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Acute Brochitis

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CLINICAL PRACTICE

Acute Bronchitis

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

A 40-year-old man with no underlying lung disease has a 7-day history of mild shortness of breath with exertion, as well as cough that is now productive of purulent sputum. He reports no paroxysms of cough and no contact with ill persons in his community. He does not appear to be in distress. His temperature is 37°C, his pulse 84 beats per minute, and his respiratory rate 17 breaths per minute. On auscultation of the lungs, no rales are heard; scattered wheezes are heard in the lung bases. How should he be evaluated and treated?

THE CLINICAL PROBLEM

Acute bronchitis is a clinical term implying a self-limited inflammation of the large airways of the lung that is characterized by cough without pneumonia. The disorder affects approximately 5% of adults annually,[1,2] with a higher incidence observed during the winter and fall than in the summer and spring. In the United States, acute bronchitis is the ninth most common illness among outpatients, as reported by physicians.[3]

Viruses are usually considered the cause of acute bronchitis but have been isolated in a minority of patients.[1,4] Those isolated in acute bronchitis (from the most to the least common in large series) include influenza A and B viruses, parainfluenza virus, respiratory syncytial virus, coronavirus, adenovirus, and rhinovirus. Human metapneumovirus has been identified as a causative agent.[5-7] A recent French study involving adults who had been vaccinated against influenza showed a viral cause in 37% of 164 cases of acute bronchitis, of which 21% were rhinovirus.[4] Thus, the yield of specific pathogens varies according to several factors, including the presence or absence of an epidemic, the season of the year, and the influenza vaccination status of the population.

Bacterial species commonly implicated in community-acquired pneumonias are isolated from the sputum in a minority of patients with acute bronchitis.[1] However, the role of these species in the disease or its attendant symptoms remains unclear, because bronchial biopsies have not shown bacterial invasion. In some cases, atypical bacteria are important causes, including *Bordetella pertussis*, *Chlamydophila* (*Chlamydia*) *pneumoniae*, and *Mycoplasma pneumoniae*.[1] Some data have suggested that *B. pertussis* may underlie 13 to 32% of cases of cough lasting 6 days or longer, although in a recent prospective study, *B. pertussis* comprised only 1% of cases of acute bronchitis.[8]

PATHOBIOLOGY

Acute bronchitis is thought to reflect an inflammatory response to infections of the epithelium of the bronchi. Epithelial-cell desquamation and denuding of the airway to the level of the basement membrane in association with the presence of a lymphocytic cellular infiltrate have been demonstrated after influenza A tracheobronchitis[9];

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microscopical examination has shown thickening of the bronchial and tracheal mucosa corresponding to the inflamed areas. Such pathological findings are consistent with reports of proximal lower airway inflammation confined to the bronchi, as detected by positron-emission tomography with ^{18}F-fluorodeoxyglucose as a tracer, in the setting of acute bronchitis.[10]

However, there are wide variations in the anatomical distribution of many pathogens that cause acute bronchitis. In a study involving volunteers exposed to rhinovirus infections, for example, virus was detected in specimens of induced sputum obtained from all the subjects, in approximately one third of bronchial biopsy specimens, in almost a quarter of bronchoalveolar lavage specimens, and in more than a third of bronchial brushing specimens.[11] Such data indicating viral infection of the lower airways may help to explain the relationship observed between rhinovirus infection (and other presumed upper respiratory viral infections) and exacerbation of asthma.[12] Thus, although its name suggests only large-airway disease, acute bronchitis may be accompanied by an array of symptoms, depending on the degree of viral involvement of the large and small airways.

NATURAL HISTORY

During the first few days of infection, the symptoms of mild upper respiratory infections cannot be distinguished from those of acute bronchitis. However, with acute bronchitis, coughing persists for more than 5 days, and during this protracted period the results of pulmonary function testing may become abnormal. Forty percent of patients have significant reductions in the forced expiratory volume in 1 second (i.e., a value below 80% of the predicted value)[13] or bronchial hyperreactivity, as measured by bronchial provocation,[14] with improvement during the following 5 to 6 weeks.

