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# Combatting the cough that won't quit

By the time patients come to see you, they've often tried a host of OTC remedies. This review and handy algorithm will help you detect and treat the cause of persistent cough without delay.

## PRACTICE RECOMMENDATIONS

› Always include post-nasal drip, asthma, and gastroesophageal reflux disease in the differential diagnosis for persistent cough, regardless of clinical signs and symptoms. **B**

› Do not rely on a patient's description of the character and timing of the cough or the absence (or presence) of sputum to narrow down the differential diagnosis. **B**

### Strength of recommendation (SOR)

- A** Good-quality patient-oriented evidence
- B** Inconsistent or limited-quality patient-oriented evidence
- C** Consensus, usual practice, opinion, disease-oriented evidence, case series

**CASE ►** Margaret M, a 52-year-old nonsmoker, came to our clinic because of a persistent cough that had started about 4 weeks earlier. She had tried multiple over-the-counter cough suppressants, including dextromethorphan and guaifenesin, as well as cough drops, but none had been effective.

Margaret denied having had a cold or respiratory infection in the past few months or being in close contact with anyone with a chronic cough, and she had never had an asthma diagnosis. In response to a question about previous coughing episodes, the patient recalled having had several bouts of chronic cough in the past, including one about a year ago.

While Margaret had no known allergies, she did have occasional heartburn, which an antacid—or, at times, a drink of water—always relieved. Thyroid medication and calcium were the only things she took on a regular basis, separated by several hours to avoid problems with absorption.

Patients like Margaret, who seek help from their primary care physician only after attempting to combat a persistent cough on their own, may be quite frustrated by the time they arrive in your office. They're counting on you to provide a cure. Fortunately, you're likely to find it, as the differential diagnosis for subacute cough (a cough of 3-8 weeks' duration) is limited.

Nonetheless, finding the cause of a subacute or chronic cough (lasting >8 weeks) is sometimes a matter of trial and error. Postnasal drip (also known as upper airway cough syndrome, or UACS), asthma, and gastroesophageal reflux disease (GERD) are the most common causes,<sup>1,2</sup> followed by postinfectious cough, nonasthmatic eosinophilic bronchitis (NAEB), and pertussis.<sup>3</sup> Although these conditions are all relatively well known, they are not always easy to detect: Some disorders, including UACS, asthma, and GERD, may be



The most effective approach? Start with trials of empiric therapy for the most common causes of persistent cough, and bring in sequential therapy and diagnostic tests, as needed.

“silent,” with persistent cough the only presenting sign or symptom.<sup>4</sup> In other cases, more than one condition may be contributing to the cough.

Starting with trials of empiric therapy for the most common causes of persistent cough—with sequential therapy and diagnostic tests, as needed—is far more effective than searching for relatively uncommon or obscure conditions. Following such a protocol, as detailed in the algorithm (FIGURE)<sup>4-7</sup> we’ve developed and in the text that follows, can help you combat subacute and chronic cough in a cost-effective, timely way.

### Treat all patients for upper airway cough syndrome

Postnasal drip—renamed UACS by the guideline committee of the American Association of Chest Physicians because it isn’t clear whether the cough is caused by irritation from direct contact with postnasal drip or by inflammation of cough receptors in the upper airway—is the most common cause of chronic cough.<sup>6</sup>

The differential diagnosis for UACS, which is implicated in about 34% of cases of persistent cough, includes allergic, postinfectious, and occupational rhinitis; rhinitis due to anatomic abnormalities or physical or chemical irritants, rhinitis medicamentosa, and rhinitis of pregnancy; bacterial sinusitis; and allergic fungal sinusitis.<sup>8</sup>

The signs and symptoms of UACS are nonspecific, and a definitive diagnosis typically cannot be made from the medical history and physical examination alone. What’s more, the absence of any of the usual clinical findings—eg, rhinorrhea and excess sputum production—should not preclude an empiric trial with a first-generation antihistamine-decongestant combination such as brompheniramine/sustained-release pseudoephedrine. Second- and third-generation combination products, such as fexofenadine/pseudoephedrine, should not be used, as they are not effective in treating UACS.<sup>4</sup>

**CASE ►** Margaret’s physical exam was unremarkable. Her vital signs were stable, she

**➤ Postnasal drip, often referred to as upper airway cough syndrome, is the leading cause of persistent cough.**

had no cervical lymphadenopathy, and her chest was clear on auscultation. She had a dry cough that occurred twice during the exam, but not on inspiration.

