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## Acute Asthmatic Bronchitis: A New Twist to an Old Problem

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In 1986, Dr Harold Williamson, Jr, wrote an editorial published in *The Journal of Family Practice* entitled "Acute Bronchitis: A Homely Prototype for Primary Care Research,"<sup>1</sup> in which he argued that much of what we know about this common syndrome has come from the research efforts of family physicians. Williamson defined "homely" conditions as those common clinical syndromes which we as practicing primary care physicians encounter frequently and recognize as important but which are hard to define and elicit little interest from the nonprimary care research community. For example, palpitations, dyspepsia, and chest wall pain are homely; ventricular tachycardia, ulcers, and myocardial infarction are not. Bronchitis is homely; pneumonia is not. Williamson concluded his editorial remarks with the suggestion that primary care researchers would do well to apply sound research principles to important "homely" diseases and thereby help establish a knowledge base for primary care.<sup>1</sup>

In this issue of *The Journal*, Dr William J. Hueston<sup>2</sup> provides clinically useful information derived from an ongoing study designed to compare the short-term (1 week) symptomatic effects of inhaled bronchodilator, erythromycin, or placebo in patients with bronchitis. In his article entitled "Albuterol Delivered by Metered-Dose Inhaler to Treat Acute Bronchitis,"<sup>2</sup> Hueston presents results suggesting that inhaled bronchodilator therapy for acute bronchitis may be superior to placebo in (1) reducing coughing after 1 week, and (2) enhancing the probability of return to work after 4 days. These endpoints are clinically relevant and important to patients. In a subgroup analysis of patients with and without abnormalities noted on initial lung examination who were treated with inhaled albuterol, Hueston found no differences in the percentages of patients who were cough-free in 7 days, although

his study did not provide data on whether differences in initial pulmonary function were associated with outcomes. This negative finding contrasts with previous work suggesting that clinically beneficial effects of bronchodilator treatment can be predicted on the basis of initial physical findings or objective measures of pulmonary function, or both.<sup>3,4</sup>

Using serial spirometry in a prospective study, Williamson<sup>3</sup> has provided more clear-cut evidence for two subgroups of patients with acute bronchitis: a "normal" group having initial FEV<sub>1</sub> (as percent predicted) of greater than 80% and an "abnormal" group with FEV<sub>1</sub> of 80% or less. During the course of Williamson's observational study, FEV<sub>1</sub> and peak expiratory flow rates returned to normal in both groups by 5 weeks post-illness, although midflow rate (FEF 25% to 75%) remained depressed in the abnormal group. The abnormal patient group (low FEV<sub>1</sub>) reported significantly more days off from work than did the group with normal FEV<sub>1</sub> (2.3 days vs 0.3,  $P < .04$ ). Melbye et al<sup>4</sup> performed a randomized study comparing the symptomatic effect of inhaled fenoterol to placebo in patients with acute bronchitis and found marked symptomatic improvement by the second day of fenoterol treatment in the subgroup of patients who had either wheezes, bronchial hyperresponsiveness, or an FEV<sub>1</sub> < 80% of predicted at randomization. Taken together, the studies of Williamson,<sup>3</sup> Melbye et al,<sup>4</sup> and Hueston<sup>2</sup> suggest that inhaled bronchodilator therapy may offer short-term symptomatic benefit in a specific subgroup of patients suffering the ill effects of acute bronchitis, but several questions remain unanswered.

How do we identify bronchitis in our practices? Once we decide who has bronchitis, how can we determine which patients are likely to benefit from a bronchodilator? How common is the type of bronchitis for which bronchodilator therapy may be helpful? Are there any long-term consequences to acute bronchitis that also merit our attention? Answers to these questions raised by Hueston's study will help guide the practical application of these

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research findings. Further, consideration of these issues may also have important ramifications for the management of chronic asthma.

As noted by Hueston, the definition of bronchitis is ambiguous. His study and others<sup>3,4</sup> have included productive cough in the inclusion criteria for bronchitis, but the criterion of production is admittedly arbitrary,<sup>4</sup> as it is not associated with all bronchitis diagnosed in the community.<sup>5</sup> I have doubts about the utility of insisting on the presence of productive cough to diagnose bronchitis. Should we accept any report of coughing up anything, anytime? Must we insist on production in a sputum cup in the office to make the diagnosis? ("Gee, doc, I could have a minute ago but now I can't"). Or may one confidently diagnose bronchitis in a patient with other systemic signs and symptoms of infection (fever, cough and a negative chest radiograph, for example) but without production? Having performed studies on patients with acute cough considered to be infectious in nature, I conclude that verifiable production of sputum is the exception, not the rule. (I would make the same statement about community-acquired pneumonia, but that is another subject.) In my experience, nonasthmatic adults with acute wheezing illness, who also have objective evidence of reversible airway obstruction, often fail to produce sputum. Exclusion of patients without sputum production may affect the proportion of patients likely to benefit from inhaled bronchodilator in research studies that include only patients with productive cough.

