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A Comparative Analysis of Antimicrobial Resistance Patterns in Ventilator-Associated Pneumonia Pathogens: Pre- and During the COVID-19 Pandemic-A Cohort Study

Ventilatör İlişkili Pnömoni Etkenlerinin Antimikrobiyal Direnç Paternlerinin Karşılaştırmalı Analizi: COVID-19 Pandemisi ve Öncesinde-Bir Kohort Çalışması

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This study was presented as an oral presentation at 24th Turkish Clinical Microbiology and Infectious Diseases Congress (KLIMIK 2024), March 6-9, 2024, Antalya, Türkiye.

ABSTRACT Objective: During the coronavirus disease-2019 (COVID-19) pandemic, antibiotics were widely used in many countries without regard for the general rules of antibiotic use. This intense antibiotic use is thought to have caused antimicrobial resistance in agents that cause ventilator-associated pneumonia (VAP). This study aimed to compare antimicrobial resistance patterns of VAP agents before and during the COVID-19 pandemic. **Material and Methods:** This retrospective cohort study involved patients diagnosed with VAP before and during COVID-19 in a training and research hospital. The antimicrobial resistance patterns of VAP agents were examined in endotracheal aspirate samples. **Results:** The results were compared between the COVID-19 and pre-COVID-19 groups. From 178 patients who met the VAP diagnostic criteria in the intensive care unit, the COVID-19 group comprised 107, and the pre-COVID-19 group, 71. In both periods, *Acinetobacter baumannii* was the most common infectious agent, followed by Pseudomonas aeruginosa (35.2%) in the pre-COVID-19 period. During the COVID-19 pandemic, *Klebsiella pneumoniae* was the second most common infectious agent (20.6%). During the COVID-19 pandemic, there was an increase in antimicrobial resistance to piperacillin-tazobactam, ciprofloxacin, amikacin, and cefepime antibiotics compared to before. **Conclusion:** The results of this study demonstrated increased antimicrobial resistance in some microorganisms that caused VAP in COVID-19 patients receiving mechanical ventilator support in the intensive care unit. The increased resistance pattern may have contributed to the failure to treat VAP. Determination of the antibiotic resistance patterns is essential concerning reducing treatment failures and preventing antimicrobial resistance.

Keywords: *Acinetobacter baumannii;* antimicrobial resistance; critical care; ventilator-associated pneumonia

ÖZET Amaç: Koronavirüs hastalığı-2019 [coronavirus disease-2019 (COVID-19)] salgını sırasında antibiyotikler, antibiyotik kullanımının genel kurallarına bakılmaksızın birçok ülkede yaygın olarak kullanıldı. Bu yoğun antibiyotik kullanımının, ventilatör ilişkili pnömoniye (VİP) neden olan etkenlerde antimikrobiyal dirence neden olduğu düşünülmektedir. Bu çalışma, COVID-19 salgını öncesi ve sırasında VİP etkenlerinin antimikrobiyal direnç paternlerini karşılaştırmayı amaçlamaktadır. **Gereç ve Yöntemler:** Bu retrospektif kohort çalışmasına, bir eğitim ve araştırma hastanesinde COVID-19 öncesi ve sırasında VİP tanısı konulan hastalar dâhil edildi. VİP etkenlerinin antimikrobiyal direnç modelleri, endotrakeal aspirat örneklerinde incelendi. **Bulgular:** Sonuçlar COVID-19 ve COVID-19 öncesi gruplar arasında karşılaştırıldı. Yoğun bakım ünitesinde VİP tanı kriterlerini karşılayan 178 hastadan 107'si COVID-19 grubunda, 71'i ise COVID-19 öncesi grubunda yer aldı. Her iki dönemde de en sık görülen enfeksiyon etkeni *Acinetobacter baumannii* iken COVID-19 öncesi dönemde bunu Pseudomonas aeruginosa (%35,2) izledi. COVID-19 pandemisi sırasında ise *Klebsiella pneumoniae* ikinci en sık görülen enfeksiyon etkeniydi (%20,6). COVID-19 pandemisi sırasında, pandemi öncesi döneme göre piperasilin-tazobaktam, siprofloksasin, amikasin ve sefepim antibiyotiklerine karşı antimikrobiyal dirençte artış görüldü. **Sonuç:** Bu çalışmanın sonuçları, yoğun bakımda mekanik ventilatör desteği alan COVID-19 hastalarında VİP etkeni olan bazı mikroorganizmalarda antimikrobiyal direncin arttığını göstermiştir. Artan direnç paterni, VİP tedavisindeki başarısızlığa katkıda bulunmuş olabilir. Antibiyotik direnç paternlerinin belirlenmesi, tedavi başarısızlıklarının azaltılması ve antimikrobiyal direncin önlenmesi açısından önemlidir.

