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ORIGINAL ARTICLE

Initial Empirical Antibiotic Treatment in Patients with COVID-19 is Associated with Excess Adverse Drug Reactions without Clinical Benefit

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ABSTRACT

Objectives: Empirical antibiotic use is common among hospitalized patients with coronavirus disease-2019 (COVID-19) pneumonia because it is difficult to differentiate it from concurrent bacterial pneumonia. The aim of this study was to determine risk factors for concurrent bacterial community-acquired pneumonia (b-CAP) and the need for initial empirical antibiotic coverage in patients with pulmonary involvement caused by Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) infection.

Materials and Methods: This prospective observational study was conducted at a tertiary university hospital between March 2020 and April 2021. Patients aged over 18 years who were hospitalized due to COVID-19 were included. Risk factors and outcomes were compared between patients who initially received empirical antibiotics and those who did not.

Results: The presence of respiratory viral pathogens other than SARS-CoV-2 was investigated *via* respiratory panel multiplex polymerase chain reaction in 295 patients and potential bacterial respiratory pathogens in 306 patients admitted to the hospital. The co-infection rate was low (17.4%) and half of the patients (205/409, 50.1%) were administered initial empirical antibiotics for suspected concurrent b-CAP. Antibiotic use was higher in patients with multiple comorbidities, severe to critical pneumonia, and patients older than 65 years ($p < 0.001$). The overall 30-day mortality rate was significantly higher (26.3% and 2.0%, $p < 0.001$), and the duration of hospital stay was longer (median 13.0 and 5.5 days, $p < 0.001$) in patients who received empirical antibacterial agents compared to those who did not.

Conclusion: Initial empirical antibiotic treatment is common among patients infected with SARS-CoV-2, although the coinfection rate is low. Empirical antibiotic(s) did not improve the clinical course in COVID-19 patients.

Keywords: SARS-CoV-2, COVID-19, antimicrobial, empirical therapy, co-infections, community-acquired pneumonia

INTRODUCTION

Differential diagnosis of bacterial co-infections may be challenging in patients with severe to critical coronavirus disease-2019 (COVID-19) on hospital admission because the clinical presentation of COVID-19 may mimic atypical bacterial pneumonia, and pulmonary consolidation develops later during the disease.[1] In addition, physicians overwhelmed by pandemic conditions might tend to cover all potential causes of community-acquired pneumonia (CAP) and leave no button unturned.[2,3]

The World Health Organization guidelines recommend empirical antibiotic therapy based on local epidemiology for bacterial pneumonia in patients with severe COVID-19, older patients, and long-term nursing home residents,[4] but a few studies have shown that the rate of antibiotic usage is high despite low microbiological evidence. In most of these studies, empirical antibacterial treatment of suspected hospital-acquired and ventilator-associated pneumonia was investigated.[5,6] A meta-analysis emphasized that the incidence of co-infection was low (8%) at hospital admission, yet empirical antibacterial

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therapy was started in 48.6% to 72% of these patients.[7] During the COVID-19 pandemic in Türkiye, antibacterial drug sales decreased by 24.30% in 2020 compared with 2019, which was probably associated with the quarantine.[8] However, a study conducted on Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2)-infected patients in Türkiye showed that 71.2% of the patients were prescribed inappropriate antibiotics.[9]

Antibiotic misuse/abuse is well known to have a negative impact, such as increased antimicrobial resistance and adverse events related to the medication.[10] Therefore, the aim of this study was to determine the risk factors for concomitant bacterial CAP (b-CAP) and the need for initial empirical antibiotic coverage in patients with SARS-Cov-2 infection.

MATERIALS AND METHODS

This prospective, observational, and single-center study was conducted at an tertiary university hospital between March 20, 2020, and April 15, 2021. This study was conducted by the Declaration of Helsinki, and the study protocol was reviewed and approved by the Hacettepe University Non-Interventional Clinical Research Ethics Committee and the Ministry of Health (approval number: GO 22/520, date: 31.05.2022). All participants provided informed consent.

In this hospital, authorization to use carbapenems, ceftazidime, cefepime, piperacillin-tazobactam, polymyxins, quinolones (except oral forms), glycopeptide antibiotics (vancomycin and teicoplanin), daptomycin, and linezolid as well as more than three days of treatment with the 3rd generation cephalosporins and intravenous fluoroquinolones requires infectious diseases (ID) approval because of reimbursement rules by the Social Security Institution. There is a close collaboration between the department of ID and other clinical departments in the management of patients with suspicious infections. Routine clinical practice includes daily clinical rounds of patients treated with an antimicrobial agent by an ID specialist, residents, and a clinical pharmacist during antimicrobial treatment.

