

# Chronic cough management: Practical guidelines and PICO-based evidence for screening and investigation

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## Abstract

Chronic cough is a common clinical condition requiring comprehensive assessment. This review employs a symptom-focused approach, prioritizing the presenting symptom of “chronic cough” to mirror real-world clinical practice. Ten key questions regarding the investigations 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. Practical diagrams were developed to facilitate clinical decision-making. The initial evaluation involves screening for red flag signs requiring urgent attention, followed by a detailed history-taking and physical examination. A chest radiograph is recommended as the first-line investigation. The primary objective of the initial evaluation is to identify the cause and initiate appropriate treatment. If history and physical examination prove insufficient for a definitive diagnosis, referral to a specialist is advised for further specific testing. The recommendations on specific testing include fractional exhaled nitric oxide for cough variant asthma, nasal endoscopy or digital endoscopy (optional) for upper airway cough syndrome, paranasal sinus computed tomography (CT) for chronic rhinosinusitis, and laryngoscopy for hoarseness. Spirometry is for the diagnosis of obstructive airway diseases, and peak flow variability or bronchial challenge tests are complements particularly if asthma is suspected. Gastroesophageal reflux (GERD) investigations are for patients with chronic cough without typical GERD symptoms. Sinus radiographs and chest CT are not routinely recommended. Our guideline distinguishes itself by prioritizing a symptom-based clinical evaluation to guide clinicians toward the most probable diagnosis, streamlining the diagnostic process.

**Key words:** cough, chronic cough, diagnosis, persistent cough, evidence-based, guideline, gastroesophageal reflux, primary care, refractory chronic cough, respiratory, unexplained chronic cough

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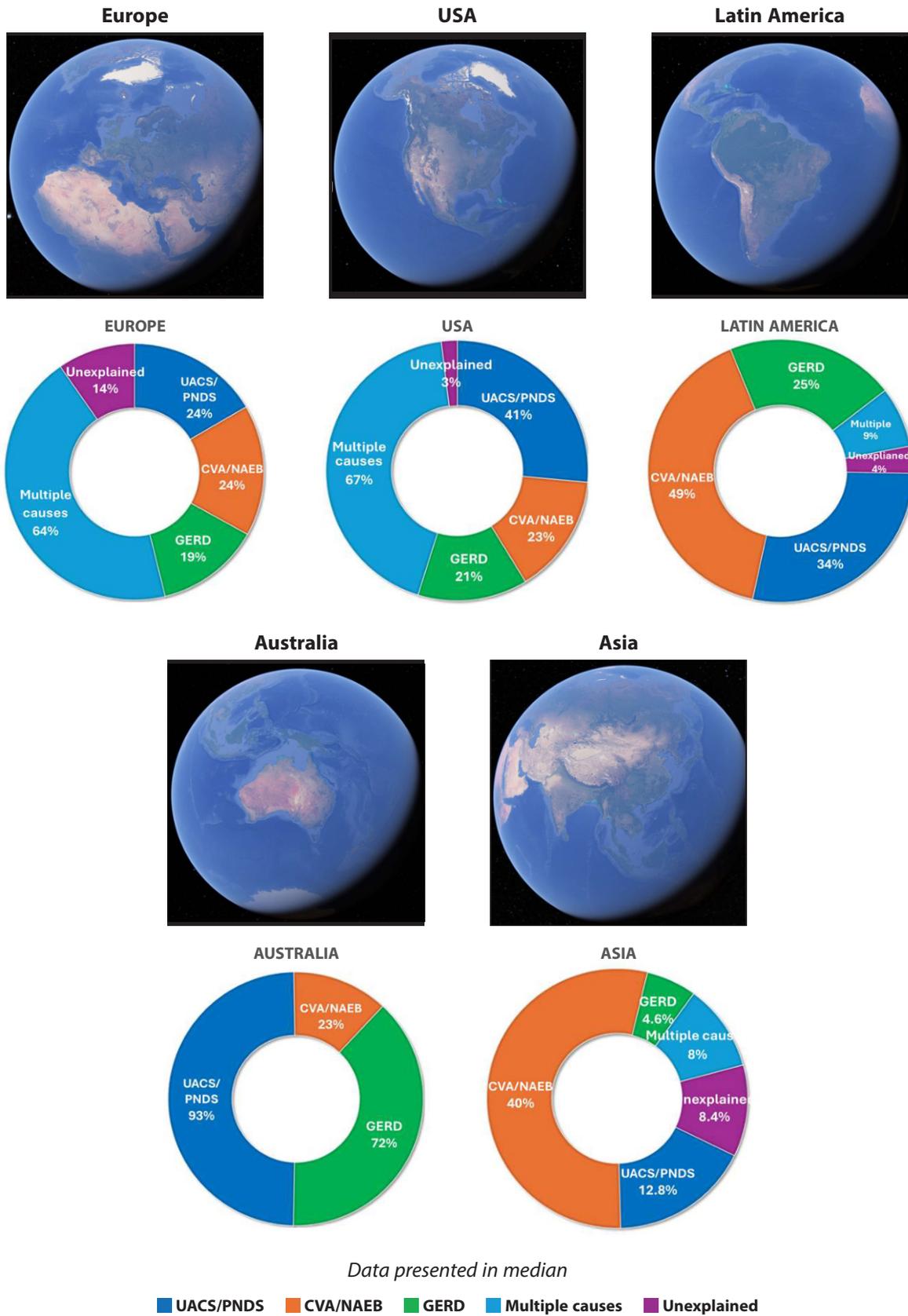
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**Introduction**

