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Antibiotic use and Influencing Factors Among Hospitalized Patients with COVID-19: A Multicenter Point-Prevalence Study from Turkey

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Background: Broad-spectrum empirical antimicrobials are frequently prescribed for patients with coronavirus disease 2019 (COVID-19) despite the lack of evidence for bacterial coinfection.

Aims: We aimed to cross-sectionally determine the frequency of antibiotics use, type of antibiotics prescribed, and the factors influencing antibiotics use in hospitalized patients with COVID-19 confirmed by polymerase chain reaction.

Study Design: The study was a national, multicenter, retrospective, and single-day point prevalence study.

Methods: This was a national, multicenter, retrospective, and single-day point-prevalence study, conducted in the 24-h period between 00:00 and 24:00 on November 18, 2020, during the start of the second COVID-19 peak in Turkey.

Results: A total of 1500 patients hospitalized with a diagnosis of

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COVID-19 were included in the study. The mean age ± standard deviation of the patients was 65.0 ± 15.5, and 56.2% (n = 843) of these patients were men. Of these hospitalized patients, 11.9% (n = 178) were undergoing invasive mechanical ventilation or ECMO. It was observed that 1118 (74.5%) patients were receiving antibiotics, of which 416 (37.2%) were prescribed a combination of antibiotics. In total, 71.2% of the patients had neither a clinical diagnosis nor microbiological evidence for prescribing antibiotics. In the multivariate logistic regression analysis, hospitalization in a state hospital ($p <$ 0.001), requiring any supplemental oxygen ($p = 0.005$), presence of moderate/diffuse lung involvement ($p < 0.001$), C-reactive protein > 10 ULT coefficient ($p < 0.001$), lymphocyte count < 800 ($p = 0.007$), and clinical diagnosis and/or confirmation by culture ($p < 0.001$) were found to be independent factors associated with increased antibiotic use.

Conclusion: The necessity of empirical antibiotics use in patients with COVID-19 should be reconsidered according to their clinical, imaging, and laboratory findings.

INTRODUCTION

Coronavirus disease-2019 (COVID-19) is an infectious disease that started toward the end of 2019 and spread rapidly worldwide, affecting populations globally. From the onset of this disease, various challenges have been encountered and different approaches have been suggested regarding its diagnosis and treatment. One of the key issues is that broad-spectrum empirical antimicrobials are frequently prescribed for patients with respiratory tract infections due to severe acute respiratory syndrome-coronavirus 2 (SARS CoV-2) despite the lack of evidence for bacterial coinfection.[1] The severity of the disease, possibility of bacterial coinfection, increased workload of physicians, progression of COVID-19 pneumonia, difficulties in clinically distinguishing bacterial/fungal superinfections, and laboratory facilities being allocated to the diagnosis of COVID-19 have led to significant challenges in antimicrobial management for clinicians. Some of the concerns regarding bacterial coinfection in COVID-19 is based on previous experiences with influenza.[2] Considering all these issues, it is not surprising that antibacterial drugs are being overprescribed.[3,4] A meta-analysis reported that only 7% of hospitalized patients with COVID-19 had a bacterial coinfection. A higher proportion of patients in the intensive care unit (ICU) had bacterial coinfections than those treated in the wards (14% versus 4%).[5] In another meta-analysis, bacterial coinfection was detected in 3.5% of the patients, and secondary bacterial infection in 14.3% of the patients. The overall proportion of patients with COVID-19 who had a bacterial infection was 6.9%. Bacterial infection was common in critically ill patients (8.1%). However, a study report that 71.9% of patients with COVID-19 received antibiotics.[6] Rawson et al.[1] also reported that broad-spectrum antibiotics were widely used, i.e., in 72% of patients with COVID-19.

There is a need to focus on the measures that can be taken to ensure the rational use of antibiotics and to understand the factors influencing the prescription of antibiotics by physicians during the COVID-19 period. In this study, we aimed to cross-sectionally determine the frequency of antibiotics use, type of antibiotics prescribed, and the factors influencing antibiotics use in hospitalized patients with COVID-19 confirmed by polymerase chain reaction (PCR) test.

