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Evaluation of Antibiotic Management in the Reduction of Recurrent Chronic Obstructive Pulmonary Disease (COPD) Exacerbations

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ABSTRACT:

Background: Antibiotic use is recommended within the 2015 guidelines during chronic obstructive pulmonary disease (COPD). However, controversy remains as to whether they truly lead to improved outcomes.

Objective: The primary objective is a reduction in 30-day readmission rate for those receiving antimicrobial therapy for a COPD exacerbation. Secondary objectives include 90-day readmission rate, time to next COPD exacerbation and length of hospital stay.

Methods: 322 subjects were evaluated in this Institutional Review Board approved, retrospective study. Patients ≥18 years-old admitted to the hospital in non-intensive care nursing units for a primary or secondary diagnosis of a COPD exacerbation were included. Exclusion criteria included transfer from an outside hospital, evidence of acute decompensated heart failure, immunocompromised state, diagnosis of pneumonia and/or influenza, documented past medical history of other lung disease(s), hospitalization within the past 90 days, code status of comfort measures only or expectation of death within 48 hours, active pregnancy or lactation, current status as a prisoner, and patients with miscoded records.

Results: 30-day readmission rates were no different for those who did/did not receive antibiotic therapy (12.7% vs. 10.3%, p=1.00). Additionally, there was no difference in 90-day readmission rate (11.3% vs 13.8%, p=0.74) and time to next exacerbation (104.7 days vs 138.1 days, p=0.41). Length of stay was no different (3.6 days vs 3.0 day) but a trend toward significance was noted (p=0.06)

Conclusion: The exact role of antibiotics on the reduction of readmission rates and length of stay in the management of recurrent COPD exacerbations remains uncertain.

Keywords: antimicrobial, chronic obstructive pulmonary disease, readmission

INTRODUCTION

The use of antibiotics during an acute moderate to severe chronic obstructive pulmonary disease (COPD) exacerbation is common practice. Currently, antibiotic use is recommended within the Global Initiative for COPD (GOLD) guidelines for specific patients in an attempt to achieve improved outcomes and symptom management.[1] The three cardinal symptoms of a COPD exacerbation include the presence of increased dyspnea, sputum purulence, and/or increased sputum volume.[1,2] These three cardinal symptoms are more specifically referred to as the Anthonisen type I criteria, with type II criteria including a change in any two of the cardinal symptoms.[2] Antibiotic therapy is recommended if all three or two of the

three symptoms are present, provided sputum purulence or the need for mechanical ventilation is one of them.[1,3] A recent trial investigating the use of the Anthonisen criteria to guide therapy found that increased sputum purulence was a predictor of clinical failure in patients not treated with antibiotics.[4] The study also demonstrated that C-reactive protein (CRP) measurements significantly increased the predictive accuracy of clinical failure.[4] Given that most exacerbations are due to bacterial infections that result in airway and systemic inflammation; a reduction in CRP can be an indication that antimicrobial therapy is effectively eradicating the infectious organism(s).[5,6]

Approximately 50% of all COPD exacerbations are secondary to bacterial infections.[1,2] Whereas the airways of a majority of patients with stable COPD can be colonized with bacteria, exacerbations are thought to be triggered by acquisition of new bacterial strains.[1,6] The common pathogens present during COPD exacerbations were , , and .[1,6] is present in up to 30% of all COPD exacerbations and compared to colonizing strains, strains of present during exacerbations are capable of increased adherence to epithelial cells and increased production of inflammatory markers.[5] For this reason the presence of purulent sputum during an exacerbation is highly correlated with a bacterial infection. Recent studies have shown that sputum purulence alone may be a sufficient indicator to initiate antibiotics.[1,6] Obtaining sputum cultures prior to initiating antimicrobial therapy is not always possible and inaccuracies in sampling techniques and/or assessment of quality of the sputum specimens may lead to the overuse of broad-spectrum therapy.[7] However, current guidelines do recommend that, if a COPD exacerbation has not improved after treatment with antibiotics, a sputum culture be obtained to assist in assessing bacterial eradication.[2]

Furthermore, five-year all-cause mortality rates as high as 50% have been found following a hospital admission for a COPD exacerbation.[1] In addition, the frequency of exacerbations increases as COPD progresses, with patients experiencing an average of 1-2 exacerbations per year.[5] A systematic review published by Ram and colleagues evaluating antimicrobial therapy in COPD exacerbations demonstrated reductions in short-term mortality by 77%, treatment failure by 53% and sputum purulence by 44%.[8] Along with disease progression, health status of hospitalized patients declined more quickly following a hospital admission, resulting in an elevated risk of mortality during the subsequent 90 days following each severe episode.[8]

Once the decision has been made to initiate antimicrobial therapy, many treatment options exist. Several recent studies having shown that early initiation of antibiotic therapy is beneficial in improving patient symptoms but specific antibiotic choice does not affect overall clinical outcomes.[9-11] However, given previous studies of varying quality and patient populations, controversy still remains over whether or not antibiotics truly lead to improved clinical outcomes in patients experiencing a COPD exacerbation and if beneficial, which antibiotic regimen results in the best clinical outcomes.