Can we as practitioners predict which patients with bronchitis will benefit from a bronchodilator? My clinical experience, supported by the studies cited above, suggests that a combination of careful history-taking, auscultation, and an in-office administration of inhaled bronchodilator, preferably but not necessarily accompanied by an objective test of airway function, may be helpful in selecting appropriate patients. Symptoms most likely to indicate bronchospasm in acute bronchitis are probably the same as those indicative of bronchospasm in chronic asthma: wheezing, shortness of breath, chest tightness or tight cough that particularly occurs at night or is triggered by exercise or cold air. These symptoms should be carefully sought by the physician. Auscultation of diffuse wheezing, a prolonged expiratory phase, or both suggest, but do not prove, the existence of reversible airway obstruction. Likewise, auscultatory changes after bronchodilator are not always a reliable indicator of effectiveness but may be helpful. It is my practice at the time of the index visit for bronchitis to administer two puffs of albuterol using a metered-dose inhaler (MDI) with a spacer device to patients with acute bronchitis in whom there is clinical evidence of bronchospasm. I offer a prescription for MDI albuterol to patients reporting subjective improvement.

As an adjunct to ongoing research, I also use computerized spirometry in this evaluation, but measurement of peak flow rates or simply clinical evaluation may be equally helpful. The validity of patient self-report of both acute<sup>6,7</sup> and chronic<sup>8</sup> changes in respiratory status have been documented, supporting the impression that my patients' self-assessment of improvement after bronchodilator almost always accurately reflects objective changes in pulmonary function. (This observation may not be generalizable to all patient populations.) Therefore, reliance on patient self-assessment in practices without access to objective measurements of pulmonary function may be a viable alternative, as suggested by Hueston's preliminary observations<sup>2</sup> and other studies.<sup>6-8</sup>

The issue of availability and interpretation of pulmonary function testing in the primary care setting merits discussion. I agree with Barach<sup>9</sup> that every office should have a peak flow meter to assess the need for hospitalization in acute exacerbations of asthma, and there is evidence that many primary care offices also have spirometers available.<sup>10</sup> The necessity for peak flow meters or spirometry in any office likely to encounter asthmatic emergencies allows their use in the assessment of inhaled bronchodilator response in acute bronchitis, as long as costs can be moderated. It is important to note that the magnitude of reversible airway obstruction necessary to predict benefit from bronchodilator treatment in bronchitis patients is less than the amount currently required for the diagnosis of asthma. American Thoracic Society (ATS) criteria for a significant bronchodilator response include an improvement in FEV<sub>1</sub> of 12% or more, with an absolute improvement of 200 mL or greater, whereas the American College of Chest Physicians (ACCP) insists on a change of between 15% and 25%.<sup>11</sup>

The ATS and the ACCP criteria are not homely in that they miss many patients with milder degrees of clinically significant reversible airway obstruction. The upper 95th percentile for response to inhaled bronchodilator in asymptomatic nonsmokers was 9% in a large population-based study.<sup>12</sup> A bronchodilator response of 9% or more was also predictive of symptomatic improvement after bronchodilator treatment in acute bronchitis.<sup>4</sup> One authority<sup>13</sup> states that relative changes are inappropriate and suggests that absolute changes of 190 mL for FEV<sub>1</sub> and 60 L per minute for peak flow rate represent significant reversibility. For offices unable to measure FEV<sub>1</sub>, it will be important to determine what amount of reversibility, as measured by peak flow meter in absolute or relative terms, is associated with symptomatic improvement following bronchodilator treatment in acute bronchitis. Such studies seem ideally suited to collaborative primary care research. Incidentally, many research studies employing a single posttreatment value measure pulmonary function

20 minutes after bronchodilator administration. To obtain meaningful results in the busy clinic setting, however, it is often sufficient to wait only 5 or 10 minutes to document a response meeting or exceeding chosen criteria for reversibility.

Given that we may be able to identify patients with acute bronchitis likely to benefit from a prescription for an inhaled bronchodilator, is it worth our time and effort? How often will we find such patients? The answer is that at least 15% to 30% of primary care patients with bronchitis have associated clinical or spirometric evidence of reversible airway obstruction.<sup>3,14-16</sup> Exceptions are a community-based study,<sup>5</sup> which found that wheezing was noted by 62% of patients but heard on auscultation in only 31%, and Hueston's current study, in which 41% of patients wheezed on initial examination. This high frequency suggests that it is worthwhile to identify and treat the subgroup of bronchitis patients likely to benefit from bronchodilator therapy. The high frequency of this type of bronchitis is also one justification for naming the condition.

