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RESEARCH ARTICLE OPEN ACCESS

Screening of Intensive Care Unit Patients for the Presence of Carbapenem-resistant *Enterobacterales* (CRE) on Admission as a Measure of Infection Control

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Abstract

The global spread of carbapenem-resistant *Enterobacteriaceae* (CRE) has been fostered by the lack of preemptive screening of patients in healthcare facilities that could prevent patient-to-patient transmission. To screen patients admitted to Medical Intensive Care Unit (MICU) for CRE carriage to take appropriate infection control measures. This prospective surveillance study was conducted in the MICU of a tertiary healthcare hospital between September to December 2022. Patients more than 18 years of age admitted to the MICU were included in the study. Patients transferred from different units within the hospital to MICU were excluded. Immediately after admission, two rectal swabs were collected after obtaining consent from the patients. These patients were selected based on the questionnaire framed from Centers for Disease Control and Prevention (CDC) CRE tool kit. The samples were further analyzed and the antimicrobial susceptibility test was performed. The present study included 91 study subjects of which 53% were males. Of selected participants, 63.7% did not have any specified medical intervention or device placed and 78% had not used antibiotics previously. Of the tested isolates, Of the tested isolates, 12 (13.2%) were observed to be CRE colonized. These isolates were found to be resistant to both imipenem and meropenem. An association was reported between CRE and device placement (p = 0.000) as well as between CRE and previous use of antibiotics (p = 0.000). Current use of antibiotics (p = 0.6381) and gender (p = 0.6066) did not show any association with CRE colonisation. The study concludes that the presence of CRE is an existing danger for patients in ICUs and that there is a possible association between CRE and device placement as well as previous use of antibiotics which can be further studied.

Keywords: Carbapenem Resistant *Enterobacteriaceae*, Drug Resistance, Screening, Intensive Care Unit

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INTRODUCTION

Antimicrobial resistance has been a health-related problem that has consequences on a global scale and has only increased with time. Massive industrial manufacturing of antibiotics, their use in humans, animals, and agriculture, as well as the ensuing environmental contamination, all have an impact on the formation and spread of antibiotic resistance, reducing the efficacy of chemotherapy and poses a huge public health concern. Research on bacterial antibiotic resistance has been continuously expanding over the past few decades and is currently one of the microbiological sciences disciplines with the highest rate of growth. The belief that there is an urgent need to address a problem that could have catastrophic effects on human health is the primary force propelling research in that direction.[1]

One such type of antibiotic resistance is Carbapenem-resistant *Enterobacteriaceae* (CRE) infection which leads to longer lengths of stay, increased healthcare costs, and higher mortality than carbapenem-susceptible infections.[2,3] CRE is defined as an *Enterobacteriaceae* isolate that is resistant to ertapenem, imipenem, meropenem, or doripenem according to the current Clinical and Laboratory Standards Institute (CLSI) breakpoints or documentation that the isolate produces a carbapenemase.[2,4] There are at least three major mechanisms of Carbapenem resistance (CR) in *Enterobacteriaceae*: (a) production of carbapenemase which are enzymes that hydrolyze carbapenems to render them inactive, these are typically found in the periplasm. (b) production of efflux pumps, actively expelling carbapenems from the bacterial cell; (c) due to a porin mutation or deletion, the bacterial cell is left without the typical carriers that allow carbapenem to pass through its outer membrane.[5]

Healthcare professionals, who treat patients with CRE infection are unquestionably faced with a difficult choice: either they continue using older medications, whose features and drawbacks are well known, or they switch to new antibiotics despite the lack of evidence on their effectiveness against CRE and higher cost.[5] Intensive Care Unit (ICU) patients are at a high risk of colonization and infection caused by multidrug-resistant organisms (MDROs). Recently, among MDROs, CRE, like *Escherichia coli* and *Klebsiella pneumoniae*, has emerged as a major threat to the health of ICU patients because of limited treatment options and high mortality rates.[6]

To counter the issue of CRE outbreaks in ICU settings, a proactive approach by active surveillance and a strong compliance with infection control measures would be needed to prevent the spread of CRE transmission particularly in a critical care unit (CCU) setup. Laboratory methods to screen for CRE have been developed, leading to improved detection of CRE carriage.[7]

There is a lack of evidence on the different aspects of antibiotic resistance, especially CRE which could help in enforcing antimicrobial stewardship policies necessary to avoid unnecessary use of broad-spectrum antibiotics which could result in the formation of antimicrobial resistance.[8] To fulfill this gap in knowledge, the present study was conducted with the aim of screening patients admitted in Medical Intensive Care Unit (MICU)s for carriage of CRE so that necessary infection control measures could be taken. This aim was fulfilled by the following objectives:

1. By processing rectal swabs for the presence of CRE using Centers for Disease Control and Prevention (CDC) protocol.
2. By confirming the identification of isolated bacteria by conventional biochemical tests.
3. To analyze the risk factors associated with CRE colonization.