MATERIALS AND METHODS

Study Design and Setting

This was a national, multicenter, retrospective, and single-day point-prevalence study, conducted in the 24-h period between 00:00 and 24:00 on November 18, 2020, during the beginning of the second COVID-19 peak in Turkey.[7] The study was conducted in 13 hospitals, including five state hospitals and eight training and research hospitals, to enhance its ability to represent antibiotic use in patients diagnosed with COVID-19. All adult patients diagnosed with severe acute respiratory syndrome coronavirus-2 (SARS CoV-2) infection by PCR and hospitalized in the ward or ICU with a diagnosis of COVID-19 were included in the study. Individuals aged < 18 years, those who were diagnosed with COVID-19 during hospitalization for another cause, and those who were diagnosed with the disease based on clinical findings but were negative for SARS CoV-2 by PCR test were excluded from the study.

The study was approved for compliance by the scientific research platform of the Ministry of Health with the code 2021-01-03T19_17_44 on January 12, 2021. It was subsequently approved by the Ethics Committee of University of Health Sciences Turkey, Dışkapı Yıldırım Beyazıt Training and Research Hospital on January 25, 2021, with number 103/20, and signed informed consent was waived.

Data Collection

The patients' clinical and laboratory data and data pertaining to their treatments were retrieved from the hospital automation systems and recorded online in the form prepared for this purpose. The details included in the online form included age, gender, type of hospital in which the patient was treated, the clinic (ward or ICU) in which the patient was hospitalized on November 18, 2022, the day of hospitalization in the ward and/or ICU, and the intubation day for the intubated patients. The presence of lung involvement and its extent were determined according to imaging results, and whether imaging was performed using posteroanterior lung radiography or computed tomography was also determined. In addition, whether antibiotic was administered and whether the decision was based on clinical or laboratory evidence were documented. Antibiotic group, clinical and/or microbiological diagnosis of bacterial infection, leukocyte and lymphocyte counts, C-reactive protein (CRP), and procalcitonin (PCT) values were also recorded.

Clinical scores for the study day were classified as follows according to the World Health Organization Ordinal Scale for Clinical Improvement: 1- hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection control or other nonmedical reasons); 2- hospitalized, not requiring supplemental oxygen, but requiring ongoing medical care (related to COVID-19 or other medical conditions); 3- hospitalized and requiring supplemental oxygen; 4- hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices; 5- hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO).[8]

Statistical Analysis

Statistical analysis was performed using the IBM SPSS version 23 (Release 23.0.0.0) software. Statistical significance was defined as $p < 0.05$. Descriptive statistics were presented as percentage distributions and mean ± standard deviation (SD). Univariate analysis was conducted to determine the factors influencing antibiotic use and expressed as odds ratio with 95% confidence interval. A multivariate linear regression model was established to evaluate the factors affecting the duration of antibiotic use. Age, hospital unit, intubation status, clinical category, lung involvement, clinical diagnosis, length of hospital stay, CRP coefficient, lymphocyte level, and PCT coefficient were included in the model. Interactions and confounding factors were explored.

RESULTS

A total of 1500 patients hospitalized with a diagnosis of COVID-19 were included in the study. The mean age ± SD of the patients was 65.0 ± 15.5, and 56.2% (n = 843) of these patients were men. Of these hospitalized patients, 11.9% (n = 178) were undergoing invasive mechanical ventilation or ECMO. Mean ± SD for days of hospitalization was 6.6 ± 6.1 as of the study day. It was observed that 1,118 (74.5%) patients were receiving antibiotics, of which 416 (37.2%) were prescribed a combination of antibiotics. Demographic characteristics of the study group are listed in Table 1. The distribution of the antibiotics used is shown in Figure 1. Among the antibiotics, respiratory fluoroquinolones were the most preferred, followed by piperacillin-tazobactam, second and third generation cephalosporins, and carbapenems (41.0%, 16.6%, 16.4%, and 13.7%, respectively). Of the patients who used antibiotics, 28.2 % (n = 315) had a clinical diagnosis as an indication for antibiotic use, and 7.1% (n = 79) had a culture-antibiogram. In total, only 28.8% (n = 322) of patients had a clinical diagnosis and/or culture requiring antibiotic prescription.

In the univariate analysis, age ($p = 0.005$), hospitalization in an ICU ($p < 0.001$), intubation ($p < 0.001$), clinical category [being a patient receiving invasive mechanical ventilation or ECMO ($p < 0.001$), being a patient requiring the use of noninvasive ventilation or high-flow oxygen devices ($p < 0.001$), being a patient requiring any supplemental oxygen ($p < 0.001$)], moderate and diffuse radiological lung involvement ($p < 0.001$), increased number of hospitalization days ($p < 0.001$), upper limit of normal (ULT) CRP coefficient ≥ 11 in laboratory values ($p < 0.001$), ULT PCT

TABLE 1. Demographic Characteristics of the Study Group, n = 1500.

