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AIRWAY INFECTION

Mitra Niroumand, MD, and Ronald F. Grossman, MD, FRCPC

ACUTE BRONCHITIS

Acute bronchitis is an inflammatory condition of the tracheobronchial tree that is especially familiar to primary care physicians. As with chronic bronchitis, the definition of *acute tracheobronchitis* is descriptive. The original American Thoracic Society definition stressed that, in acute bronchitis, no physical or radiographic findings compatible with pneumonia could be present.⁵ In that context, acute tracheobronchitis is part of a continuum that includes nasopharyngeal infection, bronchitis, bronchiolitis, and pneumonitis. Symptomatically, these processes may be indistinguishable. Acute tracheobronchitis also implies site-specific airway inflammation between the glottis and the bronchioles.

Acute bronchitis occurs most commonly during the winter months, when acute respiratory tract infections are prevalent. The mean annual attack rate in the United States for acute bronchitis is approximately 87 cases per 100,000 persons per week, peaking in winter at approximately 150 cases per 100,000 persons per week.¹² Acute bronchitis accounts for an estimated 12 million physician visits per year, with an annual cost of \$200 million to \$300 million for physician visits and prescriptions.⁹⁶ In a national survey of more than 1500 practicing physicians in the United States, 66% of patients with the diagnosis of bronchitis were treated with antibiotics.⁵² Risk factors for increased antimicrobial prescribing were female sex and rural practice location, whereas black race was associated with a lower prescribing rate.

Etiology

The syndrome of acute bronchitis is most often associated with respiratory viruses, including common cold viruses, such as rhinovirus and coronavirus, in addition to more invasive viruses of the lower respiratory tract, such as influenza and adenovirus. Other viral causes of acute bronchitis include measles, respira-

From the Division of Respiratory Medicine, Mount Sinai Hospital, Toronto, Ontario, Canada

tory syncytial virus (RSV), parainfluenza virus, and herpes simplex virus.^{22, 104, 105} A small proportion of cases of acute bronchitis is of nonviral etiology. *Mycoplasma pneumoniae*, *Bordetella pertussis*, and *Chlamydia pneumoniae*, Taiwan acute respiratory (TWAR) strain, are recognized bacterial causes of acute bronchitis.^{53, 54} The etiologic role of *Streptococcus pneumoniae* and *Haemophilus influenzae* in acute bronchitis is not clear because these bacteria may represent resident flora of the upper respiratory tract of normal individuals. To examine the role of secondary bacterial infection in the pathogenesis of acute bronchitis, it is necessary to obtain samples from tracheobronchial trees without contamination by nasopharyngeal flora.⁵⁸

Acute tracheobronchitis may also be a consequence of the inhalation of irritating, toxic substances as a result of air pollution or occupational exposures to ammonia, chlorine, sulfur dioxide, nitrogen dioxide, or ozone.^{51, 100}

Pathogenesis

During acute bronchial infection, the mucous membrane of the tracheobronchial tree is hyperemic and edematous, with increased bronchial secretion being a common feature. Although extensive destruction of the respiratory epithelium may be seen with influenza, other viral agents, such as rhinovirus, cause minimal epithelial injury.^{73, 121} Impaired mucociliary function is seen in patients with all infections, even in those without overt mucosal damage.⁵⁹ Determining the pathogenesis of acute tracheobronchitis is complicated by several factors. Studies seeking an infectious cause frequently fail to isolate a specific pathogen. A delay in seeking medical care after the onset of symptoms, which may bring the patient to medical attention beyond the period of viral shedding, may be one explanation. Determination of a causative agent is further complicated in patients with chronic lung diseases who may have tracheobronchial colonization by potentially pathogenic bacteria, including *H. influenzae*, *S. pneumoniae*, and *Moraxella catarrhalis*. An increase in serum antibody titers to bacteria associated with acute bronchitic symptoms suggests that bacteria may have a causative role,⁸² although analysis of antibody coating of bacteria in sputum is not helpful.¹²⁵ In addition, severity of attacks of acute bronchitis may be increased by exposure to cigarette smoke and air pollutants. These substances in association with recurrent acute bronchial infection may result in permanent injury to the bronchial tree. Some epidemiologic studies support the potential role of acute respiratory infections in the pathogenesis of chronic obstructive lung disease.^{70, 79} The relationship between acute bronchitis and heightened airway reactivity has also been studied extensively. Increased airway reactivity and airway resistance, usually manifested as a bothersome cough, may persist for 6 to 8 weeks.^{43, 99} The elevated airway resistance observed after a bronchial infection is largely reversible with β -sympathomimetic and anticholinergic bronchodilators.

