

Antibacterials and Acute Exacerbation of Chronic Bronchitis

Issues for Formulary Decision Makers

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Abstract

The utility of antibacterials in the management of acute exacerbations of chronic bronchitis (AECB) and the related lung pathology, chronic obstructive pulmonary disease (COPD), has been debated for decades. Data presented in this article document that more expensive antimicrobials may be favored in AECB treatment to prevent adverse outcomes to patients, namely antimicrobial failure and hospitalization. Identified patient-specific variables that may lead to treatment failure include right- or left-sided heart failure and ≥ 4 exacerbations/year. Risk factors for hospitalization include age ≥ 65 years and severe pulmonary and nonpulmonary dysfunction. However, these risk factors have never been formally validated in a prospective, randomized trial. Drug-resistant organisms have not been documented to cause antimicrobial failure or hospitalization, however, more data are needed in this growing area.

It has been reported that chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the US.^[1] Estimates show COPD results in 14 million office visits and 500 000 hospitalizations annually.^[2] Costs associated with treatment of acute exacerbations of chronic bronchitis (AECB) are in excess of \$US2 billion/year (1994 values). The goals of treatment of AECB are the prompt resolution of symptoms and the minimization of failure rates.

1. Causes of Acute Exacerbations of Chronic Bronchitis (AECB)

The organisms most implicated as causes of exacerbations are based on the severity of the disease. Nontypeable *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae*, *Staphylococcus aureus*, viruses (rhinoviruses, influenza A and B virus, parainfluenza, coronavirus, herpes simplex virus, respiratory syncytial virus, and adenovirus), Gram-negative pathogens including *Pseudomonas aeruginosa* and, in recent years, atypical pathogens (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*) have all been reported in investigations of AECB.^[3] The three bacterial pathogens, *H. influenzae*, *S. pneumoniae* and *M. catarrhalis*, were estimated to account for 70% of all episodes of AECB in one report.^[4] Other Gram-negative pathogens are recovered less commonly from bronchial secretions of patients with mild to moderate lung dysfunction and

AECB; however, these organisms indicate particularly severe impairment of lung function, with forced expiratory volume in 1 second (FEV₁) values $\leq 35\%$ of predicted.^[5,6] Viral causes of AECB have been estimated to cause up to 30% of exacerbations.^[7] The common pathway for viral pathogenesis is to disrupt respiratory mucal defenses, allowing bacteria to attach to damaged epithelial cells in patients with AECB.^[8] Chronic *Chlamydia pneumoniae* infection has been shown to occur in patients with COPD. In one report where *C. pneumoniae* was determined by two of three methods (namely serum antibodies to *C. pneumoniae*, sputum immunoglobulin A antibodies to *C. pneumoniae* and polymerase chain reaction of sputum for *C. pneumoniae* DNA), the incidence was 71% in severe COPD and 46% in mild to moderate COPD.^[9] Finally, other atypical bacteria can precipitate up to 10% of bronchial exacerbations.^[10]

2. Antibacterial Use in AECB

Current questions regarding the use of antibacterials for the treatment of AECB are whether all AECB are pathophysiologically similar to each other, and whether antibacterials used to treat AECB can prevent hospitalization and its associated morbidity and mortality? Furthermore, in patients that require hospitalization for their AECB treatment, is this because of patient-specific variables or an antibacterial-resistant pathogen? A vicious cycle of infection, inflammation and injury promoting further infection

has been proposed, but the contribution of repeated episodes of infection to the progressive loss of lung function remains controversial.^[11,12]

The use of antibacterials in the treatment of AECB has been under considerable debate since the early 1970s. Some placebo-controlled antibacterial trials for this condition have shown no positive results for antibacterials and some have shown moderate results in favor of antibacterials.^[13] Certainly, economic variables enter into the decision-making process when selecting an antibacterial for AECB. As discussed by other investigators, the use of older agents – which have low per-dose costs – may in turn increase the total costs of treating this condition because of more office visits, noncompliance, treatment failure and adverse events.^[14,15]

