ORIGINAL ARTICLE

Antimicrobial susceptibility patterns among community and health care acquired carbapenem resistant Enterobacteriaceae, in a tertiary care hospital of Lahore

Qanita Fahim,[1] Irfan Ali Mirza,[2] Anum Imtiaz,[3] Ayesha Khalid,[4] Asad Ahmad,[5] Ayesha Imtiaz[6]

Abstract

Objective: To compare the disk susceptibility pattern of healthcare-acquired carbapenem-resistant enterobacteraceae with that of community-acquired isolates and their associated clinical presentations.

Methods: The cross-sectional study was conducted at the Department of Microbiology, Combined Military Hospital, and the Institute of Dentistry, Lahore, Pakistan, from November 2017 to July 2018. Patients with positive carbapenem-resistant enterobacteraceae cultures from clinical specimens were included. All the isolates were identified through conventional methods and standard biochemical tests. Antibiotic susceptibility testing was performed by Kirby Bauer Disk Diffusion method on Muller Hinton Agar plates. Data was analysed using SPSS 23.

Result: Of the 123 isolates identified, 97(79%) were healthcare-acquired and 26(21%) were community-acquired. Statistically significant susceptibility patterns ($p<0.001$) of community-acquired isolates were observed against cefoperazone-sulbactum and amikacin, while a low significance was observed with gentamycin ($p<0.05$). Significant results were obtained in case of colistin against both the groups ($p<0.001$).

Conclusion: There was low antimicrobial resistance in community-acquired carbapenem-resistant enterobacteraceae isolates.

Keywords: Community-acquired CRE, Hospital-acquired CRE. (JPMA 70: 1130; 2020)

DOI: https://doi.org/10.5455/JPMA.14072

Introduction

Carbapenem-resistant rnterobacteriaceae (CRE) are a family of micro-organisms resistant to almost all the available antibiotics and are difficult to treat.[1] Normally they are part of human gut flora that may become resistant to carbapenems due to acquisition of resistant mechanism which could be either the production of carbapenemases (beta-lactamase),[2,3] reduced permeability of outer membrane, the altered affinity of penicillin-binding proteins (PBP) or modifying enzymes involving plasmid mediated resistance.[3,4]

Amongst enterobacteriaceae, most common organisms are Klebsiella (K.) species and Escherichia (E.) coli which can be taken as an example of CREs.[5] Healthy people are not the primary targets of CRE. Patients residing in nursing homes and other healthcare settings whose treatment/management requires devices like ventilators, urinary catheters, naso-gastric tubes or intravenous (IV) catheters are their prime targets. They also attack patients with persistent infections and taking antibiotics for a long time.[6-8] These CRE infections which are acquired from hospitals or healthcare settings are called healthcare acquired (HCA). On the other hand, community at large suffers from drug-susceptible enterobacteriaceae infections and it is speculated that this resistance of HCA-CRE might spread to enterobacteriaceae responsible for community infections. This impending danger of community transmission promulgates the need of proper epidemiological data regarding the prevalence of CRE in individuals in the community who have never been exposed to healthcare settings.[9]

CREs have been classified into community-acquired (CA) and HCA. According to the Centers for Disease Control and Prevention (CDC), if a patient has CRE culture positive after 48 hours of hospitalisation or a resident of a healthcare facility looking after terminally ill patients, these CRE isolates would fall into the category of HCA. In case of CA-CRE, patients are usually harbouring infection at the time of reporting in out-patient department (OPD) with no history of hospitalisation.[10] Moreover, a lower level of antimicrobial resistance is associated with CA-CRE, while HCA-CRE is known for its devastating nature and outrageous antimicrobial resistance, like multi-drug resistance (MDR) which is common amongst them.[3,11] For the purpose of achieving absolute results in CRE-infected patients, it is mandatory to have local microbiological data regarding susceptibility patterns of CA-CRE and HCA-CRE in hand, so that an appropriate

[1-4]Department of Microbiology, Combined Military Hospital Medical College, Lahore, [5]3rd Year MBBS Student, Avacinna Medical College Lahore, [6]Department of Health Care, Combined Mili-tary Hospital, Sialkot, Pakistan.