Variables	N	%
Age (mean ± SD)	65.0 ± 15.5	
Gender		
Male	843	56.2
Female	657	43.8
Type of hospital		
State hospital	413	27.5
Training and research hospital/university hospital	1087	72.5
Clinic		
Medical ward	1069	71.3
Intensive care unit	431	28.7
Intubation		
Yes	187	12.5
No	1313	87.5
Intubation days (mean ± SD)	5.8±7.8	
Clinical status		
Hospitalized, not requiring supplemental oxygen, and no longer requiring ongoing medical care	42	2.8
Hospitalized, not requiring supplemental oxygen, but requiring ongoing medical care	235	15.7
Hospitalized, requiring any supplemental oxygen	874	58.3
Hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices	171	11.4
Hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)	178	11.9
Antibiotic use		
No	382	25.5
1	702	46.8
2	372	24.8
≥ 3	44	2.9
Antibiotic combination		
No	702	62.8
Yes	416	37.2
Radiology		
Thorax CT	1316	90.4
Chest X-ray	140	9.6
Lung involvement		
No	96	6.4
Low	304	20.3
Moderate	606	40.4
Diffuse	493	32.9
CRP (ULT coefficient)		
> 20	559	38.1
11-20	330	22.5
1-10	481	32.8
Normal	96	6.5

TABLE 1. Continued.

Procalcitonin (ULT coefficient)		
> 20	101	10.6
11-20	41	4.3
1-10	389	40.8
Normal	422	44.3
Lymphocyte (mm³) (mean ± SD)	1223.6 ± 3664.9	
Leucocyte (mm³) (mean ± SD)	9026.6 ± 4988.4	
Length of hospital stay (days) (mean ± SD)	6.6 ± 6.1	
Clinical diagnosis and/or culture for antibiotic prescribing		
Yes	340	22.7
No	1,160	77.3
Clinical diagnosis of infection		
Bacterial pneumonia	272	18.1
Bloodstream infection	28	1.9
Urinary tract infection	22	1.5
COPD exacerbation	11	0.7
Skin-soft tissue infection	11	0.7
Ventilator-associated pneumonia	8	0.5
Intra-abdominal infection	6	0.4
Neutropenic fever	2	0.1
Culture-antibiogram		
Yes	82	5.5
No	1,418	94.5

CI: confidence intervals; SD: standard deviation; CT: computed tomography; CRP: C-reactive protein; ULT: upper limit of normal; COPD: Chronic Obstructive Pulmonary Disease.

coefficient ≥ 1 ($p < 0.001$), low mean lymphocyte count ($p < 0.001$), high mean leukocyte count ($p < 0.001$), and clinical diagnosis and/or confirmation by culture ($p < 0.001$) were found to be the factors associated with increased antibiotic use in patients with COVID-19 (Table 2).

On the study day, the duration of antibiotic use was found to be 5.0 ± 3.4 days (mean ± SD) in total, and 8 days (mean ± SD, 8.1 ± 7.1) in the patients hospitalized in the ICU. Antibiotic use was longer in patients with a clinical diagnosis requiring antibiotic use (mean ± SD, 11.2 ± 9.7), CRP ULT coefficient > 20 (mean ± SD = 7.4 ± 6.4) and PCT ULT coefficient > 20 (mean ± SD, 8.1 ± 5.8), patients with diffuse lung involvement (mean ± SD, 8.3 ± 7.3), and patients with clinical category ≥ 3 (mean ± SD, 9.1 ± 7.5).

In the multivariate logistic regression analysis, hospitalization in a state hospital ($p < 0.001$), requiring any supplemental oxygen ($p = 0.005$), presence of moderate/diffuse lung involvement ($p < 0.001$), CRP > 10 ULT coefficient ($p < 0.001$), lymphocyte count < 800 ($p = 0.007$), and clinical diagnosis and/or confirmation by culture ($p < 0.001$) were found to be independent factors associated with increased antibiotic use (Table 3). Hospitalization in a state hospital ($p < 0.001$) and being a patient who clinically required any supplemental oxygen were the factors associated with the increased use of cephalosporin + quinolone, while ULT PCT coefficient > 10 was found to be a factor associated with the decreased use of quinolones. Factors influencing the use of carbapenem and glycopeptide/linezolid are shown in Table 4.

