoms. (Strong recommendation, Moderate quality of evidence) *However, some side effects such as nasal irritation and burning sensation can be observed in hypertonic saline administration.*

Rationale

There are no clinical trials on saline nasal irrigation in adults with chronic non-specific cough. One RCT study compared normal saline solution nasal-pharyngeal irrigation (NSNPI) and fluticasone propionate nasal spray (FPNS) for treating chronic cough associated with allergic rhinitis. This study enrolled patients with AR who were allergic to house dust mites; the outcome of interest was cough symptom score, Leicester Cough Questionnaire, and cough response to capsaicin. The results showed that the cough score, Leicester Cough Questionnaire, and capsaicin cough threshold improved after NSNPI, but did not change after FPNS.[17]

Three systematic reviews and meta-analyses were conducted to address the efficacy of saline irrigation: the first included 7 RCTs comparing saline irrigation with no saline irrigation in 112 adults, and 332 children with AR. The results showed that saline irrigation may reduce patient-reported disease severity, compared with no saline irrigation at up to three months in adults and children, with no reported adverse effects.[18] The second review included 7 RCTs or quasi-RCTs comparing isotonic saline with hypertonic saline in 454 patients with chronic rhinosinusitis. The evidence showed that relative to isotonic saline, hypertonic saline irrigation improved nasal symptom scores particularly nasal secretion (without heterogeneity), and nasal congestion with high heterogeneity (I^2 = 80%) across the studies.[19] The third review including 9 RCTs of 740 patients with sinonasal diseases (chronic rhinitis and rhinosinusitis) demonstrated the benefit of hypertonic over isotonic saline nasal irrigation in reducing symptom severity. However, a risk of minor side effects, such as nasal irritation and a burning sensation in hypertonic saline, compared to isotonic saline was reported.[20]

Inhaled corticosteroids

Question 16: Should ICS be used empirically to treat patients with chronic cough?

Statement

We suggest that an empirical trial with ICS can be considered in patients with chronic cough if there is a normal chest radiograph and no clinical suspicion of other conditions such as postnasal drip or GERD. (Weak recommendation, Moderate quality of evidence)

Rationale

A systematic review and meta-analysis including 6 RCTs in 496 adult patients with chronic cough reported small to moderate treatment effects of ICS, compared with placebo.[21] For cough reduction outcome, a mean difference (95%CI) in cough symptom score was -0.37 (95%CI -0.55, -0.19), favoring ICS. Notably, when comparing before and after placebo treatment, a mean difference (95%CI) in cough symptom score was -0.46 (-0.72, -0.21), suggesting a moderate placebo effect. In addition, the therapeutic gain of ICS showed a high heterogeneity across the included studies.

A prospective observational study of 33 adult patients with unexplained chronic cough with normal chest radiograph, no evidence of asthma as indicated by normal methacholine challenge testing, and no prior experience of wheezing showed a 50% (IQR, 20 to 70) reduction in cough frequency compared to baseline after treatment with 2 weeks of ICS (fluticasone propionate 250 mcg bid by diskus device or budesonide 400 mcg bid by Turbuhaler device).[22] One RCT compared inhaled beclomethasone (1,500 mcg/day) with a placebo for 2 weeks in 44 adult patients with chronic cough, excluding those with postnasal drip and GERD. All patients had normal chest and plain sinus radiographs. The results showed that complete resolution of cough (assessed via daily cough score and VAS) was observed in 82% in the treatment group and 15% in the placebo group. The cough score decreased (3 to 0 ± 1) in the treatment group and remained unchanged (3 to 3 ± 1) in the placebo group ($p < 0.002$). VAS score improved from 94 (range, 87–100) at baseline to 3 (range, 0–10) in the treatment group and remained unchanged from 93 (range, 85–100) to 91 (range, 76–100) in the placebo group ($p < 0.01$). The reason for the high therapeutic effect of ICS is that this study included a higher proportion of positive methacholine tests (50%) and a high dose of ICS use up to 1500 mcg/day of beclomethasone.[23] In addition, these studies did not measure biomarkers for ICS responses.