Correspondence: Qanita Fahim. Email: qanita_fahim@yahoo.com

empirical therapy can be instituted promptly. Moreover, if clinical cultures be taken prior to the initiation of antibiotics therapy, proper options could be offered for treatment. As for now, most HCA-CRE bacteria can be devastating for patients. According to a study, these are responsible for the deaths of 50% patients who acquire them.[11,12] Recently, pan-resistance to all antibiotics, including colistin and tigecycline, has also been reported.[12,13] CDC[3,11] has labelled CRE as "a serious threat to public health", and by the World Health Organisation (WHO) as "one of the three greatest threats to human health,".[13,14]

Unfortunately, this association of CRE with MDR is the cornerstone of all the failures of treatment in infected patients. The current study was planned to differentiate between the antimicrobial susceptibilities associated with CA-CRE and HCA-CRE.

Materials and Methods

The cross-sectional study was conducted at the Department of Microbiology, Combined Military Hospital (CMH), and the Institute of Dentistry, Lahore, Pakistan, from November 2017 to July 2018. After approval from the ethics committees of CMH, the Institute of Dentistry and the National University of Medical Sciences (NUMS), Rawalpindi, The sample size was calculated using WHO calculator, with a population proportion of 70.5%, 8.1% margin of error and 95% confidence interval (CI).[15]

Patients having infection due to CRE at the time of hospital admission were labelled as having CA-CRE infection, and those who acquired infection during stay in the hospital were labelled as having HA-CRE infection. Samples were collected using non-probability convenience technique. Isolates which were resistant to carbapenem (meropenem, imipenem),[3,11] were selected for the study. Data collection was done on daily basis and analysed.

After obtaining written consent from the patients, relevant data regarding age, gender, ward and disease was noted along with history of any prior medical admission and antibiotics used, associated diseases, like diabetes mellitus, liver cirrhosis, chronic kidney disease, malignancy etc. Information regarding the use of medical devices like urinary catheters, IV lines, ventilators, central venous pressure (CVP) catheters was carefully registered. In addition, antimicrobial susceptibility patterns were noted.

All CRE isolates were divided into CA-CRE and HCA-CRE groups and were further scrutinised to rule out duplication. If during hospitalisation, two or more than two isolates were identified from the same patient, only the first isolate was included for analysis. In case of two CRE isolates from the same patient, only one with higher resistance was chosen.

The samples from which the strains were isolated included pus, pus swab, blood, urine, sputum, catheter tip, broncho-alveolar lavage (BAL), endotracheal secretions and body fluids. Isolation of organism was done by streaking the samples on appropriate agars as per requirement e.g MaConkey's agar, Blood agar, Cystein lactose electrolyte agar (CLED) plates etc. Further identification was done by gram's staining (gram-negative bacilli), catalase (positive), oxidase (negative), lactose fermentation, and hanging drop preparation (motility). All gram-negative isolates were identified by standard biochemical tests using commercial identification kit 20E (bioMerieux, France).

Antibiotic susceptibility testing was performed on Muller Hinton Agar plates by Modified Kirby Bauer Disk Diffusion method as defined by Clinical and Laboratory Standards Institute (CLSI)[15,16] against following antibiotics: Extended-spectrum β-lactam/β-lactamase inhibitor combinations; ampicillin, amoxicillin/ clavulanate (30/10μg/disc), piperacillin tazobactam (100μg/10 μg disc) ceftazidime (30μg/disc), cefipime (75μg/disc), cefaperazone+sulbactum (75+30μg/disc). Carbapenems tested were imipenem (10μg/disc), meropenem (10μg/disc). non β-lactam agents tested included gentamycin (10μg/disc), amikacin (230μg/disc), tobramycin (40μg/disc), ciprofloxacin, tetracyclin, tigecycline and colistin (100 units/disc).

In case of tigecycline susceptibilities, guidelines of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) were considered,[16,17] while for the rest of antimicrobials, updated CLSI guidelines[14,16] were considered.

Data was analysed using SPSS 23. Chi-square test was used to compare two sets of isolates. $P<0.05$ was considered statistically significant.

Results

Of the 123 CRE isolates identified, 97(79%) were HCA and 26(21%) were CA. Dissimilar conditions were found between CA and HCA CRE isolates (Table-1).

