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## The diagnosis and treatment of cough

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### Abstract (Document Summary)

It is not generally recognized that the common cold, like chronic postnasal-drip syndromes arising from a variety of rhinosinus conditions, can present as a syndrome of cough and phlegm.<sup>17,18</sup> Consequently, physicians tend too frequently to diagnose such a syndrome as bacterial bronchitis and to prescribe antibiotics.<sup>19</sup> We do not diagnose bronchitis in patients with a syndrome of cough and phlegm along with acute upper respiratory tract symptoms, and with few exceptions we do not initially prescribe antibiotic...

### Full Text (4291 words)

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COUGH is one of the most common symptoms for which patients seek medical attention from primary care physicians and pulmonologists,<sup>1</sup> probably because cough can so profoundly and adversely affect the quality of patients' lives.<sup>2</sup> In this review, we present an approach to managing cough in adults. With a systematic approach based on the guidelines we describe, it should be possible to diagnose and treat cough successfully in the great majority of cases. The cause of chronic cough can be determined in 88 to 100 percent of cases, and determination leads to specific therapies with success rates that range from 84 to 98 percent.<sup>1</sup> Because of this high degree of success, there is only a limited role for nonspecific therapy for cough, which has been reviewed comprehensively elsewhere.<sup>1</sup>

### DURATION OF COUGH

Estimating the duration of cough is the first step in narrowing the list of possible diagnoses. There is controversy about how best to define chronic cough.<sup>1</sup> We propose that cough be divided into three categories: acute, defined as lasting less than three weeks; subacute, lasting three to eight weeks; and chronic, lasting more than eight weeks. Since all types of cough are acute at the outset, it is the duration of the cough at the time of presentation that determines the spectrum of likely causes.

### ACUTE COUGH

For diagnosing the cause of acute cough, we recommend a clinical approach based on trials of empirical therapies. The physician should take a history and perform a physical examination while keeping in mind the estimated frequency of conditions. Although there have been no studies of the spectrum and frequency of causes of acute cough, clinical experience suggests that the most common causes are upper respiratory tract infections such as the common cold, acute bacterial sinusitis, pertussis in some communities, exacerbations of chronic obstructive pulmonary disease, allergic rhinitis, and rhinitis due to environmental irritants.<sup>1</sup>

Viral infections of the upper respiratory tract are the most common causes of acute cough. In the absence of any treatment, the prevalence of cough due to the common cold ranges from 83 percent within the first 48 hours of the cold to 26 percent on day 14.<sup>3</sup> Cough appears to arise from the stimulation of the cough reflex in the upper respiratory tract by postnasal drip, clearing of the throat, or both.<sup>3</sup>

The common cold is diagnosed when patients present with an acute respiratory illness characterized by symptoms and signs related primarily to the nasal passages (e.g., rhinorrhea, sneezing, nasal obstruction, and postnasal drip), with or without fever, lacrimation, and irritation of the throat, and when a chest examination is normal. In such cases, diagnostic testing is not indicated, because it has a low yield. For instance, in immunocompetent patients with these symptoms and signs, more than 97 percent of chest radiographs will be normal.<sup>4</sup>

For treating acute cough due to the common cold, we recommend medications that have been shown in randomized, double-blind, placebo-controlled studies (Table 1) to be efficacious in decreasing cough. These include dexbrompheniramine plus pseudoephedrine<sup>3</sup> and naproxen.<sup>5</sup> Although the effect on cough was not specifically assessed in a study that showed that intranasal ipratropium provided relief of rhinorrhea and sneezing due to the common cold,<sup>6</sup> the drug may be helpful for patients who cannot take or tolerate the older-generation antihistamines or naproxen. There is no convincing evidence that intranasal or systemic corticosteroids are beneficial,<sup>7,8</sup> or that zinc lozenges are consistently beneficial,<sup>9-11</sup> and the relatively nonsedating histamine H<sup>1</sup> antagonists (e.g., loratadine), either alone or combined with a decongestant, are likely to be ineffective.<sup>1,12</sup> These H<sup>1</sup> antagonists have failed to alleviate cough in patients with the common cold, probably because they have little or no anticholinergic activity and the common cold is not mediated by histamine. On the other hand, when cough is due to a histamine-mediated condition such as allergic rhinitis (Table 1), it is significantly improved by the nonsedating antihistamines.<sup>13</sup> We do not recommend pharmacologic therapy as a substitute for the avoidance of offending allergens.

