



# Risk Factors for Presence of Resistant Microorganisms in Sputum Cultures of Patients with Infectious Exacerbations of Chronic Obstructive Lung Disease

## Kronik Obstrüktif Akciğer Hastalığının Enfeksiyöz Alevlenmelerindeki Hastaların Balgam Kültürlerinde Dirençli Mikroorganizma Varlığı İçin Risk Faktörleri

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### ABSTRACT

**Introduction:** Antibiotics reduce the risk of short-term mortality. Certain bacteria may be resistant to initial regimens which is related to mortality. The aim of this study was to find risk factors for the presence of resistant bacteria during exacerbation of Chronic Obstructive Pulmonary Disease (COPD).

**Materials and Methods:** Ethics committee approval was obtained for the study. The patients hospitalized with an exacerbation of COPD between 2015 and 2020 were retrospectively reviewed. The patients with a sputum culture result were divided into: Group A with conventional microorganisms (susceptible to initial antibiotic regimen) and Group B with non-conventional microorganisms (resistant to initial antibiotic regimen). The risk factors for Group B microorganisms were investigated.

**Results:** One hundred and nineteen patients were included in the study. Median age was 68 (40-88) years. There were 22 patients in Group A and 97 in Group B. Most common microorganism in Group A was *Haemophilus influenzae* (12.6%). Most encountered microorganisms in Group B were *Pseudomonas aeruginosa* (49.6%). Male sex (HR= 2.9; 95% CI= 0.9-9.5; p= 0.073), age >61 (HR=4.8; 95% CI= 1.7-13.6; p= 0.003), and >5 hospitalizations last year (HR= 8.2; 95% CI= 0.9-67.7; p= 0.051) were found to be independent risk factors for resistant microorganisms.

**Conclusion:** Proposed risk factors for the isolation of multidrug resistant microorganism in patients hospitalized with COPD exacerbations should be considered when choosing the initial antibiotic regimen.

**Key Words:** Risk factors; Resistant microorganisms; Infectious exacerbation of COPD

## ÖZ

**Kronik Obstrüktif Akciğer Hastalığının Enfeksiyöz Alevlenmelerindeki Hastaların Balgam Kültürlerinde Dirençli Mikroorganizma Varlığı İçin Risk Faktörleri**Melih BÜYÜKŞİRİN<sup>1</sup>, Güneş ŞENOL<sup>2</sup>, Gülrü POLAT<sup>1</sup>, Aysu AYRANCI<sup>3</sup>, Filiz GÜLDAVAL<sup>1</sup>, Damla SERÇE UNAT<sup>1</sup><sup>1</sup> Sağlık Bilimleri Üniversitesi Dr. Suat Seren Göğüs Hastalıkları ve Cerrahisi Eğitim ve Araştırma Hastanesi, Göğüs Hastalıkları Anabilim Dalı, İzmir, Türkiye<sup>2</sup> Sağlık Bilimleri Üniversitesi Dr. Suat Seren Göğüs Hastalıkları ve Cerrahisi Eğitim ve Araştırma Hastanesi, İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı, İzmir, Türkiye<sup>3</sup> Bakırçay Üniversitesi Tıp Fakültesi, Bakırçay Üniversitesi Çiğli Eğitim ve Araştırma Hastanesi, Göğüs Hastalıkları Anabilim Dalı, İzmir, Turkey

**Giriş:** Kronik obstrüktif akciğer hastalığı (KOAH) dünya çapında önemli bir ölüm nedenidir. Antibiyotiklerin kısa süreli ölüm riskini azalttığı gösterilmiştir. Bununla birlikte, bazı bakteriler, tedavi başarısızlığı ve mortalite ile ilgili olan bu başlangıç rejimlerine dirençli olabilir. Bu çalışmanın amacı, hastaneye yatış gerektiren KOAH alevlenmesi sırasında bu dirençli bakterilerin varlığı için olası risk faktörlerini bulmaktır.

