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RESEARCH

An observational study on factors influencing antibiotic use in chronic obstructive pulmonary disease at Universitas Academic Hospital, Bloemfontein

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Background: Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are often precipitated by excessive airway inflammation caused by viral or bacterial infections. Current guidelines suggest prescribing antibiotics to patients with AECOPD and purulent sputum production, but this may lead to unnecessary or inappropriate antibiotic use. The aim of this study was to identify clinical and laboratory variables influencing antibiotic prescriptions of clinicians managing patients hospitalised for AECOPD.
Methods: An observational study was conducted among patients hospitalised with AECOPD. Antibiotic prescriptions were compared with sputum appearance, white blood cell count, C-reactive protein (CRP) levels and sputum cultures. Treatment outcomes were assessed on days 3 and 5 after admission.
Results: Thirteen patients were included in the study, from July to October 2013, at Universitas Academic Hospital, Bloemfontein. Antibiotics were prescribed in seven out of eight patients with an elevated CRP level. None of the patients with reported sputum purulence received antibiotics. White blood cell count and sputum cultures did not seem to influence antibiotic prescription habits.
Conclusions: Clinicians managing patients with AECOPD do not follow guidelines that suggest prescribing antibiotics to patients presenting with purulent sputum production. Further studies on whether biomarkers such as CRP may be more acceptable as a deciding factor on which to base antibiotic prescriptions are required.

Keywords: acute exacerbation, antibiotic use, C-reactive protein, chronic obstructive pulmonary disease, COPD, CRP

Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease characterised by progressive and irreversible air flow limitation.[1] COPD is associated with significant morbidity and is the fourth leading cause of death worldwide.[2] According to the GOLD (Global Initiative for Obstructive Lung Disease) classification of COPD, the prevalence of GOLD grade ≥ 2 COPD in South Africa is 17% and 23% among women and men, respectively.[3]

Chronic inflammation of the lungs and airways is considered a key feature in COPD.[1] Excessive inflammation, frequently precipitated by irritants or infections of the airways, often results in acute exacerbations of COPD (AECOPD).[4] Approximately 50% of acute exacerbations are caused by infections with bacterial organisms such as *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae* and *Pseudomonas aeruginosa*.[5] Acute exacerbations of COPD contribute significantly to hospitalisation, deterioration in quality of life, morbidity and mortality, all of which also contribute to the escalating costs of managing patients with COPD.[1] Patients with COPD are often treated with broad-spectrum antibiotics, which may lead to increased antibiotic resistance and treatment failures if used indiscriminately.[6]

Antibiotic stewardship is a strategy attempting to preserve the armamentarium of antibiotics that is currently available. Key principles of antibiotic stewardship are that antibiotics be prescribed only when clear signs of infection are present and that specimens are routinely sent for microbial culture in order to prescribe the narrowest spectrum of antibiotics to which the identified organisms are susceptible.[7] This approach, however, may be challenging for clinicians, because patients with COPD often produce purulent sputum as part of the clinical phenotype of chronic bronchitis, and the airways of patients with COPD are often colonised with potentially pathogenic bacteria that may not require antibiotic treatment.[8] The GOLD committee recommends the use of antibiotics in patients with AECOPD who produce purulent sputum,[1] although it may result in inappropriate and unnecessary use of antibiotics if the precipitating factor is not a bacterial infection.

The aim of this study was to identify the factors influencing antibiotic prescriptions in patients admitted with AECOPD, and to compare this to treatment outcomes at days 3 and 5.

Methods

A prospective observational study design was used. The study sample consisted of adult patients older than 40 years of age with at least a 10 pack year smoking history or a history of exposure to high levels of biomass fuel smoke, who were admitted to hospital with a diagnosis of AECOPD. All consecutive qualifying patients admitted to Universitas Academic Hospital between 30 July 2013 and 30 October 2013 were included in the study. Patients were excluded if there was any evidence of congestive heart failure at admission, pulmonary infiltrates suggesting pneumonia or cancer, or when mechanical ventilation was required at the time of admission.

Standard therapy for patients hospitalised with AECOPD included oxygen via facemask or nasal prongs, nebulised short-acting bronchodilators and systemic corticosteroids. Antibiotics could be

added at the attending doctor's discretion if the exacerbation was deemed to be precipitated by bacterial airway infection. The investigators were not allowed to provide any input in the treatment of patients, but merely to document results from special investigations as well as antibiotics prescribed by the treating physicians.

Results of special investigations such as sputum microbial culture results, C-reactive protein (CRP) values and lung functions were retrieved from patient files. Information on risk factors for COPD, frequency of exacerbations and sputum purulence was collected by interviewing the study participants within 24 h of admission.

