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## Authors:

**Samuel H.F. Lam, MD, RDMS,** FACEP, Department of Emergency Medicine, Advocate Christ Medical Center, Oak Lawn, IL.

**Conal Roche, MD,** Department of Emergency Medicine, John H. Stroger, Jr. Hospital of Cook County, Chicago, IL.

## Peer Reviewer:

**John Sarko, MD,** Maricopa Medical Center, Assistant Professor, Emergency Medicine, University of Arizona–Phoenix Medical School, Phoenix, AZ.

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## Evaluation and Management of Coughs and Hiccups

Coughs and hiccups are common emergency department complaints. While the majority of their causes are benign, patients with these symptoms can suffer from significant distress and impaired quality of life. Most patients with these symptoms can be effectively managed by understanding the pathophysiology and differential diagnosis of these symptoms and by using evidence-based therapy. It is important for the physician to be aware of the emergent conditions that may present with these seemingly benign complaints.

### Cough

Cough is one of the most common chief complaints in the emergency department.<sup>1-3</sup> Cough is categorized as acute if it lasts less than three weeks, subacute if it lasts three to eight weeks, and chronic if it lasts more than eight weeks. Most coughing episodes are acute, but in nonsmokers, there is about a 12-14% incidence of cough lasting longer than three weeks, and the incidence of chronic cough is about 1%.<sup>4</sup> Illnesses that produce cough impair the quality of life and are responsible for over 20 million lost days of work in the United States each year.<sup>5-6</sup>

### Pathophysiology

A cough may be either a pure reflex or a volitional response. Laryngeal, or reflex cough, is often triggered by aspiration, with minimal associated inspiration. Tracheobronchial cough is initiated by receptors distal to the larynx and may occur voluntarily or by a reflex arc. Coughing is obviously protective, preventing aspiration and enhancing ciliary action and debris clearance.

Afferent receptors for the “cough pathway” are located throughout the upper and larger airways. Afferent arcs are mediated by the vagus nerve. In the proximal airways, the afferent receptors are predominantly mechanoreceptors that shift primarily to chemoreceptors in the distal airways. In some individuals with variant vagus nerve innervation to the tympanic membrane, cough response can be triggered by stimulation to the external ear canal. The central and brainstem cough centers are subject to extensive and poorly understood modulation from other respiratory reflex arcs, sleep state, and voluntary initiation and suppression. The efferent pathway initiates laryngeal and respiratory muscles, as well as reflexive pelvic sphincters.

Causes of cough are often divided into upper and lower airway sources, but research has shown similarly elevated levels of inflammatory markers in the lower airways in most conditions, leading to a more unified airway theory.<sup>7</sup>

Pathologic states that potentially result in chronic cough may work by increased airway receptor exposure to stimulating tachykinins, upregulation or sensitization of receptors, or by central modulation of the reflex arc. More recently in the pulmonary literature, it has been suggested that, rather than fitting chronic cough into established diseases, it should be defined as a separate diagnosis of cough hypersensitivity syndrome.<sup>8</sup>

## Executive Summary

- The most common causes for chronic cough in non-smoking patients not taking ACE inhibitors are upper airway cough syndrome, asthma, or gastroesophageal reflux disease.
- The evaluation of subacute cough should include consideration for pertussis.
- Cough suppressants have limited effectiveness.
- Chlorpromazine is the only FDA-approved medication to treat intractable or persistent hiccups.

## Etiology and Differential Diagnosis

### Cough as the Chief Complaint in Life-threatening Diagnoses.

Coughs are typically found in patients with tracheobronchial infections, such as pneumonia, bronchial inflammation, and chronic obstructive pulmonary disease (COPD) exacerbations. A potentially life-threatening condition, pulmonary embolism (PE) is an established mimic of community-acquired pneumonia.<sup>9,10</sup> Cough was also identified as an independent predictor of delay in diagnosis of PE in emergency department patients.<sup>11</sup> In a large 2008 retrospective review, cough was present in 12–43% of elderly patients with PE.<sup>12</sup> In addition, PE has been shown repeatedly to be present in at least 20% of patients with atypical presentations of COPD exacerbation.<sup>13</sup> Therefore, the presence of cough and even sputum production does not rule out the diagnosis of PE, especially in an older population.<sup>10</sup> This same level of caution should apply to patients known to have increased risk for thromboembolic disease when cough is not explained by infectious or post-infectious causes.<sup>14</sup>

Experienced clinicians are aware that cough can be associated with heart failure (HF).<sup>15</sup> In patients who present with persistent non-productive cough, HF should be considered in the context of suggestive findings on history and physical exam.

Significant correlation has been found between chronic cough and myocardial infarction (MI).<sup>16</sup> In another study, 15% of patients who subsequently were found to have anterior MI complained of cough in

addition to their chest pain. Patients with inferior and lateral MI were significantly less likely to have cough (3–6% incidence).<sup>17</sup> Cough is also commonly seen with development of cardiac shock and pulmonary edema in the infarcting patient.

**Acute Cough.** Acute cough is commonly caused by upper respiratory tract infection (sinusitis, rhinitis, pharyngitis, laryngitis), lower respiratory tract infections (bronchitis, pneumonia), pertussis, allergic reactions, chemical or toxic exposure, as well as exacerbation of chronic conditions such as asthma, COPD, or interstitial lung disease.

**Subacute Cough.** Subacute cough is most commonly attributed to postinfectious etiology. Postinfectious cough is thought to be due to excessive inflammatory and hypersecretory changes to the upper and lower airways, along with cough receptor hypersensitivity after a viral infection.<sup>18</sup>

**Chronic Cough.** In a nonsmoking, immunocompetent patient with chronic cough, with no apparent infectious etiology, and not taking angiotensin-converting enzyme inhibitors (ACEI), greater than 90% will be attributed to upper airway cough syndrome, asthma, or gastroesophageal reflux disease, in this order of prevalence.<sup>2,19,20</sup> Many patients have more than one process involved, further complicating evaluation.

**Upper Airway Cough Syndrome (UACS).** UACS is the most common cause of chronic cough and is implicated in up to 85% of chronic cough in nonsmokers.<sup>20,21</sup> The diagnosis encompasses post-nasal drip syndrome and other

**Table 1:** Conditions Encompassed by Upper Airway Cough Syndrome (UACS)

- Post-nasal drip syndrome
- Acute bacterial sinusitis
- Allergic fungal sinusitis
- Allergic rhinitis
- Nonallergic rhinitis with eosinophilia (NARES)
- Occupational rhinitis
- Postinfectious rhinitis
- Rhinitis due to anatomic abnormalities
- Rhinitis due to physical or chemical irritants
- Rhinitis medicamentosa (rebound rhinitis after use of nasal decongestants)
- Rhinitis of pregnancy
- Vasomotor rhinitis

common causes of rhinitis. (See Table 1.) The most commonly proposed mechanism involves draining nasal or sinus secretions into the hypopharynx and larynx causing recurrent irritation and stimulation of cough receptors.<sup>22</sup> There is also evidence that patients diagnosed with UACS have a hypersensitive cough reflex.<sup>23</sup> Patients with UACS typically present with a globus sensation, nasal secretions, or frequent throat clearing. However, absence of these symptoms does not necessarily exclude the diagnosis. Physical exam findings might include a visible draining trail of mucous or clear secretion in the posterior oropharynx, or cobblestoning and inflammation to the posterior pharyngeal mucosa.

