Chronic Cough Due to Asthma
ACCP Evidence-Based Clinical Practice Guidelines

Peter V. Dicpinigaitis, MD, FCCP

Background: Asthma is among the most common causes of chronic cough in adult nonsmokers. Although cough usually accompanies dyspnea and wheezing, it may present in isolation as a precursor of typical asthmatic symptoms, or it may remain the predominant or sole symptom of asthma. The latter condition is known as cough-variant asthma (CVA).

Methods: Data for this review were obtained from a National Library of Medicine (PubMed) search, performed in April 2004, of the English language literature from 1975 to 2004, limited to human studies, using the search terms “cough” and “asthma.”

Results: The diagnosis of cough not associated with typical asthmatic symptoms (ie, CVA) presents a challenge, because physical examination and spirometry findings may be entirely normal. Methacholine inhalation challenge testing can demonstrate the presence of bronchial hyperresponsiveness; however, the diagnosis of cough due to asthma is only confirmed after the resolution of cough with antiasthmatic therapy. In general, the therapeutic approach to asthmatic cough is similar to that of the typical form of asthma. Most patients will respond to inhaled bronchodilators and inhaled corticosteroids. A subgroup of patients will require the addition of leukotriene receptor antagonists and/or a short course of oral corticosteroids.

Conclusions: Asthma should be considered as a potential etiology in any patient with chronic cough, because asthma is a common condition that is commonly associated with cough. Because the subgroup of asthmatic patients with CVA presents with no other symptoms of asthma, clinical suspicion must remain high. Cough due to asthma responds to standard antiasthmatic therapy.

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Key words: asthma; bronchial challenge tests; bronchial responsiveness; capsaicin; cough; cough reflex sensitivity; cough-variant asthma; eosinophilic bronchitis; leukotriene receptor antagonists; methacholine

Abbreviations: CVA = cough-variant asthma; LTRA = leukotriene receptor antagonist; MIC = methacholine inhalation challenge

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Multiple prospective studies1–3 have shown that asthma is among the most common etiologies of chronic cough (24 to 29%) in adult nonsmokers. Usually, cough is associated with the more typical symptoms of dyspnea and wheezing. Alternatively, an isolated cough may serve as a harbinger of future asthmatic episodes.4 In a subgroup of asthmatic patients, however, cough is the predominant or sole symptom.5 This condition has been termed cough-variant asthma (CVA). The therapeutic approach to CVA is similar to that of the typical form of asthma.

Recommendation

1. In a patient with chronic cough, asthma should always be considered as a potential etiology because asthma is a common condition with which cough is commonly associated. Quality of evidence, fair; net benefit, substantial; grade of recommendation, A

Recent data support the concept that patients with CVA comprise a distinct subgroup of individuals with asthma, rather than simply being asthmatic patients who cough. For example, subjects with the typical form of asthma do not differ from healthy volunteers in terms of experimentally measured cough reflex sensitivity, whereas those with CVA have a significantly more sensitive cough reflex.6–8 Interestingly, despite the presence of hypersensitive cough receptors, subjects with CVA demonstrate a lesser degree
of bronchial hyperresponsiveness to inhaled methacholine compared to those with the typical form of asthma.9

Further important developments since the publication of the first American College of Chest Physicians Consensus Panel report10 include the demonstration that the infiltration of airway smooth muscle by mast cells is associated with the disordered airway function of asthma11; that subepithelial layer thickening, a pathologic feature of airway remodeling, is present in CVA12; and that the leukotriene receptor antagonists (LTRAs) appear to be particularly effective in treating cough due to asthma.6 Data for this review were obtained from a National Library of Medicine (PubMed) search, performed in April 2004, of the English language literature from 1975 to 2004, limited to human studies, using the search terms “cough” and “asthma.”

**Evaluation**

If reversible airflow obstruction is demonstrated in a patient with chronic cough, empiric therapy for asthma is appropriate. However, a patient with chronic cough due to asthma may present a diagnostic challenge, because physical examination and pulmonary function test results can be entirely normal. In this setting, bronchoprovocation testing with inhaled methacholine should be used to document the presence of bronchial hyperresponsiveness and, therefore, the diagnosis of asthma. It must be stressed, however, that the presence of bronchial hyperresponsiveness in a patient with chronic cough is merely consistent with, but is not diagnostic of, CVA.13 A definitive diagnosis of CVA can only be made after the documented resolution of cough with specific treatment of asthma. Conversely, given its very high negative predictive power, a negative methacholine inhalation challenge (MIC) test result essentially excludes asthma from the differential diagnosis of chronic cough.14

