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Antimicrobial Resistance Patterns of Bacterial and Fungal Isolates in COVID-19

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Abstract

Background: The pattern of bacterial infection in coronavirus disease 2019 (COVID-19) patients differ worldwide.
Objectives: This study aimed to determine the patterns of bacterial infections and the antibiotic resistance profile by VITEK 2 (bioMérieux, France) in the culture of blood samples from hospitalized patients with COVID-19.
Methods: This retrospective descriptive cross-sectional was conducted on a total of 25 patients with critical COVID-19 admitted to Imam Reza Hospital in Mashhad, Iran, during the first three COVID-19 peaks (2019 - 2020).
Results: Among Gram-positive bacteria, two strains isolated from *Staphylococcus aureus* were methicillin-resistant *S. aureus* at a concentration of > 2 μg/mL. *Enterococcus* was vancomycin-resistant *Enterococcus* at a concentration of higher than 4 μg/mL (the minimum inhibitory concentration [MIC] ≥ 32). Among Gram-negative bacteria, three strains of *Acinetobacter baumannii* complex were extensively drug-resistant.
Conclusions: There is evidence of the remarkable increase of various antibiotics' MIC during the COVID-19 pandemic, which highlights the impact of the use of steroids on the risk of developing antimicrobial resistance during the COVID-19 pandemic.

Keywords: COVID-19, Carbapenemase-Producing *Enterobacteriaceae*

1. Background

Antibiotic-resistant bacterial infections are among the leading causes of morbidity and mortality in hospitalized patients with viral respiratory infections (1). In this regard, the coincidence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic with the global antibiotic resistance crisis has complicated the problem. The SARS-CoV-2 is the cause of coronavirus disease 2019 (COVID-19), which is characterized by mild to severe respiratory problems and low blood oxygen levels (2, 3). In COVID-19 patients, there is also evidence of an increase in the erythrocyte sedimentation rate and susceptibility to bacterial infections. Respiratory viral infections, such as COVID-19, can progressively impair the immune system by reducing peripheral blood lymphocytes, decreasing macrophage phagocytic capacity, diminishing antigen-presenting capabilities by dendritic cells and macrophages, altering pulmonary epithelial cells' functions, and increasing mucus thickening (4, 5). Therefore, concerns about bacterial infections in COVID-19 patients have led to increased antibiotics administration and an augmented risk of antimicrobial resistance (AMR), which is a significant global public health issue, with estimates that it will kill 10 million individuals by 2050 (2, 6).

The AMR was introduced as the most important health crisis worldwide before the COVID-19 pandemic (7). However, the prevalence of COVID-19 with bacterial coinfection is still unknown, even in critical patients (8). Based on the findings of a meta-analysis, secondary bacterial infections in COVID-19 were reported only in 8.02% of the cases (9). The results of a study conducted in India revealed that the most common isolates were coagulase-negative *Staphylococci* and *Staphylococcus aureus* in critical COVID-19 patients. Methicillin-resistant *S. aureus* (MRSA) was observed in 60% of urine and blood isolates. The AMR increased to 40% during the COVID-19 period, compared to that of the

pre-COVID-19 time (10).

According to the evidence, the pattern of bacterial infection in COVID-19 patients differs worldwide, implying the importance of adapting antibiotic therapy to the epidemiological pattern of the region (5, 11). On the other hand, a lack of reliable epidemiological data in the early phases of a pandemic raises the risk of common bacterial infections in hospitalized patients. It is still unclear whether antibiotics have been administered to the majority of severe COVID-19 hospitalized patients. The risk of AMR appears to be increasing due to the strong association between mortality and the use of empiric broad-spectrum antibiotics, especially in the case of sepsis (12-14). Since most studies have focused on understanding and controlling the COVID-19, not enough attention has been paid to AMR during the COVID-19 pandemic (10).

Due to the COVID-19 pandemic and the high hospitalization rate of COVID-19 patients, it is vital to determine the antibiotic and antifungal sensitivity pattern in this population to bring about the necessary reforms in health guidelines.

2. Objectives

The present study aimed to determine the patterns of bacterial and fungal infections and the antibiotic resistance profile by VITEK 2 (bioMérieux, France) based on the culture of blood samples from hospitalized patients with acute COVID-19 at Imam Reza Hospital in Mashhad, Iran, during the first three COVID-19 peaks.

3. Methods

3.1. Ethical Considerations

This experimental study was conducted under the Declaration of Helsinki for medical research involving human subjects (15). In addition, the research protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences, Mashhad, Iran (approval no.: IR.MUMS.MEDICAL.REC.1400.074.). The present study extracted from a thesis with approval number 992018.

