

# DIAGNOSIS AND THERAPY OF CHRONIC COUGH

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## Abstract

A cough that lasts for more than 8 weeks in adults (those older than 15 years) and more than 4 weeks in children is considered chronic and poses a significant health problem, as it can lead to feelings of fatigue, sleep disturbances, hoarseness, disruption of daily activities, vomiting, and often in women, even incontinence. The differential diagnosis of chronic cough in adults and children has its specificities. In certain cases, the etiological factor remains unknown when referring to unexplained (idiopathic) chronic cough. The study aimed to review contemporary European and American guidelines and published works related to the diagnosis and treatment of chronic cough in both children and adults.

This paper presents the results of a systematic review of publications in medical databases (PubMed) and guidelines from the European Respiratory Society (ERS) and the American College of Chest Physicians (CHEST), related to the diagnosis and treatment of chronic cough.

Diagnostic investigations should be focused on the most common causes of chronic cough. In adults, these include asthma, chronic obstructive pulmonary disease, bronchiectasis, interstitial lung disease, lung malignancy, non-asthmatic eosinophilic bronchitis, gastroesophageal reflux disease, and upper airway cough syndrome. In children, the most common causes of chronic cough are asthma, protracted bacterial bronchitis, cystic fibrosis, primary ciliary dyskinesia, bronchiectasis, tracheobronchomalacia, pertussis, habitual (psychogenic) cough, and foreign body aspiration. The treatment primarily involves excluding medications that might have

chronic cough as an adverse effect. Therapy is directed toward treating the underlying cause of chronic cough. If the cough persists despite treatment (refractory cough) or if it's idiopathic, neuromodulatory medications are employed (opioids, gamma-aminobutyric acid analogs, tricyclic antidepressants). Therapeutic options also include breathing and vocal techniques, superior laryngeal nerve blocks, and vocal cord medialization injections. Drugs directly inhibiting sensory receptors (P2X3, TRPV-1, and NK-1 inhibitors) are currently under clinical trial investigation. The use of validated tests is crucial for assessing therapeutic effectiveness.

The etiological factors of chronic cough can have both infectious and non-infectious origins and are not always related to lung diseases. Considering that chronic cough is regarded as a condition of hypersensitivity, when causal treatment does not yield satisfactory results or when dealing with idiopathic chronic cough, therapy is directed towards central or peripheral neuromodulation, as well as techniques involving breathing and vocal production.

**Keywords:** chronic cough, diagnosis, therapy

## Introduction

While fundamentally serving as a protective reflex, coughing can pose a significant health issue due to its often accompanying sensations of fatigue, sleep disturbances, hoarseness, disruption of daily activities, vomiting, and frequently in women, even incontinence. Depending on the presence or absence of mucus, a cough can be productive or dry.

Acute cough, by definition, lasts for less than 3 weeks, subacute cough lasts from 3 to 8 weeks, while chronic cough is considered to persist for more than 8 weeks in adults, with individuals above the age of 15 being classified as adults<sup>1,2</sup>. The definition, diagnostic protocol, and treatment of chronic cough differ for children under the age of 15.

Chronic cough can result from lung malignancy, but in cases where the lung X-ray findings are normal, the most common causes are medications, asthma, non-asthmatic eosinophilic bronchitis, gastroesophageal reflux disease (GERD), and upper airway cough syndrome (UACS)<sup>1</sup>. In a

certain number of patients, despite thorough diagnostic tests, the etiology cannot be determined, leading to the term “unexplained” or “idiopathic” chronic cough<sup>3,4</sup>. In cases where the causative factor is known but sufficiently prolonged, therapy doesn't yield satisfactory results, it's referred to as chronic refractory cough.