Clinical Presentation

Cough is uniformly found in patients with acute bronchitis, and it may be productive of mucoid or purulent sputum. The cough may be accompanied by variable amounts of hemoptysis or retrosternal pain that is often described as a burning sensation. It is usually accentuated on inspiration. Generally, the temperature is only minimally to moderately elevated. Physical examination often shows harsh breath sounds, rhonchi, and variable amounts of expiratory wheezing. Occasionally, focal areas of diminished breath sounds are present, which

suggest that inspissated mucus has caused atelectasis. Atelectasis may be relieved by the use of humidifiers; bronchodilators; vigorous coughing; and, if needed, tracheal suction. Sometimes, diffuse diminution of air intake or inspiratory stridor is present. These findings indicate obstruction of major bronchi or the trachea. Most viral acute tracheobronchitis runs a benign, self-limited course. However, herpes simplex type 1 has been associated with severe febrile tracheobronchitis and respiratory failure in "normal," immunocompetent adults.¹⁰⁴

Diagnosis

Bronchitis may be suspected in patients with an acute respiratory tract infection associated with cough; however, bronchitis must be considered a diagnosis of exclusion because more serious diseases of the lower respiratory tract are associated with cough. A complete history should include information on exposure to toxic substances and cigarette use, epidemiologic considerations, and vaccination history. A thorough physical examination is essential to exclude other causes of cough, including cardiovascular and parenchymal lung diseases. Routine bacterial cultures of expectorated sputum are not helpful because of the sampling problem of contamination by nasopharyngeal flora and the usual technical difficulties with collecting, transporting, and interpreting an adequate lower respiratory tract sample. Occasionally, the nature of sputum may provide some diagnostic clues. For instance, except for adenovirus infections, the sputum in viral infections almost always shows a marked predominance of mononuclear cells on Gram or Wright's stain. In contrast, in bacterial infections, the sputum shows a predominance of polymorphonuclear leukocytes. Mycoplasma infections are usually associated with mononuclear cells, but a predominant polymorphonuclear cell population may be present. Culture methods and a microimmunofluorescence test have been developed for the laboratory diagnosis of *C. pneumoniae*. The use of a gamma M immunoglobulin (IgM)-specific conjugate helps detect current infection. Patients in whom cough persists beyond the expected duration of the acute illness should have further diagnostic examination, including chest radiography, sputum cytology, and bronchoscopy, to exclude other diseases of the tracheobronchial tree and lungs.

Treatment

In most cases of acute bronchitis, only symptomatic treatment is needed; however, patients with underlying chronic cardiopulmonary diseases who contract influenza or other severe forms of bronchitis may develop serious symptoms requiring hospitalization, oxygen therapy, and ventilatory assistance. Cough suppressants, adequate hydration to prevent drying of bronchial secretions, and symptomatic treatment of mild fever and malaise associated with some influenza-like syndromes is the cornerstone of treatment of acute bronchitis in otherwise healthy individuals. If bronchospastic symptoms are dominant, there may be a role for inhaled β_2 -adrenergic bronchodilators.

The value of antibiotics in the treatment of otherwise healthy individuals with acute bronchitis has not been established, and the use of these agents is not recommended as a general practice. This uncertainty stems from conflicting results of clinical trials, which may be explained based on variations in type of antibiotics, dosage schedule, duration of follow-up, the season of the year (reflecting prevalence of different pathogens), and lack of a placebo-controlled

design in many of these studies. Factors that may prompt the use of antibiotics include patient's age, significant underlying medical illnesses, and severe or persistent (e.g., > 1 week in duration) symptoms.¹⁶ Under these circumstances, treatment with tetracycline or a macrolide to cover the suspected pathogens, *M. pneumoniae*, *C. pneumoniae*, and *S. pneumoniae*, should be considered.^{16, 58} During epidemics known to be caused by influenza A virus, treatment with amantidine is recommended for patients with suspected influenza if the illness is less than 48 hours in duration.