3.2. Study Population and Sampling

This retrospective descriptive cross-sectional study was conducted on patients with severe COVID-19 who were hospitalized in the intensive care unit (ICU) of Imam Reza Hospital in Mashhad, Iran, during the first three COVID-19 peaks (2019 - 2020). The participants were chosen based on the information found in the medical records of patients diagnosed with COVID-19 by laboratory diagnostic tests and positive polymerase chain reaction (PCR) tests within March 2019 to March 2020. The inclusion criteria were (1) decreased level of consciousness, (2) breathing more than 24 times per minute, (3) blood pressure less than 90/60 mmHg, (4) hypoxemia (oxygen saturation level less than 93%), (5) positive blood culture, (6) antimicrobial susceptibility test performed by VITEK 2, and (7) positive lung computed tomography scan (including unilateral diffuse or bilateral diffuse ground-glass opacities or scattered alveolar). Additionally, the patient's incomplete medical record was a criterion for exclusion. Moreover, the demographic and clinical characteristics of patients, including age, gender, duration of hospitalization, duration of mechanical ventilation, and prescribed antibiotic regimen, were recorded.

3.3. Microbial Identification and Antibiotic Susceptibility Testing by VITEK 2 System

The automated VITEK 2 system (bioMérieux, France) was employed for bacterial identification and antibiotic susceptibility testing (AST). For this purpose, the blood samples from patients were placed in BacT/Alert. Then, the positive samples were cultured on an appropriate culture medium, such as blood agar, chocolate agar, or MacConkey agar, and incubated for 24 hours at 37°C. For choosing appropriate identification (ID) and AST cards to use on the VITEK 2 system, gram staining was performed on all colonies grown on agar plates. Afterward, a bacterial suspension with a turbidity of 0.5 McFarland standard was prepared directly from each pure bacterial colony. The bacterial suspensions and the ID and AST cards were then all placed into the VITEK 2 system equipment simultaneously. Once the bacteria have been identified, the VITEK 2 system automatically selects the appropriate antibiotics according to the Clinical and Laboratory Standards Institute guidelines for AST and sets the minimum inhibitory concentration (MIC) for each antibiotic (16). In addition, methylene blue staining and microscopic examination were used to identify fungal infections with green, purple, and blue colors confirming *Candida albicans*, *Candida glabrata*, and *Candida tropicalis*, respectively. Antifungal medications, including amphotericin B, voriconazole, and caspofungin, were also used to test susceptibility to antifungals.

3.4. Statistical Analysis

The SPSS software (version 23.0; IBM Corp., Chicago, IL, USA) was used to analyze the data. The results were expressed as percentages and mean $\pm$ standard deviation values for nominal and continuous variables, respectively. In addition, a P-value of less than 0.05 was considered statistically significant. Intergroup comparisons were performed using the Mann-Whitney U test as a nonparametric

test, and the student's *t*-test as a parametric test was run after confirming the normality of quantitative data distribution using the Kolmogorov-Smirnov test.

4. Results

The information of 25 patients (including 21 male and 4 female) was collected. The ratio of male to female subjects was 6.2: 1. The source of culture was blood in all the patients (n = 25). The mean analysis time was 7.04 $\pm$ 3.21 hours. All the patients suffered from severe COVID-19.

4.1. Identification of Microorganisms

The identified microorganisms isolated from the patients were Gram-negative aerobic bacteria (n = 12, 46%) or Gram-positive aerobic bacteria (n = 14, 54%). Table 1 shows the frequency of identified agents isolated from the patients. *Acinetobacter baumannii* complex and *Staphylococcus epidermidis* were the most common Gram-negative and Gram-positive bacteria, respectively.

Table 1. Frequency of Identified Agents Isolated from Patients

Gram-Negative Bacteria	No. (%)
Escherichia coli	1 (4)
Klebsiella pneumoniae ssp. *pneumoniae*	1 (4)
Citrobacter freundii	1 (4)
Achromobacter xylosoxidans	1 (4)
Pseudomonas aeruginosa	1 (4)
Enterobacter cloacae	1 (4)
Pantoea dispersa	1 (4)
Acinetobacter baumannii complex	3 (12)
Serratia marcescens	1 (4)
Stenotrophomonas maltophilia	1 (4)
Gram-Positive Bacteria	
Enterococcus faecalis	1 (4)
Staphylococcus aureus	2 (8)
Staphylococcus epidermidis	5 (20)
Staphylococcus haemolyticus	4 (16)
Staphylococcus hominis ssp. *hominis*	2 (8)

In general, 411 strains of 15 microorganisms were assessed in terms of resistance or sensitivity to various antibiotics. Nonfermenting Gram-negative bacteria (i.e., *Pseudomonas aeruginosa*, *A. baumannii* complex, and *Stenotrophomonas maltophilia*) were observed in five cases. Other identified Gram-negative bacteria included *Escherichia coli*, *Klebsiella pneumoniae* ssp., *Citrobacter freundii*, *Achromobacter xylosoxidans*, *Enterobacter cloacae*, *Pantoea dispersa*, and *Serratia marcescens*. The identified Gram-positive bacteria were *Enterococcus faecalis*, *S. aureus*, *S. epidermidis*, and *Staphylococcus haemolyticus*.

