6

Infectious Bronchitis

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INTRODUCTION

It has been estimated that approximately 18 million episodes of bronchitis are treated in an ambulatory care setting in the United States each year.[1] These inflammatory events produce troublesome symptoms, often result in absenteeism from work, and, on occasion, threaten the life of the patient. With the introduction of new culture and serological techniques, the infectious organisms contributing to actue bronchitis and the exacerbation of chronic bronchitis are being more completely defined. This chapter reviews contemporary concepts pertaining to the pathogenesis, microbiology, clinical features, differential diagnosis, therapy, and prevention of bronchitis in adults.

ACUTE BRONCHITIS

Acute bronchitis is an inflammatory disorder of the bronchi that occurs most commonly during the winter. The disease is usually preceded by or associated with coryza, pharyngitis, and headache and is frequently caused by viruses, particularly rhinovirus, coronavirus, adenovirus, and influenza virus, less commonly by *Mycoplasma pneumoniae,* and rarely by bacterial pathogens including *Legionella* sp. and *Bordetella pertussis.* Both *Legionella pneumophila* and *Legionella feeleii* produce a self-limiting influenzalike illness known as Pontiac fever.

Pontiac fever occurs in epidemic form in individuals exposed to droplet nuclei of aerosols of contaminated water.[2] The disease is ushered in acutely, and the clinical manifestations consist of shaking chills, headache, myalgias, sore throat, and a nonproductive cough. Patients demonstrate a leukocytosis, but the

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chest x ray does not reveal an infiltrate. Pontiac fever is a self-limiting disorder, and secondary spread does not occur among family members.

Recently, a new respiratory pathogen capable of causing both acute bronchitis and pneumonia in adults has been identified.[3] The pathogen is a new strain of *Chlamydia psittaci* known as the TWAR agent. Currently, the ability to detect this organism, by culture or serological tests, remains restricted to a very small number of reference laboratories.

The hallmark of acute bronchitis is cough, and approximately one half of the patients with acute bronchitis produce sputum. As a general rule, when acute bronchitis is caused by rhinovirus or coronavirus, patients remain afebrile. When the disease is caused by adenovirus, influenza, or *M. pneumoniae,* patients are often febrile. In evaluating a patient with acute bronchitis, there is no need to analyze the sputum or blood. Chest x rays are indicated only for those elderly patients with fever and/or rales.

Acute bronchitis is usually a self-limiting infection. Bronchitis caused by influenza, however, can be complicated by viral pneumonia or a secondary bacterial pneumonia, both life-endangering diseases.

During the last year, cases have been reported of patients who developed staphylococcal-induced toxic shock syndrome in the wake of influenza-B-related acute bronchitis.[4] This sequence of events was first described by Thucydides, Greek historian of the fifth century BC.

Antibiotics are not indicated for the management of acute bronchitis. A placebo-controlled study failed to identify any advantage with the use of an antibiotic.[5] Treatment is directed at controlling cough and fever. Codeine is the preferred antitussive medication. Glyceryl guaiacolate has no documented ability to reduce cough frequency.[6]

Physicians should consider prescribing amantadine hydrochloride, 100 mg orally twice daily, for patients with suspected influenza-A-related bronchitis. Amantadine shortens the duration and severity of the symptoms and has been found to be more effective than aspirin in relieving signs and symptoms. In addition, amantadine accelerates resolution of the altered function of the peripheral airways that occurs as a result of influenzal bronchitis. To be effective, amantadine must be prescribed within 48 hr of the onset of symptoms. Adverse reactions attributed to amantadine include anxiety, lethargy, and anorexia, and in those predisposed patients, this medication can induce a seizure. Amantadine should not be administered to patients who are pregnant, have a seizure disorder, are performing work requiring constant alertness, or are receiving chlopheniramine. The dose of amantadine must be reduced in the patient with renal insufficiency.[7]

There are data to indicate that ribavirin is an effective oral therapy for disease caused by influenza A and B. This compound is not currently FDA approved for this indication, however.