**Materyal ve Metod:** Çalışmanın etik kurul onayı alınmıştır. 2015-2020 yılları arasında üçüncü basamak bir hastaneye başvuran ve KOAH alevlenmesi ile yatırılan hastalar retrospektif olarak incelendi. Balgam kültürü sonucu olan hastalar, konvansiyonel mikroorganizmaları olan Grup A (ilk antibiyotik rejimine duyarlı olması beklenen) ve konvansiyonel olmayan mikroorganizmaları olan Grup B (başlangıçtaki antibiyotik rejimine dirençli olması beklenen) olarak ayrıldı. Balgam kültürlerinde (Grup B) konvansiyonel olmayan mikroorganizma varlığı için risk faktörleri araştırıldı.

**Bulgular:** Çalışmaya 119 hasta dahil edildi. Ortanca yaş 68 (40-88) yılı. Erkekler daha fazla idi (%84.0). En sık eşlik eden hastalık konjestif kalp yetmezliği idi (%14.3). Hastalar sık atak geçiren hastalardan oluşmakta idi. Grup A'da 22, Grup B'de 97 hasta vardı. Grup A'da en sık görülen mikroorganizma *Haemophilus influenzae* idi (n= 15; %12.6). Grup B'deki suşlar ilk antibiyotik rejimine dirençliydi. En çok karşılaşılan mikroorganizmalar *Pseudomonas aeruginosa* idi (59; %49.6). Çok değişkenli lojistik regresyon analizinde erkek cinsiyet (HR= 2.9; %95 GA= 0.9-9.5; p= 0.073), yaş >61 (HR= 4.8; %95 GA= 1.7-13.6; p= 0.003), geçen yıl >5 hastaneye yatış (HR= 8.2; %95 GA= 0.9-67.7; p= 0.051) dirençli mikroorganizmalar için bağımsız risk faktörü olarak bulundu.

**Sonuç:** Başlangıç antibiyotik rejimi seçilirken KOAH alevlenmeleri ile hastaneye yatırılan hastalarda çoklu ilaca dirençli mikroorganizma izolasyonu için önerilen risk faktörleri göz önünde bulundurulmalıdır. Antibiyotiklere başlamadan önce balgam kültürü alınmalıdır.

**Anahtar Kelimeler:** Risk faktörleri; Dirençli mikroorganizmalar; İnfeksiyöz KOAH alevlenmesi

**INTRODUCTION**

Chronic obstructive pulmonary disease (COPD), as a preventable disease, is a major cause of mortality worldwide. The burden is increasing especially in middle- and low-income countries; it is estimated that the disease will be the fourth leading cause of death by 2030, worldwide<sup>[1-3]</sup>. Mortality in COPD mainly occurs during severe exacerbations, the average case-fatality rate of an exacerbation ranges between 11.4% and 19.0%<sup>[4]</sup>. Infections (viral and bacterial) may cause an exacerbation, so the use of antibiotics is encouraged in certain conditions<sup>[5]</sup>. The choice of empirical antibiotic regimen is usually amin-

openicillin with clavulanic acid, 2<sup>nd</sup>/3<sup>rd</sup> generation cephalosporins, macrolide, and tetracycline. Antibiotics are shown to reduce the risk of short-term mortality. However, certain bacteria may be resistant to those initial regimens which is related to treatment failure and mortality<sup>[6]</sup>. The aim of this study was to find possible risk factors for the presence of those resistant bacteria during an exacerbation of COPD requiring hospitalization.

**MATERIALS and METHODS**

The patients who had admitted to a tertiary care hospital and hospitalized with an exacerbation of COPD between 2015 and 2020 were retrospectively reviewed. The patients who had at

least two of the three cardinal symptoms (dyspnea, increase in sputum amount and purulence) and had given any antibiotic with recommended treatments for exacerbation were involved in the study<sup>[5]</sup>. The data of existing sputum culture results of first 72 hours were evaluated.