Permission to conduct the study was obtained from the Head of Clinical Services at Universitas Academic Hospital, the Head of the Department of Internal Medicine, and the Ethics Committee of the Faculty of Health Sciences at the University of the Free State (ETOVS STUD 25/2013). Written informed consent was obtained from participating patients.

Results

Thirteen patients were included in the study. The mean age was 61 years, ranging between 50 and 74 years. As shown in Table 1, eight patients were male and nine were Caucasian. Smoking was the main risk factor for COPD with nine of the patients having a smoking history of at least 20 pack years. Exposure to biomass fuel was apparent in eight of the patients. None of the patients had any history of prior tuberculosis.

Nine patients had a history of exacerbation in the 12 months preceding the study, with six of them reporting more than one episode. Four of the 13 patients reported definite sputum purulence during the current acute exacerbation episode.

Table 2 summarises each patient's white blood cell count and CRP value on admission, sputum appearance, sputum culture results and antibiotics used in the treatment of their current episode of AECOPD. In six patients, no sputum specimen was collected for further laboratory investigation, while in four patients only normal flora was cultured. In the remaining three patients, *Acinetobacter baumannii*, *Haemophilus parainfluenzae* and *Pseudomonas aeruginosa* were cultured from the sputum specimens. Of the three patients with positive sputum cultures, one (patient 03; Table 2) was treated with antibiotics for the current episode of exacerbation. This patient was treated empirically with amoxicillin/clavulanic acid at the time of admission. *A. baumannii* was eventually cultured and was most likely a hospital acquired airway coloniser, unlikely to respond to amoxicillin/clavulanic acid. Concomitant therapy was therefore the most likely reason for the successful treatment in patient 03. None of the patients who reported purulent sputum production received any antibiotics, despite two of them (patients 09 and 11; Table 2) having positive sputum cultures that yielded *H. parainfluenzae* and *P. aeruginosa* respectively.

Of the eight patients with elevated CRP levels (> 5 mg/L), seven were prescribed antibiotics, compared with none of the four patients with normal CRP levels. Six of the 11 patients with white blood cell counts exceeding 10 x 10^9/L (normal range 4–10 x10^9/L) were treated with antibiotics, while one patient with a normal white blood cell count also received antibiotics.

Treatment was considered to be successful based on clinical assessment of an improvement in symptoms as judged by the attending physician, or when the patient was discharged by day 5 after admission. Treatment failures at day 3 or 5 were defined by the development of new pulmonary infiltrates suggesting pneumonia (chest imaging studies being requested at the

Table 1: COPD patients' demographic and clinical details

Variable	*n*
Demographic information	
Gender	
Male	8
Female	5
Ethnicity	
Black	4
White	9
Employment status	
Unemployed	3
Retired	8
Other	2
Risk factors for COPD	
Smoking status	
Current smoker	4
Previous smoker	9
Pack year history	
< 10	2
10–19	1
20–29	2
30–39	2
≥ 40	5
Unknown	1
Biomass fuel exposure	
Yes	8
No	5
Previous tuberculosis	
Yes	0
No	13
Exacerbation profile	
History of exacerbation during previous 12 months	
Yes	9
No	4
Number of exacerbations during previous 12 months	
≤ 1 episode	2
> 1 episodes	6
Not recorded	1
Antibiotic use during previous 30 days	
Yes	4
No	9
Patient-reported sputum appearance	
Purulent	4
Not purulent	5
Unknown	4
Current treatment outcome	
Successful treatment	
Day 3	4
Day 5	9
Treatment failure	
Day 3	1
Day 5	0

discretion of the treating physicians), change in antibiotic therapy as a result of poor response to treatment, worsening dyspnoea, development of respiratory failure requiring mechanical ventilation or death by any cause.[9] Based on these definitions, 4 and 9 out of the 13 patients were treated successfully by day 3 and 5, respectively. Only one patient (patient number 08; Table 2) was considered to be a treatment failure at day 3 because of worsening dyspnoea, whereas no treatment failures were present by day 5.

Discussion

The study was conducted among patients hospitalised with acute exacerbation of COPD during one mild winter season at a single public sector academic hospital, which provided a fairly low number of participants. The hospital where the study was conducted functions as a tertiary level referral hospital where, in general, mainly higher risk patients are managed.

