MARMARA
MEDICAL JOURNAL

Original Article

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Relationship between COVID-19 and antimicrobial resistance

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Submitted: 12.11.2022 **Accepted:** 02.03.2023

ABSTRACT

Objective: Bacterial and fungal infections, antimicrobial resistance (AMR) results of bacterial agents, and the effect of the pandemic on AMR were evaluated in hospitalized COVID-19 patients. In addition, the detected AMR rates were compared with the AMR rates of the pre-pandemic period.

Patients and Methods: The isolates grown in respiratory and blood samples of adult patients hospitalized with the diagnosis of COVID-19 between March 2020 and December 2020 were evaluated retrospectively. The same data in hospitalized patients before the pandemic, between March and December 2019, were evaluated retrospectively.

Results: A total of 724 samples were included in the study. The superinfection rate was found to be 15.3%. The most frequently isolated microorganisms are; *Acinetobacter baumannii* (34.4%), *Staphylococcus aureus* (10.8%), *Klebsiella pneumoniae* (9.7%) and *Pseudomonas aeruginosa* (7.3%). The lowest resistance rates in Klebsiella pneumoniae isolates were found for aminoglycosides, in *Acinetobacter baumannii* isolates were found for trimethoprim-sulfamethoxazole, in *Pseudomonas aeruginosa* isolates were found for amikacin. When pre-pandemic and pandemic AMR rates were compared; a significant increase in amikacin resistance was detected only in *Klebsiella pneumoniae* isolates during the pandemic period (P:0.049).

Conclusion: The data we have presented may help clinicians in the selection of antimicrobials for empirical therapy by revealing the effect of the pandemic on AMR.

Keywords: Antimicrobial resistance, Bacterial infection, COVID-19, Fungal infection

1. INTRODUCTION

The new coronavirus, named severe acute respiratory syndrome-coronavirus-2 (SARS-COV-2), was declared a pandemic on 11 March 2020 by the World Health Organization (WHO) [1]. While more than 32.7 million people were affected by the disease, more than 1 million died [2]. However, the main problem that has been overlooked is the antimicrobial resistance (AMR) that will emerge after the pandemic [3].

The relationship between SARS-CoV-2 and bacterial infections can be summarized in three scenarios; 1-Secondary SARS-CoV-2 infection following bacterial infection or colonization, 2-Combined viral and/or bacterial pneumonia, 3 – Bacterial superinfection following SARS-CoV-2 infection. These scenarios vary due to the complex time-dependent interactions between virus, host, and bacteria [4]. Bacterial infections in patients infected with SARS-CoV-2 have been reported to cause an increase in disease severity, resource use, and deaths [5]. However, the rate of bacterial or fungal superinfection in patients with coronavirus disease 2019 (COVID-19) is unclear [6]. It has been reported that 25-70% of severe COVID-19 patients have symptoms of sepsis. Therefore, it is very difficult to exclude the diagnosis of bacterial superinfection with symptoms, physical examination findings, imaging and laboratory results. This has led to the widespread use of antimicrobials during the pandemic period [4]. Widespread antimicrobial use is predicted to increase AMR rates in the coming years [5]. There is also limited data on the results of antibiotic susceptibility tests of bacteria in bacterial superinfection [6]. In this article, bacterial and fungal infections in hospitalized patients infected with COVID-19 and AMR results were evaluated. In addition, the detected AMR rates were compared with the AMR rates of the pre-pandemic period.

How to cite this article: Muderris T, Kaya S, Bilman Bayindir F, et al. Relationship between COVID-19 and antimicrobial resistance. Marmara Med J 2023: 36(3):312-318. doi: 10.5472/marumj.1367895

ISSN: 1309-9469

http://doi.org/10.5472/marumj.1367895
Marmara Med J 2023;36(3): 312-318

2. PATIENTS and METHODS

Study design

This retrospective study was conducted in Izmir Katip Celebi University Ataturk Training and Research Hospital with an 1149-bed capacity, having six ICUs. All adult patients hospitalized with the diagnosis of COVID-19 between March and December 2020 were included in the study.

