

Determine phenotypical patterns of resistance to antibiotics in COVID-19 patients with associated bacterial infection: largest medical center in Iran

Esmail Mohammadnejad¹, Arash Seifi², Reza Ghanei Gheshlagh³, Amir Aliramezani⁴, Samrand Fattah Ghazi⁵, Mohammadreza Salehi², Seyed Ali Dehghan Manshadi⁶, Amirhossein Orandi^{5*}

¹Research Center for Antibiotic Stewardship and Antimicrobial Resistance, Department of Medical-Surgical Nursing and Basic Sciences, School of Nursing and Midwifery, Tehran University of Medical Sciences, Tehran, Iran

²Research Center for Antibiotic Stewardship and Antimicrobial Resistance, Department of Infectious Disease, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

³Social Determinants of Health Research Center, Research Institute for Health Development, Kurdistan University of Medical Sciences, Sanandaj, Iran

⁴Department of Microbiology, Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University, Krakow, Poland

⁵Department of Anesthesiology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

⁶Department of Infectious Disease and Tropical Medicine, School of Medicine, Iranian Research Center for HIV/AIDS, Iranian Institute for reduction of High- Risk Behaviors, Tehran University of Medical Sciences, Tehran, Iran

Received: April 2023, Accepted: May 2023

ABSTRACT

Background and Objectives: Antibacterial resistance (AMR) is a serious threat and major concern, especially in developing countries. Therefore, we aimed to determine phenotypical patterns of resistance to antibiotics in COVID-19 patients with associated bacterial infection in intensive care units.

Materials and Methods: In this cross-sectional study, 6524 COVID-19 patients admitted for more than 48 h in the ICUs of Imam Khomeini Complex Hospital (IKCH) in Tehran from March 2020 to January 2022 were included in the study with initial diagnosis of COVID-19 (PCR test and chest imaging). Data were collected regarding severity of the illness, primary reason for ICU admission, presence of risk factors, presence of infection, length of ICU and hospital stay, microbial type, and antibiotic resistance. In this study, the pattern of antibiotic resistance was determined using the Kirby–Bauer disk diffusion method.

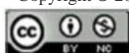
Results: In this study, 439 (37.5%) were ventilator-related events (VAEs), and 46% of all hospitalized patients had an underlying disease. The most common microorganisms in COVID-19 patients were carbapenem resistant *Klebsiella pneumoniae* (KPCs) (31.6%), *Escherichia coli* (*E. coli*) (15.8%), and *Acinetobacter baumannii* (*A. baumannii*) (15.7%), respectively. Prevalence of vancomycin-resistant enterococci (VRE) and KPCs were 88% and 82%, respectively.

Conclusion: A study on AMR surveillance is the need of the hour as it will help centers to generate local antibiograms that will further help formulate national data. It will guide doctors to choose the appropriate empiric treatment, and these studies will be the basis for establishing antimicrobial surveillance and monitoring and regulating of the use of antimicrobials.

Keywords: Pneumonia; COVID-19; Intensive care unit; Antimicrobial resistance; Surveillance

*Corresponding author: Amirhossein Orandi, MD, Department of Anesthesiology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran. Tel: +98-9128396143 Fax: +98-2166581537 Email: horandi@sina.tums.ac.ir

Copyright © 2023 The Authors. Published by Tehran University of Medical Sciences.



This work is licensed under a Creative Commons Attribution-Non Commercial 4.0 International license (<https://creativecommons.org/licenses/by-nc/4.0/>). Noncommercial uses of the work are permitted, provided the original work is properly cited.

INTRODUCTION

The pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been one of the most important challenges of our time and has affected healthcare systems worldwide (1). After the coronavirus pandemic, there is a possibility of an increase in hospital infections due to the hospitalization of these patients in the intensive care unit (2). Hospital infections, especially in intensive care units (ICU), are associated with different risk aspects, including increased mortality and hospitalization costs, and are considered one of the most important health problems. The successful management of these cases requires knowledge of hospital-related problems and proper planning (3, 4).

Management of such patients includes ensuring appropriate infection control and providing supportive care. In addition, these patients need serious care and intubation during treatment. Additionally, there is a possibility of pneumonia in these people, depending on the disease and care method. Therefore, secondary bacterial infections can contribute to an increase in the severity of the disease (3).