In the multiple linear regression analysis, presence of moderate or diffuse lung involvement ($p = 0.004$), clinical diagnosis of bacterial infection and/or presence of bacterial infection confirmed

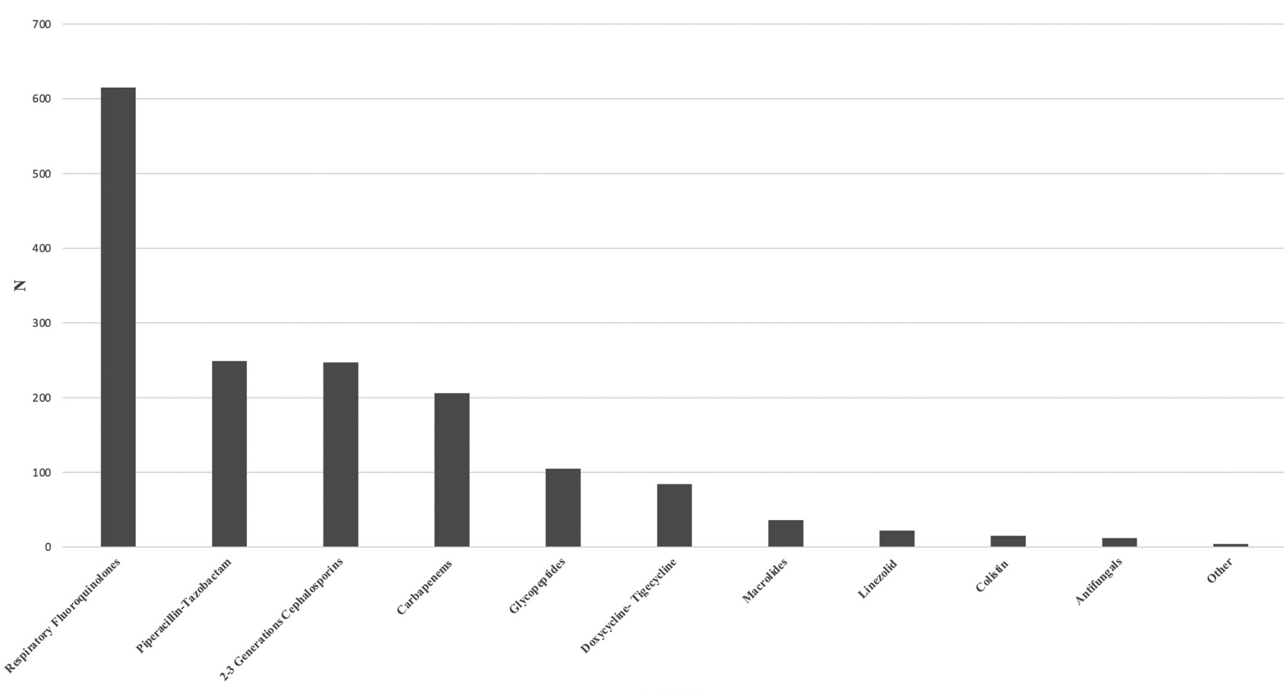

FIG. 1. The distribution of antibiotics use.

TABLE 2. Factors Influencing Antibiotic use in Patients with COVID-19, n = 1,500.

