

The Persistently Troublesome Cough

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Over the past 25 years, a great deal has been learned about the management of cough (1); this information has been summarized recently in an evidence-based consensus panel report primarily written for cough specialists (2) that includes diagnostic algorithms for chronic cough and in a practical review article primarily directed at primary care physicians (3) that includes specific evidence-based recommendations for drug therapy and its dosing. When investigators have faithfully followed diagnostic and treatment protocols that have been shown to be successful, the cause of chronic cough has been determined 88 to 100% of the time, leading to successful therapy in 84 to 98% of the patients. Multiple studies have shown that in approximately 95% of cases involving immunocompetent patients, chronic cough results from postnasal drip syndrome, asthma, gastroesophageal reflux disease (GERD), chronic bronchitis due to cigarette smoking or other irritants, bronchiectasis, eosinophilic bronchitis, or the use of an angiotensin-converting enzyme inhibitor (2). In the remaining 5% of cases, chronic cough is caused by a variety of other diseases, such as bronchogenic carcinoma, metastatic carcinomatosis, sarcoidosis, left ventricular failure, tuberculosis, and aspiration due to pharyngeal dysfunction. A more comprehensive listing of causes has been reviewed elsewhere (4).

The focus of this commentary is on the management of the adult immunocompetent patient who has a persistently troublesome cough for a duration of at least 2 months. Because, by definition, the so-called postinfectious cough resolves spontaneously within 2 months (2), that diagnosis is not considered herein. However, when a respiratory infection precedes the development of chronic cough, it is presumed that the infection led to or exacerbated other conditions commonly causing chronic cough, such as postnasal drip syndrome, symptomatic asthma, and GERD.

GENERAL PRINCIPLES OF MANAGEMENT

Our general management approach to a patient with a persistently troublesome cough is to resist the temptation to diagnose him or her as having psychogenic cough; repeat and extend the diagnostic workup previously performed; determine if the patient meets the clinical profile that predicts that postnasal drip syndrome, asthma, GERD, and/or eosinophilic bronchitis are the likely causes; address the most common potential pitfalls of management; and evaluate the patient's home and/or work environment.

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RESISTING THE TEMPTATION TO DIAGNOSE A PATIENT AS HAVING A PSYCHOGENIC COUGH

Because at least 23% of patients with a persistently troublesome cough referred to a cough specialist have been misdiagnosed as having psychogenic cough (5), we initially resist making this diagnosis. Previously, it was suggested that patients who failed to cough at night and coughed with a barking or honking character met the criteria for the diagnosis of psychogenic cough (2). However, more recent prospective studies have demonstrated that these clinical characteristics are not diagnostically helpful. It has been shown that cough due to chronic bronchitis (6) and GERD in the context of a normal chest radiograph (7) are unlikely to occur once patients fall asleep, and barking and honking coughs can be due to a variety of organic diseases (8). Because chronic cough itself so adversely affects psychosocial health (9), clinicians should be cautious when concluding that any psychosocial dysfunction is the cause rather than a consequence of the cough. By using the Adverse Cough Outcome Survey (9), clinicians can accurately determine the spectrum and severity of complications associated with cough.

REPEATING AND EXTENDING THE DIAGNOSTIC WORKUP

Repeating diagnostic evaluations can be important because the causative disease(s) may have changed over time and the original testing may not have been performed or interpreted appropriately. For example, a repeat high-resolution computerized tomography scan of the chest in a patient of ours with chronic cough that had improved by a modest degree with treatment for GERD showed patchy, ground glass attenuation in the upper lobes that had not been present in an earlier study. This led to an additional evaluation of the patient's work environment and ultimately established a diagnosis of flock worker's lung (10).

Similarly, reinterpreting or repeating 24-hour esophageal pH monitoring can be diagnostically helpful if the original test had not been interpreted according to the most sensitive guidelines (11). In this regard, it is important to be aware that conventionally used diagnostic indices of GERD (e.g., percentage of time that pH value is less than 4) can be normal when the cough is due to GERD, and gastroesophageal reflux-induced coughs can be observed and be the only part of the test that is diagnostic (11, 12). Therefore, until future studies provide better guidelines, the test should only be read as normal when conventional indices for acid reflux are within normal range, and no suspicious reflux-induced coughs appear during the monitoring session. It is also important to be aware that a 24-hour esophageal pH monitoring study can uncommonly be entirely normal at a time when GERD is the cause of cough and that barium esophagography can be the only test to reveal gastroesophageal reflux of potential pathologic significance in this situation (11, 12). Barium esophagography

can reveal reflux to the midesophagus or higher when refluxate from the stomach has a pH value similar to that of the normal esophagus, thus preventing its detection in the esophageal pH tracing.