Chronic cough, defined as a cough lasting for more than eight weeks, is a prevalent medical condition that affects a large portion of the population, significantly diminishing quality of life and overall well-being.<sup>1-4</sup> Challenges in diagnosis and management can be attributed to its diverse underlying causes. The incidence of chronic cough varies across different populations, influenced by several factors like region, ethnicity, gender, genetics, climate, lifestyle, pollution, and smoking.<sup>5</sup> A recent systematic review and meta-analysis of 90 studies from 16 countries reported an overall prevalence of 9.6% among Europeans and Americans, higher than Asians and Africans.<sup>1</sup> In Southeast Asia, various factors—including high temperatures, humidity, dust mite sensitization, high tuberculosis rates, and smoking prevalence in certain countries—contribute to respiratory diseases, including chronic cough.<sup>6</sup> Studies in Vietnam indicate a higher prevalence of chronic cough in rural areas (Bavi, 18.1%) compared to urban areas (Hanoi, 12.0%), with current smoking identified as a significant risk factor (OR, 1.45; 95%CI, 1.16–1.80).<sup>7</sup> In Malaysia and the Philippines, the reported prevalence of chronic cough was 9.9%, with 4.6% of individuals having a history of tuberculosis.<sup>8</sup> Although research on chronic cough prevalence in Thailand remains limited, the number of patients with chronic cough and respiratory issues has increased in recent years due to possible factors like pollution, infections, and allergies.

Common causes of chronic cough include asthma and non-asthmatic eosinophilic bronchitis (NAEB), with prevalence rates ranging from 14.6% to 66.0%. Upper airway cough syndrome (UACS), or post-nasal drip syndrome (PNDS), is also common, with prevalence rates between 9% and 93%, especially in regions like the USA and Australia. Gastroesophageal reflux disease (GERD) is another significant contributor, with a wide range of rates from 1.4% to 85.4%. ACE inhibitor-induced cough, a common medication-related cause, affects 11.5% of cases and can often be excluded through detailed patient history. Combined causes account for 5.5% to 72% of chronic cough cases. Additionally, unexplained chronic cough varies across regions, with rates from 2.7% to 46%, and psychogenic cough, while less common, has a prevalence of 1.4%. **Figure 1** and **Table 1** show the prevalence of chronic cough according to etiologies across regions.

Previous research has focused on identifying chronic cough of specific causes, resulting in limited evidence and low-quality recommendations for managing chronic cough as a stand-alone condition. As a result, previous guidelines posed limited clinical questions for evidence identification.<sup>5,9,10</sup> Over the last few decades, significant advances have been made in understanding and managing chronic cough, particularly in cases where no clear medical explanation exists.<sup>11</sup> In some countries, a considerable number of patients visiting referral clinics for chronic cough have cases that remain unexplained or refractory, previously labeled as ‘idiopathic,’ ‘unexplained,’ or ‘refractory’ cough.<sup>12</sup>



**Figure 1. Worldwide prevalence of chronic cough.**

ACEI: angiotensin-converting enzyme inhibitor; CXR: chest radiograph; FeNo: fractional exhaled nitric oxide; GERD: gastroesophageal reflux disease; ppb: parts per billion; TB: tuberculosis

**Table 1. Summary of evidence: Investigation.**

Question	Investigation	Statement	Level of evidence
PICO Question 1: Should nasal endoscopy be performed on chronic cough patients to evaluate the cause of upper airway cough syndrome?	Nasal endoscopy	Nasal endoscopy is a valuable diagnostic modality for patients with chronic cough, particularly those suspected of having chronic rhinosinusitis.	Weak recommendation, Low quality of evidence
PICO Question 2: Should plain paranasal sinus radiograph be performed in patients with chronic cough?	Sinus radiograph	We recommend against the routine use plain paranasal sinus radiograph for the evaluation of chronic cough.	Weak recommendation, Low quality of evidence
PICO Question 3: Should computed tomography scans of the paranasal sinuses be performed in patients with chronic cough?	Paranasal sinuses computed tomography	Computed tomography scans of the paranasal sinuses may be considered in patients with chronic cough accompanied by nasal symptoms suggestive of rhinosinusitis.	Weak recommendation, Low quality of evidence
PICO Question 4: Should laryngoscopy be performed in patients with chronic cough?	Laryngoscopy	Laryngoscopy can be considered for patients with chronic cough and associated symptoms of laryngeal dysfunction, such as throat clearing or hoarseness.	Weak recommendation, Low quality of evidence
PICO Question 5: Should FENO be used to assist in the diagnosis of chronic cough patients?	Fractional exhaled nitric oxide (FeNO)	We suggest FeNO is helpful for the diagnosis of cough variant asthma in adult patients with chronic cough.	Strong recommendation, Moderate quality evidence
PICO Question 6: Should variable airflow obstruction assessed by peak flow variability be performed in patients with chronic cough with normal chest radiographs and physical examination?	Peak flow variability	Variable airflow obstruction assessed by peak flow variability can be considered in chronic cough patients with normal chest radiographs and physical examination.	Weak recommendation, Low quality of evidence
PICO Question 7: Should spirometry be performed in patients with chronic cough with normal chest radiographs and physical examination?	Spirometry	Spirometry can be a valuable diagnostic tool for common lower airway conditions in patients with chronic cough, especially when chest radiographs and physical examination are normal.	Weak recommendation, Low quality of evidence
PICO Question 8: Should bronchial challenge test be assessed in patients with chronic cough with normal chest radiographs and physical examination?	Bronchial challenge test	Bronchial challenge test can be considered in chronic cough patients with normal chest radiographs and physical examination to identify bronchodilator-responsive cough.	Weak recommendation, Low quality of evidence
PICO Question 9: Should computed tomography scans of the chest be performed in patients with chronic cough with normal chest radiography?	Chest computed tomography	We do not recommend routinely performing computed tomography scans of the chest in chronic cough patients with normal physical examination and normal chest radiographs. Chest CT scans can be considered in patients with risk factors identified through their medical history and physical examination.	Weak recommendation, Low quality of evidence
PICO Question 10: Should definitive diagnosis of gastroesophageal reflux disease using special investigation should be routinely done before using anti-reflux drugs in adult patients with chronic cough?	Gastroesophageal reflux disease investigation	Adult patients with chronic cough without typical GERD symptoms (heartburn, acid regurgitation, non-cardiac chest pain) should undergo 24-hr pH impedance monitoring as it is the most studied investigation before prescribing proton-pump inhibitors.	Weak recommendation, Low quality of evidence

