Factors predictius, pronòstics i resposta inflamatòria del fracàs de tractament a les Aguditzacions de la Malaltia Pulmonar Obstructiva Crònica (AMPOC) i del reingrés als 30 dies de l'alta hospitalària

Mónica Guerrero Pérez

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ORIGINAL RESEARCH

Predicting In-Hospital Treatment Failure (≤7 days) in Patients with COPD Exacerbation Using Antibiotics and Systemic Steroids

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Abstract

Although pharmacological treatment of COPD exacerbation (COPDE) includes antibiotics and systemic steroids, a proportion of patients show worsening of symptoms during hospitalization that characterize treatment failure. The aim of our study was to determine in-hospital predictors of treatment failure (≤7 days). Prospective data on 110 hospitalized COPDE patients, all treated with antibiotics and systemic steroids, were collected; on the seventh day of hospitalization, patients were divided into treatment failure ($n = 16$) or success ($n = 94$). Measures of inflammatory serum biomarkers were recorded at admission and at day 3; data on clinical, laboratory, microbiological, and severity, as well data on mortality and readmission, were also recorded. Patients with treatment failure had a worse lung function, with higher serum levels of C-reactive protein (CRP), procalcitonin (PCT), tumour necrosis factor-alpha (TNF-α), interleukin (IL) 8, and IL-10 at admission, and CRP and IL-8 at day 3. Longer length of hospital stay and duration of antibiotic therapy, higher total doses of steroids and prevalence of deaths and readmitted were found in the treatment failure group. In the multivariate analysis, +1 mg/dL of CRP at admission (OR, 1.07; 95% CI, 1.01 to 1.13) and use of penicillins or cephalosporins (OR, 5.63; 95% CI, 1.26 to 25.07) were independent variables increasing risk of treatment failure, whereas cough at admission (OR, 0.20; 95% CI, 0.05 to 0.75) reduces risk of failure. In hospitalized COPDE patients CRP at admission and use of specific class of antibiotics predict in-hospital treatment failure, while presence of cough has a protective role.

Introduction

Chronic obstructive pulmonary disease (COPD) is a disease with a considerable worldwide prevalence (1) and is characterized by periodic episodes of acute deterioration of symptoms, recognized as exacerbations (2). According to Anthonisen's clinical criteria (2), a COPD exacerbation (COPDE) is defined by a progressive worsening of patients' symptoms and signs (increased dyspnea, increased sputum production and purulence). Although the cause cannot be identified in about one-third of severe COPDE, acute infections of the respiratory tract (viral or bacterial) are considered frequent triggers (3).

Generally, COPDE that require hospitalization have an elevated risk of morbidity (4) and, consequently, considerable disease-related costs (5); in these patients, a prompt outcome with success of treatment is an expected key point (6). In hospitalized COPDE patients, after an increase in dose and frequency of bronchodilators, consensus guidelines recommend systemic steroids for all patients, whereas antibiotics are recommended in patients

Keywords: Chronic obstructive pulmonary disease, disease exacerbation, inflammatory response, predictors, treatment failure

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with signs of airway infections (7,8). Despite inconsistent results (9), antibiotics are frequently prescribed in clinical practice, demonstrating a beneficial effect on reducing the risk of mortality, particularly in severe patients admitted to the intensive care unit (ICU) (9,10). In terms of duration of therapy (11), systemic steroids have proved their efficacy in reducing length of hospital stay (LOS) (12,13), increasing the success of non-invasive mechanical ventilation (NIMV) (14), and improving functional characteristics and symptoms of patients (12,13).

However, a clinical worsening of symptoms defined as treatment failure has been reported in between 10% and 39% of hospitalized COPDE patients treated with both antibiotics and systemic steroids (15–17). The factors predicting treatment failure during hospitalization, however, have not yet been described. The hypothesis of our study is that COPD patients who show treatment failure while receiving adequate treatment have a characteristic clinical and inflammatory pattern that can be detected at the beginning of hospitalization.

The primary aim of our observational study was, therefore, to determine clinical and inflammatory predictors of in-hospital treatment failure in patients with moderate-to-severe COPDE needing a hospitalization; moreover, differences in outcomes including mortality, readmission at 30, 90 days and at 1 year were also examined.

Methods

Study population and definitions

Prospective data on consecutively hospitalized adult patients with COPDE was collected in two tertiary university hospitals in Spain (in a respiratory ward and in a respiratory ICU for the Hospital Clinic, Barcelona and in a general medical ICU for the Hospital La Fe, Valencia); the study period considered was between January 2004 and June 2006. The study was approved by the Ethics Committee of both hospitals (project numbers CEIC 2003/0048 and CEIC 2004/1855 for Hospital La Fe and Hospital Clinic, respectively) and conducted in accordance with good clinical practice and the declaration of Helsinki. Written informed consent was obtained from enrolled patients. In accordance with the guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (7) an expert pneumologist defined the diagnosis and severity of COPD, based on spirometry performed at least 6 months prior to hospital admission in a stable phase.