ACUTE EXACERBATION OF CHRONIC BRONCHITIS

Chronic obstructive lung disease afflicts 20% of the population and is the fourth leading cause of death in the United States.^{114, 122} Acute bronchitis and acute exacerbation of chronic bronchitis (AECB) are frequently encountered by general and family physicians, accounting for approximately 14 million physician visits per year.^{50, 115} Chronic bronchitis, airflow obstruction, or both were found in 14% of men and 8% of women in Tecumseh, Michigan, in a population-based survey.⁶¹ In the United Kingdom, one fourth of all primary care visits are related to respiratory disease, and more than half of these are caused by upper and lower respiratory tract infections.⁸⁰ Bronchitis is associated with 28 million lost working days and 5% of deaths per year in the United Kingdom.¹¹³ In 1992, approximately 12 million prescriptions were given for lower respiratory tract infections, accounting for £47.2 million (\$78.3 million) in expenditures.⁶⁵ In Europe, more than 80% of all lower respiratory tract infections are treated with antibiotics.⁶³ Most physicians do not differentiate acute bronchitis, acute exacerbations of chronic bronchitis, community-acquired pneumonia, and viral respiratory tract infections. The pattern of antibiotic prescribing for these infections varies from country to country, but there is rationale for these antimicrobial choices exists.³⁸

Chronic obstructive pulmonary disease (COPD) is a progressive disease characterized by reduced expiratory airflow that is relatively stable over several months of observation.⁶ Chronic bronchitis is defined clinically as excessive cough, with productive of sputum on most days, for at least 3 months during at least 2 consecutive years.⁷⁶ The major risk factor for chronic bronchitis is cigarette smoking, and cumulative smoking history is most closely related to symptom development.²¹ Other factors implicated in the development of chronic bronchitis include occupational and environmental exposures (e.g., to dust, air pollution, sulfur dioxide, or nitrogen dioxide) and childhood respiratory tract infection.^{23, 75, 124} Passive smoking may also be a risk factor for chronic bronchitis, but the evidence to suggest this is less clear.⁴⁶ The prognosis of COPD is affected most when lung function as reflected by the forced expiratory volume in 1 second (FEV₁) falls below 50% of predicted values.¹⁰ When the FEV₁ falls below 1 L, the 5-year survival rate is approximately 50%.¹¹² Very poor correlation exists between the amount of sputum produced and the degree of airflow obstruction.^{66, 91} Frequent acute exacerbations of bronchitis have not been associated with an accelerated decline in FEV₁.^{19, 49}

Role of Bacterial Infection

An acute exacerbation of chronic obstructive lung disease is usually defined as an episodic respiratory decompensation without an objectively documented cause, such as pneumonia. The role of bacterial infection in acute exacerbation

of chronic bronchitis is controversial. Many patients are treated with antibiotics, but whether this treatment is efficacious is debatable.¹¹¹ Several groups have demonstrated increased numbers of bacteria and neutrophils in sputum during exacerbations.^{48, 77} A causal relationship can be inferred by the appearance of an acute antibody response in serum to these bacteria and an increase in inflammatory mediators in purulent sputum.^{82, 109} The relationship between bacterial infection and symptoms is complicated by a high spontaneous remission rate; this can be expected because bacterial exacerbations are usually limited to the bronchial mucosa.⁸¹ In a landmark study, Anthonisen and co-workers⁹ demonstrated for the first time that patients could be stratified according to symptoms to predict a response to antimicrobial therapy. In patients with at least two of increased dyspnea, sputum volume, and sputum purulence, broad-spectrum antibiotics (e.g., amoxicillin, trimethoprim-sulfamethoxazole, or doxycycline) lead to improved clinical outcomes, fewer therapeutic failures, and a more rapid rate of lung function recovery compared with placebo. Overall, the length of illness was 2 days shorter for the antibiotic-treated group compared with the group receiving placebo. A meta-analysis of nine randomized, placebo-controlled trials of patients treated with antibiotics for acute exacerbations of chronic bronchitis concluded that a small but statistically significant clinical and physiologic improvement could be expected in antibiotic-treated patients.^{20, 41, 42, 86, 90, 92, 97} Table 1 demonstrates the results in seven of the nine trials and a recently completed,

Table 1. SUMMARY OF RANDOMIZED, PLACEBO-CONTROLLED CLINICAL TRIALS EXAMINING THE ROLE OF ANTIMICROBIAL THERAPY IN ACUTE EXACERBATION OF COPD

