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Guidelines for the Treatment of Acute Exacerbations of Chronic Bronchitis*

Ronald F. Grossman, MD, FCCP

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Chronic obstructive lung disease is the fourth leading cause of death in the United States. Approximately 20% of the population are afflicted with this disorder. Acute bronchitis and acute exacerbations of chronic bronchitis account for approximately 14 million physician visits per year and are among the most common illnesses encountered by general and family physicians. Acute exacerbations of chronic obstructive lung disease are usually defined as episodic respiratory decompensation without an objectively documented cause such as pneumonia. The role of bacterial infection in acute exacerbations of chronic bronchitis is controversial. Many of these patients are treated with antibiotics, but the efficacy of this treatment has been questioned. A causal relationship is implied by the presence of increased numbers of bacteria and neutrophils in sputum during exacerbations. Musher et al documented an acute antibody response to such bacteria while Stockley and Burnett have demonstrated an increase in inflammatory mediators in purulent sputum. Bacterial exacerbations are usually limited to the bronchial mucosa and many cases resolve spontaneously. Anthonisen and coworkers demonstrated that, in patients having increased dyspnea, sputum volume, and sputum purulence, broad-spectrum antibiotics (amoxicillin, trimethoprim-sulfamethoxazole, or doxycycline) led to improved clinical outcomes, fewer therapeutic failures, and a more rapid rate of lung function recovery compared with placebo. A recently published meta-analysis of all randomized, placebo-controlled trials of patients treated with antibiotics for acute exacerbations of chronic bronchitis concluded that a small but statistically significant improvement could be expected in antibiotic-treated patients.

Bacterial Pathogens

Gump et al demonstrated that two thirds of all exacerbations are bacterial in origin. Haemophilus influenzae is the most commonly isolated organism from sputum in patients with acute exacerbations of chronic obstructive lung disease, but other Haemophilus species, Streptococcus pneumoniae, and Moraxella catarrhalis may also be found. Two studies utilizing the protected specimen brush technique, in which pure lower respiratory tract samples were obtained, indicated that the organisms associated with acute exacerbations were the same, albeit in higher number. B-1actamase-mediated amoxicillin resistance can be expected in 20 to 40% of H influenzae strains in North America and Europe and in almost 100% of M catarrhalis strains.

Definition of Risk Factors

It would be preferable to define a target population at risk based on severity of disease as has been done for patients with pneumonia. For example, patients with significant compromise of lung function may develop acute respiratory failure as a consequence of an acute exacerbation. Among these patients, 20 to 60% require mechanical ventilation, average hospital and ICU length of stay are long and expensive, and hospital mortality rates range from 10 to 30%. In North America, factors associated with inhospital mortality include age of 65 years or older, severity of respiratory and nonrespiratory organ system dysfunction, and hospital length of stay before ICU admission. Severity of the underlying respiratory function also substantially influences mortality following hospital discharge. In patients with COPD followed up for 3 years, the major determinants of survival were the patient’s age and degree of airway obstruction. Performance status and oral steroid medication usage have also been linked to survival. The risk of dying increases almost four times if a patient is confined to bed for >50% of waking hours and is increased two times if the patient reports being confined to bed part of the time but up and about for >50% of the waking hours. Coexistent cardiopulmonary disease and the number of previous exacerbations have been identified as risk factors for hospitalization or returning to the physician following institution of antibiotic therapy. From these data, it appears that a population of patients with COPD at high risk for treatment failure exists. These patients can be defined as being elderly, with signifi-
significant impairment of lung function, having poor performance status with other comorbid conditions, having frequent exacerbations, and often requiring oral corticosteroid medication. An aggressive approach to the treatment of exacerbations of COPD in this targeted population might lead to improved outcomes.

**Stratification of Patients According to Risk Factors**

Therapeutic failure might be expected to lead to more hospitalizations, increased costs due to extra physician visits, prolonged absences from work, further diagnostic tests, and repeated courses of antibiotics in high-risk individuals. Routine chemotherapy fails in 13 to 25% or more of exacerbations. Simple stratification of patients into risk categories should allow the physician to identify high-risk individuals and select targeted antimicrobial therapy to prevent some of these consequences. Although several stratification schemes have been proposed, to my knowledge, none have been validated in a prospective randomized trial.

Balter and coworkers suggested that five categories could adequately describe this population. They proposed that group 1 patients had acute simple bronchitis with no previous respiratory problems. They indicated a no treatment option or for those with persistent symptoms, a macrolide to deal with the suspected pathogens, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *S pneumoniae*. Group 2 patients had simple chronic bronchitis with little or no impairment of lung function and without other risk factors. Treatment with an aminopenicillin was suggested. Group 3 patients had moderate to severe chronic bronchitis, were elderly (≥65 years), and had frequent exacerbations (≥4/yr). Treatment with an antibiotic 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, and quinolone was suggested. Group 4 patients were similar to group 3 patients 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 but sputum cultures were suggested for this group to tailor therapy to the isolated pathogen.