Cough after acute bronchitis typically persists for 10 to 20 days but occasionally may last for 4 or more weeks. In a recent report on a clinical trial of the efficacy of an acellular pertussis vaccine involving 2781 healthy adults, the median duration of cough from acute bronchitis due to all causes was 18 days (mean, 24).[8] In addition, approximately 50% of patients with acute bronchitis report the production of purulent sputum. In otherwise healthy patients, purulent sputum usually indicates the presence of sloughed tracheobronchial epithelium and inflammatory cells, and its positive predictive value for the presence of alveolar disease is low (approximately 10%).[15]

A study of the quality of life of patients with upper respiratory tract infections, some of whom had received a diagnosis of acute bronchitis, showed significant decrements in seven subscales of the Medical Outcomes Study 36-item Short-Form General Health Survey, including vitality and social functioning,[16] but such decrements are presumed to be transient. Data on short- or long-term outcomes are limited, but one study indicated that within a month after the initial visit, up to 20% of patients had reconsulted their physicians because of persistent or recurrent symptoms.[1] The effect of an episode of acute bronchitis on a patient's subsequent lung health is uncertain. In one study, 34% of patients with acute bronchitis received a new diagnosis of chronic bronchitis or asthma at 3 years of follow-up.[17] In another study, mild bronchial asthma was diagnosed on the basis of spirometry or bronchial provocation in 65% of patients with recurrent episodes of acute bronchitis.[18] However, these studies lacked control groups, and it is unclear whether acute bronchitis led directly to the chronic condition or whether the chronic disorder or the propensity for its development was present at the time of the inflammation of the large airway.

STRATEGIES AND EVIDENCE

DIAGNOSIS

Acute bronchitis should be differentiated from acute inflammation of the small airways — asthma or bronchiolitis — which typically presents as progressive cough accompanied by wheezing, tachypnea, respiratory distress, and hypoxemia. It should also be distinguished from bronchiectasis,[19] a distinct phenomenon associated with permanent dilatation of bronchi and chronic cough. The diagnosis of chronic bronchitis is reserved for patients who have cough and sputum production on most days of the month for at least 3 months of the year during 2 consecutive years.[20] The acute exacerbation of chronic bronchitis, identified by the worsening air flow and symptoms in such patients, is not discussed here.

A careful history taking, including reports of contact with ill people, and physical examination may suggest a specific cause (Table 1). A common presentation of pertussis is cough of 2 to 3 weeks'

Table 1. Recognized Causes of Acute Bronchitis and Options for Therapy.*

Pathogen	Comments†	Options for Therapy
Virus		
Influenza virus	Precipitous onset with fever, chills, headache, and cough. Myalgias are common and may be accompanied by myositis, myoglobinuria, and elevated serum levels of muscle enzymes.	Oseltamivir (Tamiflu, Roche) for 5 days at a dose of 75 mg twice daily[21] or zanamivir (Relenza, GlaxoSmithKline) for 5 days at a dose of two puffs (5 mg/puff) twice daily, for a total daily dose of 20 mg[21]
Parainfluenzavirus	Epidemics may occur in autumn. Outbreaks may occur in nursing homes. Croup in a child at home suggests the presence of the organism.	None available
Respiratory syncytial virus	Family history is important: approximately 45% of family members exposed to an infant (≤1 yr of age) with bronchiolitis become infected.[22] Outbreaks occur in winter or spring. Twenty percent of adults have ear pain.[23]	None available
Coronavirus	Pathogen can cause severe respiratory symptoms in elderly patients. Epidemics of strain 0C43 with high attack rates have been reported among military recruits.[24]	None available
Adenovirus	Infection is clinically similar to influenza, with abrupt onset with fever.	None available
Rhinovirus	Fever is uncommon, and infection is generally mild.	None available
Atypical bacteria		
Bordetella pertussis	Incubation period is 1–3 wk. Primarily affects adolescents and young adults. In some series, 10 to 20% of patients have cough with a duration of >2 wk.[13] Whooping occurs in a minority of patients.[19] Fever is uncommon. A marked leukocytosis with lymphocytic predominance can occur.	Macrolides as first-line therapy[25]: Azithromycin (Zithromax, Pfizer) for 5 days at a dose of 500 mg on day 1 and 250 mg on days 2–5 or Erythromycin (Ery-Tab, Abbott) for 14 days at a dose of 500 mg 4 times daily or Clarithromycin (Biaxin, Abbott) for 7 days at a dose of 500 mg twice daily Second-line therapy[25]: Trimethoprim–sulfamethoxazole (Bactrim, Roche) for 14 days at a dose of 1600 mg once daily or 800 mg twice daily
Mycoplasma pneumoniae	Incubation period is 2–3 wk. Gradual onset (2–3 days) distinguishes this infection from influenza. Clusters occur among military recruits and students in boarding schools.	Azithromycin for 5 days at a dose of 500 mg on day 1 and 250 mg on days 2–5 or doxycycline (Vibramycin, Pfizer) for 5 days at a dose of 100 mg twice daily or no therapy‡
Chlamydophila pneumoniae	Incubation period is 3 wk. Onset of symptoms, which include hoarseness before cough, is gradual. Clusters reported among military recruits, college students, and patients in nursing homes.	Azithromycin for 5 days at a dose of 500 mg on day 1 and 250 mg on days 2–5 or doxycycline for 5 days at a dose of 100 mg twice daily or no therapy‡