The common cold is a viral rhinosinusitis<sup>14</sup> that often cannot be distinguished clinically from bacterial sinusitis.<sup>15</sup> Because viral rhinosinusitis is the more common of the two, we recommend giving antibiotics to patients with findings that are suggestive of acute sinusitis only if their symptoms fail to show progressive improvement when treated with antihistamines and decongestants and if they have at least two of the following signs and symptoms: a maxillary toothache; purulent nasal secretions; abnormal findings on transillumination of any sinus; and a history of discolored nasal discharge (Table 1). It is usually not necessary to perform imaging studies of the sinuses in order to begin antibiotic therapy.<sup>16</sup>

It is not generally recognized that the common cold, like chronic postnasal-drip syndromes arising from a variety of rhinosinus conditions, can present as a syndrome of cough and phlegm.<sup>17,18</sup> Consequently, physicians tend too frequently to diagnose such a syndrome as bacterial bronchitis and to prescribe antibiotics.<sup>19</sup> We do not diagnose bronchitis in patients with a syndrome of cough and phlegm along with acute upper respiratory tract symptoms, and with few exceptions we do not initially prescribe antibiotic therapy in these instances. We do prescribe antibiotics for patients with an exacerbation of chronic obstructive pulmonary disease (Table 1) if the acute cough is accompanied by worsening shortness of breath, wheezing, or both.<sup>20</sup> We also prescribe antibiotics for patients with acute upper respiratory tract symptoms who have had close contact with a patient with a known case of pertussis (Table 1) and for patients with coughing and vomiting suggestive of *Bordetella pertussis* infection.<sup>1</sup> In the absence of chronic obstructive pulmonary disease, the failure to diagnose bronchitis when it is present will probably not adversely affect the patient, because most acute respiratory infections are viral.<sup>21</sup>

Acute cough can be the presenting manifestation of pneumonia, left ventricular failure, asthma, or conditions that predispose patients to the aspiration of foreign matter.<sup>1,22</sup> It is especially important to have a high index of suspicion for these disorders in elderly patients, because classic signs and symptoms may be nonexistent or minimal.

#### SUBACUTE COUGH

For diagnosing the cause of subacute cough, we recommend a clinical approach based on trials of empirical therapies and limited laboratory testing. When cough is subacute and is not associated with an obvious respiratory infection, we evaluate patients in much the same way as those with chronic cough (see below). For a cough that began with an upper respiratory tract infection and has lasted for three to eight weeks, the most common conditions to consider are postinfectious cough, bacterial sinusitis, and asthma.

Postinfectious cough is defined as cough that begins with an acute respiratory tract infection that is not complicated

by pneumonia (i.e., the chest radiograph is normal) and that ultimately resolves without treatment.<sup>1</sup> It may result from postnasal drip or clearing of the throat due to rhinitis, tracheobronchitis, or both, with or without transient bronchial hyperresponsiveness. If the patient reports having a postnasal drip or frequently clears his or her throat or if mucus is seen in the oropharynx, we recommend an initial course of treatment similar to that for the common cold (Table 2). If the cough has not disappeared after one week of this therapy, we perform imaging studies of the sinuses to determine whether bacterial sinusitis is present. If these studies reveal a mucosal thickening of more than 5 mm, air-fluid levels, or opacification,<sup>23</sup> we prescribe a nasal decongestant for five days and an antibiotic for three weeks (Table 2), and then reassess the patient's condition.

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TABLE 1.

