Antibiotics Are Associated With Lower Relapse Rates in Outpatients With Acute Exacerbations of COPD*

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Background: COPD is a complex disease with exacerbations characterized by worsening of symptoms resulting in deteriorating lung function.

Study objective: To assess predictive factors of relapse for patients with acute exacerbations of COPD (AECB).

Design: Retrospective cohort analysis of visits for AECB.

Setting: Veterans Affairs Medical Center.

Patients: Three hundred sixty-two visits (173 patients) with documented COPD treated as outpatients for AECB.

Measurements: Severity of underlying COPD, severity of AECB, comorbid conditions, therapy, and relapse rates (return visit within 14 days with persistent or worsening symptoms).

Results: Each visit was analyzed individually (referred to as a patient-visit). One group received antibiotics (270 patient-visits), and the second group (92 patient-visits) did not. Both groups had similar demographics and severity of underlying COPD. The overall relapse rate was 22%. The majority of patient-visits (95%) with severe symptoms at presentation were prescribed antibiotics vs only 40% of those with mild symptoms. Twenty-nine of 92 patient-visits (32%) were followed by relapse in the group that was not given antibiotics, whereas only 50 of 270 (19%) treated with antibiotics relapsed (p < 0.001). Those treated with amoxicillin had an even higher relapse rate (20 of 37 patient-visits, or 54%) than those who did not receive antibiotics (p = 0.006).

Conclusions: Relapse from AECB was not related to the severity of underlying disease or to the severity of the acute exacerbation. Patients treated with antibiotics had significantly lower relapse rates than those who did not receive antibiotics. However, the specific choice of antibiotic is important because those treated with amoxicillin had the highest relapse rates of all groups.

Key words: acute exacerbation of chronic bronchitis; antibiotics; bronchitis; COPD; pulmonary function; recurrence; relapse

Abbreviations: AECB = acute exacerbations of COPD; ED = emergency department; PFT = pulmonary function test

COPD is a prevalent disease, with an estimated 14 million Americans affected. It is the fourth leading cause of death in the United States with approximately 90,000 deaths reported annually.1

Acute exacerbations of COPD (AECB) are defined as a worsening of COPD symptoms commonly characterized by increases in cough, sputum production, purulence, and dyspnea. Although several insults may lead to acute exacerbations, respiratory tract infections are often considered to be the most common cause. Several studies have demonstrated that patients with stable COPD are frequently (25 to 83%) colonized with bacteria.2–8 However, the specific role that bacterial infections play in AECB is controversial and has been debated in the literature for many years.9–18 Bronchoscopic studies (performed in patients with chronic lung disease either when exacerbating or when clinically stable), using a protected specimen brush, isolated significant...
amounts of bacterial infections in approximately 50% of patients. The most commonly isolated bacterial organisms include Haemophilus species, Moraxella catarrhalis, and Streptococcus pneumoniae.

The efficacy of antibiotic therapy in AECB is also controversial and has been the focus of an extensive review. Several schemes have been proposed to stratify patients with AECB on the basis of various combinations of risk factors. Although these proposed classifications have not been validated by a prospective randomized trial, some of these criteria have been studied in an attempt to identify risk factors predictive of failure to recover from an AECB. Thus, we studied patients with AECB in an attempt to identify the factors associated with failure of therapy resulting in relapse within 14 days.

**Materials and Methods**

All patients with discharge diagnostic codes for COPD and bronchitis from our emergency department (ED) from December 1, 1995, to June 30, 1997, were included for review. Patients' charts were evaluated if they had a pulmonary function test (PFT) within 3 years of their visit that met the criteria for COPD defined as FEV1 $\leq 80\%$ predicted and FEV1 to FVC ratio $\leq 75\%$. The severity of each patient's COPD was classified as stage I (mild) if FEV1 was $\geq 50\%$ predicted, stage II (moderate) if FEV1 was 35 to 49% predicted, or stage III (severe) if FEV1 was $< 35\%$ predicted.

The vast majority of exclusions were because no PFTs were available to support the diagnosis of COPD, even though they were coded as, and treated for, AECB.