Sputum, tracheal aspirate, and blood cultures of these patients were evaluated. In addition, the microorganisms reproduced in respiratory and blood samples of patients hospitalized between March and December 2019 before the pandemic, and antibiotic susceptibility test results were evaluated retrospectively. The study was approved by Izmir Katip Celebi University non-interventional clinical research ethics committee (Decision/protocol number: 930, Approval date: 17.09.2020).

Data collection

The data were collected from the hospital's medical records using an electronic database. These data included the patient's gender, age, admitting department, microorganism that caused the infection, and antibiotic susceptibility test results of bacterial agents.

Microbiologic methods

Blood samples were incubated in the automated blood culture system (BACTEC FX, BD, USA). Passages were made on Eosin-Methylene Blue agar (Becton Dickinson, USA), 5% sheep blood agar (Becton Dickinson, USA) and chocolate agar media (Becton Dickinson, USA) from vials with bacteria detected in Gram stain made from bottles that gave a positive signal during incubation. Agar plates were incubated at 37˚C for 24-48 hours. Vials with yeast or hyphae detected in Gram stain made from bottles were additionally passaged to sabouraud dextrose agar (Becton Dickinson, USA) in duplicate and incubated at room temperature and 37°C. Only one growth was taken into account from the repetitive growth of the same microorganism in more than one blood sample of the same patient.

In sputum samples, sputum quality was evaluated initially. Samples that have mucus in macroscopic examination and Bartlett score above zero were included in the study [7]. In addition, dominant microorganisms have been investigated in Gram staining. In more than one respiratory tract sample of the same patient, only one growth from repeated growths of the same bacteria showing the same AMR pattern was taken into account. Sputum and tracheal aspirate samples were planted in 5% sheep blood agar, chocolate agar media, Eosin Methylene Blue agar, and incubated at 37˚C for 18-24 hours. In addition, samples with yeast or hyphae in Gram staining were passaged to sabouraud dextrose agar in duplicate and incubated at room temperature and 37°C.

Strains found to be bacteria in Gram staining were evaluated by colony morphology and biochemical tests (oxidase, coagulase, and catalase test, three sugar iron test, urea hydrolysis test, Indole, Methyl Red, citrate test). Identification and antibiotic susceptibility test of isolated bacteria were done using an automated system (Phoenix, BD, USA). The results of the antibiotic susceptibility test were evaluated according to the European Committee on Antimicrobial Susceptibility Testing criteria [8]. Antimicrobials that were found to be moderately sensitive as a result of antimicrobial susceptibility tests were accepted as resistant.

Strains found to be yeast in Gram staining were evaluated by colony morphology, germ tube test, urease test, and automated system (PhoenixTM 100-yeast ID, BD, USA). Automated system was used for definition of all types. Conventional methods were used for the verification of the automated system. If it was impossible to define the species with conventional methods, they were defined only with the automated system.

Colony structure and colony color of mold-growing colonies on Saboraud dextrose agar were examined macroscopically. Preparations were prepared using lactophenol cotton blue for microscopic examination. For identification, details such as the number of sterigmata, vesicle structure, odd-even phyalite, and color, structure, and location of conidiophores were examined.

Definitions

Bloodstream infection was defined as the growth of a non-skin flora commensal from ≥ 1 blood culture in a patient with systemic signs of infection. To distinguish bloodstream infection from contamination caused by a common skin colonizer such as coagulase-negative staphylococci or *Corynebacterium*, we required ≥2 blood cultures drawn from different sites. Results that were considered as contamination were excluded from the study.

Statistical analysis

SPSS version 22.0 (IBM Corp., USA) package program was used for statistical analysis. For descriptive analyses, mean ± standard deviation, number and percentage distributions were calculated. Pearson's chi-square test was used for statistical analysis of categorical variables. Fisher's exact test was used for analyzing variables among the groups. A value of $\mathbf{P}< 0.05$ was considered to be significant.