With respect to extending the workup, assessing airway inflammation in induced sputum can aid in the diagnosis and management of chronic cough (13). Obtaining reliable and meaningful information requires considerable expertise in sputum collection, processing, and interpretation (13). Whereas its role in diagnosing a spectrum of causes of cough is unknown, this assessment can be instrumental in diagnosing non-asthmatic eosinophilic bronchitis (14), a condition that can be the cause of chronic cough in up to 13% of patient referrals (15), and it is likely to be helpful in suggesting the presence of chronic cough due to clinically "silent" bacterial suppurative airway disease (i.e., a bacterial suppurative airway infection that is not clinically obvious) (16). Although the role of bronchoscopy in evaluating cough has been reviewed elsewhere (17), it is important to stress that it should always be performed when the cough has remained undiagnosed. It can be useful, albeit uncommonly, in immunocompetent patients with chronic cough and normal chest radiographs in diagnosing conditions such as exposed endobronchial sutures in patients who have had previous thoracic surgery (18), dynamic collapse of large airways (19), and "silent" bacterial suppurative airway disease (16). On the other hand, it is important to be cautious in attributing any gross or nonspecific microscopic inflammatory changes of the vocal cords or tracheobronchial tree to any specific disease because these changes can merely be due to the act of coughing itself (20).

Whereas cough challenge testing has been useful from a research standpoint (2, 20), there are no controlled studies showing that it provides clinically useful information in managing patients with a persistently troublesome cough.

DETERMINING IF THE PATIENT MEETS THE CLINICAL PROFILE THAT PREDICTS POSTNASAL DRIP SYNDROME, ASTHMA, GERD, AND/OR EOSINOPHILIC BRONCHITIS

Based on the outcomes of eight prospective studies (5, 8, 9, 14, 15, 21–23), there is a clinical profile that can diagnose approximately 90% of the time when patients have chronic cough due to one or more of these conditions (Table 1). Whether or not the cough is dry or productive is irrelevant to this clinical profile. All these diseases can present as a cough–phlegm syndrome just like chronic bronchitis from cigarette smoking (8, 22).

When patients present with this clinical profile, first review the patient's prior evaluations and ask how these diseases have been diagnosed and treated, singly or in combination, before concluding that they have been ruled out. When diagnostic and treatment protocols other than those that have been consistently shown to be successful have been used, poorer rates of success have been reported (2).

TABLE 1. CLINICAL PROFILE OF PATIENTS WITH COUGH DUE TO POSTNASAL DRIP SYNDROME, ASTHMA, GASTROESOPHAGEAL REFLUX DISEASE, AND/OR EOSINOPHILIC BRONCHITIS

Patients will:

- Complain of a dry or productive cough for a duration of at least 2 mo
- Not be immunocompromised
- Have a normal or near-normal chest radiograph that shows nothing more than stable and inconsequential changes
- Not be smoking or be exposed to other environmental irritants
- Not be taking an angiotensin-converting enzyme inhibitor

ADDRESSING THE MOST COMMON POTENTIAL PITFALLS OF MANAGEMENT

Failure to avoid common errors in management is the most common reason why chronic cough remains troublesome. This can occur in at least 23% of patients (5) referred to a cough clinic. The most common errors will be discussed under the most common specific diseases. Patients will also fail to get better if clinicians do not consider that the most common diseases (e.g., postnasal drip syndrome, asthma, and GERD) may be the cause of cough even in the presence of another seemingly "obvious" cause (e.g., chronic interstitial pneumonia, persistent smoking) (2). Although nearly all habitual smokers have a cough, it should not be assumed that the cough is due to the smoking unless smoking ceases and the cough goes away. It is also important to recognize that multiple conditions often simultaneously contribute to cough. A persistently troublesome cough can be due to more than one condition up to 93% of the time; two conditions up to 53% of the time; three conditions up to 35% of the time; and five conditions up to 4% of the time (2, 9).