Anahtar Kelimeler: *Acinetobacter baumannii*; antimikrobiyal direnç; yoğun bakım; ventilatör-ilişkili pnömoni

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Antibiotics were widely used in many countries to treat secondary bacteria infections seen during the coronavirus disease-2019 (COVID-19) pandemic without regard to the general rules of antibiotic use.[1] In patients hospitalized with severe COVID-19 symptoms and those affected by healthcare-associated infections, antibiotics became a generally integral part of treatment. In addition to broad-spectrum antibiotics in the treatment of ventilator-associated pneumonia (VAP), empirical antibiotics were often used, especially in patients with poor clinical conditions, although this is not supported in the literature. Studies have shown that increased antibiotic use during the pandemic led to a rise in antibiotic-resistant bacteria.[2-4] It has been thought that microorganisms causing VAP could have developed antibiotic resistance during the COVID-19 pandemic.[5]

Determining the effect of the COVID-19 pandemic on antibiotic resistance patterns could contribute to reducing treatment failures and preventing antimicrobial resistance. This study aimed to analyze and compare the distribution of VAP pathogens and antimicrobial drug resistance in intensive care unit (ICU) patients before and during the COVID-19 pandemic.

MATERIAL AND METHODS

The study received approval from the Karamanoğlu Mehmetbey University Non-Interventional Ethics Committee of the University Medical Faculty, with decision number 08-2021/16 (date: November 15, 2021). Since the study was retrospective, informed consent was waived. The COVID-19 group included adult patients with a positive specific polymerase chain reaction test result used in the diagnosis of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection, who received mechanical ventilator support in ICU and were diagnosed with VAP between 1 March 2020 and 1 January 2021. The pre-COVID-19 group included patients in ICU who required mechanical ventilation and were diagnosed with VAP in the same period the year before the pandemic, 1 March 2019-1 January 2020. The study excluded individuals who were under the age of 18, pregnant or diagnosed with a known immune deficiency. The demographic information of the patients and the microbiologic data were retrieved from the patient files and were analyzed retrospectively.

The diagnosis of VAP was made according to the Centers for Disease Control and Prevention workgroup (2011) definition of the diagnosis of VAP.[6] Clinical and laboratory criteria: fever with temperature greater than 38°C, leukopenia (≤4,000 cells/mm^3), or leukocytosis (≥12,000 cells/mm^3) were used. Although radiological findings such as new infiltration seen on pulmonary radiographs and/or thorax computed tomography were not included among the new VAP criteria, this study considered them supportive. Endotracheal aspirate (ETA) samples were also examined for microbiological diagnosis. In the analysis of the ETA sample obtained from the respiratory tract, quantitative microbial growth above the threshold value of 10^5 colony-forming units in the culture was accepted as the criterion for microbiological diagnosis.[6,7] VAP was accepted as pneumonia that developed at least 48 hours after endotracheal intubation when no pneumonia was present during intubation. Only the first VAP attack meeting the diagnosis criteria was included in the study. The steroid and anti-cytokine treatments used in the COVID-19 patient group were recorded.

The study included patients who were followed up with mechanical ventilation in ICU for at least three days, and those with a shorter stay in ICU were not included. The signs and symptoms of infection that emerged at least 48 hours after admission to ICU were accepted as healthcare-associated infections. The APACHE II prognostic score was calculated for all patients on admission to ICU. All the patients were evaluated in respect of VAP by the same consulting infectious diseases specialist. This study adhered to the ethical principles of the Helsinki Declaration in all of its procedures.

STATISTICAL ANALYSIS

The study's data analysis was performed using SPSS software (Version 22, SPSS Inc., Chicago, IL,

USA). Descriptive statistics were reported as frequency (n) and percentage (%) for categorical data. Numerical data were summarized as either mean±standard deviation (SD) or median (interquartile range: Q1-Q3) values based on the assumption of normal distribution. When comparing the proportions of categorical variables, we utilized either the Chi-squared test or Fisher's Exact test based on the sample sizes in the cross-tabulation cells. The normal distribution of numerical data was assessed using the Kolmogorov-Smirnov test and Q-Q plots. The Levene test was applied to test the homogeneity of variances. When conventional tests were applicable, we utilized the Student's t-test to compare data from two independent groups. When standard tests were inappropriate, we turned to the Mann-Whitney U test. In all cases, we regarded a p-value of less than 0.05 as indicative of significance.

RESULTS

A total of 178 patients were evaluated, with 71 (39.9%) in the pre-COVID-19 group and 107 (60.1%) in the COVID-19 patient group. Among the patients, 107 (60.1%) were males and 71 (39.9%) were females, with a mean age of 74.3±11.6 years (range, 21-97 years). The characteristics of all the patients are shown in Table 1.