| Comparators | No. of Patients | Outcome of Therapy | Reference |
|---|-----------------|---|-------------------------------------|
| Placebo versus oxytetracycline | 37 37 | Treated patients lost half as much time from work, and exacerbations were shorter | Elmes et al, 1957 ⁴¹ |
| Placebo versus oxytetracycline | 27 26 | Treated patients recovered sooner and deteriorated less often | Berry et al, 1960 ²⁰ |
| Placebo versus ampicillin | 28 28 | No significant difference in clinical response | Elmes et al, 1965 ⁴² |
| Placebo versus physiotherapy versus chloramphenicol | 10 10 9 | No significant differences in clinical outcome | Peterson et al, 1967 ⁹⁰ |
| Placebo versus chloramphenicol versus tetracycline | 86 84 89 | Antibiotic therapy superior to placebo but no differences in clinical outcome between antibiotics | Pines et al, 1972 ⁹² |
| Placebo versus tetracycline | 20 20 | 100% versus 100% clinical response | Nicotra et al, 1982 ⁸⁸ |
| Placebo versus either co-trimoxazole, amoxicillin, or doxycycline | 180 182 | 55% versus 68% success ($p < 0.01$) | Anthonisen et al, 1987 ⁹ |
| Placebo versus co-amoxiclav | 179 190 | 50.3% versus 86.4% success ($p < 0.01$) | Allegra et al, 1991 ⁴ |

large, randomized, placebo-controlled Italian trial that was not included in the meta-analysis.⁴ A beneficial impact of antibiotics was demonstrated in studies that included the largest number of patients. In the six trials that reported peak expiratory flow rates, an improvement of 10.75 L/min favoring the antibiotic group was noted. Although this improvement is small, it may be clinically relevant, particularly in patients with limited respiratory reserve. Design flaws in the earlier studies, such as small number of study patients, unclear selection criteria, uncertain microbiology, nonstandard evaluation criteria, and lack of stratification of patients, may account for the discrepancy in outcomes.

Bacterial Pathogens

Bacterial pathogens can be isolated from sputum in 50% to 60% of patients having an AECB, with *H. influenzae* being the most commonly isolated organism from sputum (Table 2). *Haemophilus parainfluenzae*, *S. pneumoniae*, and *M. catarrhalis* are also found frequently.^{3, 13, 18, 26, 27, 32, 57, 71, 78, 83} Studies utilizing the protected specimen brush technique, in which lower respiratory tract samples are not contaminated with oropharyngeal flora, have confirmed the important role in ACEB for bacterial pathogens. Organisms associated with acute exacerbations are similar (e.g., *H. influenzae*, *H. parainfluenzae*, *S. pneumoniae*, or *M. catarrhalis*), but quantitative cultures indicate a greater number of organisms.^{44, 57} The log colony count of organisms is of the same magnitude associated with ventilator-associated pneumonia, suggesting a significant bacterial load. Exacerbations can be caused by endogenous or exogenous reinfection by *H. influenzae*. Persistently infected patients keep the same *H. influenzae* strain for longer periods, and antibiotic therapy may not be effective in eradicating *H. influenzae*.⁵⁵ In patients with AECB, there appears to be a relationship between severity of the underlying pulmonary disease and sputum bacteriology. Eller and co-workers⁴⁰ have observed, that with declining lung function, prevalence of enteric gram-negative organisms and pseudomonas increases.⁴⁰ *H. parainfluenzae* has been isolated from sputum in as many as 41% of patients with acute exacerbation of chronic bronchitis. Colony counts as high as 9.6×10^8 cfu/mL in sputum cultures and a serum antibody response suggest a potential role for this organism as a true respiratory pathogen.⁶² β -lactamase mediated amoxicillin resistance is seen in 20% to 40% of *H. influenzae* strains in North America and Europe and in almost 100% of *M. catarrhalis* strains.^{34, 68, 69} In a United States survey conducted between

Table 2. BACTERIAL PATHOGENS ISOLATED FROM SPUTUM IN PATIENTS WITH ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS

| Reference | No. of Isolates | % of Total Isolates | | |
|-----------------------------------|-----------------|-------------------------------|------------------------------|---------------------------------|
| | | <i>Haemophilus influenzae</i> | <i>Moraxella catarrhalis</i> | <i>Streptococcus pneumoniae</i> |
| Davies et al, 1986 ³² | 127 | 58.5 | 15.0 | 16.5 |
| Basran et al, 1990 ¹⁸ | 60 | 43.3 | 3.3 | 25.0 |
| Chodosh, 1992 ²⁷ | 214 | 37.9 | 22.4 | 22.4 |
| Aldons, 1991 ³ | 53 | 70.0 | 13.0 | 15.0 |
| Bachand, 1991 ¹³ | 84 | 30.0 | 10.7 | 21.4 |
| Lindsay et al, 1992 ⁷¹ | 398 | 49.7 | 19.0 | 17.0 |
| Neu and Chick, 1993 ⁸³ | 84 | 46.4 | 28.6 | 25.0 |

1992 and 1993, 30% of all *H. influenzae* isolates were β -lactamase producing, although a few β -lactamase-negative, ampicillin-resistant strains were isolated.¹⁷ Of almost 700 strains of *M. catarrhalis*, β -lactamase production was found in 92%. Of nearly 800 isolates of *S. pneumoniae*, 15% demonstrated intermediate susceptibility to penicillin, whereas 7% were penicillin resistant ($MIC_{90} > 2.0 \mu\text{g/mL}$).