Chronic cough in adults is considered to reflect a state of hypersensitivity, meaning that it results from the mucous membranes' heightened sensitivity to minor mechanical, thermal, or chemical stimuli. The term “cough hypersensitivity syndrome” was introduced by the European Respiratory Society (ERS) in 2014. This syndrome can occur in the context of both known and unknown etiologies, encompassing idiopathic and refractory cough. Temperature changes, perfumes, aerosols, strong odors, speech, laughter, or singing often trigger chronic coughs. The exact reason for the existence of cough hypersensitivity syndrome is still unknown, but it is hypothesized that central and peripheral neural mechanisms play a role, forming the basis for the use of neuromodulatory drugs in the treatment of chronic cough<sup>1,5</sup>.

The initial step in determining the etiology of chronic cough involves collecting historical data related to the microclimatic conditions of the living and working environment, as well as the use of medications with cough as a common side effect. Further diagnostics depend on the patient's age, risk factors, and associated symptoms.

The guidelines from the European Respiratory Society (ERS) and the American College of Chest Physicians (CHEST) provide a solid foundation for the diagnosis and treatment of chronic cough.

To assess the effects of treatment in patients with chronic cough, the use of validated tests to evaluate cough severity and quality of life is crucial. In the professional literature, the following questionnaires are most commonly applied: Visual analog scale, Leicester Cough Questionnaire, Cough Severity Index, and Cough Specific Quality of Life Questionnaire<sup>6-10</sup>.

## Anatomy and Physiology of the Cough Reflex

Cough is a protective reflex aimed at clearing foreign substances from the respiratory tract. However, coughing is also a partially voluntary action involving subcortical and cortical brain structures.

The cough reflex is triggered by mucosal infection, secretion, or foreign bodies within the aerodigestive tract. Mechanical and chemical stimuli lead to the activation of cough receptors, which are primarily located on the mucosa of the larynx, trachea, and large bronchi<sup>11</sup>. The stimulation of these receptors is transmitted to the respiratory center in the *medulla oblongata* by afferent sensory fibers of the

*vagus nerve*. It is further relayed through the *nucleus tractus solitarius* to the paratrigeminal nuclei, and then to the thalamus and the primary somatosensory cortex<sup>1</sup>. Efferent motor fibers extend to the larynx, respiratory muscles, and diaphragm. The ultimate effect is the interruption of the normal breathing rhythm. Following inhalation, there is forceful adduction of the vocal cords, contraction of expiratory muscles, and a rapid expulsion of foreign contents from the respiratory tract.

For a cough to be effective, proper glottic closure (adduction of the vocal cords in the midline) is necessary, which, after inhalation, allows the creation of sufficient subglottic and intrathoracic pressure to expel foreign content with adequate force. Due to this, patients with inadequate glottic closure (vocal cord paralysis, surgical interventions in the larynx, etc.) encounter difficulties in clearing their airways through coughing. Additionally, given that forceful vocal cord adduction is a part of coughing, chronic cough over time can lead to vocal muscle fatigue, resulting in hoarseness and fatigue during prolonged speech.

## The Etiology of Chronic Cough

Chronic cough can be triggered by environmental factors such as tobacco smoke, microclimatic conditions in the workplace or living environment (vapors, gases), and air pollutants. Chronic cough is caused by a wide range of lung diseases such as asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis, interstitial lung disease, and lung malignancy. In cases where the chest X-ray appears normal, chronic cough is most commonly attributed to medications, asthma, non-asthmatic eosinophilic bronchitis, GERD, and upper airway cough syndrome<sup>1</sup>.

The medications that most commonly induce cough are angiotensin-converting enzyme (ACE) inhibitors. However, literature reports are indicating that chronic cough can also be triggered by sitagliptin, phenytoin, and topiramate<sup>1</sup>. Prolonged cough often occurs after respiratory viral infections (rhinoviruses, SARS-CoV-2, influenza H1N1 virus), which is considered a consequence of post-infectious hypersensitivity.

The differential diagnosis of chronic cough must include tuberculosis in endemic areas or high-risk patients, even in cases with a normal lung X-ray result<sup>2</sup>. Other infectious causes leading to chronic cough include *Mycobacterium avium* complex, other mycobacteria, fungal infections, and infections with certain parasites (e.g. paragonimiasis)<sup>12</sup>.