	Any antibiotic use					
Variables	Yes		No			
	N = 1,118	%	N = 382	%	OR (95% CI)	p
Age (mean ± SD)	65.7 ± 14.7		62.9 ± 17.3		-	0.005
Gender						
Male	632	56,5	211	55.2	1.1 (0.8-1.3)	0.666
Female	486	43,5	171	44.8		
Clinic						
Medical ward	767	68.6	302	79.1	0.6 (0.4-0.8)	< 0.001
Intensive care unit	351	31.4	80	20.9		
Intubation						
Yes	168	15.0	19	5.0	3.4 (2.1-5.5)	< 0.001
No	950	85.0	363	95.0		
Intubation days (mean ± SD)	5.9 ± 8.1		5.5 ± 3.6		-	0.802
Clinical status						
Hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)	160	14.3	18	4.7	10.7 (4.9-23.5)	< 0.001
Hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices	147	13.1	24	6.3	7.4 (3.5-15.6)	< 0.001
Hospitalized, requiring any supplemental oxygen	658	58.9	216	56.5	3.7 (2.0-6.9)	< 0.001
Hospitalized, not requiring supplemental oxygen, but requiring ongoing medical care	134	12.0	101	26.4	1.6 (0.8-3.1)	0.157
Hospitalized, not requiring supplemental oxygen, and no longer requiring ongoing medical care	19	1,7	23	6,0	1	
Radiology						
Thorax CT	1005	91.0	311	88.4	1.3 (0.9-2.0)	0.137
Chest x-ray	99	9.0	41	11.6		
Lung involvement						
No	40	3.6	56	14.7	1	
Low	188	16.8	116	30.4	2.3 (1.4-3.6)	< 0.001
Moderate	467	41.8	139	36.4	4.7 (3.0-7.4)	< 0.001
Diffuse	422	37.8	71	18.6	8.3 (5.2-13.4)	< 0.001
CRP (ULT coefficient)						
> 20	487	44.2	72	19.7	7.7 (4.8-12.3)	< 0.001
11-20	254	23.1	76	20.8	3.8 (2.4-6.3)	< 0.001
1-10	315	28.6	166	45.5	2.2 (1 4-3.3)	< 0.001
Normal	45	4.1	51	14.0	1	
Procalcitonin (ULT coefficient)						
> 20	93	12.6	8	3.8	4.9 (2.3-10.4)	< 0.001
11–20	35	4.7	6	2.8	2.5 (1.1-5.9)	0.037
1–10	316	42.6	73	34.4	1.8 (1.3-2.5)	< 0.001
Normal	297	40.1	125	59.0	1	
Lymphocyte (mm^3) (mean ± SD)	1175.9 ± 3988.7		1363.5 ± 2482.2		-	< 0.001**
Leucocyte (mm^3) (mean ± SD)	9465.8 ± 5259.9		7772.3 ± 3818.0		-	< 0.001**
Length of hospital stay (days) (mean ± SD)	6.7 ± 6.3		6.2 ± 5.7		-	0.001**
Clinical diagnosis for antibiotic prescribing						
Yes	315	28.2	16	4.2	9.1 (5.3–14.3)	< 0.001
No	803	71.8	366	95.8		

TABLE 2. Continued.

Clinical diagnosis of infection						
Urinary tract infection	20	1.8	2	0.5	3.5 (0.8–14.9)	0.076
Bacterial pneumonia	262	23.4	10	2.6	11.4 (6.0–21.7)	< 0.001
Intra-abdominal infection	6	0.5	-	-	4.1 (0.2–74.0)	0.347*
COPD exacerbation	11	1.0	-	-	7.6 (0.4–129.5)	0.076*
Bloodstream infection	26	2.3	2	0.5	4.5 (1.1–19.2)	0.025
Skin-soft tissue infection	9	0.8	2	0.5	1.5 (0.3–7.2)	0.739*
Neutropenic fever	2	0.2	-	-	1.4 (0.1–30.4)	1.000*
Ventilator-associated pneumonia	8	0.7	-	-	5.5 (0.3–96.1)	0.214*
Culture-antibiogram						
Yes	79	7.1	3	0.8	9.6 (3.0–30.6)	< 0.001
No	1039	92.9	379	99.2		
Clinical diagnosis and/or culture for antibiotic prescribing						
Yes	322	28.8	17	4.5	8.7 (5.3–14.3)	< 0.001
No	796	71.2	365	95.5		

*Fisher test **Mann-Whitney U Test
CI: confidence intervals; SD: Standard deviation; CT: computed tomography; CRP: C-reactive protein; ULT: upper limit of normal; COPD: Chronic Obstructive Pulmonary Disease.

TABLE 3. Multivariate Logistic Regression Analysis of Factors Influencing Antibiotic Use in Patients with COVID-19, n = 1,465.

	OR_{adj} (95% CI)	p*
Type of hospital		
State hospital	3.4 (2.4–4.9)	< 0.001
Training and research hospital/university hospital	1	
Clinical status		
Receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)	2.0 (1.1–3.7)	0.034
Requiring noninvasive ventilation or use of high-flow oxygen devices	2.0 (1.1–3.5)	0.019
Requiring any supplemental oxygen	1.6 (1.2–2.3)	0.005
Not requiring supplemental oxygen	1	
Lung involvement		
Moderate/diffuse	1.9 (1.4–2.6)	< 0.001
No/low	1	
CRP (ULT coefficient)		
> 10	1.8 (1.3–2.3)	< 0.001
≤ 10		
Lymphocyte		
< 800	1.5 (1.1–2.0)	0.007
≥ 800		
Clinical diagnosis and/or culture for antibiotic prescribing		
Yes	7.4 (4.4–12.5)	< 0.001
No	1	

*Wald test
CI: confidence intervals; CRP: C-reactive protein; ULT: upper limit of normal.

by culture ($p = 0.003$), days of hospitalization ($p < 0.001$), CRP > 10 ULT coefficient ($p = 0.006$), and lymphocyte count ($p < 0.001$) were found to be the factors influencing the duration of antibiotic use (Table 5).