Wilson suggested a slightly different classification. He proposed patients be divided into three groups. “First degree” patients were defined as having a relatively short history, rare exacerbations, normal lung function, and the usual pathogens, namely, *H influenzae* and *S pneumoniae*. He suggested oral amoxicillin, doxycycline, co-trimoxazole, or the macrolides for these patients. “Second degree” patients were defined as having a longer history of chronic obstructive lung disease, several exacerbations per year, and impaired lung function. Because of a concern for additional Gram-negative pathogens, he 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 chronic obstructive lung disease, severe functional impairment, and frequent infections with Gram-negative pathogens. He suggested oral therapy with cephalosporins, amoxicillin-clavulanic acid, quinolones and, in hospitalized patients, these same drugs IV or aminoglycosides in combination with β-lactams.

Recently an ad hoc group of international pulmonary and infectious disease physicians have been meeting to carefully redefine these risk groups (Peter Ball, MD, Robert Wilson, MD, Sanford Chodosh, MD, and Ronald Grossman, MD; personal}

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**Table 1—Proposed Classification of Patients**

<table>
<thead>
<tr>
<th>Baseline Clinical Status</th>
<th>Criteria/Risk Factors</th>
<th>Pathogens</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Acute tracheobronchitis</td>
<td>No underlying structural disease</td>
<td>Usually viral</td>
<td>None, consider macrolide or tetracycline</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>H influenzae, M catarrhalis, S pneumoniae</em></td>
<td>Aminopenicillin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(possible β-lactam resistance)</td>
<td></td>
</tr>
<tr>
<td>2. Simple chronic bronchitis</td>
<td>FEV₁ &gt;50%, increased sputum volume and purulence</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>H influenzae, M catarrhalis, S pneumoniae</em></td>
<td>Quinolone, penicillin + β-lactam inhibition, second- or third-generation cephalosporin, second-generation macrolide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(resistance to β-lactams common)</td>
<td></td>
</tr>
<tr>
<td>3. Complicated chronic bronchitis</td>
<td>As for class 2 + any one of: FEV₁ &lt;50%, advanced age, ≥4 exacerbations/yr, significant comorbidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Chronic bronchial infection</td>
<td>Class 3 + continuous sputum throughout year</td>
<td>Above + Enterobacteria, <em>P aeruginosa</em></td>
<td>Ciprofloxacin</td>
</tr>
</tbody>
</table>

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communication; 1996). A new classification based on a better understanding of risk factors and treatment outcome with antibiotics has been proposed (Table 1).

Group 1 patients have acute bronchitis that is usually viral in etiology. Since there is no underlying lung disease in this group, the illness is usually self-limited and benign. In the face of persistent symptoms, treatment with a macrolide or doxycycline is recommended to deal with potential infection of M pneumoniae or C pneumoniae.

Group 2 patients are younger, have only mild to moderate impairment of lung function (FEV1 ≥50% predicted), and have less than four exacerbations per year. In this group of patients, typical organisms found are H influenzae, S pneumoniae, and M catarrhalis, although viral infections often precede bacterial superinfection. Treatment with a β-lactam is usually successful, and the prognosis is excellent.

Group 3 patients are older, with poor underlying lung function (FEV1 ≤50% predicted), or only moderate impairment of lung function (FEV1 between 50% and 65% predicted) but with concurrent significant medical illnesses (diabetes mellitus, congestive heart failure, chronic renal disease, chronic liver disease, etc.), and/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 and/or hospitalization. Treatment with medications directed toward resistant organisms, such as a quinolone, amoxicillin-clavulanic acid, second- or third-generation cephalosporin, or second-generation macrolide is indicated.

Group 4 patients suffer from chronic bronchial infection with frequent exacerbations characterized by increased sputum production, increased sputum purulence, cough, and worsening dyspnea. These individuals tend to have a chronic progressive course and an aggressive therapeutic approach should be offered. Besides the usual respiratory organisms, other Gram-negative organisms, including Enterobacteriaceae and Pseudomonas sp, 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.

Future studies of new antimicrobials should examine their efficacy in patients falling into the last two categories. Only in these patients can the potential benefits of broad-spectrum, β-lactamase-stable, potent antibiotics be demonstrated. The inclusion of patients from the first two categories can only dilute the results and minimize the advantages of more potent antibiotics. The benefit of this proposed classification needs to be validated in a randomized, prospective trial examining clinical and economic outcomes.

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