Furthermore, since most ICU patients often use broad-spectrum antimicrobials, this creates antibiotic selection pressure, leading to AMR among ICU microorganisms (5). Therefore, the microbiological profile of HAIs in the ICU often shows multidrug-resistant ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus* including methicillin-resistant *S. aureus* (MRSA), *Klebsiella pneumoniae* carbapenemases (KPCs), *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.) (6).

Antimicrobial resistance is becoming a global health challenge and problem that threatens many medical achievements of the last century and causes serious damage to the health system. Since the 1940s, when antibiotics entered the health system and the field of medicine, health and the well-being of people around the world has improved significantly (7). The development of resistant strains with high potential for infection occurs as a result of mutation or re-assortment of pre-existing microbial strains, rendering drugs, vaccines, and therapeutic measures ineffective in some cases (8, 9). This issue clearly causes danger for people who had a simple infection and could have recovered well if treated under the supervision of a doctor, but with the irrational use

of antibiotics in the past, these drugs have become ineffective (10). Unfortunately, due to the extended duration of the epidemic, several threats are emerging for human health. One of the most important is the risk of acquisition of new antimicrobial-resistant genes (11). Antimicrobial resistance is becoming a global health challenge and problem that threatens many medical achievements of the last century and causes serious damage to the health system. Since the 1940s, when antibiotics entered the health system and the field of medicine, health and the well-being of people around the world has improved significantly (12-14).

The studies conducted on co-infections of COVID-19 and related antibiotic resistance patterns in each province provide a clearer prognosis of the disease and, ultimately, reduce antibiotic resistance and treatment costs, which happen to be very high. On the other hand, today, more attention is paid to hospital infections and AMR due to mortality, morbidity, and many accompanying side effects in recent years (12). In some emerging infectious diseases such as the coronavirus and in sexually transmitted diseases such as hepatitis B, AIDS, and TB (13, 14), antimicrobial resistance may be ignored and is considered a big challenge for human society. The purpose of our study was to determine phenotypical patterns of resistance to antibiotics in COVID-19 patients with associated bacterial infection in the intensive care units (ICUs) of the largest medical center in Iran.

MATERIALS AND METHODS

Study design and setting. A retrospective study was done on laboratory records of the positive cultures of patients with nosocomial infection who were admitted to the ICU of IKCH in Tehran, a 1400-bed tertiary care hospital affiliated with the Tehran University of Medical Sciences during a 21-month period (March 2020 to January 2022). This study was approved by the ethics committee of the university. The participants, who were all patients admitted to the ICU of the mentioned hospital and met the inclusion criteria, were selected by census sampling. The inclusion criteria were referring to this healthcare center as a suspected COVID-19 patient for the first time and being admitted to the ICU afterward.

Data and sample collection. Data were obtained from the Iranian Nosocomial Infections Surveillance (INIS), COVID Online System of the Ministry of Health, and medical files of the patients. In addition, data were collected using a demographic characteristics questionnaire, which included name, age, gender, date of hospitalization, hospital ward (ICU), underlying diseases, date of discharge and date of death or discharge, sample submission date, and PCR results. In addition, the standard form of the Ministry of Health was the diagnosis of NIS in patients hospitalized in medical centers, with questions such as type of NIS, history of hospital infection, type of microorganism, and type of antibiogram. In this research, the pattern of antibiotic resistance was determined using the Kirby–Bauer disk diffusion method.

Identification of bacterial isolates. All specimens were cultured in a distinct range of media, including blood agar, triple sugar iron agar (TSI), sulfide indole motility (SIM), citrate agar, mannitol salt agar, and DNase (Merck, Germany) to distinguish the most important organisms. Isolation and characterization of our isolates was done using a combination of phenotypic and biochemical methods, such as colony morphology, Gram staining, oxidase, catalase, methyl red (MR)/Voges–Proskauer (VP), urease, coagulase, and API systems (bioMérieux, France).