Gender distribution was statistically similar in both groups (p=0.250). The mean age of patients in the pre-COVID-19 group was significantly higher than that of those in the COVID-19 group (76.71±12.15 years vs. 72.71±11.05 years) (p=0.024). The length of stay in ICU, the duration of follow-up on mechanical ventilation, and the time to diagnosis of VAP were significantly longer in the pre-COVID-19 group than in the COVID-19 group (p<0.001 for all) (Figure 1). The APACHE scores reveal no notable differences between the groups (p=0.855). The mortality rate was higher in the pandemic period than in the pre-pandemic period (p=0.040; 55.14% vs 39.44%, respectively).

The comorbidity rate was higher in the pre-pandemic period (p<0.001). The rates of comorbid chronic obstructive pulmonary disease, renal failure, congestive heart failure, ischaemic cerebrovascular event, and Alzheimer's disease were determined to be higher in the pre-COVID-19 group (Table 1). The rate of hypertension seen was determined to be significantly higher in the COVID-19 patient group compared to the pre-COVID-19 group (p=0.006). Diabetes mellitus and coronary artery disease were seen at similar rates in both groups (p=0.878, p=0.283, respectively). The rate of patients receiving immunosuppressive and steroid treatment was higher in the COVID-19 patients (p<0.001, p<0.001, respectively). No dexamethasone, low-dose methylprednisolone, high-dose methylprednisolone, or tocilizumab treatment was administered to any patient in the pre-pandemic period (Table 1).

The groups showed significant differences in the distributions of respiratory pathogens causing VAP before and during the COVID-19 pandemic (p<0.001) (Figure 2). In both periods, *Acinetobacter baumannii* was the most commonly seen causative microorganism, and in the pre-pandemic period, this was followed by *Pseudomonas aeruginosa* (35.2%) and *Klebsiella pneumoniae* (18.3%) (Table 2). In the COVID-19 patient group, the causative microorganisms following *A. baumannii* were *K. pneumoniae* (20.6%), *P. aeruginosa* (2.8%), *Escherichia coli* (1.9%), and others (2.8%).

Antimicrobial resistance to piperacillin-tazobactam, ciprofloxacin, amikacin, and cefepime antibiotics was higher during the pandemic compared to the pre-pandemic period (Table 3). The groups showed similar resistance and sensitivity rates to imipenem and cefoperazone-sulbactam antibiotics (p=0.737, p=0.466, respectively).

Antibiotic resistance of *P. aeruginosa* was determined to be similar in both groups (p>0.05) (Table 4). Resistance of the *A. baumannii* pathogen to imipenem decreased during the COVID-19 pandemic, and there was determined to be increased resistance to piperacillin-tazobactam and amikacin antibiotics. Resistance of *K. pneumoniae* to piperacillin-tazobactam increased during the COVID-19 pandemic (p=0.014).

TABLE 1: Statistical results for the comparison of demographic and clinical characteristics of the patients between the pre-COVID-19 and during-COVID-19 periods.

		Pre COVID-19 (n=71)	During COVID-19 (n=107)	p values
Gender	Male	39 (54.9%)	68 (63.6%)	0.250[a]
	Female	32 (45.1%)	39 (36.4%)	
Comorbidity	Yes	69 (97.2%)	83 (77.6%)	**<0.001**[a]
	No	2 (2.8%)	24 (22.4%)	
DM	Yes	22 (31%)	32 (29.9%)	0.878[a]
	No	49 (69%)	75 (70.1%)	
Hypertension	Yes	21 (29.6%)	54 (50.5%)	**0.006**[a]
	No	50 (70.4%)	53 (49.5%)	
CAD	Yes	21 (29.6%)	24 (22.4%)	0.283[a]
	No	50 (70.4%)	83 (77.6%)	
CHF	Yes	14 (19.7%)	7 (6.5%)	**0.008**[a]
	No	57 (80.3%)	100 (93.5%)	
COPD	Yes	19 (26.8%)	14 (13.1%)	**0.021**[a]
	No	52 (73.2%)	93 (86.9%)	
Alzheimer's disease	Yes	18 (25.4%)	5 (4.7%)	**<0.001**[a]
	No	53 (74.6%)	102 (95.3%)	
Cerebrovascular event	Yes	23 (32.4%)	7 (6.5%)	**<0.001**[a]
	No	48 (67.6%)	100 (93.5%)	
Kidney failure	Yes	11 (15.5%)	2 (1.9%)	**0.001**[a]
	No	60 (84.5%)	105 (98.1%)	
Immunosuppressive therapy	Yes	0 (0%)	59 (55.1%)	**<0.001**[b]
	No	71 (100%)	48 (44.9%)	
Steroid treatment	Yes	0 (0%)	53 (49.5%)	**<0.001**[b]
	No	71 (100%)	54 (50.5%)	
Dexamethasone treatment	Yes	0 (0%)	31 (29%)	**<0.001**[b]
	No	71 (100%)	76 (71%)	
Low-dose methylprednisolone treatment	Yes	0 (0%)	11 (10.3%)	**0.003**[b]
	No	71 (100%)	96 (89.7%)	
High-dose methylprednisolone treatment	Yes	0 (0%)	15 (14%)	**<0.001**[b]
	No	71 (100%)	92 (86%)	
Tocilizumab treatment	Yes	0 (0%)	15 (14%)	**<0.001**[b]
	No	71 (100%)	92 (86%)	
Age (years)		76.71±12.15	72.71±11.05	**0.024**[c]
Length of stay in the intensive care unit (days)		60 (24-95) (73.69±68.44)	14 (9-23) (17.59±14.08)	**<0.001**[d]
Duration of mechanical ventilation (days)		45 (23-80) (64.9±62.55)	11 (7-18) (14.63±11.68)	**<0.001**[d]
Time to culture growth from initiation of mechanical ventilation (days)		16 (7-30) (24.71±30.78)	6 (4-9) (7.68±4.83)	**<0.001**[d]
APACHE score		23.88±6.56	23.66±8.78	0.855[c]