METHODS

This is an Institutional Review Board approved retrospective study, evaluating all patients ≥ 18 years-old admitted to non-intensive care nursing units for a primary or secondary diagnosis of COPD at a 335-bed, tertiary academic medical center. Exclusion criteria included transfer from an outside hospital, evidence of acute decompensated heart failure, immunocompromised state (i.e. solid organ transplant recipients, presence of HIV or AIDS, the use of any biologic agent within the past 60 days, use of high-dose corticosteroids for ≥2 weeks (20 mg/day prednisone or equivalent within the past 3 months)), concomitant diagnosis of pneumonia or influenza, documented past medical history of other lung disease(s) (i.e. tuberculosis, cystic fibrosis, primary ciliary dyskinesia, bronchiectasis), active malignancy, previous hospitalization within the past 90 days for any reason, code status of comfort measures only or expectation of death within 48 hours of admission, active pregnancy or lactation, current status as a prisoner, and patients with miscoded records. ICD-9 codes were utilized for patient identification and data collection. Data was collected for patients admitted between 1/01/2013 and 12/31/2014. Patients were stratified into two groups according to whether or not they received antibiotics during their hospital admission. In addition to the presence of the above-mentioned information, the following information was collected: age, gender, place of residence, smoking status, number of previous admissions for COPD exacerbation within the past 12 months of admission, use of oral and/or intravenous (IV) antibiotics and/or corticosteroids within the past 30 days of admission, as well as all baseline comorbid conditions, presence/absence of cardinal COPD symptoms, and most recent documented forced expiratory volume (FEV).

The primary outcome of the study was to evaluate the impact of antibiotic therapy on reducing 30-day readmission rates for a recurrent COPD exacerbation. Secondary outcomes included readmission rates within 90 days for a recurrent COPD exacerbation, length of hospital stay, in-hospital mortality, and time to next exacerbation.

Statistical analysisData collected included discrete and continuous variables. The Chi-square or Fisher exact tests were used to compare categorical variables. The Student's t-test and Wilcoxon rank-sum test were used to compare normally distributed and non-normally distributed variables, respectively. A p-value of <0.05 was considered a statistically significant difference. Statistical analysis was generated using Statistical Analysis Software (SAS), Version 9.2 for Windows. Copyright© 2002-2008. SAS Institute Inc., Cary, NC, USA.

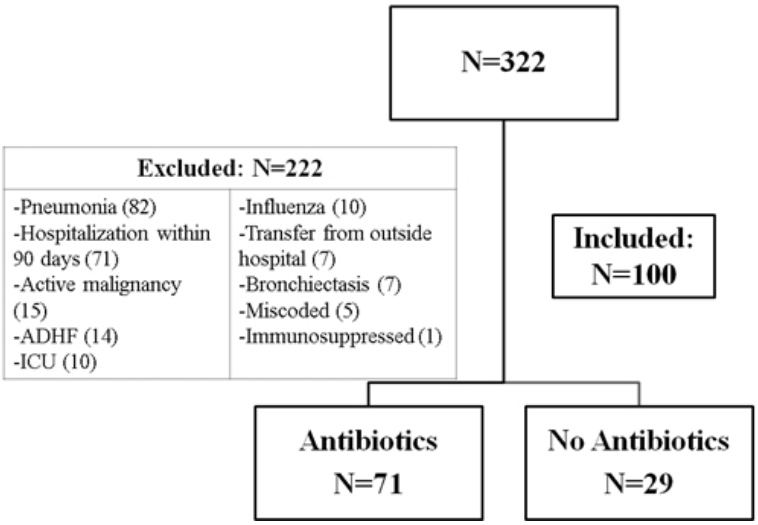

Figure 1: Patient Enrollment

RESULTS

A total of 322 patients were screened for study inclusion, and 100 patients met all inclusion and exclusion criteria (Figure 1). The majority of excluded patients had concomitant diagnosis of pneumonia (25%) or were hospitalized within the preceding 90 days (22%). Baseline characteristics are shown in Table 1. No significant differences were found between the two groups with regards to their baseline characteristics; however, there was a non-significant increase in the percentage of patients in the no antibiotic group having been treated with either antibiotics (37.9%) or corticosteroids (51.7%) in the 30 days prior to admission. The mean age of the patient population was 74 years (range 24-87) with a slightly larger percentage of patients being female (58.6%) in the no-antibiotic group vs. those receiving antibiotics (51.2%). The majority of patients were former smokers (66.2% in the antibiotic group, 72.4% in the no antibiotic group) and the median Charlson Comorbidity Index was 2 (range 0-9). The median CRP was 61.5 mg/L in the antibiotic group and 37.5 mg/L in the no antibiotic group. In those patients who did receive antibiotics upon admission, 68% (N=48) did not present with the Anthonisen criteria and had a median CRP value was 85.6 mg/L.