MATERIALS AND METHODS

The present prospective surveillance study was conducted in a 20-bed MICU of a tertiary care hospital located in Coimbatore between September 2022 through December 2022. Patients more than 18 years of age admitted to the MICU were included in the study. Patients transferred from different units within the hospital to MICU were excluded as these patients were not screened for CRE at the time of admission. The study was initiated after obtaining clearance from the Institutional Human Ethics Committee (IHEC) with reference number PSG/IHEC/2022/Appr/

FB/030 and patients were selected after obtaining necessary informed consent. A sample size of 100 participants was considered for the study based on the results of a study conducted by Wattal *et al.*[9]

p = 50%, n = 4pq/d2, q = 100-p = 100-50 = 50, d = 20% of the p = 20/50*100 = d = 10

n = 4*50*50/10*10 = 100

n = 100

During the study period 91 patients were included in the study were included in the study for analysis. Two rectal swabs were collected simultaneously soon after admission from patients getting admitted to the MICU. Patient information was collected using a predetermined questionnaire which included duration of stay in the other hospital, exposure to high-end antibiotics (Carbapenem, Colistin, Tigecycline, Polymyxin B, Vancomycin and Teicoplanin), devices inserted, surgical procedure performed in the past 3 months and history of colonization and infection with CRE were collected. Swabs were then immediately transferred to the laboratory for processing.

The screening for CRE was done based on the CDC protocol[7]: the rectal swab was inoculated in 5 ml of trypticase soy broth containing 10 µg of ertapenem. After overnight incubation at 35°C, subculture of 100 µl of the broth culture was done in MacConkey agar.

Plates were incubated overnight at 37°C in an incubator and then interpreted. The colonies grown in culture plate were further characterized for identification by biochemical methods. Lactose fermenting colonies were identified as pink, mucoid or non-mucoid colonies on MacConkey agar plate and non-lactose fermenting colonies as colorless colonies. All these colonies were identified and confirmed by conventional biochemical tests. Carbapenem resistance of Enterobacteriales from screen agar was then confirmed by antimicrobial susceptibility for imipenem and meropenem on Muller-Hilton agar plate by Kirby Bauer disc diffusion method. Susceptibility was determined using the 2022 breakpoint criteria of the Clinical and Laboratory Standards Institute. Isolates non-susceptible to either Imipenem or Meropenem were defined as CRE positive.

Storage & disposal procedures of biological/ hazardous material

After usage, materials were discarded according to Hospital Bio-medical Waste Management rules.

Potential risks & benefits

There are no potential risks involved in this project.

Statistical analysis

Analysis was done using SPSS v24.0. Descriptive statistics were performed and results were shown in frequency and percentage. Test for association was performed using the Chi-square test and p-value <0.05 was considered statistically significant.

RESULTS

The present study included 53% males and 47% females (Figure) with a mean age of 58.60 ± 14.61 years. Most participants (63.7%) did not have any specified medical intervention or device placed, while the remaining isolates had different devices or interventions present, with varying frequencies. Most of the participants reported previous hospital admission (52.7%), majority of participants reported that they did not previously use antibiotics (78%). The data shows that the majority of isolates (86.8%) had

