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ORIGINAL RESEARCH

Factors Associated with Initial Treatment Failure in Inpatients with Exacerbation of Chronic Obstructive Pulmonary Disease: A Cohort Study

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Purpose: Some patients do not respond to initial therapy for exacerbation of chronic obstructive pulmonary disease (ECOPD), resulting in treatment failure that requires antimicrobial changes or advanced therapies. Appropriate treatment is possible if patients at a high risk of treatment failure at the start of treatment are properly identified. Therefore, this study examined the factors associated with initial treatment failure in patients with ECOPD.

Patients and Methods: We conducted a cohort study involving patients with ECOPD admitted to our hospital. The primary outcome was initial treatment failure, defined as a composite of treatment intensification for ECOPD and in-hospital mortality. Uni- and multivariate analyses were performed to identify the factors associated with initial treatment failure.

Results: The analysis included data of 152 patients with a mean age of 76±8 years (mean±standard deviation); 81% of them were male patients. Treatment failure occurred in 26 (17%) patients. These included nine, two, one, and 14 patients who changed antimicrobial agents, received additional non-invasive positive pressure ventilation therapy due to non-improvement or symptom exacerbation, received additional invasive positive pressure ventilation therapy, and died in the hospital, respectively. Using multivariable analysis, home oxygen therapy (odds ratio, 5.335; 95% confidence interval, [1.542–18.457]), neutrophil count ≥7000 cells/μL (3.550; [1.007–12.519]), and acidemia (3.129; [1.009–9.698]) were significant factors associated with treatment failure. In patients treated with narrow-spectrum antibiotics as the initial antibacterial therapy, the treatment failure rate in patients receiving home oxygen therapy was significantly higher than in those receiving none.

Conclusion: Home oxygen therapy, high neutrophil count, and acidemia on admission were risk factors for treatment failure. Particularly, patients receiving home oxygen therapy were at a higher risk of treatment failure with the use of narrow-spectrum antibiotics.

Keywords: home oxygen therapy, acidemia, neutrophils, antibacterial

Introduction

Exacerbation of chronic obstructive pulmonary disease (ECOPD), such as symptom enhancement, requires additional treatment for stable management. ECOPD requiring hospitalization occurs in 15–31% of patients with chronic obstructive pulmonary disease (COPD).[1,2] The in-hospital mortality of patients with ECOPD is 2.6–20.1%;[3] therefore, ECOPD requiring hospitalization has a poor prognosis.

Antimicrobials, bronchodilators, and steroids are the basic treatments of ECOPD. However, cases wherein initial treatment is unsuccessful exist. In such cases, antimicrobial agents may need to be changed, advanced medical care such as ventilation or intensive care unit (ICU) management may be required, or death in hospital might occur. Initial treatment failure rates are 10% and 15% at the three- and seven-day admission assessments, respectively.[4,5] If patients at

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a high risk of initial treatment failure are identified at the start of initial treatment, they may be able to receive appropriate treatments.

Many studies have reported on factors and comorbidities associated with in-hospital mortality during ECOPD and readmission.[3,6] Various outcomes have been used to evaluate the effectiveness of treatment in patients with ECOPD.[7] The composite outcome of intensified treatment, including antimicrobial change and ventilatory management, and in-hospital mortality is a high consensus outcome for determining the effectiveness of treating ECOPD.[8,9] Research using the composite outcome can reveal factors that affect the effectiveness of initial treatment as well as the factors causing death, leading to improved treatment of ECOPD. However, few reports have examined the factors associated with the composite outcome of antimicrobial changes, ventilatory management, and in-hospital mortality after the initial treatment of hospitalized patients with ECOPD.[5]

Therefore, to select patients at a high risk of treatment failure at the start of initial treatment, this study examined the factors associated with initial treatment failure in patients hospitalized for ECOPD.

Methods

Study Design

This study is a cohort study based on a review of medical records and an exploratory analysis of risk factors.

Patients

This observational study enrolled patients diagnosed with ECOPD who were admitted to the Department of Allergology and Respiratory Medicine at Showa Medical University Hospital between January 1, 2013, and December 31, 2019. Respiratory specialists diagnosed patients with COPD and ECOPD according to the Japanese Respiratory Society Guidelines for the Management of COPD.[10] The diagnostic criteria for COPD included exposure factors such as long-term smoking, post-bronchodilator forced expiratory volume in one second (FEV_1) to forced vital capacity ratio <0.7, and exclusion of other diseases that might cause airflow obstruction.[10,11] ECOPD is characterized by increased shortness of breath, cough, and sputum production, and appearance or intensification of chest discomfort, which requires a change in therapy.[10,11] The exclusion criteria were patients admitted owing to treatment of lung cancer, patients hospitalized for less than one day, patients transferred from another hospital after initial inpatient treatment of ECOPD, patients whose primary treatment during hospitalization was of heart failure and severe infection such as sepsis.

