Ann Med Res 2021;28(8):1520-4

Annals of Medical Research

DOI: 10.5455/annalsmedres.2020.09.968

Original Article

Short term results comparison of antibiotic resistance in COPD patients with exacerbation

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Abstract

Aim: To obtain data which could be of guidance in the selection of empirical antibiotic treatment through bacteria isolation from sputum and antibiotic sensitivity tests in patients hospitalised because of exacerbation of chronic obstructive pulmonary disease (COPD).

Materials and Methods: Sputum samples were induced before antibiotherapy in patients hospitalised because of COPD exacerbation. In addition to routine tests and infection markers, sputum cultures and antibiotic resistance tests were applied.

Results: The study included 101 patients. Production was determined in the sputum cultures of 28 (27.7%) patients. In the group with bacteria isolated in the sputum, there was determined to be a high number of exacerbations in the last year, partial oxygen pressure (PaO2) was low, and procalcitonin (PCT), the neutrophil ratio, white blood cell count (WBC) and the modified Medical Research Council Dyspnea Score (mMRC) were found to be higher than in the patients with negative sputum ($p<0.05$). The three leading bacteria produced in the positive culture group were *Streptococcus pneumonia,Pseudomonas aeruginosa* and *Acinetobacter spp.*

Conclusion: *S. pneumoniae, P.aeroginosa* and *Acinetobacter spp.* are still the most common organisms which were isolated in acute exacerbation of COPD in our country population. Ceftriaxone is still considered a highly sensitive and effective antibiotic drug against these common micro-organisms in our society, besides that procalcitonin value is the most useful tracking parameter for these patients. Consequently, intermittent surveillance regarding improving of resistance pattern for these common pathogens against commonly prescribed drugs is necessary.

Keywords: Antibiogram; COPD; exacerbation; sputum culture

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a widespread, preventable, treatable disease, characterised by respiratory symptoms and permanent restricted airflow associated with airway and alveolar abnormalities caused by severe exposure to generally harmful particles or gases. COPD is a disease which is seen with exacerbations, which are defined as an acute worsening of respiratory symptoms which require additional treatment. COPD exacerbations are important in a global dimension as they accelerate the progression of the disease, have long-term negative effects on the patient, lead to a deterioration in quality of life, increase the risk of mortality and increase the healthcare costs (1,2).

Although there are many infectious and non-infectious causes of COPD exacerbations, generally the most common cause is respiratory tract infections. Bacteria with a leading role in infectious exacerbations are *S. pneumoniae, H. influenzae* and *M. catarrhalis*. In approximately one-third of infected COPD exacerbations the cause of infection is respiratory viruses. Although the majority of bacteria with a role in COPD exacerbations are in a similar spectrum, differences are seen in incidence and antibiotic resistance from country to country . Therefore, there is a need for countries to have their own specific data to direct empirical antibiotic treatment in COPD exacerbations and to test differences in resistance characteristics in specific time periods (3-6).

The aim of this study was to obtain data which could be of guidance in the selection of empirical antibiotic treatment through bacteria isolation from sputum and antibiotic sensitivity tests in patients hospitalised because of COPD exacerbation.

MATERIALS and METHODS

Patient Selection

The study included patients who were hospitalised

Received: 20.09.2020 **Accepted:** 04.11.2020 **Available online:** 18.08.2021
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because of COPD exacerbation between January 2019 and July 2019 in the Chest Diseases Clinic of Selcuk University Medical Faculty. Local Ethic commitee approval was obtained before the research (Selcuk university approval number 2017/382). The patients included in the study that 1) clinical diagnosis of COPD, defined by American Thoracic Society (ATS); 2) any history of asthma disease; 3) no exacerbation in the month prior to admission; 4) smoker history ; 5) baseline pre-bronchodilator forced expiratory volume in one second (FEV1) 25-85% of predicted; 6) no maintenance treatment of oral steroids or antibiotics; 7) no medical history of psychiatric morbidity 8) absence of any other active lung disease. Exacerbations were defined as worsening of respiratory symptoms that needed treatment with a short course of oral corticosteroids or antibiotics. The stable state was definedas a period of 4 weeks with no change in pulmonary symptoms (7).

Sputum Collection

On the first day of hospitalisation, after rinsing the mouth and larynx with plenty of water, the patients were given a 3% sterile solution with an ultrasonic nebuliser. During and after the nebulisation, the patients were instructed to cough and expectorate sputum at 5-minute intervals. When at least 2 ml sputum had been obtained, the procedure was terminated and the sputum bottle was sent to the pathology laboratory.