The first sputum or bronchial aspiration samples taken after hospitalization were included in the study. Respiratory samples were cultured with standard microbiological methods, identification was performed using Phonix (BD, USA) automated system and conventional microbiological methods. Antimicrobial susceptibility tests were made with Phonix automatic system and disk diffusion method, and EUCAST criteria were used for antibiotic sensitivity.

*Chlamydia pneumoniae*, *Legionella pneumophila* and *Mycoplasma pneumoniae* cannot be identified in our routine microbiological procedures. Therefore, in this study, *C. pneumoniae*, *L. pneumophila*, *M. pneumoniae* and viral panel were excluded from the study parameters.

The patients with a sputum culture result were divided into two groups: Group A with conventional microorganisms (expected to be susceptible to initial antibiotic regimen-*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*) and Group B with non-conventional microorganisms (expected to be resistant to initial antibiotic regimen- *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii* etc.). Initial antibiotic regimens consist of aminopenicillin with clavulanic acid, 2<sup>nd</sup>/3<sup>rd</sup> generation cephalosporins, or macrolides. All patients received standard care for COPD exacerbation. Several features of the cases were collected retrospectively. The risk factors for presence of non-conventional microorganism in sputum cultures (Group B) were investigated. All patients were admitted by out-patient setting. The patients with a history of immunosuppression were excluded.

Statistical analysis was performed using the IBM SPSS for Windows<sup>®</sup> version 20.0 software (IBM Corp., Armonk, NY, USA). Descriptive statistics were expressed in mean  $\pm$  standard deviation (SD) or median (25-75 percentiles) for

continuous variables and in number and frequency for categorical variables. Comparison between categorical variables was done with Chi-squared test and between continuous variables with independent samples t test or Mann-Whitney U test, where applicable. Significant variables in univariate analyses were involved in multivariate logistic regression analysis. A p value of <0.05 was considered statistically significant. This retrospective study was approved by the Ethics Committee of the tertiary care hospital where the study was conducted (28.09.2020/No: 20).

## RESULTS

A total of 119 patients who were hospitalized with an exacerbation of COPD and had a sputum culture involved in the study. Several features of the patients were summarized in Table 1. Median age was 68 (40-88) years. Males were predominant (84.0%). Most common comorbidities were congestive heart failure (14.3%), followed by hypertension, diabetes mellitus and coronary artery disease (9.2%, 5.9%, and 4.2%, respectively). Patients were mostly frequent exacerbators: a history of exacerbations last year and last three months were 86.6% and 12.6%, respectively. The rate of hospitalization during the last year was also high. Almost half of the patients were under long term oxygen therapy and a quarter had been receiving noninvasive ventilation at home.

There were 22 patients in Group A and 97 patients in Group B. The microorganisms regarding groups were given in Table 2. Most common microorganism in group A was *H. influenzae* (n= 15; 12.6%). The strains in group B were resistant to initial antibiotic regimen. Most encountered microorganisms were *P. aeruginosa* (59; 49.6%), *A. baumannii* (12; 10.1%) and *K. pneumoniae* (8; 6.7%), which were resistant to commonly used empirical antibiotics during an exacerbation of COPD.

Several features were compared between the groups. Mean age was higher in Group B. A cut-off value of >61 years was found to be discriminative for being in Group B (AUC= 0.645; 95% CI= 0.522-0.730; p= 0.035). Odds ratio of >61 years of age was 4.5 (95% CI= 1.7-12.0).