* The cause of many cases remains uncertain. The presence or absence of a community epidemic, the time of year, the population affected, and influenza immunization status are important risk factors for specific pathogens. Viruses generally have an incubation period of 2 to 7 days, whereas the three atypical bacteria have longer incubation periods. Such information may be helpful if the interval after contact with ill persons is known. A gradual onset of symptoms (2 to 3 days) is more characteristic of bacterial causes than of most viral causes.
† Diagnostic testing is most useful for identifying treatable causes when an infectious agent is circulating in the community and for identifying a cause in an outbreak.
‡ There are no compelling data suggestive of improved outcomes of acute bronchitis as a result of treatment with antibiotic agents.

duration in an adolescent or young adult; fever is less common in pertussis than in viral bronchitis.[18,26] However, in the absence of an epidemic, the positive predictive value of young age, prolonged cough, or the absence of fever is low for pertussis. During an epidemic of influenza, the finding of both cough and fever was reported to have a positive predictive value of 79% for this condition.[27]

DIAGNOSTIC TESTING

At the bedside, cough in the absence of fever, tachycardia, and tachypnea suggests bronchitis, rather than pneumonia. In fact, the presence of normal

vital signs and the absence of rales and egophony on chest examination minimize the likelihood of pneumonia to the point at which further diagnostic testing is usually unnecessary.[28] An exception, however, is cough in elderly patients; pneumonia in elderly patients is often characterized by an absence of distinctive signs and symptoms. Among patients 75 years of age or older who had community-acquired pneumonia, only 30% had a temperature above 38°C, and only 37% had a heart rate of more than 100 beats per minute.[29]

Rapid diagnostic tests exist for several pathogens currently linked to acute bronchitis. However, not all the rapid tests are widely available, and their routine use is not cost-effective in an outpatient setting. Rapid tests should be used primarily when the suspected organism is treatable, the infection is known to be circulating in the community, and the patient has suggestive symptoms or signs (e.g., testing for influenza during influenza season in patients with cough and fever) (Table 1). Multiplex polymerase-chain-reaction (PCR) testing of nasopharyngeal swabs or aspirates is being developed to diagnose infections resulting from *B. pertussis*, *M. pneumoniae*, or *C. pneumoniae* with clinically useful sensitivity and specificity, as compared with culture or monoplex PCR.[30]

TREATMENT

Antimicrobial Therapy

Antimicrobial agents are not recommended in most cases of acute bronchitis. Systematic analyses of clinical trials have suggested that antibiotics may reduce the duration of symptoms, but at best modestly. Specifically, a meta-analysis of eight trials involving patients with acute bronchitis suggested that symptoms were reduced by a fraction a day with the use of erythromycin, doxycycline, or trimethoprim–sulfamethoxazole. The results were statistically significant but clinically trivial.[31] Results of a randomized, double-blind trial comparing a 5-day course of azithromycin in 112 patients with vitamin C in 108 patients (total dose of each agent, 1.5 g), published after the meta-analysis had been completed, showed no difference between groups in the health-related quality of life at 7 days (the primary outcome) or in the proportion of patients who returned to work, school, or usual activities at home on day 3 or 7.[32]

A Cochrane Review of nine randomized, controlled trials of antibiotic agents (including three trials not included in the previous review[31]) also showed a significant but minor reduction in the duration of cough (0.6 day).[33] There was a nonsignificant reduction in the number of days of feeling ill and a nonsignificant increase in adverse events attributed to antibiotics (relative risk of adverse events, 1.22; 95% confidence interval, 0.94 to 1.58).

Antimicrobial therapy may be more beneficial when a treatable pathogen is identified than when a treatable pathogen is not identified. For example, anti-influenza agents (including oseltamivir and zanamivir) decrease the duration of symptoms by approximately 1 day and result in an earlier return to normal activity (by 0.5 day) among patients with infections caused by susceptible viruses. Prompt antibiotic treatment of patients with pertussis is indicated to limit transmission, but (with the possible exception of therapy initiated during the first week of symptoms) there are no compelling data to support the prospect that cough will be less severe or less prolonged with antibiotic therapy. Similarly, although several classes of antibiotics have in vitro activity against *M. pneumoniae* and *C. pneumoniae*, it is unclear whether antibiotic treatment of bronchitis linked to these organisms influences outcomes. Table 1 includes suggested antimicrobial therapy for cases in which such therapy is considered.