Study population

Patients aged over 18 years who tested positive by SARS-CoV-2 polymerase chain reaction (PCR) were included. Those with negative PCR test results but diagnosed presumptively based on characteristic findings on chest computed tomography (CT) and/or positive anti-SARS-CoV-2 immunoglobulin M (IgM) antibodies were also included in the analysis.[11,12] Chest imaging and respiratory panel multiplex PCR test (Seegene, South Korea[6]) were used to diagnose concurrent b-CAP (Supplement 1). Patients younger than 18 years, those with nosocomial pneumonia (pneumonia that developed 72 hours or more after hospital admission), or those without pulmonary involvement were excluded.

Data collection

Data on patient characteristics, diagnostic and clinical parameters, such as changes in oxygen requirement and fever, and antimicrobial therapy were collected. Patients were followed until the discontinuation of antimicrobial agents, discharge from the hospital, or death.

CURB-65 scores and pneumonia severity index (PSI) were used to predict mortality and determine severity of CAP. The CURB-65 and PSI scores at hospital admission were calculated. The severity of COVID-19 was classified according to the World Health Organization-China Joint Mission definitions.[13] Patients with tachypnea, oxygen saturation ≤ 93% or PaO_2/FiO_2 ratio < 300 mmHg, respiratory failure requiring mechanical ventilation, and septic shock were defined as severe to critical COVID-19 pneumonia. Patients with mild pneumonia were classified as mild to moderate COVID-19 patients.

Fever was defined as body temperature ≥ 38 °C, whereas oxygen demand was defined as SaO_2 < 90% and/or the need for oxygen supplementation. Changes in the fever pattern and oxygen demand were recorded. A leukocyte count of less than 4.1 x 10^3/μL was defined as leukopenia, whereas a leukocyte count of more than 11.2 x 10^3/μL was defined as leukocytosis. C-reactive protein (CRP) values greater than 0.8 mg/dL and a procalcitonin (PCT) value greater than 0.1 ng/mL were considered abnormal/high.

The Kidney Disease: Improving Global Outcomes (KDIGO) criteria were used to define drug-related nephrotoxicity. To summarize, nephrotoxicity was defined as an increase in serum creatinine (SCr) by ≥ 0.3 mg/dL within 48 hours or an increase in SCr by ≥ 1.5 times the baseline within seven days after the initiation of the antibacterial agent. According to KDIGO guidelines, an increase in SCr to 1.5-1.9 times the baseline or an increase in SCr of > 0.3 mg/dL was considered stage 1, and an increase in SCr to 2.0-2.9 times the baseline was considered stage 2, and an increase in SCr to ≥ 3.0 times the baseline or > 4.0 mg/dL or the initiation of renal replacement therapy was considered stage 3.[14] The Cancer Therapy Evaluation Program of the National Cancer Institute of the National Institutes of Health, which has been accepted as the common toxicity criteria for adverse events, was used to determine drug-induced hepatotoxicity.[15] The Sanford Guide to Antimicrobial Therapy recommendations were used to determine the appropriateness of antimicrobial doses.[16] "Drugs.com Drug Interactions Checker" (https://www.drugs.com/drug_interactions.html) database was used to detect potential drug-drug interactions (pDDIs) among antibacterial agents, and pDDIs were classified as "minor", "moderate" and "major" interactions.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 23.0 for patients who were given empirical antibiotic treatment for b-CAP within 72 hours of admission and those who were not. In addition, SARS-CoV-2 PCR-positive patients were compared with those who tested negative but had highly suggestive CT findings or were SARS-CoV-2 IgM antibody-positive. The Shapiro-Wilk goodness-of-fit test will test whether the distributions related to the numerical variables match the normal distribution. Descriptive statistics, such as mean, standard deviation, median [IQR], minimum, and maximum, were used for

numerical variables that conformed to the normal distribution. For categorical variables, percentage values and frequency tables are given. Categorical variables were compared with the χ^2 tests. Mann-Whitney U non-parametric test was used to compare two independent groups. Univariate and multivariate logistic regression models were used to identify risk factors associated with antibiotic treatment. The logistic regression models included independent variables found to be significant predictors ($p < 0.05$).

RESULTS

A total of 262 patients (262/409, 64.1%) with positive PCR for COVID-19 and 147 (147/409, 35.9%) PCR-negative but diagnosed with COVID-19 according to clinical and CT imaging findings were evaluated. The median age of the patients was 62 years [IQR: 48-75 years], and 58.7% were males. The most common comorbidity was hypertension, followed by diabetes mellitus and coronary artery disease (Table 1).