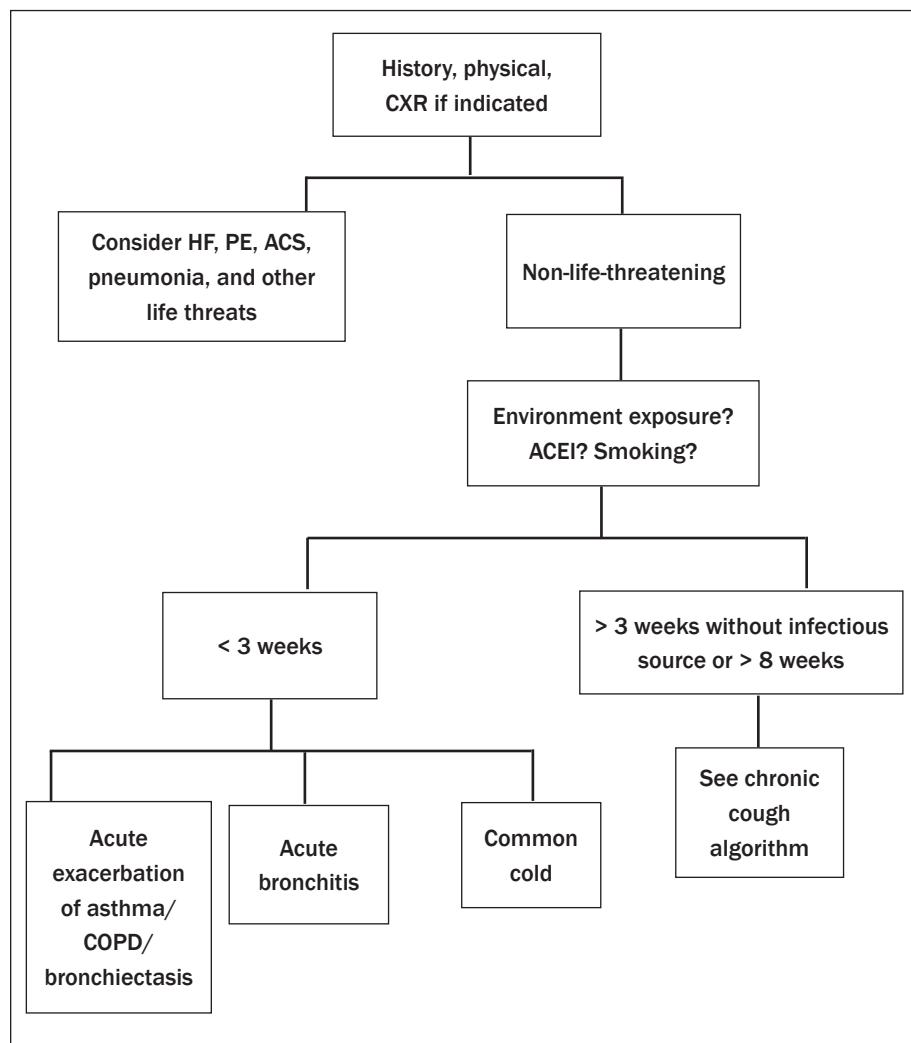
**Asthma and Non-Asthmatic Eosinophilic Bronchitis (NAEB).** After UACS, asthma is the second most common cause of chronic cough in adults, affecting 24-29% of patients in the outpatient setting.<sup>24</sup> Many of these patients will present with typical wheezing and asthma symptoms. In up to 57% of asthma cases, cough may be the only presenting complaint.<sup>25,26</sup> This cough-variant asthma may present without the expected physical exam finding of wheezing, but will invariably respond to inhaled bronchodilators.

Patients with NAEB have eosinophilic airway inflammation (like asthma) but (unlike asthma) lack airway hyperresponsiveness.<sup>27</sup> Bronchodilator therapy is typically ineffective, but they do respond to treatment with oral and inhaled corticosteroids. Diagnosis of NAEB is more suitably left to specialists. Nevertheless, it can be appropriate to initiate empiric therapy with inhaled corticosteroids in the emergency department so that an assessment of effectiveness is possible when the patient sees the specialist after discharge.

**Gastroesophageal Reflux Disease (GERD).** GERD is commonly thought to cause cough by micro-aspiration. However, numerous studies have now demonstrated an esophageal-tracheobronchial initiation of the cough reflex, elicited by lowered pH in the distal esophagus.<sup>28</sup>

GERD has been considered a common cause of chronic cough, but recent literature suggests that this is rarely an isolated cause of chronic cough.<sup>29,30</sup> Cough caused by reflux disease was believed to be present without classic reflux symptoms up to 75% of the time.<sup>30</sup> This was largely derived from a study of coughing patients who were questioned about typical GERD symptoms after empiric therapy for GERD led to improvement in cough.<sup>28</sup> A Cochrane review in 2011 left significant doubt regarding the validity of this assumption, although significant improvement in cough scores was noted after two to three months of empiric therapy with proton pump

**Figure 1: Acute Cough**



inhibitors compared with placebo.<sup>31</sup>

### Diagnostic Approach to the Coughing Patient

**Acute Cough.**<sup>32,33</sup> (See Figure 1.) Evaluation of acute cough should focus on diagnosis of an upper or lower respiratory infection, an exacerbation of a chronic respiratory condition, environmental or ACEI exposure, and whether the presentation could represent atypical HF, acute coronary syndrome (ACS), or PE presentation.