4.2. Antimicrobial Sensitivity Patterns of Gram-Positive Bacteria

Table 2 shows the details of the in vitro sensitivity profiles of the isolated Gram-positive bacteria. Among Gram-positive bacteria, two strains isolated from *S. aureus* were MRSA at a concentration of > 2 μg/mL (oxacillin); nevertheless, *S. aureus* was sensitive to cefoxitin. Of these two strains of *S. aureus*, one strain was glycopeptide-resistant *S. aureus* (GRSA) at a concentration of higher than 8 μg/mL (MIC $\geq$ 32), and the other strain was sensitive to vancomycin (MIC $\leq$ 2).

Staphylococcus hominis ssp. *hominis*, *S. aureus*, and *S. haemolyticus* were clindamycin resistant (MIC = Positive). *Staphylococcus epidermidis* was clindamycin resistant in three strains and sensitive in two strains (MIC = Negative). Moreover, *S. hominis* spp. *hominis*, *S. haemolyticus*, and *S. epidermidis* were sensitive to vancomycin (MIC $\leq$ 2).

All *S. hominis* ssp. *hominis*, *S. aureus*, and *S. haemolyticus* strains were clindamycin resistant (MIC = Positive). *Staphylococcus epidermidis* was clindamycin resistant in three strains and sensitive in two other strains (MIC = Negative). *Enterococcus* was vancomycin-resistant *Enterococcus* (VRE) at a concentration of higher than 4 μg/mL (MIC $\geq$ 32). Table 3 shows the MIC values of antimicrobials for Gram-positive bacteria.

4.3. Antimicrobial Sensitivity Patterns of Gram-Negative Bacteria

Table 4 shows the details of the in vitro sensitivity profiles of the isolated Gram-negative bacteria. Based on the obtained results, three strains of *A. baumannii* complex were extensively drug-resistant (XDR) (resistant to cefepime and ceftazidime) (MIC $\geq$ 64). They were resistant to meropenem and imipenem at concentrations of $\geq$16 and $\geq$ 4 μg/mL, respectively; however, they were sensitive to tigecycline and colistin (MIC $\leq$ 0.5).

Pseudomonas aeruginosa was carbapenemase-producing *P. aeruginosa* (resistant to penicillins, cephalosporins, carbapenem, and monobactams). It was resistant to meropenem and imipenem at a concentration of $\geq$ 16 μg/mL.

Serratia marcescens was sensitive to cefepime at a concentration of $\leq$ 1 μg/mL, and *K. pneumoniae* was carbapenem-sensitive *K. pneumoniae* (sensitive to meropenem and imipenem at concentrations of $\leq$ 0.25 and 2 μg/mL, respectively). In addition, *K. pneumoniae* was resistant to cefepime and ceftazidime (MIC $\leq$ 1).

Table 2. Details of in vitro Sensitivity Profiles of Isolated Gram-Positive Bacteria

Antibiotic	*Enterococcus faecalis*	*Staphylococcus hominis* ssp. *hominis*	*Staphylococcus aureus*		*Staphylococcus haemolyticus*				*Staphylococcus epidermidis*				
Aztreonam	S	-	-	-	-	-	-	-	-	-	-	-	-
Ciprofloxacin	R	R	R	R	R	R	R	R	R	R	R	S	S
Gentamicin	R	R	R	R	R	R	R	R	R	R	R	R	R
Levofloxacin	R	R	R	R	R	R	R	R	R	S	S	I	I
Piperacillin/ Tazobactam	-	S	-	-	-	-	-	-	-	-	-	-	-
Trimethoprim-sulfamethoxazole	-	-	R	R	R	R	R	R	R	R	S	S	S
Moxifloxacin	R	I	R	S	S	I	I	I	R	S	S	S	S
Erythromycin	R	R	R	R	R	R	R	R	R	R	R	R	S
Clindamycin	R	R	R	R	R	R	R	R	R	R	R	S	S
Daptomycin	S	-	S	-	S	S	S	S	S	S	S	S	-
Vancomycin	R	S	R	S	S	S	S	S	S	S	S	S	I
Doxycycline	I	S	I	I	R	S	I	I	R	S	S	I	I
Tetracycline	R	R	R	R	R	R	R	S	R	R	R	R	S
Tigecycline	S	S	S	S	S	S	-	-	S	S	S	S	S
Nitrofurantoin	S	S	S	S	S	S	S	I	S	S	S	S	S
Streptomycin	R	-	-	-	-	-	-	-					
Cefoxitin	-	S	S	S	S	S	S	S	R	R	S	S	S
Oxacillin	-	R	R	R	R	R	R	R	R	R	R	S	S
Inducible Clindamycin Resistance	-	R	R	R	R	R	R	R	R	R	R	R	S
Linezolid	-	S	S	S	-	-	-	-	S	S	S	S	S
Rifampicin	-	S	R	S	R	S	S	S	R	S	S	S	S

