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Treating acute exacerbations of chronic bronchitis in the face of antibiotic resistance

ABSTRACT

Antibiotics can be effective against acute exacerbations of chronic bronchitis and chronic obstructive pulmonary disease, but with bacterial resistance to multiple antibiotics increasing worldwide, appropriate antibiotic selection is critical. Categorizing patients with acute exacerbations according to age, number of exacerbations per year, disease severity, degree of pulmonary impairment, and presence of comorbid conditions helps to direct therapy.

KEY POINTS

When selecting an antibiotic for treatment, sputum analysis to identify the causative organism is advisable because bacterial resistance is continuing to emerge.

Resistance of *Streptococcus pneumoniae* isolates to multiple drugs is expected to reach 40% or 50% in the United States within the next few years.

When initial antibiotic treatment fails, try an antimicrobial without the same gaps in the spectrum as the first agent.

CAREFUL SELECTION of antibiotic therapy for acute exacerbations of chronic bronchitis is essential in the face of increasing bacterial resistance to multiple antibiotics. Treatment should be based on the severity of the exacerbation and on the causative organism's susceptibility to the antibiotic selected. Categorizing patients according to disease severity helps to direct therapy.

COPD MORTALITY ON THE RISE

Acute exacerbations of chronic bronchitis cause significant morbidity and even death[1] in patients with chronic obstructive pulmonary disease (COPD),[2–5] including chronic obstructive bronchitis, asthma, and emphysema. COPD is estimated to affect close to 15 million Americans and is now the fourth leading cause of death in the United States.[1] Of the five major causes of death, COPD is the only one for which the mortality rate has increased significantly over the last several years[2,3]: the age-adjusted mortality rate for COPD increased 47% (from 53 to 78 per 100,000) from 1979 to 1993.[3]

Factors thought to contribute to acute exacerbations include bacterial or viral infection, industrial pollutants, and environmental allergies, but the presence of pathogenic bacteria in large numbers in the sputum in most patients with acute exacerbations suggests that bacterial infection plays a key role.

MICROORGANISMS INVOLVED

Of the specific microorganisms associated with acute exacerbations:

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- *Haemophilus influenzae* and *H parainfluenzae* account for up to 50% of organisms isolated from sputum, with *H influenzae* accounting for 28% to 38%[6–10]
- *Moraxella catarrhalis* and *Streptococcus pneumoniae* together account for approximately one third of isolates, with *M catarrhalis* accounting for 18% to 22% and pneumococci for 7% to 22% in various studies[6–10]
- Atypical organisms such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* may be associated with 5% to 15% of all exacerbations,[11] although the true incidence is not known.

RESISTANCE IS INCREASING

The problem of bacterial resistance in this setting continues to increase, and the mechanisms of resistance vary. For example, bacteria that produce beta-lactamase can render penicillins, cephalosporins, and monobactams ineffective. Some experts estimate that 20% to 40% of *H influenzae* and 75% to 100% of *M catarrhalis* produce beta-lactamase.[12] Hoffmann et al[13] reported a 25% prevalence of penicillin-resistant *S pneumoniae* isolates and a 9% prevalence of cephalosporin-resistant isolates among 431 patients with invasive pneumococcal infections. Between 16% and 22% of acute exacerbations of chronic bronchitis have been associated with *S pneumoniae*.[6–10]

In acute exacerbations, up to 50% of organisms in the sputum are *H influenzae* and *H parainfluenzae*

Multidrug resistance among *S pneumoniae* isolates has progressively increased and is expected to reach 40% or 50% in the United States within a few years. One half of these *S pneumoniae* strains exhibit high levels of resistance, even to non-beta-lactams.[14] Trends of increasing antimicrobial resistance have been reported for respiratory isolates obtained throughout the United States and Europe,[15–17] and resistance to commonly used antibiotics such as erythromycin, tetracyclines, and co-trimoxazole is more commonly found in penicillin-resistant strains of *S pneumoniae*.[14,15]

The emergence of bacterial pathogens resistant to older antibiotics and the appearance of *Pseudomonas* and other gram-negative infections in the community have stimulated the search for more effective agents and for a definition of the therapeutic adequacy of available antimicrobials.