DISCUSSION

In our study, it was observed that two-thirds of the patients hospitalized with a diagnosis of COVID-19 received antibiotics. A culture was present in 7.1% of the patients using antibiotics, and a clinical diagnosis was given as the justification for antibiotic use in 28.2% of them. In total, only 28.8% of patients had a clinical diagnosis and/or culture that provided an indication for prescribing antibiotics. Therefore, antibiotics were prescribed inappropriately in 71.2% of the patients. We identified five independent factors (hospitalization in a state hospital, requiring any supplemental oxygen, presence of moderate/diffuse lung involvement, lymphocyte count < 800, and clinical diagnosis of bacterial infection and/or confirmation by culture) associated with increased antibiotic use. Moreover, two of these were also identified as factors influencing the duration of antibiotic use (presence of moderate or diffuse lung involvement, clinical diagnosis of bacterial infection and/or presence of bacterial infection confirmed by culture). The other factors affecting the duration of antibiotic use were long hospitalization, CRP > 10 ULT coefficient, and lymphocyte count < 800.

Low rates of microbiologically proven coinfection and superinfection have also been reported in the literature.[9-11] In a study conducted in the United Kingdom, 37 (2.7%) of 1396 patients with COVID-19 were reported to have a clinically significant bacterial infection within 48 h of hospitalization. Nevertheless, 98% of randomly selected patients without coinfection received empirical antibiotic therapy.[12] A survey of 166 physicians from 23 countries reported that 61.8% of them prescribed antibiotics for

TABLE 4. Multivariate Logistic Regression Analysis of Factors Influencing any Antibiotic Use, Carbapenem Use, Glycopeptide/Linezolid Use, and Cephalosporin + Quinolone Use in Patients with COVID-19, n = 948.

	Any antibiotics		Carbapenem		Glycopeptide/Linezolid		Cephalosporin + Quinolone	
	OR_{adj} (95% CI)	p*	OR_{adj} (95% CI)	p*	OR_{adj} (95% CI)	p*	OR_{adj} (95% CI)	p*
Type of hospital								
State hospital	7.0 (3.7–13.1)	< 0.001	0.9 (0.6–1.4)	0.676	0.8 (0.5–1.4)	0.470	4.5 (3.1–6.6)	< 0.001
Training and Research Hospital/university hospital	1		1		1		1	
Clinical status								
Receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)	1.4 (0.7–3.0)	0.339	11.4 (3.8–34.4)	< 0.001	3.7 (1.3–10.6)	0.017	0.7 (0.4–1.3)	0.287
Requiring noninvasive ventilation or use of high-flow oxygen devices	2.3 (1.1–4.5)	0.022	8.2 (2.7–24.7)	< 0.001	5.4 (1.9–15.2)	0.002	0.8 (0.5–1.3)	0.334
Requiring any supplemental oxygen	2.0 (1.3–3.2)	0.002	3.6 (1.3–10.3)	0.017	2.0 (0.8–5.4)	0.162	1.9 (1.2–2.8)	0.002
Not requiring supplemental oxygen	1		1		1		1	
Lung involvement								
Moderate/diffuse	1.9 (1.2–2.8)	0.003	1.6 (0.8–3.2)	0.146	1.8 (0.9–3.9)	0.119	1.3 (0.9–1.9)	0.179
No/low	1		1		1		1	
CRP (ULT coefficient)								
> 10	1.2 (0.8–1.8)	0.292	1.5 (0.9–2.4)	0.109	0.6 (0.4–1.1)	0.076	1.2 (0.9–1.6)	0.182
≤ 10	1				1		1	
Procalcitonin (ULT coefficient)								
> 10	1.6 (0.8–3.0)	0.188	1.5 (0.9–2.3)	0.113	1.6 (0.9–2.7)	0.091	0.5 (0.3–0.8)	0.002
≤ 10	1				1		1	
Lymphocyte								
< 800	1.8 (1.3–2.6)	0.002	1.7 (1.2–2.6)	0.007	2.1 (1.3–3.4)	0.001	1.2 (0.9–1.6)	0.182
≥ 800	1				1		1	
Clinical diagnosis and/or culture for antibiotic prescribing								
Yes	6.9 (3.9–12.3)	< 0.001	1.6 (1.1–2.3)	0.032	3.5 (2.2–5.6)	< 0.001	1.1 (0.8–1.5)	0.649
No	1		1		1		1	