In a more recent survey conducted between 1994 and 1995, 36.4% of *H. influenzae* strains produced β -lactamase.³⁶ Another 2.5% of *H. influenzae* isolates were β -lactamase-negative but ampicillin resistant. β -lactamase-producing *M. catarrhalis* increased to 95.3% of all isolated strains, while the overall frequency of penicillin-resistant *S. pneumoniae* increased to 23.6%.^{35, 37} Overall, 14.1% of *S. pneumoniae* isolates demonstrated intermediate resistance, while 9.5% demonstrated high-level resistance. Of concern was the observation that 9.1% of strains demonstrated multiple drug resistance.

Pathogenesis of Bronchial Infections

Cigarette smoking is the most common cause of chronic bronchitis.¹⁰³ The mucociliary system forms a primary defense mechanism of the respiratory tract against all inhaled particles, including bacteria.⁸⁴ Viral infection and cigarette smoke frequently damage ciliated epithelium, which, in turn, impairs mucociliary clearance.^{107, 119} Mucociliary function may also be reduced by increased mucous volume, and altered mucous rheology.^{25, 98} Viral infections result in the release of inflammatory mediators, such as kinins, increasing local permeability that may predispose the respiratory mucosa to bacterial colonization.⁹³ Loss of large areas of ciliated epithelium occurs during viral and bacterial infections and contributes to impaired mucociliary clearance.^{59, 117} Delayed mucociliary clearance affords bacteria the opportunity to multiply and attach, first to mucous and then to mucosal surfaces.¹¹⁶ An organism that is uniquely designed to take advantage of this is nontypable *H. influenzae*. It expresses pili, and piliated isolates of nontypable *H. influenzae* adhere to human nasopharyngeal epithelial cells very well.^{11, 14} Organisms such as *H. influenzae* produce substances that impair ciliary function, stimulate mucous production, destroy local immunoglobulins, impair phagocytic function, and damage the tracheobronchial epithelium.^{1, 45, 89, 108} *H. influenzae* synthesizes histamine and releases an uncharacterized factor which impairs human neutrophil function.^{30, 102} When these bacteria loiter in the airways, a host inflammatory response is stimulated. With the movement of large numbers of neutrophils and their subsequent release of proteinases and toxic oxygen radicals, mucous production and epithelial surface damage may be enhanced.^{7, 31} The neutrophils are attracted by chemoattractant bacterial products.⁹⁴ Proteinase enzymes, such as elastase, are released from neutrophils and can be found in the sputum of patients with chronic bronchitis.¹⁰⁹ Progressive airway damage may occur from the products of the bacteria themselves or from the host response to these bacteria. Local host defense may be further impaired, leading to an ever-greater chance of bacterial colonization and thus further damage. This process has been termed the *vicious circle hypothesis* and may account for the insidious progression of airway disease.²⁹

Risk Stratification

Patients with significant compromise of lung function may develop acute respiratory failure as a consequence of an acute exacerbation. Therefore, it is

prudent to identify this high-risk population for which an aggressive approach can be applied from the outset, hoping to avoid this important complication. Mechanical ventilation is required in 20% to 60% of these patients, and long and expensive intensive care unit (ICU) care and hospital mortality rates of 10% to 30% have been reported.³³ Factors reported to be associated with in-hospital mortality include age of more than 65 years, comorbid respiratory and nonrespiratory organ dysfunction, and hospital length of stay before ICU admission.¹⁰¹ Patient age and severity of airway obstruction in patients with COPD were identified as the major determinants of survival in patients followed for 3 years after discharge from the hospital.¹⁰