Table 1. Baseline Characteristics

	Antibiotics N=71	**No antibiotics N=29**	**p-value**
Age (years), mean [range]	75 [24-94]	73 [48-90]	0.70
Gender (male), %	47.9	41.4	0.66
Smoker, %:			
• **Current**	28.2	24.1	0.80
• **Former**	66.2	72.4	
• **Never**	5.6	3.4	
Forced expiratory volume in 1 second (FEV1) prior to admit, median	49	46.5	0.72
Charlson comorbidity index, median	2	2	0.44
Antibiotics 30 days before admission, %	18.3	37.9	0.07
Steroids 30 days before admission, %	31	51.7	0.07
Hospitalization for COPD exacerbation over			

past 12 months, %	12.7	17.2	0.52
# COPD exacerbations over past 12 months, mean:			
• **1-3**	45.1	48.3	0.43
• **>3**	4.2	10.3	
Anthonisen criteria, N (%)			
• **Yes**	23 (32)	7 (24)	0.48
• **No**	48 (68)	22 (76)	

Of the 100 patients included in the study, 71% (N=71) were treated with antibiotics, while 29% (N=29) were not. Specifically, 67.6% (N=48) received azithromycin monotherapy, 12.7% (N=9) received doxycycline monotherapy and 19.7% (N=14) received levofloxacin monotherapy, In the antibiotic group, 12.7% of patients were readmitted for a recurrent COPD exacerbation within 30 days compared to 10.3% in the no antibiotics group (p=1.0) (Figure 2). No significant differences were found between those patients who received antibiotics and those that did not with regards to the secondary outcomes (Table 2). Specifically, the 90 day readmission rate for a COPD exacerbation was 11.3 % (received antibiotics) versus 13.8% (did not receive antibiotics), p=0.74 and mean time to next COPD exacerbation 104.6 days versus 138.1 days, (p=0.41). There was a non-statistically significant trend toward reduction in the mean length of hospital stay for those who did not receive antibiotics (3.0 days) versus those that did (3.6 days), p=0.06. In addition to the use of antibiotics, the majority of patients in each group were prescribed steroids during admission (97% in the antibiotic group and 96.6% in the no antibiotic group). Lastly, there were no instances of in-hospital mortality in either of the groups.

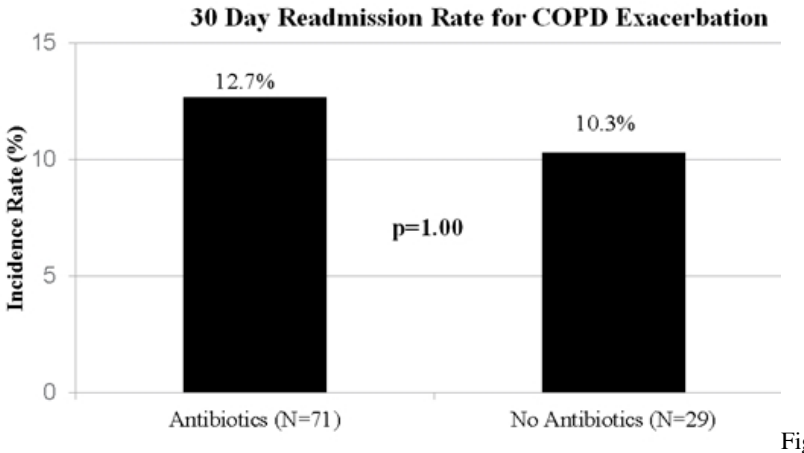

Figure 2: Primary Outcome

Table 2: Secondary Outcomes

	Antibiotics N=71	**No antibiotics N=29**	**p-value**
90-day readmission rate for COPD exacerbation, %	11.3	13.8	0.74
Length of hospital stay (days), mean	3.6	3.0	0.06
Time to next COPD exacerbation (days), mean	104.7	138.1	0.41

CONCLUSION/DISCUSSION

Overall, no statistically significant difference in the 30-day readmission rate for a recurrent COPD exacerbation was found between those subjects that received antibiotics and those that did not in this study. In addition, no significant difference was found between the two groups with regards to the secondary outcomes including 90-day readmission rate and time to next exacerbation. However, a trend toward a significantly shorter mean length of hospital stay was seen in the patients who did not receive antibiotics compared to those who did receive antibiotics. Additionally, it can be seen that approximately two-thirds of those patients who received antibiotics did not have the presence of one, or more, of the cardinal symptoms of COPD. Thus, in this cohort of patients the guidelines do not support the use of antibiotics, exposing these patients to, potentially, unnecessary adverse effects, increased risk of drug resistance and overall antibiotic exposure.