[a]Chi-square test with n (%); [b]Fisher's exact test with n (%); [c]Student's t-test with mean±SD; [d]Mann-Whitney U test with median (Q1-Q3) and (mean±SD); DM: Diabetes mellitus; CAD: Coronary artery disease; CHF: Congestive heart failure; COPD: Chronic obstructive pulmonary disease; APACHE: Acute physiology and chronic health evaluation; SD: Standard deviation.

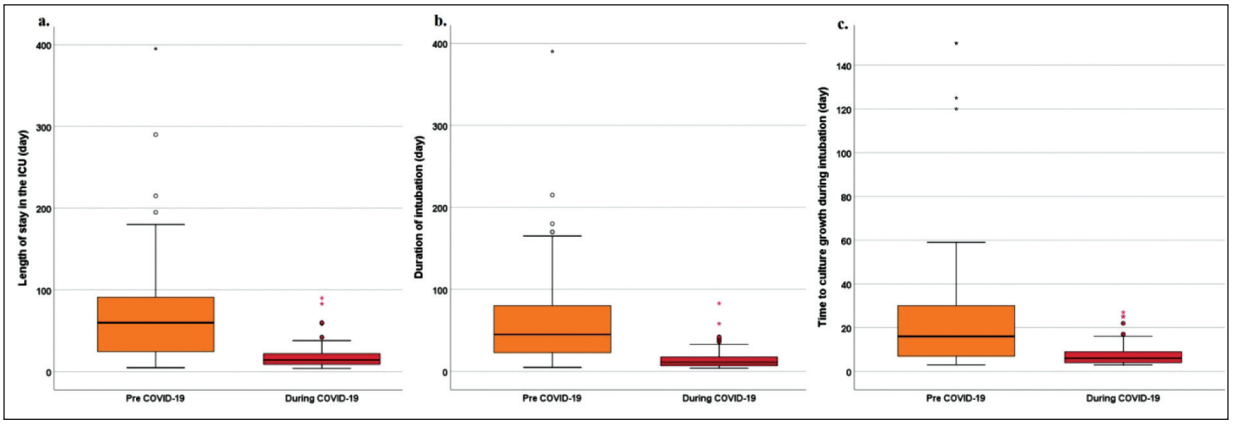

FIGURE 1: Box plots comparing the distributions of length of stay in the intensive care unit (a), duration of intubation (b), and time to culture growth from the initiation of mechanical ventilation (c) between pre COVID-19 and during COVID-19 periods.

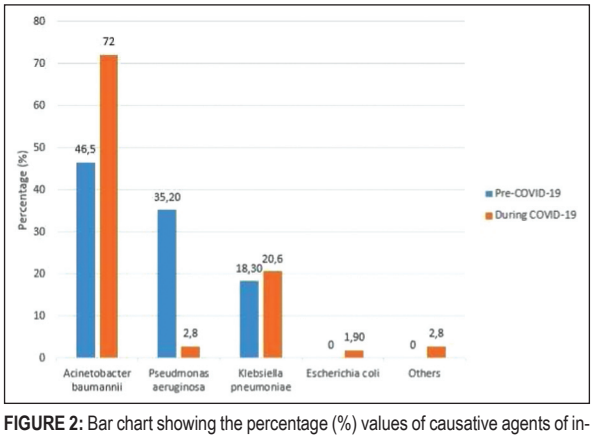

FIGURE 2: Bar chart showing the percentage (%) values of causative agents of infection between pre-COVID-19 and during COVID-19 periods.

DISCUSSION

The results of this study demonstrated that the antimicrobial resistance to piperacillin-tazobactam, ciprofloxacin, amikacin, and cefepime antibiotics increased during the COVID-19 pandemic compared to the period before the pandemic. The most frequent causative pathogen of VAP in both groups was *A. baumannii*, followed by *K. pneumoniae* in the COVID-19 group, and *P. aeruginosa* in the pre-COVID-19 group.