Other factors linked to survival are performance status and use of oral corticosteroids.¹¹⁰ Following institution of antibiotic therapy for an acute exacerbation of chronic bronchitis, factors predicting failure of initial antimicrobial therapy (return to the prescribing physician for more treatment) or need for hospitalization include coexistent cardiopulmonary diseases and the number of previous exacerbations.¹⁵ The presence of cardiovascular comorbidity and more than four exacerbations in the previous year has a sensitivity of 75% and specificity of 47% in predicting return to the prescribing physician for further treatment. Advanced age, significant impairment of lung function, poor performance status, comorbid conditions, and history of previous frequent exacerbations requiring systemic corticosteroid medications characterize a high risk group of patients. Because the cost of failure of treatment of these patients is high, an aggressive approach to treatment of this high-risk group may improve outcome. Routine antimicrobial therapy fails in 13% to 25% or more of exacerbations.^{15, 74} Therapeutic failure leads to increased cost of care because of extra physician visits, further diagnostic tests, and repeated courses of antibiotics. It may also lead to more hospitalizations and prolonged absence from work. Stratification of patients into risk categories may allow the physician to select targeted antimicrobial therapy to prevent some of these consequences. This approach has become increasingly more important because of increasing rates of resistance to standard antimicrobial therapy. Several stratification schemes have been proposed to improve initial antimicrobial selection.

Balter and co-workers in Canada suggested that patients could be categorized into five groups¹⁶ (Table 3). Group 1 had acute simple bronchitis, likely viral induced, with no previous respiratory problems. Antimicrobial therapy was not recommended for this group. In patients with persistent symptoms (> 1 week in duration), a macrolide to treat the suspected pathogens, *M. pneumoniae*, *C. pneumoniae*, and *S. pneumoniae*, was recommended. Group 2 patients had simple chronic bronchitis with minimal or no impairment of pulmonary function and without any other risk factors. Treatment was recommended because Anthonisen and co-workers⁹ demonstrated a beneficial effect of antibiotics. An aminopenicillin was suggested as first-line therapy for an acute exacerbation because the consequences of a treatment failure were expected to be relatively few. Group 3 patients were described as having moderate to severe chronic bronchitis. They may be elderly (> 65 years), and were likely to have frequent exacerbations (four or more/year). Treatment with antibiotics directed toward β -lactamase-producing strains of *H. influenzae* and *M. catarrhalis*, such as a second- or third-generation cephalosporin, trimethoprim-sulfamethoxazole, amoxicillin-clavulanic acid, second-generation macrolide, or quinolone was suggested. Group 4 was similar to group 3 but had other significant comorbid illness, such as congestive heart failure, diabetes mellitus, chronic renal failure, or chronic liver disease. Treatment regimens similar to those suggested for group 3 were advised. Group 5 patients were classified as having bronchiectasis.

Table 3. PROPOSED PATIENT STRATIFICATION BY BALTER ET AL¹⁶

| Category | Characteristics | Suggested Treatment |
|----------|---|--|
| Group 1 | Acute simple bronchitis; no previous respiratory problems | No treatment Macrolide for persistent symptoms |
| Group 2 | Simple chronic bronchitis; little or no lung impairment; no other risk factors | Aminopenicillin |
| Group 3 | Moderate-severe chronic bronchitis; elderly (>65 years of age); ≥ 4 exacerbations/year | Second- or third-generation cephalosporin TMP/SMX Amoxicillin-clavulanic acid Second-generation macrolide Fluoroquinolones |
| Group 4 | Similar to group 3, plus significant comorbid illnesses: CHF, diabetes mellitus, chronic renal failure, chronic liver disease | Similar to group 3 |
| Group 5 | Bronchiectasis | According to sputum culture |

TMP-SMX, trimethoprim-sulfamethoxazole; CHF, congestive heart failure.

Sputum cultures were recommended for this group to tailor therapy to the isolated pathogen.

Lode proposed patients be divided into three groups⁷² (Table 4). "First-degree" patients were defined as those with a relatively short duration of chronic bronchitis; rare exacerbations; normal lung function; and infection with the usual pathogens, namely, *H. influenzae* and *S. pneumoniae*. The suggested antimicrobial choices for this group included oral amoxicillin, doxycycline, co-trimoxazole, or a macrolide. "Second-degree" patients were defined as having a longer history of chronic obstructive lung disease, several exacerbations each year, and impaired lung function. Because of the concern of gram-negative pathogens, Lode

Table 4. STRATIFICATION SCHEME SUGGESTED BY LODE⁷²

| Category | Characteristics | Suggested Treatment |
|---------------|--|---|
| First degree | Short history of symptoms; rare exacerbations; normal lung function | Amoxicillin Doxycycline Co-trimoxazole Macrolide |
| Second degree | Longer history of COPD; several exacerbations/year; impaired lung function | Cephalosporins Amoxicillin-clavulanic acid Fluoroquinolones |
| Third degree | Hospitalized patient with significant comorbidity; prolonged history of COPD; severe functional impairment; frequent infections with gram-negative pathogens | Cephalosporins Amoxicillin-clavulanic acid Fluoroquinolones Aminoglycosides β -lactams intravenously in hospitalized patients |

COPD, chronic obstructive pulmonary disease.

proposed the use of oral cephalosporins, amoxicillin-clavulanic acid, or quinolones. "Third-degree" patients were described as hospitalized patients with significant comorbidity, prolonged history of COPD, severe functional impairment, and frequent infections with gram-negative pathogens. He suggested oral therapy with cephalosporins, amoxicillin-clavulanic acid, or quinolones. In hospitalized patients, these same drugs, administered intravenously or an aminoglycoside in combination with β -lactam antibiotic, were recommended.