**Table 1. Several features of the patients involved in the study**

Features	All patients (N= 119)	Group A (n= 22)	Group B (n= 97)	p
Age [Med. (min-max)]	68 (40-88)	58.5 (40-86)	70 (48-88)	0.034
Sex [Male n(%)]	100 (84.0)	14 (83.6)	86 (88.7)	0.008
BMI [Med. (min-max)]	N= 9422.38 (13.10- 42.00)	n= 1924.00 (14.00- 42.00)	n=7524.00 (13.10-37.20)	0.914
Presence of comorbidity [n (%)]	48 (40.3)	6 (27.3)	42 (43.3)	0.253
History of exacerbation (last year) [n (%)]	103 (86.6)	17 (77.3)	86 (88.7)	0.173
Number of exacerbations (last year) [Med. (min-max)]	3.0 (0-15)	2 (0-7)	3 (0-15)	0.037
History of exacerbation (last three months) [n (%)]	15 (12.6)	4 (18.2)	11 (11.3)	0.475
History of hospitalization (last year) [n (%)]	98 (82.4)	15 (68.2)	83 (85.6)	0.066
Number of hospitalizations (last year) [Med. (min-max)]	1 (0-6)	1 (0-5)	2 (0-6)	0.015
Smoking (active and ex-smokers) [n (%)]	108 (90.8)	21 (95.5)	87 (89.7)	0.687
Smoking (packyears)	N= 4150 (5-200)	n=350 (30-100)	n=3850 (5-200)	NA
Long term oxygen supply [n (%)]	60 (54.1)	13 (61.9)	47 (52.2)	0.576
Non-invasive ventilation at home [n (%)]	30 (27.0)	6 (28.6)	24 (26.7)	0.860
FEV <sub>1</sub> % [Med. (min-max)]	31.5 (20-67) n= 76	29.5 (22-67) n= 16	32.0 (20-67) n= 60	0.944
FVC% [Med. (min-max)]	45 (22-79) n= 76	48 (28-75) n= 16	45 (22-79) n= 60	0.721
FEV <sub>1</sub> /FVC% [Med. (min-max)]	56 (30-73) n= 76	58.5 (38-73) n= 16	55.5 (30-73) n= 60	0.275
WBC (per mm <sup>3</sup> ) [Med. (min-max)]	10800 (2900-34000)	10000 (6500-34000)	10800 (2900-32000)	0.264
Neutrophils (per mm <sup>3</sup> ) [Med. (min-max)]	8500 (300-30000)	8150 (4100-29000)	8600 (300-30000)	0.429
Eosinophils (per mm <sup>3</sup> ) [Med. [min-max]]	100 (50-3900)	100 (50-500)	100 (50-3900)	0.425
Hemoglobin (g/dL) [Med. (min- max)]	12.0 (8.6-20.0)	12.9 (9.2-17.0)	12.0 (8.6-20.0)	0.204
Platelets (x10 <sup>3</sup> per mm <sup>3</sup> ) [Med. (min-max)]	314000 (40000- 721000)	300000 (149000- 721000)	324000 (40000- 675000)	0.390
C-reactive protein (mg/dL) [Med. (min-max)]	6.70 [0.05-42.00]	3.85 [0.53-42.00]	7.90 [0.05-34.00]	0.314
Length of hospital stay (days) [Med. (min-max)]	10 (3-44)	8 (3-20)	12 (3-44)	0.006

BMI: Body mass index, F: Female, FEV<sub>1</sub>: Forced expiratory volume in 1 second, FVC: Forced vital capacity, M: Male, n/a: Not applicable, WBC: White blood cell, Mann-Whitney U Test used continue variable, Chi-squared test used categorical variable.

**Table 2. Classification of patients according to sputum culture**

	n (%)
<b>Group A</b>	
<i>Haemophilus influenzae</i>	15 (12.6)
<i>Streptococcus pneumoniae</i>	5 (4.2)
<i>Moraxella catarrhalis</i>	2 (1.7)
<b>Group B</b>	
<i>Pseudomonas aeruginosa</i>	59 (49.6)
<i>Acinetobacter baumannii</i>	12 (10.1)
<i>Klebsiella pneumoniae</i>	8 (6.7)
Gram negative enteric bacillus	6 (5.0)
<i>Escherichia coli</i>	6 (5.0)
<i>Stenotrophomonas maltophilia</i>	3 (2.5)
Methicillin-resistant <i>Staphylococcus aureus</i>	2 (1.7)
Gram negative non-fermentative bacillus	1 (0.8)