Recent evidence suggests that cough reflex hypersensitivity is often a common underlying mechanism in these cases, supporting the view of chronic cough as a disease entity.<sup>13</sup>

This guideline aims to incorporate a thorough review of investigations and treatments, particularly for patients with nonspecific chronic cough. By integrating this evidence into clinical practice through diagnosis-driven approaches, the guideline provides key recommendations based on the latest evidence and expert consensus. This valuable resource assists clinicians in effectively managing patients with chronic cough and improving their quality of life. The guideline is divided into two parts: Part I: Screening and Investigations, and Part II: Treatment.

## Methodology

This guideline follows the dual-model approach, combining the scientific rigor of the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework<sup>14</sup> for key questions with a narrative component to the consensus of the Chronic Cough Guidelines Working Group without supporting evidence. The summary of the GRADE framework is provided in the supplementary materials. The narrative addresses clinically important aspects of chronic cough, while the key questions systematically explore the evidence in areas of clinically important controversy. Based on these findings, a management algorithm was developed. 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. The working group compiled a list of 10 key clinical questions related to the screening and diagnosis and arranged them into the Population, Intervention, Comparator, and Outcomes (PICO) format. Discussion and consensus among the chairs and members determined the number of questions to be addressed in the guidelines.

### 1) Population

The guideline focuses on adult patients aged 18 years or older with chronic cough lasting at least 8 weeks, which defines chronicity. Patients with a specifically identified cause of cough with chronic cough as presenting symptoms i.e., cough variant asthma, non-asthmatic eosinophilic bronchitis, upper airway cough syndrome including allergic rhinitis, and chronic rhinosinusitis were also considered. Chronic cough due to specific etiologies will be discussed in detail in each PICO statement and included in the approach scheme diagram.

### 2) Interventions and Comparators

The working group determined the relevant topics for screening and investigations of chronic cough.

### 3) Outcomes

All relevant outcomes associated with the diagnosis of cough i.e., the performance of the tests, and change in treatment decision.

## Evaluating chronic cough: A step-by-step approach

Chronic cough, defined as a cough lasting more than eight weeks,<sup>4</sup> requires a comprehensive evaluation. The initial assessment should involve a detailed medical history, physical examination, and a chest radiograph. **Figure 2** reveals a step-by-step approach to chronic cough and further specific investigations to identify the common causes of chronic cough.

### Red Flag Symptoms and Signs

It is crucial to screen for urgent and severe conditions when the key red flags are present as follows: hemoptysis, chest pain, hoarseness, dyspnea, dysphagia, weight loss, fever, recurrent pneumonia, oxygen desaturation, clubbing of fingers, and abnormal respiratory findings on examination.

### Detailed History and Severity Assessment

If no red flags are present, a detailed history is necessary to identify potential causes and comorbidities. Additionally, assessing cough severity through tools such as the Leicester Cough Questionnaire (LCQ) or Visual Analog Scale (VAS) is critical for informed treatment planning.

### Initial Investigations

A chest radiograph is a valuable initial diagnostic tool to identify common causes of chronic cough.