In the United Kingdom, Wilson¹⁸ classified patients into four groups (Table 5). Group 1 patients have acute bronchitis that is usually viral in origin. Because no underlying lung disease is present in this group, the illness is usually self-limited and runs a benign course. Group 2 patients have simple chronic bronchitis, are younger, have only mild to moderate impairment of lung function ($FEV_1 > 50\%$ predicted value) and have less than four exacerbations per year. In this group of patients, typical pathogens, including *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis* are present, although viral infection often precedes bacterial superinfection. Treatment with a β -lactam is usually successful, and the prognosis is excellent. Group 3 patients are older and may have poor underlying lung function ($FEV_1 < 50\%$ predicted). Alternatively, they may demonstrate only moderate impairment of lung function (FEV_1 50%–65% predicted) but have significant comorbidity (e.g., diabetes mellitus, congestive heart failure, chronic renal disease, or chronic liver disease) or, experience four or more exacerbations per year. *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis* continue to be the predominant organisms. In this group of patients, initial treatment failure has major implications for the patient and health-care system, including increased time lost from work, hospitalization, or both. Treatment with medications directed toward resistant organisms, such as a quinolone, amoxicillin-clavulanic acid, second- or third-generation cephalosporins, or a second-generation macrolide should perform better than amoxicillin. Group 4 patients suffer from chronic bronchial infection with frequent exacerbations characterized by increased spu-

Table 5. STRATIFICATION SCHEME SUGGESTED BY WILSON¹⁸

| Category | Characteristics | Suggested Treatment |
|----------|---|--|
| Group 1 | Postviral tracheobronchitis; previously healthy person | None |
| Group 2 | Simple chronic bronchitis; young person; mild-moderate impairment of lung function ($FEV_1 > 50\%$ predicted); < 4 exacerbations/year | β -lactam antibiotics |
| Group 3 | "Chronic bronchitis plus" older person; $FEV_1 < 50\%$ predicted or FEV_1 50%–60% predicted but concurrent medical illnesses; CHF, diabetes mellitus, chronic renal disease, chronic liver disease, >4 exacerbations/year | Fluoroquinolones Amoxicillin-clavulanic acid Second- or third-generation cephalosporins Second-generation macrolide |
| Group 4 | "Chronic bronchial sepsis," bronchiectasis, chronic airway colonization | Tailor antimicrobial treatment to airway pathogens |

FEV_1 , forced expiratory volume in 1 second; CHF, congestive heart failure.

tum production, increased sputum purulence, cough, and worsening dyspnea. Many of these patients have evidence of bronchiectasis if subjected to high-resolution CT scanning. These individuals tend to have a chronic progressive course, and an aggressive therapeutic approach should be offered. In addition to the usual respiratory organisms, other gram-negative organisms, including Enterobacteriaceae and *Pseudomonas* spp., should be considered as potential pathogens. Ciprofloxacin is the agent with the most activity against these species and should be considered the agent of choice when they are identified.²⁸

These and other classification systems emphasize identifying the high-risk population so they can be treated, from the outset, with antibiotics designed to deal with potential resistant organisms. This approach may reduce risk for treatment failure, which, especially in high-risk population, has significant medical and economical implications.

In a recently completed study, patients with at least three treated exacerbations in the past year (class 3 patients) were randomized to receive either ciprofloxacin or any non-quinolone-based therapy for their next acute exacerbation of chronic bronchitis.⁵⁶ In this prospective health economic study, clinical endpoints (i.e., days of illness, hospitalizations, and time to next exacerbation) were blended with quality-of-life measurements (Nottingham Health Profile, St. George's Hospital Respiratory Questionnaire, Health Utility Index) and total respiratory costs from a societal perspective. Although the overall results indicated no preference for either treatment arm, in patients with risk factors (i.e., severe underlying lung disease, more than four exacerbations/year, duration of bronchitis > 10 years, elderly, or significant comorbid illness), the use of ciprofloxacin led to improved clinical outcome, higher quality of life, and lower costs. The results of this study suggest that aggressive antimicrobial therapy directed especially toward resistant organisms in high-risk patients may be a more effective strategy than no therapy or therapy with older antimicrobials that are not effective particularly against β -lactamase-producing *H. influenzae*.