When a patient presents with wheezes, rhonchi, or crackles on physical examination, a chest radiograph should be obtained. If it is normal, we prescribe inhaled bronchodilators and corticosteroids and consider antibiotics only if we suspect a recent *B. pertussis* infection. In such cases, improvement does not mean the diagnosis is asthma, because these drugs may have alleviated the cough by increasing mucociliary clearance and decreasing the production of mucus or by decreasing transient bronchial hyperresponsiveness after a viral infection. However, cough may be the sole presenting manifestation of asthma (as in so-called cough variant asthma). This diagnosis is suggested by the presence of bronchial hyperresponsiveness (e.g., a positive result on methacholine challenge) and is confirmed only when cough resolves during asthma therapy (Table 2) and follow-up proves the chronic nature of the disease.<sup>1</sup>

If *B. pertussis* infections have recently been reported in the community, if there is a history of contact with a patient who has a known case, or if the patient presents with the characteristic but infrequently heard whoop or with coughing and vomiting, empirical therapy for this infection should be considered (Tables 1 and 2).<sup>1</sup> The later in the illness antibiotics are prescribed, the less likely it is that they will be efficacious. The laboratory diagnosis of pertussis is difficult to establish because there is usually a delay between the onset of cough and the suspicion of the disease and because there is no readily available, reliable serologic test for *B. pertussis*.<sup>24,25</sup> Cultures of nasopharyngeal secretions are usually negative after two weeks, and reliable, serologic confirmation of a recent *B. pertussis* infection requires evidence of an elevated level of antibodies against one of the various virulence factors of the organism, as revealed by an enzyme-linked immunosorbent assay.

CHRONIC COUGH

Although cough that lasts longer than eight weeks can be caused by many different diseases,<sup>26</sup> most cases are attributable to one of only a few diagnoses. Consequently, we recommend a systematic evaluation that initially assesses the likelihood of the most common causes by means of trials of empirical therapy and trials involving the avoidance of irritants and drugs, along with focused laboratory testing (e.g., chest radiography or methacholine challenge), followed by additional testing and consultation with a specialist, if necessary. The definitive diagnosis of the cause of chronic cough is then established on the basis of an observation of which specific therapy eliminates the cough. Because chronic cough can result simultaneously from more than one condition (as is the case in 18 to 93 percent of instances),<sup>1,2</sup> therapy that is partially successful should not be stopped but should instead be sequentially supplemented.

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TABLE 2.

Multiple studies<sup>1, 17, 18, 27-32</sup> have shown that in approximately 95 percent of cases in immunocompetent patients, chronic cough results from postnasal-drip syndrome from conditions of the nose and sinuses, asthma, gastroesophageal reflux disease, chronic bronchitis due to cigarette smoking or other irritants, bronchiectasis, eosinophilic bronchitis, or the use of an angiotensin-converting-enzyme inhibitor. In the remaining 5 percent of cases, chronic cough results from a variety of other diseases, such as bronchogenic carcinoma, carcinomatosis, sarcoidosis, left ventricular failure, and aspiration due to pharyngeal dysfunction. In our experience, psychogenic, or "habit," coughs are rare conditions best diagnosed by exclusion.<sup>1, 26</sup> For example, a postnasal-drip syndrome with continual clearing of the throat can be misdiagnosed as a habit cough.<sup>1</sup>

Diagnosis and Clinical Evaluation

Physicians can narrow the list of possible diagnoses by reviewing the patient's history and physical examination and focusing on the most common causes of chronic cough (i.e., postnasal-drip syndromes, asthma, and gastroesophageal reflux disease); obtaining a chest radiograph; and determining whether the symptoms conform to the clinical profile that is usually associated with a diagnosis of postnasal-drip syndrome, asthma, gastroesophageal reflux disease, or eosinophilic bronchitis, alone or in combination. If the cough is productive of blood, the patient should be evaluated according to published guidelines for hemoptysis.<sup>33</sup>