Postnasal Drip Syndrome from Rhinosinus Conditions

Most patients with postnasal drip–induced cough will have symptoms or evidence of one or more of the following: postnasal drainage, throat clearing, nasal discharge, cobblestone appearance of the oropharyngeal mucosa, or mucus in the oropharynx. However, failure to observe these clues at the time one sees the patient should not dissuade one from considering the diagnosis because a minority of patients will have no upper respiratory symptoms or signs (23). On the other hand, when upper respiratory complaints and findings do suggest the diagnosis of a postnasal drip syndrome but cough does not respond to appropriate therapy, consider environmental (nonallergen) irritant–induced upper respiratory tract disease, and GERD (5, 24) that can mimic a postnasal drip syndrome from rhinosinus disease.

The best treatment of postnasal drip syndrome depends on the etiology. Bacterial suppurative sinus disease should not be excluded because it is not clinically obvious; allergic rhinitis should not be excluded because symptoms are perennial. Although computerized tomography scanning of the sinuses is considered the most sensitive sinus imaging technique, it appears to add little to routine sinus radiographs in implicating sinusitis as the potential cause of chronic cough (25). The testing characteristics of routine sinus radiographs in diagnosing sinusitis as the cause of chronic cough have been reviewed elsewhere (2). Based on prospective descriptive studies, patients with chronic cough due to chronic sinusitis appear to do best when initially treated with nasal decongestant sprays for 3–5 days, first-generation antihistamine–decongestant agents for at least 3 weeks, and antibiotics directed against mouth anaerobes and *Hemophilus influenzae* (2). When the cough appears to be due to nonallergic, recurrent exacerbations of sinusitis in association with nasal polyps, it has been our practice to routinely consider aspirin therapy, when rhinosinus surgery and all other therapeutic interventions have failed to control the problem. In this context, we have patients undergo a standard aspirin challenge and desensitization if necessary (26) and, unless it is contraindicated, begin aspirin therapy following desensitization. In some of our patients, the addition of aspirin therapy has been the only intervention to eliminate recurrent cough on a long-term basis (e.g., years). Aspirin challenge, desensitization, and therapy have been extensively reviewed elsewhere (26).

A common error is to assume that all histamine₁ (H₁)-antagonists are equally efficacious in treating postnasal drip syn-

dromes. For instance, based on prospective descriptive studies and a double-blind, randomized, placebo-controlled trial (2), the first-generation antihistamines, often in combination with a decongestant, are considered the most consistently effective sole form of therapy in treating patients with postnasal drip-induced cough not due to sinusitis. Because the newer, relatively non-sedating H₁-antagonists are considered less effective than the first-generation agents in treating cough due to non-histamine-mediated postnasal drip syndromes (2), the first-generation agents should be used preferentially in nonallergic postnasal drip syndromes (2). Before prescribing the first-generation agents, patients should be cautioned about their potential sedating effects. Whereas it is possible that the efficacy of the first-generation agents is related to their sedating (antitussive) effect on the cough center, it is the anticholinergic activity of these agents that is probably responsible for their efficacy (2). Therefore, intranasal ipratropium bromide is our next agent of choice when the first-generation antihistamines are contraindicated (e.g., glaucoma, benign prostatic hypertrophy).

Asthma

There is nothing distinctive about the clinical characteristics of cough associated with asthma (8), and the clinical diagnosis of asthma is unreliable (27). Because methacholine challenge has a negative predictive value of 100% (2) in the context of cough, the test is extremely useful in ruling out asthma. If the test is negative, do not treat for asthma as the cause of cough; rather, evaluate for other conditions. On the other hand, it should not be assumed that a positive challenge, in and of itself, is diagnostic of asthma as the cause of cough. Because a positive test has been observed in conditions other than asthma, and cough has disappeared with treatment for these conditions after asthma therapy failed, it has been determined that the positive predictive value of methacholine challenge ranges between 60 and 82% (2) for predicting whether chronic cough will improve with asthma therapy.