*Adult acute asthmatic bronchitis* is a term which, like the early Homeric epics, appears to have had a long and well-recognized verbal tradition in the primary care community but is not yet written down, in the sense that I have been unable to find a textbook of pulmonology in which adult acute asthmatic bronchitis is defined or acknowledged to exist. A provisional definition of asthmatic bronchitis includes the presence of symptoms, signs and objective evidence of acutely reversible airway obstruction (bronchospasm) in an adult with acute infectious bronchitis who does not have a history of adult asthma. The term *acute asthmatic bronchitis* (AAB) must be carefully distinguished from *chronic asthmatic bronchitis* (CAB), which refers to a different clinical entity. CAB refers to patients for whom the diagnoses of chronic bronchitis and asthma coexist, or are difficult to distinguish.<sup>17</sup> An additional criterion for chronic bronchitis is that a patient must produce sputum for at least 3 months of the year for 2 consecutive years, making this condition, compared with AAB, rare in my experience as a primary care clinician. The striking inverse relationship between the frequencies of AAB and CAB in primary care and their documentation in textbooks of pulmonology underscores the need for primary care physicians to continue to "establish a knowledge base for primary care," as advocated by Williamson<sup>1</sup> and as exemplified by the work of Hueston<sup>2</sup> in this issue of *The Journal*.

Apart from the immediate benefits of appropriate symptomatic treatment, are there any long-term consequences to acute bronchitis that also merit our attention? There are associations between acute bronchitis and asthma that may be etiologically important. *Wheezy bron-*

*chitis*<sup>18</sup> refers to episodes of wheezing during acute bronchitis. This definition has been applied mainly to children in whom associations between viral infections,<sup>19</sup> exacerbations of asthma<sup>20</sup> and an atopic disposition<sup>21</sup> have been well documented. Some children with wheezy bronchitis, however, do not have chronic asthma, and it has been suggested that acute bronchitis in adults may be the clinical analog of this type of childhood wheezy bronchitis.<sup>3</sup> Relationships between acute bronchitis and the subsequent development of chronic asthma have been less extensively documented in adults than in children but appear to exist. For example, Hallett and Jacobs<sup>22</sup> reported that two thirds of patients with recurrent acute bronchitis referred to an allergy clinic actually had asthma, and Williamson<sup>15</sup> found that, of a group of relatively unselected primary care adult outpatients with acute bronchitis, 16% were diagnosed with asthma in the 5 years subsequent to their bronchitis episode, compared with 1.7% of a control group ( $P=.01$ ). Although it is possible that previous episodes diagnosed as bronchitis in these reports could simply have been misdiagnosed asthma, clinical evidence suggests otherwise,<sup>3</sup> raising the possibility of an etiologic link between infectious bronchitis and subsequent asthma.

Not only may a general etiologic association exist between infectious bronchitis and subsequent chronic asthma, recent evidence has suggested that a specific respiratory pathogen may play an important role in the development of asthma from bronchitis.<sup>14,23-27</sup> While exploring the prevalence of acute *Chlamydia pneumoniae* infection as a cause for acute bronchitis and pneumonia, my colleagues Ruth Dodge and Rjurik Golubjatnikov and I made the serendipitous discovery of extremely strong serologic associations between antibody suggesting chronic *C pneumoniae* infection and wheezing, asthmatic bronchitis, and adult-onset asthma.<sup>14</sup> Our original report also included the observation that adult-onset asthma often developed after one or more episodes of acute asthmatic bronchitis, and we reported a few patients in whom appropriate antichlamydial antimicrobial therapy successfully eradicated or ameliorated established asthma.<sup>14</sup> Prospective studies have subsequently confirmed these *C pneumoniae* serologic associations in adult acute asthmatic bronchitis and pulmonary function-confirmed asthma,<sup>26</sup> the development of asthma from asthmatic bronchitis,<sup>26</sup> and the positive therapeutic effects of antichlamydial antimicrobial therapy.<sup>27</sup> This may be one reason for the popularity of erythromycin among clinicians in the community who treat bronchitis. Although additional confirmatory evidence is beginning to accumulate from a variety of sources,<sup>28</sup> a *C pneumoniae*-asthma etiologic association must be regarded as unproven at this time largely because of the difficulty in isolating the organism to prove Koch's postulates, and the lack of an

animal model in which to study pathophysiologic mechanisms.