K. pneumoniae was the most common pathogen, followed by E. coli and others (Figure).

Surgical site infections were 40(32.5%), followed by

Table-1: Antimicrobial susceptibilities pattern of community-acquired (CA) and healthcare-acquired (HCA) carbapenem-resistant enterobacteraceae-(CRE) n=123.

Antibiotics	% Non-Susceptible Rate					P-value
	ALL	CA-CRE n=26		HCA-CRE n=97		HA Vs CA
		Sensitive	Resistant	Sensitive	Resistant	
Ampicillin	123(100)	0(0)	26(100)	0(0)	97(100)	NSS
Augmentin	123(100)	0(0)	26(100)	0(0)	97(100)	NSS
TMP/SMZ	123(100)	0(0)	26(100)	0(0)	97(100)	NSS
Tetracyclin	123(100)	0(0)	26(100)	0(0)	97(100)	NSS
Doxycyclin	123(100)	0(0)	26(100)	0(0)	97(100)	NSS
Gentamycin	108(87.8)	14(53.8)	12(46.1)	1(01)	96(98.9)	0.015*
Amikacin	97(78.8)	24(92.3)	2 (7.6)	2(2.0)	95(98.9)	<0.001*
Ciprofloxacin	110(89.4)	10(38.4)	16(61.5)	3(3.09)	94(96.9)	>0.99
Ceftazidime	123(100)	0(0)	26(100)	0(0)	97(100)	NSS
Imipenem	120(97.5)	3(11.5)	23(88.4)	0(0)	97(100)	0.217
Meropenem	123(100)	0(0)	26(100)	0(0)	97(100)	NSS
TZP	122(99.1)	1(3.84)	25(96.1)	0(0)	97(100)	0.897
SCF	119(96.7)	2(7.6)	24(92.3)	2(2.0)	95(98.9)	<0.001*
Colistin	02/123(0.01)	26(100)	0(0)	95(98.9)	2(2.0)	<0.001*
Fosfomycin	47/80(58.7)	10/20(50.0)	10/20(50.0)	23/60(38.3)	37/60(61.6)	0.250
Nitrofurantoin	2/17(11.7)	7/7(100)	0/7(0)	8/10(80)	2/10(20)	0.426

*$p < 0.05$ indicator of statistical significance; NSS, not statistically significant.
TZP, Tazobactam piperacillin and SCF, Cefoperazone sulbactam.