Ethics

This study was conducted in accordance with the principles of the Declaration of Helsinki. This study was approved by the Ethics Committee of Showa Medical University School of Pharmacy, Japan (No.: 373), which waived the requirement for informed consent owing to the nature of the study. The patients were informed on the website of the Showa Medical University Hospital that they could opt out of using their data for research purposes. To protect personal information, it was processed so that individuals could not be identified and then used appropriately for research.

Treatment

Respiratory specialists treated patients during hospitalization for ECOPD according to the Japanese Respiratory Society guidelines for the diagnosis and treatment of COPD,[10] based on the ABC approach using antibacterial agents, bronchodilators, and corticosteroids.

Data Collection

The following patient information was collected from medical records: age, sex, body weight, body mass index (BMI), smoking history, pack-year, comorbidities (bronchiectasis, heart failure, diabetes, and asthma), FEV_1 (% predicted), global initiative for chronic obstructive lung disease (GOLD) grade (GOLD 1: $FEV_1 \geq 80\%$, GOLD 2:$79\% \geq FEV_1 \geq 50\%$, GOLD 3:$49\% \geq FEV_1 \geq 30\%$, GOLD 4:$30\% > FEV_1$),[11] hospitalization due to ECOPD in the previous year, and treatment received for stable phase COPD (home oxygen therapy, inhaled corticosteroid, long-acting muscarinic antagonist, and

long-acting β_2-agonist). Asthma was diagnosed according to the guidelines.[12] Comorbidities included those diagnosed at other hospitals.

The following patient data were also collected at admission: dyspnea, respiratory rate, heart rate, systolic blood pressure, diastolic blood pressure, body temperature, SpO_2, arterial blood gas analysis data (pH, $PaCO_2$, PaO_2, HCO_3^-), and blood test results (white blood cell, eosinophil, neutrophil, lymphocyte counts, hemoglobin, albumin, C-reactive protein, glucose, creatinine, estimated glomerular filtration rate, blood urea nitrogen, sodium, potassium, and chloride levels).

The data obtained during hospitalization included the treatment received for ECOPD (antibiotics, bronchodilators, corticosteroids, and mechanical ventilation), admission to intensive care unit, and length of hospital stay. The initial dose of corticosteroids and increase in corticosteroids dose were collected. The dose of corticosteroids was expressed in prednisone equivalents, as follows: prednisone (4 mg) = methylprednisone (5 mg) = hydrocortisone (20 mg) = betamethasone (0.6 mg).[13]

Outcome

The primary outcome was initial treatment failure, which was defined as a composite of treatment intensification for ECOPD and in-hospital mortality. Initial treatment was defined as treatment of ECOPD initiated within 24 h after admission. Therapy intensification was defined as a switch from narrow-spectrum antibiotics to broad-spectrum antibiotics and addition of non-invasive mechanical ventilation (NPPV) or invasive mechanical ventilation (IPPV) because of non-improvement in exacerbation symptoms. Narrow-spectrum antibiotics, including intravenous ceftriaxone, levofloxacin, and sulbactam/ampicillin, were defined as the recommended antimicrobial agents for mild cases during inpatient treatment.[14] Broad-spectrum antibiotics, intravenous tazobactam/piperacillin, meropenem, doripenem, cefepime, and ceftazidime, were defined as the recommended antimicrobial agents for severe cases.[14] Increase in corticosteroids dose was not included in the treatment failure because the patient characteristics were considered different.

Statistical Analysis

Sample Size

We calculated that the required sample size was 131 patients to detect an odds ratio (OR) of 2.0, with 80% power at a significance level of 0.05, using a logistic regression model[15] and assuming an initial treatment failure rate of 15% based on a previous study.[5]

Definitions

Continuous variables were categorized based on the clinical definitions. Based on the World Health Organization definition, patients were allocated into two groups according to the cutoff values for BMI (underweight, 18.5 kg/m^2) and hemoglobin levels (anemia, <13 g/dL in men and <12 g/dL in women). Based on the definition of the phenotype marker of ECOPD, the patients were categorized into two groups according to the cutoff eosinophil and neutrophil counts of 2% and 7000 cells/μL, respectively.[16] Based on the other blood test results, the patients were divided into two or three groups according to the upper and/or lower limit of the reference range for clinical laboratory values established by the Japanese Committee For Clinical Laboratory Standards.[17] Patients were divided into two groups based on median age (77 years).