EVIDENCE THAT ANTIBIOTICS WORK

The use of antibiotics to treat acute exacerbation of bronchitis has been controversial. An earlier study[18] showed either no benefit or only minimal benefit. More recent studies,[19–22] including a meta-analysis,[23] demonstrate a benefit of antibiotics during an acute exacerbation but no benefit in preventing exacerbations.

Studies reporting benefits of antibiotic therapy

Anthonisen et al[19] conducted a large-scale placebo-controlled study of the effectiveness of antibiotics in the treatment of acute exacerbations of chronic bronchitis. This study helped to define the condition and offered the first widely accepted classification of severity of presenting symptoms. They evaluated 173 patients with chronic bronchitis and followed them for 3.5 years, during which 362 exacerbations occurred. Three levels of severity were described:

- Severe exacerbations (approximately 40% of cases)—worsening dyspnea, increased sputum volume, and sputum purulence
- Moderate exacerbations (40%)—any two of the above three symptoms
- Mild exacerbations (20%)—only one of the above three symptoms plus at least one of the following: upper respiratory symptoms, wheezing, an increase of 20% in the heart rate or respiratory rate, or fever without another cause.

Patients with the most severe exacerbations benefited significantly from antibiotic therapy, whereas no significant difference was seen between antibiotic treatment and placebo in patients with mild exacerbations. Furthermore, patients who received antibiotics had a more rapid improvement of peak expiratory flow, more clinical successes, and a smaller percentage of clinical failures (ie, recurrence).

A major criticism of this study was that no microbiological testing was performed.

Allegra et al[17] found significant benefit with the use of amoxicillin-clavulanic acid vs placebo in patients with severe exacerbations. Patients treated had a higher success rate than the placebo group (86.4% vs 50.3%, $P < .01$),

and the frequency of recurrent exacerbations was lower.

Saint et al,[23] in a meta-analysis of nine placebo-controlled, randomized studies published between 1957 and 1992, found a statistically significant overall benefit of antibiotic treatment. In addition, analysis of studies that provided data on expiratory flow rates noted an improvement of 10.75 L/minute in antibiotic-treated groups. They concluded that this antibiotic-associated improvement might be clinically significant, particularly in patients with low baseline peak flow rates and limited respiratory reserve.

Antibiotics are not equivalent

Given the potential benefits, it is not only important to use antibiotics, but also to use the appropriate one. This has not always been the goal. For example, in the study by Anthonisen et al,[19] the assumption was that antibiotics were equivalent and, therefore, the choice of agent was not important.

Unfortunately, no prospective randomized trial to date has directly compared the effectiveness of different antibiotics in treating this problem. Retrospective studies,[21,22] however, indicate that the rising rates of antimicrobial resistance probably have significant clinical implications and should influence our choice of antibiotic. A retrospective study[21] of outpatients with COPD conducted at our institution found not only that the major risk factor for treatment failure within 14 days of initial treatment was the lack of antibiotic therapy, but that the type of antibiotic used was also important. Patients treated with amoxicillin had a 54% failure rate vs 5% to 20% ($P < .01$) for the other antibiotics (ie, macrolides, trimethoprim-sulfamethoxazole, cephalosporins).[21] Patients treated with antibiotics who experienced treatment failure within 14 days had a significantly higher hospital admission rate. There may be many explanations for these findings, but the most likely is that the pathogens were resistant to amoxicillin and thus were associated with treatment failure.

