The emergence of antibiotic-induced resistant microbiomes among severe COVID-19-infected patients correlates with a high case fatality rate

Zina Alshami[1]*, Haidar Jiham[2] and Ahmed Alshammari[3]

[1]Pathology and Forensic Medicine Department, Faculty of Medicine, Jabir Ibn Hayyan University of Medical and Pharmaceutical Sciences, AlNajaf, Iraq.
[2]Community Medicine Department, Faculty of Medicine, Jabir Ibn Hayyan University of Medical and Pharmaceutical Sciences, AlNajaf, Iraq.
[3]Medical Microbiology Department, Faculty of Medicine, Jabir Ibn Hayyan University of Medical and Pharmaceutical Sciences, AlNajaf, Iraq.
Email: z.shami@jmu.edu.iq

ABSTRACT

Aims: The coronavirus disease 2019 (COVID-19) is a contagious respiratory disease. The massive use of antibiotics during COVID-19 treatment induced the problem of antibiotic resistance among different strains of microbiome. The current study was conducted to evaluate the level of antibiotic resistance among pathogenic and microbiome bacteria isolated from the blood and upper respiratory tract of COVID-19 patients and its correlation with the case fatality rate in each patient.

Methodology and results: COVID-19 patients were diagnosed using real-time reverse transcription-polymerase chain reaction (RT-PCR) technique. Swabs and blood samples were collected from each patient to isolate bacteria and every isolate identification was performed using the bioMérieux VITEK® 2 system. The case fatality rate among the study group was 50% for patients whose isolates were highly antibiotic-resistant. Blood culture was positive in 2.5% compared to nasal swab culture in 65%. Results of nasal swab culture revealed growth of Gram-positive bacteria isolated from 17.1% of patients, Gram-negative isolates were found in 9.75% and fungal isolates formed 9.75%. Most of the isolates were reflective of normal microbiomes; unfortunately, isolates were 100% resistant to penicillins, cephalosporins, azithromycin and amoxicillin-clavulanate. On the other hand, isolates were 100% sensitive to daptomycin.

Conclusion, significance and impact of study: Results were alarming and there is a need to take measures to prevent the increase in bacterial resistance to antibiotics and limit the excessive use of it. It is crucial to monitor the rise in fungal infections among patients and consider it a risk factor for increasing the case fatality rate.

Keywords: Case fatality rate, COVID- 19, lymphopenia, multidrug-resistant microbiomes

INTRODUCTION

After the emergence of multiple cases of pneumonia among the residents of Wuhan City in China, the laboratory work identified the causative agent as a new *Betacoronavirus* and it was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that caused coronavirus disease 2019 (COVID-19) global pandemic (She *et al.*, 2019). In March 2020, this new disease was declared a pandemic by the World Health Organization (WHO) and in December 2022 there were more than 650,588,360 million recorded cases of COVID-19 and more than 6,648,420 million deaths reported globally (WHO, 2022).

The United States of America and India were the most affected worldwide, while Iraq was the most affected country in the Arabian region. In Iraq, the first case of COVID-19 was diagnosed in February 2020 in the holly city of Al-Najaf, linked to a person who had recently returned from Iran (World Bank, 2020). Iraq recorded 2,464,375 confirmed cases and 25,366 deaths, according to the World Health Organization (WHO) dashboard (WHO, 2022).

The drivers' pathology of COVID-19 remains to be elucidated, but a hyperinflammatory response is associated with worse-case fatality. Other viral respiratory tract infections, best characterized by influenza, can be complicated by bacterial coinfections that raise inflammatory markers and are associated with high mortality. However, distinguishing severe viral pneumonia from bacterial coinfection is challenging (WHO, 2022). Several studies on COVID-19 have found bacterial

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coinfection to be rare and unnecessary because upper respiratory tract routine microbiological culture takes several days, lacks sensitivity, and does not readily distinguish bacterial colonization from infection (World Bank, 2020).