Table 3. Details of Minimum Inhibitory Concentration of Antimicrobials for Gram-Positive Bacteria [a]

Antibiotic	*Enterococcus faecalis*	*Staphylococcus hominis* ssp. *hominis*	*Staphylococcus aureus*		*Staphylococcus haemolyticus*				*Staphylococcus epidermidis*				
Aztreonam	2	-	-	-	-	-	-	-	-	-	-	-	-
Ciprofloxacin	≥ 8	≥ 8	≥ 8	4	≥ 8	≥ 8	≥ 8	≥ 8	≥ 8	4	4	≤ 0.5	≤ 0.5
Gentamicin	-	≥ 64	≥ 16	≥ 16	≥ 16	≥ 16	≥ 16	≥ 64	4	≤ 0.5	≤ 0.5	≤ 0.5	8
Levofloxacin	≥ 8	≥ 8	≥ 8	≥ 8	≥ 8	≥ 8	≥ 8	≥ 8	≥ 8	4	4	≤ 12	≤ 0.12
Trimethoprim-sulfamethoxazole		20	160	160	≥ 320	≥ 320	≥ 320	≥ 320	≤ 0.5	≤ 10	≤ 10	≤ 10	160
Moxifloxacin	≥ 8	4	≥ 8	2	4	4	4	2	≤ 0.25	≤ 0.25	≥ 8	1	1
Erythromycin	≥ 8	≥ 8	≥ 8	≥ 8	≥ 8	≥ 8	≥ 8	≥ 8	≤ 0.25	≥ 8	≥ 8	≥ 8	≤ 4
Daptomycin	2		0.25		0.25	0.5	0.5	0.5	2	1	0.25	0.5	≤ 0.12
Vancomycin	≥ 32	1	2	≥ 32	2	2	2	≤ 0.5	2	1	≤ 0.5	≤ 0.5	≤ 0.5
Doxycycline	8	2	8	8	≥ 16	1	8	8	2	≥ 64	≤ 0.5	8	8
Tetracycline	≥ 16	≥ 64	≥ 16	≥ 16	≥ 16	≥ 16	2	≥ 64	≥ 16	≥ 16	≥ 64	≥ 64	≤ 1
Tigecycline	≤ 0.12	≤ 0.12	0.5	0.5	0.5	0.5			0.25	0.5	0.5	0.5	≤ 0.12
Nitrofurantoin	≤ 16	≤ 16	≤ 16	32	≤ 16	≤ 16	64	32	8	≤ 16	≤ 16	≤ 16	≤ 16
Streptomycin	8	-	-	-	-	-	-	-	-	-	-	-	-
Cefoxitin	-	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Negative	Negative	Positive	Positive	Positive
Oxacillin	-	≥ 4	≥ 4	≥ 4	≥ 4	≥ 4	≥ 4	≥ 4	≥ 4	≥ 4	≥ 4	≤ 0.25	≤ 0.25
Inducible Clindamycin Resistance	-	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Positive
Clindamycin	≥ 4	≥ 4	≥ 4	≥ 4	≥ 4	≥ 4	≥ 4	≥ 4	≥ 4	≥ 4	0.25	0.25	≤ 0.12
Linezolid		2	2	1	2	2	2	≤ 0.5	2	2	1	1	1
Rifampicin	-	≤ 0.5	≤ 0.5	≥ 32	≤ 0.5	≤ 0.5	≤ 0.5	≥ 32	≤ 0.5	≤ 0.5	≤ 0.5	≤ 16	≥ 32

[a] All the values are reported in μg/mL.

Table 4. Details of In Vitro Sensitivity Profiles of Isolated Gram-Negative Bacteria