In a prospective study of patients with chronic cough and FeNO ≥ 25 ppb, the response rate to high-dose ICS treatment (defined as a ≥ 1.3-point increase in LCQ scores) was 68% at 3 weeks, with significant improvements in cough severity, LCQ scores, and FeNO levels post-treatment. However, as an improvement in cough with ICS treatment may be gradual, oral steroids might be considered in cases of severe cough and high FeNO.[24] Therefore, a biomarker for type 2 inflammation, such as FeNO or eosinophils, is likely useful for identifying responders to ICS treatment in one narrative review.[25]

Leukotriene receptor antagonists

Question 17: Should LTRA be used empirically to treat patients with chronic cough?

Statement

We suggest against the empirical use of LTRAs in patients with chronic cough. (Weak recommendation, Low quality of evidence) *However, a short-term LTRA trial (2-4 weeks) may be considered in adult patients with chronic cough resulting from cough variant asthma.* (Weak recommendation, Moderate quality of evidence)

Rationale

A small observational comparative study in 14 chronic cough patients evaluated the cough score after 2 weeks of montelukast treatment. The LCQ scores improved from 12.4 ± 3.4 to 16.6 ± 3.1, and the cough threshold significantly increased.[26]

Evidence from an RCT and a systematic review and meta-analysis demonstrated the positive effect of montelukast on chronic cough in patients whose cough was associated with asthma. A small RCT assessing the effects of montelukast in 75 patients with chronic cough diagnosed as CVA and atopic cough showed that montelukast decreased cough score in CVA but not in atopic cough patients.[27] A systematic review and meta-analysis included 15 RCTs of montelukast as an add-on treatment with ICS/LABA in patients with CVA. Montelukast as an adjuvant therapy increased the response rate in cough symptoms and recurrences, with no significant differences in adverse events, compared with ICS/LABA alone.[28]

One prospective cohort study in 247 CVA patients who received montelukast monotherapy or montelukast in combination with ICS or ICS/LABA showed that montelukast alone or in combination with ICS or ICS/LABA improved cough scores after 4 weeks of treatment; there were no differences between the three treatment groups.[29] It was noted that patients in the montelukast-ICS group had a higher proportion of AR, but this was not considered for adjustment in statistical analysis.

Anti-reflux medications

Question 18: Should anti-reflux medications (PPIs or antacids) be empirically used to treat patients with chronic cough suspected of GERD?

Statement

We recommend against the empirical use of PPIs in chronic cough. (Strong recommendation (against), moderate quality of evidence) *because the effect of PPIs in patients with chronic cough suspected of GERD was comparable to placebo. Empirical treatment in adult patients with chronic cough suspected of GERD with PPIs is less likely to have benefit.*

There is no evidence for prokinetics in adult patients with chronic cough suspected of GERD.

Rationale

A meta-analysis included 9 studies of adults with dry, non-productive cough that lasted longer than 3 weeks, without other respiratory symptoms or systemic illness. The results showed no significant difference between treatment and placebo in total resolution of cough (OR 0.46; 95%CI, 0.19–1.15). Additionally, there was no overall significant improvement in cough outcomes at the end of the trial or change in cough scores compared to baseline. The authors concluded that there is insufficient evidence to conclude that PPI is universally beneficial for cough associated with GERD.[30]

Two additional RCTs provided consistent results, demonstrating that PPIs did not have a clinically important effect greater than placebo in patients with cough.[31,32]

Symptoms or signs suggestive of acid reflux may help identify treatment responders in patients with GERD-associated chronic cough. An observational study found that patients reporting heartburn were 2.7 times more likely to respond to acid suppression therapy (95%CI: 1.3 to 5.6).[33] Notably, heartburn or acid regurgitation symptoms are not uncommon in Asian patients with chronic cough.[34]

Cough suppressants

Question 19: Should cough suppressants be used to treat patients with chronic cough?