The patient's work-up included office spirometry, which was normal; a nasopharyngeal culture for *Bordetella pertussis* was negative. We prescribed a 2-week course of therapy with brompheniramine/sustained-release pseudoephedrine and scheduled a return visit shortly after it was completed.

There is no gold standard diagnostic test to confirm or rule out postnasal drip as the cause of cough. CT scanning of sinuses has a poor positive predictive value and is no longer recommended as part of an initial work-up,<sup>9</sup> but may be useful for patients whose symptoms persist longer than 3 weeks.

### **Consider bronchodilator Tx when asthma is suspected**

Cough-variant asthma is the second most common cause of persistent cough, and is responsible for an estimated 28% of cases.<sup>6</sup> Asthma is the easiest of the conditions included in the differential diagnosis for persistent cough to establish in an office setting. The challenge is to remember to consider it in patients who present with cough but no sign of the classic expiratory wheezing. When you suspect that a patient has asthma, consider empiric bronchodilator therapy—or conduct spirometry testing.

Spirometric values of forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) <70% and a positive bronchodilator response ( $\geq 12\%$ ) are consistent with an asthma diagnosis. Management of asthma depends on severity, and patients should be evaluated based on the National Heart, Lung, and Blood Institute's National Asthma Education and Prevention Program Guidelines for the Diagnosis and Management of Asthma.<sup>10</sup>

It is crucial to ask patients with asthma (and, indeed, to ask all patients with a persistent cough) about exposure to secondhand smoke, and to stress the importance of avoiding smoking and secondary exposure. Individuals who are regularly exposed to

secondhand smoke report more nasal symptoms and greater use of nasal decongestants compared with people with no exposure to smoke;<sup>11</sup> they also have poor control of asthma.<sup>12-14</sup>

### **Cough unresolved? Add therapy for GERD**

Although GERD is primarily associated with heartburn and gastrointestinal distress, it is not unusual for cough to be its only sign or symptom.<sup>15</sup> In fact, GERD is the third most common cause of subacute cough—affecting about 21% of patients who seek help for cough at primary care practices.<sup>3</sup>

**CASE ▶** Margaret returned to the clinic shortly after completion of a 2-week course of brompheniramine/sustained-release pseudoephedrine, and reported that she was still coughing frequently—and that the medication had brought little improvement. Because of her history of heartburn, we added a 2-week trial with a proton pump inhibitor (PPI)—omeprazole 20 mg/d.

While there are diagnostic tests for GERD, including a pH probe of the esophagus, a barium esophagogram, and manometry testing, empiric therapy with a PPI—starting with a trial of at least 2 weeks—often eliminates the troublesome cough.<sup>16</sup> If the patient responds to treatment, the medication can be continued. Risks associated with long-term PPI therapy include osteoporosis and interference with calcium and magnesium absorption,<sup>17</sup> so it is important to monitor patients taking them and to discontinue treatment as soon as the cough symptoms resolve.