Risk Factors of Initial Treatment Failure

Continuous data are expressed as mean±standard deviation or median (min-max), and categorical data are expressed as numbers and percentages. Categorical variables were compared between patients with and without treatment failure using the chi-squared test or Fisher's exact test. Multivariate logistic regression analysis was performed using the significant factors from the univariate analysis. No correlations were found between these factors. A stepwise selection method was used for identifying the factors associated with initial treatment failure in patients with ECOPD. $P<0.05$ was considered statistically significant. All statistical analyses were performed using the SPSS software version 28 (IBM, Tokyo, Japan). Missing values were not imputed.

Relationship Between Antimicrobial Agents and the Risk Factors

To gain an insight into the selection of antimicrobial agents, we assessed the factors contributing to treatment failure for each type of antimicrobial agent used for the initial treatment. Antimicrobial agents were classified into two categories: narrow- and broad-spectrum. We stratified patients according to the type of antimicrobial agent they received and evaluated the association between the factors of treatment failure determined by multivariate analysis and outcomes using the chi-square test or Fisher's exact test.

Results

Patients

Patient characteristics are presented in Table 1. Ten patients were excluded from the 162 patients; data of 152 patients were included in the final analysis (Figure 1). The mean age was 76±8 years, and 123 (81%) were male patients. The rates of patients with bronchiectasis, heart failure, diabetes, and asthma were 2%, 16%, 20%, and 23%, respectively. Patients with GOLD grade 3 or higher were 82 (61%). Thirty-five cases (23%) had a history of hospitalization for ECOPD within the past year. Fifty-five (36%) patients were treated with home oxygen therapy for stable-phase COPD. The mean pH and neutrophil count were 7.383±0.103 and 8.2±4.7 ($\times 10^3$ cells/μL), respectively. As an initial treatment of ECOPD, 135 (89%), 144 (95%), and 138 (91%) patients received antibacterial agents, bronchodilators, and corticosteroids, respectively. All patients received antimicrobials, bronchodilators, or corticosteroids.

Table 1 Characteristics of Hospitalized Patients with Exacerbation of Chronic Obstructive Pulmonary Disease (ECOPD)

Variables	n (%), Mean±Standard Error, or Median (Min–Max) n=152			
Age (years)	152	76	±	8
Sex, male	152	123		(81)
BMI (kg/m²)	151	20.4	±	4.4
Smoking history	151	149		(99)
Pack-year	146	65	±	39
Comorbidities				
Bronchiectasis	152	3		(2)
Heart failure	152	24		(16)
Diabetes	152	30		(20)
Asthma	152	35		(23)
FEV_1(% predicted)	124	49.2	±	21.9
GOLD grade	135			
1		14		(10)
2		39		(29)
3		55		(41)
4		27		(20)
Hospitalized ECOPD in the previous year	152	35		(23)
Treatment of stable phase COPD				
Home oxygen therapy	152	55		(36)
ICS	152	50		(33)
Without both of LAMA and LABA	152	38		(25)
LAMA or LABA		30		(20)
LAMA+LABA-ICS		45		(30)
LAMA+LABA+ICS		39		(26)
Oral systemic corticosteroids at admission	152	10		(7)
Prednisone equivalent (mg/day)	10	20		(3–30)
Dyspnea	152	140		(92)
Respiratory rate (breaths/min)	142	24	±	6

(*Continued*)

Table 1 (Continued).