The presence of a post-bronchodilator ratio between forced expiratory volume in the 1st second (FEV_1) and forced vital capacity (FVC) less than 0.70 confirm the presence of persistent airflow obstruction and then diagnosis of COPD. All COPD patients were considered, independently from severity of airflow obstruction. A threshold of 10 pack-years was considered as a positive smoking habit. Anthonisen's criteria were used to define COPD exacerbation and patients were then classified as type I if patients presented all three symptoms, type II with any two of the three symptoms, and type III if any one of these symptoms was present (2). The severity of COPDE was based on the severity of respiratory symptoms/signs and/or presence of potential indications needing an admission to hospital (7), whereas the choice to use antibiotics and the class of antibiotics used were decided according guidelines for the management of adult lower respiratory tract infections (8). We considered only COPDE patients who were treated with both antibiotics and systemic steroids on admission.

Exclusion criteria

At admission to hospital (day 1), the following patients were excluded: *a)* those with a different diagnosis other than COPD or those with a not confirmed diagnosis of COPD by a spirometry; *b)* those with a documented history of concomitant chronic respiratory conditions (asthma and bronchiectasis); *c)* those with a severe respiratory impairment needing NIMV or admitted directly to ICU; *d)* those with clinical evidence of signs and symptoms of acute heart failure; *e)* those with suspected community-acquired pneumonia (CAP) or health care associated pneumonia (HCAP) or aspiration pneumonia, based on compatible clinical signs and symptoms of lower respiratory tract infection plus a new pulmonary infiltrate by means of chest x-ray on admission to hospital; *f)* those with a diagnosis of active cancer; *g)* those with an immunosuppression due to chemotherapy or HIV; *h)* those with a previous hospitalization for COPDE and/or with domiciliary use of antibiotics or oral steroids in a period of four weeks prior to hospitalization. Moreover, patients treated with antibiotics/systemic steroids only or patients in whom antibiotics/systemic steroids were used in a period after day 1 of hospitalization were also excluded from data collection.

Study end-point

In our study, in-hospital treatment failure was considered the main end-point. By adaptation of previously described criteria (12,15), in-hospital treatment failure was defined by the occurrence in a period of up to 7 days from day 2 of at least one of the following conditions: *a)* need for NIMV or admission to the ICU, indicated according guidelines (7); *b)* clinical persistence of signs of infection after 72 hours of the first line (either empiric of pathogen directed) antibiotic therapy requiring a new course of antibiotic treatment with a different class; *c)* deaths from any causes. In accordance with documented evidence of efficacious length of antibiotic and systemic steroid therapy during COPDE (7,8, 9,11,12), in all enrolled patients, the evaluation of treatment success or failure was established using a comparable period of care of seven days (from day 2 to day 7) with a criteria of success or failure defined at day 7 of hospitalization. Patients with a treatment failure occurring after day 7 of hospitalization were not considered for the study.

Clinical and laboratory measurements

Data on demographic variables, presence of any associated co-morbidities (chronic heart, renal failure, neurologic, non-cirrhotic liver disease, diabetes, and non-active cancer), baseline dyspnea grade evaluated by modified medical research council (mMRC) scale, need for long-term oxygen therapy (LTOT) and domiciliary inhaled bronchodilators (short-acting β_2 agonist [SABA]; long-acting β_2 agonist [LABA]; anticholinergics), inhaled corticosteroids and theophylline were recorded on admission to hospital. Rates of exacerbation and exacerbation requiring hospitalization occurring in the preceding year were also recorded at admission.

Symptoms and signs of acute exacerbation (fever, chills, cough, pleuritic pain, dyspnea, and sputum characteristics), gas analysis variables (pH, partial arterial carbon dioxide pressure-$PaCO_2$, ratio of partial arterial oxygen pressure to fraction of inspired oxygen-PaO_2/FiO_2, serum bicarbonate [HCO^3], and base excess [BE]) and serum laboratory measurements (total leukocytes counts, hematocrit, glucose, creatinine, sodium, potassium, aspartate transaminase-AST, alanine transaminase-ALT, total bilirubin, creatine phosphokinase-CPK, and lactate dehydrogenase-LDH) were recorded at admission to hospital.

Measurements of C-reactive protein (CRP), procalcitonin (PCT), tumor necrosis factor-alpha (TNF-α), and cytokines (interleukin [IL] 1, IL-6, IL-8, and IL-10) were performed on admission to hospital and after three days. A commercial immunoturbidimetric method (Bayer Diagnostics, Leverkusen, Germany) was used to measure CRP, while an immunoluminometric technique using a LUMItest assay (BRAHMS Diagnostica GmbH) was used to determine PCT levels. Levels of TNF-α, IL-1, IL-6, IL-8, and IL-10 were measured using a microtiter plate with coated wells and antibodies; TNF-α/IL-6 and IL-1/IL-8/IL-10 were determined using the Medgenix and PerSeptive commercial enzyme immunoassays, respectively.

LOS, prevalence of patients with abnormal mental status, duration of antibiotic treatment, and total doses of systemic steroids were recorded during hospitalization. Follow-up of mortality and re-admission for a new episode of COPDE at 30 days, 90 days, and 1 year were also monitored.

Statistical analysis

Analyses were carried out using a statistical software package (SPSS 17 for Windows), and a prior Shapiro–Wilk test for normal data distribution was performed. Results were expressed as percentage for categorical variables and mean ± SD (standard deviation) for continuous variables with normal distribution or as median (1^{st} quartile; 3^{rd} quartile) for those with non-normal distribution. Differences in continuous variables were analyzed using the *t*-test for unpaired analysis; otherwise, the nonparametric Mann–Whitney U-test was used. Categorical variables were compared using the χ^2 test or Fisher's exact test.