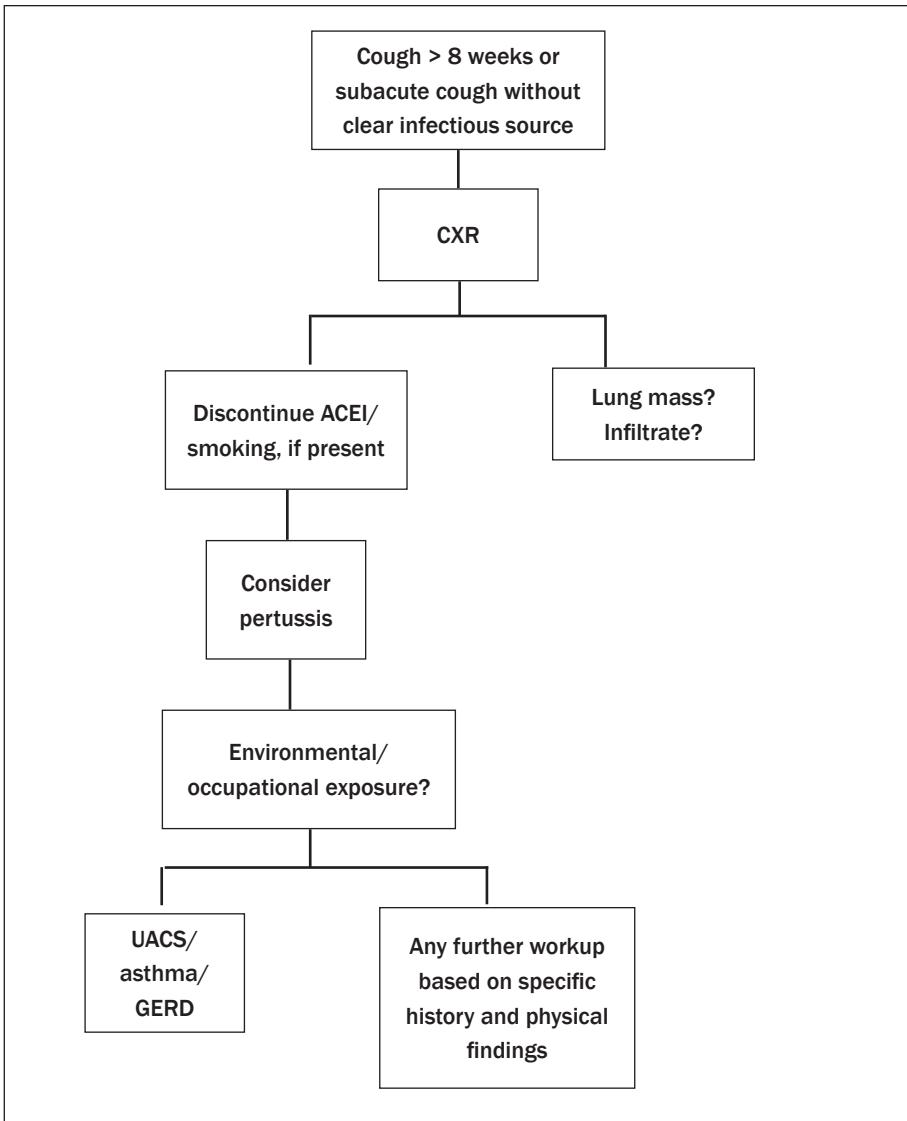
Acute bronchitis is one of the most common emergency department diagnoses provided for the coughing patient, but is thought to be overused.<sup>34</sup> The diagnosis of acute bronchitis should only be considered in a patient with cough less than three weeks, in the absence of exacerbation of chronic reactive airway

disease or nasal and upper respiratory tract symptoms more consistent with the common cold, and without evidence for pneumonia on chest radiography.<sup>34</sup>

**Subacute Cough.** Similar to acute cough evaluation, subacute cough assessment should focus on identifying post-infectious or ongoing infectious sources. Suspicion for pertussis and post-viral bacterial pneumonia should be higher in these patients. If no infectious source is apparent, these patients should be evaluated as chronic cough patients.

**Chronic Cough.**<sup>24,29,33,35</sup> (See Figure 2.) Patients presenting with chronic cough should be asked about risk factors and symptoms that might suggest the presence of HIV/AIDS, tuberculosis, cancer, and any other immunocompromised status. It is appropriate to obtain a chest

**Figure 2: Chronic Cough**



radiograph, primarily to assess for radiopaque foreign body, bronchogenic carcinoma, or mediastinal mass.

### Environmental and Occupational Causes

Current data suggest that up to one in six cases of adult asthma and chronic cough can be attributed to occupational exposure.<sup>36,37</sup> Along with questions about smoking and ACEI use, it is reasonable to screen patients with chronic cough for occupational exposures. Questions about co-workers with similar symptoms, whether there is improvement of complaints on the weekend or vacation, or if the patient can recall a sentinel event (spill, explosion), are all appropriate in the evaluation.

At-risk groups include mine

workers, farmers, painters, cleaners, bakers, and lumber industry workers, among others exposed to high levels of aerosolized substances.<sup>38</sup> The most common agents found to contribute to occupational chronic cough and asthma symptoms are: adhesives, metals, resins, flour and grain dust, latex, animals, aldehydes, and wood dust.<sup>36</sup> Farming is associated with numerous respiratory hazards and results most commonly in asthma and rhinitis. Exposure to wet winter conditions and high mold counts in stored crops can lead to fungal pneumonias and hypersensitivity syndromes. Several severe acute cough syndromes are also associated with high nitrite gas or organic dust exposure.<sup>39</sup> Symptom monitoring of 9/11 World Trade Center

responders suggests a 12-fold rate of chronic cough and bronchitis symptoms in exposed individuals.<sup>40</sup>

Patients should be informed of the risks of continued exposure to inciting toxins or triggers and referred to an occupational medicine or pulmonary clinic if available. Work restriction, personal protective measures, or appropriate trigger avoidance should be suggested.

### Evaluation for Pertussis

The presence of prolonged cough and upper respiratory infectious symptoms should raise suspicion for pertussis. Studies have shown up to 20% of urban adult patients presenting for greater than two weeks of cough have positive pertussis antibody on testing.<sup>41,42</sup> Paroxysmal cough, inspiratory whoop, or post-tussive emesis is less likely to be present in a previously vaccinated population.

Microbial culture has been the gold standard to diagnose pertussis, but may miss more than 50% of cases (sensitivity 12-60%), especially when symptoms have been present for two weeks or more. Polymerase chain reaction (PCR) is much more sensitive (70-99%), but may return up to 14% false positives. Direct fluorescent antibody (DFA) testing gives results within minutes, but has highly variable sensitivity and specificity, and is not recommended by the Centers for Disease Control and Prevention. In general, if the patient presents in the first three weeks of disease, nasopharyngeal swabs should be sent for PCR or DFA, depending on the individual lab, along with microbial culture. If the patient presents after three weeks, serologic testing may be more appropriate, as the nasopharyngeal swabs become even less sensitive at this point. However, if the clinician has high pre-test suspicion for pertussis based on the presence of classic symptoms or known exposure in an unvaccinated individual, treatment should be initiated regardless of testing results due to limited sensitivity in all of the available tests.<sup>43</sup> Furthermore, these tests should not be used to screen patients in whom

there is very low or no suspicion for pertussis, as this will result in high false-positive rates and unnecessary antibiotic use.