Variables	n (%), Mean±Standard Error, or Median (Min–Max) n=152			
Heart rate (beats/min)	151	100	±	20
Systolic blood pressure (mmHg)	152	134	±	28
Diastolic blood pressure (mmHg)	152	79	±	19
Body temperature (°C)	151	37.0	±	1.0
SpO_2 (%)	151	92.2	±	6.7
Arterial blood gas analysis				
pH	123	7.383	±	0.103
$PaCO_2$ (mmHg)	124	51.3	±	21.7
PaO_2 (mmHg)	123	82.8	±	39.6
HCO_3^-(mEq/L)	122	28.4	±	7.3
Blood test data				
WBC (×10^3 cells/μL)	151	10.2	±	5.3
Eosinophils (%)	103	1.5	±	1.7
Neutrophils (×10^3 cells/μL)	148	8.2	±	4.7
Lymphocytes (×10^3 cells/μL)	148	1.2	±	1.1
Hemoglobin (g/dL)	150	13.2	±	2.2
Albumin (g/dL)	145	3.7	±	0.5
C-reactive protein (mg/dL)	152	7.5	±	9.1
Glucose (mg/mL)	152	141	±	51
Creatinine (mg/mL)	152	0.88	±	0.79
eGFR (mL/min/1.73m^2)	152	78.0	±	32.3
Blood urea nitrogen (mg/dL)	151	21.2	±	13.7
Sodium (mEq/L)	152	137.7	±	4.9
Potassium (mEq/L)	149	4.3	±	0.7
Chloride (mEq/L)	152	100.2	±	5.4
Initial therapy for ECOPD				
Antibiotics	152	135		(89)
Bronchodilators	152	144		(95)
Corticosteroid	152	138		(91)
Prednisone equivalent (mg/day)	152	40		(0–206)
Intensive care unit	152	9		(6)
Invasive mechanical ventilation	152	7		(5)
Non-invasive mechanical ventilation	152	32		(21)

Note: Data are presented as mean±standard deviation or n (%).

Abbreviations: ECOPD, exacerbation of chronic obstructive pulmonary disease; BMI, body mass index; FEV_1, forced expiratory volume in one second; GOLD, global initiative for chronic obstructive lung disease; LAMA, long-acting muscarinic antagonist; LABA, long-acting β-agonist; ICS, inhaled corticosteroid; WBC, white blood cell; eGFR, estimated glomerular filtration rate.

Outcome

Treatment failure occurred in 26 patients (17%), comprising nine, two, one, and 14 patients who changed their antimicrobial agents, received additional NPPV, received additional IPPV, and died during hospitalization, respectively (Table 2). The median time to treatment failure was 8 days (range, 1–58), and the median length of hospital stay was 11 days (range, 1–163). Of the 138 patients, four patients required an increase in corticosteroid dose on the second, fourth, fifth, and ninth days, respectively. Two of these four patients died in hospital.

Comparison Between Patients with and without Treatment Failure

Table 3 compares the characteristics of patients with and without treatment failure. The rates of patients with low BMI (58% vs 33%, P=0.017), history of hospitalization due to ECOPD within one-year (42% vs 19%, P=0.010), home oxygen therapy for stable phase of COPD (65% vs 30%, P=0.001), acidemia (52% vs 26%, P=0.014), hypercarbia (71% vs 44%, P=0.018), high neutrophil count (77% vs 51%, P=0.015), low hemoglobin (62% vs 36%, P=0.017), low albumin (50% vs

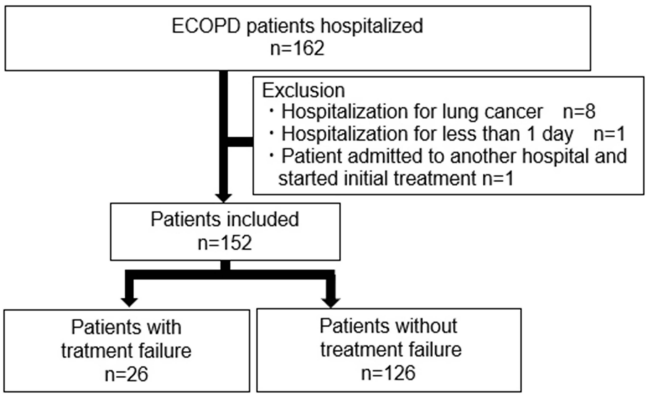

Figure 1 Study population flowchart.

28%, P=0.037), high K (20% vs 7%, P=0.044), and low Cl levels (73% vs 51%, P=0.038) were significantly higher in the non-treatment failure group than that in the treatment failure group. Bronchiectasis, heart failure, diabetes, asthma, and COPD severity were not significantly associated with treatment failure.

Risk Factors of Initial Treatment Failure

Logistic regression analysis revealed that the factors for initial treatment failure were home oxygen therapy for stable phase COPD (OR, 5.335; 95% confidence interval [CI], 1.542–18.457; P=0.008), high neutrophil count (≥7000 cells/μL) (OR, 3.550; 95% CI, 1.007–12.519; P=0.049), and acidemia (OR, 3.129; 95% CI, 1.009–9.698'; P=0.048) (Table 4).