Univariate and multivariate logistic regression analyses were performed to identify variables predictive of patients with in-hospital treatment failure as a dependent variable. Due the limited number of patients in the group of treatment failure and in order to exclude bias related to overestimation or underestimation of regression coefficient variance we set the limit for including univariate variables in a multivariate logistic regression backward stepwise model to $p < 0.05$. Strongly correlated variables ($r > |\pm 0.3|$) were excluded from the multivariate analyses. The Hosmer-Lemeshow goodness-of-fit test was performed to assess the overall fit of the models (18). Internal validation of the prediction model was conducted using ordinary nonparametric bootstrapping with 1000 bootstrap samples and bias-corrected, accelerated 95% confidence intervals (CIs). Receiver operating characteristic (ROC) curves were constructed for the ability to predict in-hospital treatment failure using significant variables derived from logistic regression model. In all statistical tests, the significance level was set at 0.05 two-tailed.

Results

General characteristics

In total, 110 patients admitted to two Spanish university hospitals for COPDE were considered as our prospective study cohort. At day seven of hospitalization, 16 (14.5%) and 94 (85.5%) patients were considered as having in-hospital treatment failure and success, respectively. In the treatment failure group, a change with a new course of antibiotics was required in 8 patients (50%), while the need for noninvasive/invasive mechanical ventilation and deaths from any cause during hospitalization involved 5 (31.2%) and 3 (18.8%) patients, respectively. Figure 1 shows the study flow diagram.

In comparison to treatment success, the treatment failure group was represented by patients with more severe airflow obstruction and a higher rate of prior exacerbations and exacerbations requiring hospitalization. Prevalence of any evaluated co-morbidities, need for LTOT, domiciliary use of inhaled medications, and theophylline were similar between patients with in-hospital treatment failure and success (see data on Table 1).

Admission and hospitalization variables

Evaluation of clinical and microbiological variables at admission (Table 2) showed a lower prevalence of patients presenting cough at admission (56.3% versus 83%, $p = 0.015$), a greater prevalence of confirmed microbiological etiology rate (62.5% versus 26.6%, $p = 0.004$) and different class of antibiotic class used ($p = 0.043$), with a greater use of penicillins and less use of fluoroquinolones, macrolides and cephalosporins in patients with in-hospital treatment failure and success, respectively. Data on specific etiological bacteria, clinical characteristics, physiological parameters, and