**Recommendation**

2. In a patient suspected of having CVA but in whom physical examination and spirometry findings are nondiagnostic, MIC testing should be performed to confirm the presence of asthma. However, a diagnosis of CVA is established only after the resolution of cough with specific antiasthmatic therapy. If MIC testing cannot be performed, empiric therapy should be given; however, a response to steroid therapy will not exclude nonasthmatic eosinophilic bronchitis as an etiology of the patient’s cough. Quality of evidence, good; net benefit, substantial; grade of recommendation, A

Other conditions may suggest the diagnosis of asthmatic cough. Postviral or postinfectious cough (discussed in detail elsewhere in this supplement) typically presents as a persistent, dry cough in a previously healthy person in whom all other symptoms of the inciting upper respiratory tract infection resolved weeks or months earlier. Although this condition is not asthma, the patient with postviral cough may have dyspnea and wheezing, reversible airflow obstruction as demonstrated by spirometry, and a positive MIC test result due to transient, viral upper respiratory tract infection-induced bronchial hyperresponsiveness.

**Treatment**

In general, the therapeutic approach to CVA is similar to that of the typical form of asthma. Partial improvement is often achieved after 1 week of inhaled bronchodilator therapy, but the complete resolution of cough may require up to 8 weeks of treatment with inhaled corticosteroids.13,15

**Recommendation**

3. Patients with cough due to asthma should initially be treated with a standard antiasthmatic regimen of inhaled bronchodilators and inhaled corticosteroids. Quality of evidence, fair; net benefit, substantial; grade of recommendation, A

A potential pitfall of inhaled steroid therapy in patients with CVA is that the treatment itself may induce or exacerbate cough, which is likely due to a constituent of the aerosol. For example, the more common occurrence of cough after the inhalation of beclomethasone dipropionate, compared to after the inhalation of triamcinolone acetonide, is thought to be due to a component of the dispersant in the former mixture.16 For cough that is severe or only partially responsive to inhaled corticosteroids, oral therapy (ie, prednisone 40 mg or equivalent daily for 1 week), alone or followed by inhaled therapy, may be necessary.17 However, the possibility of inhaled steroid-induced cough, improper use of the inhaler device, or the presence of another etiology, such as gastroesophageal reflux disease, making asthma difficult to control, should be excluded before the escalation of therapy.
In those patients in whom cough remains refractory to inhaled corticosteroids, an assessment of airway inflammation is helpful. The presence of airway eosinophilia demonstrated by the evaluation of induced sputum or BAL fluid will identify those patients who may benefit from more aggressive antiinflammatory therapy (\textit{ie}, higher dose inhaled corticosteroids or oral steroid therapy).\textsuperscript{18}

\textbf{Recommendation}

4. In patients whose cough is refractory to inhaled corticosteroids, an assessment of airway inflammation should be performed whenever available and feasible. The demonstration of persistent airway eosinophilia during such an assessment will identify those patients who may

\textbf{Table 1—Treatment of Chronic Cough Associated With Asthma}\textsuperscript{*}

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Age, yr</th>
<th>Study Design</th>
<th>Patients, No.</th>
<th>Treatment</th>
<th>Response Rate, %</th>
<th>Other Details</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corrao et al\textsuperscript{5}/1979</td>
<td>16–40</td>
<td>Prospective, descriptive</td>
<td>6</td>
<td>Terbutaline (inhaled)</td>
<td>100</td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Irwin et al\textsuperscript{4}/1997</td>
<td>55 ± 16†</td>
<td>PRDBPC crossover</td>
<td>15</td>
<td>Metaproterenol (inhaled)</td>
<td>60</td>
<td>In 40%, cough due to other etiologies</td>
<td>Fair</td>
</tr>
<tr>
<td>North American Tilade Study Group\textsuperscript{20}/1990</td>
<td>12–70 (35.2)‡</td>
<td>PRDBPC</td>
<td>121</td>
<td>Nedocromil sodium</td>
<td>Improvement in treated patients. (p = 0.02)</td>
<td>Patients also on theophylline and oral β-agonists</td>
<td>Fair</td>
</tr>
<tr>
<td>Dicpinigatis et al\textsuperscript{8}/2002</td>
<td>27–62</td>
<td>PRDBPC crossover</td>
<td>8</td>
<td>Zafirlukast</td>
<td>88</td>
<td>Suppression of cough reflex sensitivity 100%</td>
<td>Fair</td>
</tr>
<tr>
<td>Irwin et al\textsuperscript{4}/1997</td>
<td>55 ± 16†</td>
<td>PRDBPC crossover</td>
<td>15</td>
<td>Beclomethasone dipropionate (inhaled)</td>
<td>60</td>
<td>In 40%, cough due to other etiologies</td>
<td>Fair</td>
</tr>
<tr>
<td>Cheriyan et al\textsuperscript{13}/1994</td>
<td>Retrospective, descriptive</td>
<td>10</td>
<td>Prednisone 7–14 d, followed by beclomethasone dipropionate</td>
<td>100</td>
<td>Improvement in treated patients (p &lt; 0.01) Compared to placebo and albuterol Subsequent therapy with ICSs</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Di Franco et al\textsuperscript{8}/2001</td>
<td>36 ± 16†</td>
<td>PRDBPC</td>
<td>36</td>
<td>Beclomethasone dipropionate (and albuterol)</td>
<td>Improvement in treated patients (p &lt; 0.01)</td>
<td></td>
<td>Fair</td>
</tr>
<tr>
<td>Doan et al\textsuperscript{17}/1992</td>
<td>4–71</td>
<td>Prospective, descriptive</td>
<td>10</td>
<td>Prednisone (20–60 mg/d)</td>
<td>100</td>
<td>Subsequent therapy with ICSs</td>
<td>Low</td>
</tr>
<tr>
<td>Shioya et al\textsuperscript{21}/1998</td>
<td>25–63 (47.1)†</td>
<td>Prospective, unblinded, uncontrolled</td>
<td>22</td>
<td>Azelastine hydrochloride</td>
<td>Improvement in treated patients (p &lt; 0.001)</td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Shioya et al\textsuperscript{22}/2002</td>
<td>22–69 (44.7)†</td>
<td>PRDBPC</td>
<td>20</td>
<td>Suplatast tosilate</td>
<td>Improvement in treated patients (p &lt; 0.01)</td>
<td></td>
<td>Fair</td>
</tr>
</tbody>
</table>