### Specific Causes and Treatment

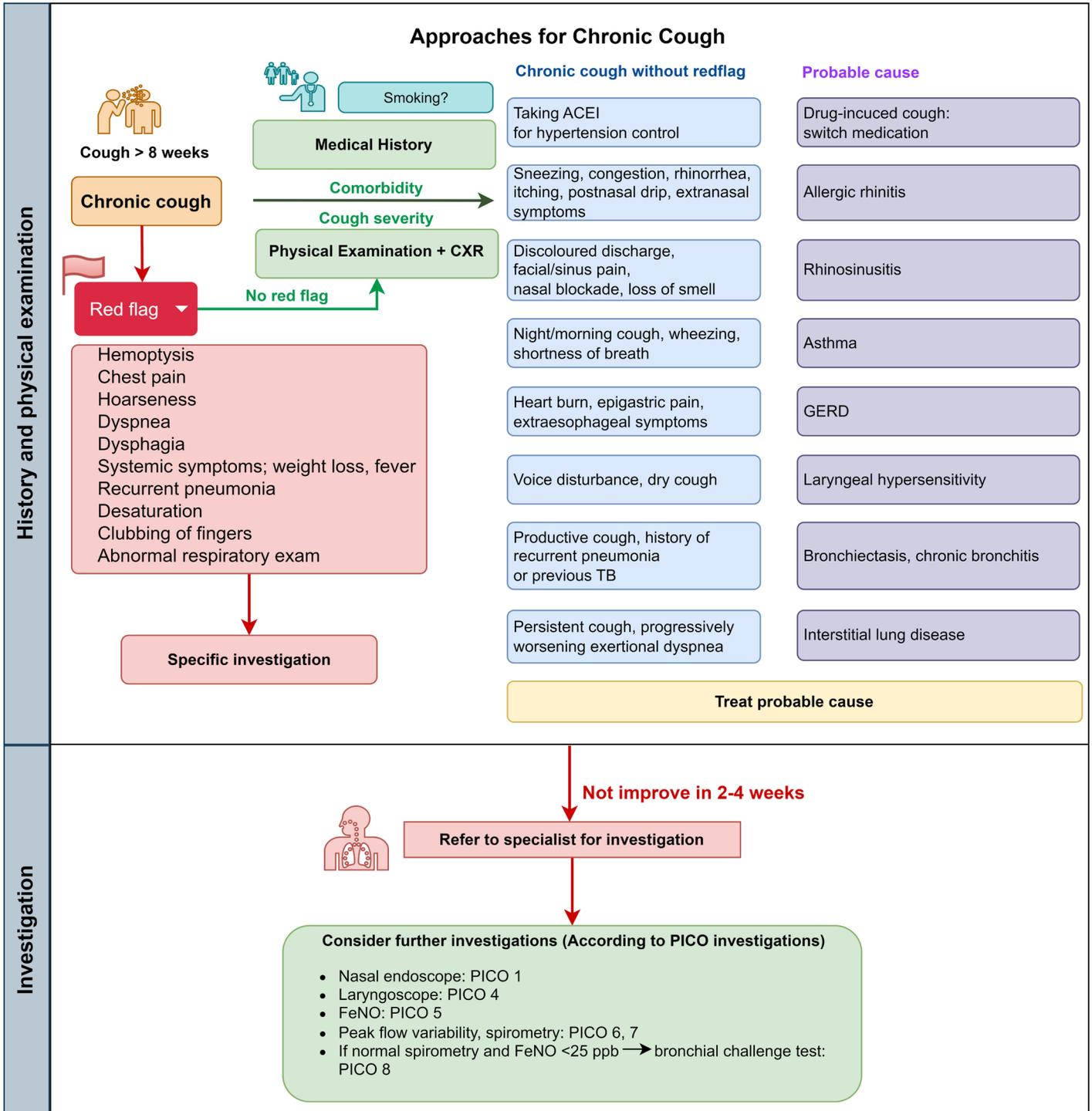
Common causes of chronic cough include:

- Drug-induced cough
- Allergic rhinitis (AR)
- Chronic rhinosinusitis (CRS)
- Asthma/Cough Variant Asthma (CVA)/non-asthmatic eosinophilic bronchitis (NAEB)
- Gastroesophageal reflux disease (GERD)
- Laryngeal hypersensitivity
- Bronchiectasis
- Chronic bronchitis
- Interstitial lung disease (ILD)

The history, symptoms, and signs can guide the diagnosis of these common causes, as outlined in **Figure 2**. Once a specific diagnosis is made, targeted treatment can be initiated.

### Referral to Specialist

If no specific cause of persistent cough can be identified, or further investigations are required, referral to a specialist is recommended. The evidence supporting the use of specific investigations is demonstrated in the next section.



**Figure 2. Chronic Cough: Screening and Special Investigations.**

ACEI: Angiotensin-converting enzyme inhibitors; CXR: chest radiograph; FeNO: fractional exhaled nitric oxide; GERD: gastroesophageal reflux disease; ppb: parts per billion; TB: tuberculosis

## Investigations in chronic cough

### Chest radiograph

*We recommend a chest radiograph as an initial evaluation for patients with chronic cough to exclude common causes of chronic cough.*

A chest radiograph is a common and safe initial evaluation for chronic cough. It can suggest lung pathologies such as lung neoplasms, tuberculosis, bronchiectasis, emphysema, and interstitial lung disease, which may help guide a more comprehensive diagnosis and focused treatment. A prospective study of 131 patients with chronic cough, which included a chest radiograph in an algorithm-based approach identified the cause of cough in 93% of cases.<sup>15</sup> Another prospective study involving 112 chronic cough patients who underwent chest radiographs achieved a 66% successful treatment rate based on the diagnosis made.<sup>16</sup> A larger retrospective cohort study involving 404 chronic cough patients in a primary care setting in which chest radiographs were included as part of the initial investigation demonstrated improved cough symptoms following treatment according to the identifiable causes.<sup>17</sup>

### Nasal endoscopy

Question 1: Should nasal endoscopy be performed on chronic cough patients to evaluate the cause of upper airway cough syndrome?

#### Statement

*Nasal endoscopy is a valuable diagnostic modality for patients with chronic cough, particularly those suspected of having chronic rhinosinusitis. While its role in diagnosing allergic rhinitis and related conditions is less clear, it may be considered an optional tool. (Weak recommendation, Low quality of evidence)*

#### Rationale

Nasal endoscopy improves diagnostic sensitivity, especially for screening for AR-associated conditions,<sup>18</sup> and improves specificity and positive predictive value for diagnosis of CRS.<sup>19</sup> A cross-sectional study evaluated 172 patients presenting with chronic cough using clinical data, spirometry, and nasal endoscopy, 58 (33.7%) were diagnosed with CRS.<sup>20</sup> Another retrospective study demonstrated the benefit of flexible nasopharyngoscopy in 20 chronic cough patients, 10 (50%) were diagnosed with AR, and 8 (40%) were diagnosed with laryngeal/gastroesophageal reflux.<sup>21</sup>

Digital nasal endoscopy is a potential option for examining inferior turbinate hypertrophy in AR. However, currently, there is a lack of research on its use. It is important to note that digital nasal endoscopy should be limited to the inferior turbinate head under direct vision to avoid damage to surrounding structures. It should not be considered a substitute for formal nasal endoscopy.