Antibiotic susceptibility testing. The susceptibility of isolates to antibiotics was determined using disk diffusion according to CLSI guidelines. The antibiotics tested were oxacillin (1 µg), imipenem (10 µg), meropenem (10 µg), clindamycin (2 µg), linezolid (30 µg), vancomycin (5 µg), ampicillin (2 µg), ceftazidime (30 µg), cefotaxime (30 µg), ceftriaxone (30 µg), amikacin (30 µg), gentamicin (10 µg), tigecycline (15 µg), piperacillin (100 µg), piperacillin/tazobactam (110 µg), ampicillin/sulbactam (20 µg), ciprofloxacin (5 µg), levofloxacin (5 µg), trimethoprim/sulfamethoxazole (25 µg), and colistin sulphate (25 µg) (Mast Group Ltd., Bootle, UK).

Statistical analysis. Data analysis was performed using descriptive statistics (percent, mean, standard deviation, and median) of every variable. The analysis was done using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

Ethical considerations. The study was also ap-

proved by the research council and ethics committee of TUMS (code of ethics: IR.TUMS.VCR.REC.1399.169). All patients signed an informed consent for giving the specimens for research. No intervention has been done in diagnosis or treatment of COVID-19 cases. All methods were performed in accordance with the relevant guidelines and regulations.

RESULTS

Patient characteristics. This study was performed on 6524 patients in the ICUs of IKCH from March 2020 to January 2022, of whom 1168 (17.90%) had NISs. In terms of gender, 58.9% of the participants were male and the mean (SD) age of the patients was 52 ± 14.4 years old. Out of 1168 NISs, 37.5% were ventilator-related events (VAEs), 33% Urinary Tract Infections (UTI) and 26% Bloodstream Infections (BSI).

This study shows that 46% of all hospitalized patients had an underlying disease. Out of 1168 patients with NISs, 613 (52.4%) individuals had underlying diseases, the most common of which were hypertension (43.1), diabetes (28.4), cardiac diseases (22.64), hyperlipidemia (19.4%), and cancers (14.8%). In addition, 2961 patients (45.3%) had positive RT-PCR COVID-19 results, and out of the study participants, the median hospital stay was 12 days.

Bacterial characteristics. Table 1 shows that the most common microorganisms in COVID-19 patients were KPCs (31.6%), *E. coli* (15.8%), and *A. baumannii* (15.7%), respectively.

DISCUSSION

The present study aimed to evaluate the phenotypical patterns of resistance to antibiotics in COVID-19 patients with associated bacterial infection admitted to the intensive care units at the largest medical center in Iran. The results of our study show that the most common microorganisms in COVID-19 patients were KPCs (31.6%), *E. coli* (15.8%), and *A. baumannii* (15.7%), respectively. In the study conducted at Al-Zahra Hospital Isfahan, the data showed that *Pseudomonas aeruginosa* (13.9%), KPCs (11%), and *E. coli* (6.4%) were the most common bacterial

Table 1. Antibiotic resistance among identified isolates

Microorganisms	Percent	Antibiotic	Resistance (%)	
<i>Staphylococcus aureus</i>	4.26	Oxacillin	45	MRSA
		Clindamycin	72.2	
		Vancomycin	21.9	
<i>Enterococcus</i> spp.	8.06	Linezolid	1.06	VRE
		Vancomycin	62.8	
		Ampicillin	76.6	
<i>Klebsiella pneumoniae</i> carbapenemases (KPCs)	31.06	Third- and fourth-generation cephalosporins1	91.7	ESBL
		Fluoroquinolone2	85.04	
		Beta-lactamase inhibitors3	66.52	
		Carbapenem	82.93	
<i>Escherichia coli</i>	15.8	Third- and fourth-generation cephalosporins	75.89	ESBL
		Fluoroquinolone	71.54	
		Beta-lactamase inhibitors	74.16	
		Carbapenem4	24.13	
<i>Pseudomonas aeruginosa</i>	6.29	Ceftazidime	74.71	
		Fluoroquinolone	58.95	
		Aminoglycosides5	61.53	
		Piperacillin/Tazobactam	63.43	
		Carbapenem	74.36	
<i>Acinetobacter baumannii</i>	15.7	Ceftazidime	97.36	
		Fluoroquinolone	95.74	
		Aminoglycosides	91.53	
		Piperacillin/Tazobactam	92.63	
		Carbapenem	96.23	
		Colistin	7.3	

infections (15). Some studies have reported a higher rate of infections in the ICUs, which is due to the severity of the disease as well as some life-saving measures (16). One of the current challenges in Iranian hospitals, especially ICUs, is the high prevalence of Gram-negative bacteria. NIs with MDR, especially in the ICU, is a significant social, economic, and medical complication worldwide. They can spread various infections in society or cause longer hospitalization and impose more costs on patients (17, 18).