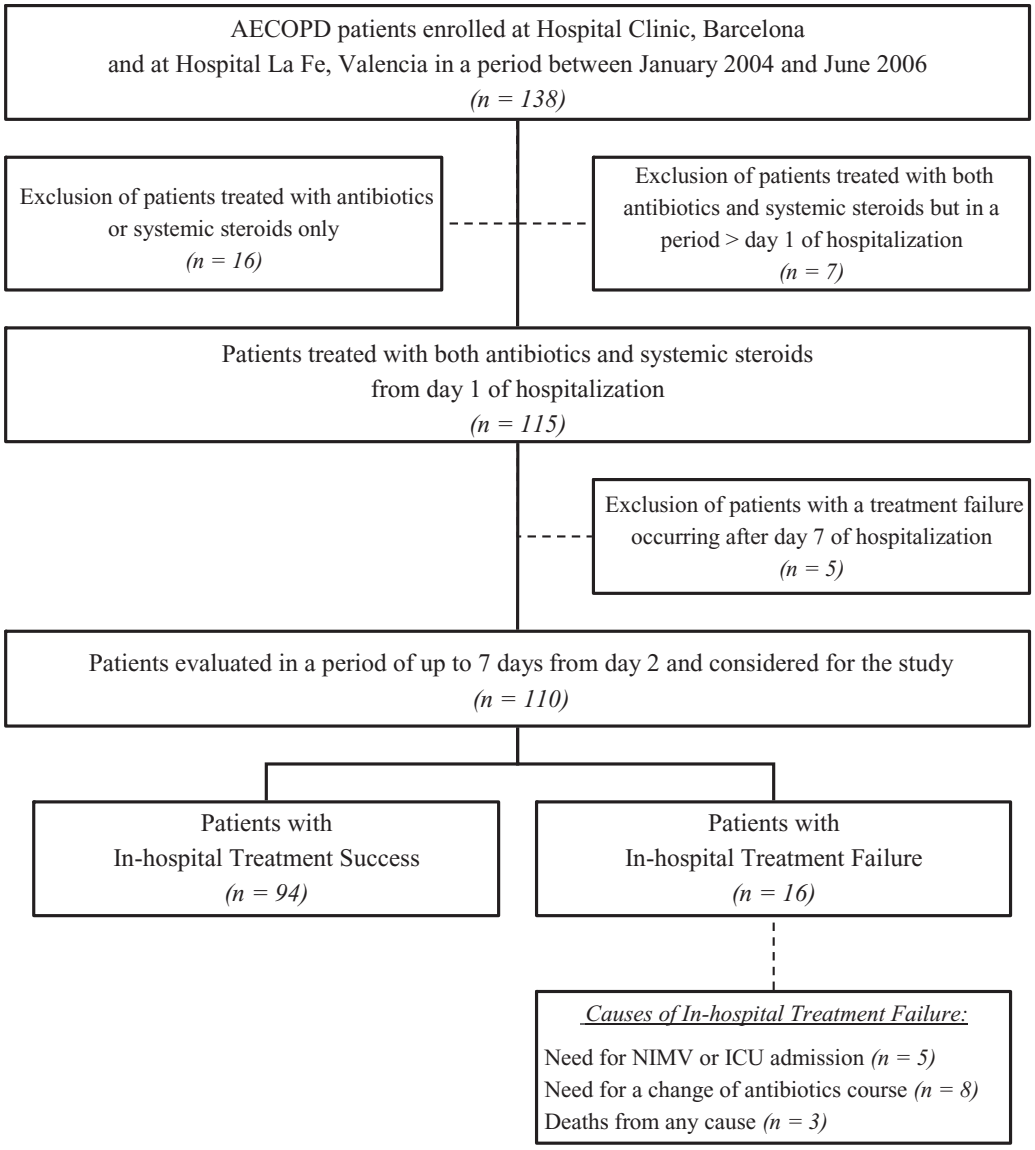

Figure 1. Study flow diagram.

gas analysis variables were similar between in-hospital treatment failure and success groups. In the comparison of serum laboratory data measured at day one of admission (Table 3), non-significant differences between groups were also found.

Early inflammatory response

Table 3 report data on assessment of systemic inflammatory response comparing patients with in-hospital treatment failure and success. At day 1 serum levels of C-reactive protein (CRP), procalcitonin-PCT, tumor necrosis factor-alpha (TNF-α), interleukin (IL) 8, and IL-10 were higher in the treatment failure group than in the treatment success group; the remaining inflammatory biomarkers (IL-1 and IL-6) were similar between the two groups. At day 3, higher levels of CRP and IL-8 were confirmed in patients with treatment failure in comparison to patients with treatment success.

Multivariate logistic regression analysis and internal validation of model

Several variables were significantly associated with in-hospital treatment failure in the univariate logistic regression analyses (Table 4). Among these variables +1 mg/dL of CRP (OR, 1.07; 95% CI, 1.01 to 1.13) and use of penicillins or cephalosporins (versus fluoroquinolones or macrolides) (OR, 5.63; 95% CI, 1.26 to 25.07) were independent variables predicting risk of in-hospital treatment failure, while presence of cough at admission was a protective variable on treatment failure (OR, 0.20; 95% CI, 0.05 to 0.75). Data of internal validation of logistic regression model, conducted using bootstrapping with 1000 samples, are presented in Table 5. Two of three variables included in the model demonstrated robust results, with small 95% CIs around the original coefficients, while the class of antibiotics used appeared to be less reliable, with wider 95% CIs around the original coefficients. The area under the ROC curve

Table 1. Baseline characteristics of enrolled patients according to treatment failure criteria

Variables	All patients ($N = 110$)	Patients With In-Hospital Treatment Success ($N = 94$)	Patients With In-Hospital Treatment Failure ($N = 16$)	P
Male, %	93.6	93.5	93.8	0.976
Age, years	70.5 ± 9.6	70.2 ± 9.3	72.1 ± 11.5	0.471
FEV_1, liters	1.07 (0.90; 1.55)	1.09 (0.92; 1.52)	0.88 (0.59; 1.25)	**0.036**
FEV_1, % predicted	45 (36; 58)	49 (36; 60)	39 (23.7; 48.5)	**0.033**
COPD-GOLD stage: A/B/C/D, %	1.1/36.6/45.6/16.7	1.3/39.2/45.6/13.9	0/18.1/45.5/36.4	0.238
mMRC dyspnea grade: I/II/III/IV	4.5/33.6/53.6/8.3	5.3/37.2/51.1/6.4	0/12.5/68.8/18.8	0.082
LTOT, %	20.9	19.1	31.3	0.271
Rate of previous events (events per patient)[†]				
Exacerbations	1.74	1.60	2.50	**0.002**
Exacerbations requiring hospitalizations	0.94	0.89	1.44	**0.032**
Chronic co-morbidities, %				
Congestive heart failure	25.7	23.4	40	0.172
Chronic renal failure	0.9	1.1	0	0.679
Diabetes	15.5	14.9	18.8	0.693
Non-cirrhotic liver disease	1.8	2.1	0	0.556
Neurologic disease	8.2	9.6	0	0.196
Non-active cancer	8.2	7.4	12.5	0.495
Use of inhaled medications, %				
SABA (salbutamol/terbutaline, % of users)	71.3 (94.4/5.6)	69.6 (93.3/6.7)	81.3 (100/0)	0.340
LABA (formoterol/salmeterol, % of users)	64.5 (29.2/70.8)	66.3 (27.6/72.4)	53.3 (42.9/57.1)	0.330
Anticholinergics (ipratropium/tiotropium, % of users)	69.2 (41.6/58.4)	71.4 (38.8/61.2)	56.3 (60/40)	0.225
ICS (budesonide/fluticasone, % of users)	63.2 (40/60)	63 (39.3/60.7)	64.3 (44.4/55.6)	0.928
Use of theophylline, %	7.5	6.5	13.3	0.352
Vaccination, %				
Anti-pneumococcal	23.5	24.7	15.4	0.459
Flu	69.6	68.5	76.9	0.539

Data are shown as percentage of patients, mean ± SD or median (1st quartile; 3rd quartile), unless otherwise stated. Percentages calculated on non-missing data.
[†]In a period of 1 year previous the hospitalization index.
Abbreviations: FEV_1 indicates forced expiratory volume in the 1st second; mMRC, modified medical research council dyspnea scale; LTOT, long-term oxygen therapy; SABA, short action β_2 agonist; LABA, long action β_2 agonist; ICS, inhaled corticosteroids.

was 0.81 (95% CI, 0.70 to 0.92) for the model predictive of in-hospital treatment failure.