*Wald test
CI: confidence intervals; CRP: C-reactive protein; ULT: upper limit of normal.

patients with COVID-19.[3] Many studies from different countries have reported high rates of empirical antibiotics use in patients with COVID-19.[13,14] In two other studies, antibiotic use was found in more than 70% of COVID-19 cases.[5,6] Ghazi et al.[15] reported that 65.5% of adult patients who were admitted in their institution during the 2012-2013 and 2013-2014 flu seasons with a diagnosis of influenza were prescribed an antibiotic empirically on admission. In our study, 74.5% of the hospitalized patients with COVID-19 received antibiotics. It is obvious that clinicians have continued their antibiotics-prescribing habits with COVID-19 as it was with influenza, although studies show that bacterial coinfection is less common in COVID-19 than influenza.[16,17]

A major challenge faced during the COVID-19 pandemic is the lack of evidence on reliable treatment options.[18] Concurrent clinical suspicion of bacterial pneumonia and anxiety associated with it, evidence of superinfection, or elevations in inflammation

TABLE 5. Multiple Linear Regression Analysis of Factors Influencing the Duration of Antibiotic Use in Patients with COVID-19, n = 947.

	Standardized beta	Partial correlation coefficient	p*
Moderate and diffuse lung involvement	0.084	0.095	0.004
Infection confirmed by clinical diagnosis and/or culture	0.089	0.098	0.003
Length of hospital stay	0.452	0.464	< 0.001
CRP (> 10 ULT coefficient)	0.082	0.090	0.006
Lymphocyte (< 800)	0.133	0.150	< 0.001
Procalcitonin (> 10 ULT coefficient)	-0.043	-0.047	0.146
Stable			0.777

*When age, hospitalization, presence of intubation, and clinical category are controlled.
ULT: upper limit of normal; COVID-19: coronavirus disease-2019.

markers in these patients may encourage physicians to prescribe antibiotics. Our study showed that there was a significant rate of antibiotic use without a clinical or laboratory diagnosis of bacterial infection in patients with COVID-19, and this approach can have serious consequences. Inappropriate use of antibiotics in patients with COVID-19 will lead to bacterial resistance[8], *Clostridioides difficile* infection, complications such as renal and hepatic failure, and increased costs.[19] In a study conducted in China between January and March 2020, it was reported that 6.8% of 1495 patients hospitalized with a diagnosis of COVID-19 had acquired secondary bacterial infections, of which 49.0% died during hospitalization.[20] In a study conducted in the USA, bacterial coinfection was found in 19% of the patients, and genitourinary infections, reported in 57% of the patients, were the most common.[14] In our study, the most common clinical diagnosis justifying antibiotic use was bacterial pneumonia, followed by very low rates of circulatory (1.9%) and urinary tract (1.5%) infections.

A recent multinational survey revealed that 82.9% of physicians started treatment according to the local community-acquired pneumonia guidelines in their patients with COVID-19. The use of a combination of beta-lactams and macrolides or fluoroquinolones was reported by 52.4% of the participants. For patients in the ICU, the most prescribed antibiotic was piperacillin/tazobactam.[3] In a study reported from the United Kingdom, the most prescribed antibiotics were a combination of second and third generation cephalosporins and clarithromycin (12). In a study conducted in the USA, cefepime (45%), ceftriaxone (54%), vancomycin (48%), and azithromycin (47%) were the most prescribed antibiotics.[14] In our study, respiratory tract fluoroquinolones were the most prescribed antibiotics, followed by piperacillin-tazobactam and second and third generation cephalosporins. We believe that the choice of these antibiotics is associated with the anxiety induced the suspicion of bacterial pneumonia in the patients with COVID-19.