### Sinus radiograph

Question 2: Should plain paranasal sinus radiograph be performed in patients with chronic cough?

#### Statement

*Given the limited overall benefit of plain paranasal sinus radiographs in chronic cough, coupled with the unnecessary risk of radiation exposure and the superior diagnostic value of alternative imaging modalities, we recommend against the routine use of plain paranasal sinus radiographs for the evaluation of chronic cough. (Weak recommendation, Low quality of evidence)*

#### Rationale

The benefit of plain paranasal sinus radiographs in diagnosing sinonasal disease for patients presenting with chronic cough is weak, as only 30% of such patients show abnormalities in plain sinus radiographs. In a cross-sectional study of 270 patients with rhinitis, and asthma, 57 patients reported chronic cough, 23 of whom were identified as having AR with cough, and 18 were identified as having NAR with cough. Abnormal plain sinus radiographs, including mucosal thickening, loss of sinus cavity translucency, and the presence of polyps were reported in 12 (52%) patients in the AR group, and 5 (28%) patients in the NAR group. None of the patients with such findings were clinically diagnosed with sinusitis.<sup>22</sup> Another prospective cohort study included patients with chronic cough. Abnormal plain sinus radiographs were found in 10 subjects (28%), 5 were diagnosed with sinusitis, and the remaining 5 were diagnosed with rhinitis as the cause of cough.<sup>23</sup> Such abnormal findings indicated the chronicity of the disease but did not assist with the diagnosis. There are no high-quality studies demonstrating a role for imaging in the diagnosis of AR.<sup>18</sup> Additionally, plain sinus radiographs did not play a role in the definitive diagnosis of sinonasal diseases, whereas a computed tomography scan offers an imaging modality of choice over plain sinus radiographs in CRS.<sup>19,24</sup>

### Paranasal sinus computed tomography

Question 3: Should computed tomography (CT) scans of the paranasal sinuses be performed in patients with chronic cough?

#### Statement

*Computed tomography (CT) scans of the paranasal sinuses may be considered in patients with chronic cough accompanied by nasal symptoms suggestive of rhinosinusitis. However, there is insufficient evidence to support the routine use of CT scans for chronic cough alone. (Weak recommendation, Low quality of evidence).*

### Rationale

CT scans of the paranasal sinuses are generally not recommended for patients presenting with symptoms indicative of AR or acute rhinosinusitis (ARS).<sup>18,19</sup> In patients with CRS, a CT scan may be considered under specific circumstances. These include situations where the patient exhibits symptoms suggestive of CRS, but no abnormalities are detected upon examination using a nasal speculum or an endoscope. Additionally, CT scans should be considered if the patient does not respond to appropriate medical therapy.<sup>19</sup> A study included 702 patients with chronic cough who were referred to a tertiary hospital. Of the 159 patients who were clinically suspected of having rhinosinusitis and underwent CT paranasal sinus scans, abnormalities were found in 123 cases (77%). Furthermore, 32% of these patients had fluid levels within the sinuses, indicating acute rhinosinusitis.<sup>25</sup>

### Laryngoscopy

Question 4: Should laryngoscopy be performed in patients with chronic cough?

#### Statement

*Laryngoscopy can be considered for patients with chronic cough and associated symptoms of laryngeal dysfunction, such as throat clearing or hoarseness. Laryngoscopy is particularly indicated when the cough persists beyond eight weeks, or earlier if severe laryngeal dysfunction is suspected based on clinical assessment. The potential benefits and preferences of individual patients should be considered before the procedure.* (Weak recommendation, Low quality of evidence)

#### Rationale

Laryngeal dysfunction in several terms includes laryngospasm, vocal cord dysfunction, and paradoxical vocal fold movement. More recently, inducible laryngeal obstruction or laryngeal dysfunction have been proposed as umbrella terms to encompass the wide variety of aberrant laryngeal response patterns.<sup>26</sup> Laryngoscopy is a common diagnostic tool for patients with laryngeal disorders, including those presenting with chronic cough. Four observational studies revealed abnormalities in laryngoscopy examinations of chronic cough patients, with vocal motor dysfunction identified in 47-80% of cases.<sup>27-30</sup> However, several limitations undermine its diagnostic utility. None of the studies includes a control group, which limits the ability to compare the prevalence of laryngeal abnormalities in chronic cough patients to those in the general population. The criteria for diagnosing laryngeal dysfunction via laryngoscopy are not consistently defined or standardized across the studies, leading to a variability in findings.

Of note, simple laryngoscopy at rest provides only a snapshot of laryngeal movement and may often appear completely normal when the patient is asymptomatic. Challenge laryngoscopy—using external triggers such as exercise or other environmental factors based on the patient's history—is likely more diagnostic.<sup>31</sup>

### Fractional exhaled nitric oxide (FeNO)

Question 5: Should FeNO be used to assist in the diagnosis of chronic cough patients?