The treatment of cough-variant asthma is the same as asthma in general (2). Although cough-variant asthma is usually managed easily with inhaled corticosteroids alone or with inhaled β_2 -agonists to relieve acute symptoms, an occasional patient may require the addition of systemic corticosteroids, especially if inhaled medications provoke cough (2). When cough does not respond to asthma medications, the positive methacholine challenge test should be considered a false positive, asthma therapy discontinued, and other diseases evaluated. When cough responds only partially to asthma medications or responds only to intermittent or high-dose systemic corticosteroid therapy, systematically evaluate the patient as a difficult-to-control patient with asthma (28). GERD has been the condition most frequently contributing to this difficult-to-control state (7, 28).

GERD

Accurately diagnosing and successfully treating chronic cough due to GERD is a major challenge. Although GERD is among the three most common causes of chronic cough in all age groups (2), there is nothing about the character and timing of cough due to GERD that distinguishes it from other conditions (8); moreover, it can be "silent" from a gastrointestinal standpoint up to 75% of the time (11). GERD should always be considered a possible cause of cough when patients also complain of typical and frequent gastrointestinal problems (e.g., weekly heartburn and regurgitation) and especially when the chest radiograph is consistent with aspiration. Also, it should always be considered a possibility even when there are no gastrointestinal complaints, the chest radiograph is normal, and postnasal drip syndrome, asthma, and eosinophilic

bronchitis have been ruled out. This profile for "silent" GERD (Table 2) has been prospectively shown in two small, selected cohorts of patients to be highly predictive that the patient's cough will respond to antireflux treatment (11, 29). In one study, coughs disappeared in 12 of 12 patients with intensive medical therapy (11); in the other, cough disappeared or significantly improved in 18 of 21 patients with antireflux surgery after intensive medical therapy had failed (29). It is important to stress that it can be an error in management to assume that cough cannot be due to GERD because cough is unchanged when gastrointestinal symptoms improve or disappear (29).

Although 24-hour esophageal pH monitoring is the single best test for linking GERD and cough in a cause and effect relationship, monitoring has its limitations. Because it cannot detect reflux events with a pH similar to that of the normal esophagus, it is not perfectly sensitive (11), and its specificity in the context of evaluating the cause of cough can be as low as 66% (2). Consequently, for patients who fit the clinical profile for cough due to GERD (Table 2), we recommend that treatment be initially started in lieu of testing. To determine if the therapy is not intensive enough or if medical therapy has failed (29), we do recommend performing 24-hour esophageal pH monitoring on therapy when cough does not improve within 3 months. Hopefully, in the near future, simultaneous 24-hour monitoring of intraesophageal impedance and pH will allow clinicians to more easily determine when acid and/or nonacid reflux disease is the cause of a chronic cough (30, 31). Data are mounting that acid does not have to be the sole or primary mediator of gastroesophageal reflux-induced cough (12, 27).

Whereas the optimal way to treat all patients with cough due to GERD has yet to be determined, a pilot study published in abstract form suggests that an antireflux diet, when followed, is likely to be effective (32). Based on this small study and our experience, we believe that diet should be a part of all antireflux medical treatment regimens. It appears to be the most underappreciated and often ignored part of treatment for GERD. Whereas cough may resolve within weeks in some patients with an antireflux diet or acid suppression alone (21), in others, it may take 2–3 months of diet plus prokinetic and acid suppression therapy before cough starts to improve and, on average, 5–6 months before cough resolves (5, 7). Because our referrals tend to require the most intensive medical regimens to improve, our initial medical treatment program includes the following: (1) antireflux diet and lifestyle changes; (2) a prokinetic agent (e.g., metoclopramide); and (3) acid suppression with a proton pump inhibitor. Because comorbid diseases such as obstructive sleep apnea (33) or therapy for comorbid conditions (34) (e.g.,

TABLE 2. CLINICAL PROFILE OF PATIENTS WITH COUGH DUE TO "SILENT" GASTROESOPHAGEAL REFLUX DISEASE

Patients will:

- Complain of a dry or productive cough for a duration of at least 2 mo
- Not be immunocompromised
- Have a normal or near-normal chest radiograph that shows nothing more than stable and inconsequential changes
- Not be smoking or be exposed to other environmental irritants
- Not be taking an angiotensin-converting enzyme inhibitor