3. RESULTS

A total of 4662 (3750 blood, 912 respiratory) samples from 4461 patients were analyzed retrospectively. Growth was detected in 1779 samples from 1727 patients. Growths considered as contamination were excluded from the study. Only one growth was evaluated from the repetitive growth of the same bacteria in the same patient. A total of 724 samples from 681 patients, including 381 (52.6%) respiratory samples and 343 (47.4%) blood samples, were included in the study. Of these samples, 610 (84.3%) were from patients hospitalized in ICU (Table I). In our hospital, the superinfection rate was found to be 15.3% (681/4461) in patients diagnosed with COVID-19.

http://doi.org/10.5472/marumj.1367895
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Table I. *Distribution of isolated agents*

	Respiratory samples			Blood samples			TOTAL
	Standard ward n (%)	ICU n (%)	Total n (%)	Standard ward n (%)	ICU n (%)	Total n (%)	n (%)
Acinetobacter baumannii	8 (1.1)	171 (23.6)	179 (24.7)	4 (0.6)	66 (9.1)	70 (9.7)	249 (34.4)
Klebsiella pneumoniae	6 (0.8)	28 (3.9)	34 (4.7)	6 (0.8)	30 (4.1)	36 (5)	70 (9.7)
Pseudomonas aeruginosa	6 (0.8)	38 (5.2)	44 (6)	2 (0.3)	7 (1)	9 (1.2)	53 (7.3)
Escherichia coli	2 (0.3)	10 (1.4)	12 (1.7)	6 (0.8)	6 (0.8)	12 (1.7)	24 (3.3)
Stenotrophomonas maltophilia	0	11 (1.5)	11 (1.5)	0	1 (0.1)	1 (0.1)	12 (1.7)
Enterobacter aerogenes	2 (0.3)	8 (1.1)	10 (1.4)	0	0	0	10 (1.4)
Serratia marcescens	3 (0.4)	5 (0.7)	8 (1.1)	0	0	0	8 (1.1)
Proteus mirabilis	1 (0.1)	3 (0.4)	4 (0.5)	1 (0.1)	1 (0.1)	2 (0.3)	6 (0.8)
Haemophilus influenzae	0	4 (0.6)	4 (0.6)	0	0	0	4 (0.6)
Staphylococcus aureus	3 (0.4)	26 (3.6)	29 (4)	31 (4.3)	18 (2.5)	49 (6.8)	78 (10.8)
Enterococcus faecium	1 (0.1)	3 (0.4)	4 (0.5)	10 (1.4)	23 (3.2)	33 (4.6)	37 (5.1)
Enterococcus faecalis	0	0	0	6 (0.8)	23 (3.2)	29 (4)	29 (4)
Streptococcus spp.	0	1 (0.1)	1 (0.1)	7 (1)	12 (1.7)	19 (2.6)	20 (2.8)
Streptococcus pneumoniae	0	9 (1.2)	9 (1.2)	0	10 (1.4)	10 (1.4)	19 (2.6)
Candida albicans	0	9 (1.2)	9 (1.2)	0	8 (1.1)	8 (1.1)	17 (2.3)
Candida glabrata	0	0	0	0	1 (0.1)	1 (0.1)	1 (0.1)
Candida parapsilosis	0	0	0	0	24 (3.3)	24 (3.3)	24 (3.3)
Candida trophicalis	0	1 (0.1)	1 (0.1)	0	1 (0.1)	1 (0.1)	2 (0.3)
Asgergillus fumigatus	0	3 (0.4)	3 (0.4)	0	0	0	3 (0.4)
Asgergillus flavus	0	3 (0.4)	3 (0.4)	0	0	0	3 (0.4)
Asgergillus niger	0	1 (0.1)	1 (0.1)	0	0	0	1 (0.1)
Other	5 (0.7)	10 (1.4)	15 (2.1)	4 (0.6)	35 (4.8)	39 (5.4)	54 (7.5)
TOTAL	37 (5.1)	344 (47.5)	381 (52.6)	77 (10.6)	266 (36.7)	343 (47.4)	724

ICU: Intensive care units, CNS: Coagulase negative staphylococcus. Other: In this group; Citrobacter koseri, Enterobacter cloacae, Klebsiella oxytoca, Pseudomonas putita, Pseudomonas fluorescens, Serratia odorifera, Streptococcus vestibularis, Hafnia alvei, Delftia acidovorans, Achromobacter spp. is located.