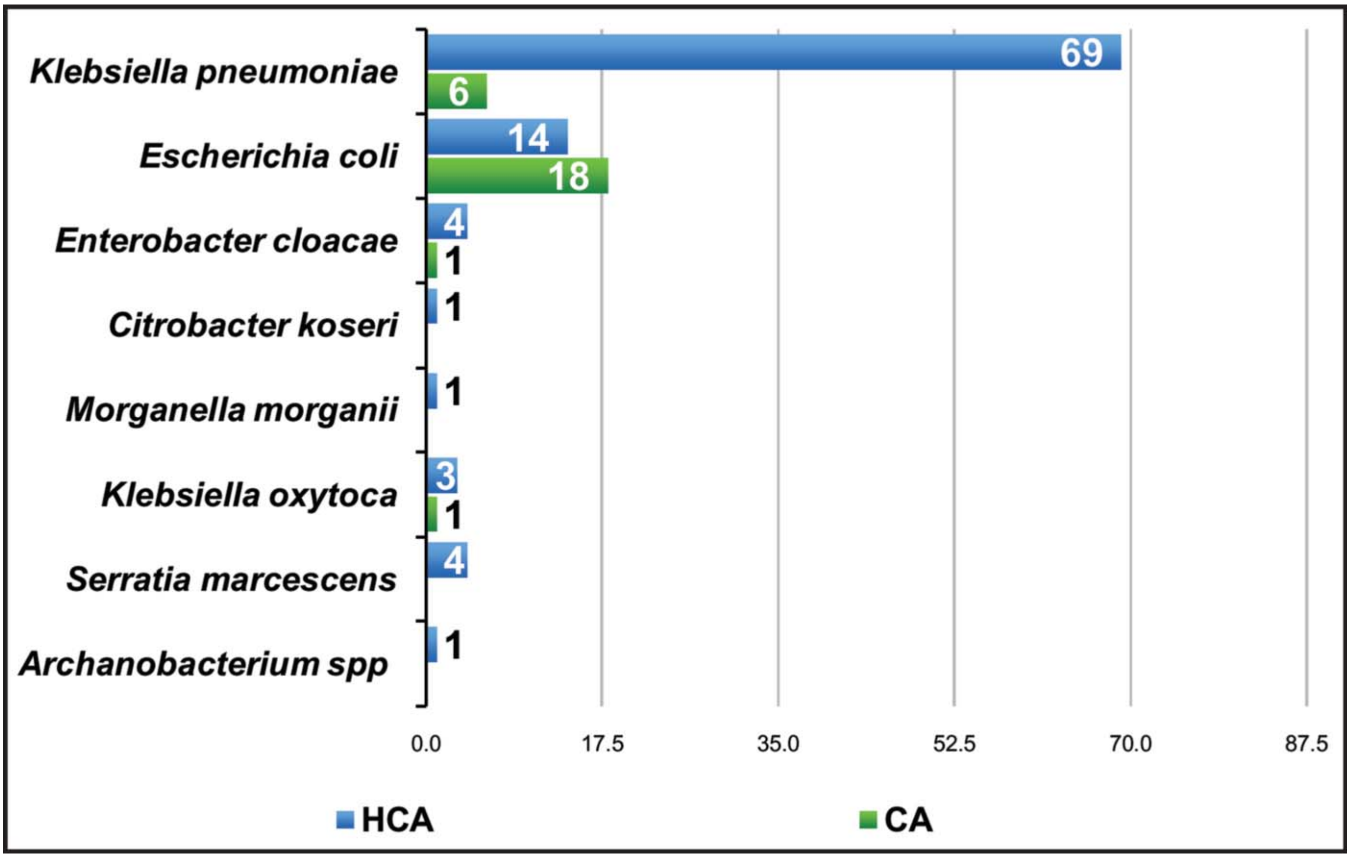

Figure: Total no of isolates in community-acquired (CA) and healthcare-acquired (HCA) carbapenem-resistant enterobacteraceae-(CRE); n=123.

Table-2: Clinical manifestations of n=123 patients with carbapenem-resistant enterobacteraceae (CRE).

Variables	Community Acquired n=26	Health Care Acquired n=97	P-value
Age >60	4(15.3)	26(26.8)	<0.001*
Male%	14(53.8)	61(62.8)	<0.001*
Female%	12(46.1)	36(37.1)	<0.002*
ISOLATES			
Escherichia coli	18(66.6)	14(10.7)	0.570
Klebsiella pneumoniae	6(22.2)	69(75.3)	<0.001*
Klebsiella oxytoca	1(5.55)	3(3.07)	0.621
Enterobacter cloacea	1(5.55)	4(4.6)	0.369
Citrobacter koseri	0(0.0)	1(1.5)	NSS
Morganella morganii	0(0.0)	1(1.5)	NSS
Serratia marsesence	0(0.0)	4(3.07)	NSS
Achanobacterium spp	0(0.0)	1(1.5)	NSS
SPECIMENS			
Blood	3(11.5)	9(9.2)	0.136
Pure pus	2(7.6)	11(11.3)	0.0191
Pus swab	7(26.9)	30(30.9)	<0.001*
Sputum	1(3.8)	11(11.3)	<0.0052*
Urine	7(26.9)	10(10.3)	0.616
BAL	1(3.8)	1(1.03)	>0.99
ETT	3(11.5)	22(22.6)	<0.001*
Catheter tip	1(3.8)	2(2.06)	>0.99
Asciticfluid / drain fluid	1(3.8)	3(3.09)	0.621
DISEASES			
Sepsis	2(7.6)	9(9.2)	0.059*
SSI	0(0.0)	40 (41.2)	NSS
VAP	0(0.00)	19(19.5)	NSS
Pneumonia	5(19.2)	13(13.4)	0.084
UTI	7(26.9)	10(10.3)	0.463
Meningitis	2(7.6)	0(0.0)	0.498
Peritonitis	1(3.8)	0(0.0)	NSS
Abcess	1(3.8)	0(0.0)	NSS
Diabettic foot	0(0.0)	1(1.03)	NSS
Intra cranial bleed	0(0.0)	1(1.03)	NSS
Bed sores	0(0.0)	2(2.06)	NSS
Wounds	8(30.7)	0(0.0)	NSS