Clinical outcomes during hospitalization and follow-up

In the evaluation of clinical outcomes (Table 6), a longer length of hospital stay (13 days [7.5-25] versus 7 [6-8]; $p < 0.001$), a higher prevalence of patients presenting abnormal mental status (25% versus 6.5%; $p = 0.018$), a longer duration of antibiotic therapy (11 days [8-16] versus 6 [4-8]; $p < 0.001$), and higher total doses of systemic steroids (456 mg [264-1200] versus 300 [212-396]; $p = 0.033$) were evident in the treatment failure group compared to the treatment success group. Moreover, a higher prevalence of patient deaths at day 30, day 90 and at 1 year (18.1% versus 1.1%, $p = 0.001$; 25% versus 2.2%, $p < 0.001$; 40% versus 14%, $p < 0.001$) were evident between the in-hospital treatment failure and success groups. Similarly, a higher prevalence of re-admitted patients in a period of 30 and 90 days and at 1 year was evident in treatment failure group (46.2% versus 18.3%, $p = 0.022$; 53.8% versus 20.4%, $p = 0.009$; 54.5% versus 25.8%, $p = 0.047$).

Clinical evaluation and outcomes according to specific classes of antibiotics

The clinical comparison among patients categorized according to use of specific classes of antibiotic at the start of hospitalization (Table 7) in the group of penicillins or cephalosporins versus fluoroquinolones or macrolides shows a higher rate of documented antibiotic resistance (n = 19, 17.2% in all patients versus n = 0; $p < 0.001$), a higher prevalence of patients requiring a change with a new course of antibiotics (n = 7 versus n = 1, $p = 0.018$), higher levels of CRP at day 1 (13 mg/dL [3.21; 18.7] versus 5 mg/dL [1.15; 12]), and higher levels of PCT at day 1 (0.15 ng/mL [0.09; 0.47] versus 0.09 ng/mL [0.09; 0.21]). The prevalence of identified bacterial pathogens, PaO_2/FiO_2, CRP and PCT at day 3, LOS,

Table 2. Clinical, microbiological and antibiotic-related variables

Variables	All patients	Patients With In-Hospital Treatment Success	Patients With In-Hospital Treatment Failure	*P*
Temperature, °C	37 (36.5; 37.5)	37 (36.5; 37.5)	36.7 (36.2; 37.4)	0.473
Chills, %	30.0	31.9	18.8	0.288
Cough, %	79.1	83	56.3	**0.015**
Pleuritic pain, %	11.8	12.8	6.3	0.455
Dyspnea, %	97.3	96.8	100	0.469
Characteristics of sputum, % Absence/mucous/purulence	10/9.1/80.9	9.6/9.6/80.9	12.5/6.3/81.3	0.868
Anthonisen criteria, % Type I/type II/type III	40.6/31.1/28.3	42.2/30/27.8	31.3/37.5/31.3	0.702
Respiratory rate, breaths per minute	24 (20; 30)	24 (20; 30)	27.5 (20; 30.5)	0.202
Heart rate, beat per minute	95 (82.5; 105)	95 (82.5; 104)	100.5 (81; 123.7)	0.224
Systolic arterial pressure, mmHg	149.5 (131.2; 165.7)	150 (132.5; 166.5)	149 (114; 165)	0.355
Diastolic arterial pressure, mmHg	80 (71; 90)	80 (71; 90)	80 (71; 86)	0.719
pH	7.41 (7.38; 7.43)	7.41 (7.38; 7.43)	7.37 (7.35; 7.40)	0.087
PCO_2, mmHg	46 (40.6; 53.1)	46 (39; 52)	50 (46; 60)	0.086
PaO_2/FiO_2	266 (233; 280)	266 (238; 280)	233 (214.2; 328)	0.641
HCO^3, mmol/L	28 (25.8; 31.7)	28 (25; 31.7)	28.9 (27; 32)	0.425
BE, mmol/L	3 (1.3; 5.8)	3 (1.3; 5.7)	3.7 (1.9; 6.2)	0.574
Bacterial pathogen identified, *n* (%)*	35 (100)	25 (26.6)	10 (62.5)	**0.004**
Bacterial etiology, *n* (%)**				0.599
Streptococcus pneumoniae	5 (14)	3 (12)	2 (20)	
Staphylococcus aureus	3 (9)	3 (12)	0 (0)	
Haemophilus influenzae	8 (23)	6 (24)	2 (20)	
Haemophilus parainfluenzae	4 (11)	3 (12)	1 (10)	
Pseudomonas aeruginosa	7 (20)	4 (16)	3 (30)	
Moraxella catarrhalis	3 (9)	2 (8)	1 (10)	
Chlamydia pneumoniae	1 (3)	1 (4)	0 (0)	
Enterobacteriaceae†	3 (9)	3 (12)	0 (0)	
Legionella pneumophila	1 (3)	0 (0)	1 (10)	
Class of antibiotics used, %				**0.043**
Penicillins, *n* (%) *Amoxicillin/Clavulanate*	47 (42.7)	35 (37.2)	12 (75)	
Cephalosporins, *n* (%) *Ceftriaxone, Cefotaxime, Cefuroxime and Cefepime*	13 (11.8)	12 (12.8)	1 (6.3)	
Fluoroquinolones, *n* (%) *Ciprofloxacin, Moxifloxacin, Levofloxacin*	45 (40.9)	42 (44.7)	3 (18.7)	
Macrolides, *n* (%) *Azithromycin, Clarithromycin*	5 (4.5)	5 (5.3)	0 (0)	

