Nobel Med 2025; 21(2): 105-110

RESISTANCE PATTERNS OF MULTI-DRUG-RESISTANT GRAM-NEGATIVE ISOLATES TO CARBAPENEMS: AN EMERGING PROBLEM

Mehdi Meskini Heydarlou[1], Ayşe Demet Kaya[1], Kevser Atalık[1], Tuğrul Erbaydar[2]

[1]*Istanbul Okan University, Faculty of Medicine, Department of Medical Microbiology, Istanbul, Türkiye*
[2]*Istanbul Okan University, Faculty of Medicine, Department of Public Health, Istanbul, Türkiye*

ABSTRACT

Objective: *Infections caused by multidrug-resistant (MDR) Gram-negative bacteria and resistance to carbapenems constitute a major public health problem worldwide, due to limited treatment options and high mortality rates. In this study, we aimed to determine the resistance profiles of MDR Gram-negative bacilli isolated from clinical samples to carbapenems.*

Material and Method: *Specimens, from which MDR Gram-negative bacteria were isolated, were cultured onto 5% sheep blood and EMB agar, and VITEK 2 automated system (bio Mérieux, France) was used for identification and antimicrobial susceptibility testing. Data were analyzed using chi-square and Fisher's exact tests.*

Results: *1072 MDR bacterial strains were isolated from the specimens of 272 patients, with the majority of transtracheal aspirates (64%) sent predominantly from palliative care (49.8%) and intensive care (42%) units. The leading pathogens were Pseudomonas aeruginosa (42,1%), Acinetobacter baumannii (31,2%), and Klebsiella spp (22,5%). The highest resistance rate among carbapenems was detected to meropenem (91,6%), followed by imipenem (44,3%) and ertapenem (25%). While ertapenem resistance was significantly lower in P. aeruginosa strains ($p<0,01$), meropenem resistance was significantly higher in A. baumannii strains when compared to other antibiotics.*

Conclusion: *Since Gram-negative MDR bacteria continue to spread rapidly, monitoring resistance profiles through active hospital surveillance is crucial to determine the appropriate treatment. The data obtained in this study once again highlight the importance of resistance to carbapenems and is considered to contribute to epidemiological data.*

Keywords: *Multidrug resistance, gram-negative bacteria, carbapenems.*

CORRESPONDING AUTHOR: Kevser Atalık İstanbul Okan University, Faculty of Medicine, Department of Medical Microbiology, 34959, Akfırat-Tuzla, İstanbul, Turkiye
kevser.atalik@okan.edu.tr

MMH https://orcid.org/0000-0001-5858-8079 ADK https://orcid.org/0000-0001-8224-8242 KA https://orcid.org/0000-0002-7021-7227

TE https://orcid.org/0000-0002-7778-7521

DELIVERING DATE: 31 / 07 / 2024 • **ACCEPTED DATE:** 19 / 08 / 2024

ÇOKLU İLAÇ DİRENÇLİ GRAM-NEGATİF İZOLATLARIN KARBAPENEM GRUBU ANTİBİYOTİKLERE DİRENÇ DURUMLARI: GÜNCEL BİR SORUN

ÖZET

Amaç: Çoklu ilaç dirençli (MDR) Gram-negatif bakterilerin neden olduğu enfeksiyonlar ve karbapenem direnci, sınırlı tedavi yaklaşımları ve yüksek mortalite oranları nedeniyle Dünya çapında önemli bir toplum sağlığı sorunu oluşturmaktadır. Bu çalışmada, klinik örneklerden izole edilen MDR Gram-negatif basillerin karbapenem grubu antibiyotiklere direnç profillerini belirlemek amaçlanmıştır.

Materyal ve Metot: MDR Gram-negatif bakteri izole edilen örnekler, %5 koyun kanlı agar ve EMB agar besiyerlerine ekimi yapıldıktan sonra bakterilerin tanımlanması ve antibiyotik duyarlılık profili belirlenmesinde VITEK 2 (bio Mérieux, Fransa) otomatize sistemi kullanıldı. Veriler Ki-kare ve Fisher's exact testleri kullanarak irdelendi.