Patients should be isolated from unvaccinated or under-vaccinated individuals, especially infants, at least until 5-7 days of therapy are completed, but ideally for four weeks. Therapy will not decrease the duration of symptoms once patients have reached a paroxysmal cough stage, but will decrease the rate of transmission.<sup>43</sup>

## Management of Chronic Cough

**ACEI Use and Smoking.** Studies have shown that cough is present in up to 10-12% of patients taking ACEIs. Patients with chronic cough and ACEI use for less than one year should have them discontinued, preferably in conjunction with their primary physicians.<sup>33,44</sup> ACEI-induced cough should be expected to resolve from two days to two weeks after cessation, but may take as long as four weeks to see improvement.<sup>44</sup>

Smokers should be offered counseling for quitting and should expect improvement in coughing within four weeks after smoking cessation.<sup>33</sup>

**UACS, Asthma, and GERD.** (See Table 2.) Studies have shown that patients' descriptions of duration of symptoms, quality of cough, and sputum production are unreliable in establishing an eventual diagnosis.<sup>45</sup> Therefore, these conditions are now defined by a response to therapy, rather than a classic constellation of symptoms. If one diagnosis appears most likely based on brief questioning, it is appropriate to treat this etiology first. Otherwise, therapy should be directed to each cause in order of prevalence.

**UACS.** In the undifferentiated patient, initial treatment should be directed at this potential cause. Therapy should involve a combination of a first-generation antihistamine and a decongestant.<sup>46</sup> A minimum of two weeks' therapy is recommended, although complete symptom resolution might not be seen for several weeks or months.<sup>33</sup>

**Table 2:** Treatment Choices for Undifferentiated Chronic Cough

Condition	Medication	Dosage
UACS	First-generation antihistamines	Chlorpheniramine 4 mg PO every 4-6 hours, diphenhydramine 25- 50 mg PO every 4-6 hours
	Decongestant	Pseudoephedrine 60 mg PO every 4-6 hours
Asthma	B2-agonist inhaler	Albuterol MDI 2 puffs as needed
	Steroid inhaler	Beclomethasone MDI 2 sprays (80 mcg/spray) once daily
GERD	Behavioral modification	Avoid common dietary triggers, large meals, meals before bed
	Proton pump inhibitor	Omeprazole 40 mg PO once daily
	Prokinetic agent	Metoclopramide 10 mg PO 3 times a day

**Table 3:** Conditions Where Evidence Supports Antibiotics in the Coughing Patient<sup>46</sup>

Evidence for Antibiotics Use	No Improved Outcomes with Antibiotics
<ul style="list-style-type: none"> <li>Pneumonia</li> <li>COPD exacerbation with fever or purulent sputum character<sup>61,62</sup></li> <li>Bacterial sinusitis</li> <li><i>Bordetella pertussis</i> infection</li> </ul>	<ul style="list-style-type: none"> <li>Common cold</li> <li>Acute bronchitis</li> <li>Acute or chronic bronchitis in smokers without severe features</li> <li>Environmental exposures</li> </ul>

**Table 4:** Choosing Suppressive Therapy<sup>63</sup>

Medication	Acute cough/URI	Subacute/chronic cough
Dextromethorphan	Mixed, suggest benefit	Benefit in chronic bronchitis/COPD*
Codeine	Mixed, suggest no benefit	Mixed, suggest benefit
Guaifenesin	Mixed, suggest benefit	Mixed, suggest benefit
Inhaled ipratropium bromide	Benefit in URI	Benefit in COPD

\*small sample (i.e., N ≤ 15)

**Asthma.** In a patient who has failed a trial of antihistamines and a decongestant, it is appropriate to initiate a trial of inhaled albuterol in the emergency department, even in the absence of wheeze or prolonged expiratory respiration on exam. If the patient has improvement of symptoms, he or she may be discharged with an inhaled beta-agonist and inhaled corticosteroids with the

presumptive diagnosis of cough-variant asthma and a referral back to the primary care physician or a specialist for follow-up and more extensive testing as needed.<sup>24,26</sup> Even with normal spirometry and hyperresponsiveness testing, current recommendations allow for exclusion of cough-variant asthma as a source of chronic cough only after a trial of typical therapy has failed.<sup>26</sup>

**Table 5:** Etiology of Hiccups

<b>Central Nervous System Disorders</b>	
Ischemic/ hemorrhagic stroke	General anesthesia
Arteriovenous malformation	Intubation (stimulation of glottis)
Temporal arteritis	Neck extension (stretching of phrenic nerve roots)
Encephalitis	Traction on viscera
Meningitis	
Brain abscess	
Neurosyphilis	
Intracranial neoplasms	
Brainstem neoplasms	
Multiple sclerosis	
Hydrocephalus	
Syringomyelia	
Head trauma	
<b>Cardiovascular Disorders</b>	
Myocardial infarction	
Pericarditis	
Abdominal aortic aneurysm	
<b>Gastrointestinal Disorders</b>	
Aerophagia	
Gastric distension	
Esophageal distension	
Esophagitis	
Gastritis	
Hepatitis	
Inflammatory bowel disease	
Pancreatitis	
Peptic ulcer disease	
Pancreatic cancer	
Gastric carcinoma	
Abdominal abscess	
Gallbladder disease	
Peritonitis	
<b>Medications</b>	
Alpha methyldopa	
Steroids	
Benzodiazepines	
Short-acting barbiturates	
Chemotherapy agents	
Post-operative	
Gastric distension	
<b>Psychogenic</b>	
Stress	
Excitement	
Conversion reaction	
Malingering	
<b>Thoracic Disorders</b>	
Empyema	
Pneumonia	
Pleuritis	
Asthma	
Bronchitis	
Aortic aneurysm	
Mediastinitis	
Chest trauma	
Mediastinal and lung tumors	
Thoracic adenopathy secondary to infection/neoplasm	
<b>Toxic-metabolic</b>	
Alcohol	
Uremia	
Hyperglycemia	
Hyponatremia	
Hypocalcemia	
Hypocapnia	
<b>Vagus and Phrenic Nerve Irritation</b>	
Goiter	
Pharyngitis	
Laryngitis	
Foreign body irritation of tympanic membrane	
Neck cyst or tumor	

Adapted from: Lembo AJ. Overview of hiccups. UptoDate. [www.uptodate.com](http://www.uptodate.com). Accessed 4/7/2012.