Thus, we studied patients with AECB in an attempt to identify the factors associated with failure of therapy resulting in relapse within 14 days. The outcome of interest was the relapse rate, which refers to visits that ended in relapse and those that did not. For differences between groups, $\chi^2$ and analysis of variance were used. The level of significance was set at 5%; p values are two-tailed. Univariate and multivariate analyses were performed to investigate the historical and clinical variables that may be used to predict an increased risk of relapse. A logistic regression model was constructed to determine independent predictors of relapse for AECB. The hypothesis of a significant influence of a variable was assessed by the likelihood ratio test. Data were entered into a customized database, and all statistical analyses were performed using Statistical Analysis Software (SAS Institute, Cary, NC). Results are expressed as mean $\pm$ SD.

**Results**

A total of 1,754 visits to the ED were assigned diagnostic codes for COPD or bronchitis during the 18-month study period. There were 632 patient-visits (36%) for which PFTs were available; 506 had criteria for COPD, and 362 of these met the study criteria and qualified for this analysis. Table 1 summarizes the specific reasons for excluding visits. The table shows the details of exclusions. The vast majority of exclusions were because no PFTs were available to support the diagnosis of COPD, even though they were coded as, and treated for, AECB.

The 362 patient-visits (173 individual patients) were analyzed in two groups: 79 patient-visits (22%) that were followed by relapse and 283 patient-visits (78%) that were not followed by relapse within 14 days of the initial ED presentation. We analyzed each exacerbation (patient-visit) individually, rather than grouping all exacerbations for each patient. Figure 1 demonstrates the relationship between the number of exacerbations for each patient and the number of relapses. Although a small proportion of patients had multiple relapses (16 of 173 patients), many patients had multiple exacerbations (patient-visits) during the study period but did not have a relapse (34 of 173 patients).

**Table 1—Visits Excluded From Analysis**

<table>
<thead>
<tr>
<th>No. Excluded</th>
<th>Reason for Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,122</td>
<td>No PFTs available</td>
</tr>
<tr>
<td>60</td>
<td>Normal PFTs</td>
</tr>
<tr>
<td>37</td>
<td>Restrictive lung disease*</td>
</tr>
<tr>
<td>12</td>
<td>Asthma</td>
</tr>
<tr>
<td>11</td>
<td>PFT $&gt; 3$ years old</td>
</tr>
<tr>
<td>18</td>
<td>Admitted to hospital</td>
</tr>
<tr>
<td>18</td>
<td>Visit unrelated to AECB</td>
</tr>
<tr>
<td>12</td>
<td>Charts not available</td>
</tr>
</tbody>
</table>

*Restrictive lung disease defined as FEV1/FVC $> 75\%$ and total lung capacity $< 80\%$.
†Visits for medication refill, abdominal complaints, urinary tract infections, etc.

Statistical Analysis

The outcome of interest was the relapse rate, which refers to the proportion of ED dismissions ending in relapse. Historical, diagnostic, and treatment variables in the ED were compared for visits that ended in relapse and those that did not. For differences between groups, $\chi^2$ and analysis of variance were used. The level of significance was set at 5%; p values are two-tailed. Univariate and multivariate analyses were performed to investigate the historical and clinical variables that may be used to predict an increased risk of relapse. A logistic regression model was constructed to determine independent predictors of relapse for AECB. The hypothesis of a significant influence of a variable was assessed by the likelihood ratio test. Data were entered into a customized database, and all statistical analyses were performed using Statistical Analysis Software (SAS Institute, Cary, NC). Results are expressed as mean $\pm$ SD.

**Clinical Investigations**
Patient demographics and comorbid conditions of the two study groups are summarized in Table 2. According to COPD severity, 38% of visits included patients with stage I (mild), 49% with stage II (moderate), and 13% with stage III (severe) COPD. There were no differences between the study groups. Cardiovascular disease (including coronary artery disease and congestive heart failure) was significantly more common in the group of patients who had relapses. However, there were no differences in other comorbid conditions. No association was found between multiple comorbidities and the risk of relapse. The group of visits followed by relapse did have more patients who were actively