Sputum Analysis

Sputum samples were collected in sterile bottles and handled in the laboratory within 6 hours. Sputums were homogenized by incubation at 37 for 15 min with anequal volume of 0.1% dithiothreitol. In line with the European Society of Microbiologists (ESM) criteria, sputum samples with < 105m squamous epithelial cells were accepted as representative samples and were revealed as insufficient samples. An area on the sputum gram staining preparates at x100 magnification containing <10 epithelial cells and >25 leukocytes was accepted as an appropriate sputum sample for culture. Sputum samples with these characteristics were seeded with the single colony seeding method in chocolate agar, bacitracin chocolate agar, sheep blood Columbia agar and McConkey agar media. By incubating the media at 37˚C for 24-48 hrs in an environment with 5% CO2, the produced bacteria were identified with traditional methods and the VITEK-2 automated system. Gram dying and semi-quantitative culture were applied for all collected sputum samples.. The sensitivity to antibiotics of the bacteria was tested with the disc diffusion method or the VITEK-2 automated system, and was evaluated according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria (8).

Statistical Analysis

All statistical analysis was performed using R 3.6.0 (www.r-project.org). Anderson Darling normality test and Q-Q plot were used to check the data normality. Continuous variables were presented as mean ± standard deviation, median (interquartile range), or median (minimum – maximum), and analyzed using student's t test or Mann-Whitney U test, as appropriate. Categorical variables were described as numbers (n) and percentages (%), and analyzed using Chi-square test. A p-value less than 0.05 was considered as statistically significant.

RESULTS

Evaluation was made of 101 patients. Bacteria were produced in the sputum cultures of 28 (27.7%) patients. When the variables were examined between the groups, no statistically significant difference was determined in respect of age, partial carbon dioxide pressure (PaCO2), forced expiratory volume in the first second (FEV1) and C-reactive protein (CRP). In the group with positive cultures, there was determined to have been a higher number of exacerbations, partial oxygen pressure (PaO2)

Table 1. Comparison of variables between groups

	Positive	Negative	p-value
Age (years), mean ± SD	67.54 ± 9.32	68.36 ± 7.94	.659
Gender, n (%)			.774
Female	24 (85.7)	60 (82.2)	
Male	4 (14.3)	13 (17.8)	
Exacerbation, median (min – max)	3 (2 – 8)	2 (1 – 7)	.040*
Pa02, median (IQR)	55 (52 – 59.50)	61 (57 – 70)	.003*
PaCO2, median (IQR)	38.50 (34 – 45)	38 (35 – 43)	.843
Fev1 (L), mean ± SD	1.49 ± 0.55	1.46 ± 0.62	.818
Fev1 (%), median (IQR)	55.50 (48.25 – 63)	56 (37 – 70)	.724
CRP, median (IQR)	25.40 (14.75 – 54)	24 (16 – 37)	.471
PCT, median (IQR)	1.36 (0.15 – 2.52)	0.13 (0.05 – 0.40)	<.001*
Neutrophil, mean ± SD	82.42 ± 8.13	78.05 ± 9.39	.032*
WBC, mean ± SD	13.60 ± 4.78	10.70 ± 3.65	.001*
MMRC, n (%)			.417
1	0 (0)	1 (1.4)	
2	11 (39.3)	40 (54.8)	
3	11 (39.3)	23 (31.5)	
4	6 (21.4)	9 (12.3)	

SD: standard deviation, IQR: interquartile range, min: minimum, max: maximum; *p<0.05 was considered as statistically significant

was lower, and procalcitonin (PCT), the neutrophil ratio, white blood cell count (WBC) and the modified Medical Research Council Dyspnea Score (mMRC) were found to be higher than in the patients with negative sputum ($p<0.05$) (Table 1). The three leading bacteria produced in the positive culture group were Streptococcus pneumonia, Pseudomonas aeruginosa and Acinetobacter spp.. (Figure 1). In the antibiogram, S.pneumonia was determined to be most resistant to erythromycin, gentamicin, clyndamycin, tetracycline and trimethoprim. P. aeruginosa was found to be most resistant to piperacillin-tazobactam (TZP), cefepime and ciprofloxacin. Klebsiella pneumonia showed the most resistance to ampicillin (Table 2,3).

Table 2. Antibiotic resistance for S.pneumonia, P. Aeruginosa and Acinetobacter spp..