When all samples were evaluated, the most frequently isolated microorganisms were; *Acinetobacter baumannii* 34.4%, *Staphylococcus aureus* 10.8%, *Klebsiella pneumoniae* 9.7%, *Pseudomonas aeruginosa* 7.3% and *Enterococcus faecium* (5.1%). The most isolated bacteria were *Acinetobacter baumannii* (24.7%), *Pseudomonas aeruginosa* (6%), *Klebsiella pneumoniae* (4.7%), *Staphylococcus aureus* (4%) and *Escherichia coli* (1.7%) in respiratory samples. The most isolated bacteria were *Acinetobacter baumannii* (9.7%), *Staphylococcus aureus* (6.8%), *Klebsiella pneumoniae* (5%), *Enterococcus faecium* (4.6%) and *Enterococcus faecalis* (4%) in blood samples. In addition, fungal growth was detected in 51 samples. Of these, 34 were blood samples and 17 were respiratory samples. The most isolated fungi were *Candida parapsilosis* (3.3%) and *Candida albicans* (2.3%) (Table I).

Amikacin, daptomycin, vancomycin, teicoplanin and linezolid resistance were not detected in *Staphylococcus aureus* isolates. The first three antimicrobials with the highest resistance rate were; erythromycin (15.4%), clindamycin (12.8%), and gentamicin (10.3%). In *Klebsiella pneumoniae* isolates, the lowest resistance rate was found in aminoglycosides (amikacin 24.3%, gentamicin 17.1%), while the first two antimicrobials with the highest resistance rate were cephalosporins (ceftazidime 82.9%, cefuroxime 82.1%, ceftriaxone 81.4%, cefepime 75.4%) and quinolones (ciprofloxacin 78.6%, levofloxacin 77.1%). While the lowest resistance rate was found in trimethoprim-sulfamethoxazole (TMP/SMX) (68.7%) in *Acinetobacter baumannii* isolates, resistance rates were quite higher in the other antimicrobials. The first two antimicrobials with the lowest resistance rate in *Pseudomonas aeruginosa* isolates were; cephalosporins (ceftazidime 30.6%, cefepime 28.9%) and amikacin (22.6%). The highest resistance rate in these isolates was found in carbapenems (imipenem 60.4%, meropenem 60.4%) (Table II).

When the resistance rates of patients in standard wards and ICU were compared for *Staphylococcus aureus* isolates; the resistance rates of fosfomycin, fusidic acid and gentamicin were higher among patients in standard wards, and the resistance rates of clindamycin, erythromycin, tetracycline and oxacillin were higher patients in ICU. In *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* isolates, antibiotic resistance was found to be higher among the patients in ICU than the patients in standard wards.

When the AMR rates detected in the year 2019 before the pandemic were compared with our findings based on more than 10% change; amikacin and TMP/SMX have increased in

http://doi.org/10.5472/marumj.1367895
Marmara Med J 2023;36(3): 312-318

Acinetobacter baumanni isolates, and gentamicin, amikacin, ciprofloxacin and carbapenem resistance were increased in *Pseudomonas aeruginosa* isolates [9]. In addition, erythromycin resistance in *Staphylococcus aureus* isolates and gentamicin and TMP/SMX resistance rates in *Klebsiella pneumoniae* isolates were decreased. However, a significant increase in amikacin resistance was detected only in *Klebsiella pneumoniae* isolates during the pandemic period (P:0.049).