If the patient has a history of smoking or of exposure to other environmental irritants or is currently being treated with an angiotensin-converting-enzyme inhibitor, the first step in the evaluation of cough becomes straightforward; elimination of the irritant or discontinuation of the drug for four weeks should be encouraged because it will reveal whether the cough is partially or entirely due to chronic bronchitis or to the angiotensin-converting-enzyme inhibitor. Cough due to these factors should substantially improve or resolve within this time (Table 3).<sup>1</sup> A comprehensive review of cough due to angiotensin-converting-enzyme inhibitors has been published elsewhere.<sup>1</sup> In the absence of exposure to irritants, a diagnosis of chronic bronchitis is untenable even if the cough is productive. The character of the cough (e.g., paroxysmal, loose and self-propagating, productive, or dry), the quality of the sound (e.g., barking, honking, or brassy), and the timing of the cough (e.g., at night or with meals) have not been shown to be diagnostically useful.<sup>18</sup>

Although a history of postnasal drip or clearing of the throat and physical findings of mucus, a cobblestone appearance to the mucosa of the oropharynx, or both suggest postnasal-drip syndrome, these symptoms and signs are not specific to this diagnosis<sup>32</sup> nor do they always appear even when this syndrome is the cause of cough. A minority of patients may have no upper respiratory symptoms or signs yet may have a favorable response to combination therapy with a first-generation H1 antagonist and a decongestant (these patients have "silent" postnasal-drip syndrome).<sup>31</sup> Although frequent heartburn and regurgitation suggest that gastroesophageal reflux disease is the cause of cough, these symptoms may be absent in up to 75 percent of cases (i.e., in patients with "silent" gastroesophageal reflux disease).<sup>34</sup>

Because cough can be the sole manifestation of asthma in up to 57 percent of cases<sup>35</sup> (i.e., with cough variant asthma or "silent" asthma) and because the clinical diagnosis of asthma is unreliable even when there is a history of wheezing and a current physical finding of wheezing,<sup>36</sup> it is inadvisable to diagnose asthma on clinical grounds alone. Although the presence of other abnormal sounds such as crackles and rhonchi suggests that testing for lower respiratory tract disease is indicated, these findings, with or without confirmatory laboratory-test results (e.g., chest radiography showing chronic interstitial pneumonia), should not be relied on exclusively in the determination of the ultimate cause of cough. A definitive diagnosis can be made only when cough responds to specific therapy.

Chest Radiography

The chest radiograph is useful for the initial ranking of possible diagnoses and for guiding trials of empirical therapies and laboratory testing.1 A normal radiograph in an immunocompetent patient, or a radiograph that shows no abnormality other than one consistent with an old and unrelated process, makes postnasal-drip syndrome, asthma, gastroesophageal reflux disease, chronic bronchitis, and eosinophilic bronchitis likely and bronchogenic carcinoma, sarcoidosis, tuberculosis, and bronchiectasis unlikely. If the chest radiograph is abnormal, the physician should next evaluate the possibility of the diseases suggested by the radiographic findings.

### The Most Common Causes

The clinical profile associated with postnasal-drip syndrome, asthma, gastroesophageal reflux disease, eosinophilic bronchitis, or some combination of these conditions is that of a nonsmoking patient with a chronic cough who is not taking an angiotensin-converting-enzyme inhibitor and has a normal or nearnormal and stable chest radiograph.

Because there is no diagnostic test for postnasaldrip syndrome and because it is the most common cause of chronic cough, the patient should be evaluated for this condition first. The outcome of specific therapy will depend on the determination of the correct cause and the choice of the correct specific therapy (Table 3).1 The differential diagnosis of postnasal-drip syndrome includes sinusitis and the following types of rhinitis, alone or in combination: nonallergic, allergic, postinfectious, vasomotor, drug-induced, and environmental-irritant-induced. If the specific therapy that is chosen fails, it does not necessarily mean that there is no postnasal-drip syndrome; cough may have failed to improve because the wrong antihistamine was given.1 The newer-generation H<sup>1</sup> antagonists do not appear to be effective when cough induced by postnasal drip is not mediated by histamine.1