Antibiotic	*Citrobacter freundii*	*Achromobacter xylosoxidans*	*Pseudomonas aeruginosa*	*Enterobacter cloacae*	*Pantoea dispersa*	*Stenotrophomonas maltophilia*	*Escherichia coli*	*Klebsiella pneumoniae*	*Serratia marcescens*	*Acinetobacter baumannii* Complex		
Amikacin	R	R	R	S	S	R	S	S	S	I	-	-
Aztreonam	R	R	-	R	S	-	-	R	-	R	R	-
Cefepime	R	R	R	S	S	R	S	R	S	R	R	R
Ceftazidime	R	S	R	R	S	R	S	R	S	R	R	R
Ciprofloxacin	R	R	R	S	S	S	S	S	S	R	R	R
Colistin	R	S	S	R	S	-	-	R	-	S	S	-
Gentamicin	R	R	R	S	S	S	S	S	S	R	S	S
Imipenem	S	S	R	S	S	R	S	S	S	R	R	R
Levofloxacin	R	I	R	S	S	S	S	S	S	R	R	R
Meropenem	S	S	R	S	S	-	-	S	-	R	R	-
Piperacillin	S	S	R	S	S	-	-	R	-	R	R	-
Piperacillin/tazo	S	S	R	-	S	R	S	I	S	R	R	R
Ticarcillin	I	S	R	S	S	-	-	R	-	-	-	-
Tobramycin	R	R	R	S	S	-	-	S	-	R	R	-
Trimethoprim-sulfamethoxazole	R	S	R	S	S	S	S	R	S	R	S	S
Ticarcillin/clavu acid	-	-	R	-	-	-	-	-	-	R	R	-
Tigecycline	-	-	-	-	-	S	S	-	S	S	-	-
Nitrofurantoin	-	-	-	-	-	R	S	-	S	R	-	-
Streptomycin	-	-	-	-	-		-		-			
Cefoxitin	-	-	-	-	-	R	S	-	S	R	-	-
Ampicillin	-	-	-	-	-	R	S	-	S	R	-	-
Extended-spectrum beta-lactamases	-	-	-	-	-	S	S	-	S	S	-	-
Cefazolin	-	-	-	-	-	R	S	-	R	R	-	-
Ceftriaxone	-	-	-	-	-	R	S	-	S	R	-	-
Ertapenem	-	-	-	-	-	R	S	-	S	R	-	-
Rifampicin	-	-	-	-	-	-	-	-	-	S	S	-

Stenotrophomonas maltophilia was sensitive to tigecycline and trimethoprim-sulfamethoxazole (MIC $\leq$ 2.37). Table 5 shows the MIC values of antimicrobials for Gram-negative bacteria.

5. Discussion

The most commonly isolated organisms from all the clinical specimens of critical COVID-19 patients were two Gram-positive bacteria, including *S. haemolyticus* and *S. epidermidis*, which were reported in 9 (36%) cases. Of 12 Gram-negative bacteria, nonfermenting Gram-negative bacteria were detected in five cases.

5.1. Methicillin-Resistant Staphylococcus Aureus

Colonization or infection with MRSA or VRE is the main sign for contact precautions in the United States (17). Any strain of *S. aureus* developing multiple drug resistance to beta-lactam antibiotics (i.e., penicillin derivatives, such as amoxicillin, penicillin, oxacillin, and other common antibiotics known as cephalosporins, such as cefoxitin) is known as MRSA. Probably, MRSA is associated with 44% of hospital-acquired infections in Europe, and the mortality rate has been estimated at about 20% (18).

In one study conducted on patients with community-acquired pneumonia (CAP), the prevalence of MRSA was estimated at 3.6% (19). A cohort study conducted on patients with positive SARS-CoV-2 PCR test indicated that the prevalence of MRSA in respiratory cultures increased from 0.6% on the 3rd day to 5.7% on the 28th day (20). Due to the uncertain line between community-acquired and hospital-acquired pneumonia during the COVID-19 pandemic, determining the prevalence of MRSA in respiratory cultures of patients with COVID-19 is highly critical. The MRSA was reported in 13.9% of patients with COVID-19 (n = 340) in a study performed on an Iranian population (21). In the present study, two *S. aureus* strains isolated from different clinical specimens were MRSA (resistance to oxacillin) with MIC > 2 μg/mL (oxacillin); nevertheless, *S. aureus* was sensitive to cefoxitin. In another study conducted on COVID-19 patients admitted to an ICU in Iran, *S. aureus* isolates were detected to be MRSA, which were resistant to peni-

Table 5. Details of Minimum Inhibitory Concentration of Antimicrobials for Gram-Negative Bacteria [a]

