Acute Exacerbations of Chronic Bronchitis: Diagnosis and Therapy

Case Study and Commentary, Fernando J. Martinez, MD, MS

Abstract

- **Objective:** To review the diagnosis and treatment of acute exacerbations of chronic bronchitis (AECB).
- **Methods:** Qualitative assessment of the literature.
- **Results:** The physician must first make an accurate determination of the cause of the AECB. Antibiotics are appropriate only for patients proven or suspected of having a bacterial infection. Patients with purulent sputum and multisymptom exacerbations have a greater likelihood of a bacterial pathogen and will benefit most from antibiotic therapy. When choosing an antibiotic, it is important to stratify patients with regard to clinical features suggesting a higher likelihood of treatment failure or of a shorter disease-free interval. Various classes of antibiotics are available for treatment of uncomplicated and complicated AECB, which allows the physician flexibility in treating the patient who recently has been exposed to a class of antibiotics. Given the increased likelihood of resistant isolates in such a patient, an agent from an alternate class may be ideal. Oral steroids are also an important component of therapy in AECBs, particularly in exacerbations of greater severity. Measures to reduce the risk of recurrence (ie, bronchodilators, steroids) should be considered as a means to prevent deterioration in health status and pulmonary function.
- **Conclusion:** Given the negative effects of AECBs on patients’ health status, appropriate treatment of AECBs and institution of interventions to prevent recurrent exacerbations is an important component in the management of patients with chronic obstructive pulmonary disease.

Approximately 6% of the U.S. adult population has chronic obstructive pulmonary disease (COPD) [1], while the prevalence of chronic bronchitis has been estimated at 3.2% [2]. Acute exacerbations of disease in patients with chronic bronchitis account for about 13 million office visits each year [3,4]. Over the past several years, it has become increasingly evident that appropriate management of acute exacerbations of chronic bronchitis (AECB) is of paramount importance in managing patients with chronic airway disease because of the implications of these episodes on the natural history of disease.

**CASE STUDY**

**Initial Presentation**

A 55-year-old man presents to his primary care physician with a change in his chronic cough.

**History**

The patient gives a history of chronic cough with clear sputum production on a daily basis for the past 4 years. He also suffers from chronic, exertional breathlessness that has been gradually worsening for the past 2 years. As a result of this breathlessness, he has been gradually decreasing his daily activities, which he attributes to “getting older.” Five days ago he noted coryza, a low-grade temperature, and a sore throat. Two days ago, he noted increased cough with green sputum and worsening shortness of breath. His past medical history is significant for hypertension, hyperlipidemia, coronary artery disease status post–myocardial infarction 7 years earlier, and a history of documented chronic airflow obstruction (forced expiratory volume in 1 sec [FEV₁] 48% predicted). He has experienced 2 similar disease exacerbations within the past 12 months, one of which required hospitalization 2 months earlier; he was treated with oral prednisone and antibiotics at that time. He has smoked 2 packs of cigarettes per day for 30 years and continues to smoke. His current medications include lisinopril, aspirin, atorvastatin, inhaled ipratropium/albuterol, and inhaled salmeterol. He is up to date with influenza vaccination.

**Physical Examination**

Physical examination reveals a temperature of 37.1°C, blood pressure of 132/76 mm Hg, pulse of 88 bpm, and a respiratory rate of 18 breaths/min. Oxygen saturation while breathing...
The room air is 92%. The patient is not in apparent respiratory distress. His chest examination reveals scattered wheezes and rhonchi, while the cardiovascular examination and abdominal examination are normal. There is no cyanosis or peripheral edema.

- What constitutes an AECB?
- What is the impact of an AECB on current and future health status and pulmonary function?

The exact definition of an AECB remains controversial [5], but a generally accepted definition is that of “a sustained worsening of the patient’s condition from the stable state and beyond normal day-to-day variations that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD” [6]. The case patient’s history includes a smoking history (60 pack-years and counting) and documented airflow obstruction, which confirm a diagnosis of COPD [7]. The increasing cough, breathlessness, and change in sputum character strongly support the diagnosis of an acute exacerbation of underlying COPD. This triad of symptoms classically has been used to describe a symptom-based definition of an AECB [5,8].

It is important to exclude other infectious causes that could account for the current symptoms. The absence of fever and tachypnea with nonfocal chest findings strongly argues against a diagnosis of community-acquired pneumonia [9]. If clinical concern remains, a chest radiograph is the most definitive way to exclude this diagnosis [10]. The absence of fever and the previous influenza vaccination decreases the likelihood of acute influenza [11–13], although the diagnosis of this viral infection in patients with underlying COPD may be difficult [14]. Noting the time of the year and the presence of influenza infection in the community could alter the diagnostic and therapeutic approach.