Data are shown as number of patients (percentage), mean ± SD or median (1st quartile; 3rd quartile), unless otherwise stated. Percentages calculated on non-missing data.
*Percentage calculated in total patients for each group.
**Percentage calculated in total patients with etiological diagnosis confirmed for each group.
†Including Escherichia coli and Proteus mirabilis.
Abbreviations: BE indicates base excess; HCO^3, serum bicarbonate; $PaCO_2$, partial arterial carbon dioxide pressure; PaO_2/FiO_2, ratio of partial arterial oxygen pressure to the fraction of inspired oxygen.

abnormal mental status, duration of antibiotic therapy, and total doses of systemic steroids were similar between groups.

Discussion

The main findings of our prospective observational study concern the predictive role of some clinical variables (cough, class of antibiotics used) and systemic biomarker (CRP) variables in the identification of in-hospital treatment failure in patients with moderate-to-severe COPDE needing a hospitalization and treated with both antibiotics and systemic steroids. The differences in inflammatory response, in-hospital clinical variables/outcomes and short-term/long-term evaluations between patients with treatment success and failure suggest that the early detection of a sub-group of patients with increased risk of failure may be a useful goal in the pharmacological management of COPDE.

Usually, the failure of treatment is defined by persistence or worsening of disease symptoms (19). Similar to other studies (15,16), the treatment-failure rate of our patients was 14.5%. Another recent randomized, placebo-controlled study (17) using doxycycline in addition to systemic steroids reported a higher rate of failure (about 39%) in the treated group but at day 30 after

Table 3. Laboratory and serum biomarker measurements

Variables	Sample	Patients With In-Hospital Treatment Success	Patients With In-Hospital Treatment Failure	*P*
Assessment at day 1				
Total leukocytes, counts x 10^9/L	*n = 109*	10.1 (7.6; 13.2)	9.7 (8.1; 11.3)	0.637
Hematocrit, %	*n = 109*	45 (41.2; 49)	44.5 (41.5; 46.6)	0.513
Glucose, mg/dL	*n = 108*	126.6 (108; 159)	126.3 (99.2; 133.5)	0.528
Creatinine, mg/dL	*n = 109*	0.9 (0.8; 1.1)	1 (0.7; 1.3)	0.737
Sodium, mmol/L	*n = 109*	136.6 (134; 138.9)	135 (131; 138.7)	0.245
Potassium, mEq/L	*n = 109*	4.4 (4; 4.8)	4.2 (3.5; 4.9)	0.480
AST, IU/L	*n = 88*	22 (18; 30)	25 (19; 35)	0.682
ALT, IU/L	*n = 89*	18.5 (13.6; 25.7)	17 (11; 20)	0.284
Total bilirubin, mg/dL	*n = 75*	0.8 (0.6; 1.2)	0.6 (0.6; 0.9)	0.456
CPK, mcg/L	*n = 84*	74 (43.3; 115.1)	107.5 (63.3; 216)	0.252
LDH, IU/L	*n = 88*	363.5 (247.7; 474.2)	278 (198; 435.2)	0.291
CRP (mg/dL)	*n = 109*	6.7 (1.65; 15.85)	16.1 (7.37; 27.99)	**0.007**
PCT (ng/mL)	*n = 109*	0.09 (0.09; 0.27)	0.32 (0.14; 0.66)	**0.009**
TNF-α (pg/mL)	*n = 108*	10 (6; 20)	19 (11.2; 40.7)	**0.009**
IL-1 (pg/mL)	*n = 109*	4 (0; 11)	6.5 (3; 20.2)	0.081
IL-6 (pg/mL)	*n = 109*	9 (0; 78.5)	51 (3.5; 123.7)	0.134
IL-8 (pg/mL)	*n = 108*	2 (0; 14.5)	12 (2.2; 45.5)	**0.044**
IL-10 (pg/mL)	*n = 109*	0 (0; 7.7)	7 (0.5; 17.2)	**0.020**
Assessment at day 3				
CRP (mg/dL)	*n* = 108	1.22 (0.30; 3.60)	2.80 (1.12; 6.17)	**0.043**
PCT (ng/mL)	*n* = 108	0.09 (0.09; 0.29)	0.09 (0.09; 0.78)	0.386
TNF-α (pg/mL)	*n* = 108	11 (6.5; 22.5)	17 (8.2; 22.7)	0.242
IL-1 (pg/mL)	*n = 108*	4 (0; 8)	6 (2.2; 33.2)	0.136
IL-6 (pg/mL)	*n* = 108	6 (0; 28)	10 (0; 56)	0.659
IL-8 (pg/mL)	*n* = 105	0 (0; 3)	2 (0; 21)	**0.049**
IL-10 (pg/mL	*n* = 107	9 (0; 18.2)	11.5 (0.5; 34.7)	0.331

Data are shown as median (1st quartile; 3rd quartile).
Abbreviations: ALT indicates alanine *transaminase*; AST, aspartate transaminase; CPK, *creatine phosphokinase;* CRP, C-reactive protein; IL, interleukin; LDH, Lactate dehydrogenase; PCT, procalcitonin; TNF-α, tumour necrosis factor-alpha; IL, interleukin.