In 1987, a landmark study was reported by Anthonisen et al.^[16] In this study, patients with a diagnosis of AECB and COPD were randomized to antibacterial therapy or placebo for the treatment of their chronic bronchitis exacerbation. Upon subsequent exacerbations, patients enrolled in this study were crossed over to the other arm of the study. The antibacterials used in this trial included cotrimoxazole (trimethoprim-sulfamethoxazole), amoxicillin (amoxycillin) or doxycycline in standard doses. Patients were stratified in the study by severity of exacerbation based on clinical criteria. The results demonstrated that the success rate in antibacterial-treated exacerbations was 1.24 times higher than in the placebo-treated arm. Of importance from an outcome standpoint, 34% of placebo-treated patients experienced deterioration of their condition compared with 18% in the antibacterial-treated arm. Additionally, differences in the success rate between the antibacterial arm and the placebo arm were greatest in patients with the most severe disease (type I or II) and deterioration was more than twice as much with placebo compared with antibacterials. The authors present their interpretation of the study results and a comparison with previously published AECB antibacterial trial results.^[17-23] In 1995, Saint et al.^[13] published the results of a meta-analysis of nine randomized, placebo-controlled antibacterial trials that demonstrated a small statistically significant benefit with the use of antibacterials in the treatment of AECB. Currently, there are numerous antibacterials that are approved for the treatment of AECB.

Previous studies of antibacterials for AECB have not accounted for differences in disease severity among patients. Additionally, several randomized, controlled clinical trials investigating the usefulness of antibacterials for AECB were performed in the early 1980s and could not account for the current rates of antimicrobial resistance. The utility of bronchial specimens for culture has been questioned. Antibacterial selection for AECB is often empiric.

Destache et al.^[24] have published a retrospective review of 60 outpatients treated for AECB. Pulmonologists categorized the antibacterial used to treat patients with AECB on initial, second and third presentations if they were separated by 2 to 4 weeks. Correspondingly, antibacterials were categorized as first-line (amoxicillin, cotrimoxazole, tetracyclines and erythromycin), second-line (cefradine, cefuroxime, cefaclor and cefprozil), and third-line (amoxicillin clavulanic acid, azithromycin and ciprofloxacin). Antibacterial failure was defined as failure of the patient to respond to initial antibacterials and requirement of further antibacterials within 2 weeks. Hospitalization rates were gathered from the records of patients who were hospitalized within 2 weeks of initial outpatient treatment for AECB. Economic variables and time between AECB intervals were also captured.

Medical records indicated that approximately 95% of patients received first-line antibacterials at their first outpatient visit. Twenty-three percent of patients who were given second-line antibacterials on the second visit were switched to third-line agents if conditions required a third visit.

Data analysis revealed that 34% of patients who were treated failed to respond within 2 weeks of treatment initiation. Patients who received first-line agents failed to respond significantly more often than those receiving third-line antibacterials (19 vs 7%). Patients who received first-line antibacterials were hospitalized significantly more often within 2 weeks of outpatient treatment than those given third-line agents (18 vs 5.3%). Finally, the use of third-line antibacterials was associated with significantly longer time intervals between exacerbations compared with both first-line and second-line antibacterials (34 vs 17 weeks). There was a statistically insignificant trend toward lower mean total cost of AECB treatment with the use of third-line agents, although the pharmacy cost alone was significantly lower for first-line antibacterials.

This was the first study to document possible differences between patients based on the antibacterial prescribed to them. Adams et al.^[25] have documented in their study that patients relapse significantly more often when not given antibacterials compared with patients who received an antibacterial. Additionally, this study also documented that the highest relapse rates were in those patients who received amoxicillin. Therefore, these two studies suggest that the choice of certain antibacterials may decrease relapse rates and hospitalizations and their associated high costs.