Four hundred and five patients received antiviral treatment in accordance with the recommendations of the Turkish Ministry of Health at the time of diagnosis: favipiravir (76.8%, n= 311), redeliver (3.2%, n= 13), and hydroxychloroquine (20%, n= 81). Antiviral therapy was not prescribed to four patients because of severe liver failure. Oseltamivir was added in 14 (6.8%) patients empirically.

Pulmonary co-infection was detected in 71 (17.4%) patients. Among the coinfecting agents, 83.1% (n= 59) were bacteria and 16.9% (n= 12) were respiratory viruses. The most common bacterial pathogen was *Haemophilus influenzae* (n= 36, 60.0%), followed by *Streptococcus pneumoniae* (n= 20, 33.3%) (Table 2). Urinary *Legionella* antigen was positive in one patient despite a negative respiratory multiplex PCR.

In total, 205 (50.1%) patients received initial empirical antibiotics for suspected b-CAP (Table 2). Antibacterial treatment with atypical coverage was given in 178 patients (86.8%). Chest CT did not suggest concurrent bacterial pneumonia in 66.8%

Table 1. Demographic and clinical characteristics of patients with COVID-19 pneumonia

	Total (n= 409)	Initial antibiotic therapy (n=205)	Not initially receiving antibiotic therapy (n= 204)	*p* value
Age				
Age (years), median (IQR)	62 (48-75)	70 (57.5-80.0)	54 (40.5-67.0)	**< 0.001**
> 65 years, n (%)	184 (45.0)	126 (61.5)	58 (28.4)	**< 0.001**
Sex, n (%)				
Male	240 (58.7)	134 (65.4)	106 (52.0)	**0.006**
Vaccination rate, n (%)				
Influenza vaccine	17 (4.2)	9 (4.4)	8 (3.9)	0.085
Pneumococcal vaccine	9 (2.2)	7 (3.4)	2 (0.98)	0.692
Comorbidities, n (%)				
Hypertension	166 (40.6)	103 (50.2)	63 (30.9)	**< 0.001**
Diabetes mellitus	111 (27.1)	73 (35.6)	38 (18.6)	**< 0.001**
Coronary artery disease	106 (25.9)	66 (32.2)	40 (19.6)	**0.004**
Malignancy	63 (15.4)	48 (23.4)	15 (7.4)	**< 0.001**
Neurological disease	56 (13.7)	48 (23.4)	8 (3.9)	**< 0.001**
COPD	44 (10.8)	38 (18.5)	6 (2.9)	**< 0.001**
Congestive heart failure	37 (9.0)	29 (14.1)	8 (3.9)	**< 0.001**
Benign prostatic hyperplasia	30 (7.3)	19 (9.3)	11 (5.4)	0.133
Chronic kidney disease	25 (6.1)	19 (9.3)	6 (2.9)	**0.008**
Asthma	25 (6.1)	8 (3.9)	17 (8.3)	0.061
Atrial fibrillation	23 (5.6)	20 (9.8)	3 (1.5)	**< 0.001**
Rheumatological diseases	19 (4.6)	8 (3.9)	11 (5.4)	0.474
Liver failure	7 (1.7)	4 (2.0)	3 (1.5)	1.000
Presence of comorbidity	308 (75.3)	189 (92.2)	119 (58.3)	**< 0.001**
Number of comorbidities, median (IQR)	2 (1-3)	3.0 (1.0-4.0)	1.0 (0.0-2.0)	**< 0.001**