**GERD.** Empiric treatment in the absence of typical GERD symptoms should not be instituted unless the patient has already failed an adequate trial of therapy for UACS and asthma. It is reasonable to suggest common lifestyle modifications that have been shown to improve

reflux symptoms, while initiating therapy for UACS or asthma.<sup>30</sup> If medical therapy is initiated from the emergency department, a proton pump inhibitor with or without a prokinetic agent is preferred.<sup>30,47,48</sup> Treatment of up to 2-3 months might be necessary for effectiveness

to be seen and responsiveness determined. However, the benefit of such an approach has been called into question by two recent publications.<sup>49,50</sup>

## Role for Antibiotics in the Coughing Patient

Evidence supports antibiotic treatment for pneumonia, COPD exacerbation, and pertussis infections. (See Table 3.) Severe cases of acute sinusitis and sinusitis with symptoms lasting longer than a week may be assumed to be bacterial, and antibiotic therapy is often recommended. Severe sinusitis is characterized by high fever, exquisite tenderness to palpation of sinuses, or overlying cellulitis, in addition to the usual symptoms of nasal discharge, congestion, and sinus pain. Most other cases of sinusitis are due to viral sources that will likely resolve without antibiotic therapy.<sup>51</sup>

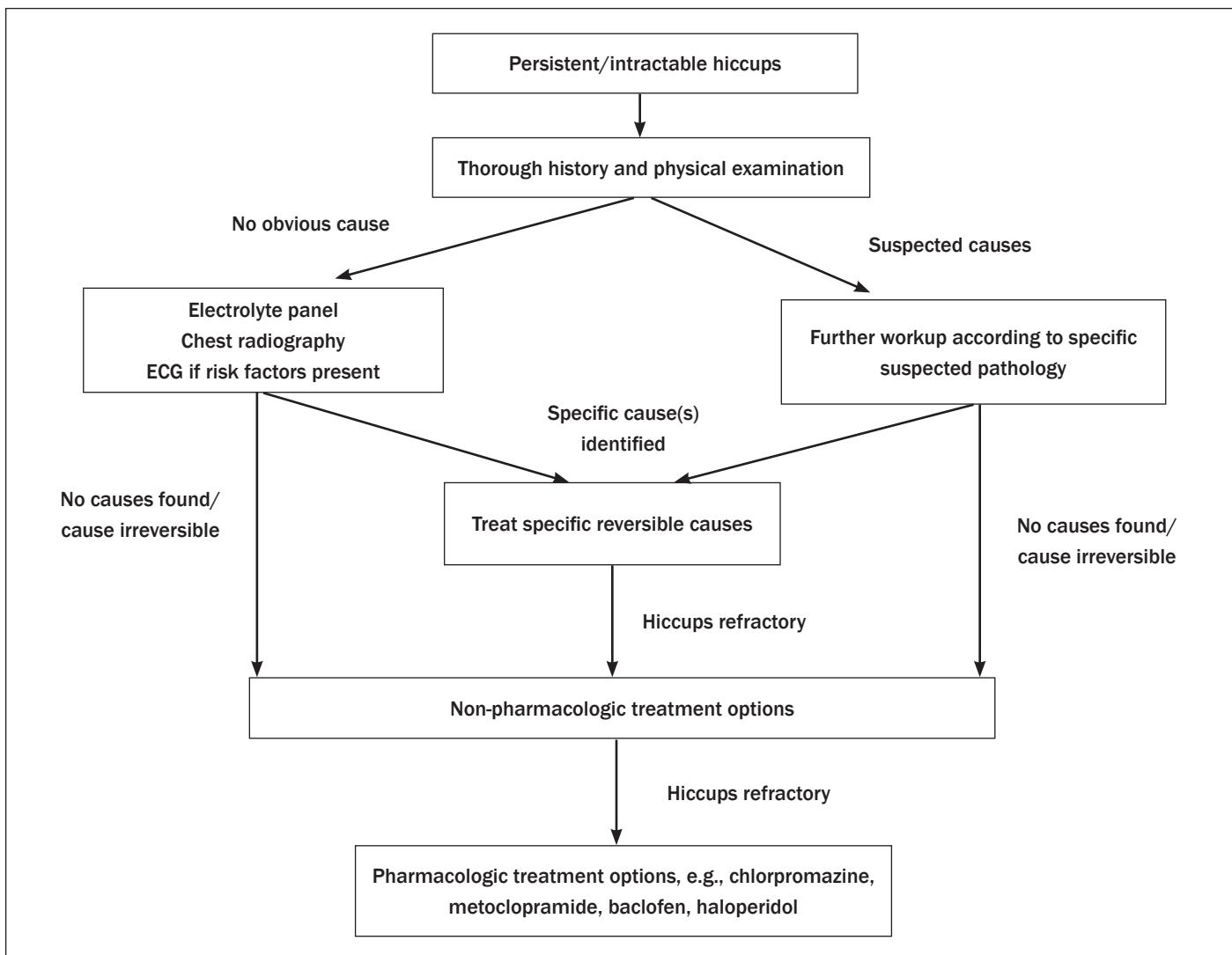
Acute bronchitis is a common diagnosis in the emergency department and is often associated with antibiotic prescription, contrary to recommendations of published guidelines.<sup>34,52,53</sup> In a 2012 study, 74% of emergency department patients with a diagnosis of acute bronchitis were prescribed antibiotics, 77% of those being broad spectrum.<sup>54</sup>

Physicians were more likely to prescribe antibiotics if they thought the patient was expecting them. The practice of delayed antibiotic prescription has been suggested as a way to decrease unnecessary antibiotic use while preserving satisfaction scores. A Cochrane review in 2010 determined that there was little evidence to suggest improved patient satisfaction with delayed antibiotic prescribing compared with having the difficult conversation up front.<sup>55</sup>

## Role for Cough Suppressants

Despite their widespread use, studies on the effectiveness of various cough suppressants are surprisingly scant and often contradictory. (See Table 4.) A recent Cochrane review found no good evidence for or against the effectiveness of

**Figure 3:** Diagnostic Approach to Hiccups in the Emergency Department



over-the-counter remedies in adults with acute cough.<sup>56</sup>

Opioids are believed to suppress cough via their action on the central nervous system. Codeine is a commonly prescribed drug in this class, yet evidence on its effectiveness is limited at best.<sup>57-60</sup> Hydrocodone is recommended for cancer-related cough, but its use in cough of other etiologies is mostly inferred. Dextromethorphan has a more favorable side-effect profile, although clinical studies have yielded mixed results. More recently, slow-release morphine was found to be effective in patients with chronic cough in a double-blind, crossover, placebo-controlled trial.<sup>61</sup>

In terms of peripherally acting medications, inhaled ipratropium seems to be useful in suppressing

acute and chronic cough in small studies. Guaifenesin has also been found to be generally effective. In a recent study, the addition of benzonatate to guaifenesin in patients with viral cough resulted in improved cough suppression, the first new evidence on its effectiveness in more than half a century.<sup>62</sup>

### Disposition

Patients with cough may be discharged home from the emergency department if no serious or life-threatening pathology is found. Further outpatient workup, if indicated, should be coordinated with the patients' primary physicians or referral specialists.