\textsuperscript{*}PRDBPC = prospective, randomized, double-blind, placebo-controlled study; ICS = inhaled corticosteroid.

†Values are given as mean ± SD.

‡Values in parentheses are the mean.
benefit from more aggressive antiinflammatory therapy. Quality of evidence, low; net benefit, substantial; grade of recommendation, B

The LTRA zafirlukast has been shown to improve subjective cough scores as well as to inhibit experimentally induced cough in subjects with CVA, including a subgroup of patients whose cough had been refractory to therapy with inhaled steroids. The ability of zafirlukast to suppress cough that was previously resistant to treatment with bronchodilators and inhaled steroids suggests that, in patients with CVA, treatment with LTRAs might more effectively modulate the inflammatory milieu of the sensory cough receptors within the airway epithelium. The mechanism by which this antitussive effect occurs remains unclear.

Despite the demonstrated efficacy of therapy with LTRAs in patients with CVA, the question of whether these agents are sufficient as monotherapy, or whether they should be used in addition to inhaled steroids, remains unresolved at this time. Subepithelial layer thickening, a pathologic feature of airway wall remodeling, is present in CVA, although to a lesser extent than in the typical form of asthma. Hence, chronic antiinflammatory therapy seems appropriate for patients with CVA, but the issue of whether treatment with LTRAs alone is sufficient to prevent the sequelae of chronic airway inflammation awaits further elucidation.

Recommendations

5a. For patients with asthmatic cough that is refractory to treatment with inhaled corticosteroids and bronchodilators, in whom poor compliance or another contributing condition has been excluded, an LTRA may be added to the therapeutic regimen before the escalation of therapy to systemic corticosteroids. Quality of evidence, fair; net benefit, intermediate; grade of recommendation, B

5b. Patients with severe and/or refractory cough due to asthma should receive a short course (1 to 2 weeks) of systemic (oral) corticosteroids followed by inhaled corticosteroids. Quality of evidence, low; net benefit, substantial; grade of recommendation, B

Other agents shown in prospective trials to be effective in treating asthmatic cough include inhaled terbutaline, metaproterenol, theophylline, nedocromil sodium, azelastine hydrochloride, a second-generation H1-receptor antagonist, and suplatast tosilate, a Th2 cytokine inhibitor (see Table 1). There are no data to suggest that these agents offer added benefit to a regimen of an inhaled bronchodilator and inhaled corticosteroid, with or without an LTRA.

Summary of Recommendations

1. In a patient with chronic cough, asthma should always be considered as a potential etiology because asthma is a common condition with which cough is commonly associated. Quality of evidence, fair; net benefit, substantial; grade of recommendation, A

2. In a patient suspected of having CVA but in whom physical examination and spirometry findings are nondiagnostic, MIC testing should be performed to confirm the presence of asthma. However, a diagnosis of CVA is established only after the resolution of cough with specific antiasthmatic therapy. If MIC testing cannot be performed, empirical therapy should be administered; however, a response to steroid therapy will not exclude nonasthmatic eosinophilic bronchitis as an etiology of the patient’s cough. Quality of evidence, good; net benefit, substantial; grade of recommendation, A

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4. In patients whose cough is refractory to treatment with inhaled corticosteroids, an assessment of airway inflammation should be performed whenever available and feasible. The demonstration of persistent airway eosinophilia during such an assessment will identify those patients who may benefit from more aggressive antiinflammatory therapy. Quality of evidence, low; net benefit, substantial; grade of recommendation, B

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