Male sex was more common in Group B. Male sex increased the risk of resistant microorganism by 4.4 folds (95% CI= 1.5-13.0). A history of exacerbation was similar; however, number of exacerbations since last year was higher in group B. A cut-off value of >5 exacerbations was found to be discriminative for being in Group B (AUC= 0.642; 95% CI= 0.548-0.727; p= 0.021). Odds ratio of >5 exacerbations was 8.5 (95% CI= 1.09-66.4). Although a history of hospitalization was similar between groups,

number of hospitalizations since last year was higher in Group B. A cut-off value of >1 hospitalization was found to be discriminative for being in Group B (AUC= 0.662; 95% CI= 0.569-0.746; p= 0.008). Odds ratio of >1 hospitalization was 3.0 (95% CI= 1.11-8.5). The patients in group B stayed at hospital almost six days longer. A cut-off value of >11 days was found to be discriminative for being in Group B (AUC= 0.687; 95% CI= 0.596-0.769; p< 0.001). Odds ratio of >11 days of hospitalization was 6.4 (95% CI= 1.79-23.2) (Table 3). In multivariate logistic regression analysis, only age >61 (HR= 4.8; 95% CI= 1.7-13.6; p= 0.003) was found to be independent risk factor for presenting resistant microorganisms (Table 4).

## DISCUSSION

Exacerbations are related to mortality in COPD. Severe exacerbations result in a case-fatality rate of 15.6% (11.4-19.0%), which seems to be higher in certain populations<sup>[4]</sup>. Especially, the presence of multidrug resistant microorganisms increases the risk of exacerbations and mortality<sup>[7]</sup>. Prior use of antibiotics, a history of endotracheal intubation, corticosteroid use, and severely affected lung function are the risk factors for severe exacerbations related to multidrug resistant microorganisms<sup>[8]</sup>. In our study, we found that multidrug resistant microorganisms were commonly observed in patients who were

**Table 3. Univariate analysis of the parameters**

Grup B/A	Odds Ratio	%95 CI Lower Upper	p
Gender (Male/Female)	4.47	1.53-13.05	0.008
Age (>61/≤61)	4.54	1.71-12.04	0.003
Number of attacks in the last year (>5/≤5)	8.52	1.09-66.43	0.034
Number of hospitalizations in the last year (>1/≤1)	3.08	1.11-8.54	0.046
Length of hospital stay (>11)	6.40	1.79-23.2	0.001

**Table 4. Multivariate logistic regression analysis of the parameters**

Grup B/A	Odds Ratio	%95 CI Lower - Upper	p
Sex (Male/Female)	2.93	0.90-9.50	0.073
Age (>61/≤61)	4.83	1.71-13.64	<b>0.003</b>
Number of attacks in the last year (>5/≤5)	8.20	0.99-67.77	0.051
Constant (-0.518).			

hospitalized for severe COPD exacerbation. This finding pushes us to question the optimal initial antibiotic regimen for severe COPD exacerbations, which should offer a broader spectrum in some patients with certain risk factors. In our study, the factors related to increased risk for multidrug resistant microorganisms were age over 61 years, male gender, a history of hospitalization since last year, total number of exacerbations and length of hospital stay. Yet, only age was found as an independent risk factor.