Table II. *Distribution of AMR rates of isolated bacteria*

	Staphylococcus aureus					*Klebsiella pneumoniae*					*Acinetobacter baumannii*					*Pseudomonas aeruginosa*				
	PP n: 78			PPP n:189		PP n: 70			PPP n:490		PP n: 249			PPP n:446		PP n: 53			PPP n:227	
	SW	**ICU**	**Total**	**Total**	***P**	**SW**	**ICU**	**Total**	**Total**	***P**	**SW**	**ICU**	**Total**	**Total**	***P**	**SW**	**ICU**	**Total**	**Total**	***P**
GEN	8.9	1.4	10.3	6.9	>0.05	2.9	14.2	17.1	35.3	>0.05	4	93.2	97.2	88.3	>0.05	2	33.8	35.8	13.7	>0.05
AMK	0	0	0	3	NA	4.3	20	24.3	19.4	**0.049**	2.8	92.4	95.2	83.2	>0.05	1.9	20.7	22.6	10.1	>0.05
CLI	2.6	10.2	12.8	20.6	>0.05	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ERY	3.8	11.6	15.4	27	>0.05	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
DAP	0	0	0	0	NA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
FA	5.1	2.6	7.7	6.3	>0.05	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CIP	2.6	2.5	5.1	4.8	>0.05	14.3	64.3	78.6	79.6	>0.05	4.8	93.6	98.4	91	>0.05	2	43.3	45.3	24.2	>0.05
LVX	2.6	2.5	5.1	4.8	>0.05	12.9	64.2	77.1	-	NA	3.2	93.2	96.4	-	NA	6	53.2	59.2	-	NA
MXF	2.6	2.5	5.1	0	NA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
OXA	3.8	10.3	14.1	21.2	>0.05	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
TE	2.6	6.4	9	18	>0.05	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
VA	0	0	0	0	NA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
TEC	0	0	0	0	NA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
TMP/SMX	1.3	1.3	2.6	3.2	>0.05	7.1	40	47.1	60.4	>0.05	2.4	66.3	68.7	52.5	>0.05	-	-	-	-	-
LZD	0	0	0	0	NA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
FOF	3.8	0	3.8	3.7	>0.05	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
AMC	-	-	-	-	-	14.3	57.1	71.4	78.2	>0.05	-	-	-	-	-	-	-	-	-	-
SAM	-	-	-	-	-	12.9	62.1	75	-	NA	-	-	-	-	-	-	-	-	-	-
CAZ	-	-	-	-	-	14.3	68.6	82.9	79.2	>0.05	-	-	-	-	-	7.5	23.1	30.6	25.6	>0.05
CRO	-	-	-	-	-	14.3	67.1	81.4	78.8	>0.05	-	-	-	-	-	-	-	-	-	-
CXM	-	-	-	-	-	12.9	69.2	82.1	81.6	>0.05	-	-	-	-	-	-	-	-	-	-
FEP	-	-	-	-	-	10	65.4	75.4	79.2	>0.05	-	-	-	-	-	3.8	25.1	28.9	27.3	>0.05
TPZ	-	-	-	-	-	12.9	61.4	74.3	76.5	>0.05	-	-	-	-	-	7.5	26.5	34	27.8	>0.05
ETP	-	-	-	-	-	12.9	55.7	68.6	68.6	>0.05	-	-	-	-	-	-	-	-	-	-
IPM	-	-	-	-	-	12.9	54.2	67.1	61.4	>0.05	2.8	95.6	96.4	92.8	>0.05	6	54.4	60.4	44.1	>0.05
MEM	-	-	-	-	-	11.4	47.2	58.6	61.4	>0.05	2.8	95.6	96.4	91.9	>0.05	7.5	52.9	60.4	46.3	>0.05

*SW: Standard ward, ICU: Intensive care units, PP: Pandemic period; During the period in March 2020 and December 2020, PPP: Pre-pandemic period; During the period in March-December 2019, *P: It was obtained by comparing the total resistance rates of the pandemic and prepandemic period. NA: Not available, GEN: Gentamicin, AMK: Amikacin, CLI: Clindamycin, ERY: Erythromycin, DAP: Daptomycin, FA: Fusidic acid, CIP: Ciprofloxacin, LVX: Levofloxacin, MXF: Moxifloxacin, OXA: Oxacillin, TE: Tetracycline, VA: Vancomycin, TEC: Teicoplanin, TMP/SMX: Trimethoprim-Sulfamethoxazole, LZD: Linezolid, FOF: Fosfomycin, AMC: Amoxicillin-clavulanate, SAM: Ampicillin-sulbactam, CAZ: Ceftazidime, CRO: Ceftriaxone, CXM: Cefuroxime, FEP: Cefepime, TPZ: Piperacillin-tazobactam, ETP: Ertapenem, IPM: Imipenem, MEM: Meropenem*