Respiratory droplets transmit COVID-19; the virus is very light, spreads in the air for over 2 meters and remains viable for a few days on different media. One of the significant problems during the COVID-19 attack is severe lymphopenia among some patients, especially in the elderly, which gives rise to severe immunosuppression correlated with disease severity and poor prognosis, making the patient vulnerable to coinfections, especially bacterial and fungal infection (Mathieu et al., 2020; Peñuelas et al., 2021). Focusing on antibiotics during viral pandemic may be strange, on the other hand, ignoring secondary bacterial infection caused by antibiotic-resistant pathogens will make COVID-19 more severe (Nguyen et al., 2021). Proliferations of resistant microbiome and pathobiont can aggravate inflammatory manifestations, trigger autoimmune diseases and lead to severe life-threatening conditions. An example is the emergence of Clostridium difficile. Such conditions will threaten the lives of many patients, especially those who are immunocompromised (Chandra et al., 2021; Lami et al., 2022). Hence, this study was aimed to evaluate the frequency of antibiotic resistance from bacteria isolated from the blood and upper respiratory tract of COVID-19 and correlate the level of antibiotic resistance of isolates with the patient's case fatality rate.

MATERIALS AND METHODS

A follow-up cohort study comprised forty COVID-19 patients diagnosed with real-time reverse transcription-polymerase chain reaction (RT-PCR); patients were hospitalized in Al-Amal Hospital for Communicable Diseases in AlNajaf Province. Patients included in the study were hospitalized for more than a week and followed up for five months; different parameters were recorded for each patient. Data collected included age, gender, admission date, occupation, marital status, oxygen supplementation method, different blood test results, type of treatment and fate. Samples collected included:

Nasal swab collection

A total of 40 swab samples were collected from COVID-19 confirmed cases. To collect the swab sample patients' heads were tilted back 70° and the back of the head was supported by the non-dominant hand. Nasal passages were inspected for obstruction, and specimen was not collected from an obstructed nostril. Nasal swabs were collected in a sterile way with no contact with any surface. Swabs were inserted into the nostril parallel to the palate until the tip was roughly at the level of the anterior ear. Swabs were removed and placed in a collection tube and closed tightly. Samples were cultured on different culture media, including (MacConkey agar, mannitol salt agar, brain heart infusion broth, brain heart agar and nutrient agar). All incubations were performed at 35 ± 1 °C unless indicated otherwise; culture results were initially identified using Gram-stain.

Blood culture

A total of 40 blood samples were collected from confirmed COVID-19-infected patients. Ten (10) mL of venous blood was drawn from each patient and cultured in BACTEC blood culture system aerobic blood culture bottles. Blood culture bottles were examined and incubated at 35 °C in 5% carbon dioxide for 4-24 h and an aliquot of the culture fluid was Gram-stained.

Microbial identification

Bacteria and yeast identification (ID) and antibiotic susceptibility testing (AST) were performed using bioMérieux VITEK® 2 system according to manufacturer instructions. Culture results containing Gram-negative bacilli were inoculated on bioMérieux VITEK 2 ID-GNB (identification-Gram-negative bacilli), while Gram-positive bacterial growth on ID-GPC (identification-Gram-positive cocci) and bioMérieux VITEK® 2 AST-P580 and AST-N222 cards (antimicrobial susceptibility testing cards) were used to identify antibiotic susceptibility. Imipenem disc was used to identify carbapenemase-producing organisms.

Ethical approval and patient consent

The study was approved by the ethical approval committee of the Faculty of Medicine in Jabir Ibn Hayyan University for Medical and Pharmaceutical Sciences with protocol number (1/4/2020); written informed consent was obtained from patients before data collection. Information obtained from the study participants was kept confidential and used only for this study.

Statistical analysis

Results were analyzed using MS Excel and SPSS version 21. The P value had been calculated by chi-square test at alpha = 0.05.