If thorough investigations exclude the aforementioned etiological factors of chronic cough, one of the presumed mechanisms underlying cough hypersensitivity syndrome is laryngeal dysfunction. Laryngeal dysfunction can manifest as laryngeal hypersensitivity, involving sensory pathways, or laryngeal motor dysfunction affecting the motor neural pathways of the larynx<sup>13</sup>. Moreover, chronic cough could

also be a manifestation of "Vocal cord dysfunction", a condition characterized by paradoxical vocal cord movement during respiration<sup>14</sup>.

In literature, a rare cause of cough has been described as the "Superior Thyroid Cornu Syndrome"<sup>15</sup>. In this case, the cause of the cough is the displacement of the superior horn of the thyroid cartilage from the medial position towards the lateral wall of the hypopharynx. It is presumed that this positional change leads to irritation of sensitive nerves and triggers the cough reflex.

## The diagnostic protocol for chronic cough

The initial step of the diagnostic algorithm for chronic cough involves a detailed medical history. Primarily, information about cigarette smoking, medications the patient is taking, allergies to respiratory allergens, microclimatic conditions in the living and working environment, and associated symptoms and signs are crucial. These details will guide further diagnostic investigations.

In adults with chronic cough, symptoms and signs that might indicate life-threatening conditions are of utmost importance and require urgent diagnostic assessment<sup>2</sup>. These include hemoptysis, pronounced dyspnea especially at rest or during the night, hoarseness, the presence of systemic symptoms (fever, weight loss, peripheral edema with weight gain), vomiting, difficulty swallowing solids or liquids, and recurrent pneumonia. When the previously mentioned symptoms and signs are not present, specific diagnostics will be focused on confirming or excluding the most common causes of cough (asthma, GERD, upper airway cough syndrome, non-asthmatic eosinophilic bronchitis)<sup>1</sup>.

Information about wheezing, difficulty breathing, allergies, nighttime cough, and triggering factors such as physical activity and cold air are suggestive of asthma. If it's an upper airway cough syndrome, patients might complain of postnasal drip, frequent sinusitis, nasal secretion and/or congestion, with the back of the throat showing a rough "cobblestone" appearance due to postnasal drainage. Frequent heartburn, dyspepsia, hoarseness, or worsened cough in a supine position or when bending forward may indicate GERD. A productive cough is generally associated with bronchiectasis, chronic bronchitis, eosinophilic bronchitis, and pneumonia.

In the medical history, it's also crucial to gather information about possible aspiration - whether the cough occurs during or shortly after eating, if the patient chokes on liquids, experiences difficulty swallowing solid food, etc. Such information might necessitate further in-depth investigations by ear, nose, and throat specialists (otorhinolaryngologists) and gastroenterologists.

The standard of otorhinolaryngological diagnostics is a fiberoptic examination of the upper aerodigestive tract,

which most adequately observes changes in the mucous membrane and examines the mobility of the vocal cords, sensitivity of the larynx and possible aspiration.

The initial radiological diagnosis for chronic cough involves a chest X-ray (posteroanterior and lateral views) to identify structural changes. According to the ERS protocol, if the chest X-ray is normal, computed tomography (CT) of the chest is not indicated<sup>1</sup>. If all investigations do not reveal the cause of chronic cough, it is considered unexplained (idiopathic).

## The treatment of chronic cough

In the treatment of chronic cough, it's important to eliminate known risk factors such as cigarette smoking and medications that can cause cough as a side effect. When chronic cough is associated with conditions like pneumonia, COPD, bronchiectasis, cystic fibrosis, and similar respiratory disorders, treatment is causal, aiming to address the underlying condition. The goal of therapy is to reduce cough to a level that doesn't significantly impair the quality of life, without eliminating it, as cough serves as a protective reflex.

In cases where treatment of the underlying disease does not yield an adequate therapeutic response, specific neuromodulatory therapy can be applied. Given that chronic cough is considered a state of hypersensitivity due to disruptions in central and/or peripheral neural pathways, therapy involves medications that achieve central neuromodulation (opioids, gabapentinoids, tricyclic antidepressants), direct inhibition of sensory receptors (P2X3, TRPV-1, and NK-1 inhibitors), and nerve inhibition (blocking the superior laryngeal nerve). These medications are used exclusively in adults<sup>16</sup>.