Antibiotics	S.pneumonia		P. aeruginosa		spp	
	Number	%	Number	%	Number	%
Rifampicin	0	0	-	-	-	-
Erythromycin	2	40	-	-	-	-
Ampicillin	1	20	-	-	-	-
Gentamicin	2	40	1	25	2	50
Clindamycin	2	40	-	-	-	-
Chloramphenicol	0	0	-	-	-	-
Levofloxacin	0	0	1	25	2	50
Linezolid	0	0	-	-	-	-
Moxifloxacin	0	0	0	0	0	0
Ceftriaxone	0	0	-	-	-	-
Cefotaxime	0	0	-	-	-	-
Penicillin	1	20	-	-	-	-
Tetracycline	2	40	-	-	-	-
TMP-SMX	2	40	-	-	-	-
Vancomycin	0	0	-	-		
Tobramycin	-	-	0	0	1	25
Netilmicin	-	-	0	0	1	25
Amikacin	-	-	0	0	1	25
TZP*	-	-	2	50	2	50
Ceftazidime	-	-	1	25	3	75
Cefepime	-	-	2	50	1	25
Ciprofloxacin	-	-	2	50	3	75
Imipenem	-	-	1	25	2	50
Meropenem	-	-	1	25	1	25
Aztreonam	-	-	1	25	1	25

(-): Antibiotic without culture antibiogram.
TZP: Piperasilin-Tazobaktam; TMP-SMX: Trimetoprim sulfametoxazol

Table 3. Antibiotic resistance for E. Coli, Klebsiella spp., E. cloacae complex, Serratia marcescens

	E. coli		Klebsiella spp.		E. loacae		Serratia marcescens	
	Number	%	Number	%	Number	%	Number	%
Ampicillin	1	50	2	66	1	100	1	100
AMC*	1	50	1	33	1	100	1	100
TZP**	1	50	1	33	0	0	0	0
Gentamicin	0	0	0	0	0	0	0	0
Amikacin	1	50	0	0	0	0	0	0
Colistin	0	0	0	0	0	0	0	0
Cefuroxime	1	50	0	0	1	100	1	100
Cefuroxime / Aksetil	1	50	0	0	1	100	1	100
Cefepime	1	50	0	0	0	0	0	0
Ceftriaxone	1	50	0	0	0	0	0	0
Ceftazidime	1	50	0	0	0	0	0	0
Ciprofloxacin	2	100	0	0	0	0	0	0
Ertapenem	0	0	0	0	0	0	0	0
Meropenem	0	0	0	0	0	0	0	0
Tigecycline	0	0	0	0	0	0	0	0
TMP-SMX	1	50	1	33	0	0	0	0

AMC: Amoxicillin-Klavulunat; TZP: Piperacillin-Tazobactam; TMP-SMX: Trimethoprim sulfametoxazole

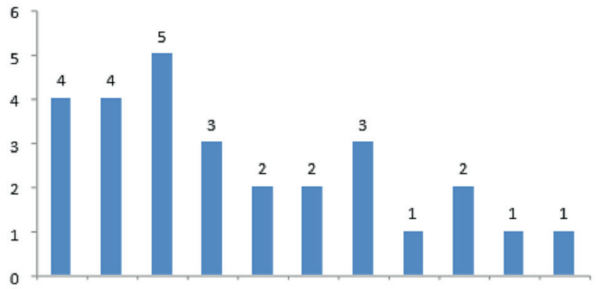

Figure 1: Bacteria growing in sputum cultures

DISCUSSION

Chronic obstructive pulmonary disease (COPD) is a majorcause of chronic morbidity and mortality throughout the world. Morbidity and mortality among patients with COPDare for a large part related to acute exacerbations of COPD, which occur on average 1-3 times a year. It is accepted that tracheobronchial infections are responsible for 50%-70% of COPD exacerbations (6). Bacterial agents are responsible at the rate of 40-50%, viral agents at the rate of 30-40% and atypical bacterial agents at the rate of 5-10% (9). In the current series, bacteria were isolated in only 27.7% of the patients. The most significant reasons for COPD exacerbations in Turkey are thought to be treatment incompatibility, a high rate of misuse of inhalation devices, and air pollution in both internal and external environments.

The pathogens most responsible for COPD infectious exacerbations are *Haemophilus influenzae, Streptococcus pneu¬moniae, Moraxella catarrhalis, Enterobacteriaceae* family members, *Pseudomonas aeruginosa, Staphylococcus aureus* and *Chlamydia pneumoniae*. It is not easy to understand whether or not there is new infection from the bacteria isolated from sputum in COPD exacerbations because there may be colonisation of pathogens at a rate in parallel with disease severity and duration in the respiratory tract of stable COPD patients. Therefore, it has been suggested that pathogens isolated in sputum in infected COPD exacerbations are caused by excessive proliferation of colonised bacteria (11). Thus in patients at a severe stage of COPD where there is a high risk of colonisation, the risk of developing infectious excerbation will be high .