RESULTS AND DISCUSSION

The COVID-19 pandemic started three years ago and still threatens the lives of millions of people and affects the economic activity of many countries. Fears remain despite the decline in the number of cases and the availability of vaccines; the reason is the lack of a definite treatment and the emergence of new variants (Galeotti and Bayry, 2020). Empirical treatment and the inadequate use of antibiotics in this era has led to changes in antibiotic resistance pattern among bacteria and increased the concern about the emergence of bacterial strains resistant to colistin, which is the last drug of choice

Table 1: Distribution of patients according to gender and age.

Age distribution/Sex		Male	Female	Frequency	Percent (%)
Valid	<60	8	3	11	27.5
	≥60	11	12	23	57.5
	Total	19	15	34	85
Missing	System	3	3	6	15
Total		22	18	40	100

Table 2: The association between the patient's gender and fate.

Fate	Gender		Case fatality rate		Total
	Male	Female	Male	Female	
Recovered	12 (60%)	6 (37%)	40%	63%	18 (50%)
Dead	8 (40%)	10 (63%)			18 (50%)
Total	20 (100%)	16 (100%)			36 (100%)
P-value	0.180 non-significant				

Table 3: Culture results for blood and swab samples.

Culture results		Nasal swab frequency (%)	Blood culture frequency (%)
Valid	Bacterial or fungal growth	26 (65.0)	1 (2.50)
	No growth	14 (35.0)	25 (96.15)
	Total	40 (100.0)	26 (100.0)
	P-value	<0.001	

for resistant bacteria (Yanez *et al.*, 2020; Damayanthi *et al.*, 2021). The current study collected samples from 40 patients, including 23 males (57.5%) and 17 females (42.5%). The male-to-female ratio was 1.35:1. Patients with an age less than 60 years old formed 27.5% of all participants and patients with an age equal to or more than 60 years old were 57.5%. Thirty-six patients were followed up for final fate (either recovery or death); however, the fate of 6 patients was missed. The admission rate was higher among the male group in contrast to the case fatality rate (CFR), which was higher among the female group (63%) with a non-significant difference (Table 1 and Table 2).

The results of our study contradicted the results of Nguyen, who stated that the death rate was higher among the male gender (Nguyen *et al.*, 2021). The difference might be due to the low number of participants in our study or because females seek medical care in a late stage of the disease and are mostly admitted to hospitals with severe conditions. Traditions and customs also play a role in this issue, especially in rural areas (World Bank, 2020). The data collected so far does not accurately indicate the difference between the CFR among male and female groups in Iraq; generally, the highest CFR was (10%) recorded in March 2020, while the lowest percentage (1.08%) was recorded in April 2022 (Mathieu *et al.*, 2020). However, in the current study, the male group recorded a higher hospitalization rate with a lower CFR than the female group, 40% and 60%, respectively, (Table 2). Our results were partially incompatible with the results of Nguyen and colleagues, who found that male gender is a predictor of high hospitalization and mortality rate among patients with COVID-19 as well as older age

(Nguyen *et al.*, 2021).

Age of ≥60 years was a risk factor for increasing CFR among our patients in both male and female groups (Table 2). Similar results appeared in several studies and found that depletion of immunity, low Barthel index and severe intellectual decline were critical risk factor in increasing the CFR among elderly (Galeotti and Bayry, 2020; Yanez *et al.*, 2020; Damayanthi *et al.*, 2021). Although there was a non-significant difference between the age and fate of patients, which could be attributed to the low number of cases involved, however, our results were compatible with the results of different studies like Sepulveda *et al.* (2020) and Estrada *et al.* (2021) who enrolled a large study sample size.

Culture results of Twenty-six swab samples revealed positive bacterial growth (65%) out of the total samples. Blood culture was positive for one patient only (3.85%) (Table 3). Our results showed a significant difference between blood and swab culture results (P<0.001). The current result confirms the substantial role in upper respiratory tract infection among COVID-19 patients compared to bloodstream infections, which were recorded by different studies around the world (Damayanthi *et al.*, 2021; Sreenath *et al.*, 2021). Treatment of COVID-19 patients relies on a guideline for treatment that makes the patient receive high doses of different broad-spectrum antibiotics that are continuously changed to avoid the problem of antibiotic resistance, which may at the same time be a reason for inducing antibiotic resistance among microbiomes in lymphopenia patients. Mentioning that the percentage of bacteremia is very low among COVID-19 patients (Sepulveda *et al.*, 2020; Damayanthi *et al.*, 2021; Estrada *et al.*, 2021).