Relationship Between Antimicrobial Agents and the Risk Factors

Overall, the type of antimicrobial agent used during the initial treatment was not significantly associated with treatment failure (Table 3). In the patient population treated with narrow-spectrum antibiotics as the initial antibacterial therapy, the treatment failure rate in those receiving home oxygen therapy was significantly higher than that in participants receiving none (69% vs 24%, P<0.001) (Table 5). In patients using broad-spectrum antibiotics, neutrophil count (≥7000 cells/μL) was significantly associated with treatment failure (Table 5). Furthermore, patients using home-based oxygen therapy tended to switch from narrow- to broad-spectrum antibiotics (Table 6).

Table 2 Clinical Outcomes of Exacerbation of Chronic Obstructive Pulmonary Disease (ECOPD) Evaluated During Hospitalization

Variables	Number (%) n=152	Length (Days) Median (Min-Max)
Treatment failure	26 (17.1)	8 (1–58)
Intensification of treatment	12 (7.9)	7 (1–23)
Change from narrow-spectrum antibiotics to broad-spectrum antibiotics	9 (5.9)	7 (1–23)
Addition of NPPV	2 (1.3)	7.5 (6–9)
Addition of IPPV	1 (0.7)	2 –
Deaths from any cause	14 (9.2)	9 (1–58)
Length of stay in hospital	–	11 (1–163)

Notes: Fourteen deaths occurred without intensification of treatment. Three patients died after changing antimicrobials and two died after the addition of non-invasive mechanical ventilation (NPPV). The total number of deaths during hospitalization was 19 (12.5%). Narrow-spectrum antibiotics, including intravenous ceftriaxone, levofloxacin, and sulbactam/ampicillin, were defined as the recommended antimicrobial agents for mild cases during inpatient treatment. Broad-spectrum antibiotics are defined as the recommended antimicrobial agents for severe cases, including intravenous tazobactam/piperacillin, meropenem, doripenem, cefepime, and ceftazidime.
Abbreviations: ECOPD, exacerbation of chronic obstructive pulmonary disease; NPPV, non-invasive mechanical ventilation; IPPV, invasive mechanical ventilation.

Table 3 Comparison of Patient Characteristics Between Hospitalized Exacerbation of Chronic Obstructive Pulmonary Disease (ECOPD) Patients with Treatment Failure and Without Treatment Failure

Variables	With Treatment Failure n=26	Without Treatment Failure n=126	P Value
Age (years), ≥77	16 (62)	63 (50)	0.284
Sex, male	24 (92)	99 (79)	0.168
BMI (kg/m²), <18.5	15 (58)	41 (33)	0.017
Smoking history	26 (100)	123 (98)	1.000
Pack-year	53 (1–205)	58 (10–150)	0.225
Comorbidities			
Bronchiectasis	1 (4)	2 (2)	0.433
Heart failure	3 (12)	21 (17)	0.768
Diabetes	5 (19)	25 (20)	0.943
Asthma	3 (12)	32 (25)	0.126
GOLD grade			
1	3 (17)	11 (9)	0.459
2	5 (28)	34 (29)	
3	5 (28)	50 (43)	
4	5 (28)	22 (19)	
Hospitalized ECOPD in the previous year	11 (42)	24 (19)	0.010
Treatment of stable phase COPD			
Home oxygen therapy	17 (65)	38 (30)	0.001
ICS	12 (46)	38 (30)	0.114
Neither LAMA nor LABA	3 (12)	35 (28)	0.220
LAMA or LABA	6 (23)	24 (19)	
LAMA+LABA	17 (65)	67 (53)	
Oral systemic corticosteroids at admission	0 (0)	10 (8)	0.212
Dyspnea	25 (96)	115 (91)	0.692
Respiratory rate (breaths/min), ≥30	6 (26)	23 (19)	0.572
Heart rate (beats/min)			
≤59	0 (0)	1 (1)	1.000
60–99	13 (50)	63 (50)	
≥100	13 (50)	61 (49)	
Systolic blood pressure (mmHg)			
≤100	3 (12)	10 (8)	0.830
101–139	14 (54)	69 (55)	
≥140	9 (35)	47 (37)	
Diastolic blood pressure (mmHg)			
≤60	5 (19)	19 (15)	0.862
61–89	15 (58)	78 (62)	
≥90	6 (23)	29 (23)	
Body temperature (°C), ≥37.5	6 (23)	39 (31)	0.410
SpO_2 (%), ≤88	5 (19)	22 (18)	0.785
Arterial blood gas analysis			
pH, <7.35	12 (52)	26 (26)	0.014
$PaCO_2$ (mmHg), >45	17 (71)	44 (44)	0.018
PaO_2 (mmHg), ≤55	4 (17)	10 (10)	0.295
HCO_3^- (mEq/L), >26	16 (67)	50 (51)	0.168