Nonantimicrobial Treatment

Treatment of acute exacerbation of chronic bronchitis falls into two general approaches of preventive and symptomatic therapies.

Preventive Measures

Smoking cessation has been identified as a major cornerstone of management of patients with chronic bronchitis. The recent Lung Health Study⁸ confirmed that smoking cessation greatly reduces the rate of decline of FEV₁. The benefit of smoking cessation is seen even in patients over the age of 60 years.⁶⁰ Chronic sputum production often clears within 4 weeks of smoking cessation.¹²³ Nicotine-replacement therapy is an effective approach to smoking cessation, although counseling by a physician has been shown to be the most potent intervention.^{47, 67, 106}

Annual influenza vaccination reduces morbidity and mortality of influenza in the elderly by 50%.⁸⁵ This beneficial effect is believed to be the result of prevention of airway epithelial damage predisposing to subsequent bacterial infection caused by the virus.³⁹ The beneficial effect of pneumococcal vaccine in patients with chronic bronchitis has not been firmly established; however, current recommendations are that patients with COPD receive Pneumovax (23 valent pneumococcal vaccine) at least once in their lives and considerations be

given to repeating the vaccine every 5 to 10 years, especially in high-risk patients or those that have a rapid decline in pneumococcal antibody levels.^{24, 64}

Orcel and co-workers⁸⁸ showed a 40% reduction in the incidence of acute exacerbation of chronic bronchitis after oral immunization with lyophilized fractions of the eight most common pathogens isolated in respiratory tract infections.⁸⁸ This was a randomized, double-blind, placebo-controlled trial. At the present time, however, oral vaccination for patients with chronic bronchitis remains an experimental approach.

Symptomatic Therapy

Generally a combination of inhaled anticholinergic with inhaled β -agonist is used in the treatment of acute exacerbation of chronic bronchitis. Oxygen therapy to maintain a PO_2 of more than 60 mm Hg or an arterial oxygen saturation of more than 90% may be required. Excessive use of oxygen should be avoided because it may lead to progressive hypercapnia, either by decreasing hypoxic ventilatory drive or by worsening ventilation-perfusion mismatching within the lung.

Aminophylline in acute exacerbation of chronic bronchitis adds little to the bronchodilating potential of inhaled medications and increases side effects.⁹⁵ Retrospective reviews of patients presenting to the emergency room with acute exacerbation of COPD show a clear benefit in the group treated with corticosteroids.⁸⁷ Albert and co-workers² reported faster improvement of pulmonary function tests in a randomized, placebo-controlled, double-blind clinical trial of parenteral corticosteroids during acute exacerbations of COPD.² The results of the current Systemic Corticosteroids in COPD Exacerbation (SCCOPE) clinical trial being conducted by the Veterans' Affairs Medical Research Service will better define the role for oral corticosteroids. Currently, the weight of clinical evidence supports use of a course of systemic corticosteroids in the management of acute exacerbation of chronic bronchitis.

SUMMARY

Bronchitis in its acute and chronic forms with recurrent acute exacerbations is one of the most common reasons for physician visits, accounting for a significant cost to the health-care system, lost work days, and increased morbidity and mortality. Smoking and recurrent lower respiratory tract infections are major risk factors for chronic bronchitis. Therefore, smoking cessation and vaccination strategies are cornerstones of management in terms of halting disease progression and reducing the frequency of infectious exacerbations. Bacterial infection is the main culprit in acute flares of the disease. Routine antimicrobial therapy fails in a significant number of patients, and therapeutic failures lead to increased costs. Several stratification schemes have been proposed to improve initial antimicrobial selection. These schemes identify patient's age, severity of underlying pulmonary dysfunction, frequency of exacerbations, and the presence of comorbid illnesses as predictors for likely pathogens and to guide antimicrobial selection. This approach may reduce the risk for treatment failure, which would have significant medical and economic implications. Improved understanding of the roles of airway inflammation and infection in the pathogenesis of progressive airway disease, in addition to future studies examining the efficacy of newer classes of antimicrobials, should guide physicians to target early and effective treatment to high-risk patients.

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Address reprint requests to

Ronald F. Grossman, MD, FRCPC
Mount Sinai Hospital, Suite 640
600 University Avenue
Toronto, Ontario, Canada
M5G 1X5