Statement

We suggest that cough suppressants such as dextromethorphan, levodropropizine, and codeine may be considered for treating refractory cough. However, the evidence supporting their use is restricted based on small numbers of high-quality studies. Therefore, the decision to use cough suppressants should be made on a case-by-case basis, considering individual patient circumstances. (Weak recommendation, Low quality of evidence)

Rationale

A meta-analysis included 13 studies in adult patients with unexplained or refractory chronic cough. Opioids and dextromethorphan reduced cough severity compared to placebo, with a mean difference of 0.55; 95%CI: 0.38 to 0.72), and 0.37; 95%CI: 0.19 to 0.56), respectively, while mucolytics showed no effect. Regarding cough frequency, opioids, and dextromethorphan showed beneficial effects relative to placebo with an RR of 0.57; 95%CI: 0.36 to 0.91, and 0.40; 95%CI: 0.18 to 0.85, respectively.[35]

A small RCT compared the efficacy of codeine 60 mg and levodropropizine 180 mg in 88 adults with chronic cough. Levodropropizine was significantly better than codeine in total cough symptom score (2.96 ± 2.35 and 1.26 ± 1.89), and nighttime cough symptom score (1.51 ± 1.49 and 0.47 ± 1.14).[36]

In another small RCT, the LCQ scores in 27 patients with refractory chronic cough being treated with morphine vs. placebo, were better in the psychological and social domains in the morphine group compared to the placebo group.[37]

A major strength of opiates is their rapid onset of anti-tussive action, enabling quick differentiation between responders and non-responders. The anti-tussive effects may be rapid, strong, and typically apparent within 1 or 2 weeks after initiation of therapy in responders.[37] However, less than 50% of patients with refractory chronic cough show a good response and no strong predictors of treatment response have been identified.[37,38]

Neuromodulating agents

Question 20: Should neuromodulating agents be used to treat patients with chronic cough?

Statement

We suggest that gabapentin or pregabalin as neuromodulating agents may be used for treating chronic refractory cough in adults. (Weak recommendation, Low quality of evidence) *Close monitoring for adverse events is advised*. (Strong recommendation, Low quality of evidence)

Rationale

A meta-analysis of 6 studies showed that gabapentin in patients with chronic refractory cough significantly improved LCQ scores with a mean difference and 95%CI of 4.0 (3.3, 4.8), reduced cough severity (assessed via VAS), with a mean difference and 95%CI of -29.36 (-39.5, -19.3), and lowered cough frequency with a mean difference and 95%CI of -29.9 (-43.8, -15.9), relative to placebo. However, the heterogeneity was observed across the studies ($I^2 > 50\%$). Gabapentin's safety is comparable to placebo with an RR and 95%CI of 1.32 (0.47, 3.7). The most reported side effects were dizziness, drowsiness and fatigue, gastrointestinal reactions, disorientation/confusion, and dry mouth. No heterogeneity was found across the included studies ($I^2 = 0\%$). Gabapentin appears effective and relatively safe for treating chronic refractory cough, compared to other neuromodulating agents.[39] The potential biases in the studies assessing side effects of gabapentin were lacked allocation concealment, and non-blinding during outcome measurement. Additionally, some studies had incomplete outcome data and selective reporting.

Narrative components of other treatments of chronic cough

Intranasal corticosteroids

There is no evidence supporting the use of INCS in unexplained chronic cough. However, given its high safety profile, INCS may be considered in patients with rhinitis-associated chronic cough for alleviating symptoms, especially daytime symptoms.

An open-label trial that compared Mometasone Furoate nasal spray with a placebo in 122 patients with chronic cough due to seasonal allergic rhinitis showed INCS significantly improved overall daytime symptoms and cough scores.[40]

Additionally, a study comparing a variety of intranasal treatments including Azelastine nasal spray, INCS, and ipratropium in 266 patients with rhinitis-associated cough (seasonal AR 3%, non-allergic rhinitis 65%, and mixed rhinitis 32%) demonstrated an improvement in 76% of the patients.[41]

A systematic review of 40 studies included adult patients with chronic cough from chronic sinusitis using mometasone furoate nasal spray. Mometasone nasal spray improved quality of life, sense of smell, and reduced daytime cough, with a high safety profile.[42]

Bronchodilators

There is no evidence supporting an empirical use of inhaled or oral bronchodilators as the standalone therapy for non-specific chronic cough.