Other Therapy

The few randomized, placebo-controlled trials that have examined the effect of β_2-agonists administered orally or by aerosol for cough associated with acute bronchitis have involved small numbers of patients and have had mixed results.[34-36] In these studies, among patients without preexisting lung disease, daily cough scores and the likelihood of persistent cough after 7 days did not differ significantly between the active treatment and placebo groups. However, in one trial, a subgroup of patients with evidence of airflow limitation had significantly lower scores for symptoms on day 2 after treatment with β_2-agonists.[34] A recent Cochrane Review of five trials involving 418 adults showed that even among patients with airflow obstruction, the potential benefit of β_2-agonists is not well supported and should be balanced against the adverse effects of treatment.[37] In practice, a brief trial (7 days) of inhaled or oral corticosteroids may be reasonable for troublesome cough (i.e., cough persisting for more than 20 days), but there are no clinical trial data to support this approach. Data

from clinical trials are also not available to support the use of mucolytic or antitussive agents.

AREAS OF UNCERTAINTY

Distinguishing the minority of cases of acute bronchitis due to a treatable cause from those due to currently nontreatable viruses is often challenging. Recently, the measurement of serum levels of procalcitonin, which is typically elevated in bacterial infections, has been proposed as a means of identifying patients in whom treatment with antibiotics is warranted. In one clinical trial, low levels of procalcitonin (<0.1 μg per liter) were used to discriminate safely between patients with cough or dyspnea who did not require antibiotic therapy, such as those with acute bronchitis,[38] and patients who did require such therapy. However, more data are needed to validate the usefulness of the procalcitonin test for discriminating between patients with bronchitis and those with pneumonia.

Although clinicians might argue that the pressure of time influences the prescribing of antibiotics, the data do not support this contention. A recent study involving almost 4000 adults with upper respiratory tract infections showed that the mean duration of an office visit was 14.2 minutes when antibiotics were prescribed, as compared with 15.2 minutes when no prescription for antibiotics was given.[39]

Previous studies involving volunteers exposed to rhinovirus showed that nonsteroidal drugs alone or in combination with antihistamines reduced the severity of symptoms, including cough.[40] However, the effects of either drug alone or their combination in naturally occurring acute bronchitis have not been evaluated. Results of a single randomized trial involving 486 adults with acute bronchitis suggested a clinical benefit of an extract of the roots of *Pelargonium sidoides,* but the data require confirmation.[41]

GUIDELINES

According to the 2001 guidelines of the American College of Physicians for the treatment of uncomplicated acute bronchitis, antibiotic treatment is "not recommended, regardless of duration of cough."[42] According to the 2006 guidelines of the American College of Chest Physicians (ACCP) for treating acute bronchitis, routine treatment with antibiotics is not justified, antitussive agents are only occasionally useful, and there is no routine role for inhaled bronchodilators or mucolytic agents.[43] However, these guidelines note that subgroups of patients with chronic airflow obstruction at baseline or wheezing at the onset of illness do have a benefit from β_2-agonists. Inhaled anticholinergic agents are not recommended. These guidelines have been criticized on the grounds that many of the recommendations were based "more on opinion than on evidence."[44]

Both the ACCP guidelines and guidelines of the Centers for Disease Control and Prevention (CDC) recommend macrolides as first-line therapy for pertussis.[25,43] For infection with influenza A virus, in January 2006 the CDC recommended therapy with either oseltamivir or zanamivir,[21] noting that the circulating H3N2 strains of influenza A virus were almost uniformly resistant to both first-generation drugs (amantadine and rimantadine).

SUMMARY AND RECOMMENDATIONS

The patient described in the vignette most likely has a viral infection causing uncomplicated acute bronchitis. On the basis of data from clinical trials, antibacterial agents are not recommended. Chest radiography is not indicated, given the absence of signs of pneumonia on physical examination. In the absence of an influenza outbreak in the community, no rapid testing for viral causes should be ordered, and no antiviral therapy should be prescribed; influenza is especially unlikely in a patient who is afebrile. In the absence of a history of contact with a person with suspected pertussis (or a person with a history of persistent cough), this diagnosis is unlikely. If paroxysms of cough developed later or if whooping or post-tussive vomiting occurred, testing for pertussis would be reasonable. The patient should be advised that the cough may persist for an additional 10 to 21 days and that infrequently, it persists longer. For his wheezing and shortness of breath with activity, clinical experience suggests that a β_2-agonist such as albuterol may provide relief, although data from clinical trials are inconsistent. On the basis of clinical experience, the patient might be offered short-term use of codeine or hydrocodone-containing preparations or inhaled corticosteroids if the cough is persistent, although data from trials to support their use are lacking.

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