The current South African guidelines for the management of COPD state that antibiotics should be prescribed to patients with purulent sputum production during an acute exacerbation.[10] Based on these guidelines, antibiotics would be indicated in these patients without necessarily requiring confirmatory results of a pathogenic organism on sputum culture. However, in our study cohort, none of the patients with purulent sputum received antibiotics. The main predictor for antibiotic therapy seems to have been an elevated CRP (> 5 mg/L), since seven of the eight patients with an elevated CRP (> 5 mg/L) were treated with antibiotics. Eleven of the 13 patients had an increased white cell count (> 10 x 10^9/L), although this finding did not seem to influence the decision to prescribe antibiotic therapy. Sputum for microbiological investigations was collected in only 7 of the 13 patients. *H. parainfluenzae* was not considered pathogenic. Only two of the sputum samples therefore cultured potentially pathogenic organisms, and only one of these patients received antibiotics.

Because of the limited number of participants, definite associations between clinical or laboratory variables and antibiotic use could not be determined. Although treating physicians could have simply been asked which factors influence their decisions to prescribe antibiotics, we attempted to identify objective evidence of the factors guiding clinicians' antibiotic prescription decisions. The antibiotic prescription habits of the physicians managing the patients in this study cohort seem to correlate more with the CRP level than with any of the other factors evaluated.

Although sputum purulence is predictive of bacterial infection,[11] patients' self-reported sputum purulence is subjective. Using the guideline 'recommended appearance of sputum as reported by patients' as the deciding factor to institute antibiotics may lead to either overtreatment of patients with antibiotics and thereby

Table 2: Infection markers, sputum appearance and culture, and antibiotic therapy of patients hospitalised for acute exacerbation of COPD

Patient	WBC count (x 10^9/L)[a, b]	CRP (mg/L)[c, d]	Purulent sputum (Yes/No)	Sputum culture	Antibiotic therapy for current episode	Treatment outcome
01	11.73	61.9	No	Normal flora	Amoxycillin/ clavulanic acid	Successful, day 5
02	12.41	32.8	No	Normal flora	Cefuroxime plus erythromycin	Not successful by day 5
03	10.94	9.1	No	*Acinetobacter baumannii*	Amoxycillin/ clavulanic acid	Successful, day 3
04	10.10	2.4	Yes	Not collected	None	Successful, day 3
05	29.24	296.4	Unknown	Not collected	Amoxycillin/ clavulanic acid plus erythromycin	Successful, day 5
06	12.20	17.4	No	Not collected	Amoxycillin/ clavulanic acid plus erythromycin	Successful, day 5
07	10.58	2.4	Unknown	Normal flora	None	Successful, day 5
08	13.50	51.0	Unknown	Not collected	Ertapenem	Successful, day 5
09	11.81	1.3	Yes	*Haemophilus parainfluenzae*	None	Not successful by day 5
10	6.24	37.2	No	Not collected	Ciprofloxacin	Not successful by day 5
11	14.37	< 1	Yes	*Pseudomonas aeruginosa*	None	Successful, day 3
12	11.53	15.5	Yes	Normal flora	None	Successful, day 3
13	8.37	ND[e]	Unknown	Not collected	None	Not successful by day 5
Mean	12.54	44.0				
Median	11.73	16.5				
Range	6.24–29.24	< 1–296.4				

[a]WBC: white blood cell.
[b]Normal range: 4–10 x 10^9/L.
[c]CRP: C-reactive protein.
[d]Normal range: < 5 mg/L.
[e]ND: Not determined.

contribute to antimicrobial resistance, or undertreatment with potentially poor outcomes. None of the patients in this cohort were deemed to have been treatment failures after 5 days.

Previous research demonstrated the modifying effects that rapid CRP testing has on general practitioners' antibiotic prescription habits when treating patients with COPD.[12] Our study similarly points to the possible value of CRP as a biomarker that may be more acceptable to clinicians than reported sputum purulence when deciding to prescribe antibiotics to acutely ill hospitalised patients with AECOPD. Patients in whom antibiotics are deferred might be monitored for a few days, and antibiotics prescribed later based on sputum culture results should the patient show a poor response to standard bronchodilator and corticosteroid treatment.[13]

Limitations of this study include the small sample size and the poor compliance of the primary physicians in collecting sputum specimens for microbial culture. The criteria for successful treatment were also subjective, which complicated comparison of treatment outcomes between antibiotic treated and untreated groups of patients. Although the results of this study reveal certain potential associations, a larger randomised control study will have to be conducted in order to determine definite associations between antibiotic therapy, biomarkers of inflammation and treatment outcomes. In conclusion, clinicians managing patients with AECOPD at Universitas Academic Hospital do not follow guidelines suggesting antibiotics for patients with purulent sputum production. The use of biomarkers such as CRP may be a more acceptable tool on which to base antibiotic prescription decisions, if immediately available at the point of care. Larger randomised control studies conducted among hospitalised COPD patients are required to evaluate the role of CRP as part of antibiotic stewardship policies.

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