CHRONIC BRONCHITIS

Chronic bronchitis, a disease characterized by mucosal inflammation of the cartilaginous airways, represents a response to chronic bronchial irritation. Patients experience a chronic or recurrent productive cough. To satisfy the official definition, the productive cough should be present almost every day for a minimum of 3 months in 1 year and for not less than two successive years.[8] Approximately 7.5 million Americans have chronic bronchitis.

There are a number of alternative diseases that cause chronic cough and sputum production over a period of years. These diseases, such as cystic fibrosis, bronchietasis, and asthma, need to be excluded before the diagnosis of chronic bronchitis is accepted.

Among American women a disturbing trend has developed over the last 20 years. More women now are considered "heavy" smokers, and these women inhale deeply. In fact, there is 300% more bronchitis and emphysema among women who smoke, and lung cancer has become the leading cause of cancer death in women. In 1983 there were 41,000 new cases of lung cancer and 35,000 deaths from cancer among American women. The risk for fatal and nonfatal cardiac events is also enhanced for women who smoke.[9]

For patients with bronchitis, the prognosis is related to the degree of airflow obstruction and the age at which spirometric abnormalities are first identified.[8] Smoking cessation is the single most important therapeutic maneuver that can alter the course of chronic bronchitis with airflow obstruction.[10,11] Among the identifiable causes of chronic bronchitis are cigarette smoking, air pollution, and perhaps respiratory illness in early life.[12]

Physicians should encourage their patients to stop smoking. It is important, however, to appreciate that nicotine is six to eight times more addictive than alcohol and that patients are concerned with the withdrawal syndrome, which consists of increased appetite and decreased ability to concentrate.

An exacerbation of chronic bronchitis is considered to have occurred when the patient experiences a worsening cough accompanied by purulent or mucopurulent sputum. Inconsistent manifestations of the exacerbation consist of malaise. increasing dyspnea, fever, and leukocytosis.During the exacerbation there can be rhonchi, coarse rales, wheezes, or decreased breath sounds. There can be no abnormality detected. Since the abnormalities can be present when the patient's condition is stable, the detection of these ausculatory findings has no diagnostic value. Objective findings that develop with the exacerbation of chronic bronchitis include an elevated sedimentation rate, a decreased vital capacity, and a decreased forced expiratory volume in the first second. The exacerbation of chronic bronchitis has attracted considerable medical attention, because for the patient it often results in incapacitation, medical costs, lost work time, and, less commonly, hospitalization, respiratory failure, and even death.

A number of factors are considered to be able to precipitate an exacerbation of chronic bronchitis: infection, hypersensitivity with acute bronchospasm, and environmental irritants. With regard to the "infectious" exacerbation of chronic bronchitis, this is believed to develop because of the combined effects of retained secretions, diminished cough, decreased mucociliary activity, and unrestrained multiplication of respiratory pathogens.

Whether infection contributes to the onset or perpetuation of the exacerbation has been disputed for a number of years, since there are studies that both support and refute a role for viruses, *M. pneumoniae, Streptococcus pneumoniae, Haemophilus influenzae,* and *Branhamella catarrhalis.* In fact, the resolution of this issue has been hampered by the assumption that patients with chronic bronchitis invariably have bacteria colonizing their bronchi. A more recent investigation, however, indicates that patients with chronic bronchitis do not invariably have a tracheobronchial microflora but that colonizing of the bronchi occurs selectively in those patients who continue to smoke.[13]

There are three lines of evidence that indicate that specific bacterial respiratory pathogens, such as *H. influenzae* and *S. pneumoniae,* contribute to the infectious exacerbation of chronic bronchitis. When transtracheal aspiration is performed on patients experiencing an exacerbation, *S. pneumoniae* and *H. influenzae,* as well as α-hemolytic *Streptococcus* and *Neisseria* spp. (? *B. catarrhalis*), are the bacteria most commonly isolated.[14] *Branhamella catarrhalis,* a gram-negative diplococcus that resembles two other respiratory pathogens by Gram stain, namely, *Neisseria meningitidis* and *Acinetobacter* sp., has been incriminated as a cause of exacerbation of chronic bronchitis. Antibody develops in patients who manifest purulent bronchitis associated with the recovery of *H. influenzae.*[15] Antibiotic therapy has been documented to be effective treatment for a specific segment of patients with an exacerbation of chronic bronchitis.[16]