Cough associated with COPD

A meta-analysis of 5 RCTs including 3,325 COPD patients revealed that inhaled indacaterol (150-300 µg once daily) did not show a significant cough reduction compared to placebo over 12 weeks.[43] A Phase 3b RCT including 414 moderate-to-severe-COPD patients demonstrated that inhaled aclidinium (400 µg twice daily) significantly improved lung function and daily COPD symptoms (cough and sputum), to a greater extent than tiotropium at 6 weeks.[44] A Phase 4 RCT in 269 moderate COPD patients showed that inhaled aclidinium (400 µg twice daily) over 8 weeks improved cough and sputum scores compared to placebo in patients with severe cough indicated by cough VAS > 30 mm; however, the change of LCQ scores was not significantly different from placebo.[45]

Cough associated with asthma

An RCT in 158 patients with CVA showed that oral procaterol added to inhaled budesonide over 8 weeks significantly improved cough symptoms but marginally improved LCQ.[46] Bronchodilators should be used with ICS to improve lung function, breathlessness/wheezing and to relieve cough, even though the benefits for cough control may be marginal.

Post-infectious cough

An RCT in 74 patients with post-infectious cough did not show a significant reduction in cough symptoms (assessed by LCQ score) after treatment with oral procaterol for 2 and 4 weeks compared to placebo.[47]

Non-pharmacological therapy

Non-pharmacological therapies may be considered for the management of persistent chronic cough. However, further research is needed to establish the optimal treatment approach and identify the patients likely to benefit from these interventions.

Non-pharmacological therapies include education, cough suppression techniques, counseling, physiotherapy, speech therapy, and language therapy. A systematic review included one RCT and four observational studies found that 2 to 4 sessions of speech pathology management, psychoeducation, strategies to reduce cough, and vocal hygiene education significantly reduced cough frequency, cough reflex sensitivity, and improved LCQ scores compared to placebo.[48] Another RCT compared the speech pathology evaluation, which included education, laryngeal hygiene and hydration, cough suppression techniques, breathing exercises, and psychoeducational counseling. vs. healthy lifestyle advice. The results showed a greater improvement in LCQ and cough frequency in the intervention group.[49]

Cough management process

The concept of the cough management process is to guide practitioners to assess chronic cough using a holistic approach. (**Figure 3**) The "Assess" process is to evaluate cough severity by LCQ or VAS scores, and then to assess comorbidities by taking a history of red flag symptoms including hemoptysis, chest pain, hoarseness, dyspnea, dysphagia, systemic symptoms (e.g. weight loss, fever), recurrent pneumonia, desaturation, and abnormal respiratory exams. Taking a history of cough triggers and complications is also useful.

The relevant investigations and treatments can be chosen according to information obtained from the patient. Once treatment is initiated, adjusting the treatment to control cough and to treat specific diseases is required. Education and counseling are also important to facilitate successful treatment. On follow-up visits, the practitioners should review whether the diagnosis is correct. Practitioners should also review responses to treatment and adverse events related to treatment. The cough management process should be repeated until the cough is resolved. Scoring cough severity, using a 0-10 numerical rating or a 0-100 VAS scale, is recommended as a routine tool to assess changes in cough during management.[50] A cough-specific quality-of-life assessment may also be useful in referral clinics.