### Hiccups

A hiccup, also known as a

hiccup or singultus, is due to sudden inspiration followed by abrupt closure of the glottis (Latin singult = a gasp or a sob). Hiccups are more common in children than adults, more common in adult men than in women, and more common in those with co-morbid conditions.<sup>64,65</sup> While hiccups are often benign and self-limiting in most individuals, they can be debilitating and cause significant distress if prolonged. Hiccups are termed bouts if they last for less than 48 hours, persistent if they last for more than 48 hours, and intractable if they last for more than a month.

### Pathophysiology

Hiccups are caused by involuntary, rhythmic contractions of the diaphragm and other accessory respiratory muscles. Their function is

**Table 6:** Non-pharmacologic Treatment Options for Persistent or Intractable Hiccups

• Biting on lemon
• Breath-holding/breathing into paper bag
• Direct stimulation of nasopharynx or uvula with cotton swab/catheter
• Drinking from the opposite side of the glass
• Fright
• Ice water gargle
• Noxious odors (inhaling ammonia)
• Pulling knee to chest
• Swallowing granulated sugar/peanut butter
• Tongue traction
• Vagal maneuver (Valsalva, pressing on eyeballs, carotid sinus massage)

**Table 7:** Common Drug Treatment Options for Persistent or Intractable Hiccups

Drug Name	Initial Dose	Maintenance Dose
Chlorpromazine (Thorazine®)	25-50 mg IV/IM	25-50 mg PO three to four times a day
Baclofen (Lioresal®)	10 mg PO	10-20 mg PO three times a day
Metoclopramide (Reglan®)	10 mg IV/IM	10-20 mg PO three to four times a day
Haloperidol (Haldol®)	2-5 mg IM	1-4 mg PO three times a day
Gabapentin (Neurontin®)	100 mg PO	100-400 mg PO three times a day
Valproic acid (Depakote®)	15 mg/kg PO	15 mg/kg/day PO divided two to three times a day. Increase by 250 mg every 2 weeks until hiccough cease or side effects develop
Nifedipine (Procardia®, Adalat®)	10-20 mg PO	10-20 mg PO three to four times a day

unknown, and the exact neurologic pathway has yet to be elucidated. Nevertheless, they were thought to be mediated by a reflex arc with involvement of the central nervous system, the vagus nerve, and the phrenic nerve. A “hiccup center” is postulated to be located in the brainstem or the spinal cord, receiving afferent input from the vagus nerve, the phrenic nerve, and the sympathetic chain. Efferent outputs are transmitted mostly via the phrenic nerve. Multiple neuroreceptors (dopamine, serotonin, opioid, gamma-aminobutyric acid [GABA], and calcium channels) are hypothesized to be involved. Stimulation or pathology anywhere along the reflex

arc can result in hiccups.

### Etiology and Differential Diagnosis

Gastric distension from food, carbonated beverage, or aerophagia is a common cause of benign, self-limiting hiccups. Persistent hiccups are usually due to injury or irritation to the central nervous system, the vagus nerve, or the phrenic nerve. Since the vagus and phrenic nerves innervate or course near multiple head, neck, thoracic, and abdominal organs and structures, the differential diagnosis can be extensive. In addition, hiccups can be psychogenic, metabolic, or pharmacologic in etiology. (See Table 5.)

### Diagnostic Approach in the Emergency Department

Patients with hiccups should be asked about onset, severity, and duration of symptoms, modifying factors, recent trauma or surgery, co-morbid conditions, alcohol and illicit drug use, and current medications. A concise review of systems may help uncover unsuspected causes. Associated neurologic, cardiac, respiratory, and gastrointestinal symptoms should be specifically sought. In general, hiccups that persist during sleep suggest an organic cause, while hiccups that resolve during sleep suggest a psychogenic cause, although this distinction is not absolute.

A careful physical examination should be performed in search of an underlying etiology. In particular, one should look for signs of potentially life-threatening conditions such as central nervous system pathology, myocardial injury, vascular dissection, acute surgical abdomen, and malignancy. The head and neck should be examined carefully to look for signs of trauma, infection, goiter, and other masses. An otoscopic exam should be diligently performed, since a rare but easily treatable cause of hiccups is a foreign body (usually hair) on the tympanic membrane stimulating the auricular branch of the vagus nerve.

An electrolyte and renal function panel can detect causes such as uremia, hypocalcemia, and hyponatremia. (See Figure 3.) Chest radiography may help identify intrathoracic pathology. A screening electrocardiogram (ECG) is prudent in patients with risk factors or significant co-morbidities for ischemic heart disease, since there have been case reports of hiccups as a presenting symptom in patients with myocardial infarction<sup>66</sup> or ischemia.<sup>67,68</sup>

### Management

Specific reversible causes should be treated when found. The following pertains to management of idiopathic or unrelenting cases of hiccups.

Many of the non-pharmacologic

treatments suggested by various authors are based on stimulation of the vagus nerve or disruption of the normal respiratory cycle in the hope of interrupting the hiccup reflex arc. (See Table 6.) However, most of them have not been tested by rigorous scientific trials, and no one method seems to be more effective than others.

A myriad of pharmacologic agents have been reported to be effective in treatment of hiccups, lending support to the theory that multiple neuroreceptor types are involved in the postulated hiccup reflex arc. Chlorpromazine, a phenothiazine antipsychotic, is the only medication approved by U.S. Food and Drug Administration (FDA) for treatment of hiccups based on small case series. It is postulated to work by antagonism of central dopamine neuromodulators. Haloperidol (non-FDA approved) likely has a similar mechanism of action.

Other off-label drugs reported to be effective hiccup treatment in case series consisting of more than 10 patients include gabapentin, baclofen, and metoclopramide.<sup>69-72</sup> Valproic acid and nifedipine were also used to treat hiccup with some success in case series of five and seven patients, respectively.<sup>73,74</sup> In addition, there have been numerous case reports attesting to successful hiccup therapy with various classes of medications such as anticonvulsants (phenytoin, carbamazepine), antidepressants (amitriptyline, sertraline), central nervous system agents (methylphenidate, amantadine, olanzapine), steroids (dexamethasone), benzodiazepines (midazolam), and antiarrhythmics (quinidine, lidocaine). To date there has not been any published clinical trial comparing the effectiveness of different hiccup medications. Hence, the choice of pharmacologic therapy is somewhat empirical and clinician-dependent. Most drug treatments are prescribed for 7-10 days and may be discontinued upon cessation of symptoms. (See Table 7.) Potentially serious side effects include hypotension, arrhythmias, glaucoma, and delirium.

For refractory or debilitating hiccups, more invasive treatment options such as phrenic nerve block, controlled phrenic and vagal nerve stimulation, and phrenic nerve crushing via surgery can be considered in consultation with the appropriate specialists. Alternative medicine treatments such as hypnosis and acupuncture have also been found to be effective in some cases.<sup>75-78</sup>

## Disposition

Generally, patients with hiccups can be discharged home if no significant pathology is found during an emergency department screening examination.