Table 1. Continued

	Total (n= 409)	Initial antibiotic therapy (n=205)	Not initially receiving antibiotic therapy (n= 204)	*p* value
Severity of COVID-19, n (%)				
Severe-to-critical patient	168 (41.1)	129 (62.9)	39 (19.1)	< 0.001
Mild-moderate patient	241 (58.9)	76 (37.1)	165 (80.8)	
Corticosteroid therapy, n (%)				
Yes	158 (38.6)	125 (61.0)	33 (16.2)	< 0.001
No	251 (61.4)	80 (39.0)	171 (83.8)	
Risk factors for CAP, n (%)				
Risk factors	239 (58.4)	167 (81.5)	72 (35.3)	< 0.001
Number of patients monitored for biochemical markers, n (%)				
PCT	348 (85.1)	191 (93.2)	157 (77.0)	< 0.001
CRP	383 (93.6)	195 (95.1)	188 (92.2)	0.219
Erythrocyte sedimentation rate	302 (73.8)	157 (76.6)	145 (71.1)	0.205
Development of nosocomial infections during hospitalization, n (%)				
Presence of nosocomial infections	103 (25.2)	80 (39.0)	23 (11.3)	< 0.001
Hospital stay [median (IQR)]				
Duration of hospital stay: day	9.0 (5.0-17.0)	13.0 (8.0-27.5)	5.5 (4.0-10.0)	< 0.001
Criteria for evaluating the severity of the disease, [median (IQR)]				
CURB-65 score	2.0 (0.0-2.0)	2.0 (1.0-3.0)	0.0 (0.0-1.0)	< 0.001
PSI	94 (51.0-139.0)	132 (104.5-164.0)	54 (39.25-88.0)	< 0.001
Adverse events				
Acute kidney injury	46 (11.2)	37 (18.0)	9 (4.4)	< 0.001
ALT elevation	203 (49.6)	108 (52.7)	95 (46.6)	0.236
AST elevation	214 (52.3)	119 (58.0)	95 (46.6)	0.023
Mortality, n (%)				
30-day mortality	58 (14.2)	54 (26.3)	4 (2.0)	< 0.001
Mortality (in hospital)	79 (19.3)	70 (34.1)	9 (4.4)	< 0.001

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CAP: Community-acquired pneumonia, PCT: Procalcitonin, CRP: C-reactive protein, IQR: Interquartile range, COPD: Chronic obstructive pulmonary disease, COVID-19: Coronavirus disease-2019, PSI: Pneumonia severity index

(n= 138) of the patients. Patients with high PCT and CRP levels, leukocytosis, oxygen demand, and fever were more likely to receive initial empirical antibiotic therapy (Table 3). Corticosteroid use was also significantly more common in patients who received antibiotic treatment (61%, n= 125) compared to those who did not (16.2%, n= 33, $p < 0.001$). Anti-inflammatory treatment was given to 3 patients due to cytokine storm (tocilizumab in 2 patients, pulse corticosteroid in one). All three patients also received empirical antibiotics at admission to the hospital. Initial empirical antibiotic coverage was 5.338 (95% CI: 2.130-13.379) times more frequent in patients with chronic obstructive pulmonary disease (COPD), 4.457 (95% CI: 1.220-16.276) times with atrial fibrillation (AF), and 1.784 (95% CI: 1.060-3.004) times with diabetes mellitus. The PSI was higher in patients who received antibiotic treatment than in those who did not [132 (range: 104.5-164.0) versus 54 (range: 39.25-88.0); $p < 0.001$]. However, discontinuation of oxygen supplementation, clinical improvement, and defervescence were similar between patients who received antibiotics and those who did not (Table 3). Thirty-day mortality was significantly higher in patients who received initial antibiotics (26.3%) than in those who did not (2.0%) ($p < 0.001$) (Table 1). The mortality rate increased with older age (1.028-fold), severe to critical patients (3.411-fold), antibiotic therapy (5.726-fold), and nosocomial infection (3.557-fold) (Table 4).

Administration of antibiotics was comparable between SARS-CoV-2 PCR-positive (131/262, 50.0%) and PCR-negative patients (74/147, 50.3%) (p= 0.947). In the severe to critical disease subgroup, empirical antibiotics were administered more frequently in patients with positive PCR than in those with

Table 2. Initial empirical antibiotic treatment for CAP in patients with COVID-19 confirmed *via* PCR positive for SARS-CoV-2 and those with suggestive clinical and radiological findings