#### Statement

*We suggest FeNO is helpful for the diagnosis of cough variant asthma in adult patients with chronic cough.* (Strong recommendation, Moderate quality evidence)

#### Rationale

Fractional exhaled nitric oxide (FeNO) is a non-invasive test used to assess the degree of type 2 inflammation in the airways, particularly in asthma.<sup>32</sup> FeNO is also an important tool for monitoring compliance with corticosteroid therapy in chronic airway diseases, especially asthma. However, FeNO is ineffective in detecting non-type 2 inflammatory airway conditions.<sup>33-34</sup> A prospective cohort study of 52 non-smoker patients with chronic cough including those with CVA, NAEB, GERD, and UACS, were evaluated for FeNO levels. The FeNO values of CVA were similar to NAEB ( $54.0 \pm 21.0$  and  $47.3 \pm 15.5$  ppb), and both were higher than GERD and UACS ( $18.1 \pm 13.5$  and  $20.2 \pm 8.3$  ppb). Using a cut-off of 33 ppb to differentiate CVA/NAEB from GERD/UACS, the sensitivity was 92% and the specificity was 88%.<sup>35</sup> Another prospective cohort study recommended a FeNO cut-off of 39 ppb to distinguish asthma (including classical asthma and CVA) from other causes, achieving a sensitivity of 79% and specificity of 91%.<sup>36</sup> In the larger two retrospective studies involving 450, and 328 patients with chronic cough, one-third of the patients in both studies had CVA. A FeNO cut-off of 25 ppb was proposed to separate CVA from non-CVA cough, with an AUC of 0.87, sensitivity of 81%, and specificity of 84%.<sup>37</sup> The latter study had lower sensitivity and specificity (66% and 74%), with an AUC of 0.77.<sup>38</sup>

A systematic review and meta-analysis of 25 studies involving 3,983 subjects with chronic cough assessed FeNO as a diagnostic tool for asthma.<sup>39</sup> The pooled sensitivity and specificity were 72% and 78%, respectively. However, high heterogeneity was observed ( $I^2 = 78\%$ ). The FeNO cut-off varied from 13 to 41 ppb. Another systematic review and meta-analysis included 15 studies with 2,187 subjects (13 studies on CVA) and reported pooled sensitivity and specificity for FeNO in diagnosing CVA as 72% and 85%. Optimal cutoff levels varied from 16 to 55 ppb.<sup>40</sup> A recent meta-analysis including 12 studies and 1,968 subjects analyzed the accuracy of FeNO for diagnosing CVA. The FeNO cut-off ranged from 16 to 55 ppb. The pooled sensitivity and specificity were 74% and 82%, and the pooled positive likelihood ratio (LR) and negative LR were 4.1 and 0.3 respectively.<sup>41</sup>

Therefore, the performance of FeNO for diagnosis of chronic cough due to asthma is variable depending on the cut-off. False-negative results can occur in approximately 20 to 25%, particularly in patients using inhaled corticosteroid (ICS). In such cases, ICS should stop before remeasurement for at least 2 weeks. If results are negative, further investigations such as a bronchial challenge test, or variability of peak expiratory flow may be needed if available.

## Peak flow variability

Question 6: Should variable airflow obstruction assessed by peak flow variability be performed in patients with chronic cough?

### Statement

*Variable airflow obstruction assessed by peak flow variability can be considered in chronic cough patients. (Weak recommendation, Low quality of evidence)*

### Rationale

Peak expiratory flow (PEF) variability can help confirm the diagnosis of asthma by identifying variable expiratory airflow limitation, especially if the average daily diurnal PEF variability exceeds 10%. Additionally, PEF variability can be used to assess asthma control.<sup>42</sup> A prospective cohort of 221 adult patients with chronic cough was assessed for diurnal peak flow variability (DPV) during 2 weeks, as well as spirometry. Patients were diagnosed with asthma if they had respiratory symptoms for more than three weeks in the past year, accompanied by a positive methacholine provocation test. A DPV of 20% for at least three days increased the prior probability of having asthma from 45% to more than 70%.<sup>43</sup>

## Spirometry

Question 7: Should spirometry be performed in patients with chronic cough?

### Statement

*Spirometry can be a valuable diagnostic tool for common lower airway conditions in patients with chronic cough. Despite the limited number of high-quality studies supporting its use, the low risk associated with spirometry makes it a reasonable consideration for chronic cough patients. (Weak recommendation, Low quality of evidence)*

### Rationale

Spirometry is useful in identifying common causes of chronic cough, particularly in patients with clinically suspected asthma (young age, shortness of breath, chest tightness, wheezing, and symptoms responsive to bronchodilator treatment). It helps to confirm chronic obstructive pulmonary disease (COPD) diagnosis in patients with a smoking history. If spirometry shows a bronchodilator response (an increase in FEV<sub>1</sub> or FVC from baseline of  $\geq 12\%$  and  $\geq 200$  mL), this finding suggests a diagnosis of asthma.<sup>42</sup> If spirometry shows a reduced post-bronchodilator FEV<sub>1</sub>/FVC ratio ( $<$  the lower limit of normal or  $< 0.7$ ) along with the presence of risk factors such as smoking, this confirms a diagnosis of COPD.<sup>44</sup> COPD can be excluded in cases with normal spirometry, but not for asthma in cases with a high clinical probability of asthma. In such cases, a bronchial challenge test can be considered to confirm the diagnosis.