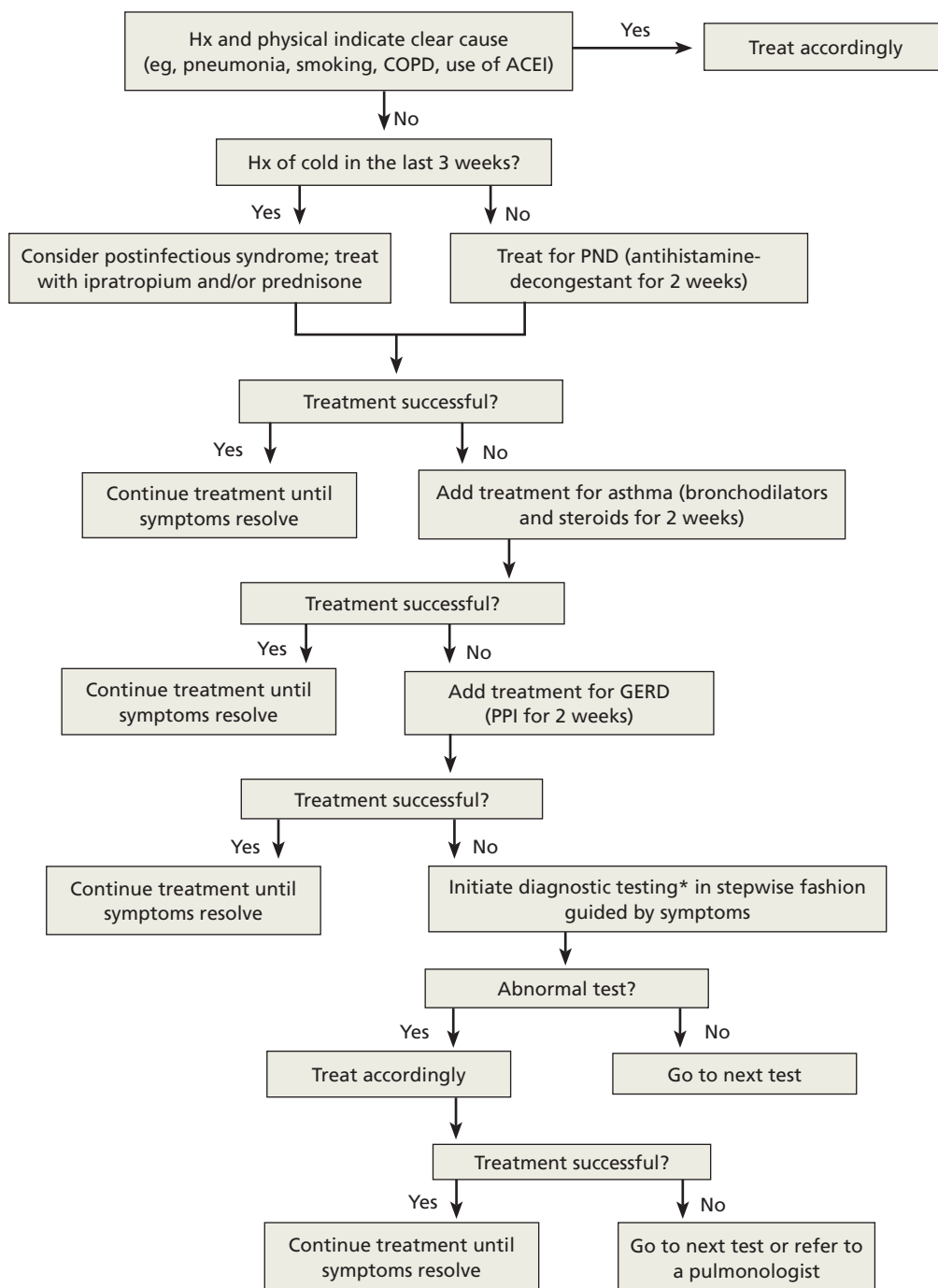
### **Have you ruled out postinfectious cough?**

If a patient has a cough that has lingered for 3 to 8 weeks after his or her recovery from an acute upper respiratory infection (URI), postinfectious cough may be the reason.<sup>18,19</sup> Such a cough is subacute and self-limiting. (If the cough lasts >8 weeks after an acute illness, other diagnoses, such as chronic infection, are more likely.)