(*Continued*)

Table 3 (Continued).

Variables	With Treatment Failure n=26	Without Treatment Failure n=126	P Value
Blood test data			
WBC (×10^3 cells/μL), >9	17 (65)	62 (50)	0.143
Eosinophils (%), ≥2	3 (16)	23 (27)	0.388
Neutrophils (×10^3 cells/μL), ≥7	20 (77)	62 (51)	0.015
Hemoglobin (g/dL), male <13, female <12	16 (62)	45 (36)	0.017
Albumin (g/dL), <3.5	11 (50)	34 (28)	0.037
C-reactive protein (mg/dL), >0.14	23 (89)	113 (90)	0.739
Glucose (mg/mL), ≥109	16 (62)	91 (72)	0.277
Creatinine (mg/mL), >1.2	4 (15)	13 (10)	0.494
eGFR (mL/min/1.73m^2), <30	2 (8)	5 (4)	0.343
Blood urea nitrogen (mg/dL), ≥22	9 (35)	36 (29)	0.555
Sodium (mEq/L), ≥145	4 (15)	6 (5)	0.069
Potassium (mEq/L), >5.1	5 (20)	8 (7)	0.044
Chloride (mEq/L), ≤101	19 (73)	64 (51)	0.038
Initial therapy for ECOPD			
Antibiotics	25 (96)	110 (87)	0.308
Narrow-spectrum	16 (64)	71 (67)	0.683
Broad-spectrum	9 (36)	33 (32)	
Bronchodilators	25 (96)	119 (94)	1.000
Corticosteroid	25 (96)	113 (90)	0.466
Prednisone equivalent (mg/day)	50 (0–100)	40 (0–206)	0.057

Note: Data are presented as n (%).

Abbreviations: ECOPD, exacerbation of chronic obstructive pulmonary disease; BMI, body mass index; GOLD, global initiative for chronic obstructive lung disease; ICS, inhaled corticosteroid; LAMA, long-acting muscarinic antagonist; LABA, long-acting β-agonist; WBC, white blood cell; eGFR, estimated glomerular filtration rate. Narrow-spectrum antibiotics; intravenous ceftriaxone, levofloxacin, and sulbactam/ampicillin. Broad-spectrum antibiotics; intravenous tazobactam/piperacillin, meropenem, doripenem, cefepime, and ceftazidime.

Table 4 Multivariable Analysis of Risk Factors for Treatment Failure for the Initial Treatment of Hospitalized Patients with Exacerbation of Chronic Obstructive Pulmonary Disease (ECOPD)

Variables	Odds Ratio	95% Confidence Interval		P Value
Home oxygen therapy	5.335	1.542	18.457	0.008
Neutrophils (≥7000 cells/μL)	3.550	1.007	12.519	0.049
pH (<7.35)	3.129	1.009	9.698	0.048

Notes: BMI (<18.5), hospitalized ECOPD in the previous year, home oxygen therapy, pH (<7.35), $PaCO_2$ (>45 mmHg), neutrophil count (≥7000 cells/μL), hemoglobin (male<13 g/dL, female<12 g/dL), albumin (<3.5 g/dL), K (>5.1 mEq/L), and Cl (≤101 mEq/L) were subjected to multivariable analysis.

Abbreviations: ECOPD, exacerbation of chronic obstructive pulmonary disease; BMI, body mass index.

Discussion

In this study, we found that the home oxygen therapy for stable phase COPD, high neutrophil count (≥7000 cells/μL), and acidemia were factors associated with initial treatment failure in patients with ECOPD requiring hospitalization. Particularly, patients receiving home oxygen therapy are at a higher risk of treatment failure with the use of narrow-spectrum antibiotics. To the best of our knowledge, this is the first study to identify the factors associated with the composite outcome of antimicrobial change, intensified therapy, and in-hospital mortality. These factors may be indicators for selecting patients at high risk of treatment failure at the start of initial treatment. Treatment considering the possibility of treatment failure might lead to promptly intensified therapy in patients with these factors.