In a previous study comparing VAP data from six different centers in Türkiye, the average patient age was lower during the pandemic.[8] The results obtained in the current study were similar. In our study, the average age of patients with VAP during the pandemic was also lower.

In a study that examined secondary bacterial respiratory infections in COVID-19 patients hospitalized in the ICU, the mean length of stay in ICU was determined to be approximately 15 days.[9] Another study in Türkiye reported the mean length

TABLE 2: Statistical findings of the comparisons of the distributions of causative agents of infection between the pre-COVID-19 and during-COVID-19 periods.

		Pre COVID-19 (n=71)	During COVID-19 (n=107)	p values[a]
Causative Pathogens of Ventilator-associated pneumonia	*Pseudomonas aeruginosa*	25 (35.2%)	3 (2.8%)	**<0.001**
	Acinetobacter baumannii	33 (46.5%)	77 (72%)	
	Klebsiella pneumoniae	13 (18.3%)	22 (20.6%)	
	Escherichia coli	0 (0%)	2 (1.9%)	
	Others	0 (0%)	3 (2.8%)	

[a]Fisher's exact test with n (%).

TABLE 3: Statistical findings of the comparisons of susceptible and resistance rates of antibiotics used in the treatment of bacterial infections between the pre-COVID-19 and during-COVID-19 periods.

		Pre COVID-19 (n=71)	During COVID-19 (n=107)	p values
Imipenem	Susceptible	36 (50.7%)	57 (53.3%)	0.737[a]
	Resistant	35 (49.3%)	50 (46.7%)	
Piperacillin-tazobactam	Susceptible	18 (25.4%)	6 (5.6%)	**<0.001**[a]
	Resistant	53 (74.6%)	101 (94.4%)	
Ciprofloxacin	Susceptible	26 (36.6%)	2 (1.9%)	**<0.001**[a]
	Resistant	45 (63.4%)	105 (98.1%)	
Amikacin	Susceptible	55 (77.5%)	40 (37.4%)	**<0.001**[a]
	Resistant	16 (22.5%)	67 (62.6%)	
Cefoperazone-sulbactam	Susceptible	44 (62%)	72 (67.3%)	0.466[a]
	Resistant	27 (38%)	35 (32.7%)	
Cefepime	Susceptible	19 (26.8%)	12 (11.2%)	**0.007**[a]
	Resistant	52 (73.2%)	95 (88.8%)	

[a]Chi-square test with n (%).

of stay in ICU to be 13.49±8.03 days in the pandemic period and 33.59±32.89 days in the pre-pandemic period.[10] The current study results were similar, as the mean length of stay in the ICU was determined to be 14 days in the COVID-19 patient group and 60 days in the pre-pandemic group. The study's findings indicated that the duration of ICU stays and the time required for mechanical ventilation were longer in the pre-pandemic period. This may attributed to the differing mortality rates of patients with respiratory failure for reasons unrelated to COVID-19 infection. When comparing the mortality rates in our study, it was evident that the mortality rates of patients in the pandemic period were higher (55.14% vs 39.44%). The high mortality rates in our study during the pandemic period also support the ideas mentioned above.

In contrast to COVID-19 infection, the lung tissue damage rate was lower due to other causes of respiratory failure. The cause of damage to the lung tissue in the majority of COVID-19 patients treated in the ICU was acute respiratory distress syndrome (ARDS).[11] This is also a reason for the longer time of VAP occurring from the initiation of mechanical ventilation in patients before the COVID-19 pandemic compared to COVID-19 patients. As ARDS status creates a predisposition for the occurrence of VAP, it shortens this period.[12] Moreover, this may also be caused by suppression of the immune system by the steroids and anti-cytokines used in treatment in addition to the direct immunosuppressive effect of COVID-19 infection.[13,14] A review that investigated the occurrence of VAP during the COVID-19 pandemic noted that most VAP cases in COVID-19 patients were diagnosed eight to twelve days after the initiation of invasive mechanical ventilation.[12] Similarly, in the current study, VAP during the pandemic was occured at a mean of six days after the initiation of mechanical ventilation. In the pre-pandemic period, this was seen to be much longer at approximately a mean of 16 days. The reasons mentioned above could have been effective in these results.

When the comorbid diseases in the patients diagnosed with VAP were compared between the groups, hypertension was seen at a higher rate during the COVID-19 pandemic, and other diseases in the period before the pandemic. This was thought to be due to a greater need for treatment in ICU because of the worse course of COVID-19 infection in patients with hypertension.[15,16]

Although studies conducted during the COVID-19 pandemic have shown different results related to

TABLE 4: Statistical findings of the comparisons of susceptible and resistance antibiotics rates according to causative agents of infection between the pre-COVID-19 and during-COVID-19 periods.