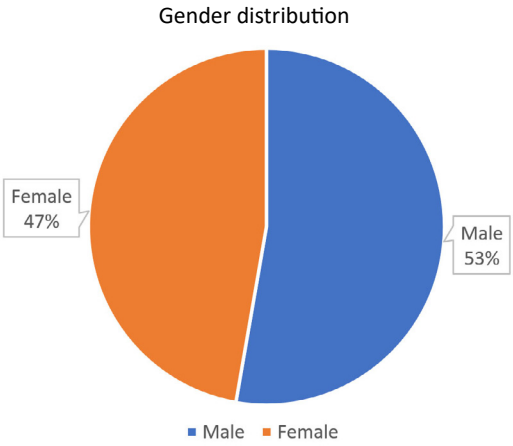

Figure. Pie chart depicting gender distribution of participants

Table 1. Demographic details of participants

Variable		Frequency	Percent (%)
Frequency For Device Placed	No	58	63.7
	Yes (Central Line)	3	3.3
	Yes (Endotracheal Tube)	3	3.3
	Yes (Foley Catheter)	27	29.7
Previous Hospital Admission	No	43	47.3
	Yes	48	52.7
Previous Use of Antibiotics	No	71	78.0
	Yes (Meropenem)	11	12.1
	Yes (Colistin)	3	3.3
	Yes (Vancomycin)	6	6.6
Rectal Swab Culture (CRE)	Negative	79	86.8
	Positive	12	13.2
Biochemical Reactions			
	Test Conducted	12	13.2
	Test Not Conducted	79	86.8
Disc Diffusion Test	Imipenem-resistant, Meropenem-resistant	12	86.8
	None	79	13.2

Table 2. Table assessing for association between CRE and sex

		Rectal Swab Culture (CRE)		
		Negative	Positive	p-value
Sex	Female	36	7	0.6066
	Male	43	5	

*- statistically significant ($p < 0.05$)

"NEGATIVE" results, indicating that Carbapenem-Resistant *Enterobacteriaceae* was not detected in their rectal swab cultures. On the other hand, 12 (13.2%) were positive for CRE colonization (Table 1).

Among the 12 CRE isolates 4 wereidentified as *Escherichia coli* and 8 were *Klebsiella pneumoniae* by standard conventional biochemical tests.

Out of the total 91 isolates, 79 (86.8%) of them exhibited no growth at all. Out of the tested CRE isolates, 12 isolates (13.2%) were found to be resistant to both imipenem and meropenem (Table 1).

Out of 12 CRE colonized patients, 5 patients were referred from outside healthcare facility and 7 were from community directly.

Test for association between CRE testing and sex was conducted and the results showed that there was no association ($p > 0.05$), a similar result was observed when assessing for association between CRE testing and current use of antibiotics ($p > 0.05$) (Table 2 and 5) An association was found between CRE and device placement ($p = 0.000$*) as well as between CRE and previous use of antibiotics ($p = 0.000$*) (Table 3 and 4).

DISCUSSION

Drug-resistant bacteria come in many different forms, including vancomycin-resistant *Enterococci* (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA), among others. However, the Centers for Disease Control and Prevention (CDC) in the US has emphasized that immediate action is needed to combat carbapenem-resistant bacteria.[8] The studies done by Wattal et al showed the prevalence of CRE was around 57%.[9] Drugs like imipenem and meropenem are the last-resort drugs for the treatment of multidrug-resistant organisms and have emerged as viable options for the treatment of CRE and have been studied extensively.[10,11] However, resistance to these drugs has also been detected in some cases which is a major cause for concern. In 2017, Mohan *et al.* reported that the prevalence rate of CRE in India was 18.7%.[9,12]

The present study was conducted to assess the extent of consequences associated

Table 3. Table assessing for association between CRE and device placement

		Rectal Swab Culture (CRE)		Total	p-value
		Negative	Positive		
Device Placed	No	55	3	58	0.000*
	Yes (Central Line)	0	3	3	
	Yes (Endotracheal Tube)	1	2	3	
	Yes (Foley Catheter)	23	4	27	
Total		79	12	91	

*- statistically significant ($p < 0.05$)

Table 4. Table assessing for association between CRE and previous use of antibiotics

		Rectal Swab Culture (CRE)		Total	p-value
		Negative	Positive		
Previous use of Antibiotics	No	68	3	71	0.000*
	Yes (Meropenem)	0	3	3	
	Yes (Endotracheal Tube)	1	2	3	
	Yes (Foley Catheter)	23	4	27	
Total		79	12	91	

*- statistically significant ($p < 0.05$)

with CRE formation and the different factors that could affect it. The present study included 53% males and 47% females with a mean age of 58.60 ± 14.61 years. This result was found to be similar to that of a study conducted based on the report from the China CRE network, which stated that it included a majority of males (67.8%). It also reported that a large proportion of the patients with CRE were 65 years or older which is within the range set forth by the results obtained in the present study.[11] Similar gender distribution was reported in a study by Rajni *et al.* with a reported mean age of 41 years which was comparatively very low.[13] Another Thai study also reported a predominance of male patients with regard to CRE colonization in samples.[14]