Table 4: Isolates and rate of mortality and recovery connected to each isolate.

Isolates	No.	Death (CFR)	Recovery
No growth	13	5 (38.46%)	6 (2 *)
Gram-positive isolates			
Aerococcus viridans	1	1 (100%)	0
Staphylococcus aerocularis	1	0	1 (100%)
Staphylococcus epidermidis	6	2 (33.33%)	4 (66.67%)
Staphylococcus hominis	2	2 (100%)	0
Staphylococcus scuri	1	0	1 (100%)
Staphylococcus haemolyticus	3	2 (66.67%)	1*
Leuconostoc mesentroidis	2	0	2 (100%)
Total (percentage out of 41)	16 (39%)	7 (17.1%)	9 (22%)
Gram-negative isolates			
Acenitobacter bomani complex	1	*	*
Raoultella ornithinolytica	2	2 (100%)	0
Enterobacter aurogenes	1	1 (100%)	0
Klebseilla pneumoni spp *pneumoni*	1	0	1 (100%)
Morganella morganii	1	0	1 (100%)
Salmonella typhi + E. coli	1	1 (100%)	0
Total (percentage out of 41)	7 (17.1%)	4 (9.75%)	2 (4.87%) + 1 *
Fungi			
Candida albicans (out of 41)	5 (12.2%)	4 (9.75%)	1 (2.43%)
Total (percentage out of 41)	41 (100%)	20 (48.8%)	17+ 4 * (51.2%)

*= No data; CFR, Case fatality rate.

Table 5: Antibiotic susceptibility testing results for a total of 28 patients and the associated resistance rates.

Antibiotic	Resistance rate	Antibiotic	Resistance rate
Penicillin group	100	Cefoxitin screen	100% positive
Cephalosporin group	100	Imipenem	68.0
Oxacillin	100	Ciprofloxacin	72.0
Azithromycin*	100	Gentamycin	76.1
Amoxicillin-clavulanate	100	Daptomycin	00.0

*Strains resistant to azithromycin are also resistant to clarithromycin and erythromycin.

The bacteria isolated from swab samples included different Gram-positive and Gram-negative bacteria in addition to *Candida albicans*. The high rate of these isolates was reflective of normal microbiota, Gram-positive bacteria and *Candida* species recorded 39% and 12.2%, respectively, and isolates were highly resistant to antibiotics (Table 4 and Table 5). Different studies evaluated the rate of coinfection among SARS-CoV-2 infected patients; however, most of these studies neglected the microbiota isolates and did not consider them significant or to play an important role in the pathogenesis, so isolates antibiotic sensitivity has not been evaluated. A study performed by Sreenath *et al.* (2021) was in concordance with our results; blood cultures in their study were negative compared to swab results in which coinfections were identified in 47.1% (90/191) of swab cultures. *Staphylococcus aureus* (*S. aureus*) was frequently isolated, followed by *Klebsiella pneumoniae* and the least frequency recorded by *Pneumocystis jirovecii* or *Legionella pneumophila*. Mixed infection was also found between *Acinetobacter baumannii* and *K. pneumoniae* (Alvi *et al.*, 2021). Nasal carriage of methicillin-resistant *S. aureus* among healthy individuals was frequently recorded in Iraq and other

countries before the COVID-19 pandemic, but COVID-19 treatment that requires excessive use of antibiotics and continuous change of these antibiotics led to a reduction in the nasal carriage pattern among those patients leading to the replacement of normal flora with a highly resistant strains (NIH, 2020; Alvi *et al.*, 2021; Sreenath *et al.*, 2021; Terreni *et al.*, 2021; Shamsuddin *et al.*, 2022). This scenario led to the emergence of a multidrug-resistant microbiome because of a change in the healthy microbiome and complex interactions of various microbial, exposomal, genetic and host factors that lead to their selection and expansion (Buret *et al.*, 2019; Belal, 2020).