Parameters	Total (n= 409)	COVID-19 patients with positive PCR (n= 262)	COVID-19 patients with suggestive CT imaging & negative PCR (n= 147)	*p* value
Antibiotic use, n (%)				
Rate of antibiotic use	205 (50.1)	131 (50.0)	74 (50.3)	0.947
Coverage of atypical pathogens during treatment	178 (86.8)	112 (85.5)	66 (89.2)	0.453
Antibacterial treatment duration (day), median (IQR)	7 (6-10)	7.5 (6.0-10.0)	7 (6.75-10.0)	0.999
Preference of antibiotics for the treatment of CAP, n (%)				
Cefuroxime	5 (2.4)	2 (1.5)	3 (4.1)	0.354
Ceftriaxone	73 (35.6)	48 (36.6)	25 (33.8)	0.682
Amoxicillin-clavulanic acid	10 (4.9)	5 (3.8)	5 (6.8)	0.501
Ampicillin-sulbactam	45 (22.0)	26 (19.8)	19 (25.7)	0.333
Piperacillin-tazobactam	81 (39.5)	50 (38.2)	31 (41.9)	0.600
Meropenem	51 (24.9)	37 (28.2)	14 (18.9)	0.138
Fluoroquinolones	9 (4.4)	5 (3.8)	4 (5.4)	0.725
Macrolides	23 (11.2)	15 (11.5)	8 (10.8)	0.889
Doxycycline	147 (71.7)	92 (70.2)	55 (74.3)	0.532
Respiratory multiplex PCR at admission, n (%)				
Bacteria (n= 295)	59 (20.0)	33 (18.0)	26 (23.2)	0.280
Detected pathogens (n= 60)				
Haemophilus influenzae	36 (60.0)	18 (52.9)	18 (69.2)	
Streptococcus pneumoniae	20 (33.3)	14 (41.2)	6 (23.1)	
Dual pathogen†	4 (6.7)	2 (5.9)	2 (7.7)	
Virus (n= 306)	12 (3.9)	8 (4.2)	4 (3.5)	1.000
Detected viruses (n= 12)				
Human rhinovirus	3 (25.0)	1 (12.5)	2 (50.0)	
Influenza A	2 (16.7)	2 (25.0)	0 (0.0)	
Influenza B	2 (16.7)	1 (12.5)	1 (25.0)	
Bocavirus	2 (16.7)	1 (12.5)	1 (25.0)	
Adenovirus	2 (16.7)	2 (25.0)	0 (0.0)	
Dual pathogen‡	1 (8.3)	1 (12.5)	0 (0.0)	
COVID-19 severity, n (%)				
Severe-to-critical	168 (41.1)	112 (42.7)	56 (38.1)	0.359
Mild-moderate	241 (58.9)	150 (57.3)	91 (61.9)	
Nosocomial infections during hospitalization, n (%)				
Presence of nosocomial infections	103 (25.2)	76 (29.0)	27 (18.4)	**0.017**
Mortality, n (%)				
30-day mortality	58 (14.2)	41 (15.6)	17 (11.6)	0.256
Mortality (in hospital)	79 (19.3)	58 (22.1)	21 (14.3)	0.054

†Dual pathogens in bacterial respiratory, PCR: *Haemophilus influenza* and *Streptococcus pneumoniae*, ‡Dual pathogens in viral respiratory PCR: Human rhinovirus and Influenza B, COVID-19: Coronavirus disease 2019, CT: Computed tomography, PCR: Polymerase chain reaction, IQR: Interquartile range, CAP: Community-acquired pneumonia, SARS-CoV-2: Severe acute respiratory syndrome-Coronavirus-2

Table 3. Antibiotic treatment and clinical, biochemical, and microbiological parameters

		Total	Initial antibiotic therapy	Not receiving initial antibiotic therapy	*p* value
Baseline inflammatory marker levels, n (%)					
PCT (n= 397)	≥ 0.1 ng/mL	167 (42.1)	133 (65.5)	34 (17.5)	**< 0.001**
	< 0.1 ng/mL	230 (57.9)	70 (34.5)	160 (82.5)	
CRP (n= 405)	≥ 0.8 mg/dL	345 (85.2)	197 (97.0)	148 (73.3)	**< 0.001**
	< 0.8 mg/dL	60 (14.8)	6 (3.0)	54 (26.7)	
Leukocyte count (n= 409)	< 4.1 x 10^3/µL	53 (13.0)	20 (9.8)	33 (16.2)	**< 0.001**
	4.1-11.2 x 10^3/µL	269 (65.8)	114 (55.6)	155 (76.0)	
	> 11.2 x 10^3/µL	87 (21.3)	71 (34.6)	16 (7.8)	
Inflammatory markers at antibiotic discontinuation, n (%)					
PCT (n= 147)	No change	47 (32.0)	34 (28.3)	13 (48.1)	**0.046**
	Improved	100 (68.0)	86 (71.7)	14 (51.9)	
CRP (n= 321)	No change	97 (30.2)	42 (22.8)	55 (40.1)	**0.001**
	Improved	224 (69.8)	142 (77.2)	82 (59.9)	
Leukocyte (n= 136)	No change	61 (44.9)	36 (39.6)	25 (55.6)	0.078
	Improved	75 (55.1)	55 (60.4)	20 (44.4)	
Baseline clinical parameters, n (%)					
Oxygen saturation (n= 409)	SaO_2 ≥ 90 mmHg	200 (48.9)	35 (17.1)	165 (80.9)	**< 0.001**
	SaO_2 < 90 mmHg	209 (51.1)	170 (82.9)	39 (19.1)	
Fever (n= 409)	< 38 °C	130 (31.8)	48 (23.4)	82 (40.2)	**0.001**
	≥ 38 °C	279 (68.2)	157 (76.6)	122 (59.8)	
Clinical parameters at antibiotic discontinuation, n (%)					
Oxygen saturation (n= 209)	No change	96 (45.9)	77 (45.3)	19 (48.7)	0.699
	Improved	113 (54.1)	93 (54.7)	20 (51.3)	
Fever (n= 279)	No change	95 (34.1)	48 (30.6)	47 (38.5)	0.164
	Improved	184 (65.9)	109 (69.4)	75 (61.5)	
Respiratory PCR monitoring, n (%)					
Bacterial multiplex PCR (n= 295)	Positive	59 (20.0)	28 (17.9)	31 (22.3)	0.351
	Negative	236 (80.0)	128 (82.1)	108 (77.7)	
Viral multiplex PCR (n= 306)	Positive	12 (3.9)	8 (5.0)	4 (2.8)	0.320
	Negative	294 (96.1)	153 (95.0)	141 (97.2)	
Bacterial culture within 72 hours of hospitalization, n (%)					
Growth of the sputum culture (n= 52)	Yes	9 (17.3)	8 (17.8)	1 (14.3)	1.000
	No	43 (82.7)	37 (82.2)	6 (85.7)	
Growth of the blood culture (n= 272)	Yes	11 (4.0)	10 (6.0)	1 (1.0)	0.055
	No	261 (96.0)	157 (94.0)	104 (99.0)	