Table 4. Significant univariate and multivariate logistic regression analyses predicting the probability of early in-hospital treatment failure

	Univariate			Multivariate*		
Variables	OR	95% CI	*P*	OR	95% CI	*P*
No of previous exacerbations† (≥2 *vs.* ≤1)	3.55	1.05 to 11.97	0.041	–	–	–
mMRC (+1 point)	3.10	1.25 to 7.66	0.014	–	–	–
Cough at admission (Yes *vs.* No)	0.26	0.08 to 0.81	0.020	0.20	0.05 to 0.75	**0.018**
Class of antibiotics used (Penicillins or Cephalosporins *vs.* Fluoroquinolones or Macrolides)	4.33	1.15 to 16.20	0.029	5.63	1.26 to 25.07	**0.023**
CRP day 1 (+1 mg/dL)	1.08	1.02 to 1.13	0.003	1.07	1.01 to 1.13	**0.014**
TNF-α day 1 (+1 pg/mL)	1.06	1.02 to 1.10	0.002	–	–	–
IL-1 at day 3 (+1 pg/mL)	1.02	1.00 to 1.04	0.043	–	–	–
IL-8 at day 3 (+1 pg/mL)	1.03	1.00 to 1.07	0.034	–	–	–

*Hosmer and Lemeshow test: $p = 0.723$.
†In a period of 1 year previous the hospitalization index.
Abbreviations: OR indicates odds ratio; CI, confidence interval; mMRC, modified medical research council dyspnoea scale; CRP, C-reactive protein; TNF-α, tumour necrosis factor-alpha; IL, interleukin.

Table 5. Internal validation of prediction model using nonparametric bootstrap technique

Variables	Original	Bias	SE	95% BCa CI
Cough at admission (Yes *vs.* No)	–1.594	–0.207	1.604	–3.434 to –0.222
Class of antibiotics used				
(Penicillins or Cephalosporins *vs.* Fluoroquinolones or Macrolides)	1.729	0.931	4.009	0.270 to 20.073
CRP day 1 (+1 mg/dL)	0.073	0.008	0.039	0.013 to 0.171

Abbreviations: SE indicates standard error; BCa, adjusted bootstrap confidence interval; CI, confidence interval; CRP, C-reactive protein.

discharge, while a rate about 20% was reported in the patients evaluated at day 10.

In the comparison of general characteristics, we detected a population of patients with differences in disease severity and previous exacerbations. A preview observational trial (20) performed on COPDE patients attended in outpatients defines host factors such as severity of airflow obstruction and frequency of exacerbation as specific to poor treatment outcome. Our results in inpatients confirm, in terms of in-hospital treatment failure, that severity of COPD (evaluated by FEV_1 (21)) and susceptibility of exacerbation (22) are features that, in hospitalized patients with COPDE, also require more attention in the choice of a correct pharmacological approach.

The low prevalence of patients presenting cough at admission and the protective role of cough in the multivariate predictive analysis is probably related to a defensive mechanism of the airways, improving mucus clearance and thus having a potentially beneficial effect on treatment (23).

CRP, an acute non-specific phase reactant, is a protein produced by the liver in response to IL-6 stimulation (24); in COPD patients, CRP levels are associated with poor clinical outcomes (25) and are a strong and independent predictor of prognosis (26). A Spanish study (27) recognized CRP measured at admission as a useful biomarker that can identify adverse short-term negative clinical outcomes, although it was not sensitive and showed no specific statistical characteristics; this study, however, did not include episodes strictly linked to treatment failure, such as need for a new antibiotic course. The high early inflammatory response measured by CRP levels in our patients, expression of pan-airway inflammation (28), may represent a strong immunological response, conditioning the effect of treatment and hence the in-hospital severe outcomes (25,26). Moreover, related to the greater prevalence of a confirmed infection in group of treatment failure, elevated serum CRP levels are seen with bacterial exacerbation (29).

Antibiotics are commonly used during COPDE (30). Several prospective trials have tested the clinical effects of some fluoroquinolones in comparison to standard therapy (penicillins or cephalosporins) in COPDE (31,32) or chronic bronchitis (33–35) and have found generally similar clinical and anti-bacterial activity against likely pathogens (31–35). To our knowledge, for the first time, our study demonstrates a specific role of penicillins or cephalosporins in increasing the risk of in-hospital treatment failure during the first seven days of antibiotic treatment. As discussed above, the early inflammatory response conditioning some outcomes in COPD patients (25–28), evident in the group of penicillin/cephalosporin users, together with a greater

Table 6. Clinical outcomes evaluated during hospitalization and in the follow-up

Variables	Patients With In-Hospital Treatment Success	Patients With In-Hospital Treatment Failure	*p*
LOS†, days	7 (6; 8)	13 (7.5; 25)	**<0.001**
Mental status alteration†	6.5	25	**0.018**
Duration of antibiotic therapy†, days	6 (4; 8)	11 (8; 16)	**<0.001**
Total doses of systemic steroids†, mg	300 (212; 396)	456 (264; 1200)	**0.033**
Mortality, %			
On day 30	1.1	18.1	**0.001**
On day 90	2.2	25	**<0.001**
At 1 year	14.0	40	**0.014**
Re-hospitalization for a new episode, %			
In a period of 30 days	18.3	46.2	**0.022**
In a period of 90 days	20.4	53.8	**0.009**
In a period of 1 year	25.8	54.5	**0.047**

Data are shown as percentage of patients or median (1st quartile; 3rd quartile), unless otherwise stated. Percentages calculated on non-missing data.
†Calculated during total period of hospitalization.
Abbreviations: LOS indicates length of stay in hospital.