Subsequent to the Destache et al. study,^[24] Grossman^[26] published a review of the treatment of AECB. In the article, he presented evidence that treatment success or failure may be based on specific patient variables. Patient-specific variables that have been identified include cardiopulmonary disease and the

number of exacerbations/year. The cardiopulmonary diseases of importance include right- or left-sided heart failure. It appears from other studies, that patients with four or more exacerbations/year may be at risk of antibacterial failure and may require a third-line antibacterial, namely azithromycin, amoxicillin clavulanic acid or ciprofloxacin.^[27,28] Additionally, there are identified risk factors that place a patient at increased risk of hospitalization during an acute exacerbation, e.g. age ≥ 65 years. Finally, significantly compromised lung function and severe non-pulmonary dysfunction places a patient at increased risk for hospitalization.^[5,6] In his article, Grossman^[26] offered a proposed classification of patients and suggested treatment options for patients with acute exacerbations of chronic bronchitis. However, it is important to realize that none of the patient-specific factors have been prospectively determined to present an increased risk of antibacterial failure or prevent hospitalization. Indeed patients with the most severe exacerbations (type I from Anthonison et al.^[16]) were more likely to experience a benefit from antibacterials compared with patients with less severe exacerbations.^[29]

Additionally, no study to date has documented whether the risk of hospitalization is related to the prevalence of a resistant pathogen. This needs to be determined, as it will have a major impact on the prescription of more costly antibacterials for patients that have severe lung dysfunction and are ≥ 65 years.

Several studies were presented at the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) meeting. Ball et al.^[30] presented an abstract comparing gemifloxacin, a new investigational quinolone, with clarithromycin. This study was a double-blind, randomized trial in patients with AECB who were followed for 26 weeks after enrollment. Patients who received gemifloxacin for AECB treatment had significantly fewer relapses compared with patients who received clarithromycin (71% success compared with 59%, $p < 0.02$). Additionally, 5 of 214 gemifloxacin recipients compared with 14 of 224 clarithromycin recipients required hospitalization ($p = 0.059$). Differences between the treatment groups may have been related to the isolation of *Haemophilus influenzae*; more study is necessary to confirm these results. Niederman et al.^[31] presented an abstract comparing the antibacterial treatment intervals in patients with AECB receiving antimicrobial therapy. Patients were divided into those that received β -lactams ($n = 185$), macrolides ($n = 180$) and quinolones ($n = 131$). When the prescribing physician documented that the antimicrobial was used to treat a relapse, there was a significant difference in treatment intervals between patients who received quinolones compared with the other groups (27.5, 17.5 and 18 days for quinolones, macrolides and β -lactams, respectively, $p = 0.03$).

Table I. Treatment of acute exacerbations of chronic bronchitis according to classification. (Reproduced from Grossman,^[33] with permission)

Classification	Disease characteristics	Treatment
Simple chronic bronchitis	FEV ₁ >50% of predicted, \uparrow sputum volume and purulence	Aminopenicillin, erythromycin, doxycycline, cotrimoxazole (trimethoprim-sulfamethoxazole)
Complicated chronic bronchitis	FEV ₁ <50% of predicted or age ≥ 60 years, or ≥ 4 exacerbations/year, or significant comorbidity	Quinolone, β -lactam/ β -lactamase inhibitor, second generation macrolide, second or third generation cephalosporin

FEV₁ = forced expiratory volume in 1 second; \uparrow = increased.

3. Conclusion

The research described points to a need to evaluate further the effect that exacerbation severity has on making an appropriate choice of antibacterial for the treatment of AECB. Certainly, an infection-free interval may be appropriate to use to compare differences between antibacterials in this patient population. Anueztó et al.^[32] have written an editorial that outlines a protocol to test whether the infection-free interval is a valid outcome measurement for patients with AECB.

The choice of antibacterial in the treatment of an AECB episode remains controversial (see table I). More research needs to be gathered on whether newer antimicrobials prevent treatment failure and hospitalization to a greater extent than older antimicrobials. Finally, if newer antimicrobials do have a positive effect on outcomes, is this because of better coverage of the resistant organisms that may be causing the exacerbation? Investigating whether resistant organisms cause AECB as frequently as sensitive organisms, and determining whether resistance is a factor in the outcome of AECB would be of interest to all who treat these patients.

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