A majority of participants (63.7%) did not have any specified medical intervention or device placed, while the remaining isolates had different devices or interventions present, with varying frequencies. This was in contrast to the results obtained by a previously conducted study by Zhang *et al.* wherein 64.8% of patients had undergone placement of urinary catheter whereas in the present study, only 29.7% had a Foley catheter placed prior to admission.[11]

Most of the participants reported previous hospital admission (52.7%), this was higher than the percentage reported in a previously conducted study which showed that 37.1% of patients with CRE had undergone hospitalization in the past year.[11] The result obtained here was also higher than that reported by a study conducted in Jodhpur which showed that 40% of patients had a history of previous hospitalizations.[13] Previous hospitalization increases the chances of developing resistance to antibiotics as a hospital setting would be teeming with resistant strains of bacteria and this can be elicited from the results of the present study.

In the present study, only 22% of participants reported previous use of antibiotics, this was dissimilar to the results of a previously conducted study which reported that 90.9% of patients had used antibiotics 30 days prior to culture.[11] A study conducted among ICU patients in Jodhpur showed that 53% of CRE carrier patients had a history of antibiotic usage which

Table 5. Table assessing for association between CRE and current use of antibiotics

		Rectal Swab Culture (CRE)		Total	p-value
		Negative	Positive		
Current use number of antibiotics	No	6	0	6	0.6381
	One	44	6	50	
	Two	26	5	31	
	Three	3	1	4	
Total		79	12	91	

*- statistically significant ($p < 0.05$)

is higher than reported in the present study.[13] A study previously conducted study in Thailand also reported that 69.9% of patients positive for CRE had a history of antimicrobial use 3 months prior to admission which is much higher than reported in the present study. The use of antimicrobials should be much higher when we consider that overuse of antibiotics is associated with the presence of antimicrobial resistance, however, the number of patients using antibiotics is close to the amount of positive CRE isolates.

The data shows that a smaller proportion of isolates (13.2%) tested positive for colonization, indicating the presence of CRE in their rectal swab cultures. This was a much lower level of CRE carriage than that obtained by Rajni *et al.* wherein a carriage rate of 37% was obtained in the fecal swabs that were collected and tested.[13] A study conducted in an ICU setting in Mumbai reported an alarmingly high rate of CRE-positive isolated with 51.85% of the patients admitted there.[15] A surveillance study conducted in Thailand reported that 15.5% patients had shown to be positive to CRE colonization upon admission, this is similar to the results obtained in the present study. However, the previous study was conducted over a period of 3 years and included 582 patients.[14] A study conducted in Tamil Nadu by Ramanathan *et al.* reported that 7.8% selected patients were identified with CRE colonization.[16] The difference in results can be explained by the differing duration of study periods and sample size.

Out of a total of 12 CRE isolates, 4 (33.33%) were identified as *Escherichia coli* (I+, MR+, Vi, C-), and 8 (66.67%) were identified as *Klebsiella pneumoniae* (I-, MR-, Vi+, C+). This was close to the results obtained by a previously conducted study wherein the CRE isolated had harbored 39.2% *Escherichia coli* and 42.8% *Klebsiella pneumoniae* organisms.[15] Another previously conducted study showed that from 25 isolates, 22% were *E. coli* and 42% belonged to the *Klebsiella* species, this was lower than the levels reported in the present study.[17] Another previously conducted study reported that among the detected isolates, 75% were *K. pneumoniae* and 25% were *E. coli.*[16] This difference in results can be explained by the difference in sample sizes between all the involved studies.

Out of the tested CRE isolates, 12 isolates (13.2%) were found to be resistant to both imipenem and meropenem. This resistance pattern suggests that these isolates are highly resistant to carbapenem antibiotics, which are potent antibiotics often used to treat serious bacterial infections. Among the tested CRE isolates, 79 isolates (86.8%) did not exhibit resistance to either imipenem or meropenem. These isolates were susceptible to these carbapenem antibiotics. Another study reported that all detected isolates showed resistance toward cotrimoxazole, imipenem, and meropenem.[17] This massive difference in results points to variations in the presence of resistant bacteria between studies and should be studied further.