Table 5 Relationship Between Antimicrobial Agents and the Risk Factors

Variables	With Treatment Failure n=16	Without Treatment Failure n=71	P Value
Narrow-spectrum antibiotics group			
Home oxygen therapy	11 (69)	17 (24)	<0.001
Neutrophils (≥7000 cells/μL)	11 (69)	36 (52)	0.230
pH (<7.35)	6 (43)	12 (21)	0.166
Broad-spectrum antibiotics group			
Home oxygen therapy	6 (67)	13 (39)	0.257
Neutrophils (≥7000 cells/μL)	9 (100)	20 (63)	0.039
pH (<7.35)	6 (75)	10 (39)	0.110

Notes: Data are presented as n (%). Narrow-spectrum antibiotics; intravenous ceftriaxone, levofloxacin, and sulbactam/ampicillin. Broad-spectrum antibiotics; intravenous tazobactam/piperacillin, meropenem, doripenem, cefepime, and ceftazidime.

Table 6 Relationship Between the Risk Factors and Antibiotics Change in the Narrow-Spectrum Antibiotics Group

Variables	With Antibiotics Change n=9		Without Antibiotics Change n=78		P Value
Home oxygen therapy	9	6 (67)	78	22 (28)	0.028
Neutrophils (≥7000 cells/μL)	9	6 (67)	76	41 (54)	0.725
pH (<7.35)	8	4 (50)	63	14 (22)	0.189

Notes: Data are presented as n (%). Antibiotic changes were defined as a change from narrow-spectrum antibiotics (intravenous ceftriaxone, levofloxacin, and sulbactam/ampicillin) to broad-spectrum antibiotics (intravenous tazobactam/piperacillin, meropenem, doripenem, cefepime, and ceftazidime).

Home oxygen therapy is used in patients with COPD whose respiratory function has declined to a stable level and who have hypoxemia. The presence or absence of home oxygen therapy can be confirmed even in patients transported to the emergency room, and this information is objective and does not depend of the patient's subjective complaints. In this study, home oxygen therapy was associated with hypercarbonemia at admission (r=0.37, P<0.0001). Therefore, patients receiving home oxygen therapy might have died or required further treatment after the initial therapy due to their impaired respiratory function during the stable phase and the severity of exacerbations. The use of long-term oxygen therapy was reported to be approximately twice as common in the group of patients who died in the hospital as in those who survived,[18] which is consistent with the results of this study. Therefore, the presence or absence of home-based oxygen therapy is a versatile and useful indicator for treatment failure, including in-hospital mortality.

A cause of neutrophilia is bacterial infection. Among patients with severe ECOPD requiring hospitalization, those with neutrophilia have higher rates of ICU admission and in-hospital mortality than do those with eosinophilia.[19] In this study, the in-hospital mortality rate was also higher in patients with neutrophilia than in those with eosinophilia (18.3% [15/82] vs 3.8% [1/26]). Additionally, in patients with ECOPD, the higher the neutrophil count was, the lower the FEV_1 and the more severe the disease were.[20] Thus, patients with bacterial infections were likely to develop severe disease with reduced respiratory function and may have bad outcomes after the initial treatment.

Acidemia reflects ECOPD severity. In addition to chronic respiratory dysfunction, acidemia represents a condition that is not covered by renal compensation, either because of severe hypercarbonemia due to alveolar hypoventilation triggered by infection or other factors or because of renal impairment. Acidemia is a predictor of in-hospital mortality,[18] which is consistent with the results of the present study. Acidemia is also a significant factor associated with prolonged hospitalization in patients with ECOPD.[6] Therefore, the presence of acidemia at admission is a versatile and useful predictor for treatment failure, including in-hospital death.

In patients receiving home oxygen plus therapy, the use of narrow-spectrum antimicrobials is associated with a high risk of treatment failure and a high likelihood of switching to broad-spectrum antimicrobials. Therefore, in patients undergoing home oxygen therapy, the risk of treatment failure may be reduced by selecting broad-spectrum antibiotics as the initial antibacterial agents. The use of broad-spectrum antibiotics in patients with high neutrophil counts at the time of hospitalization has been associated with a higher risk of treatment failure. This may reflect the fact that broad-spectrum antibiotics are selected for the initial treatment of severely ill patients.