In a retrospective cohort study of 7,150 patients with chronic cough, spirometry was performed in 56.5% of cases. Airflow obstruction was detected in 12.8% of the tested patients, with a positive bronchodilator response (increase in FEV<sub>1</sub>  $\geq 12\%$  and  $\geq 200$  mL) observed in 3.3%.<sup>45</sup> In another cross-sectional study 218 adults aged 15 and older with chronic cough reported abnormal spirometry results indicating asthma and COPD in 21.1% and 33.5% of tested patients.<sup>46</sup>

## Bronchial challenge test

Question 8: Should bronchial challenge test be assessed in patients with chronic cough with normal chest radiographs and physical examination?

### Statement

*Bronchial challenge test can be considered in chronic cough patients with normal chest radiographs and physical examination to identify bronchodilator-responsive cough. (Weak recommendation, Low quality of evidence)*

### Rationale

An accurate diagnosis of asthma is crucial for ensuring appropriate therapy. Bronchial challenge test can be used to confirm the diagnosis for patients with clinically suspected asthma, but spirometry results are normal. Furthermore, cough variant asthma, characterized by chronic cough without wheezing, can be identified with a positive bronchial challenge test.

A retrospective study of 100 patients with chronic cough identified bronchodilator-responsive cough (BRC) in 63% of cases.<sup>47</sup> BRC was defined as a reduction in cough severity of 30% or more on a visual analog scale (VAS) following bronchodilator therapy. In this study, a decrease in flow-volume curves measuring the expiratory flow of the partial flow-volume curve 40% above residual volume (PEF40) by 35% during methacholine challenge testing, was considered a positive result. For predicting a BRC, a cut-off value of 24 for the PEF40 showed a sensitivity of 71% and a specificity of 89%, with an AUC of 0.82.

This highlights the utility of bronchial challenge testing in the diagnosis of BRC. However, its diagnostic value in patients with isolated chronic dry cough, without any history of breathlessness or wheezing, remains unclear.

## Chest computed tomography

Question 9: Should computed tomography (CT) scans of the chest be performed in patients with chronic cough with normal chest radiography?

### Statement

We do not recommend routinely performing computed tomography (CT) scans of the chest in chronic cough patients with normal physical examination and normal chest radiographs. Most of these scans do not reveal any significant abnormalities associated with chronic cough, and they expose patients to potential risks associated with radiation exposure. Chest CT scans can be considered in patients with risk factors identified through their medical history such as smoking, exposure to chemicals/PM2.5, and physical examination. (Weak recommendation, Low quality of evidence)

### Rationale

Based on two guidelines, there was no strong evidence to support the use of chest CT in the initial evaluation of patients with chronic cough. However, chest CT scans can be considered if symptoms persist despite initial clinical assessment, especially when risk factors such as smoking, exposure to chemicals/PM2.5, or red flags are present.<sup>5,48</sup>

Evidence suggested that a routine chest CT scan may not be recommended for chronic cough patients with normal chest radiography. A prospective study included patients with chronic cough who underwent the chronic-cough algorithm-based approach, including history, physical examination, chest radiograph, and spirometry, and excluded post-viral upper respiratory tract infection and currently used ACE-Inhibitor. Chest CT scans showed abnormalities in 59% of patients tested. Most abnormalities observed in CT scans were not serious. Bronchiectasis, interstitial lung disease, COPD, and lung cancer were found in 8%, 8%, 5%, and 1.5% of cases, respectively. The majority of patients with significant abnormalities had chronic productive cough. Given the low diagnostic yield, the authors suggested that CT is unlikely to be cost-effective but may be considered in patients with persistent chronic productive cough.<sup>15</sup> Similarly, another retrospective study in chronic cough patients examined the utility of chest CT. The results revealed abnormal findings in chest CT for 37.3% of patients with normal chest radiographs. Common abnormalities observed were focal fibrosis (6.9%), focal infiltrates (5.9%), subsegmental atelectasis (5.9%), and bronchial wall thickening (4.5%). Other findings were bronchiectasis (4.1%), emphysema (2.3%), pneumonia (0.4%), tuberculosis (0.2%), and lung cancer (0.12%).<sup>49</sup> Lastly, a retrospective analysis of paired chest radiographs and CT chest results was performed in 189 consecutive adults with chronic cough. Negative CT findings were found in 85% of patients with normal chest radiography. Patients with false-negative chest radiography results were statistically older than those with true-negative results. No differences were found in other characteristics such as gender, duration of cough, smoking history, comorbidities, or BMI.<sup>50</sup>

Overall, based on the studies above, we do not recommend routine chest CT, but it may be considered in patients with persistent cough, especially productive cough, presence of risk factors, and older age.

### Gastroesophageal reflux disease (GERD) investigation

Question 10: Should a definitive diagnosis of gastroesophageal reflux disease (GERD) using special investigation should be routinely done before using anti-reflux drugs in adult patients with chronic cough?