A test for the association between CRE testing and certain variables was conducted and the results showed that an association was found between CRE and device placement ($p = 0.000$*) as well as between CRE and previous use of antibiotics ($p = 0.000$*). A previously conducted study by Wang *et al.* concluded that cumulative antibiotic exposure history, especially for previous use of beta-lactams and carbapenems, was

considered a risk factor associated with CRE infections.[18] This result can be emphasized by a previous study showing that 90.9% of patients with CRE had recent antimicrobial therapy exposure.[11] Another previously conducted study did not detect an association between CRE colonization and previous antibiotic use but found one with older age (40+ years) with a p-value of 0.009. This difference could be due to most of the participants in the present study belonging to an older age group. A study conducted in Thailand compared patients with and without CRE colonization and reported that there was a significant difference between the patients with regard to previous hospitalization and use of antimicrobials within 3 months ($p<0.001$), this can help reinforce the results of the present study with regard to use of antibiotics.[14] A study conducted in Tamil Nadu also reported that high-end antibiotic exposure ($p = 0.0029$), history of surgery in the past 90 days ($p = 0.0167$), and systemic infection ($p = 0.00001$) showed a statistical association with CRE colonization.[16]

The present study was not without any limitations; the single-centered nature of the study puts into question the generalizability of the study. The study duration is also a matter of concern with the three-month period not facilitating analysis of CRE infections acquired after admission. Lastly, the study could have also included an assessment of carbapenemases which is a major reason for resistance formation in bacteria. The clinical implications of the results of the study are that carbapenem resistance are a cause for concern as they can result in a 26-44% mortality rate in patients with *Enterobacteriaceae* infections.[19] Intestinal colonization of multidrug-resistant Enterobacterales in hospitalized patients serves as a reservoir for disseminating Enterobacterales in the hospital setting, this can be used for diagnosis which makes rectal swab samples a good avenue to diagnose CRE.[14] Hence, it is essential to conduct testing of rectal swabs for CRE at admission to avoid the spread of infection as well as to initiate a specific treatment protocol for the management of the infection.[20-22]

CONCLUSION

The results of the present study help conclude that overall CRE colonization rates in hospital settings were found to be low,but it cannot be disregarded due to the associated morbidity and mortality. Diagnosis of the infection by means of rectal swabs at admission can help in the management of CRE infection and help curb the disease at its incipient stages itself. This study can also lead to modification of infection control practices to initiate empiric contact isolation precautions and active surveillance for the patients with risk factors in MICUs.

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None.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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DATA AVAILABILITY

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

This study was approved by the Institutional Human Ethics Committee (IHEC) with reference number PSG/IHEC/2022/Appr/FB/030.

INFORMED CONSENT

Written informed consent was obtained from the participants before enrolling in the study.