It has been suggested that the elaboration of an IgA protease enzyme by *H. influenzae* and *S. pneumoniae* inactivates secretory IgA in the bronchial epithelium, thereby permitting these respiratory pathogens to adhere to and invade the bronchial epithelium.[17] This mechanism would not explain the role of *B. catarrhalis,* however, since this bacterium does not produce IgA protease.[18] It has also been suggested that secretory IgA blocks the bactericidal and opsonizing effect of antibody to nontypable *H. influenzae,* thereby allowing for colonization and subsequent invasive bronchitis by this organism.[19]

Since 1974, an increasing number of *H. influenzae* strains, both typable and nontypable, have been noted to be resistant to ampicillin. The most common ampicillin-resistant mechanism is explained by the elaboration in the periplasmic space of a β-lactamase enzyme mediated by a plasmid. The β-lactamase hydrolyzes the amide bond of the β-lactam nucleus, thereby rendering ampicillin inactive. Some strains of type B *H. influenzae* are resistant to ampicillin because of altered penicillin-binding proteins in the bacterium's plasma membrane, and

presumably others are resistant because of an alteration of the organisms's outer membrane proteins (porins) that regulate drug diffusion. Many strains of *B. catarrhalis* also elaborate an inactivating enzyme, but this is a chromosome-mediated β-lactamase.

In this era of cost containment, physicians have reconsidered the need to obtain a complete blood count, Gram stain of sputum, sputum culture, or blood culture when evaluating patients in an outpatient setting. Sputum culture adds to the costs and requires 48 hr for identification and susceptibility data. If sputum is not processed, however, there will be no recognition of β-lactamase-producing *H. influenzae* and *B. catarrhalis*. All patients with exacerbations of chronic bronchitis merit chest x rays to exclude coexisting pneumonia, tuberculosis, or pulmonary neoplasm. The presence or absence of fever or leukocytosis does not effectively differentiate an exacerbation from pneumonia.[20]

Traditionally, physicians have prescribed antibiotics for patients experiencing an exacerbation. Physicians are convinced that patients improve faster and are concerned that patients will develop respiratory failure. Physicians also feel that antibiotics can forestall progressive pulmonary deterioration. Since the introduction of the sulfonamides, the value of administering an antimicrobial agent for the patient with an exacerbation has been an unresolved issue. The previously published studies designed to assess the contribution of the antibiotic have had major methodological and statistical defects. Investigators have often evaluated nonhomogeneous groups, used variable adjunctive therapy, failed to randomize patient entry into the study or to use a double-blind technique, and have not monitored drug compliance. Other researchers have failed to identify the causative infectious agents, exclude patients with pneumonia, or use objective efficacy criteria in their study protocols. In addition, patient entry into the studies has been so limited that if a difference existed among patients receiving antibiotics, the merit of the drug could not be demonstrated statistically.[21]

A recent large study that enrolled 173 patients and evaluated 362 exacerbations appears to have resolved this issue.[16] This randomized placebo-controlled investigation demonstrated that antimicrobial agents, when prescribed for 10 days, were well tolerated and resulted in a more complete resolution of symptoms, less frequent clinical failures requiring intervention (new medication or the need for hospitalization), and achieved a more rapid increase in peak flow rates. Of note is the fact that the patients who benefited from the antibiotic were those individuals who had an exacerbation characterized by increasing dyspnea, sputum volume, and sputum purulence or at least two of these abnormalities. Antibiotics conferred no benefit when only one of these manifestations had occurred.