Because a negative result of methacholine challenge rules out asthma as a cause of chronic cough (except soon after an exposure to toluene diisocyanate),1 we recommend that the test be routinely performed. Although its positive predictive value ranges from 60 to 88 percent,17,12,34,37 its negative predictive value is 100 percent.17,32,34,37 Cough variant asthma should be treated the same way as asthma in general.1 If cough does not improve with asthma treatment (Table 3), the result of methacholine challenge can be considered to have been falsely positive. On the other hand, if methacholine challenge is not performed and cough disappears after the administration of systemic corticosteroids, it should not be assumed on the basis of this empirical trial alone that the patient has asthma, because other inflammatory conditions (e.g., eosinophilic bronchitis and allergic rhinitis) also respond well to corticosteroids.1

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TABLE 3.

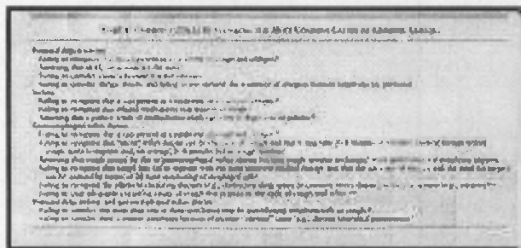
We do not routinely recommend diagnostic testing for the evaluation of patients for "silent" gastroesophageal reflux disease, for the following reasons: although 24-hour monitoring of esophageal pH is the single most sensitive and specific test, it has a negative predictive value of less than 100 percent and a positive predictive value as low as 89 percent<sup>17,32,34</sup>; 24-hour monitoring of esophageal pH is inconvenient for patients and not widely available; and there is no consensus about the best way to interpret the results obtained through such monitoring in the diagnosis of cough due to reflux disease.<sup>1,33,34</sup> Even if the attempted therapies (changes in lifestyle, acid suppression, and the addition of prokinetic drugs) do not improve cough (Table 3), it must not be assumed that gastroesophageal

reflux disease has been ruled out as the cause. The therapy may not be intensive enough or may not have been sustained long enough, or the disease may not respond to even the most intensive medical therapy; in some cases, antireflux surgery may be successful.<sup>1,38</sup> The adequacy of the regimen of medical treatment and the need for antireflux surgery can be assessed by means of esophageal pH monitoring while medical therapy continues.<sup>1,38</sup>

Eosinophilic bronchitis is a cause of chronic cough in up to 13 percent of cases.<sup>30-32,35</sup> Although an analysis of the sputum generally shows eosinophils and metachromatic cells similar to those seen in asthma, this condition is distinct from asthma because it is not associated with bronchial hyperresponsiveness.<sup>39</sup> Eosinophilic bronchitis is responsive to inhaled and especially systemic corticosteroids (Table 3).<sup>30</sup> It can be ruled out if eosinophils make up less than 3 percent of the nonsquamous cells in the induced-sputum sample as determined with the use of standard methods<sup>30,39</sup> or if cough fails to improve with empirical corticosteroid therapy.

#### PERSISTENTLY TROUBLESOME CHRONIC COUGH

Because postnasal-drip syndrome, asthma, and gastroesophageal reflux disease are the most common causes of chronic cough, the first step in managing a persistently troublesome chronic cough must be to consider the most common errors in management (Table 4). In our experience,<sup>35</sup> the failure to avoid these common pitfalls is often the reason chronic cough remains troublesome. Once potential errors in management have been addressed, additional laboratory studies (e.g., studies of sputum, modified barium esophagography, 24-hour monitoring of esophageal pH, esophagoscopy, a study of gastric emptying, high-resolution computed tomography of the chest, bronchoscopy,<sup>43</sup> or noninvasive cardiac studies) and referral to a cough specialist are indicated to assess the possibilities of intrathoracic processes (e.g., bronchiectasis,<sup>44</sup> bronchiolitis,<sup>44</sup> and left ventricular failure<sup>35</sup>) that were not suggested by the chest radiograph.



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TABLE 4.