Opioids (such as Morphine, Codeine, Tramadol) exert a central action in suppressing the cough reflex. Codeine and Tramadol are not mentioned in the ERS and CHEST guidelines for the treatment of chronic cough<sup>1,2</sup>. Morphine is about 10 times more potent than codeine, and it has side effects like drowsiness, constipation, and the potential for dependence. However, small doses of morphine are included in the recommendations of the 2020 ERS guidelines. The recommended daily dose is 5-10 mg twice a day.

Gabapentin and Pregabalin are analogs of gamma-aminobutyric acid (GABA) that bind to calcium channels, thereby inhibiting the release of central neurotransmitters. These medications are primarily used in the treatment of epilepsy and pain therapy due to their ability to pass the blood-brain barrier. When used to treat chronic cough, it's recommended to start with lower doses and gradually increase the dosage every week. According to the ERS guidelines, the initial dose of Gabapentin is 100 mg three times a day, with a maximum of 300 mg three times a day<sup>1</sup>. The initial dose of Pregabalin is 50-75 mg twice a day, gradually increasing to a maximum of 150 mg twice a day<sup>1</sup>. Possible side effects of using GABA analogs include drowsiness, dizziness,

disorientation, fatigue, nausea, dry mouth, confusion, and blurred vision. Pregabalin has faster absorption and onset of action, leading to more frequent side effects<sup>1, 17</sup>.

Amitriptyline belongs to the class of tricyclic antidepressants and works as a serotonin reuptake inhibitor. According to the ERS guidelines for the treatment of chronic cough, the recommended daily dose is 10 mg in the evening<sup>1</sup>. Possible side effects may include tremors, dry mouth, dizziness, headaches, and drowsiness.

In cases of suspected laryngeal hypersensitivity, a therapeutic option is the blockage of the superior laryngeal nerve. This is achieved by injecting a mixture of corticosteroids (such as Triamcinolone, Methylprednisolone) and a local anesthetic (such as Lidocaine, Bupivacaine) at the point of entry of the internal branch of the superior laryngeal nerve on the thyrohyoid membrane. The therapeutic effect

involved in breathing, swallowing, and speech, and that chronic cough is a result of muscle tension disturbances in the larynx. These exercises can have a significant therapeutic effect, can be used in combination with other treatment modalities, and have the advantage of having no adverse effects.

## Specifics of Chronic Cough in Childhood

Chronic cough in children (individuals under 15 years of age) has its specifics, which pertain to etiological factors, diagnosis, and treatment<sup>24</sup>. Unlike in adults, in children, chronic cough is considered to be a cough that lasts for more than 4 weeks.

Chronic productive cough in children most commonly occurs in the context of asthma, prolonged bacterial

**Table 1.** Summary overview of therapeutic options according to ERS guidelines for the treatment of chronic cough<sup>1</sup>

CAUSATIVE AGENT	THERAPY
Medications (e.g. ACE inhibitors)	- Discontinuation of medication
Asthma	- Inhaled corticosteroids ± long-acting β-2 agonists - Leukotriene antagonists - Systemic corticosteroids
COPD	- Long-acting muscarinic antagonists
Non-asthmatic eosinophilic bronchitis	- Inhaled corticosteroids - Systemic corticosteroids
GERD	- Hygienic diet regimen - PPI or H2 blockers (for 8 weeks)
Upper respiratory tract cough syndrome	- Antihistamines - Decongestants - Intranasal corticosteroids
Unexplained (idiopathic) chronic cough	- Small doses of morphine (5-10 mg, twice a day orally) - Gabapentin (up to a maximum of 300 mg, three times a day orally); start with 100 mg, three times a day - Pregabalin (up to a maximum of 150 mg, twice a day orally); start with 50 to 75 mg, twice a day - Amitriptyline (10 mg orally in the evening) - Breathing exercises and voice production