Numerous investigators have highlighted the negative implications of AECBs. Some have confirmed the negative effect of individual AECB episodes on health status [15], while others have demonstrated that recurrent AECB episodes exert significant negative effects on health status. Patients with more frequent AECBs have a worse health status than patients with less frequent exacerbations [16,17]. A recent prospective study of 336 COPD patients confirmed that more frequent exacerbations had a deleterious effect on health status in patients with moderate disease (FEV₁ 35%–50% predicted), while hospitalizations had a particularly significant impact on health status in patients with more severe disease [18]. An early recurrence of an AECB after treatment has a sustained negative effect on health status [15,19]. Two investigative groups have suggested that more frequent AECBs are associated with additional decline in lung function: 7 mL in FEV₁ per lower respiratory tract infection per year [20] and approximately 8 mL per year in patients with frequent exacerbations compared to those with infrequent exacerbations [21].

AECB episodes are a major source of health care expenditures. Total treatment costs were estimated at $1.2 billion in patients at least 65 years of age and $419 million in those younger than 65 years in 1995; these costs were predominantly for hospitalizations [22]. In a prospective study of 2414 COPD patients following an AECB, 507 patients relapsed after therapy; of these, 161 patients required emergency department treatment and 84 required hospitalization [23]. These latter patients accounted for 58% of the total cost. It is evident that AECBs, particularly those that require hospitalization, result in major health care costs.

- What are the viral and bacterial etiologies of an AECB episode?

**Table 1. Infectious Etiologies of an Acute Exacerbation of Chronic Bronchitis**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>No infectious etiology identified</td>
<td>30–50</td>
</tr>
<tr>
<td>Viral</td>
<td></td>
</tr>
<tr>
<td>Adenovirus</td>
<td>1–2</td>
</tr>
<tr>
<td>Influenza</td>
<td>5–26</td>
</tr>
<tr>
<td>Parainfluenza</td>
<td>3–29</td>
</tr>
<tr>
<td>Rhinovirus</td>
<td>5–36</td>
</tr>
<tr>
<td>Coronavirus</td>
<td>5–23</td>
</tr>
<tr>
<td>Respiratory syncytial virus</td>
<td>0–22</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>2</td>
</tr>
<tr>
<td>Bacterial</td>
<td></td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>15–33</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>30–70</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
<td>3–22</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>0–17</td>
</tr>
<tr>
<td>Enteric gram-negative organisms</td>
<td>0–44</td>
</tr>
<tr>
<td>Atypical pathogens</td>
<td></td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td>0–14</td>
</tr>
<tr>
<td>Chlamydia pneumoniae</td>
<td>4–34</td>
</tr>
</tbody>
</table>

Adapted with permission from Martinez FJ. Acute bronchitis: state of the art diagnosis and therapy. Compr Ther 2004;30:55–69.
by picornaviruses [25,26]. Respiratory syncytial virus [25] and coronaviruses [27] appear to be the second most preva-

lent. In hospitalized patients, picornaviruses remain quite prevalent [28], while some have suggested that influenza virus [29] or coronaviruses [30] are also important pathogens. The differences between studies likely relate to differences in the methodology used to define viral infection, the patient population studied, the time of the year data were recorded, and the proportion of patients who received influenza vaccination. In any case, viral infections may be associated with particularly severe AECBs. Seemungal and colleagues confirmed that patients with viral AECBs had higher symptom scores at the onset of an exacerbation and had longer times to resolution of the acute episode [25]. The symptoms that were more likely to be associated with a viral infection included colds, sore throat, and the combination of dyspnea with a cold [25]. Importantly, a previous study suggested that an acute viral infection was associated with increased colonization of the respiratory tract by bacteria [31]. The clinical scenario presented in the current case strongly suggests that a viral infection has triggered the current exacerbation.

In contrast to uncomplicated acute bronchitis, up to 70% of AECB episodes can be attributed to bacterial infection [32–35]. The presence of bacterial pathogens in the sputum while the patient is in a stable phase (ie, bacterial colonization) has been associated with a greater AECB frequency [36]. Potentially pathogenic bacteria are identified in many COPD patients at baseline and during an AECB [34]. Bronchoscopic sampling by several groups has confirmed this finding [37–41]. For example, intracellular Haemophilus influenzae was identified in 87% of bronchial biopsy samples from acutely ill patients with chronic bronchitis compared with 33% of stable patients and 0% of healthy controls in one series [42]. Interestingly, a recent report suggests that sputum cultures may underestimate the presence of colonization with H. influenzae [43]. Both local and systemic immune responses to H. influenzae [44–46] and Streptococcus pneumoniae [47] have been identified in COPD patients. A link between bacterial infection and AECB is strongly suggested by the recent work of Sethi et al, which demonstrated that the likelihood of a patient reporting an AECB was related to identification of new strains of H. influenzae, Moraxella catarrhalis, and S. pneumoniae in the sputum rather than simply the presence of these organisms [48].