4. DISCUSSION

Although, there is limited clinical experience with patients hospitalized for COVID-19, many critical decisions had to be made during the implementation of the treatment. One of these decisions is antimicrobial therapy [9]. Superinfection may increase antibacterial intolerance, inhibit the host's immune system, and thus adversely affect the prognosis of the disease [10]. The rate of superinfection in patients with a diagnosis of COVID-19 has been reported between 6.9% and 15% in various studies [5,11-15]. These rates have been reported as 5.1% to 38.9% in China and 4.8% to 27.4% in Western countries, especially in patients hospitalized in the ICU [12]. In our study, the superinfection rate was found to be 15.3%, which was consistent with the literature.

http://doi.org/10.5472/marumj.1367895
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Bacterial infections take the first place among the superinfection agents in patients infected with COVID-19. The most isolated bacteria in these patients are; *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Acinetobacter baumannii* [9,16,17]. In our study, we detected *Acinetobacter baumannii*, *Staphylococcus aureus*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa,* as the superinfection agents in COVID-19 patients, respectively, which was also consistent with the literature.

The superinfection rate in patients with COVID-19 infection followed in ICUs has been reported as 13.5-44% [18-20]. Bacterial or fungal pneumonia is the most common infection in these patients, while bloodstream and urinary tract infections have also been reported. The most isolated microorganisms are *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Enterobacter cloacae*, *Serratia marcescens*, *Aspergillus* spp. and *Candida* spp [6]. In our study, in accordance with the literature, the most isolated microorganisms in ICU hospitalized patients were *Acinetobacter baumannii*, *Staphylococcus aureus*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, respectively. Zamora-Cintas et al., reported that the most isolated microorganisms were *Candida albicans* and *Enterococcus faecalis* in blood samples, and *Candida albicans* and *Pseudomonas aeruginosa* in respiratory samples in patients infected with COVID-19 in the ICU [21].

In our study, the most isolated microorganisms in intensive care patients were; *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in blood samples, and *Acinetobacter baumannii* and *Klebsiella pneumoniae* in respiratory samples. These discordant results are thought to be due to regional differences and different treatment protocols.

It is thought that risk factors such as ICU admission, corticosteroid therapy, intubation/mechanical ventilation, underlying respiratory diseases and cytokine storm may be responsible for the increase in invasive fungal infections in COVID-19 patients [22]. While Chen et al., reported positive fungal culture from respiratory samples in 5% of 99 patients, Du et al., reported fungal infection in 10.6% of 85 COVID-19 cases [23,24]. Silva et al,. reported 25.5% *Candida* spp., and 1.4% *Aspergillus* spp. in 212 patients with COVID-19 [17]. In our study, *Candida* spp. were isolated in 6%, and *Aspergillus* spp. in 0.9% of the patients. The discordance in these results is thought to be due to differences in study populations, treatment protocols, and geographical location.