			Pre COVID-19 (n=71)	During COVID-19 (n=107)	p values
Pseudomonas aeruginosa	Imipenem	Susceptible	21 (84%)	3 (100%)	1.000[b]
		Resistant	4 (16%)	0 (0%)	
	Piperacillin-Tazobactam	Susceptible	8 (32%)	2 (66.7%)	0.284[b]
		Resistant	17 (68%)	1 (33.3%)	
	Ciprofloxacin	Susceptible	23 (92%)	2 (66.7%)	0.298[b]
		Resistant	2 (8%)	1 (33.3%)	
	Amikacin	Susceptible	24 (96%)	3 (100%)	1.000[b]
		Resistant	1 (4%)	0 (0%)	
	Cefoperazone-Sulbactam	Susceptible	7 (28%)	2 (66.7%)	0.234[b]
		Resistant	18 (72%)	1 (33.3%)	
	Cefepime	Susceptible	8 (32%)	2 (66.7%)	0.284[b]
		Resistant	17 (68%)	1 (33.3%)	
Acinetobacter baumannii	Imipenem	Susceptible	4 (12.1%)	34 (44.2%)	**0.001[a]**
		Resistant	29 (87.9%)	43 (55.8%)	
	Piperacillin-Tazobactam	Susceptible	6 (18.2%)	3 (3.9%)	**0.020[b]**
		Resistant	27 (81.8%)	74 (96.1%)	
	Ciprofloxacin	Susceptible	1 (3%)	0 (0%)	0.300[b]
		Resistant	32 (97%)	77 (100%)	
	Amikacin	Susceptible	23 (69.7%)	25 (32.5%)	**<0.001[a]**
		Resistant	10 (30.3%)	52 (67.5%)	
	Cefoperazone-Sulbactam	Susceptible	32 (97%)	67 (87%)	0.168[b]
		Resistant	1 (3%)	10 (13%)	
	Cefepime	Susceptible	6 (18.2%)	8 (10.4%)	0.349[b]
		Resistant	27 (81.8%)	69 (89.6%)	
Klebsiella pneumoniae	Imipenem	Susceptible	11 (84.6%)	19 (86.4%)	1.000[b]
		Resistant	2 (15.4%)	3 (13.6%)	
	Piperacillin-Tazobactam	Susceptible	4 (30.8%)	0 (0%)	**0.014[b]**
		Resistant	9 (69.2%)	22 (100%)	
	Ciprofloxacin	Susceptible	2 (15.4%)	0 (0%)	0.131[b]
		Resistant	11 (84.6%)	22 (100%)	
	Amikacin	Susceptible	8 (61.5%)	11 (50%)	0.508[a]
		Resistant	5 (38.5%)	11 (50%)	
	Cefoperazone-Sulbactam	Susceptible	5 (38.5%)	3 (13.6%)	0.116[b]
		Resistant	8 (61.5%)	19 (86.4%)	
	Cefepime	Susceptible	5 (38.5%)	2 (9.1%)	0.075[b]
		Resistant	8 (61.5%)	20 (90.9%)	

[a]Chi-square test with n (%); bFisher's exact test with n (%).

frequent causative pathogens of VAP, more than 70% of studies have reported that gram-negative bacteria were the agent.[12] In a multicentre study of COVID-19 patients in Europe, the agents most seen in the development of VAP were gram-negative bacilli, especially *P. aeruginosa*, *Enterobacter* spp., and *Klebsiella* spp.[11] Another multicentre study in Brazil determined *P. aeruginosa* and *A. baumannii* as the most frequent causative pathogens of VAP development during the pandemic, and *P. aeruginosa* and *Staphylococcus aureus* in the period before the pandemic.[17] A previous study in Türkiye that examined healthcare-associated infectious agents found *A. baumannii* to be the most frequent causative pathogen in both periods. In the same study, the second most common agents were found to be *K.*

pneumoniae before the COVID-19 pandemic and *P. aeruginosa* during the pandemic.[8] Another study in Türkiye also showed that *A. baumannii* was the most frequent causative pathogen in lower respiratory tract infections in ICU in both periods, followed by *K. pneumoniae*.[10] Similar to these previously reported results, *A. baumannii* was determined to be the most frequently causative pathogen of VAP in both periods of the current study, followed by *P. aeruginosa* before the pandemic and *K. pneumoniae* during the pandemic. These results also show that unlike in other countries, the prevalence of Acinetobacter infections was high in Türkiye before the COVID-19 pandemic.