No study has identified the preferred antimicrobial agent.[22] Erythromycin, prescribed as 500 mg q.i.d., is an inexpensive and safe compound that would be an appropriate selection when the exacerbation is caused by *S. pneumoniae, B.*

catarrhalis, or *M. pneumoniae.* This drug does not possess inhibitory activity for many strains of *H. influenzae,* and it interacts with theophylline, warfarin, carbamazepine, and cyclosporine.

Tetracycline, prescribed as 500 mg q.i.d., is inexpensive and has stood the test of time. There are pneumococci and *H. influenzae* strains that are resistant to tetracycline, however, and this drug can augment azotemia in patients with renal insufficiency. Alternatively, doxycycline, prescribed as 100 mg b.i.d., can be offered. This drug does not affect renal function. Ampicillin, prescribed as 500 mg q.i.d., and amoxicillin, prescribed as 500 mg t.i.d., inhibit the growth of *S. pneumoniae* and most *H. influenzae.* These antibiotics are contraindicated in the patient allergic to penicillin, can cause fever, skin rashes, and diarrhea, and fail to impede the growth of β-lactamase-producing *H. influenzae* and *B. catarrhalis.* Bacampicillin, prescribed as 800 mg b.i.d., is as effective as ampicillin, and it offers several advantages, such as twice-a-day dosage without regard to meals and fewer gastrointestinal side effects.[23] It is more expensive, however.

Trimethoprim–sulfamethoxazole possesses inhibitory activity for *S. pneumoniae* and most *H. influenzae,* including β-lactamase-producing strains. The combination agent can be prescribed as infrequently as twice a day. When prescribed in a dose of two tablets t.i.d. in a randomized blinded controlled study comparing trimethoprim–sulfamethoxazole to tetracycline, 500 mg q.i.d., deterioration in clinical status that required an alternative antibiotic occurred significantly more often in those patients receiving the tetracycline.[24] The disadvantages of this compound are its potential to cause fever and rash and its interaction with numerous other drugs, including warfarin, phenytoin, and oral hypoglycemic agents. Cefeclor possesses a spectrum of activity that includes *S. pneumoniae* and many *H. influenzae,* including β-lactamase-producing strains. This compound is expensive and contraindicated for the patient who has experienced an immediate or accelerated hypersensitivity reaction (anaphylaxis, laryngospasm, giant urticaria) from a penicillin antibiotic. The long-acting cefadroxil should not be considered as an alternative to cefaclor because the former compound does not possess inhibitory activity for *H. influenzae.*

The fixed-dose antimicrobial compound consisting of amoxicillin and clavulanic acid is known as Augmentin®. The clavulanic acid component binds irreversibly to the active sites of many β-lactamase enzymes capable of inactivating amoxicillin. Clavulanic acid functions as a true "suicide inhibitor," since it forms a complex with some β-lactamases, and the complex then decomposes. By removing some β-lactamase hydrolytic enzymes, this allows the amoxicillin component of the combination to exert its inhibitory activity on bacterial respiratory pathogens that are normally resistant to amoxicillin. In essence, the addition of clavulanic acid has extended the spectrum of amoxicillin to include β-lactamase producing strains of both *H. influenzae* and *B. catarrhalis.* The amoxicillin–clavulanic acid combination, however, is expensive, is contraindicated in the penicillin-allergic patient, and often causes diarrhea.

Physicians now have access to a new cephalosporin and a quinolone for treatment of the bacterial exacerbation of chronic bronchitis. The oral cephalosporin cefuroxime axetil possesses excellent inhibitory activity against virtually all strains of *H. influenzae,* and this compound can be administered infrequently.[25] Initial clinical studies with the quinolone ciprofloxacin for the treatment of the bacterial exacerbation of chronic bronchitis appear promising, but this compound is expensive, can interact with theophylline, and does not possess impressive *in vitro* inhibitory activity directed against *S. pneumoniae.*[26]

The conventional duration of antimicrobial therapy for the exacerbation is 10 to 14 days. Ancillary therapies consist of cessation of smoking, adequate hydration, and bronchodilators. No evidence exists, however, that hydration actually facilitates sputum production. Chest physiotherapy and expectorants have not produced consistent, significant improvement. In colder climates, humidification should be considered during the heating season.