REFERENCES

1. Baquero F. Threats of antibiotic resistance: an obliged reappraisal. *Int Microbiol.* 2021;24(4):499-506. doi: 10.1007/s10123-021-00184-y
2. Lutgring JD. Carbapenem-resistant *Enterobacteriaceae*: An emerging bacterial threat. *Semin DiagnPathol.* 2019;36(3):182-186. doi: 10.1053/j.semdp.2019.04.011
3. Bartsch SM, McKinnell JA, Mueller LE, et al. Potential economic burden of carbapenem-resistant *Enterobacteriaceae* (CRE) in the United States. *Clin Microbiol Infect.* 2017;23(1):48.e9-48.e16. doi: 10.1016/j.cmi.2016.09.003
4. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing; twenty-first informational supplement; M100-S21. Wayne, PA: Clinical and Laboratory Standards Institute; 2011.
5. Durante-Mangoni E, Andini R, Zampino R. Management of carbapenem-resistant *Enterobacteriaceae* infections. *Clin Microbiol Infect.* 2019;25(8):943-950. doi: 10.1016/j.cmi.2019.04.013
6. Doi Y. Treatment Options for Carbapenem-resistant Gram-negative Bacterial Infections. *Clin Infect Dis.* 2019;69(Suppl 7):S565-S575. doi: 10.1093/cid/ciz830
7. Richter SS, Marchaim D. Screening for carbapenem-resistant *Enterobacteriaceae*: Who, When, and How? *Virulence.* 2017;8(4):417-426. doi: 10.1080/21505594.2016.1255381
8. Akeda Y. Current situation of carbapenem-resistant *Enterobacteriaceae* and *Acinetobacter* in Japan and Southeast Asia. *Microbiol Immunol.* 2021;65(6):229-237. doi: 10.1111/1348-0421.12887
9. Wattal C, Goel N, Oberoi JK, Raveendran R, Datta S, Prasad KJ. Surveillance of multidrug resistant organisms in tertiary care hospital in Delhi, India. *J Assoc Physicians India.* 2010;58(Suppl):32-36.
10. Tompkins K, van Duin D. Treatment for carbapenem-resistant *Enterobacterales* infections: recent advances and future directions. *Eur J Clin Microbiol Infect Dis.* 2021;40(10):2053-2068. doi: 10.1007/s10096-021-04296-1
11. Pascale R, Giannella M, Bartoletti M, Viale P, Pea F. Use of meropenem in treating carbapenem-resistant *Enterobacteriaceae* infections. *Expert Rev Anti Infect Ther.* 2019;17(10):819-827. doi: 10.1080/14787210.2019.1673731
12. Mohan B, Prasad A, Kaur H, Hallur V, Gautam N, Taneja N. Fecal carriage of carbapenem-resistant *Enterobacteriaceae* and risk factor analysis in hospitalised patients: A single centre study from India. *Indian J Med Microbiol.* 2017;35(4):555-562. doi: 10.4103/ijmm.IJMM_17_144
13. Rajni E, Rajpurohit V, Rathore P, Khatri PK. Epidemiology of carbapenem-resistant *Enterobacteriaceae* colonization in ICU: a pilot study from a tertiary care hospital in Western Rajasthan, India. *Int J Res Med Sci.* 2018;6(10):3340-3345. doi: 10.18203/2320-6012.ijrms20184043
14. Wangchinda W, Thamlikitkul V, Watcharasuwanseree S, Tangkoskul T. Active Surveillance for Carbapenem-Resistant *Enterobacterales* (CRE) Colonization and Clinical Course of CRE Colonization among Hospitalized Patients at a University Hospital in Thailand. *Antibiotics* (Basel). 2022;11(10):1401. doi: 10.3390/antibiotics11101401
15. Saseedharan S, Sahu M, Pathrose EJ, Shivdas S. Act Fast as Time Is Less: High Faecal Carriage of Carbapenem-Resistant *Enterobacteriaceae* in Critical Care Patients. *J Clin Diagn Res.* 2016;10(9):DC01-DC05. doi: 10.7860/JCDR/2016/17638.8400
16. Ramanathan YV, Venkatasubramanian R, Nambi PS, et al. Carbapenem-resistant *Enterobacteriaceae* screening: A core infection control measure for critical care unit in India? *Indian J Med Microbiol.* 2018;36(4):572-576. doi: 10.4103/ijmm.IJMM_18_437
17. Balaji VK, Sudha K, Usha B, Duraipandian J, Easow JM, Muthuswamy S. Rectal Carriage of Carbapenemase Producing *Enterobacteriaceae* in Intensive Care Units of a Tertiary Care Hospital. *Int J Curr Microbiol App Sci.* 8(06):2217-2223. doi: 10.20546/ijcmas.2019.806.264
18. Wang Q, Zhang Y, Yao X, et al. Risk factors and clinical outcomes for carbapenem-resistant *Enterobacteriaceae* nosocomial infections. *Eur J Clin Microbiol Infect Dis.* 2016;35(10):1679-1689. doi: 10.1007/s10096-016-2710-0
19. Kim YA, Lee SJ, Park YS, et al. Risk Factors for Carbapenemase-Producing *Enterobacterales* Infection or Colonization in a Korean Intensive Care Unit: A Case-Control Study. *Antibiotics* (Basel). 2020;9(10):680. doi: 10.3390/antibiotics9100680
20. Ackley R, Roshdy D, Meredith J, et al. Meropenem-Vaborbactam versus Ceftazidime-Avibactam for Treatment of Carbapenem-Resistant *Enterobacteriaceae* Infections. *Antimicrob Agents Chemother.* 2020;64(5):e02313-19. doi: 10.1128/AAC.02313-19
21. van Duin D, Lok JJ, Earley M, et al. Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant *Enterobacteriaceae*. *Clin Infect Dis.* 2018;66(2):163-171. doi: 10.1093/cid/cix783
22. Pascale R, Giannella M, Bartoletti M, Viale P, Pea F. Use of meropenem in treating carbapenem-resistant *Enterobacteriaceae* infections. *Expert Rev Anti Infect Ther.* 2019;17(10):819-827. doi: 10.1080/14787210.2019.1673731