Antibiotic	*Citrobacter freundii*	*Achromobacter xylosoxidans*	*Pseudomonas aeruginosa*	*Enterobacter cloacae*	*Pantoea dispersa*	*Stenotrophomonas maltophilia*	*Escherichia coli*	*Klebsiella pneumoniae*	*Serratia marcescens*	*Acinetobacter baumannii* Complex		
Amikacin	≥ 64*	≥ 64	≥ 64	≤ 2	≥ 64	≥ 64	≤ 2	≤ 2	≤ 2	-	-	-
Aztreonam	≥ 64	≥ 64	-	≥ 64	≥ 64	-	-	≤ 1	-	≥ 64	≥ 64	32
Cefepime	32	≥ 64	≥ 64	≤ 1	≥ 64	≥ 64	≤ 1	≤ 1	≤ 1	≥ 64	≥ 64	≥ 64
Ceftazidime	32	4	≥ 64	16	≥ 64	≥ 64	≤ 1	≤ 1	≤ 1	≥ 64	≥ 64	≥ 64
Ciprofloxacin	≥ 4	≥ 4	≥ 4	≤ 0.25	≥ 4	≤ 2	≥ 1	0.5	≤ 1	≥ 4	≥ 4	≥ 4
Colistin	≥ 16	2	≤ 0.5	≥ 16	≥ 16	-	-	8		≤ 0.5	≤ 0.5	-
Gentamicin	≥ 16	≥ 16	≥ 16	≤ 1	≥ 16	≤ 8	≤ 8	≤ 1	≤ 1	≥ 16	2	≥ 64
Imipenem	≤ 0.25	1	≥ 16	≤ 0.25	≥ 16	≥ 4	≤ 0.5	2	≤ 0.25	≥ 4	≥ 16	≥ 64
Levofloxacin	≥ 8	4	≥ 8	≤ 12	≥ 8	≤ 2	1	1	≤ 1	≥ 8	≥ 8	≥ 8
Meropenem	4	≤ 0.25	≥ 16	0.5	≥ 4	-	-	≤ 0.25	-	≥ 16	≥ 64	-
Piperacillin	≤ 4	≤ 4	≥ 128	8	≥ 128	-	-	≥ 128	-	≥ 128	≥ 128	-
Piperacillin/tazı	≤ 4	≤ 4	≥ 128	-	≥ 128	≥ 128	≤ 4	64	≤ 4	≥ 128	≥ 128	≥ 128
Ticarcillin	32	≤ 8	≥ 128	≤ 8	≥ 128	-	-	≥ 128	-	≥ 128	≥ 128	-
Tobramycin	≥ 16	≥ 16	≥ 16	≤ 1	≥ 4	-	-	≤ 1	-	≥ 16	≥ 64	-
Trimethoprim-sulfamethoxazole	≥ 320	≤ 20	≥ 320	40	≥ 320	≤ 2.37	≤ 1	≥ 320	≤ 2.38	≥ 320	≤ 20	≤ 20
Ticarcillin/clavı acid	-	-	≥ 128	-	-	-	-	-	-	-	-	-
Tigecycline	-	-	-	-	-	≤ 0.5	≤ 0.5	-	≤ 0.5	≤ 0.5	-	-
Nitrofurantoin	-	-	-	-	-	≥ 128	≤ 64	-	≥ 32	≥ 128	-	-
Streptomycin	-	-	-	-	-			-				
Cefoxitin	-	-	-	-	-	32	≤ 4	-	≤ 4	32	-	-
Ampicillin	-	-	-	-	-	≥ 32	≤ 16	-	≤ 2	≥ 32	-	-
Extended-spectrum beta-lactamases	-	-	-	-	-	Positive	Negative	-	Negative	Positive	-	-
Cefazolin	-	-	-	-	-	≥ 64	≤ 16	-	≥ 8	≥ 64	-	-
Ceftriaxone	-	-	-	-	-	≥ 64	≤ 1	-	≤ 1	≥ 64	-	-
Ertapenem	-	-	-	-	-	4	≤ 0.5	-	≤ 0.5	4	-	-
Rifampicin	-	-	-	-	-	-	-	-	-	4	4	-

[a] All the values are reported in μg/mL.

cillin, cefoxitin, azithromycin, erythromycin, gentamicin, co-trimoxazole, linezolid, and ciprofloxacin (22). The evidence has shown that MRSA has marginally risen from pre-COVID-19 time (23-25). The results of a study by Saini et al. indicated that MRSA was observed in 60% of urine and blood isolates (10). Increased MRSA during the post-COVID-19 time, compared to that of the pre-COVID-19 period, is a serious warning about the overuse of antibiotics, which might lead to treatment failure among patients with MRSA infections.

The treatment options for MRSA isolates are limited due to their resistance to the main classes of antibiotics (26). *Staphylococcus aureus* can become resistant to beta-lactam antibiotics, including methicillin, by the expression of penicillin-binding proteins. Anti-MRSA agents, especially vancomycin, are considered important targets for concomitant CAP during COVID-19 (27). However, vancomycin treatment failure is not uncommon in MRSA bacteremia, even when it is susceptible to vancomycin. Based on one study, the MIC value of vancomycin for *S. aureus* ranged from 0.016 to 1 μg/mL (28). Based on the obtained results of one study, the risk of mortality associated with MRSA bacteremia increased when the empirical antibiotic was inappropriate, and strains with a vancomycin MIC of 2 μg/mL were associated with a lower risk of shock (29). A susceptible but high MIC to vancomycin is associated with increased mortality and treatment failure among patients with MRSA infections (30).