Bacteria are likely related to the symptoms of an AECB via an intensification of airway inflammation, an important component of disease [35]. Neutrophils [49,50] and eosinophils [51,52] have been implicated in this process. For example, purulent sputum, in contrast to nonpurulent sputum, contains a greater concentration of the neutrophil chemoattractants leukotriene B4 (LTB4) and interleukin (IL)-8, neutrophils, and markers of their activity, including myeloperoxidase (MPO) and neutrophil elastase (NE) [49,53,54].

Infection is likely an important trigger of airway inflammation in COPD. Sputum MPO, NE, IL-8 and LTB4 concentration in colonized patients correlates with bacterial count [36,55]. Bacterial colonization is associated with increased sputum levels of neutrophil chemoattractants [56–58]. The colonizing bacterial species influences the inflammatory response, with the greatest response associated with Pseudomonas aeruginosa and H. influenzae [55]. Bacterial pathogens in sputum during an AECB are associated with a higher concentration of neutrophil chemoattractants and with evidence of neutrophil degranulation, particularly with H. influenzae infection [59]. Importantly, antimicrobial therapy in AECBs results in decreasing neutrophil chemoattractant concentration in the sputum [54,60]. In fact, failure to eradicate organisms from sputum after treatment of an AECB is associated with persistent airflow inflammation [61].

Conventional bacteria are the principal culprits in most episodes as noted in Table 1. In addition, several host factors, including the severity of underlying pulmonary disease, likely affect the etiologic agent. Several investigators have documented that patients with decreased FEV1 (< 35%–50% predicted) have a greater likelihood of infection with enterobacteriaceae, Pseudomonas species, and H. influenzae [39,62,63]. Pseudomonas species may be particularly likely in patients who have received frequent antibiotics [64]. One group has noted that H. influenzae was more likely to be identified in the sputum of active smokers (odds ratio, 8.1 [95% confidence interval (CI), 1.9–43.0]) [62]. The role of other microorganisms remains controversial. Chlamydia pneumoniae and Mycoplasma pneumoniae infection have been implicated in approximately 5% to 10% of AECBs, although some investigators have suggested a greater prevalence [65–68]. Thus, a wide variety of pathogens can be responsible for AECB episodes, and the pathogen identified differs according to the presence or severity of underlying pulmonary disease. Unfortunately, a simple delineation of etiology is difficult to achieve in practice.

• What is the goal for the management of an AECB episode?

Optimal management of an AECB should result in rapid resolution of symptoms, eradicate the causative pathogen, and decrease the likelihood of recurrence. A recent report has confirmed that earlier treatment of an AECB is associated with faster recovery from symptoms (0.42 days/day delay) [69]. Comprehensive evidence-based reviews of the literature addressing the management of AECB have [70,71] suggested
CHRONIC BRONCHITIS

that optimal management incorporates multiple therapeutic modalities. Given the biologic nature of an AECB, the practitioner should aim to reduce the inflammatory response and target therapy to the causative pathogens. With regard to the latter, practitioners must first decide whether bacteria are the cause of a specific episode.

• Which patients should be treated with antibiotics?

Because patients with an AECB have a higher likelihood of a bacterial etiology, it is not surprising that placebo-controlled trials of antibiotics in AECBs have suggested a modest treatment effect [70,72]. Several authors have provided practical information highlighting the benefits of antibiotics for selected AECB patients [73–75]. For example, patients with severe AECBs (requiring mechanical ventilation) [74] or more severe underlying lung disease [75] are particularly likely to benefit from antimicrobial therapy. Despite these data, determining which individuals are most likely to benefit from antibiotic therapy remains difficult in clinical practice. In a sentinel study, Anthonisen et al randomly assigned 173 patients during 362 episodes of AECB to an antibiotic (trimethoprim/sulfamethoxazole, amoxicillin, or doxycycline) or placebo, stratifying the results based on the number of symptoms at presentation [8]. Patients with at least 2 symptoms (increase in dyspnea, increase in sputum production, and/or change in sputum color) experienced a benefit with antibiotic therapy. Interestingly, a recent bronchoscopic study in hospitalized patients stratified by the Anthonisen criteria confirmed a greater likelihood of bacterial infection in patients with multisymptom AECBs [76]. Thus, antibiotic therapy appears to benefit patients with multisymptom AECBs.