In cases of failed non-pharmacologic treatment, medications such as chlorpromazine, haloperidol, metoclopramide, baclofen, among others, can be initiated. Well-appearing patients with negative emergency department screening examinations can be sent home on 7-10 days of outpatient therapy.

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- ## Physician CME Questions
- In the patient with undifferentiated chronic cough, treatment should initially be directed at which of the following entities?
    - chronic bronchitis
    - asthma
    - nonasthmatic eosinophilic bronchitis
    - upper airway cough syndrome (UACS)
    - gastroesophageal reflux disease (GERD)
  - Which of the following statements is true?
    - There is evidence to support the use of broad-spectrum antibiotics for acute bronchitis.
    - Emergency physicians are more likely to prescribe antibiotics if they think the patient is expecting them.
    - Dextromethorphan has been unequivocally shown to be an effective suppressant for acute URI/cough syndromes.
    - Inhaled albuterol is an effective cough suppressant in acute URI/sough syndromes.
  - Which combination of medication is most appropriate initial therapy for a patient with uncomplicated cough for more than 3 weeks without an infectious source?
    - albuterol MDI and ranitidine 150 mg PO daily
    - loratadine 10 mg PO daily and GERD reduction lifestyle changes
    - pseudoephedrine 60 mg q 6 h and albuterol MDI
    - ipratropium bromide MDI and diphenhydramine 25 mg PO q 6 h
    - diphenhydramine 25 mg PO q 6 h and pseudoephedrine 60 mg PO q 6 h
  - Which of the following statements is true?
    - ACEI-induced cough may take up to 4 weeks to resolve after withdrawal of medication.
    - A careful history of cough description is crucial in determining the initial course of therapy from the emergency department.
    - Occupational exposure is a rare cause of cough, resulting in < 5% of cases.
    - A cough is considered "chronic" when it lasts for longer than 3 weeks.
  - Which of the following is true regarding laboratory testing for pertussis?
    - Conventional sputum culture is a sensitive screen for disease.
    - Serum testing is most useful after 2-3 weeks of symptoms when antibodies have reached high levels in the blood.
    - There is no indication for testing vaccinated adults for pertussis if they are not exhibiting either post-tussive emesis or fever.
    - The purpose of antibiotics in the patient with suspected pertussis is primarily for decreased duration of symptoms, but will not decrease transmission rates.
  - Which of the following medications is approved by the U.S. Food and Drug Administration (FDA) for the treatment of hiccups?
    - metoclopramide
    - baclofen
    - gabapentin
    - chlorpromazine
    - haloperidol
  - A thorough physical exam should be performed in patients presenting with hiccups, particularly on this part(s) of the body, because it may uncover a rare but easily treatable cause due to irritation of a branch of the vagus nerve:
    - retina
    - nasal septum
    - tympanic membrane
  - Which class of medication has both been implicated in the cause of hiccups and reported in literature as an effective treatment of hiccups?
    - calcium channel blockers
    - steroids
    - barbiturates
    - beta-blockers
    - chemotherapy agents
  - A patient with a history of diabetes, hypertension, and smoking presents with persistent hiccups and dizziness. Which of the following is a reasonable emergency department screening test to look for potentially life-threatening pathology?
    - carboxyhemoglobin level
    - electrocardiogram (EKG)
    - B-type natriuretic peptide (BNP)
    - C-reactive protein (CRP)
    - urinalysis (UA)
  - Hiccups are termed "intractable" when they:
    - are unresponsive to pharmacologic treatments
    - are unresponsive to non-pharmacologic treatments
    - last for more than 48 hours
    - last for more than a month
    - last for more than 48 hours and are unresponsive to non-pharmacologic treatments

## Emergency Medicine Reports

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*Upon completion of this educational activity, participants should be able to:*

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- apply state-of-the-art diagnostic and therapeutic techniques to patients with the particular medical problems discussed in the publication;
- discuss the differential diagnosis of the particular medical problems discussed in the publication;
- explain both the likely and rare complications that may be associated with the particular medical problems discussed in the publication.

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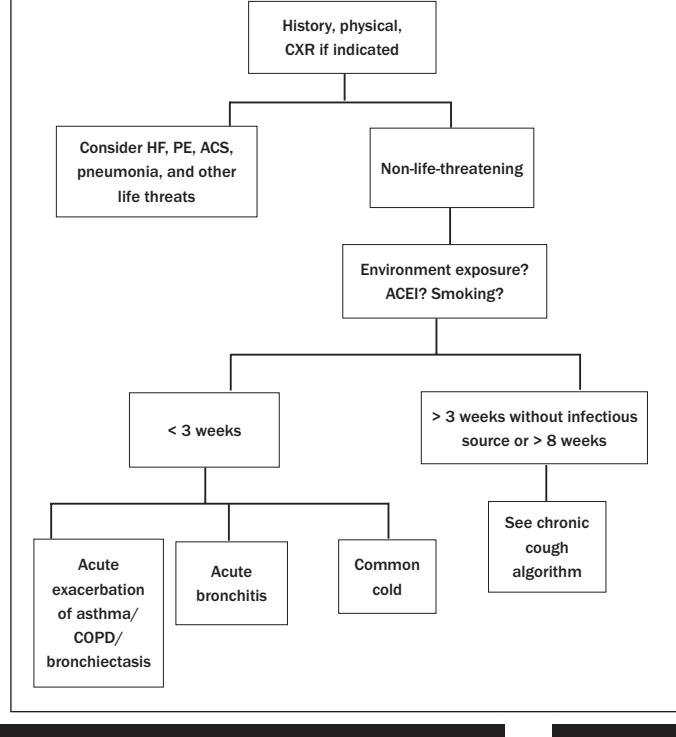
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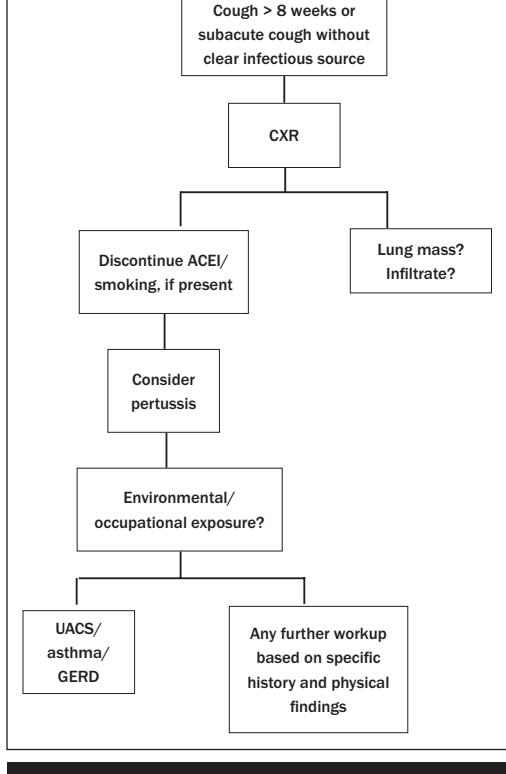
The Practical Journal for Emergency Physicians