*p < 0.05 indicator of statistical significance; NSS, not statistically significant.
BAL, broncho-alveolar lavage; ETT, endotracheal tube; SSI, surgical site infection; VAP, ventilator associated pneumonia and UTI, urinary tract infection.

ventilator-associated pneumonia (VAP) 19(15.4%), pneumonia 18(14.6%), urinary tract infections (UTIs) 17(13.8%), sepsis 11(8.9%), skin wounds 8(6.5%), meningitis 2(1.6%) and miscellaneous infections 7(5.6%) (Table-2).

Discussion

In line with earlier studies, the current study indicated that not only susceptibility patterns differ among CA-CRE and HCA-CRE isolates,[3,17,18] but also a clear difference could be marked out among clinical manifestations and antimicrobial characteristics in patients with CA-CRE and HCA-CRE infections.[19,20] In the present study, K. pneumoniae was the most prevalent organism, clearly demonstrating that antimicrobial susceptibilities of HCA-CRE were significantly dissimilar than those of CA-CRE and showed lower susceptibility to various antibiotics.[21] The results of the current study supports the findings of a recent study which emphasised that cultures for antimicrobial susceptibility testing were required irrespective of the initial empirical antibiotic therapy, especially in case of CA-CRE, for the clinicians to switch over to relatively less toxic and pertinent antibiotic therapy.[20]

The present study indicates that the most of the patients in the HCA-CRE group were more than 50 years of age and being admitted or readmitted within 30-40 days of discharge from a hospital either after being through an invasive procedure or for a serious underlining condition/co-morbidities. Significant number of these patients were kept in Intensive cares (ITCs), immunocompromised, having had an exposure to indwelling urinary catheters and devices like central line, endotracheal tube and nasogastric tube, and those kept on ventilator including exposure to multiple antibiotics, which is in concordance with previous studies.[19,20,22] Moreover, a profound difference was observed between CA and HCA CREs regarding clinical features. In most cases of CA-CRE the commonest clinical infections were pneumonia and UTIs. However, in this study a limited number of cases (18), as in previous study,[20] fell in the category of CA-CRE, and it underlines the need to conduct a large-scale study to thoroughly investigate the demographic characteristics of CA-CREs.

In comparison with HCA-CRE, patients having CA-CRE positive cultures directly reported in OPDs and had quite infrequent hospital visits. Consequently, same was the case with surgical site infections (SSI) (n=40), where patient was not hospitalised at the onset of infection, but the likely pathogens might be related to hospitals. Under such circumstances, although empirical antimicrobial agents should be the same for both HCA-CRE and CA-CRE patients, but mistake could take place if such awareness would not prevail, as in both the conditions the patient is from a community environment. Successful recognition may lead to adequate and proper treatment, and failure may even lead to adverse outcomes. Therefore, antimicrobial susceptibility testing is necessary in differentiating patients with HCA-CRE from those with CA-CRE.

The most common organism among CRE in our study was K. pneumoniae, followed by E. coli and Ent. cloacae. This frequency is consistent with previous studies.[20,23] According to a study done in Asia, Klebsiella spp happens to be most frequent organism isolated followed by Serratia spp, Enterobacter spp., Proteus spp., and Citrobacter spp.[24] This mismatch of findings suggest that CRE isolate has varied distribution depending upon their region of emergence and urges the requirement of proper investigations to be carried out by every region to find out their own epidemiological characteristics of CRE.

In line with several molecular, biological, epidemiological studies,[2,5,11,13,17,25] the findings of the current study supports the idea of using extreme care while prescribing carbapenem, cephalosporin and fluoroquinilones as empirical treatment of CA-CRE, specially in moderately to severely ill patients having long-standing CA-CRE infections. Furthermore, in case of serious CRE infections colistin can be the prime choice but only after appropriate culture testing.