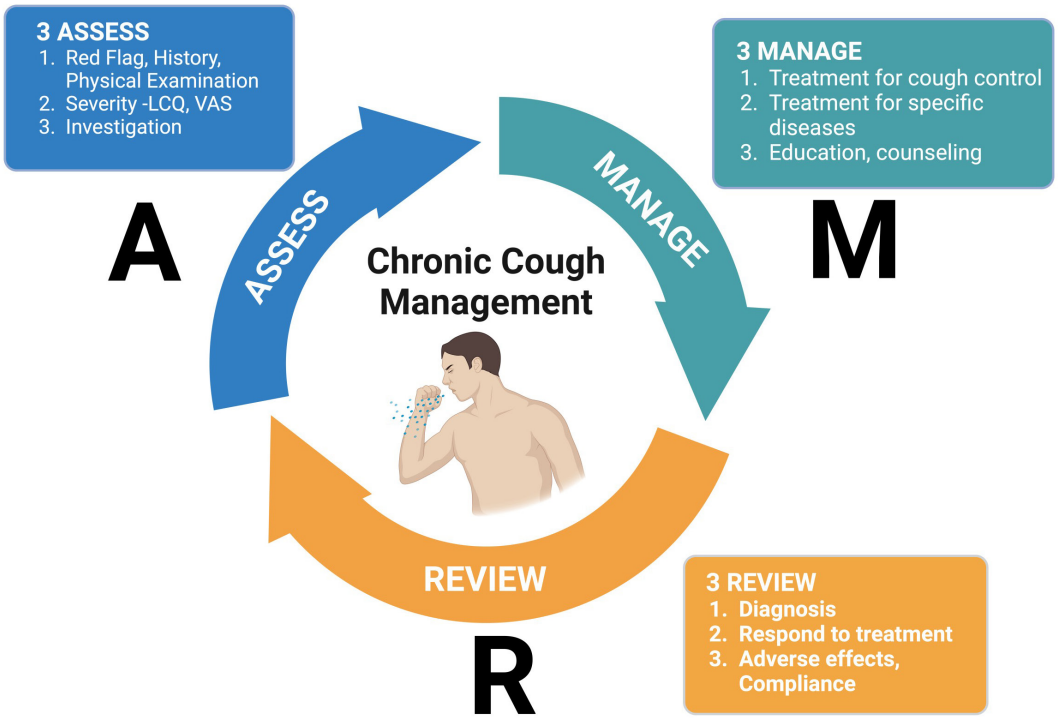

Figure 3. The Cough management process requires a combination of "assess", "adjust" and "review". Details of each process are explained in the text. The process should be repeated on each visit until the cough is resolved.

Discussion

Chronic cough is a significant clinical entity that can involve multiple systems, i.e. the upper airways (UACS, AR, rhinosinusitis), lower airways (asthma, CVA, NAEB, chronic bronchitis), and gastrointestinal system (laryngopharyngeal reflux, GERD). The diagnostic algorithm and evidence-based investigations were discussed in the previous chapter. The level of evidence regarding treatments varies across different etiologies. For UACS, saline nasal irrigation is strongly recommended. We do not recommend the routine use of antihistamines or decongestants. Empirical trial with ICS is weakly recommended for chronic cough, but the evidence supports the use of ICS in patients with high FeNO levels (≥ 25 ppb). LTRA is not recommended in chronic cough except for cough-variant asthma, in which monotherapy with LTRA or LTRA combined with ICS/LABA can be used. Lack of evidence supports the routine use of saline nasal irrigation, LTRA, and PPI in patients with non-specific chronic cough.

In this guideline, recommendations regarding anti-tussive drugs and neuromodulating agents for patients with refractory chronic cough were made. Positive clinical trials suggest that neuronal hypersensitivity is a key treatable trait in refractory chronic cough.[51] However, the current level of evidence is weak and requires novel data when available to update the recommendation for these treatments. Notably, the antitussive effects of these drugs were initially discovered and later in controlled trials demonstrated the concerns of tolerability and safety. Therefore, our guidelines should be updated once novel anti-tussive therapies are approved.