In this study, the outcome was defined as a composite of antimicrobial changes, intensification of therapy, and in-hospital mortality. Among patients with ECOPD requiring hospitalization, those with relatively mild illnesses or at low risk of developing a *Pseudomonas aeruginosa* infection received oxygen therapy, bronchodilators, and steroids, plus a narrow-range antibacterial agent as initial therapy.[10,11,14] If the initial treatment was ineffective, the patient was switched to a broad-range antibacterial agent with anti-*Pseudomonas* activity.[14] If this change or initial treatment with anti-*Pseudomonas* antimicrobial agents was ineffective, the patient may have required additional mechanical ventilation and ICU management,[10,11] or it may have resulted in in-hospital death. Therefore, the composite outcome is an indicator for comprehensively evaluating treatment effects in patients with relatively mild-to-severe ECOPD requiring hospitalization. Owing to the need for treating patients with ECOPD of various severities, examining the factors associated with such composite outcomes is of high clinical importance. Additionally, this would allow the examination of factors influencing the therapeutic effects of the initial antimicrobial agents. In patients with these factors, treatment while considering the possibility of treatment failure will be promptly intensified. These findings are expected to improve the overall success rate of ECOPD treatments.

Although studies have examined factors associated with death during hospitalization, reports examining the factors for treatment failure in ECOPD inpatient remain limited.[3] A previous study using a composite outcome was limited to the analysis of outcomes up to seven days after hospitalization based on the recommended duration of antimicrobial and steroid use.[5] Contrarily, the median length of stay in patients with ECOPD has been reported to be 10–16 days.[21,22] Additionally, exacerbation recurrence may occur during hospitalization, prolonging the hospital stay. Because seven days was insufficient to assess outcomes during hospitalization, the entire hospital stay was analyzed in this study.

Previous studies have reported that the coexistence of bronchiectasis, heart failure, diabetes, and asthma is associated with poor prognosis of COPD and readmission due to COPD exacerbation.[6] However, in this study, these comorbidities were not significantly associated with treatment failure of the initial treatment in patients hospitalized for COPD exacerbation. This difference in results is thought to be due to differences in outcomes.

This study had three limitations. First, we did not assess whether self-reported symptoms during the stable phase or disease grade were associated with treatment failure. Since 10% of cases did not have GOLD grade data, we did not analyze the effect of disease grade using the multivariate analysis. Additionally, self-reported symptoms such as the Modified Medical Research Council Dyspnea Scale or COPD assessment test, which are one of the predictors of in-hospital mortality during ECOPD,[18] were rarely recorded in the medical records. Second, we could not adequately investigate the involvement of peripheral blood eosinophil counts. Several reports have indicated that a low eosinophil count is a predictor of in-hospital mortality.[18,23] This study did not show an association between a low eosinophil count and treatment failure, which might have been influenced by the fact that the eosinophil count deficiency rate was 32%. Third, the number of patients was small. Therefore, some findings might have been mere coincidences. Further research is needed to develop predictive model and apply findings of this study in clinical practice.

Conclusion

This study identified home oxygen therapy for stable phase COPD, acidemia, and high neutrophil count (≥7000 cells/μL) at admission as factors of treatment failure for the initial treatment in hospitalized patients with ECOPD. These factors may be indicators for selecting patients at high risk of treatment failure at the start of initial treatment. Additionally, in patients undergoing home-based oxygen therapy, the risk of treatment failure may be reduced by selecting broad-spectrum antimicrobial agents as the initial treatment. Large-scale prospective studies are required to validate these findings.

Abbreviations

BMI, body mass index; CI, confidence interval; ECOPD, exacerbation of chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICU, intensive care unit; IPPV, invasive mechanical ventilation; NPPV, non-invasive mechanical ventilation; OR, odds ratio.

Data Sharing Statement

Data supporting the findings of this study are available upon reasonable request from the corresponding author. The data are not publicly available because of privacy and ethical restrictions.

Ethics Approval

The study was approved by the Ethics Committee of Showa Medical University School of Pharmacy.

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Author Contributions

All authors contributed to the conception, study design, and interpretation of data. NK performed material preparation, data collection, and analysis. NK wrote the first draft of the manuscript. All authors commented on the previous versions of the manuscript. All authors have read and approved the final manuscript, agreed with the journal to which the article has been submitted, and agreed to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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