Assessing the efficacy of therapy for the exacerbation of chronic bronchitis is crude. The patient should experience a sense of well-being and produce less sputum. There should be a change in the appearance of the sputum, from purulent to mucoid. Clinical improvement is recognized within 3 to 4 days of the onset of therapy, and complete resolution of the exacerbation occurs in approximately 11 days.[22] If clinical improvement does not ensue within 3 to 4 days of the onset of therapy, three concerns surface. Has the patient failed to comply with the therapeutic program? Has an inappropriate medication been prescribed? Should hospitalization be considered to offer an intense supervised therapy or to initiate steroid treatment? Although there are not rigid guidelines, most physicians would hospitalize the patient when the oxygen pressure at room air is <50 mm Hg and/or the carbon dioxide at room air is >50 mm Hg. For the hospitalized patient intravenous methylprednisolone improves airflow.[27] No benefit has been attributed to intravenous aminophylline, however.[28]

In addition to the conventional parameters to measure antimicrobial effectiveness, the suggestion has been made that another important dimension that merits consideration is the posttreatment infection-free period.[22] Unfortunately, this has not been precisely determined for many antimicrobial patients.

An unresolved issue is whether or not patients with chronic bronchitis should receive prophylactic antibiotic during the winter months. Limited data indicate that some patients who take prophylactic antibiotics experience fewer exacerbations and lose less work time. Certainly the data supporting the prophylactic value of influenza vaccine for patients with chronic bronchitis are compelling. The vaccine has been shown to be able to reduce the length of illness of influenza, the necessity for hospitalization, the development of pneumonia, and the number of deaths. For those patients with chronic bronchitis who fail to receive influenza immunization, amantadine should be administered continuously throughout influenza epidemics.

It is important to emphasize that recent influenza vaccines have not been

associated with the development of the Guillain–Barré syndrome and that, contrary to initial reports, influenza vaccine does not inhibit the clearance of warfarin or theophylline.

Although patients with chronic bronchitis are considered prime candidates for immunization with the 23-valent pneumococcal vaccine, there currently exist no published data indicating its prophylactic value in this population.[29] When elderly patients with chronic bronchitis receive pneumococcal vaccine, they do not achieve persistent protective antibody concentrations, and their sera fail to develop adequate opsonizing capacity.