In the current study, Gram-positive bacteria were isolated from cases with a total CFR of 17.1%, while fungal coinfection was associated with (9.75%) of the total CFR. Our findings were lower than that proposed earlier by Sharifipour *et al.* (2020). CFR was 95% for Gram-negative coinfected patients and 5% for those coinfected with Gram-positive bacteria (methicillin sensitive *S. aureus*) (Sharifipour *et al.*, 2020).

A VITEK® 2 system was used to evaluate the spectrum of resistance among the isolated microorganisms (Table 5). A 100% resistance rate of isolates was recorded for the following antibiotics

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(penicillins, cephalosporins, cefoxitin screen, oxyacillin, azithromycin and amoxicillin-clavulanate). In addition to VITEK® 2 system, the imipenem disc was used to identify carbapenemase-producing organisms; this disc method is 100% sensitive and 96% specific in determining carbapenem-hydrolysing β-lactamases strains (Benenson *et al.*, 2011). Different studies recorded the upsurge in the spread of carbapenemase production among Gram-positive and Gram-negative bacteria, and our results found that 68% of our isolates were resistant strains producing carbapenemase. Isolates included *Staphylococcus hominis*, *Raoultella ornithinolytica*, *Enterobacter aurogenes*, *Klebsiella pneumoni* and *Acinetobacter bomani* with a 100% CFR; the World Health Organization (WHO) classified such resistant strains as "a bacteria of critical priority" with an expected increase in the death rate due to infection in 2050 from 700,000 to 10 million per year (Takano *et al.*, 2009; Brauncajs *et al.*, 2022; Moubareck and Halat, 2022).

On the other hand, the results demonstrated that daptomycin was very effective and recorded 100% sensitivity. These findings support the recommendations of recent guidelines, which suggest considering the switch to alternative agents when the isolate shows a high rate of resistance during receipt of therapy (Moore *et al.*, 2012).

One isolate showed a 100% CFR among infected patients, the most important of which is the newly emerged bacteria *Raoultella ornithinolytica*. *Raoultella ornithinolytica* is a Gram-negative aerobic histamine-producing bacteria related to the Enterobacteriaceae family. This study is the first one that records this bacteria's isolation from the upper respiratory tract of Iraqi patients; however, there were other Iraqi study recorded the isolation of this organism from various clinical samples, including urine, burns, blood, wounds and stool and it was in concordance with our results (Al-Hulu *et al.*, 2009).

The research findings concluded the urgent need to rationalize the use of antibiotics and to develop new antibiotics that compete with the rapid spread and increase in antibiotic resistance among clinical isolates. The nonculture-dependent antibiotic treatment may lead to the emergence of new resistant strains, making infections that are apparently under control quickly turn into fatal threats (Alvi *et al.*, 2021; Sreenath *et al.*, 2021).

The major limitations of this study are related to the difficulty of following up on cases for a long time, as some patients are discharged before their full recovery to search for treatment at home or outside the governorate. Another limitation is the small number of patients participating in the study, either because they were afraid of the pain during deep swabbing or because they were using mechanical ventilators like Continuous Positive Airway Pressure (CPAP).

CONCLUSION

The results are alarming because of the need to take measures to prevent an increase in microbiome

resistance to antibiotics and limit their excessive use. In addition, further monitoring of the rise in the number of fungal infections among patients is required. It should be considered as a risk factor for the increasing case fatality rate. Susceptibility testing of all isolates is recommended. Neglecting local infections such as sinusitis or pulmonary fungal infection may cause an increase in hospitalization or even an increase in the case fatality rate among COVID-19 patients, especially among patients with lymphopenia.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

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