One study reported an increase in the resistance of *A. baumannii* to all tested antibiotics except colistin. Another study by Sharifipour et al. was similar to the results of our study (19). According to previous studies, AR rates were generally high, where carbapenem-resistant *A. baumannii* and carbapenem-resistant *K. pneumoniae* accounted for 91.7% and 76.6%, respectively. *S. aureus* and coagulase-negative staphylococci were resistant to methicillin (100%). The resistance of *E. coli* bacteria-producing ESBLs was 75%

(20, 21). The results of a study by Kariyavasam et al. (2022) showed that among MDR organisms, methicillin-resistant *S. aureus*, carbapenem-resistant *A. baumannii*, KPCs, *P. aeruginosa*, and multi-drug resistant *Candida auris* were most commonly reported (22). In a similar study in Iran, the highest resistance rates were seen in *E. coli* (615 samples), *K. pneumoniae* (351 samples), *P. aeruginosa* (362 samples), and *A. baumannii* (344 samples) to ampicillin (89.6%), imipenem (91.8%), and ceftazidime (94.6%), respectively (23). According to a meta-analysis by Langford et al. (2021), antibiotic prescriptions were administered in approximately 75% of cases of COVID-19, while bacterial co-infection occurred in less than 10% (24). In 2021, Moradi et al. reported that *A. baumannii* was the most prevalent bacteria isolated from the respiratory tract (15.4%) and blood (2.1%). *E. coli* (12.5%) was the most frequent bacteria in urine (25). *A. baumannii* has emerged as a major cause of nosocomial infections in critically ill patients in

the ICU. Resistance of *A. baumannii* isolates to carbapenems is a growing problem worldwide (26, 27).

In the present study, 7.3% of *A. baumannii* were resistant to colistin. Colistin is considered the most effective antibiotic for MDR *A. baumannii* (28). Actually, it is often the only treatment option for highly drug-resistant strains. Therefore, it is alarming that 7.3% of our *A. baumannii* clinical isolates were resistant to colistin in 2021-22. In a meta-analysis study by Maraki et al. (2016), the majority of *A. baumannii* clinical isolates in our hospital are MDR. The remaining therapeutic options for critically ill patients who suffer from MDR *A. baumannii* infections are severely limited, with *A. baumannii* beginning to develop resistance even against colistin (28). In this respect, the emergence of colistin resistance in our hospital is probably related to the selective pressure caused by the excessive use of colistin, as previously shown with KPCs (29). In a recent systematic review on the susceptibility of *A. baumannii* to colistin in Iran, a resistance rate of 4% had been estimated (30). Finally, in several studies, *A. baumannii* resistance to colistin is a big threat to medical centers in the next few years (31-34). The results of a study in Iran show that most clinical isolates of *A. baumannii* in our hospital are MDR. The remaining treatment options for critically ill patients with MDR *A. baumannii* infections are severely limited, and *A. baumannii* has begun to develop resistance even to colistin (35). AMR affects not only patients, but also healthy people in society. Resistant bacteria will spread rapidly among family members, classmates, and colleagues, and the health of community members will be threatened by new pathogenic species that are difficult and expensive to treat (36, 37).

The results of this study showed that antibiotic resistance among enterococci is increasing. This causes resistance in pathogenic bacteria and its spread to other bacteria. The results of this study showed that more than 60% of patients hospitalized in ICU were carriers of enterococci resistant to vancomycin. In a similar study in Iran, the rate of VRE was reported to be more than 40% (38). Enterococci are always looking for new methods to prevent the effects of antibiotics that are used (39). The global prevalence of VRSA has been steadily increasing over the past decades (40). Theories have been proposed for the persistence of VRE, such as co-selection of vancomycin resistance by other antibiotics, the common nature of enterococci in humans and animals, heavy metals,

its ubiquitous presence in the natural environment, and its compatibility and sustainability (41). Vancomycin is a glycopeptide antibiotic that is used to treat enterococcal infections and is considered as the last line of treatment for these infections (42-44).