Destache et al[22] retrospectively reviewed the impact of antibiotic selection, antimicrobial efficacy, and related costs in 224 episodes of acute exacerbation of chronic bronchitis. The antibiotics were arbitrarily divided into three groups: first-line (amoxicillin, co-trimoxazole, tetracycline, erythromycin), second-line (cephradine, cefuroxime, cefaclor, cefprozil), and third-line (amoxicillin-clavulanate, azithromycin, ciprofloxacin). Patients who received first-line antibiotics had a significantly higher failure rate at day 14 vs those who received a third-line agent ($P < .05$). Additionally, patients who received third-line agents were hospitalized significantly less often, and the time between subsequent exacerbations was significantly longer than with first-line and second-line agents ($P < .005$).

Two predictors of treatment failure

Antibiotic treatment in patients with acute exacerbations of chronic bronchitis is not always successful, as indicated by an increase in or persistence of purulence in the sputum, cough, and shortness of breath. This leads us to search for a way of predicting in which patients antibiotic treatment is most likely to fail.

In an observational study of 471 patients with acute exacerbations, Ball et al[24] found two factors that positively predicted treated patients would experience a return of similar symptoms within 4 weeks of initial presentation:

- Frequent (more than four) exacerbations within the previous year
- Significant comorbidity, such as coronary artery disease or heart failure

It is important to identify these factors to better direct therapy.

20% to 40% of *H influenzae* and 75% to 100% of *M catarrhalis* produce beta-lactamase

FOUR CRITERIA FOR ANTIBIOTIC SELECTION

We recommend that any antibiotic used for treatment of acute exacerbation of chronic bronchitis meet the following four criteria:

- **Significant activity against the most common pathogens,** including *H influenzae*, *H parainfluenzae*, *M catarrhalis*, and *S pneumoniae*, with the caveat that emerging patterns of resistance have been observed with these pathogens.[14,16,17,25]
- **Good penetration of the drug into sputum, bronchial mucosa, and epithelial lining fluid.** Antibiotics exhibit markedly differing

TABLE 1

Treatment of acute exacerbation of chronic bronchitis based on disease severity and causative organisms

CANADIAN BRONCHITIS SYMPOSIUM CLASSIFICATION	PROBABLE PATHOGEN	RECOMMENDED THERAPY
GROUP 1 **Acute bronchitis** Healthy, without previous respiratory problems	Viral	Treat symptoms with decongestants, antihistamines, antipyretics
GROUP 2 **Simple chronic bronchitis** Age ≤ 65 years old **and** < 4 exacerbations per year **and** minimal or no impairment in pulmonary function **and** no comorbid conditions	*Haemophilus influenzae* Other *Haemophilus* species *Moraxella catarrhalis* *Streptococcus pneumoniae* Perhaps atypical organisms	Doxycyline **or** A newer macrolide (eg, azithromycin, clarithromycin) **or** A newer cephalosporin
GROUP 3 **Complicated chronic bronchitis** Age > 65 years old **or** FEV_1 < 50% of predicted **or** ≥ 4 exacerbations per year	Same as for Group 2, with possible addition of *Pseudomonas* species, Enterobacteriaceae, and other gram-negative organisms	Fluoroquinolones (if at risk for *Pseudomonas* infection, use ciprofloxacin) Amoxicillin/clavulanate
GROUP 4 **Complicated chronic bronchitis with comorbid illness** *Same as for Group 3, plus:* Congestive heart failure **or** diabetes **or** chronic renal failure **or** chronic liver disease **or** other chronic disease	Same as for Group 3	Same as for Group 3

degrees of penetration into the tissues and secretions of the respiratory tract.[26,27] Higher concentrations of antibiotic in the sputum, bronchial mucosa, and epithelial lining fluid are thought to predict clinical efficacy. Compared with simultaneous serum concentrations, the concentration of most beta-lactamase antibiotics is 25% to 55% in the bronchial mucosa and 5% to 25% in the sputum.[27] In contrast, macrolides (azithromycin and clarithromycin) and quinolones may achieve concentrations of 200% to 500% in respiratory secretions and bronchial mucosa.