Among multidrug resistant microorganisms *Pseudomonas* and *Acinetobacter* species were most observed. *P. aeruginosa* is isolated in up to 15% of general COPD population in cross-sectional time points; the frequency is higher in severe disease<sup>[9,10]</sup>. However, the risk of *P. aeruginosa* colonization seems to increase in time. In a cohort by Jacobs et al, 40% of the cases with COPD have been colonized by *P. aeruginosa*<sup>[7]</sup>. Gallego et al. have found the prevalence as 34.7% in severe COPD patients<sup>[11]</sup>. In our study, *P. aeruginosa* was isolated in 59 (49.6%) patients. It seems to be higher than the data in cross-sectional studies; however, might be concluded as relevant when obtaining of sputum cultures in exacerbation of severe disease were considered. The conclusion would be similar in case of *A. baumannii*, which was isolated in 12 (10.1%) of the cases. *A. baumannii* is a microorganism which is not uncommon in infectious COPD exacerbations. In a study by Grochowalska et al., the microorganism has been isolated in 2.5% of the patients with COPD exacerbations. The frequency is remarkable as the calculated mortality related to this microorganism is reported as 29%. The authors have concluded that *A. baumannii* should be considered in selecting initial antibiotic regimen in patients experiencing severe COPD exacerbation<sup>[12]</sup>. When compared with our data, the risk of multidrug resistant microorganism in certain populations with COPD is not neglectable, hence should be considered in choosing initial antibiotic regimen.

The main point should be defining the specific sub-populations with increased risk of multidrug resistant microorganisms. There are several data on certain risk factors. Age is one of the suspe-

cted risk factors. In an observational study of a huge number of cases, the risk of *P. aeruginosa* has been found to be higher in older patients (71 vs 69 years,  $p < 0.0001$ )<sup>[6]</sup>. However, these results are shared by other studies<sup>[7,11,13,14]</sup>. The data in the literature regarding sex as a possible contributing factor for presence of resistant microorganisms have shown no relation<sup>[6,14,15]</sup>. In our study, age over 61 years was found to be an independent risk factor for multidrug resistant microorganism. Inconsistency of different results may be related to patient selection.

In their study, Eklöf et al. have reported that prior hospitalization for exacerbation of COPD since last year, is a clear factor for resistant microorganisms and mortality [adjusted HR= 2.7 (2.3-3.4);  $p < 0.0001$ ]<sup>[6]</sup>. *P. aeruginosa* and multidrug resistant microorganisms also increase readmission rates after hospitalization, which increases total number of hospitalizations per year<sup>[15,16]</sup>. So, patients with resistant microorganisms might have higher number of exacerbations and hospitalizations per year. Garcia-Vidal et al. have reviewed the data of 188 patients and showed that admission and hospital admission were higher in *P. aeruginosa* affected individuals<sup>[13]</sup>. Murphy et al. have shown no increase in exacerbations between patients with or without *P. aeruginosa*<sup>[17]</sup>. Our study showed that the risk of multidrug resistant microorganism increases when a COPD patient was a frequent exacerbator with more than five episodes and who required more than one hospitalization. This may be related to more severe disease, increased antibiotic use or higher systemic corticosteroid use for each hospitalization. Nseir et al. have reported on the importance of previous antibiotic treatment. The risk of multidrug resistant microorganism was higher in patients with a history of previous antibiotic use and previous endotracheal intubation<sup>[8,18]</sup>. They have also shown that inappropriate antibiotic use was common in patients with multidrug resistant organisms.

There are several limitations of this study. First, the number of the cases was low, which may be related to confounding results on some variables with higher Odds ratio but lack of statistical significance. There are some reports

on short term colonization of multidrug resistant microorganism which may be a factor to question the importance of culture results<sup>[9]</sup>. Although the results of culture methods in this study were in consistence with clinical features of the cases, we do not have control cultures to rule-out short-term colonization.

## CONCLUSION

Proposed risk factors for isolation of multidrug resistant microorganism in patients hospitalized with COPD exacerbations should be considered when choosing initial antibiotic regimen. Obtaining sputum cultures before initiating antibiotics should be warranted.

## ETHICS COMMITTEE APPROVAL

This study approval was obtained from XXX (Decision No: 19-25, Date: 09.04.2021).

## CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

## AUTHORSHIP CONTRIBUTIONS

Concept and Design: GP, MB

Data Collection or Processing: GŞ, AA

Analysis/Interpretation: AA, GŞ

Literature Search: DSU, GP

Writing: FG, DSU

Final Approval: MB, FG

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