Globally, the prevalence of antibiotic-resistant enterococcal infections in many countries around the world is high and on the rise, and there is a heavy burden of disease in developing and developed countries, causing problems in the health system (45-47). The importance of investigating the amount of resistant strains in the ICU is because the colonization of VRE increases in sensitive people after being admitted to this department, because VRE is more common in this department than in other hospital departments. These infections occur mostly in people colonized with this bacteria. Therefore, the risk of infections from these strains is higher in patients admitted to the intensive care unit. Considering the high prevalence of VRE in ICUs and the importance of the survival of VRE in the hospital and its spread in the community, it is recommended to apply hospital infection control and continuous training of intensive care unit personnel.

CONCLUSION

This study showed that the antibiotic resistance level in Gram-negative bacteria has still been increasing, even among COVID-19 patients. Although monitoring of antibiotic-resistant microorganisms must be continued on all sides, these valuable data might guide physicians to choose the appropriate empiric treatment when they encounter complicated patients, especially in the COVID-19 pandemic situation. In addition, these types of studies will be the basis for establishing antimicrobial surveillance and regulating the application of therapeutic agents in large referral hospitals and in developing countries.

ACKNOWLEDGEMENTS

This was a research project funded by a COVID-19 grant. Ethical approval reference number is (IR.TUMS.VCR.REC.1399.169). The authors thank Tehran University of Medical Sciences and Imam Khomeini Hospital for their financial support for this research.