Using estimation-based statistical models to evaluate the data for 2019, another study determined that lower respiratory tract infections have become the most severe infectious disease, resulting in more than one and a half million deaths with increasing antimicrobial resistance. In listing the pathogens responsible for resistance-related deaths, *K. pneumoniae* was ranked third, and *A. baumannii* was ranked fifth.[18] There is known to have been an increase in the use of antimicrobial drugs during the pandemic in both developed and developing countries. In some developing countries where this increase was at a higher rate, the importance of antimicrobial resistance can be better understood if it is taken into consideration that the presence of resistant pathogens was reported even before the pandemic.[19] It has been reported that there was an increase in the prevalence of *A. baumannii* resistant to carbapenem during the pandemic, and these strains were reported also to be resistant to both ciprofloxacin and gentamicin.[19] A previous study in Türkiye showed that resistance rates of *A. baumannii* strains to antibiotics except tigecycline increased during the pandemic.[10]

The research examined the antimicrobial resistance patterns of VAP-causative pathogens in COVID-19 patients receiving mechanical ventilation support and compared these with the equivalent period the year before the pandemic. Resistance to piperacillin-tazobactam, ciprofloxacin, amikacin, and cefepime antibiotics was higher during the COVID-19 pandemic than in the preceding period. It was thought that this could be due to the frequent use of antibiotics, especially piperacillin-tazobactam and ciprofloxacin, in the wards and the ICU during the pandemic. The study results showed increased resistance of *A. baumannii* and *K. pneumoniae* to piperacillin-tazobactam supports this view.

That the resistance pattern to imipenem and cefoperazone-sulbactam antibiotics did not change can be thought to be due to the lesser use of these antibiotics, taking the ICU guidelines into consideration. Another factor could have been the use of imipenem treatment for treatment-resistant patients with a worse clinical condition and that the period of use was shorter because the survival of these patients was lower than in the pre-COVID-19 period. Similarly, the decrease in resistance of *A. baumannii* strains to imipenem during the COVID-19 pandemic suggests that this could have been due to these same reasons.

This study has limitations that need to be considered. The study results only include patients' data in the ICU of a single hospital in Türkiye, bound by local conditions, so they cannot be generalized to other hospitals in the country or worldwide. The research was carried out before the rollout of COVID-19 vaccines and before the appearance of SARS-CoV-2 variants. Suppose it is considered that these factors could have caused variability in the results on the subject of VAP. In that case, the fact that this study was conducted in the initial period of the pandemic before these factors emerged strengthens the power of the study. By determining VAP agents and resistance patterns, the data obtained in this study in the only tertiary-level hospital in the city will contribute to establishing a targeted treatment approach for infections and thereby reduce antimicrobial resistance.

CONCLUSION

The results of this study, in which causative pathogens of VAP and antimicrobial resistance patterns were compared between the periods before and during the COVID-19 pandemic, showed that the most common agent was *A. baumannii*, and there was seen to be an increased resistance pattern to some

antibiotics during the COVID-19 pandemic. When it is considered that unnecessary and overuse of antibiotics is an important factor in increasing antimicrobial resistance, it is important that attention is paid to the general rules and guidelines of antibiotic use, even in extraordinary situations such as a pandemic. This study will likely contribute to public health protection by raising healthcare personnel's awareness of antimicrobial resistance.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Rafet Yarımoğlu;* ***Design:*** *Rafet Yarımoğlu, Saliha Yarımoğlu;* ***Control/Supervision:*** *Rafet Yarımoğlu, Saliha Yarımoğlu;* ***Data Collection and/or Processing:*** *Rafet Yarımoğlu, Saliha Yarımoğlu;* ***Analysis and/or Interpretation:*** *Rafet Yarımoğlu, Saliha Yarımoğlu;* ***Literature Review:*** *Rafet Yarımoğlu;* ***Writing the Article:*** *Rafet Yarımoğlu, Saliha Yarımoğlu;* ***Critical Review:*** *Rafet Yarımoğlu, Saliha Yarımoğlu;* ***References and Fundings:*** *Rafet Yarımoğlu, Saliha Yarımoğlu;* ***Materials:*** *Rafet Yarımoğlu, Saliha Yarımoğlu.*