Symptomatic asthma has been ruled out:

- Methacholine challenge is negative, or
- Cough has not improved with asthma medications

Postnasal drip syndrome due to rhinosinus diseases have been ruled out:

- First-generation H₁-antagonists have been used and failed to improve cough, and
- "Silent" sinusitis has been ruled out

Eosinophilic bronchitis has been ruled out:

- Properly performed sputum studies are negative, or
- Cough has not improved with inhaled/systemic corticosteroids

calcium channel blockers, nitrates, progesterone) can potentially make GERD more difficult to control, routinely try to mitigate the influences of these factors. Because coughing can induce gastroesophageal reflux events, less than optimal results may occur due to a cough–gastroesophageal reflux self-perpetuating cycle (2) unless all causes of cough are adequately treated.

Recently, an increasing number of patients with cough due to GERD have been reported (35, 36) whose coughs only resolved or significantly improved following antireflux surgery. All these patients had failed to respond to intensive antireflux medical therapy, and some even had prior antireflux surgery (29). Consequently, it cannot be assumed that GERD has been ruled out as the cause of cough because patients have failed to improve with intensive and prolonged medical therapy or with prior antireflux surgery. Determining when surgery is indicated and likely to be successful has been addressed in a recent publication (29).

Nonasthmatic Eosinophilic Bronchitis

This disease was first described in 1989 (14). Whereas it has been associated with dry as well as productive coughs (37) and a predominance of eosinophils (i.e., at least 3% of nonsquamous cells) and metachromatic cells in induced sputum similar to asthma, eosinophilic bronchitis is distinguished from asthma by the lack of bronchial hyperresponsiveness or variable airflow obstruction. It is important to consider this diagnosis in patients with negative methacholine challenges because it is corticosteroid responsive, and it can be a common cause of chronic cough (e.g., up to 13%) (15). The cough due to eosinophilic bronchitis has been reported to always respond to corticosteroid treatment (37). Although improvement usually occurs with inhaled corticosteroids, systemic therapy is sometimes required. Long-term therapy may be necessary (37). Whereas the natural history of eosinophilic bronchitis is not known (38), a recent report suggests that diagnosing and adequately treating patients with this condition is important not only to resolve the cough but also to avoid persistence of eosinophilic airway inflammation that may lead to progressive irreversible airflow obstruction (38).

It is now appreciated that the disease can present in atopic as well as nonatopic individuals, smokers with and without chronic obstructive pulmonary disease, as well as nonsmokers, and it can be associated with occupational chemical sensitizers (37). When cough due to eosinophilic bronchitis is associated with an environmental irritant (e.g., acrylic resin, allergens), avoidance is advised.

Because patients with cough due to GERD have been observed to have an increased number of eosinophils in bronchoalveolar lavage fluid (39), and intraepithelial eosinophils have been described in esophageal mucosa as being markers of reflux-induced esophageal injury (40), it remains to be determined whether or not there is an important association between GERD and eosinophilic bronchitis.

Angiotensin-Converting Enzyme Inhibitor–induced Cough

This diagnosis can only be established when cough disappears with elimination of the drug. The median time to resolution has been shown to be 26 days (41). Because these drugs are effective antihypertensive agents, vasodilators in congestive heart failure, and renoprotective agents, it is useful to know, if the angiotensin-converting enzyme inhibitor has to be continued, that the cough may be significantly improved by adding nifedipine, inhaled sodium cromoglycate, indomethacin, intermediate (500 mg/day) but not low (100 mg/day) dose aspirin, sulindac, or picotamide, a thromboxane antagonist that is not available in the United States (2, 42).

Because cough due to angiotensin-converting enzyme inhibitors is a class effect and not dose-related, substituting one angio-

tensin-converting enzyme inhibitor for another will not likely improve the cough (2). On the other hand, angiotensin-converting enzyme inhibitor–induced cough should be eliminated by substituting an angiotensin II receptor antagonist for the ACEI (41).

Suppurative Airway Diseases

There is a wide spectrum of suppurative airway diseases that includes tracheitis, bronchitis, bronchiolitis, and bronchiectasis, and these may or may not be associated with a systemic disease. Whereas the suppuration may be due to infection, this will not always be the case (e.g., inflammatory bowel disease) (43). When patients have a chronic cough due to a suppurative airway disease, it is usually clinically obvious; they usually expectorate purulent phlegm and appear ill.