REFERENCES

1. Abdollahi A, Shakoori A, Khoshnevis H, Arabzadeh M, Dehghan Manshadi SA, Mohammadnejad E, et al. Comparison of patient-collected and lab technician-collected nasopharyngeal and oropharyngeal swabs for detection of COVID-19 by RT-PCR. *Iran J Pathol* 2020; 15: 313-319.
2. Mohammadnejad E, Abbaszadeh A, Soori H, Afhami S. Prevention and control of nosocomial infections proceeding in intensive care units: A content analysis study. *Acta Med Mediterr* 2016; 32: 1295-1301.
3. Mohammadnejad E, Manshadi SAD, Mohammadi MTB, Abdollahi A, Seifi A, Salehi MR, et al. Prevalence of nosocomial infections in COVID-19 patients admitted to the intensive care unit of Imam Khomeini complex hospital in Tehran. *Iran J Microbiol* 2021; 13: 764-768.
4. Taher Al Barzin RMG, Ghafour Raheem S, Khudhur PK, Abdulkarimi R, Mohammadnejad E, Tabatabaee A. Interleukin-6 role in the severity of COVID-19 and intensive care unit stay length. *Cell Mol Biol (Noisy-le-grand)* 2020; 66: 15-18.
5. Moolchandani K, Sastry AS, Deepashree R, Sistla S, Harish B, Mandal J. Antimicrobial resistance surveillance among intensive care units of a tertiary care hospital in Southern India. *J Clin Diagn Res* 2017; 11: DC01-DC07.
6. Allameh SF, Nemati S, Ghalehtaki R, Mohammadnejad E, Aghili SM, Khajavirad N, et al. Clinical characteristics and outcomes of 905 COVID-19 patients admitted to Imam Khomeini hospital complex in the capital city of Tehran, Iran. *Arch Iran Med* 2020; 23: 766-775.
7. Podolsky SH. The evolving response to antibiotic resistance (1945–2018). *Palgrave Commun* 2018; 4: 124.
8. Getahun H, Smith I, Trivedi K, Paulin S, Balkhy HH. Tackling antimicrobial resistance in the COVID-19 pandemic. *Bull World Health Organ* 2020; 98: 442-442A.
9. Pérez de la Lastra JM, Anand U, González-Acosta S, López MR, Dey A, Bontempi E, et al. Antimicrobial resistance in the COVID-19 landscape: is there an opportunity for anti-infective antibodies and antimicrobial peptides? *Front Immunol* 2022; 13: 921483.
10. Aslam B, Wang W, Arshad MI, Khurshid M, Muzammil S, Rasool MH, et al. Antibiotic resistance: a run-down of a global crisis. *Infect Drug Resist* 2018; 11: 1645-1658.
11. Ukuhor HO. The interrelationships between antimicrobial resistance, COVID-19, past, and future pandemics. *J Infect Public Health* 2021; 14: 53-60.
12. Majumder MAA, Rahman S, Cohall D, Bharatha A, Singh K, Haque M, et al. Antimicrobial stewardship: Fighting antimicrobial resistance and protecting global public health. *Infect Drug Resist* 2020; 13: 4713-4738.
13. Rabirad N, Nejad EM, Hadizadeh MR, Begjan J, Ehsani SR. The prevalence of TB in HIV patients and risk factor with frequent referral (Iran, 2009-10). *Iran Red Crescent Med J* 2013; 15: 58-61.
14. Mohammad Nejad E, Jafari S, Mahmoodi M, Begjani J, Roghayeh Ehsani S, Rabirad N. Hepatitis B virus antibody levels in high-risk health care workers. *Hepat Mon* 2011; 11: 662-663.
15. Akbari M, Nejad Rahim R, Azimpour A, Bernousi I, Ghahremanlu H. A survey of nosocomial infections in intensive care units in an Imam Reza hospital to provide appropriate preventive guides based on international standards. *Studies Med Sci* 2013; 23: 591-596.
16. Kumar A, Chaudhry D, Goel N, Tanwar S. Epidemiology of Intensive Care Unit-acquired Infections in a Tertiary Care Hospital of North India. *Indian J Crit Care Med* 2021; 25: 1427-1433.
17. Eggimann P, Pittet D. Infection control in the ICU. *Chest* 2001; 120: 2059-2093.
18. Yallew WW, Kumie A, Yehuala FM. Risk factors for hospital-acquired infections in teaching hospitals of Amhara regional state, Ethiopia: A matched-case control study. *PLoS One* 2017; 12(7): e0181145.
19. 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: 646.
20. Li J, Wang J, Yang Y, Cai P, Cao J, Cai X, et al. Etiology and antimicrobial resistance of secondary bacterial infections in patients hospitalized with COVID-19 in Wuhan, China: a retrospective analysis. *Antimicrob Resist Infect Control* 2020; 9: 153.
21. Sang L, Xi Y, Lin Z, Pan Y, Song B, Li C-A, et al. Secondary infection in severe and critical COVID-19 patients in China: a multicenter retrospective study. *Ann Palliat Med* 2021; 10: 8557-8570.
22. 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: 45.
23. Khoshbakht R, Kabiri M, Neshani A, Khaksari MN, Sadrzadeh SM, Mousavi SM, et al. Assessment of antibiotic resistance changes during the COVID-19 pandemic in northeast of Iran during 2020–2022: an epidemiological study. *Antimicrob Resist Infect Control* 2022; 11: 121.
24. Langford BJ, So M, Raybardhan S, Leung V, Soucy J-PR, Westwood D, et al. Antibiotic prescribing in patients with COVID-19: rapid review and meta-analysis. *Clin Microbiol Infect* 2021; 27: 520-531.
25. Moradi N, Kazemi N, Ghaemi M, Mirzaei B. Frequent