Bulgular: 272 hastaya ait örneklerden izole edilmiş olan 1072 MDR bakteri suşunun çoğunluğunu transtrakeal aspirasyon örneklerinin (%64) oluşturduğu ve sıklıkla palyatif bakım merkezi (%49.8) ve yoğun bakım üniteleri (%42)'nden gönderilmiş olduğu saptandı. En sık etkenler, Pseudomonas aeruginosa (%42,1), Acinetobacter baumannii (%31,2), Klebsiella spp (%22,5) idi. En yüksek direnç oranı meropenem (%91,6), takiben imipenem (%44,3) ve ertapenem (%25) olarak belirlendi. P. aeruginosa suşlarında ertapenem direnci anlamlı derecede düşük (p<0,01), A. baumannii suşlarında ise meropenem direnci diğer antibiyotiklere göre anlamlı derecede yüksek bulundu.

Sonuç: MDR Gram-negatif bakterilerin dünya genelinde hızla yayılmaya devam etmesi nedeniyle, etkenlerin direnç durumunun hastanelerde aktif sürveyans yoluyla takip edilmesi, uygun tedavi seçeneğinin belirlenmesi açısından önem arz etmektedir. Bu çalışmada elde ettiğimiz veriler karbapenem grubu antimikrobiyallare direncin önemini bir kez daha vurgulamakta olup, epidemiyolojik verilere katkı sağlayacağı düşünülmektedir.

Anahtar kelimeler: Çoklu ilaç direnci, gram-negatif bakteri, karbapenemler.

INTRODUCTION

Infectious diseases caused by multidrug-resistant (MDR) Gram-negative bacteria pose a significant threat to public health due to limited therapeutic approaches and high mortality rates. Multidrug resistance is the resistance of bacteria to more than two of the antipseudomonal cephalosporins, antipseudomonal carbapenems, ampicillin-sulbactam, fluoroquinolones, and aminoglycosides.[1] Regarding the problem of resistance, in the early 2000s methicillin-resistant Staphylococcus aureus (MRSA) was the most important global problem, whereas today MDR Gram-negative bacteria are the leading problem.[2]

According to a study conducted in the United States, 2 million patients contract antibiotic-resistant bacterial infections every year, resulting in more than 23,000 deaths. Healthcare-associated infections with Gram-negative bacteria, particularly extended-spectrum beta-lactamase (ESBL)-producing, carbapenem-resistant Enterobacteriaceae, multidrug-resistant Acinetobacter baumannii, and Pseudomonas aeruginosa, are reported to be the most common infectious agents.[3,4]

Carbapenems are highly effective antibiotics against ESBL-producing microorganisms and are frequently used as the first choice in treatment. However, there has been an increase in resistance rates over the years, related to the frequent use of carbapenems.[5-7]

Carbapenem-resistant A. baumannii, P. aeruginosa, and members of the Enterobacteriaceae are critical priority targets for new antibiotics to fill the gap of urgently needed treatment options high on the World Health Organisation Global Priority List of antibiotic-resistant bacteria developed to guide research, discovery and development of new antibiotics.[8]

The aim of this study was to determine the distribution of MDR Gram-negative bacteria isolated from clinical specimens and examine their resistance patterns to antibiotics in the carbapenem group.

MATERIAL AND METHOD

Sample Selection and Inclusion Criteria

MDR Gram-negative bacteria isolated from samples of hospitalized patients and sent to the Microbiology Laboratory of Istanbul Okan University Hospital from various clinics between January 1, 2019, and December 31, 2020, were included. In this retrospective study, the data were obtained from the Laboratory Information Management System and analyzed by anonymizing the patients. This study was

approved by the Ethics Committee of Istanbul Okan University (Decision No. 167, dated June 14, 2023).