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TABLE 1. GUIDELINES FOR TREATING THE MOST COMMON CAUSES OF A

CAUSE	THERAPEUTIC OPTIONS	COMMENT
Common cold	Dexbrompheniramine, 6 mg, plus pseudoephedrine, 120 mg, twice daily for 1 wk, or naproxen, 500-mg loading dose, then 500 mg 3 times daily for 5 days, or ipratropium (0.06%) nasal spray, 2 42- $\mu$ g sprays per nostril 3 to 4 times daily as needed for 4 days	First-generation antihistamines are not as effective as newer agents
Allergic rhinitis	Avoidance of offending allergens Loratadine, 10 mg once a day	Other options include intranasal corticosteroids and anticholinergics
Acute bacterial sinusitis	Dexbrompheniramine, 6 mg, plus pseudoephedrine, 120 mg, twice daily for 2 wk Oxymetazoline, 2 sprays twice daily for 5 days Antibiotic directed against <i>Haemophilus influenzae</i> and <i>Streptococcus pneumoniae</i>	Choice of antibiotic depends on cost, side effects, and local resistance patterns
Exacerbation of chronic obstructive pulmonary disease	Antibiotic directed against <i>H. influenzae</i> and <i>S. pneumoniae</i> for 10 days Systemic corticosteroids tapered over 2-wk period Continuous oxygen if PaO <sub>2</sub> $\leq$ 55 mm Hg or SaO <sub>2</sub> $\leq$ 88%, or if PaO <sub>2</sub> $\leq$ 59 mm Hg and there is evidence of erythrocytosis or cor pulmonale Ipratropium, 2 18- $\mu$ g puffs, plus albuterol, 2 90- $\mu$ g puffs, 4 times daily by metered-dose inhaler with spacer Cessation of smoking	Choice of antibiotic depends on local resistance patterns If treatment with methylprednisolone or prednisone is indicated, use 20 mg daily for 10 days Oxygen therapy is indicated if resting SpO <sub>2</sub> is $\leq$ 88% Smoking cessation is the most important long-term intervention
<i>Bordetella pertussis</i> infection	Erythromycin, 500 mg 4 times daily for 14 days, or (if allergic) trimethoprim-sulfamethoxazole, 160 mg-800 mg twice daily for 14 days	Given that pertussis is a highly contagious disease, treatment of contacts is also indicated Systemic corticosteroids are not indicated

\*Specific drugs and doses are mentioned when their use is supported by double-blind, randomized trials, or when they are the standard of care. PaO<sub>2</sub> is partial pressure of arterial oxygen, and SaO<sub>2</sub> is arterial oxygen saturation.

TABLE 2. GUIDELINES FOR TREATING THE MOST COMMON CAUSES OF SUBA

CAUSE	THERAPEUTIC OPTIONS	COMMENT:
Postinfection	Dexbrompheniramine plus pseudoephedrine for 1 wk, or ipratropium (0.06%) nasal spray for 1 wk Ipratropium, 4 18- $\mu$ g puffs 4 times daily by metered-dose inhaler with spacer for 1-3 wk Systemic corticosteroids tapered over period of 2-3 wk Central antitussives	In case of to com If partial If partial tia d dextro associa ic (see siveness
<i>B. pertussis</i> infection	Erythromycin for 14 days, or (if allergic) trimethoprim-sulfamethoxazole	Dose sam with <i>B.</i> the ab provok
Subacute bacterial sinusitis	Dexbrompheniramine plus pseudoephedrine for 3 wk Oxymetazoline for 5 days Antibiotic directed against <i>Haemophilus influenzae</i> and <i>Streptococcus pneumoniae</i>	Initial tre (see Ta tistar
Asthma	Beclomethasone, 4 42- $\mu$ g puffs twice daily by metered-dose inhaler with spacer or other equivalent Albuterol, 2 90- $\mu$ g puffs as needed, up to 4 times daily by metered-dose inhaler with spacer	Equivalent sults. T vokes c costero

\*Specific drugs and doses are mentioned when their use is supported by double-blind, randomized, p