The strength of this guideline is that we compared our findings on chronic cough treatment with recent guidelines and position papers (**Table 2**). These guidelines, including a systematic review of RCTs on chronic cough management, found limited high-quality evidence.[52] Subsequent guidelines, such as BTS 2023 and CICADA 2023, also struggled to identify strong evidence and often relied on expert consensus.[53,54] While the BTS 2023 guideline focused on specific disease diagnoses, the CICADA 2023 position statement incorporated the recommendations for specific diseases, and unexplained chronic cough (UCC). Consistent with our findings, most treatment recommendations in previous guidelines are weak and disease-specific. As expected, data on empirical treatment for chronic cough as a clinical presentation is limited.

The potential limitations of this guideline are acknowledged where the low quality of evidence can be attributed to several factors. First, the search term using symptom-based chronic cough may restrict the evidence search, as many patients with chronic cough eventually receive a specific diagnosis. Second, studies with small sample sizes or limited funding support may be excluded from this review. To address these limitations, high-quality research is urgently needed to improve our understanding of chronic cough and inform future clinical practice. Researchers and clinicians should prioritize conducting well-designed studies that focus on the early diagnosis and management of chronic cough, emphasizing identifying and validating novel biomarkers and diagnostic tools.

Table 2. Comparison of treatment guidelines for chronic cough in adults.

	CHEST 2016	KAAACI 2018	ERS 2020	BTS 2023	CICADA 2023
Authors	Gibson et al.	Song et al.	Morice et al.	Parker et al.	Marchant et al.
Population	UCC RCC	Non-specific CC UCC	CC	CC	Non-specific CC UCC RCC
Duration of cough	> 8 weeks	> 8 weeks in adults > 4 weeks in children	> 8 weeks in adults > 4 weeks in children	> 8 weeks	> 8 weeks in adults > 4 weeks in children
Methodology	Systematic review of RCT on the efficacy of treatment	Clinical question and evidence review	Clinical question and evidence review	Clinical questions and evidence review	Literature review of RCT, Systematic review, guideline, and positional statement
Format of recommendation	Methodology of CHEST Guideline (Lewis 2014)	GRADE	GRADE	-	GRADE

Table 2. (Continued)

	CHEST 2016	KAAACI 2018	ERS 2020	BTS 2023	CICADA 2023
Treatment					
Antihistamines	-	For non-specific cough, empirical use: - Strong recommendation (adults) - Conditional recommendation (children)	-	-	For cough with AR: - Weak recommendation (adults); topical - Weak recommendation (children)
INCS	-	-	-	For cough with CRS: - Empirical trial of INCS	For cough with AR: - Weak recommendation (adults); INCS - Weak recommendation (adults); INCS/intranasal antihistamines - Weak recommendation (children) For cough with CRS: - Weak recommendation (adults); INCS
Saline nasal irrigation	-	-	-	For cough with CRS: - should include an intranasal steroid spray with saline irrigation	For cough with CRS: - Weak recommendation (adults)
Anti-asthmatic drugs					
Bronchodilators	-	-	-	-	For cough with asthma: - Strong recommendation (adults, children)
ICS	Not suggested if negative tests for bronchial hyperresponsiveness and eosinophilia (Grade 2B)	For non-specific cough, empirical use: - Conditional recommendation (adults, children)	Conditional recommendation	Avoid ICS in normal spirometry and low T2 biomarkers Short trial in cough with no other symptoms or airflow obstruction and raised T2 biomarkers (Eosinophilic airway disease), double dose ICS if incomplete response	For cough with asthma: - Strong recommendation (adults, children) For cough with eosinophilic bronchitis: - Strong recommendation (adults) For unexplained chronic cough: - Weak recommendation (adults) - No recommendation (children)
ICS/LABA	-	-	Conditional recommendation	-	-
LTRA		For non-specific cough empirical use: - Conditional recommendation against (adults) - no specific recommendation (children)	Conditional recommendation	For Eosinophilic airway disease: If response is incomplete, consider adding LTRA	For cough with asthma: - Weak recommendation (adults) For cough with eosinophilic bronchitis: - Weak recommendation (adults) For unexplained chronic cough - Weak recommendation (adults)

Table 2. (Continued)