PCT: Procalcitonin, CRP: C-reactive protein, PCR: Polymerase chain reaction

Table 4. Factors influencing mortality in logistic regression analysis

	Univariable analysis		Multivariable analysis	
	Odds ratio (95% CI)	***p* value**	**Odds ratio (95% CI)**	***p* value**
Male	2.485 (1.314-4.701)	**0.005**	1.997 (0.963-4.142)	0.063
Age	1.057 (1.034-1.079)	**< 0.001**	1.028 (1.003-1.053)	**0.030**
Comorbidities	7.101 (2.171-23.231)	**0.001**	1.366 (0.276-6.768)	0.702
Presence of risk factors for CAP	6.317 (2.789-14.305)	**< 0.001**	1.653 (0.533-5.126)	0.384
Severe-to-critical patient	10.614 (5.042-22.344)	**< 0.001**	3.411 (1.506-7.724)	**0.003**
Initial antibiotic therapy	17.881 (6.337-50.456)	**< 0.001**	5.726 (1.866-17.569)	**0.002**
Nosocomial infection	6.936 (3.832-12.556)	**< 0.001**	3.557 (1.826-6.930)	**< 0.001**

CAP: Community-acquired pneumonia, CI: Confidence interval

negative PCR (64.9% versus 59.5%, $p < 0.001$). Corticosteroid use (dexamethasone or methylprednisolone) was more frequent in SARS-CoV-2 PCR-positive patients (43.1% versus 30.6%, $p= 0.013$). Nosocomial infections were more common in the SARS-CoV-2 PCR-positive group than in the PCR-negative group (29.0% versus 18.4%, respectively, $p= 0.017$), and in those who received corticosteroids compared with those who did not (59.2% versus 40.8%, respectively, $p < 0.001$). The median duration of antibiotic treatment did not differ between PCR-positive and PCR-negative patients ($p= 0.999$) (Table 2). Antibiotic treatment did not improve the clinical course of patients with positive SARS-CoV-2 PCR and negative results (data not shown).

Adverse events and pDDIs during follow-up

Acute kidney injury occurred in 11.2% of patients. Thirty-seven patients who received antibiotic treatment experienced nephrotoxicity (52.8% for stage 1; 36.1% for stage 2; and 11.1% for stage 3). Nephrotoxicity was significantly higher in patients treated with antibiotics than in patients not treated with antibiotics (18.0% versus 4.4%; $p < 0.001$). Patients treated with piperacillin-tazobactam experienced more nephrotoxicity than those treated with other antibiotics (31.3% versus 9.6%, $p < 0.001$).

Elevated aminotransferase levels occurred in 60.9% (n= 249) of the patients. Elevated aspartate aminotransferase levels were observed more frequently in patients receiving antibiotic treatment than in those who were not receiving antibiotic treatment [58.0% (n= 119) versus 46.6% (n= 95), $p= 0.023$]. Alanine aminotransferase elevation was similar between patients who did and did not receive antibiotic(s) [52.7% (n= 108) versus 46.6% (n= 95), $p= 0.236$].

Antibiotic-related pDDIs were detected in 77.1% of the patients treated with antibiotics (the rate of minor pDDIs was 30.7%, the rate of moderate pDDIs was 68.3%, and the rate of major pDDIs was 15.1%) (Supplement 2). The median number of pDDIs detected with antibiotics was 2 (1-3). The 30-day mortality was similar between patients with and without antibiotic-related pDDIs (25.3% versus 29.8%, $p= 0.541$).