**Legend:** ACE - Angiotensin Converting Enzyme; COPD - Chronic Obstructive Pulmonary Disease; GERD - Gastroesophageal Reflux Disease; PPI - Proton Pump Inhibitor.

on cough is good but transient, usually lasting for a few weeks<sup>18</sup>. However, due to the use of a local anesthetic in the area of the superior laryngeal nerve, this method carries a certain risk of aspiration of liquids, which is usually short-lived. In well-selected patients, with certain success, vocal fold medialization can also be applied by otolaryngologists in cases of chronic cough<sup>19, 20</sup>.

Considering that chronic refractory cough is regarded as a disruption in the neural regulation of the cough reflex, new medications are currently being investigated in various stages of clinical trials, such as P2X3 and TRPV-1 receptor antagonists, even though initial results have shown significant side effects like taste disturbances for the former and altered temperature sensations for the latter<sup>11, 19, 21</sup>.

An alternative to pharmacological treatment for chronic cough is voice, speech, and breathing exercises provided by a speech therapist, combined with vocal hygiene measures<sup>22, 23</sup>. The therapeutic effect of this method is based on the understanding that the larynx is a complex structure

bronchitis, cystic fibrosis, primary ciliary dyskinesia, and bronchiectasis. One possible cause of chronic cough in children is significant tracheobronchomalacia, with a diagnosis confirmed through bronchoscopy<sup>25</sup>.

In childhood, chronic cough is more commonly encountered as part of pertussis. The cough in pertussis is very pronounced, occurring in the form of attacks and is often accompanied by vomiting and difficulty in breathing. In children, more so than in adults, a condition known as a habitual (psychogenic) cough can be observed, presenting as a tic-like cough. However, diagnosing this condition requires thorough prior investigation to exclude other etiological factors<sup>25</sup>. It's characterized by being frequent, repetitive, sometimes occurring with each exhalation, and absent during sleep.

In children, aspiration of a foreign body into the respiratory tract is more common and presents as a prolonged cough. Less frequently, chronic cough can be caused by the presence of a foreign body in the ear, due to reflex

stimulation of the Arnold's nerve (a branch of the vagus nerve). In some cases, enlarged palatine tonsils and adenoid vegetation can be the cause of chronic cough, and surgical treatment (tonsillectomy/adenoidectomy) is the method of choice for treating these patients.

The initial diagnosis of chronic cough in children, according to the CHEST protocol guidelines, should include a chest X-ray and spirometry testing, if age-appropriate. For suspected asthma in children aged 6 to 14, a bronchoprovocation test is recommended. Additional diagnostics (skin prick test, Mantoux test, flexible fiberoptic bronchoscopy, chest CT scan, assessment of the child's immune competence, etc.) are not performed routinely and are indicated in selected cases when clear indications exist.

Empirical treatment of postnasal drip, GERD, or asthma assuming them as the cause of chronic cough is not recommended in children. According to the CHEST protocol, in children where chronic cough is not linked to triggering

factors (such as feeding) or other associated conditions, treatment should begin with a two-week course of antibiotics targeting the most common bacteria causing respiratory infections in children (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*). If symptoms resolve after this treatment, it also serves as a diagnostic confirmation of prolonged bacterial bronchitis. If the cough persists, extending the therapy for another 2 weeks is recommended. If the cough continues or is associated with triggering factors, it's an indication for further investigations.

## Conclusion

Chronic cough can be a symptom of various conditions. In the differential diagnosis for adults, the most common considerations include asthma, chronic obstructive pulmonary disease, bronchiectasis, interstitial lung disease, lung malignancy, non-asthmatic eosinophilic bronchitis, GERD, and upper airway cough syndrome. In certain cases, the etiological cause cannot be determined, leading to unexplained (idiopathic) chronic cough. When treating the underlying cause does not yield satisfactory results or when dealing with idiopathic cough, treatment focuses on neuromodulatory therapy (medication/upper laryngeal nerve block) and techniques for breathing and voice production.

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