Just as in previous similar studies, *S. pneumonia* were the most frequently isolated bacteria in the current study. The isolation of gram negative *Pseudomonas aeruginosa* and *Acinetobacter spp*. as the second and third most common bacteria was attributed to severe exacerbations of the patients which required hospitalisation. The isolation of gram negative bacteria in COPD exacerbations is not an uncommon finding. However, *Acinetobacter spp*. was isolated in this study, which has not been greatly reported in sputum cultures of COPD exacerbations(9-14).

The use of antibiotics in patients hospitalised because of COPD exacerbation reduces mortality and treatment failure. In addition, the early administration of antibiotics can prevent a later need for ventilation and re-hospitalisation within 30 days. In a retrospective study of 53,900 patients hospitalised because of COPD exacerbation, it was reported that antibiotics were not given to 15% of the patients, and the length of stay in hospital and the mortality rates were better in the group that received antibiotics (15, 16).

In cases of COPD followed up as outpatients without hospitalisation, gram staining and sputum cultures are not mandatory. However, when there is no response to empirical treatment or there is a risk of gram negative infection, sputum tests may be necessary in outpatient treatment. Purulence is an important marker in the decision for antibiotic treatment of patients with exacerbations, treated as outpatients. Ceftriaxome for a mean period of one week are the recommended first choice antibiotic. On the other hand when the drug resistance started against to this drug, Levofloxacin could be useful for these population. In patients with an exacerbation of a severity for hospitalisation, it is recommended that antibiotic treatment is administered intravenously when possible and started immediately (17).

However, each country should determine its own standards in the selection of antibiotics, and culture-resistance studies should be repeated periodically. Antibiotic resistance properties show great differences between countries. It has been reported that *S. pneumonia* isolated in sputum cultures of patients in India with COPD exacerbation has the highest resistance to cefalosporin. In the current study, *S.pneumonia* was found to be most resistant to erthromycin, gentamicin, clyndamycin and tetracycline. In Klebsiella strains, the highest resistance rate was determined to ampicillin. In different studies, *P. aeruginosa* has been determined at a significant rate and with most resistance to AMC and cephalosporin , while in the current study, resistance to TZP, cefepime and ciprofloxacin was determined.

Acinetobacter spp. was most resistant to ceftazidime and ciprofloxacin, and *E. Coli* was also determined to be most resistant to ciprofloxacin (18). When we look at the antibiogram results we have detected that ceftriaxome is the first and also effective choice however if any resistance developed to this medicine levofloxacin should utilized for recovery and improvement in COPD exacerbation.

At the same time there was, no significant difference was determined in the CRP value, whereas procalcitonin was found to be significantly elevated compared to CRP. The CRP value is not accepted as a specific marker for the presence of pathogenic micro-organisms in sputum. For the initiation of antibiotic treatment in COPD exacerbations, the procalcitonin value can be of more guidance than CRP. Although the determination of procalcitonin is an expensive method, it is accepted as cost-effective in respect of showing exacerbations associated with serum level bacterial causes and for the decision-making of the appropriate antibiotic treatment. It has been reported that when procalcitonin is used to make the decision for antibiotic treatment, there is a reduction in antibiotic use without any increase in mortality or treatment failure (19-21).

LIMITATIONS

Limitations of this study could be said to be the low number of cases, the quantitative processing of the cultures and that culture antibiogram tests were not made for *H. influenza* and *M. catarrhalis*. Evaluation of the culture and antibiogram results together with the exacerbation history and antibiotics used by the patient would provide more robust data.

CONCLUSION

S. pneumoniae, P.aeroginosa and *Acinetobacter spp*. are still the most common organisms which were isolated in acute exacerbation of COPD in our country population. Ceftriaxone is still considered a highly sensitive and effective antibiotic drug against these common micro-organisms in our society, besides that procalcitonin value is the most useful tracking parameter for these patients. On the other hand when the drug resistance started against to ceftriaxome, Levofloxacin could be useful for these population. Consequently, intermittent surveillance regarding improving of resistance pattern for these common pathogens against commonly prescribed drugs is necessary.

Competing Interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical Approval: Ethics committee approval was received from the Ethics Committee of Selcuk University School of Medicine (no: 2017/382). .

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