![Table 2—Characteristics of the Relapse Group vs the No-Relapse Group*](image)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relapse (n = 79)</th>
<th>No Relapse (n = 283)</th>
<th>p Value</th>
<th>Relative Risk (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>66.8 ± 10.1</td>
<td>66.2 ± 10.02</td>
<td>&gt; 0.2</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>78 (99)</td>
<td>280 (99)</td>
<td>&gt; 0.2</td>
<td></td>
</tr>
<tr>
<td>&gt; 40 pack-year smoking</td>
<td>79 (100)</td>
<td>253 (100)</td>
<td>&gt; 0.2</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>18 (23)</td>
<td>60 (21)</td>
<td>&gt; 0.2</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>40 (51)</td>
<td>151 (53)</td>
<td>&gt; 0.2</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>34 (43)</td>
<td>87 (31)</td>
<td>0.03</td>
<td>1.51 (1.02–2.22)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>21 (27)</td>
<td>41 (15)</td>
<td>0.01</td>
<td>1.75 (1.15–2.66)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>8 (10)</td>
<td>22 (8)</td>
<td>&gt; 0.2</td>
<td></td>
</tr>
<tr>
<td>Liver disease</td>
<td>3 (4)</td>
<td>12 (4)</td>
<td>&gt; 0.2</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>11 (14)</td>
<td>33 (12)</td>
<td>&gt; 0.2</td>
<td></td>
</tr>
<tr>
<td>Cerebral vascular accident</td>
<td>6 (8)</td>
<td>17 (6)</td>
<td>&gt; 0.2</td>
<td></td>
</tr>
<tr>
<td>Active smoking</td>
<td>42 (53)</td>
<td>121 (43)</td>
<td>0.06</td>
<td>1.39 (0.94–2.05)</td>
</tr>
<tr>
<td>Oxygen dependence</td>
<td>16 (20)</td>
<td>36 (13)</td>
<td>0.07</td>
<td>1.51 (0.95–2.04)</td>
</tr>
<tr>
<td>Chronic steroid use</td>
<td>14 (18)</td>
<td>30 (10)</td>
<td>0.07</td>
<td>1.56 (0.96–2.53)</td>
</tr>
<tr>
<td>FEV$_1$ ≥ 50 (mild)</td>
<td>31 (39)</td>
<td>105 (37)</td>
<td>&gt; 0.2</td>
<td></td>
</tr>
<tr>
<td>FEV$_1$ = 35–49% (moderate)</td>
<td>38 (48)</td>
<td>139 (49)</td>
<td>&gt; 0.2</td>
<td></td>
</tr>
<tr>
<td>FEV$_1$ &lt; 35% (severe)</td>
<td>10 (13)</td>
<td>39 (14)</td>
<td>&gt; 0.2</td>
<td></td>
</tr>
</tbody>
</table>

*Data are presented as mean±SD or No. (%) unless otherwise indicated.
smoking, receiving chronic corticosteroids, and dependent on oxygen; however, these differences were not statistically significant (Table 2).

The severity of each exacerbation (based on the classification by Anthonisen et al\(^26\)) showed that 43% of patient-visits were type I (severe), 33% were type II (moderate), and 24% were type III (mild). There were no significant differences in acute exacerbation severity between the two study groups, and this was not associated with relapse (Fig 2). However, 95% of the patient-visits with type I (severe) exacerbations were treated with antibiotics compared with only 40% of those with type III (Fig 3). There were no significant differences in other therapies prescribed to treat the AECB (bronchodilators, corticosteroids), or laboratory variables between patients who did and did not relapse (data not shown).

Antibiotics were prescribed in 270 patient-visits (75%), and 50 of those visits (19%) were followed by relapse within 14 days. However, a much larger proportion of those visits during which antibiotics were not given, 29 of 192 (32%), ended in relapse (p < 0.001). Of those who received antibiotics and then had relapse, 21 of 50 (42%) required hospital admission, and one patient underwent mechanical ventilation during the hospital stay. This is in contrast to the group that did not receive antibiotics, in which only 5 of 29 patient-visits (17%) resulted in hospital admission, but a large proportion (3 of 5) of those patients required mechanical ventilation (Fig 4). None of the patients admitted after a relapse of AECB died of respiratory failure during that hospital stay. One patient died of a ruptured aortic aneurysm.