	CHEST 2016	KAAACI 2018	ERS 2020	BTS 2023	CICADA 2023
Anti-acids	Proton pump inhibitor therapy should not be prescribed with a negative workup for acid reflux disease (Grade 2C)	For non-specific cough, empirical use: - Conditional recommendation against (adults)	Conditional recommendation	Only treat with proton pump inhibitors if the patient has heartburn or other definitive evidence of acid reflux.	For GERD with cough alone: - Strong recommendation against (adults) Treatment for GERD should not be used when there are no gastro-intestinal clinical features: - Weak recommendation (children) For unexplained chronic cough, empirical trial of acid-suppressive therapy, proton pump inhibitors, or H2 antagonists: - Strong recommendation against (adults) For non-specific or refractory cough, empirical trial of proton pump inhibitors: - Strong recommendation against (children)
Antibiotics					
Antibiotics	-	For chronic productive cough, empirical use: - Conditional recommendation (children)	Conditional recommendation (children)	-	For protracted bacterial bronchitis: - Strong recommendation (children)
Macrolides	-	-	Conditional recommendation	For productive cough: consider low-dose macrolide therapy after assessment in secondary care	For cough with CRS: - Weak recommendation (adults) For cough with chronic bronchitis without airflow obstruction: - Weak recommendation (adults) For unexplained chronic cough: - Weak recommendation against (adults)

Table 2. (Continued)

	CHEST 2016	KAAACI 2018	ERS 2020	BTS 2023	CICADA 2023
Neuromodulating drugs					
gabapentin or pregabalin	Suggest a therapeutic trial of gabapentin as long as the potential side effects and the risk-benefit profile is discussed (Grade 2C)	For unexplained chronic cough: - Conditional recommendation (adults)	Conditional recommendation (adults)	In refractory chronic cough, addressing cough hypersensitivity and include gabapentin	For unexplained chronic cough: - Weak recommendation (adults)
Opioids	-	For unexplained chronic cough: - Conditional recommendation (adults)	Strong recommendation (adults)	In refractory chronic cough, addressing cough hypersensitivity and include low-dose morphine	For unexplained chronic cough: empirical treatment trial of opioids - Weak recommendation against (adults) For non-specific or refractory cough - Strong recommendation against (children)
Mucolytics	-	-	-	Suggest optimization of airway clearance	For cough with chronic bronchitis without airflow obstruction: - Weak recommendation (adults)
Non-pharmacology					
Therapeutic trial of multimodality speech pathology therapy	Suggested (Grade 2C)	For unexplained chronic cough: - Conditional recommendation (adults)	Conditional recommendation (adults)	In refractory chronic cough, addressing cough hypersensitivity and including non-pharmacological therapy	For cough with laryngeal hypersensitivity/ vocal cord dysfunction: - Strong recommendation (adults) For unexplained chronic cough: - Strong recommendation (adults) - No recommendation (children)
Others					
Treatment according to current ILD guidelines	-	-	-	-	Cough with ILD: - Weak recommendation (adults)
Treatment according to current COPD management guidelines	-	-	-	-	Cough with COPD: - Strong recommendation (adults)
Treatment according to current bronchiectasis management guidelines	-	-	-	-	Cough with bronchiectasis: - Weak recommendation (adults)
Tonsillectomy and adenoidectomy	-	-	-	-	For cough with OSA: - Weak recommendation (children)
Uniqueness	Systematic review of cough management	Empirical treatment focused on nonspecific cough, defines different terminology for cough	-	-	Pairing both specific conditions/unexplained chronic cough and the treatment
Limitations	-	-	-	No grading system	-

Abbreviations: CC: chronic cough, COPD: chronic obstructive pulmonary disease, CRS: chronic rhinosinusitis, ICS: inhaled corticosteroids, INCS: intranasal corticosteroids, ILD: interstitial lung diseases, OSA: obstructive sleep apnea, RCC: refractory chronic cough, UCC: unexplained chronic cough

Conclusion

This part of the guideline reviews the evidence supporting these treatments and proposes a management scheme to assist primary care physicians and specialists in managing adults with chronic cough.

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