REFERENCES

1. Huttner BD, Catho G, Pano-Pardo JR, Pulcini C, Schouten J. COVID-19: don't neglect antimicrobial stewardship principles! Clin Microbiol Infect. 2020;26(7):808-10. [Crossref] [PubMed] [PMC]
2. Ghanizadeh A, Najafizade M, Rashki S, Marzhoseyni Z, Motallebi M. Genetic diversity, antimicrobial resistance pattern, and biofilm formation in Klebsiella pneumoniae isolated from patients with coronavirus disease 2019 (COVID-19) and ventilator-associated pneumonia. Biomed Res Int. 2021;2021:2347872. [Crossref] [PubMed] [PMC]
3. Kariyawasam RM, Julien DA, Jelinski DC, Larose SL, Rennert-May E, Conly JM, et al. Antimicrobial resistance (AMR) in COVID-19 patients: a systematic review and meta-analysis (November 2019-June 2021). Antimicrob Resist Infect Control. 2022;11(1):45. [Crossref] [PubMed] [PMC]
4. Segala FV, Bavaro DF, Di Gennaro F, Salvati F, Marotta C, Saracino A, et al. Impact of SARS-CoV-2 epidemic on antimicrobial resistance: a literature review. Viruses. 2021;13(11):2110. [Crossref] [PubMed] [PMC]
5. Jamnani AN, Montazeri M, Mirzakhani M, Moosazadeh M, Haghighi M. Evaluation of bacterial coinfection and antibiotic resistance in patients with COVID-19 under mechanical ventilation. SN Compr Clin Med. 2022;4(1):19. [Crossref] [PubMed] [PMC]
6. Spalding MC, Cripps MW, Minshall CT. Ventilator-associated pneumonia: new definitions. Crit Care Clin. 2017;33(2):277-92. [Crossref] [PubMed] [PMC]
7. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the infectious diseases society of America and the American Thoracic Society. Clin Infect Dis. 2016;63(5):e61-e111. Erratum in: Clin Infect Dis. 2017;64(9):1298. Erratum in: Clin Infect Dis. 2017;65(8):1435. Erratum in: Clin Infect Dis. 2017;65(12):2161. [PubMed] [PMC]
8. Sarı S, Arslan F, Turan S, Mengi T, Ankaralı H, Sarı A, et al. Comparison of the healthcare-associated infections in intensive care units in Turkey before and during COVID-19. Egypt J Intern Med. 2023;35(1):30. [Crossref] [PubMed] [PMC]
9. Sharifipour E, Shams S, Esmkhani M, Khodadadi J, Fotouhi-Ardakani R, Koohpaei A, et al. Evaluation of bacterial co-infections of the respiratory tract in COVID-19 patients admitted to ICU. BMC Infect Dis. 2020;20(1):646. [Crossref] [PubMed] [PMC]
10. Bahçe YG, Acer Ö, Özüdoğru O. Evaluation of bacterial agents isolated from endotracheal aspirate cultures of Covid-19 general intensive care patients and their antibiotic resistance profiles compared to pre-pandemic conditions. Microb Pathog. 2022;164:105409. [Crossref] [PubMed] [PMC]
11. Rouzé A, Martin-Loeches I, Povoa P, Makris D, Artigas A, Bouchereau M, et al; coVAPid study Group. Relationship between SARS-CoV-2 infection and the incidence of ventilator-associated lower respiratory tract infections: a European multicenter cohort study. Intensive Care Med. 2021;47(2):188-98. Erratum in: Intensive Care Med. 2022;48(4):514-5. [PubMed] [PMC]
12. Fumagalli J, Panigada M, Klompas M, Berra L. Ventilator-associated pneumonia among SARS-CoV-2 acute respiratory distress syndrome patients. Curr Opin Crit Care. 2022;28(1):74-82. [Crossref] [PubMed] [PMC]
13. Giacobbe DR, Battaglini D, Enrile EM, Dentone C, Vena A, Robba C, et al. Incidence and prognosis of ventilator-associated pneumonia in critically ill patients with COVID-19: a multicenter study. J Clin Med. 2021;10(4):555. [Crossref] [PubMed] [PMC]
14. Mikulska M, Nicolini LA, Signori A, Di Biagio A, Sepulcri C, Russo C, et al. Tocilizumab and steroid treatment in patients with COVID-19 pneumonia. PLoS One. 2020;15(8):e0237831. [Crossref] [PubMed] [PMC]

15. Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, et al; China Medical Treatment Expert Group for COVID-19. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J. 2020;55(5):2000547. [Crossref] [PubMed] [PMC]

16. Peng M, He J, Xue Y, Yang X, Liu S, Gong Z. Role of hypertension on the severity of COVID-19: a review. J Cardiovasc Pharmacol. 2021;78(5):e648-e55. [Crossref] [PubMed] [PMC]

17. Porto APM, Borges IC, Buss L, Machado A, Bassetti BR, Cocentino B, et al; HAI/COVID-19 Brazilian Task Force. Healthcare-associated infections on the intensive care unit in 21 Brazilian hospitals during the early months of the coronavirus disease 2019 (COVID-19) pandemic: an ecological study. Infect Control Hosp Epidemiol. 2023;44(2):284-90. [Crossref] [PubMed] [PMC]

18. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022;399(10325): 629-55. Erratum in: Lancet. 2022;400(10358):1102. [PubMed] [PMC]

19. Arshad AR, Ijaz F, Siddiqui MS, Khalid S, Fatima A, Aftab RK. COVID-19 pandemic and antimicrobial resistance in developing countries. Discoveries (Craiova). 2021;9(2):e127. [Crossref] [PubMed] [PMC]