- cy and antimicrobial resistance pattern of bacterial isolates from patients with COVID-19 in two hospitals of Zanjan. *Iran J Microbiol* 2021; 13: 769-778.
26. Maragakis LL, Perl TM. *Acinetobacter baumannii*: epidemiology, antimicrobial resistance, and treatment options. *Clin Infect Dis* 2008; 46: 1254-1263.
 27. Bonomo RA, Szabo D. Mechanisms of multidrug resistance in *Acinetobacter* species and *Pseudomonas aeruginosa*. *Clin Infect Dis* 2006; 43 Suppl 2: S49-56.
 28. Maraki S, Mantadakis E, Mavromanolaki VE, Kofteridis DP, Samonis G. A 5-year surveillance study on antimicrobial resistance of *Acinetobacter baumannii* clinical isolates from a tertiary Greek hospital. *Infect Chemother* 2016; 48: 190-198.
 29. Souli M, Galani I, Giamarellou H. Emergence of extensively drug-resistant and pandrug-resistant Gram-negative bacilli in Europe. *Euro Surveill* 2008; 13: 19045.
 30. Moradi J, Hashemi FB, Bahador A. Antibiotic resistance of *Acinetobacter baumannii* in Iran: a systemic review of the published literature. *Osong Public Health Res Perspect* 2015; 6: 79-86.
 31. Chandra' P, V R, M S, Cs S, Mk U. Multidrug-resistant *Acinetobacter baumannii* infections: looming threat in the Indian clinical setting. *Expert Rev Anti Infect Ther* 2022; 20: 721-732.
 32. Xie R, Zhang XD, Zhao Q, Peng B, Zheng J. Analysis of global prevalence of antibiotic resistance in *Acinetobacter baumannii* infections disclosed a faster increase in OECD countries. *Emerg Microbes Infect* 2018; 7: 31.
 33. Giamarellou H, Antoniadou A, Kanellakopoulou K. *Acinetobacter baumannii*: a universal threat to public health? *Int J Antimicrob Agents* 2008; 32: 106-119.
 34. Shields RK, Clancy CJ, Gillis LM, Kwak EJ, Silveira FP, Massih RCA, et al. Epidemiology, clinical characteristics and outcomes of extensively drug-resistant *Acinetobacter baumannii* infections among solid organ transplant recipients. *PLoS One* 2012; 7(12): e52349.
 35. Mostafavi SN, Rostami S, Nokhodian Z, Ataei B, Cheraghi A, Ataabadi P, et al. Antibacterial resistance patterns of *Acinetobacter baumannii* complex: The results of Isfahan antimicrobial resistance surveillance-I program. *Asian Pac J Trop Med* 2021; 14: 316-322.
 36. Rump B, Timen A, Hulscher M, Verweij M. Ethics of infection control measures for carriers of antimicrobial drug-resistant organisms. *Emerg Infect Dis* 2018; 24: 1609-1616.
 37. Toner E, Adalja A, Gronvall GK, Cicero A, Inglesby TV. Antimicrobial resistance is a global health emergency. *Health Secur* 2015; 13: 153-155.
 38. Ghaffarpasand I, Moniri R, Kheradi E, Tehrani M. Antibiotic resistance in fecal enterococci in hospitalized patients. *Indian J Pathol Microbiol* 2010; 53: 898-899.
 39. Asnaashari M, Eghbal MJ, Yaghmayi AS, Shokri M, Azari-Marhabi S. Comparison of antibacterial effects of photodynamic therapy, modified triple antibiotic paste and calcium hydroxide on root canals infected with *Enterococcus faecalis*: an *in vitro* study. *J Lasers Med Sci* 2019; 10(Suppl 1): S23-S29.
 40. Lee M-C, Lu C-H, Lee W-Y, Lee C-M. Correlation between nosocomial carriage of vancomycin-resistant Enterococci and antimicrobial use in Taiwan. *Am J Trop Med Hyg* 2020; 104: 1131-1136.
 41. Li G, Walker MJ, De Oliveira DM. Vancomycin resistance in *Enterococcus* and *Staphylococcus aureus*. *Microorganisms* 2022; 11: 24.
 42. Nellore A, Huprikar S, AST ID Community of Practice. Vancomycin-resistant Enterococcus in solid organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant* 2019; 33(9): e13549.
 43. Linden PK. Treatment options for vancomycin-resistant enterococcal infections. *Drugs* 2002; 62: 425-441.
 44. Kauffman CA. Therapeutic and preventative options for the management of vancomycin-resistant enterococcal infections. *J Antimicrob Chemother* 2003; 51 Suppl 3: iii23-30.
 45. Markwart R, Willrich N, Haller S, Noll I, Koppe U, Werner G, et al. The rise in vancomycin-resistant *Enterococcus faecium* in Germany: data from the German antimicrobial resistance surveillance (ARS). *Antimicrob Resist Infect Control* 2019; 8: 147.
 46. Moussally M, Zahreddine N, Kazma J, Ahmadih R, Kan SS, Kanafan ZA. Prevalence of antibiotic-resistant organisms among hospitalized patients at a tertiary care center in Lebanon, 2010–2018. *J Infect Public Health* 2021; 14: 12-16.
 47. Molechan C, Amoako DG, Abia ALK, Somboro AM, Bester LA, Essack SY. Molecular epidemiology of antibiotic-resistant *Enterococcus* spp. from the farm-to-fork continuum in intensive poultry production in KwaZulu-Natal, South Africa. *Sci Total Environ* 2019; 692: 868-878.