5.2. Vancomycin-Resistant Enterococci

Enterococci species is regarded as the second causative agent of healthcare-associated infection; accordingly, ICU patients are at high risk of VRE infection (31). The VRE are bacterial strains of the genus *Enterococcus* that are resistant to the antibiotic vancomycin. Due to the resilience of *Enterococci*, they survive for prolonged periods (32) and have recently developed a different mechanism of resistance to several antibiotics, including aminoglycosides, cephalosporins, tetracyclines, quinolones, and glycopeptides (31). Although the incidence of VRE is increasing, it

is associated with remarkable mortality, especially in ICU patients and those with comorbidities, and it remains a serious problem worldwide despite the proactive measures (33-35).

Enterococci can produce beta-lactamases leading to decreased cellular permeability. The VRE occurs due to changes in the formation of murein and binds to the D-Ala-D-Ala terminus of the protein precursors to peptidoglycan, where vancomycin binds normally. The changing of the terminus to D-Ala-D-lactate leads to the development of resilience considering the bindings of vancomycin to the ligase with less affinity (31).

Based on the results of a study by Saini et al., the most common bacterium among the Gram-positive bacteria was observed to be the *Enterococcus* species (10). They showed that the resistance of *Enterococcus* species has increased during the pre-COVID-19 pandemic (10). In the present study, among Gram-positive bacteria, *S. hominis*, *S. haemolyticus*, and *S. epidermidis* were sensitive to vancomycin. One strain isolated from *Enterococcus* was VRE with MIC > 4 μg/mL. Despite intensified contact precautions during the current pandemic, this finding indicates a weak prognosis for COVID-19 patients. Similarly, Kampmeier et al. report a nosocomial cluster of *Staphylococcus*-resistant *enterococci* that occurred in COVID-19 patients hospitalized in an ICU. They used whole-genome sequence (WGS)-based typing to evaluate the genetic relatedness of VRE isolated from COVID-19 and non-COVID-19 patients, which showed two genotypically distinct VRE clusters. This finding emphasizes the importance of infection prevention measures during the COVID-19 pandemic to prevent VRE transmission (36).

5.3. Glycopeptide-Resistant Staphylococcus Aureus

Vancomycin is the most commonly used drug for severe MRSA infections. Recently, vancomycin-resistant *S. aureus* (VRSA) strains have been introduced as a serious risk for public health (37). The genetic selection of a strain variant is dependent on the consecutive occurrence of several genetic events. Therefore, the isolation of *S. aureus* strains from the VRSA phenotype related to the vanA operon is very rare. Mutations in the *ddl* gene encoding the D-Ala-D-Ala ligase are other reasons for the restriction of the expansion of vancomycin-positive *S. aureus* strains (38).

Despite personal protective equipment and isolation of COVID-19-confirmed or -suspected patients, the cluster increased during the COVID-19 pandemic. The transmission of VRE in an ICU by WGS-based typing during the COVID-19 pandemic has been reported in the findings of a study by Kampmeier et al. (36). Szymanek-Majchrzak et al. detected 11 *S. aureus* strains resistant to vancomycin that exhibited the MIC range of 4 - 8 μg/mL (37). In the present study, of the two *S. aureus* strains, one strain was VRSA at a concentration of higher than 8 μg/mL (MIC $\geq$ 32); nonetheless, the other strain was sensitive to vancomycin (MIC $\leq$ 2). There is evidence of the remarkable increase in vancomycin and teicoplanin MIC values for ST247-IA as a sequence type/clone, which might be due to antibiotic-induced pressure toward the accumulation of point mutations.

5.4. Staphylococcus Resistance to Clindamycin

Clindamycin is commonly used for the treatment of *S. aureus* infections because the agent is low-cost with limited side effects. This antibiotic is known as a proper alternative to beta-lactam antibiotics in patients with allergic problems. However, there are numerous reports of bacterial resistance to clindamycin due to its excessive use (39). According to one study conducted on the Iranian population, the rates of resistance to oxacillin and clindamycin among patients with COVID-19 were over 90% (21). In the present study, all the *Staphylococcus* strains were clindamycin resistant. Sutter et al. showed that *S. aureus* susceptibility to clindamycin decreased over the study period (40). Moreover, the susceptibility of methicillin-susceptible *S. aureus* to clindamycin decreased from 90% to 83% (40). Due to increased clindamycin resistance among methicillin-susceptible *S. aureus* strains, the agent should be used with caution.