Patients with an AECB associated with purulent sputum also may be more likely to benefit from antibiotic treatment. Stockley and colleagues noted that 32 of 34 patients with an exacerbation and mucoid sputum resolved their exacerbation without antibiotic therapy; patients with purulent sputum were more likely to have neutrophils and organisms in sputum, and 77 of 87 of these patients resolved their AECB with antibiotic therapy [49]. As such, new sputum purulence suggests that the patient may be more likely to benefit from antibiotic therapy. Interest has been growing in the use of serum procalcitonin levels as a marker of bacterial respiratory tract infection [77]. A recent systematic review suggests acceptable sensitivity (88%) and specificity (80%) in separating bacterial from nonbacterial causes of inflammation in hospitalized patients [77]. One group has suggested that serum procalcitonin levels may be a useful tool in identifying AECB patients infected with a bacterial pathogen [78].

• Which antibiotic should be administered?

Antimicrobial Therapy Options

Choosing the optimal agent can be a difficult task, as the antimicrobial must have an appropriate spectrum of activity and an adequate pharmacokinetic/pharmacodynamic profile to effectively kill the infecting organism. It has become increasingly clear that certain patients are at particularly high risk for treatment failure [73,79], a situation associated with particularly high health care costs [23]. Most recent therapeutic guidelines have taken the approach of stratifying patients according to the risk of treatment failure (Figure 1, Table 2) [73,79]. All of these schemes have identified features for a high likelihood of infection with organisms that are not covered with standard antibiotic regimens (eg, P. aeruginosa, drug-resistant bacteria) or host factors that predict treatment failure (poor lung function, frequency of exacerbation/office visits, ischemic heart disease, and other comorbid conditions) [80–82]. In fact, a recent study has prospectively confirmed that patients with a complicated AECB as stratified by an approach similar to that delineated in Table 2 experienced an inferior response rate compared with those with uncomplicated AECB [83]. Based on these data, numerous guidelines have suggested a tailored approach for the initial antimicrobial regimen in individuals at increased risk for treatment failure (Table 2).

A major component of the stratification-based schemes takes into account the likelihood of infection with unusual or resistant pathogens in selected patients. As noted above, patients with a severely impaired FEV1 or recent treatment with broad-spectrum antibiotics are more likely to harbor pathogens such as P. aeruginosa. The role of antimicrobial resistance among S. pneumoniae, H. influenzae, and Moraxella catarrhalis in treatment failures for AECB remains controversial [73,84]. Antimicrobial resistance among these pathogens has increased over the past decade [73] and is likely related to antimicrobial utilization [85]. In fact, patients exposed to β-lactams, macrolides, and quinolones within the previous 3 to 6 months have an increased likelihood of infection with a resistant pathogen [86–88]. Among S. pneumoniae isolates, a wide variability in susceptibility to penicillins [89,90], macrolides [89,91,92], and fluoroquinolones has been reported [93,94]. The in vitro activity of newer respiratory fluoroquinolones (eg, levofloxacin, moxifloxacin, gatifloxacin, gemifloxacin) has remained excellent when tested against penicillin-sensitive or penicillin-resistant S. pneumoniae isolates [95,96]. In fact, levofloxacin, moxifloxacin, and gemifloxacin have received U.S. Food and Drug Administration (FDA) approval for treatment of respiratory infections with penicillin-nonsusceptible S. pneumoniae. In addition, telithromycin, the first ketolide to
come to market, exhibits excellent in vitro and clinical activity against multidrug-resistant *S. pneumoniae* and is approved by the FDA for use in such infections [97,98]. Importantly, a recent, large multicenter study utilizing stratification of patients into severity categories has confirmed that a higher percentage of *S. pneumoniae* isolates from patients with complicated AECB versus uncomplicated AECB exhibited resistance to macrolides (45% versus 35%), penicillin (37% versus 4%), trimethoprim/sulfamethoxazole (43% versus 22%), and levofloxacin (6% versus 0%) [99].

Isolates of *H. influenzae* and *Moraxella catarrhalis* have also exhibited increasing resistance [100]. The overall prevalence of β-lactamase production has ranged from approximately 30% to 35% for *H. influenzae* and from 95% to 99% for *Moraxella catarrhalis* [84]. β-Lactamase-negative ampicillin-resistant strains [100] and amoxicillin-clavulanate-resistant strains have also been reported [101], albeit infrequently. In fact, quinolone-resistant *H. influenzae* have recently been reported in a long-term care facility, with a particularly high prevalence among COPD patients [102].

The clinical implication of antibiotic resistance in patients with AECB remains unclear, however [84]. The most convincing report involves the identification of a nosocomial outbreak of fluoroquinolone-resistant *S. pneumoniae* infection in a hospital ward in which ciprofloxacin was frequently used to treat lower respiratory tract infections; 13 patients on this ward experienced failure during treatment of an AECB with a fluoroquinolone [103]. Additional data are required to clarify whether outcomes are worse in AECB patients with infections due to resistant organisms.