REFERENCES

1. Dixon RE: Economic costs of respiratory tract infections in the United States. *Am J Med* 1985; 78(suppl 6B):45–51.
2. Glick FH, Gregg MB, Berman B, *et al:* Pontiac fever. *Am J Epidemiol* 1978; 107:149–160.
3. Grayston JT, Kuo CC, Wang SP, *et al:* A new *Chlamydia psittaci* strain, TWAR, isolated in acute respiratory tract infections. *N Engl J Med* 1986; 315:161–168.
4. MacDonald KL, Osterholm MT, Hedberg CW, *et al:* Toxic shock syndrome: A newly recognized complication of influenza like illness. *JAMA* 1987; 257:1052–1058.
5. Stott NCH, West RR: Randomised controlled trial of antibiotics in patients with cough and purulent sputum. *Br Med J* 1976: 2:556–559.
6. Kuhn JJ, Hendley JO, Adams KF, *et al:* Antitussive effect of guaifenesin in young adults with natural colds. *Chest* 1982; 82:7–13.
7. Horadam VW, Sharp JG, Similack JD, *et al:* Pharmacokinetics of amantadine hydrochloride in subjects with normal and impaired renal function. *Ann Intern Med* 1981; 94:454–458.
8. American Thoracic Society: Definitions and classification of chronic bronchitis, asthma and pulmonary emphysema. *Am Rev Respir Dis* 1962; 85:762–768.
9. Willett EC, Green A, Stampfer MJ, *et al:* Relative and absolute excess risks of coronary heart disease among women who smoke cigarettes. *N Engl J Med* 1987; 317:1303–1309.
10. Peto R, Speiger FE, Cochrane AL, *et al:* The relevance in adults of airflow obstruction, but not of mucus hypersecretion, to mortality from chronic lung disease. *Am Rev Respir Dis* 1983; 128:491–500.
11. Camilli AE, Burrows B, Knudson RJ, *et al:* Longitudinal changes in forced expiratory volume in one second in adults. *Am Rev Respir Dis* 1987; 135:794–799.
12. Britten N, Davies JMC, Colley JRT: Early respiratory experience and subsequent cough and peak expiratory flow rate in 36 year old men and women. *Br Bed J* 1987; 294:1317–1320.
13. Irwin RS, Erickson AD, Pratter MR, *et al:* Prediction of tracheobronchial colonization in current cigarette smokers with chronic obstructive bronchitis. *J Infect Dis* 1982; 145:234–241.
14. Irwin RS, Corroa WM, Erickson AD, *et al:* Characterization by transtrachaeal aspiration of the tracheobronchial microflora during acute exacerbations of chronic obstructive bronchitis. *Am Rev Respir Dis* 1980; 121(suppl):150.
15. Musher DM, Kubitscheck KR, Crennan J, *et al:* Pneumonia and acute febrile tracheobronchitis due to *Haemophilus influenzae*. *Ann Intern Med* 1983; 99:444–450.
16. Anthonisen NR, Manfreda J, Warren CPW, *et al:* Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987; 106:196–204.
17. Mulks MH, Kamfeld SJ, Plaut AG: Specific proteolysis of human IgA by *Streptococcus pneumoniae* and *Haemophilus influenzae*. *J Infect Dis* 1980; 141:450–456.

18. Mulks MH, Plaut AG: IgA protease production as a characteristic distinguishing pathogenic from harmless Neisseriaceae. *N Engl J Med* 1978; 299:973–976.
19. Musher DM, Goree A, Baughn RE, *et al:* Immunoglobulin A from bronchopulmonary secretions blocks bactericidal and opsonizing effects of antibody to nontypable *Haemophilus influenzae*. *Infect Immun* 1984; 45:36–40.
20. Raheja AK, Weiss EB: The significance of fever in acute exacerbations of chronic obstructive airways disase. *Am Rev Respir Dis* 1981; 123(Suppl):71.
21. Nicotra MB, Rivera M, Awe RJ: Antibiotic therapy of acute exacerbations of chronic bronchitis. *Ann Intern Med* 1982; 97:18–21.
22. Chodosh S: Acute bacterial exacerbations in bronchitis and asthma. *Am J Med* 1987; 82(Suppl 4A):154–163.
23. Chodosh S: Bacampicillin in chronic bronchitis: Clinical experience. *Bull NY Acad Med* 1983; 59:505–514.
24. Pines A: Trimethoprim–sulfamethoxazole in the treatment and prevention of purulent exacerbations of chronic bronchitis. *J Infect Dis* 1973; 128(Suppl):706–709.
25. Cooper TJ, Ladusans E, Williams PEO, *et al:* A comparison of oral cefuroxime axetil and oral amoxycillin in lower respiratory tract infections. *J Antimibroc Chemother* 1985; 16:373–378.
26. Rubinstein E, Segev S: Drug interactions of ciproflozacin with other nonantibiotic agents. *Am J Med* 1987; 82(Suppl 4A):119–123.
27. Albert RK, Martin TR, Lavois SW: Controlled clinical trial of methylprednisolone in patients with chronic bronchitis and acute respiratory insufficiency. *Ann Intern Med* 1980; 92:753–758.
28. Rice KL, Leatherman, JW, Duane PG, *et al:* Aminophylline for acute exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987; 107:305–309.
29. Leech JA, Gervais A, Rubin FL: Efficacy of pneumococcal vaccine in severe chronic obstructive pulmonary disease. *Can Med Assoc J* 1987; 136:361–365.