There is no clear cut decision regarding treatment of infections caused by CRE and available data stresses the use of combination therapy rather than monotherapy, while recent studies have favoured monotherapy as a better option.[25,26] The Food and Drug Administration (FDA) has approved a new ceftazidime-avibactam combination for treating complicated infections caused by CRE isolates like urinary tract and intestinal infections, but this drug is unable to counter Metallo-beta-lactamases (MBL)such as New Delhi MBL (NDM), Verona Integron-encoded MBL (VIM), or Active on Imipenem MBL (IMP).[26]

Finally, prevention and spread of CRE in healthcare settings and beyond can only be achieved by active surveillance, thorough screening of patients to detect colonisation, strict compliance with contact precautions and infection control measures.[7]

The major limitation of he current study is that it had limited number of CA-CRE cases (n=26), which could be attributed to either low prevalence of CA-CRE in the community or may be further large-scale study is required.

Conclusions

There was low antimicrobial resistance in CA-CRE isolates, indicating the need of sending appropriate samples for cultures and susceptibility prior to the initiation of definite antibiotic therapy.

Disclaimer: None.

Conflict of Interests: None.

Source of Funding: None.

References

1. US Centers for Disease Control and Prevention (CDC). Antibiotic re-sistance threats in the United States. [Online] 2013 [Cited 2018 June 04]. Available from URL: http://www.cdc.gov/drugresistance/threat-report-2013/
2. Kumarasamy KK, Toleman MA, Walsh TR, Bagaria J, Butt F, Bala-krishnan R, et al. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemio-logical study. Lancet Infect Dis 2010;10:597-602. doi: 10.1016/S1473-3099(10)70143-2.
3. US Centers for Disease Control and Prevention (CDC). Facility guid-ance for control of carbapenem-resistant Enterobacteriaceae (CRE)—November 2015 update CRE toolkit. [Online] 2015 [Cited 2018 June 04]. Available from URL: http://www.cdc.gov/hai/organisms/cre/cre-toolkit/
4. Devi PV, Reddy PS, John MS. Prevalence of Metallo-beta-Lactamases Producing Pseudomonas aeruginosa among the Clinical isolates: A study from tertiary care hospital. Int J Curr Microbiol App Sci 2015;4:955-61.
5. Gupta N, Limbago BM, Patel JB, Kallen AJ. Carbapenem-resistant En-terobacteriaceae: epidemiology and prevention. Clin Infect Dis 2011;53:60-7. doi: 10.1093/cid/cir202.
6. Munoz-Price LS, Poirel L, Bonomo RA, Schwaber MJ, Daikos GL, Cormican M, et al. Clinical epidemiology of the global expansion of Klebsiella pneumoniae carbapenemases. Lancet Infect Dis 2013;13:785-96. doi: 10.1016/S1473-3099(13)70190-7.
7. Hayden MK, Lin MY, Lolans K, Weiner S, Blom D, Moore NM, et al. Prevention of colonization and infection by Klebsiella pneumoniae car-bapenemase-producing enterobacteriaceae in long-term acute-care hos-pitals. Clin Infect Dis 2015;60:1153-61. doi: 10.1093/cid/ciu1173.
8. Thaden JT, Lewis SS, Hazen KC, Huslage K, Fowler VG Jr, Moehring RW, et al. Rising rates of carbapenem-resistant enterobacteriaceae in community hospitals: a mixed-methods review of epidemiology and microbiology practices in a network of community hospitals in the southeastern United States. Infect Control Hosp Epidemiol 2014;35:978-83. doi: 10.1086/677157.
9. Schwaber MJ, Lev B, Israeli A, Solter E, Smollan G, Rubinovitch B, et al. Containment of a country-wide outbreak of carbapenem-resistant Klebsiella pneumoniae in Israeli hospitals via a nationally implemented intervention. Clin Infect Dis 2011;52:848-55. doi: 10.1093/cid/cir025.
10. US Centers for Disease Control and Prevention (CDC). Healthcare-associated infections (HAIs). Tracking CRE infections. [Online] 2016 [Cited 2018 June 04]. Available from URL: http://www.cdc.gov/hai/organisms/cre/TrackingCRE.html#CREmap
11. van Duin D, Kaye KS, Neuner EA, Bonomo RA. Carbapenem-resistant Enterobacteriaceae: a review of treatment and outcomes. Di-agn Microbiol Infect Dis 2013;75:115-20. doi: 10.1016/j.diagmicrobio.2012.11.009.
12. Elemam A, Rahimian J, Mandell W. Infection with panresistant Klebsiella pneumoniae: a report of 2 cases and a brief review of the lit-erature. Clin Infect Dis 2009;49:271-4. doi: 10.1086/600042.
13. Wise R. The urgent need for new antibacterial agents. J Antimi-crob Chemother 2011;66:1939-40. doi: 10.1093/jac/dkr261.
14. CLSI. Performance Standards for Antimicrobial Susceptibility Testing. 26th ed. CLSI supplement M100S. Wayne, PA: Clinical and Laboratory Standards Institute; 2016.
15. Calculator.net. Sample Size Calculator. [Online] 2008-2020 [Cited 2018 June 10]. Available from URL: http://www.calculator.net/sample-size-calculator.html
16. The European Committee on Antimicrobial Susceptibility Test-