Increasingly, data are being reported supporting the concept that antimicrobial classes have varying clinical efficacy in AECB. A recent prospective study confirmed that patients stratified in a complicated AECB category experienced an inferior clinical and microbiologic response compared with patients stratified in an uncomplicated AECB category, despite similar quinolone therapy in one of the arms (levofloxacin) [83]. Differences between antimicrobial classes are particularly evident when investigating the disease-free interval (DFI), that is, the time between exacerbations [104,105]. The DFI can have important clinical and economic implications. For example, a longer DFI should translate to fewer annual episodes of AECB, which may significantly improve a patient’s health status and preserve lung function. From an economic perspective, a longer DFI and fewer AECB episodes should result in lower health care costs [105]. Although an early trial demonstrated equivalence between ciprofloxacin and cefuroxime axetil, a post hoc analysis suggested that failure to clear the organism from the baseline sputum after therapy was associated with a prolonged DFI [106].

More recently, several investigative groups have provided more compelling data. Wilson and colleagues noted a lower AECB recurrence rate in patients treated with gatifloxacin than in those treated with clarithromycin [107]. The MOSAIC study investigators identified patients with well-defined COPD and frequent AECBs and randomly assigned them at the time of an AECB to therapy with moxifloxacin or a comparator (cefuroxime, clarithromycin, or amoxicillin) [108]. Although all antibiotics were equivalent with respect

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**Figure 1.** Approach to selection of an antimicrobial agent for treatment of acute exacerbation of chronic bronchitis. *If an antimicrobial agent has been administered within the previous 3 months, an agent from a different antimicrobial class should be considered. †Active smoking increases likelihood of *Haemophilus influenzae* infection.*
to clinical response after initial therapy, moxifloxacin-treated patients required fewer additional antibiotics and experienced a longer DFI. In addition, other prospective studies have suggested a faster resolution of symptoms with quinolone-based therapy [83,109]. The totality of these data suggests that antibiotics may differ in efficacy in high-risk patients with an AECB.

**Initiation of Antimicrobial Therapy**

The case patient has severe chronic airflow obstruction (FEV₁ 48% predicted) and is experiencing a multisymptom AECB with new, purulent sputum, suggesting that an antimicrobial agent is likely to be of benefit. He is classified as experiencing a complicated AECB given the presence of cardiovascular comorbidity and an FEV₁ of less than 50% predicted. In addition, treatment during the recent hospitalization included antimicrobial therapy, which increases the likelihood of a resistant organism. As such, the physician initiates therapy with a newer respiratory fluoroquinolone (eg, gatifloxacin, gemifloxacin, levofloxacin, or moxifloxacin); amoxicillin-clavulanate could serve as an alternate agent, although its activity could be compromised if β-lactam-resistant *S. pneumoniae* is present.

- Would corticosteroid therapy be appropriate in this case?

Numerous studies have evaluated the effect of systemic corticosteroids for AECBs [110]. A review of 6 randomized,
placebo-controlled trials has suggested that a short course of systemic steroids improves pulmonary function and decreases the relapse rate in AECB [70], while a more recent systematic review suggested that systemic steroid therapy results in improvement over the first 72 hours but with increased risk of adverse drug reaction [111]. The largest study in hospitalized patients confirmed that parenteral steroids (solumedrol 125 mg/day for 3 days followed by either a 15-day or 8-week taper) was associated with more rapid improvement in \( \text{FEV}_1 \), fewer treatment failures, and a shorter length of hospital stay [112]. Both steroid doses exhibited similar efficacy, although steroids were associated with more adverse events (particularly hyperglycemia) [112]. Subsequent investigators have confirmed these findings while using lower doses for shorter periods [113,114], including patients being discharged from the emergency department [115]. An uncontrolled, prospective cohort study suggested that prednisone therapy hastened AECB recovery by 2.63 days [69]. Finally, an uncontrolled cohort study has suggested a longer DFI in patients treated with steroids (84 days) compared with those not treated with oral steroids (60 days) [16]. The case patient described would be an appropriate candidate for a short course of moderate dose prednisone (eg, 30–60 mg with a 10–14 day taper) given the severity of his underlying COPD and his history of a recent hospitalization.