## Evaluation and Management of Coughs and Hiccups

### Acute Cough



### Chronic Cough



### Conditions Encompassed by Upper Airway Cough Syndrome (UACS)

- Post-nasal drip syndrome
- Acute bacterial sinusitis
- Allergic fungal sinusitis
- Allergic rhinitis
- Nonallergic rhinitis with eosinophilia (NARES)
- Occupational rhinitis
- Postinfectious rhinitis
- Rhinitis due to anatomic abnormalities
- Rhinitis due to physical or chemical irritants
- Rhinitis medicamentosa (rebound rhinitis after use of nasal decongestants)
- Rhinitis of pregnancy
- Vasomotor rhinitis

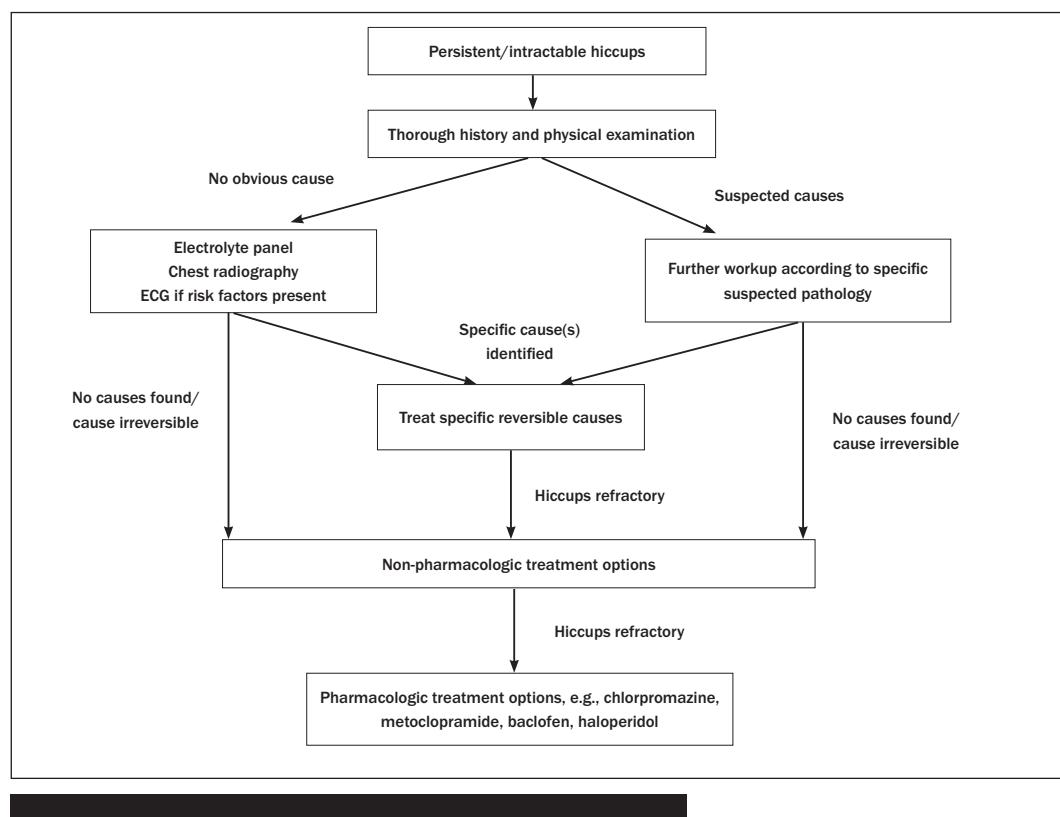
### Treatment Choices for Undifferentiated Chronic Cough

Condition	Medication	Dosage
UACS	First-generation antihistamines	Chlorpheniramine 4 mg PO every 4-6 hours, diphenhydramine 25-50 mg PO every 4-6 hours
	Decongestant	Pseudoephedrine 60 mg PO every 4-6 hours
Asthma	B2-agonist inhaler	Albuterol MDI 2 puffs as needed
	Steroid inhaler	Bclomethasone MDI 2 sprays (80 mcg/spray) once daily
GERD	Behavioral modification	Avoid common dietary triggers, large meals, meals before bed
	Proton pump inhibitor	Omeprazole 40 mg PO once daily
	Prokinetic agent	Metoclopramide 10 mg PO 3 times a day

### Conditions Where Evidence Supports Antibiotics in the Coughing Patient

Evidence for Antibiotics Use	No Improved Outcomes with Antibiotics
<ul style="list-style-type: none"> <li>• Pneumonia</li> <li>• COPD exacerbation with fever or purulent sputum character</li> <li>• Bacterial sinusitis</li> <li>• <i>Bordetella pertussis</i> infection</li> </ul>	<ul style="list-style-type: none"> <li>• Common cold</li> <li>• Acute bronchitis</li> <li>• Acute or chronic bronchitis in smokers without severe features</li> <li>• Environmental exposures</li> </ul>

# Diagnostic Approach to Hiccups in the Emergency Department



## Non-pharmacologic Treatment Options for Persistent or Intractable Hiccups

- Biting on lemon
- Breath-holding/breathing into paper bag
- Direct stimulation of nasopharynx or uvula with cotton swab/catheter
- Drinking from the opposite side of the glass
- Fright
- Ice water gargle
- Noxious odors (inhaling ammonia)
- Pulling knee to chest
- Swallowing granulated sugar/peanut butter
- Tongue traction
- Vagal maneuver (Valsalva, pressing on eyeballs, carotid sinus massage)

## Common Drug Treatment Options for Persistent or Intractable Hiccups

Drug Name	Initial Dose	Maintenance Dose
Chlorpromazine (Thorazine®)	25-50 mg IV/IM	25-50 mg PO three to four times a day
Baclofen (Lioresal®)	10 mg PO	10-20 mg PO three times a day
Metoclopramide (Reglan®)	10 mg IV/IM	10-20 mg PO three to four times a day
Haloperidol (Haldol®)	2-5 mg IM	1-4 mg PO three times a day
Gabapentin (Neurontin®)	100 mg PO	100-400 mg PO three times a day
Valproic acid (Depakote®)	15 mg/kg PO	15 mg/kg/day PO divided two to three times a day. Increase by 250 mg every 2 weeks until hiccough cease or side effects develop
Nifedipine (Procardia®, Adalat®)	10-20 mg PO	10-20 mg PO three to four times a day

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