The patient-visits during which amoxicillin was prescribed had the highest relapse rate of all study groups (54%; p < 0.001). The relapse rate was even higher for the amoxicillin group than for those patients not prescribed any antibiotic (p = 0.006).

Although there were no significant differences (p > 0.2) in relapse rates between any of the other antibiotic groups, there was a trend toward higher relapse rates for those receiving macrolides (21%) and ciprofloxacin (22%; Fig 5).

The results of the multivariate analysis are shown in Table 3. We found an interaction between coronary artery disease and active smoking (at the time of the exacerbation). Smoking appeared to significantly increase the risk of relapse in those patients who did not have a history of coronary artery disease, although it had no effect on those who did have a history of coronary artery disease. None of the following were associated with a statistically significant increase in the risk of relapse: older age, severity of underlying lung disease, or chronic corticosteroid therapy. However, the treatment of AECB with amoxicillin increased the patient’s risk for relapse within 14 days (odds ratio, 3.37; 95% confidence interval, 1.44 to 8.13). In contrast, treatment with any other antibiotic lowered the risk of relapse (odds ratio, 0.28; 95% confidence interval, 0.15 to 0.53).

**Discussion**

The major finding of our study is that patients with AECB who were given antibiotics at dismissal had a significantly lower 14-day relapse rate. The second important point is that patients who received amoxicillin had the highest relapse rate, even higher than the group not receiving antibiotics. Neither the severity of the patients’ underlying disease nor the severity of presenting symptoms were predictors of relapse. Despite their higher relapse rates, the patients who received either no antibiotics or amoxicillin had significantly milder symptoms at presentation. This study (using the multivariate analysis

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21945/ on 03/31/2017)
model) demonstrates that the type of antibiotics used to treat patients with AECB has an impact on the failure rate. Identifying that specific antibiotic therapy in AECB is an important factor in the 14-day relapse rate and is essential in providing adequate treatment for these patients.

The decision to prescribe antibiotics in patients with an AECB has been debated in the literature. Many studies have shown either no benefit, or minimal benefit, when antibiotics are prescribed for an AECB. Some problems with these early studies include a lack of consistency concerning the definition of an AECB. The study by Anthonisen et al. brought some conformity to the definition of AECB and was the first widely accepted classification for the severity of presenting symptoms. Their data demonstrated...
a significant benefit (resolution of symptoms at 21 days) in patients with moderate to severe symptoms who were treated with antibiotics (amoxicillin, trimethoprim/sulfamethoxazole, or doxycycline). However, in that study, those with mild symptoms at presentation (19% of patients) did not show statistically significant differences. A recent report by Destache et al demonstrated that outpatients with AECB treated with first-line therapy (including amoxicillin, co-trimoxazole, tetracycline, and erythromycin) had significantly higher failure rates than those treated with third-line agents (co-amoxicillin-clavulanate, azithromycin, and ciprofloxacin; 19% vs 7%; p < 0.05).

Some authors have stated that most infections in AECB are noninvasive and will eventually resolve spontaneously. However, because the relapse rate from AECB is high (11 to 32%), better strategies for treatment of an acute exacerbation are needed. Authors currently recommend treatment of AECB with antibiotics if the patient presents with moderate to severe symptoms, but these authors state that patients with mild symptoms at presentation can be treated supportively. Our data suggest that patients with documented COPD (even with mild symptoms at presentation) benefit from antibiotic therapy. However, the choice of antibiotic is important because the antibiotics were not all equally effective in lowering the risk of relapse. One possibility for the high relapse rates of patients treated with amoxicillin is related to the increasing emergence of pathogen resistance. There are a significant number of reports of antimicrobial resistance among respiratory isolates common in patients with AECB (including *Haemophilus influenzae*, *M catarrhalis*, and *S pneumoniae*). This trend of increasing resistance has been reported across the United States, Canada, and Europe. Our institution (at the time of the study) had rates of resistance to amoxicillin of 30% for *H influenzae* isolates, 34% for *S pneumoniae*, and 32% for *M catarrhalis*. The other antibiotics prescribed during the study period had