- **What therapies can be used to minimize the risk of future AECB episodes?**

### Bronchodilators

Prevention of AECB episodes has become an increasingly important component of COPD therapy. Numerous approaches have been utilized to achieve this goal. For example, bronchodilators appear to reduce the exacerbation rate [116]. In reviewing 9 placebo-controlled clinical trials including salmeterol or formoterol, Sin and colleagues reported a 21% (95% CI, 10%–31%) reduction in exacerbation rates, although the findings of the individual studies were variable (Table 3) [116]. The data regarding ipratropium have been variable, with 3 groups failing to identify a beneficial effect of ipratropium use, although their definitions of exacerbations varied [122,124,125]. Interestingly, a pharmacoeconomic analysis of 2 placebo-controlled, 3 month-long randomized studies of ipratropium versus ipratropium plus albuterol or albuterol alone has been published [126]. These investigators confirmed a significant decrease in exacerbation frequency in the ipratropium arms that translated into a marked decrease in total treatment costs compared with albuterol alone. Five large clinical trials of the novel anticholinergic agent tiotropium have uniformly demonstrated a beneficial effect of this agent in reducing exacerbations compared with placebo (relative risk [RR], 0.74 [95% CI, 0.62–0.89]) or with ipratropium (RR, 0.78 [95% CI, 0.63–0.95]) (Table 4) [116]. Although comparative data are limited, tiotropium and long-acting \( \beta \)-agonists (LABA) seem to be equivalent in decreasing AECBs (RR, 0.93 [95% CI, 0.80–1.08]) [116]. The most recent and best designed trial was recently presented at the American Thoracic Society annual meeting [132]. These investigators randomly assigned 1829

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**Table 3. Clinical Trial Data Evaluating the Effects of Long-Acting \( \beta \)-Agonists on Chronic Obstructive Pulmonary Disease Exacerbations**

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>No. of Patients</th>
<th>Drug</th>
<th>Study Duration, wk</th>
<th>Mean Age, y (SD)</th>
<th>Mean ( \text{FEV}_1 ), L (95% CI)</th>
<th>Relative Risk of Exacerbation (95% CI)</th>
<th>Favors Long-Acting ( \beta )-Agonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wadbo et al [117] 2002</td>
<td>183</td>
<td>Formoterol</td>
<td>12</td>
<td>64 (NR)</td>
<td>&lt; 1.0 (NR)</td>
<td>0.49 (0.13–1.88)</td>
<td>[ ]</td>
</tr>
<tr>
<td>van Noord et al [118] 2000</td>
<td>144</td>
<td>Salmeterol</td>
<td>12</td>
<td>64 (7)</td>
<td>1.2 (0.4)</td>
<td>0.65 (0.34–1.23)</td>
<td>[ ]</td>
</tr>
<tr>
<td>Chapman et al [119] 2002</td>
<td>408</td>
<td>Salmeterol</td>
<td>24</td>
<td>NR</td>
<td>1.2 (NR)</td>
<td>0.79 (0.58–1.07)</td>
<td>[ ]</td>
</tr>
<tr>
<td>Jones and Bosh [120] 1997</td>
<td>326</td>
<td>Salmeterol</td>
<td>16</td>
<td>63 (8)</td>
<td>1.3 (0.5)</td>
<td>NR</td>
<td>[ ]</td>
</tr>
<tr>
<td>Rossi et al [121] 2000</td>
<td>854</td>
<td>Formoterol</td>
<td>52</td>
<td>63 (NR)</td>
<td>1.4 (NR)</td>
<td>0.81 (0.64–1.03)</td>
<td>[ ]</td>
</tr>
<tr>
<td>Dahl et al [122] 2001</td>
<td>780</td>
<td>Formoterol</td>
<td>12</td>
<td>64 (8.6)</td>
<td>1.3 (0.4)</td>
<td>0.87 (0.60–1.26)</td>
<td>[ ]</td>
</tr>
<tr>
<td>Aalbers et al [123] 2002</td>
<td>687</td>
<td>Formoterol</td>
<td>12</td>
<td>63 (NR)</td>
<td>1.5 (NR)</td>
<td>0.78 (0.44–1.36)</td>
<td>[ ]</td>
</tr>
<tr>
<td>Rennard et al [124] 2001</td>
<td>405</td>
<td>Salmeterol</td>
<td>12</td>
<td>64 (8.1)</td>
<td>1.5 (0.6)</td>
<td>0.95 (0.65–1.37)</td>
<td>[ ]</td>
</tr>
<tr>
<td>Mahler et al [125] 1999</td>
<td>411</td>
<td>Salmeterol</td>
<td>12</td>
<td>63 (8.6)</td>
<td>1.5 (NR)</td>
<td>0.63 (0.42–0.95)</td>
<td>[ ]</td>
</tr>
<tr>
<td>Pooled summary</td>
<td>4198</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.79 (0.69–0.90)</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

CI = confidence interval; \( \text{FEV}_1 \) = forced expiratory volume in 1 sec; NR = not reported; SD = standard deviation. (Adapted with permission from Sin DD, McAlister FA, Man SF, Anthonisen NR. Contemporary management of chronic obstructive pulmonary disease. JAMA 2003;290:2304.)
patients at several U.S. VA medical centers to tiotropium \((n = 914)\) or placebo \((n = 915)\); all other medications except for ipratropium were allowed, and patients were followed for 6 months. As expected, the patients were almost all elderly (mean age, 68 years), male (98%), white (approximately 90%), had a heavy smoking history, and exhibited severe airflow obstruction (mean \(\text{FEV}_1\), 36% predicted). Tiotropium favorably affected the primary endpoints, which included the percentage of patients experiencing 1 or more exacerbations (27.9% for tiotropium versus 32.2% for placebo; \(P = 0.04\)) and the percentage with 1 or more hospitalizations (7.0% for tiotropium versus 9.5% for placebo; \(P = 0.06\)). Multiple clinically relevant secondary endpoints of health care utilization favored the long-acting anticholinergic agent. Given the recurrence of AECBs and 1 recent hospitalization in the patient presented, it is likely that institution of tiotropium (18 \(\mu\)g/day via HandiHaler) in place of ipratropium would be a wise move.