- **Easy to take, with minimal side effects.** Patients are more likely to comply with a once-daily or twice-daily dosage (particularly for less than 14 days) vs three or more times a day, according to a recent survey[28]: more than 54% of patients interviewed confessed to not completing the prescribed course of antibiotics or not taking tablets regularly, and more than 80% said they preferred medications that had to be taken only once or twice daily.
- **Cost-effective.** Cost considerations include not only the acquisition cost, but also the need for hospitalization, the failure rate, delayed improvement in symptoms, and increased morbidity. Destache et al[22] showed that initial pharmacy acquisition costs were lowest with the first-line agents (amoxicillin, co-trimoxazole, tetracycline, erythromycin), but that the third-line agents (amoxicillin-clavulanate, azithromycin, ciprofloxacin) showed a trend towards lower mean total costs of treating acute exacerbations of chronic bronchitis. Newer, more expensive antibiotics can be cost-effective if they prevent complications, prolong the time between acute exacer-

bations, decrease the need for other medications, and prolong the development of antibiotic resistance. Since hospitalization is a large part of the cost of acute exacerbations of bronchitis,[29] any therapy that allows patients to be treated in an outpatient setting is likely to generate significant savings.

A CLASSIFICATION SYSTEM FOR CHOOSING THERAPY

The Canadian Bronchitis Symposium,[30] a panel of experts in respiratory medicine, microbiology, and infectious disease, proposed a four-tiered classification of disease severity, using lung function and other clinical parameters. Patients are grouped according to the number and severity of acute symptoms, age, severity of airflow obstruction (measured by changes in the forced expiratory volume in 1 second [FEV_1]), frequency of exacerbations, and history of comorbid disease (TABLE 1). We find this classification scheme helpful when selecting antibiotic treatment in patients with acute exacerbations of bronchitis.

In general, the antibiotics prescribed should cover the common pathogens (ie, *H influenzae*, *H parainfluenzae*, *M catarrhalis*, and *S pneumoniae*). There is evidence, however, that other gram-negative organisms such as Enterobacteriaceae and *Pseudomonas* are important to consider in patients with the most severe obstructive lung disease ($FEV_1 \leq 35\%$ predicted).[31]

Newer, expensive drugs can still be cost-effective

Group 1: Patients who have acute tracheobronchitis but are generally healthy and have no history of respiratory problems do not require antibiotic treatment and should be treated symptomatically: eg, with decongestants, topical corticosteroids, antipyretics. In patients with acute bronchitis with more than 2 weeks of cough and clear sputum that is highly suggestive of the presence of atypical microorganisms, consider using one of the advanced macrolide antibiotics (clarithromycin or azithromycin).

Group 2: Patients with "simple" chronic bronchitis require antibiotic therapy directed at *H influenzae*, *M catarrhalis*, *S pneumoniae*, and, possibly, at atypical organisms such as *M pneumoniae* and *C pneumoniae*. When patients can provide a sputum sample, microbiologic assessment is advisable. Using the Canadian Bronchitis Symposium guidelines,[30] with some modifications due to concerns in the United States about increasing antimicrobial resistance, the specific treatment recommendation for patients with simple chronic bronchitis is doxycycline, a newer macrolide such as azithromycin or clarithromycin, or a newer cephalosporin such as cefixime or cefprozil.

Some of the recently developed quinolones have some activity against these organisms and may be the antibiotics of choice in the future. In addition, in patients who have recently received antibiotic therapy or who have had no response to an agent, the recommended treatment is another antimicrobial without the same gaps in the spectrum as the first agent.

Groups 3 and 4: Patients with complicated chronic bronchitis and patients with complicated bronchitis and comorbid illness require sputum assessment to help direct therapy, as the probability of resistance and subsequent reinfection by the same organism is high. For these patients, the recommended treatment is one of the newer macrolides, amoxicillin-clavulanate, or an oral fluoroquinolone.

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