5.5. Extensively Drug-Resistant Acinetobacter Baumannii

The bacterial pathogens related to AMR have been classified as multidrug-resistant (MDR), XDR, and pan-drug resistant. The MDR *A. baumannii* is an important ICU-acquired infection linked to high mortality (41). Recently, XDR and MDR Gram-negative bacteria have increased among COVID-19 patients (41, 42). *Acinetobacter baumannii* intestinal colonization is introduced as a predictor for infection in COVID-19 patients. The assessment of superinfections caused by Gram-negative strains in the ICU, including COVID-19 patients, has shown that XDR *A. baumannii* is a serious infection in critically-ill patients.

A rapid increase in MDR agents, including extended-spectrum beta-lactamase (ESBL)-producing *K. pneumoniae*, has been reported during the COVID-19 pandemic. The cause of this rise is multifactorial; however, it is particularly associated with the high rates of antimicrobial agent usage during the pandemic with a relatively low rate of coinfection or secondary infection (43).

Russo et al. demonstrated that the hospital course of patients with COVID-19 might be complicated with bacterial superinfections (41). They showed that the risk of MDR-*A. baumannii* infection was relatively high among patients with COVID-19. The serum lactate levels of >2 mmol/L, *A. baumannii* colonization, and steroid therapy in COVID-19

patients are related to 30-day mortality and the development of bloodstream infection in COVID-19 patients (41). In the present study, the authors detected three strains of XDR *A. baumannii* complex (resistant to cefepime and ceftazidime) (MIC $\geq$ 64). The only therapeutic option for XDR *A. baumannii* is colistin (44).

5.6. Carbapenemase-Producing Enterobacteriaceae

There is evidence of the increased risk of mortality due to carbapenemase-producing *Enterobacteriaceae* (CPE) infections in the face of multiclass antibiotic resistance, which could lead to additional burdens on health systems. *Klebsiella pneumoniae* carbapenemase (KPC)-positive *Enterobacteriaceae* have the highest frequency among CPE in Europe (45). Pascale et al. reported a shift from KPC to other CPE mechanisms during the COVID-19 pandemic (46). The CPE has increased during the COVID-19 pandemic, which might signal the reemergence of these highly resistant pathogens. This issue supports recent concerns considering the emergence of MDR bacterial coinfections in the COVID-19 pandemic (47). Gomez-Simmonds et al. confirmed the presence of multiple different ST258 lineages driving the emergence of CPE in the COVID-19 patient population (48). In the current study, CPE was reported among critical patients with COVID-19 (resistance to penicillin, cephalosporins, carbapenem, and monobactams). There are only a few available antimicrobial agents for the treatment of infections caused by MDR and CPE bacteria (49). This situation has been worsened during the COVID-19 pandemic due to the presence of some factors, including organ disruption and potential interactions with immunomodulators or other drugs, such as antiretrovirals and hydroxychloroquine (50).

5.7. Extended-Spectrum Beta-Lactamase

The most common mechanism of resistance to multiple broad-spectrum beta-lactams among the *Enterobacteriaceae* family is ESBL (51). The emergence of Enterobacterales carrying ESBL enzymes and carbapenem resistance has increased in recent years. Accordingly, it has limited the antimicrobial drugs for the management of infections. The TEM, SHV, and CTX-M are three major genetic groups of ESBLs. *Escherichia coli* and *K. pneumoniae* are the main ESBL-producing bacteria. The pathogenic potential of these bacteria and the frequent acquisition of conjugative plasmids encoding AMR genes (antibiotic resistance genes [ARGs], such as ESBL genes) lead to the fast exchange of ARGs in these bacteria (52).

A beta-lactam ring is hydrolyzed by ESBL enzymes leading to the ineffectiveness of antibiotics against ESBL (53). The dissemination of CTX-M-1 group genes has been facilitated by the horizontal gene transfer of mobile genetic elements, including plasmids, transposons, and integrons (54). Based on a study by Moremi et al., ESBL-producing Gram-negative bacteria were detected in 43.2% of the patients admitted to two hospitals in Tanzania in 2017 (55). The majority of ESBL isolates were *E. coli* (74%), and CTX-M-1 group genes were observed in about 95% of ESBL isolates (55). The resistance of CTX-M-15-producing ST131 *E. coli* strains is increasing (56). Carbapenems have been introduced as the first choice for patients with community-acquired infections due to ESBL-producing bacteria. In the present study, *K. pneumoniae* was ESBL and sensitive to meropenem and imipenem.

5.8. Conclusions

Although a considerable amount of resources has been focused on coping with the COVID-19 pandemic, the effects of long-standing infection in healthcare settings remain unclear. Dangerous organisms, including MRSA, VRE, VRSA, XDR *A. baumannii*, CPE, and ESBL, have been isolated from the clinical specimens of critical COVID-19 patients. There is evidence of the remarkable increase of various antibiotics' MIC during the COVID-19 pandemic due to the antibiotic-induced pressure toward mutations, which highlights the impact of the use of steroids on the risk of developing AMR during the COVID-19 pandemic.

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Footnotes

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