The *C pneumoniae*-asthma association must be kept in mind when interpreting the reported lack of effect at 1 week of erythromycin therapy in ameliorating bronchitis symptoms, as reported in Hueston's study.<sup>2</sup> It is likely that most patients with acute bronchitis have viral rather than bacterial infections, and a review of the current literature does not support antibiotic treatment for *all* acute bronchitis.<sup>29</sup> Studies upon which this conclusion is based did not investigate whether identifiable subtypes of acute bronchitis might have differential responses to antimicrobial therapy. In this regard a recent study isolated *C pneumoniae* in 16 (26%) of 62 acute bronchitis patients, many of whom had asthmatic bronchitis.<sup>30</sup> When assessed 6 weeks after treatment, all but 2 patients were cured (13 patients) or improved (1 patient) after receiving azithromycin, 1500 mg over 5 days. A further interesting finding in this study was that 9 (56%) patients remained culture positive after therapy despite clinical improvement and that at least two of these patients went on to develop adult-onset asthma in the ensuing months. For reference, the prevalence of *C pneumoniae* in unselected acute bronchitis is 5% or less.<sup>31</sup>

It is now well established that asthma is related to T-cell-mediated bronchial inflammation, which may resolve only very slowly after removal of the original antigenic triggers that initiated the inflammatory cascade.<sup>32</sup> Applying this concept to acute asthmatic bronchitis, if bacteria susceptible to erythromycin were causing an inflammatory reaction and bronchospasm, it is unlikely that improvement would occur within 7 days, since it should take weeks or even months for the inflammatory reaction caused by a bacterial antigen to subside after "antigen removal" by effective antimicrobial treatment. It is notable that resolution of asthma did not occur until 6 to 8 weeks after initiation of antimicrobial therapy in cases of presumed<sup>27</sup> and culture-confirmed chlamydial asthma (Hahn DL, unpublished data, 1993). These considerations suggest that longer term outcomes are to be preferred over short-term results in future randomized controlled trials of antimicrobial therapy for acute bronchitis.

Most physicians administer antibiotics to patients with acute bronchitis despite lack of evidence of effectiveness from controlled trials.<sup>29</sup> Preliminary results support the use of prolonged courses of antichlamydial antimicrobial therapy in some cases of adult-onset asthma.<sup>23,27,33</sup> Should we prescribe antibiotics for adult-onset asthmatics who are *C pneumoniae* seroreactive or, when serologic results are unavailable, for those with a history of previous episodes of acute asthmatic bronchitis? There are as yet no controlled studies to help answer this question. My clinical experience suggests that about one half of such pa-

tients will respond, some dramatically, to appropriately long courses of antichlamydial therapy. My experience involves the administration of doxycycline, 100 mg twice daily, and azithromycin, 1000 mg once weekly (a single 1-g oral dose of azithromycin is effective for uncomplicated urethritis and cervicitis caused by *C trachomatis*, a closely related organism). On the basis of *in vitro* sensitivities, clarithromycin, 500 mg twice daily, may also be effective. I avoid the use of traditional erythromycin preparations in chronic therapy because of the likelihood of adverse gastrointestinal effects and the difficulty in maintaining continuous intracellular chlamydia levels with these short half-life preparations.

The specific antibiotic may not be as important as the *duration of therapy*. In my experience, a *minimum of 3 weeks of continuous therapy* is necessary to ameliorate or eradicate symptoms and spirometric signs of early chronic asthma in some patients. *Six weeks of therapy* has often been required in established asthma, and I have obtained positive results only after *2 to 3 months of continuous therapy* in a few patients with advanced severe asthma and chronic obstructive pulmonary disease. Medication adherence has been excellent in this highly motivated patient group, and side effects have been equivalent to those of standard dosing. I have yet to encounter a patient with adult-onset asthma who did not appreciate the advantages of possible curative therapy as opposed to lifelong palliation with inhaled steroids. Clearly, however, the danger of promiscuous overuse accompanies any recommendation for empiric antibiotic treatment based solely on uncontrolled clinical observations. Proper subject selection, optimal dosing, frequency of success and risk of relapse remain topics for future research, preferably in the setting of blinded, randomized controlled trials. To paraphrase Williamson,<sup>1</sup> asthmatic bronchitis is homely, asthma is not. In regard to the entire spectrum of reactive airway diseases, we as primary care physicians may now have the opportunity both to offer improved symptomatic relief to bronchitis sufferers by the judicious prescription of inhaled bronchodilators, and to make major contributions to the understanding, treatment, and perhaps even prevention of adult asthma by applying our developing research skills to the study of this important disease whose etiology remains largely a mystery.<sup>34</sup>

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