DISCUSSION

Our results emphasize that initial empirical antibiotic treatment is mostly unnecessary in patients with COVID-19. We observed that empirical antibiotics did not affect mortality regardless of comorbidities and severity of pneumonia. In contrast, they lead to drug-related problems, such as nephrotoxicity and pDDIs. Although inflammatory markers were improved, clinical parameters remained similar between patients who did and did not receive antibiotics.

Several studies reported an incidence of 2.0-17.2% bacterial co-infection in patients with COVID-19. However, antibiotic therapy was administered to 48.6-100% of patients.[2,17-22] In our study (n= 409) antibiotics were used in 50.1% of the COVID-19 patients for presumptive b-CAP. A cross-sectional study from our center found that respiratory bacterial co-infection was present in 26 (13.1%) of 198 outpatients with COVID-19, with only 10.6% received.[23] This could be explained by the preference of the physician for antibiotic administration to patients who require hospitalization for pulmonary infection.

Whether the patient was positive by PCR for SARS-CoV-2 or diagnosed presumptively based on clinical and imaging findings did not affect the clinical decision-making of the physicians to start antibiotics. Antibiotic treatment rates and antibiotic preferences were similar between patients with and without SARS-CoV-2 PCR ($p= 0.947$). In a study by Beović et al.,[24] clinical presentation was the most common indication for antibiotic therapy in patients with COVID-19. It was also emphasized that laboratory markers and radiological evaluation were effective in the antibiotic therapy decision.[24] Similarly, in our study, antibiotic use was related to supplemental oxygen therapy, fever, and elevated acute-phase reactants.

The role of inflammatory markers in determining the efficacy of antibiotic therapy is limited. In our study, significant improvement was achieved in these parameters but not in the clinical course. The use of anti-inflammatory agents (corticosteroids or tocilizumab) and the rate of concomitant nosocomial infection are confounding factors in determining the impact of antibiotic treatment on serum levels of inflammatory markers. In our study, more patients who received empirical

antibiotics were also treated with corticosteroids (61.0% versus 16.2%; $p < 0.001$). This finding could explain the improvement in inflammatory marker levels observed in the antibiotic-treated group, despite no clinical improvement.

Empirical antibacterial therapy may have undesirable consequences. Contrary to other studies,[18,19,21] we found that the nosocomial infection rate was significantly higher in patients treated with antibiotics for CAP (39.0% versus 11.3%, respectively, $p < 0.001$). In addition, hospital stay was longer among patients treated with antibiotics ($p < 0.001$). This could also be related to a more severe initial clinical presentation, the presence of certain comorbidities, such as COPD and diabetes mellitus, which are known to have a negative effect on the hospital stay of patients with COVID-19, and the more frequent use of corticosteroids in this patient population.

Pettit et al.[2] reported that the mortality rate of patients with COVID-19 receiving empirical antibiotic therapy for CAP was 13.8%.[2] A retrospective study by Ng et al.[25] On patients with COVID-19 showed that mortality was higher in patients receiving antibiotic treatment (13.3% versus 0.5%, $p < 0.001$). Furthermore, their study did not associate antibiotic therapy with lower mortality [adjusted odds ratio 14,492, (95% CI 0.533-393.875)].[25] We found that initial empirical antibacterial treatment was an independent risk factor for mortality (Table 4).

Study limitations

This was a single-center, observational study; thus, the results may not be applicable to other centers. In some patients with positive CT imaging but negative PCR results, the absence of antibody test results makes the definitive diagnosis of COVID-19 unclear. We did our best to rule out other viral/bacterial infections and non-infectious causes, such as congestive heart failure, leaving us with a COVID-19 diagnosis during the pandemic.

CONCLUSION

Attending physicians tend to prescribe antimicrobials to prevent adverse outcomes in high-risk COVID-19 patients, *i.e.*, patients with older age, severe disease, comorbidities such as COPD, AF, and diabetes mellitus, high inflammatory marker levels, fever, and the necessity for oxygen supplementation even when there is no evidence of co-infection. Irrational use of antibiotics may cause drug-related problems and negative effects by disrupting the gastrointestinal microbiota in patients with COVID-19, including altered metabolic activity and increased antibiotic resistance. This study provides further evidence for antimicrobial stewardship efforts and recommends discontinuing empirical antibiotics, even if they are not started.