Table 7. Clinical evaluation and outcomes according class of antibiotics

Variables	Patients Using Penicillins or Cephalosporins ($N = 60$)	Patients Using Fluoroquinolones or Macrolides ($N = 50$)	P
Bacterial pathogen identified ($N = 35$), n (%)*	23 (38.3)	12 (24)	0.108
Documented antibiotic resistance ($N = 23$)			**<0.001**
To the same class of antibiotics used, n (%)	14 (60.8)	0 (0)	
To other class of antibiotics, n (%)	0 (0)	5 (21.8)	
To the same and other classes of antibiotics, n (%)	3 (13)	1 (4.4)	
Patients in who class of antibiotics was changed ($N = 8$)†			**0.018**
With penicillins or cephalosporins, n (%)	–	1 (12.5)	
With fluoroquinolones or macrolides, n (%)	6 (75)	–	
With aminoglycosides, n (%)§	1 (12.5)	0 (0)	
PaO_2/FiO_2	266 (247.6; 300)	259.5 (223; 279.2)	0.087
CRP at day 1, mg/dL	13 (3.21; 18.7)	5 (1.15; 12)	**0.017**
CRP at day 3, mg/dL	1.45 (0.5; 5.7)	1.45 (0.35; 3.2)	0.349
PCT at day 1, ng/mL	0.15 (0.09; 0.47)	0.09 (0.09; 0.21)	**0.024**
PCT at day 3, ng/mL	0.09 (0.09; 0.44)	0.09 (0.09; 0.18)	0.631
LOS†, days	6 (4; 11)	6 (4; 8.2)	0.671
Mental status alteration‡, %	11.9	6	0.291
Duration of antibiotic therapy‡, days	7 (4; 10)	6 (4; 9)	0.403
Total doses of systemic steroids‡, mg	340 (220; 471)	300 (230; 390)	0.490

Data are shown as number of patients (percentage), or median (1st quartile; 3rd quartile), unless otherwise stated. Percentages calculated on non-missing data.
*Percentage calculated in total patients for each group.
†During period of evaluation of in-hospital treatment failure (from day 1 to day 7).
§Used for a Pseudomonas aeruginosa multi-antibiotic resistance.
‡Calculated during total period of hospitalization.
Abbreviations: CRP indicates C-reactive protein; PCT, procalcitonin; LOS, length of stay in hospital.

prevalence of specific antibiotic-resistance, may explain why these classes of antibiotics increase risk of failure in our cohort of COPDE. For this reason, based on failure criteria, 7 out of 8 patients (87.5%) using penicillins or cephalosporins had to change the initial antibiotic prescription with a new course of antibiotics (fluoroquinolones or macrolides in 6 patients). However, as documented by the similar reduction of inflammatory process at day 3 and the subsequent clinical course between antibiotic users, the outcomes related to patients hospitalization (LOS, duration of total antibiotic therapy and total doses of steroids required) were comparable between users of penicillins or cephalosporins and of fluoroquinolones or macrolides.

The prediction model we have presented is the first step in establishing a more universal model; to move forward, our prediction model will need to undergo external validation with larger patient cohorts from multiple centers. We were able to apply internal validation techniques to understand how likely this model will be replicable in future studies and at other centers. Bootstrapping techniques were applied and demonstrated that the coefficients obtained from this prediction model were quite robust. The class of antibiotics used was the one factor that the bootstrap results indicated might have limited repeatability in future work. Removal of the class of antibiotics used from the model did not change which factors were significant predictors of in-hospital treatment failure. However, because of the clinical importance surrounding the class of antibiotics used, this variable was kept as a factor in this model despite some statistical limitations. In the real-world clinical setting where this prediction model could be used, the class of antibiotics used is an important clinical characteristic that can play a substantial role in decision making.

Major strengths of our research are the prospective nature of the data collection, the selection of COPDE with exclusion of patients with pneumonia and heart failure, and the systematic analysis of several serum inflammatory biomarkers. As demonstrated by internal validation of the prediction model a limitation of our study include the modest sample size, especially for patients with dependent event (in-hospital treatment failure) that not permit to reach robust conclusions. Moreover, groups are not well balanced and only one country (Spain) site was used for data collection; a confirmation of our results in a large and well balanced, international cohort of COPDE is therefore desirable. Other limitations were the lack of information regarding CRP inflammatory levels at the pre-acute stable phase of COPD, identifying patients with a persistent inflammatory response (36) and regarding virus detection as etiology in triggering COPD exacerbation (3).

Conclusion

Our prospective study performed in moderate-to-severe hospitalized COPDE patients report that high serum values of CRP at admission and the use of specific classes of antibiotics (penicillins or cephalosporins) increase the risk of in-hospital treatment failure, whereas presence of cough reduce the risk of failure.

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