### Inhaled Corticosteroids

An important potential benefit of steroid therapy is a modulation of exacerbation frequency. Two systematic reviews have suggested that inhaled corticosteroids (ICS) decrease the risk of a recurrent AECB, particularly in patients with more severe airflow obstruction [116,133]. A review of 6 placebo-controlled trials with at least 6 months of follow-up suggested that ICS led to a 24% reduction in AECBs (95% CI, 20%–28%) [116]. This effect was most likely to be seen in studies where patients exhibited a mean \(\text{FEV}_1\), below 2.0 L (approximately 70% predicted) (Figure 2). Two of the larger studies provide additional insight. The International COPD Study Group, which was powered to detect differences in exacerbation frequency, found no difference in overall incidence of AECBs; importantly, more patients treated with placebo experienced moderate or severe exacerbations (those requiring physician visits or hospitalizations) (86% versus 60%; \(P < 0.001\)) [137]. The ISOLDE study examined exacerbations as a secondary endpoint, demonstrating a decrease in AECB rate from 1.32 per year with placebo to 0.99 per year with fluticasone propionate (500 mg bid) therapy [136]. Further analysis of data from this ground-breaking trial has recently been presented. Fluticasone reduced the overall AECB rate in patients with a postbronchodilator \(\text{FEV}_1\), below 50% predicted (1.47 per year in fluticasone versus 1.75 per year in placebo) but had less effect in patients with milder COPD (0.67 per year in fluticasone versus 0.92 per year in placebo) [140].

Additional information comes from population-based studies. Sin and colleagues examined the Ontario version of the Canadian Institute for Health Information hospital discharge database [141]. These investigators examined outcomes in all 22,260 patients older than 65 years who were discharged from the hospital with a principal diagnosis of COPD between 1992 and 1996. Admission data were linked

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>No. of Patients</th>
<th>Study Duration, wk</th>
<th>Mean (SD) Age, y</th>
<th>Mean (SD) (\text{FEV}_1), L</th>
<th>Versus Long-Acting (\beta_2)-Agonist</th>
<th>Versus Ipratropium</th>
<th>Versus Placebo</th>
<th>Favors Tiotropium</th>
<th>Favors Placebo or Ipratropium</th>
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</thead>
<tbody>
<tr>
<td>Casaburi et al</td>
<td>921</td>
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<td></td>
<td></td>
<td></td>
<td>(0.4)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Donohue et al</td>
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<td>24</td>
<td>65 (8)</td>
<td>1.1</td>
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<td>24</td>
<td>64 (8)</td>
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<td>NR</td>
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<td>[129] 2003</td>
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<td>(0.4)</td>
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<tr>
<td>van Noord et al</td>
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<td>Vincken et al</td>
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<td>64 (8)</td>
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<td>NR</td>
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<td>(0.63–0.95)</td>
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</table>

CI = confidence interval; \(\text{FEV}_1\) = forced expiratory volume in 1 sec; NR = not reported; SD = standard deviation. (Adapted with permission from Sin DD, McAlister FA, Man SF, Anthonisen NR. Contemporary management of chronic obstructive pulmonary disease. JAMA 2003;290:2304.)
to subsequent ICS prescriptions and subsequent death or rehospitalization for COPD during the year after the index hospitalization. After adjustment for age, gender, other medications, and comorbidity, the group receiving ICS after hospital discharge experienced an improved COPD hospitalization-free survival. Subsequent analyses by these investigators suggested that this effect was more likely to be seen with medium- or high-dose ICS therapy (RR, 0.48 [95% CI, 0.37–0.63] for medium dose; RR, 0.55 [95% CI, 0.44–0.69] for high dose) than with low-dose therapy (RR, 0.77 [95% CI, 0.69–0.86]) [142]. Similar results have been published by another group using a separate database [143], although others have questioned the analytic techniques used in these studies [144].