### Statement

Adult patients with chronic cough without typical GERD symptoms (heartburn, acid regurgitation, non-cardiac chest pain) should undergo 24-hour pH impedance monitoring as it is the most studied investigation before prescribing proton-pump inhibitors. (Weak recommendation, Low quality of evidence)

### Rationale

Among patients with chronic cough without typical GERD symptoms, not everyone has true GERD. A prospective cohort study enrolled 100 patients with unexplained chronic cough. All participants underwent 24-hour pH impedance monitoring. Thirty-one patients had no reflux, 45 had acid reflux and 24 had weakly acid reflux. However, only 24 of them had a positive reflux-cough association. Among these patients, 7 of 24 cases had acid reflux, while 17 had weakly acid.<sup>51</sup> Additionally, 24-hour pH impedance demonstrated that patients with GERD without chronic cough had fewer symptom scores, fewer acid reflux episodes, and less proximal reflux compared to patients who had both chronic cough and typical GERD symptoms. These findings indicated that GERD symptoms when co-existing with chronic cough, increase the likelihood of acid reflux.<sup>52</sup> Recently, two societies including the American Gastroenterology Association<sup>53</sup> and Lyon Consensus<sup>54</sup> have suggested that objective GERD testing should be performed in patients with extraesophageal GERD without typical GERD symptoms before continuing long-term proton pump inhibitors. The Thailand GERD guideline<sup>55</sup> also stated that patients with extraesophageal symptoms of GERD without alarm features can be diagnosed with GERD after excluding other diseases.

### Discussion

Chronic cough is a prevalent and impactful clinical condition that often requires careful assessment and management. Its prevalence is increasing globally over time. Numerous guidelines have been published over the years to address chronic cough, generally defining it as a cough lasting more than 8 weeks in adults. A systematic review of randomized controlled trials on chronic cough management<sup>9</sup> found limited evidence and low-quality evidence. Subsequent guidelines<sup>5,10</sup> also failed to identify high-level evidence and conclusions when using the GRADE recommendation system. The recent BTS 2023 guideline developed clinical consensus based on a review of existing literature, focusing on treatable traits of chronic cough.<sup>56</sup> The latest CICADA 2023 position statement incorporated recommendations for both specific diseases and unexplained chronic cough.<sup>57</sup> A comparison of the previous guidelines is shown in **Table 2**.

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

	CHEST 2016	KAAACI 2018	ERS 2020	BTS 2023	CICADA 2023
Author	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	> 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
<b>Investigation</b>					
Chest radiography	-	Initial evaluation	Initial evaluation	Initial evaluation	Initial evaluation
Spirometry	-	Initial evaluation (if available)	Initial evaluation	Initial evaluation (if available)	Initial evaluation
FeNO	-	For predicting asthma: - Conditional recommendation (adult) - Conditional recommendation (children)  For predicting NAEB: - Conditional recommendation (adult)	Research recommendation	Should have FeNO (if available)	-
Blood Eosinophil	-	-	Research recommendation	Should have full blood count	-
CT chest	-	-	Conditional recommendation	-	-

**Abbreviation:** CC: chronic cough; UCC: unexplained chronic cough; RCT: randomized controlled trial; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations framework; FeNO: fractional exhaled nitric oxide; CT: computed tomography

These guidelines emphasize the importance of history-taking, physical examination, and chest radiography, along with identifying risk factors such as ACE inhibitor use and smoking. They also include red flags to help screen for severe conditions. Most guidelines recognize four common causes of chronic cough: UACS, asthma, NAEB, and GERD. A significant number of cases remain unexplained when a specific diagnosis cannot be made, often labeled as ‘non-specific’ chronic cough, which may require further evaluation by specialists.

Given the fact that most chronic cough cases ultimately lead to a specific diagnosis, this study re-emphasized the PICO approach, focusing on the presenting condition of “chronic cough” to define the population for systematic searching. This symptom-based approach mirrors real-world clinical practice, providing a more practical and relevant framework for research and guideline development.

We identified 10 key clinical questions on investigations of chronic cough through this process and summarized recommendations where possible. Due to the limited evidence, recommendations for some key questions were presented as narrative descriptions. Both recommendations and narrative descriptions contributed to the development of practical diagrams aimed at guiding primary care physicians in screening and assisting specialists in diagnosing chronic cough. Our current guideline stands out by incorporating clinical evaluation based on specific symptoms, guiding the clinician toward the most likely potential diagnosis.

Our step-by-step guide matches probable causes and common symptoms, which can assist in initial diagnosis, as this is often the stage at which most patients present. If a specific cause is identified, prompt treatment can be initiated. If the condition persists, a referral to a specialist is recommended for further investigations.

By following these guidelines, clinicians can improve the accuracy of diagnosis, optimize treatment strategies, and ultimately enhance patient outcomes and satisfaction. This guideline is intended to provide as a practical tool for healthcare professionals involved in the care of adult patients with chronic cough, including primary care physicians, internists, pulmonologists, allergists, and otolaryngologists.

While adhering to PICO and GRADE methodologies like previous guidelines, this guideline provides a more comprehensive approach by incorporating a wider range of special investigations, including endoscopic examination, laryngeal examination, peak flow variability, and GERD evaluation. This enhanced approach is evident when compared to existing guidelines.

### Limitations

The low quality of evidence in this guideline can be attributed to several factors. First, the symptom-based focus on chronic cough may have restricted the evidence search, as many patients with chronic cough eventually receive a specific diagnosis. Second, some investigations that are typically performed to diagnose specific diseases, such as certain imaging tests or laboratory studies, may have been overlooked, despite their potential utility in initial evaluations. Third, studies with small sample sizes or limited funding support may have been excluded from the 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, with a particular emphasis on identifying and validating novel biomarkers and diagnostic tools.

### Conclusion

Chronic cough presents a significant clinical challenge. A range of investigations are available to aid in the diagnosis of specific underlying conditions. However, a symptom-based clinical approach is also important as the initial tool guiding the possible diagnosis. Part I of the guideline reviews the evidence supporting investigations in chronic cough patients. A step-by-step approach, based on the evidence, is provided to enhance the evaluation of this common condition for primary care physicians and specialists.

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