ing. Breakpoint tables for interpretation of MICs and zone diameters, Version 7.1. [Online] 2017 [Cited 2018 June 04]. Available from URL: http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_7.1_Breakpoint_Tables.pdf
17. Almugadam BS, Ali NO, Ahmed AB, Ahmed EB, Wang L. Prevalence and antibiotics susceptibility patterns of carbapenem re-sistant Enterobacteriaceae. J Bacteriol Mycol Open Access 2018;6:187–90. doi: 10.15406/jbmoa.2018.06.00201
18. Christophy R, Osman M, Mallat H, Achkar M, Ziedeh A, Moukaddem W, et al. Prevalence, antibiotic susceptibility and charac-terization of antibiotic resistant genes among carbapenem-resistant Gram-negative bacilli and yeast in intestinal flora of cancer patients in North Lebanon. J Infect Public Health 2017;10:716-20. doi: 10.1016/j.jiph.2016.10.009.
19. Lee GC, Lawson KA, Burgess DS. Clinical epidemiology of carbapenem-resistant enterobacteriaceae in community hospitals: a case-case-control study. Ann Pharmacother 2013;47:1115-21. doi: 10.1177/1060028013503120.
20. Tang HJ, Hsieh CF, Chang PC, Chen JJ, Lin YH, Lai CC, et al. Clinical significance of community- and healthcare-acquired car-bapenem-resistant enterobacteriaceae isolates. PLoS One 2016;11:e0151897. doi: 10.1371/journal.pone.0151897.
21. El Bouamri MC, Arsalane L, El Kamouni Y, Zouhair S. Anti-microbial susceptibility of urinary Klebsiella pneumoniae and the emergence of carbapenem-resistant strains: a retrospective study from a university hospital in Morocco, North Africa. Afr J Urol 2015;21:36-40. doi: 10.1016/j.afju.2014.10.004.
22. Alotaibi FE, Bukhari EE, Al-Mohizea MM, Hafiz T, Essa EB, AlTokhais YI. Emergence of carbapenem-resistant Enterobacteriaceae isolated from patients in a university hospital in Saudi Arabia. Epide-miology, clinical profiles and outcomes. J Infect Public Health 2017;10:667-73. doi: 10.1016/j.jiph.2017.05.004.
23. Lai CC, Wu UI, Wang JT, Chang SC. Prevalence of car-bapenemase-producing Enterobacteriaceae and its impact on clinical outcomes at a teaching hospital in Taiwan. J Formos Med Assoc 2013;112:492-6. doi: 10.1016/j.jfma.2012.09.021.
24. Ling ML, Tee YM, Tan SG, Amin IM, How KB, Tan KY, et al. Risk factors for acquisition of carbapenem resistant Enterobacteriaceae in an acute tertiary care hospital in Singapore. Antimicrob Resist Infect Control 2015;4:e26. doi: 10.1186/s13756-015-0066-3.
25. Daikos GL, Tsaousi S, Tzouvelekis LS, Anyfantis I, Psichogiou M, Argyropoulou A, et al. Carbapenemase-producing Klebsiella pneu-moniae bloodstream infections: lowering mortality by antibiotic combi-nation schemes and the role of carbapenems. Antimicrob Agents Chemother 2014;58:2322-8. doi: 10.1128/AAC.02166-13.
26. Falcone M, Paterson D. Spotlight on ceftazidime/avibactam: a new option for MDR Gram-negative infections. J Antimicrob Chemother 2016;71:2713-22. doi: 10.1093/jac/dkw239