However, we have recently observed and reported in abstract form that chronic cough may be due to clinically “silent” bacterial suppurative airway disease that may only respond to prolonged (e.g., at least 3 weeks) intravenous antibiotic therapy chosen on the basis of protected specimen brush quantitative cultures (16). In a group of 14 such patients, all were noted to have copious purulent secretions at the time of bronchoscopy; yet, none appeared ill, were febrile, or had elevated white blood cell counts. In retrospect, an abnormal lung examination in 13/14 (9 had rhonchi or wheezes, 7 had crackles) was the only clinical clue that there was an intrathoracic cause of their chronic cough. Whereas 12 had a productive cough, 2 complained that their coughs were dry, and all failed to improve with multiple oral antibiotics, including quinolones. In many patients, the same antibiotics that were ineffective orally became effective once given intravenously. Based on high-resolution computerized tomography scanning of the chest and the distribution and quantitation of suppuration observed at bronchoscopy, the bacterial suppurative airway disease was primarily believed to be due to diffuse bronchitis and/or bronchiolitis. Whereas cough in some patients has been cured, it has been a recurrent problem in others that has only responded to intermittent prolonged courses of intravenous antibiotics.

Whenever patients have recurrent episodes of suppurative respiratory disease, investigations should be undertaken to determine the causative factors (44) such as immunodeficiency states or aspiration from pharyngeal dysfunction. Because we have recently observed and reported in abstract form (45) that there can be a delay (median = 43.5 months, range = 6–62 months) in the laboratory expression of common variable immunodeficiency in adults with bacterial, suppurative respiratory diseases, we periodically obtain serum immunoglobulin concentrations and assess immunoglobulin function when these are initially normal in these patients. In our personal experience, once the patient has been diagnosed with common variable immunodeficiency, improvement is likely to occur with intravenous γ -globulin.

EVALUATING THE PATIENT’S HOME AND/OR WORK ENVIRONMENT

Air pollution from a variety of different types of pollutants in the home and/or work place should always be considered a potential cause of cough (46). It can provoke cough by causing postnasal drip syndrome, tracheobronchitis, exacerbating or causing asthma, hypersensitivity pneumonitis, or nonallergic parenchymal lung disease such as flock worker’s pneumoconiosis (10). When history reveals that the patient smokes or that the cough is worse in specific environmental settings, it is relatively easy to associate air pollution with the patient’s cough and suggest a remedial course of action (47). However, the association may not be obvious even after a careful study of the history. Whereas an allergy evaluation should be performed in

the setting of difficult-to-control postnasal drip syndrome and asthma to help determine and localize the exposure source, a site inspection of the home and/or work by a knowledgeable professional, in our experience, is often needed for proper diagnosis, remediation of the problem, and resolution of the cough. A practical approach to diagnosing and treating a home air pollution problem has been published recently (48). Because we have witnessed that environmental air pollution of a nonallergic and nonsmoking nature has been the cause of cough due to a postnasal drip syndrome, we routinely arrange for home inspections when the cough remains unknown and refractory to treatment even when an allergy evaluation has been negative. In these cases, whereas we do not know what in the environment is provoking the cough, we have wondered if mycotoxins and/or endotoxins in the air from microbial growth caused cough by irritating the respiratory tract. This is an area in which further research needs to be done.

MANAGING THE REFRACTORY IDIOPATHIC COUGH

Most patients referred to a subspecialist for a persistently troublesome cough can be successfully treated with specific therapy. Nevertheless, there will be occasional patients who defy diagnosis and require nonspecific antitussive therapy for relief. For these patients, preferentially consider prescribing the limited number of drugs (e.g., dextromethorphan, ipratropium bromide, and narcotics such as codeine) that have been shown to be effective in randomized, double-blind, placebo-controlled trials in humans with chronic pathologic cough (2). Because of their addictive potential, consider prescribing narcotics when all other drugs have failed. In this regard, we will give trials of other drugs that have been suggested but not proven to be of benefit, such as baclofen (49) and nebulized local anesthetics (e.g., lidocaine, mepivacaine) (50, 51).

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