Antibacterial selection and duration of treatment are very important in respiratory bacterial or fungal infections. Many antimicrobials used in therapy have the potential to cause prolongation of the QT wave on the electrocardiogram and cardiac arrest, raising concerns about antimicrobial choice [12]. Inflammatory markers can be used to support antimicrobial decisions. However, since the data obtained with these tests may have been affected by COVID-19, it may be insufficient to diagnose bacterial infection. In addition, routine microbiological examinations with long-term patient contact may have been decreased due to the fear of getting sick by health professionals. In this instance, studies reporting AMR rates guide the selection of empirical antimicrobials. WHO has recommended that antimicrobial selection in empirical antimicrobial therapy should be based on individual and local epidemiological data [9]. In our study, resistance to amikacin, daptomycin, vancomycin, teicoplanin, and linezolid was not found in *Staphylococcus aureus* isolates. *Klebsiella pneumoniae* isolates were more sensitive to aminoglycosides, *Acinetobacter baumanni* isolates to TMP/SMX, and *Pseudomonas aeruginosa* isolates were more sensitive to 3rd and 4th generation cephalosporins and amikacin. In addition, as expected, AMR rates were found to be higher in patients hospitalized in ICU compared to patients hospitalized in other wards. It is very important for antimicrobial stewardship programs to focus on the determination of antimicrobials to be used in empirical treatment, but, studies on the AMR patterns of bacterial agents that cause infections in patients infected with COVID-19 are very limited in the literature. For this reason, we believe the data we presented in our study will make a significant contribution to the literature.

It is very difficult to exclude bacterial or fungal infections in severe COVID-19 patients only with symptoms, signs, radiological abnormalities and blood tests [6]. Although, the superinfection rate is 6.9-15% in patients infected with COVID-19, it has been reported that 58-100% of these patients received antimicrobial therapy [5,6,11,12,14,15,25]. Due to the inconsistency between the initiation of empirical antimicrobials and the rates of bacterial infection, WHO recommended that empirical antimicrobial therapy should be initiated only in severe COVID-19 patients [9]. The widespread use of antimicrobials during the pandemic period may increase resistance rates in the following years. It is expected that there will be approximately 10 million deaths worldwide in the next 30 years due to AMR in the post-COVID-19 period compared to the pre-COVID-19 period [3]. Therefore potential management interventions that support the reduction of antimicrobial prescribing in the pandemic should be evaluated urgently. Nori et al., compared the antimicrobial susceptibility results with the antimicrobial susceptibility data of the same period of 2019 before the pandemic and reported that the susceptibility to cephalosporin, ciprofloxacin, and meropenem in *Klebsiella pneumoniae* isolates decreased by more than 10% [9]. In our study, when the AMR rates detected in the same period of 2019 before the pandemic was compared with the AMR rates during the pandemic period; it was determined that the resistance rates of gentamicin, amikacin, ciprofloxacin and carbapenem in *Acinetobacter baumanni* isolates, amikacin and TMP/SMX in *Pseudomonas aeruginosa* isolates were increased by more than 10%. In addition, in our study, it was found that amikacin resistance increased significantly in *Klebsiella pneumoniae* isolates during the pandemic period. Although, it is predicted that the increasing use of antimicrobials in the pandemic will increase AMR rates in forthcoming years, studies on this subject are very limited. Our results will shed light on the limited information on this subject. In the future, the effect of the pandemic on AMR rate will be better understood with multicenter studies involving a large patient population.

The two major limitations of our study are; the study was a single-center study and the COVID-19 pandemic period was limited to the year 2020.

In conclusion; despite the high rate of empirical broad-spectrum antibiotics being prescribed in patients with respiratory tract infection with a diagnosis of SARS-CoV-2, the data supporting the association of symptoms with bacterial/fungal infection is quite low. A general evidence base for developing antimicrobial management strategies is required to prevent the undesirable consequences of antimicrobials prescribed during the COVID-19 pandemic, both on the individual and the community. This evidence can only be provided by prospective clinical and laboratory studies focusing on antimicrobial therapy. The results of the relevant study will guide researchers in future comprehensive studies on the antimicrobials to be selected in empirical antimicrobial therapy and the impact of the pandemic on AMR rate.

Compliance with the Ethical Standards

Ethics Committee Approval: The study was approved by Izmir Katip Celebi University non-interventional clinical research ethics committee (Decision/protocol number: 930, Approval date: 17.09.2020).

Conflict of Interest: The authors declare that they have no conflict of interest relevant to this article.

Financial Disclosure: This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors Contribution: TM: Planning, data collection, analysis, article writing, SK: Planning, data collection, article writing, FBB and EO: Data collection, analysis, BOP: Analysis, article writing, AAG and SGY: Planning, data collection. All authors read and approved the final version of the article.

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