In a study from Belgium, fever and a low SpO_2/FiO_2 (single peripheral blood oxygen saturation/fraction of inspired oxygen) ratio at presentation, underlying lung disease, and longer hospital stays were reported as the factors associated with antibiotics prescription for possible respiratory superinfection in patients with COVID-19.[21] Another study reported that the most important reason motivating clinicians to initiate antibiotic therapy was the clinical presentation, followed by laboratory markers of inflammation and radiological findings.[3] Based on past experiences, clinicians often make unnecessary decisions to prescribe antibiotics for patients with severe disease.[22] In our study, hospitalization in a state hospital and disease severity were found to be factors associated with the increased use of any antibiotic. The high rates of antibiotic use in state hospitals may be related to the excessive workload and increased patient population in these hospitals during this period. Invasive mechanical ventilation or ECMO were the factors associated with the increased use of carbapenem and glycopeptide or linezolid. The fact that this patient group comprised clinically severe patients suggests that the more severe the clinical condition, the more frequently the physicians use broad-spectrum antibiotics, regardless of whether the patient has any evidence of bacterial infection. This finding reveals the need to provide training on appropriate antibiotic use for teams treating severe patients. Thus, physicians treating critically ill patients during the COVID-19 pandemic should be trained in the principles of appropriate antibiotic use.

PCT levels have been investigated in different studies to differentiate bacterial respiratory tract infections from viral infections. It has been suggested that the elevated PCT levels observed in COVID-19 may be due to bacterial coinfection that causes systemic sepsis or may be a direct marker of a more severe or widespread viral infection.[23] Serum PCT may be useful for detecting secondary infections in patients with COVID-19. As in other viral infections, PCT levels usually remain within the normal range in isolated COVID-19. PCT is useful for facilitating decisions regarding antibiotic therapy in lower respiratory tract infections. In our study, the presence of PCT (> 10 ULT coefficient) was not associated with the increased use of antibiotics, but it was found to be a factor associated with the decreased use of cephalosporin and quinolone. This finding could be attributed to the fact that the participants of this study based their decision to prescribe antibiotics on elevated CRP values in the patients with COVID-19. However, CRP is not a good indicator for antibiotics prescription during the COVID-19 pandemic.[24] Damages to the respiratory tract may lead to an increase in CRP, and it is often elevated in patients with COVID-19 at presentation.[25]

During the COVID-19 pandemic period, the number of presentations to healthcare services decreased across Turkey, and accordingly, in 2020, there was a 24.30% decrease in antibacterial drug sales on a box basis compared with 2019. However, when the antibiotic groups were considered, a 1.90% decrease was observed in the fluoroquinolone group (unpublished data: IQVIA dataview program, 2020).[26] We believe that this finding may be due to the significant drop in the overall number of patients presenting to the hospitals and primary care health facilities. On the other hand, the decrease in total antibiotic consumption can be considered as a factor that favors a reduction in antibiotic resistance.

A recent study reported that the mean reported usual duration of antibiotic treatment in patients with COVID-19 was 5 days in North America, 5.44 days in the UK, 6.59 days in Spain, 7.2 days in Italy, 7.63 days in Turkey, and 8.47 days in other countries, with a mean duration of 7.12 days in all countries.[3] The duration of antibiotic use for patients who were using antibiotics on the day of this study was 5.0 ± 3.4 days (mean ± SD). Moderate or diffuse lung involvement, bacterial infection confirmed by clinical diagnosis and/or culture, days of hospitalization, CRP > 10 ULT coefficient, and lymphocyte count < 800 were found to be the factors influencing the duration of antibiotic use. In fact, it is not surprising that the duration of antibiotic use increases with the length of hospitalization days, as patients may suffer from nosocomial infections during prolonged hospitalization. Hand hygiene, aseptic techniques, and isolation should be promoted as key interventions in reducing nosocomial infections.[4]

The limitations of our study were as follows: microbiological culture results were recorded as present/absent, only inpatients were included, and antibiotics prescribed at the outpatient clinic were not included. In addition, since our study was a point-prevalence study, it is not possible to generalize the results to the entire period. However, we believe that the results are important because it is a national, multicenter study with a large number of patients.

This study found that two-thirds of the patients hospitalized with a diagnosis of COVID-19 received antibiotics. However, only 28.8% of them had a clinical diagnosis and/or culture for antibiotic prescribing. Hospitalization in a state hospital and disease severity are significant factors associated with increased antibiotic use. However, in most patients hospitalized with COVID-19, disease severity was due to viral pneumonia rather than bacterial coinfection. Physicians treating critically ill patients during the COVID-19 pandemic should be trained in the principles of appropriate antibiotic use. For the purposes of antibiotic stewardship, before empirical antibiotic use, the necessity of antibiotics should be reconsidered in the light of clinical, imaging, and laboratory findings. Prospective studies are needed to understand the risk factors for bacterial and fungal infections in patients with COVID-19 and to develop evidence-based principles for antimicrobial management.

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