The pathogenesis for postinfectious

FIGURE

Dx and treatment when persistent cough is the only symptom<sup>4-7</sup>



\*May include CXR, PPD, *B pertussis* IgG or IgA, spirometry with methacholine inhalation challenge, barium swallow, prolonged pH monitoring, sinus CT, and sputum eosinophil count, excluding any tests that have already been performed.

ACEI, angiotensin-converting enzyme inhibitor; CT, computed tomography; COPD, chronic obstructive pulmonary disease; CXR, chest x-ray; GERD, gastroesophageal reflux disease; IgA, immunoglobulin A; IgG, immunoglobulin G; PND, postnasal drip; PPD, purified protein derivative; PPI, proton pump inhibitor.

➤  
In cases of upper airway cough syndrome, asthma, and GERD, a persistent cough may be the only presenting sign or symptom.

cough may be related to postviral airway inflammation or bronchial hyperresponsiveness, and antibiotics are not indicated.<sup>4</sup> Patients may be treated with a bronchodilator such as ipratropium rather than a beta-agonist or inhaled corticosteroids; oral tapered prednisone can be prescribed, if needed, for severe paroxysms, although there is limited evidence of its efficacy.<sup>20</sup> Central antitussive agents such as codeine and dextromethorphan can be used when other measures fail to bring relief.

### Nonasthmatic eosinophilic bronchitis does not impede airflow

NAEB is less well known than the conditions discussed thus far, but it is a relatively common cause of persistent cough.<sup>21-23</sup> In some studies, up to 13% of patients with subacute cough were diagnosed with NAEB.<sup>6</sup>

Unlike asthma, NAEB is not associated with abnormalities in airway function; patients have no dyspnea and no wheezing, and no obstruction of airflow.<sup>24</sup> Patients will have FEV1 >80% and FEV1/FVC >75% on spirometric examination, a negative response to bronchoprovocation, and, typically, an elevated sputum eosinophil count of >3%. Because induced sputum or bronchoscopic washings are difficult, exhaled nitric oxide testing is another option. If these tests are not available, a trial of inhaled steroids is indicated, even if neither spirometry nor bronchoprovocation testing was abnormal.<sup>9</sup>

Patients with NAEB respond well to inhaled corticosteroids, and budesonide 400 mcg twice a day or prednisolone 30 mg daily may be prescribed. It is also important to remove airway irritants. Long-term follow-up studies of patients with NAEB have had conflicting results. One study found that most cases resolve completely;<sup>23</sup> another showed a

need for long-term treatment, and suggested that patients with NAEB may be at increased risk for asthma and chronic obstructive pulmonary disease.<sup>25</sup>

### Paroxysmal cough, whoops point to pertussis

When a patient has paroxysms of cough, posttussive vomiting, and/or an inspiratory whooping sound, *B pertussis* infection is the likely culprit.<sup>26-28</sup> A definitive diagnosis of pertussis, or whooping cough, may be based on a positive culture from a nasopharyngeal aspirate swab.<sup>29</sup> Suspected cases can be confirmed with a polymerase chain reaction test, and a presumptive diagnosis may be made as a result of a 4-fold increase in immunoglobulin G or immunoglobulin A antibodies for *B pertussis*.<sup>4</sup>

A macrolide antibiotic, usually azithromycin, is the standard treatment for pertussis.<sup>30-32</sup> Patients should be isolated for 5 days from the start of treatment. Antibiotic therapy will reduce the risk of transmission, but will not affect the duration of the cough, which may be 6 to 8 weeks. Long-acting beta-agonists, antihistamines, and corticosteroids should not be used to treat pertussis.<sup>4</sup>

**CASE ▶** After a 2-week course of omeprazole 20 mg daily, Margaret was coughing much less. We extended the prescription, and by the end of the next 4 weeks, she was no longer coughing. After 2 months, both the PPI and the antihistamine/decongestant were discontinued. We advised her to institute antireflux measures, such as elevating her head at night and not eating after 6 pm, and she has not had a relapse. **JFP**

#### CORRESPONDENCE

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