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**Table 3—Variables Identified as Risk Factors for Relapse by Logistic Regression**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Wald χ² p Value</th>
<th>Coefficient</th>
<th>SE</th>
<th>Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>0.0056</td>
<td>1.22</td>
<td>0.44</td>
<td>3.37 (1.44–8.13)</td>
</tr>
<tr>
<td>Any other antibiotic except amoxicillin</td>
<td>0.0001</td>
<td>−1.26</td>
<td>0.32</td>
<td>0.28 (0.15–0.53)</td>
</tr>
<tr>
<td>Coronary artery disease*</td>
<td>0.0002</td>
<td>1.72</td>
<td>0.46</td>
<td>5.60 (2.33–14.17)</td>
</tr>
<tr>
<td>Active smoking</td>
<td>0.0002</td>
<td>1.47</td>
<td>0.40</td>
<td>4.45 (2.09–10.13)</td>
</tr>
</tbody>
</table>

*Interaction between coronary artery disease and active smoking (see text).*
resistance rates ≤ 10%, with the exception of erythromycin (12% resistance for *S. pneumoniae*) and trimethoprim/sulfamethoxazole (18% resistance for *S. pneumoniae*). The elevated rates of resistance to amoxicillin suggest one possible explanation for the higher relapse rate observed in our patients who were treated with this medication.

Inasmuch as the relapse rates for patients with AECB are high, there are several schemes that have been proposed to risk stratify these patients. Some risk factors that have been suggested are age, presence or severity of underlying obstructive lung disease, comorbid conditions, frequency of exacerbations, and severity of symptoms at presentation.29-32-35 Although these proposed classifications have not been validated by a prospective randomized trial, some of these criteria have been studied in an attempt to identify risk factors predictive of treatment failure.36-39,49 In some trials, there were no differences in the relapse rates (defined as return visit with persistent or worsening symptoms within 48 h or 14 days) on the basis of age, severity of underlying COPD, or use of antibiotics.36-38 However, the number of previous exacerbations and previous relapses was associated with significantly increased risks of relapse. The study by Ball et al39 did not demonstrate any difference in relapse (within 4 weeks) on the basis of age, severity of underlying obstructive lung disease, number of years that the patient suffered from COPD, or the severity of symptoms of each acute exacerbation. Their study did, however, demonstrate a significantly higher risk of relapse in patients with coexisting cardiopulmonary disease, which was similar to our results.39

Our study has several limitations. Principally, this is a retrospective analysis of data. Because the information was obtained retrospectively, it is dependent on the data written by nurses and physicians caring for the patients. The diagnosis of AECB was derived from subjective interpretation of symptoms, physical examination, and laboratory tests. Because the data were obtained from patients’ charts, it is possible that some patients may have had other obstructive diseases, such as asthma or bronchiectasis. In addition, the diagnosis and treatment of AECB were not standardized. However, each chart had a record of the patients’ symptoms, physical examination, and therapy given. The data were reviewed for the initial visit before reviewing the records of subsequent visits in an attempt to minimize bias. In many circumstances, the clinician was not aware of the patient’s PFTs. Furthermore, some important factors, which could help in deciding the therapy choice, were not assessed in our study (eg, bacteriologic assessment of sputum, number of prior exacerbations). The lack of microbiologic data and *in vitro* susceptibility tests limits our ability to confirm our hypothesis about resistance contributing to the higher relapse rates of those treated with amoxicillin.

One further possible limitation of this study is that some of the patients with persistent or worsening symptoms (relapses) could have been treated at other institutions, but this is not likely because most of our patients receive all of their health care at the Veterans Medical Center or one of its satellite clinics. Furthermore, no intervention was performed to verify patient compliance with the prescribed medications. However, it is unlikely that lack of compliance with amoxicillin would have been a significant factor associated with increased recurrence.

**Conclusion**

Patients with documented COPD, even with mild symptoms at presentation, benefit from antibiotic therapy. However, the choice of antibiotic is important (because resistant organisms are increasing and are likely contributing to treatment failures) and should probably be based on the resistance profile to antibiotics in the institution where the patient is being treated. We feel that this retrospective study raises many questions about the current treatment recommendations for AECB, and supports the need for a prospective controlled trial to answer questions about the most appropriate use of antibiotics in these patients.

ACKNOWLEDGMENT: The authors thank Francisco Villegas for assisting with the collection of data for this study.

**References**


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