Combination ICS/LABA Therapy
The role of products combining an ICS and LABA in modulating AECB frequency has been evaluated. Calverley and colleagues reported on the impact of fluticasone (500 mg twice daily), salmeterol (50 mg twice daily), their combination, or placebo in 1465 COPD patients (mean FEV₁ approximately 45% predicted) [145]. The combination reduced the overall AECB rate by 25% compared with placebo; fluticasone alone (20% reduction) and salmeterol alone (19% reduction) exhibited a similar effect. In addition, the combination product reduced the rate of AECBs requiring oral steroids by 39%. Overall, the reduction in AECB rate was most evident in patients with an FEV₁ below 50% predicted (30% reduction compared with placebo); the reduction in AECB rate in patients with an FEV₁ greater than 50% predicted was only 10%. Two additional studies examined the combination of formoterol (9 mg twice daily) and budesonide (320 mg twice daily) with formoterol alone (9 mg twice daily), budesonide alone (400 mg daily), or placebo [146,147]. In the study that compared these agents without prior prednisone use, the combination product led to a greater decrease in severe AECBs compared with the individual components or placebo [147]. The second study administered a 2-week course of prednisone therapy up front, which resulted in a 210 mL increase in FEV₁ and improved health status [146]. The combination of ICS and a LABA prolonged the time to first AECB compared with placebo (254 days versus 96 days), decreased the risk of having an AECB, and decreased the AECB rate compared to all of the comparison groups [146]. The authors suggested that combination budesonide/formoterol was better able to maintain the beneficial effects of an initial course of oral steroids. The remarkable consistency between all 3 studies suggests that in patients with more severe COPD (FEV₁ < 50% predicted), the combination of a LABA and an ICS may be better able to reduce AECB frequency than the individual components. In the current patient, the severe nature of his underlying airflow obstruction (FEV₁ 48% predicted) and previous AECBs (including one requiring hospitalization) justifies the introduction of a combined product to his regimen (eg, fluticasone 250 µg/salmeterol 50 µg one actuation twice daily). Whether a further reduction in AECB rate will be seen when LABA/ICS and tiotropium are combined requires additional investigation. Furthermore, which approach will be more effective and less costly and result in fewer adverse events is currently under intensive investigation.

Figure 2. Relationship between forced expiratory volume in 1 second (FEV₁) values and effect on inhaled corticosteroids (ICS) for chronic obstructive pulmonary disease exacerbations. The relative risks have been log transformed. The inverse weighted regression line is the solid line and the dashed lines represent 95% confidence intervals. The diameter of the circle of each trial is proportional to its weight (R² = 78%; P = 0.02). (Adapted with permission from Sin DD, McAlister FA, Man SF, Anthonisen NR. Contemporary management of chronic obstructive pulmonary disease. JAMA 2003;290:2305.)
Mucolytics
Mucolytic drugs increase the expectoration of sputum by reducing hypersecretion or the viscosity of the secretions [148]. As such, these drugs would be expected to have a beneficial impact on AECBs. A detailed systematic review examining the role of oral mucolytic drugs has been published [149]. These authors examined 23 randomized placebo-controlled trials of oral mucolytic drugs taken for at least 2 months. In these studies, regular use of these agents was associated with a reduction of 0.07 exacerbations per patient-month (95% CI, −0.08 to −0.05). As such, the odds ratio for having no exacerbation in the study period with mucolytic drug therapy compared with placebo was 2.22 (95% CI, 1.93–2.54). The reduction in the exacerbation rate was greater in the 2 studies with patients with an FEV1 below 50% predicted (reduction of 0.13 per patient-month). In addition, the reduction was greater for studies that lasted 3 months or less (0.13/subject) than for those that lasted over 3 months (0.06/subject), suggesting that the benefit was seen early in the course of therapy. In addition, mucolytic therapy was associated with a reduced number of days of illness and days that subjects took antibiotics. Given the limited availability of the most active mucolytic drugs in the United States, the role of these drugs in the patient presented in the case study remains unclear.

Summary
Proper management of an AECB is an important component of COPD therapy. The practitioner first needs to make an accurate determination of the cause of the condition. Antibiotics are appropriate only for patients proven or suspected of having a bacterial infection. It is likely that patients with purulent sputum and multisymptom exacerbations have a greater likelihood of a bacterial pathogen and will benefit most from antibiotic therapy. When choosing an antibiotic, it is important to stratify patients with regards to clinical features suggesting a higher likelihood of treatment failure or of a shorter DFI. It is notable that various classes of antibiotics are suggested for treatment of uncomplicated and complicated AECB, which gives the health care provider flexibility in treating the patient who has been recently exposed to a class of antibiotics. Given the increased likelihood of resistant isolates in such a patient, an agent from an alternate class may be ideal. Such an approach should optimize antibacterial therapy for AECB episodes with the greatest likelihood of resolving the individual episode and extending the time to the next AECB. Oral steroids are also an important component of therapy in AECBs, particularly those of greater severity. Instituting measures to minimize the likelihood of a recurrence should be considered as such an approach may stave off deterioration in health status and pulmonary function.

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