In a review by Vollenweider and colleagues, the rate of treatment failure was assessed in patients experiencing a COPD exacerbation treated with, and without, antibiotics.[10] The authors evaluated three groups of patients, those admitted as non-intensive care (ICU) inpatients, intensive care unit patients, and outpatients, from sixteen trials comparing antibiotics to placebo with a primary endpoint of treatment failure between seven and thirty days. From this student it was shown that antibiotic use reduced the risk of treatment failure for hospitalized patients, including those admitted to an ICU, but not for those patients managed in an outpatient setting. In addition, there was no significant effect on in-patient mortality and length of hospital stay.[10] Severity of COPD and stratifying patients according to risk factors for prescribing antibiotics has been recommended; however, this is often not feasible especially in retrospective studies. Additionally, Vollenweider and colleagues did not collect data on risk factors and severity of COPD, consistent with the present study.[10] Additionally, a smaller study by Lode and colleagues found no significant differences in exacerbation-free interval for one year when comparing the use of levofloxacin versus clarithromycin in patients experiencing a COPD exacerbation.[11] As has been demonstrated in the literature, significant variety exists between the antimicrobial regimen(s) used to manage COPD exacerbations, making it difficult to demonstrate superiority of any one regimen.

At our institution, a patient-specific COPD order set is available to facilitate management of acute exacerbations for the non-critically ill patient. This order set guides providers to select either oral or IV azithromycin at a dose of 500 mg x one with four additional days of 250 mg or doxycycline 100 mg twice daily for 7 days. Additionally, the recommended drug, dose and duration of corticosteroid is prednisone 40 mg daily for 5 days. It should be noted that the order set provides guidance on these, and other clinical areas including, but not limited to, the use of bronchodilators but allows providers to customize the drug, dose and frequency within each choice as the clinical case dictates. For each patient, providers indicate if the use of antibiotics is warranted. If there is no evidence of a bacterial infection, then the provider would indicate that antibiotics are not needed. However, if there is evidence of a bacterial infection, then the provider would indicate on the order set that the use of antibiotics is deemed appropriate, and they have the option of choosing either macrolide therapy, which is preferred, or alternatively doxycycline may be used. The COPD order set was used in 42% of patients in the antibiotic group and only 24% of patients in the no antibiotic group, demonstrating a need for further education on its appropriate use relative to initiation of antibiotics.

Additionally, other studies assessing time to next exacerbation often compared two different antibiotic groups, rather than a treatment and control group, making it difficult to compare the results of the present study to those in which all patients received antimicrobial therapy. Impact of long-term antimicrobial therapy may also affect outcomes due to resistance patterns and overall bacterial colonization. Lastly, our study only evaluated the rate of COPD re-exacerbation for a period of time up to 90 days, whereas several studies followed patients for up to 12 months, or longer. Thus, a direct comparison cannot be made between these studies.

Limitations of this study include its retrospective design and the concern that patients may have sought care at outside facilities, and therefore documentation of a readmission would not be available as part of this review, exists. A variety of subjective assessments were present throughout this study due to patient-reported symptoms, provider documentation of these symptoms, and then investigator bias in reviewing and interpreting these documented symptoms. Additionally, the lack of other clinical markers to guide the use of antimicrobial therapy in this cohort, such as C-reactive protein, may have impacted the number of patients who inappropriately received antibiotic therapy. Lastly, the limited use of CRP to guide clinical decision making during the studied time period. A total of eight subjects had a recorded CRP during this time, limiting our ability to fully comment on the use of this biomarker to guide antibiotic therapy. Since 2014 a higher percentage of patients have a recorded CRP hospital-wide, as this was added as part of the admission laboratory process. Overall, this study did not find a difference in the 30 day readmission rate for recurrent non-critical COPD exacerbations in patients treated with antibiotics compared to those treated without antibiotics. In addition, there was a trend toward a slightly longer mean length of stay in the antibiotic group compared to the no antibiotic group. Given the small sample it is difficult to quantify this result, combined with the fact that there was no difference in Charlson Comorbidity Index or corticosteroid use between these patients. Providers may be reluctant to discharge a patient until they have received several days of antibiotics, thus increasing the length of stay in this cohort, however this is speculation. Overall, the benefit of antibiotics on the reduction of readmission rates for a recurrent COPD exacerbation and length of stay remains uncertain. Until more definitive evidence is available, clinicians should use appropriate clinical judgment in addition to the most up-to-date clinical literature when evaluating the need for antibiotic use in individual patients presenting with a COPD exacerbation.

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