Acknowledgment

This study was presented at the 16th World Intensive and Critical Care Congress (WICC), İstanbul, Türkiye, on 26-30 August 2023.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki, and the study protocol was reviewed and approved by the Hacettepe University Non-Interventional Clinical Research Ethics Committee (approval number: GO 22/520, date: 31.05.2022).

Informed Consent: All participants provided informed consent.

Authorship Contributions

Surgical and Medical Practices: P.B.E., E.K., G.T.D., M.Ç.S., Concept: P.B.E., E.K., A.Ç.İ., K.D., S.Ü., Ö.U., Design: P.B.E., G.T.D., M.Ç.S., A.C.I., K.D., S.Ü., Ö.U., Data Collection or Processing: P.B.E., E.K., G.T.D., M.Ç.S., Analysis or Interpretation: P.B.E.,E.K, A.Ç.İ, Literature Search: P.B.E., A.Ç.İ., K.D., S.Ü., Ö.U., Writing: P.B.E., E.K.

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Supplement 1. Respiratory pathogens were tested using respiratory panel multiplex PCR (Seegene, South Korea)

Viral pathogens	Bacterial pathogens
Adenovirus	*Streptococcus pneumoniae*
Bocavirus	*Haemophilus influenza*
Enterovirus	*Mycoplasma* spp.
Human rhinovirus	*Legionella* spp.
Influenza A	
Influenza B	
Metapneumovirus	
Coronavirus OC43	
Coronavirus HKU1	
Coronavirus 229E	
Coronavirus NL63	
Parainfluenza 1	
Parainfluenza 2	
Parainfluenza 3	
Parainfluenza 4	
RSV A	
RSV B	
Microbiological culture (deep tracheal aspirate or sputum)	
-	Meticillin-sensitive *Staphylococcus aureus* *Streptococcus parasanguinis* *Haemophilus influenzae* *Klebsiella pneumoniae* *Klebsiella aerogenes*

PCR: Polymerase chain reaction, RSV: Respiratory Syncytial Virus

Supplement 2. Classification of antibiotic-drug interactions

Major antibiotic-drug interactions (n= 42)*		Moderate antibiotic-drug ınteractions (n= 221)*	
Clarithromycin and atorvastatin	14.3%	Doxycyclin-piperacillin	21.7%
Clarithromycin-methylprednisolone	9.5%	Doxycycline-calcium carbonate	20.8%
Moxifloxacin-dexamethasone	9.5%	Doxycycline-insulin	16.3%
Clarithromycin, fentanyl	7.1%	Doxycycline-ampicillin	10.4%
Clarithromycin/haloperidol	4.8%	Clarithromycin and dexamethasone	6.3%
Clarithromycin and quetiapine	4.8%	Ceftriaxone-furosemide	5.9%
Clarithromycin and tamsulosin	4.8%	Clarithromycin-lactulose	2.3%
Clarithromycin and midazolam	4.8%	Doxycycline-digoxin	1.8%
Clarithromycin and amiodarone	4.8%	Clarithromycin-amlodipine	1.8%
Clarithromycin and silodosin	4.8%	Clarithromycin, lansoprazole	1.4%
Meropenem and tramadol	4.8%	Doxycycline (warfarin)	0.9%
Clarithromycin and warfarin	2.4%	Doxycycline-rocuronium	0.9%
Clarithromycin-colchicine	2.4%	Clarithromycin-ınsulin	0.9%
Clarithromycin and escitalopram	2.4%	Clarithromycin and propofol	0.9%
Clarithromycin-hydroxychloroquine	2.4%	Levofloxacin, quetiapine	0.9%
Levofloxacin-methylprednisolone	2.4%	Levofloxacin-lactulose	0.9%
Levofloxacin-dexamethasone	2.4%	Ceftriaxone (warfarin)	0.5%
Levofloxacin/haloperidol	2.4%	Cefuroxime-pantoprazole	0.5%
Levofloxacin-insulin	2.4%	Piperacillin and warfarin	0.5%
Moxifloxacin (granisetron)	2.4%	Moxifloxacin, aspirin (low strength)	0.5%
Moxifloxacin-insulin	2.4%	Moxifloxacin/famotidine	0.5%
Meropenem-valproic acid	2.4%	Moxifloxacin/ibuprofen	0.5%
		Levofloxacin, aspirin (low strength)	0.5%
		Levofloxacin, mirtazapine	0.5%
		Doxycycline-sucralfate	0.5%
		Doxycycline (primidone)	0.5%
		Doxycycline, carbamazepine	0.5%
		Clarithromycin, clopidogrel	0.5%
		Clarithromycin-sertraline	0.5%

*Indicates the total number of interactions