Isolation and Identification of Bacteria from Samples

Clinical specimens were inoculated onto 5% sheep blood agar and Eosin Methylene Blue (EMB) agar in the laboratory. After incubation at 37°C for 24 hours, the isolated microorganisms were identified by conventional methods and the VITEK 2 automated bacterial identification system (bio Mérieux, France) according to the manufacturer's recommendations.

Antimicrobial Susceptibility Testing

Antimicrobial susceptibility testing of the isolated microorganisms was performed using the VITEK 2 automated system (bio Mérieux, France), and the results were interpreted according to the criteria of the European Committee for Antimicrobial Susceptibility Testing.

Statistical Analysis

The IBM SPSS Statistics 21 package program was used to analyze the data. The numerical and percentage distributions of the data were presented. The chi-square test and Fisher's exact test were used for statistical analysis, and the *p*-value was determined when necessary. The Friedman rank test and Wilcoxon signed-rank test were used to compare the resistance rates of each bacterium to different antibiotics in the carbapenem group. The value of $p<0.05$ was considered statistically significant.

RESULTS

Our study included 1072 bacterial strains isolated from samples of 272 patients. Of the patients, 109 (40%) were female and 163 (60%) were male. The age range was 1-97 years, with a mean of 65.6 years.

When the distribution of the samples from which MDR strains were isolated according to the clinics they were sent was examined, palliative care (49.8%), and intensive care units (42%) were leading, -including general intensive care (29.3%), internal intensive care (10.4%), neonatal and premature intensive care (1.2%), surgical intensive care (1.1%) (Table 1).

In the evaluation of the type of clinical specimens, the most common growths were obtained from transtracheal aspirate (686, 64%) and urine specimens (185, 17.3%) (Table 2).

Table 1. Distribution of samples from which multidrug-resistant (MDR) strains were isolated based on the clinics.

Clinics	Number (%)
Palliative Care	534 (49.8)
General Intensive Care	314 (29.3)
Internal Intensive Care	112 (10.4)
Chest Diseases	24 (2.2)
Neonatal and Premature Intensive Care	13 (1.2)
Surgical Intensive Care	12 (1.1)
Neurosurgery	12 (1.1)
Nephrology	12 (1.1)
Interventional Radiology	10 (0.9)
Urology	8 (0.7)
Orthopedics	6 (0.5)
Cardiovascular Surgery	5 (0.4)
Emergency	4 (0.3)
Infectious Disease	3 (0.2)
Medical Oncology	2 (0.1)
Neurology	1 (0.09)
Total	1072 (100)

Table 2. Distribution of clinical samples.

Sample type	n (%)
Transtracheal Aspirate	686 (64)
Urine	185 (17.3)
Sputum	48 (4.4)
Wound Swab	68 (6.3)
Blood	57 (5.3)
Catheter	18 (1.6)
Bronchoalveolar lavage	2 (0.1)
Tissue	7 (0.6)
Nasal Swab	1 (0.09)
Total	1072 (100)

Out of the isolated bacteria, there were five members of the family Enterobacteriaceae and two non-fermenting bacilli, distributed as; 452 (42.1%) P. aeruginosa, 335 (31.2%) A.baumannii, 242 (22.5%) Klebsiella spp., 23 (2.1%) Proteus spp., 13 (1.2%) Escherichia coli, 4 (0.3%) Enterobacter spp., and 3 (0.2%) Citrobacter spp.. The distribution of MDR isolates is shown in Table 3.

Antimicrobial resistance of MDR isolates to the carbapenems showed the highest resistance rate against meropenem with 91.6%. Resistance to imipenem and ertapenem was 44.3% and 25%, respectively. The isolated strains and antimicrobial resistance rates of the carbapenem group are shown in Table 4.

Table 3. Distribution of multidrug-resistant (MDR) isolates.

Bacteria	n	(%)
Pseudomonas Aeruginosa	452	42.1
Acinetobacter Baumannii	335	31.2
Klebsiella spp.	242	22.5
Proteus spp.	23	2.1
Escherichia Coli	13	1.2
Enterobacter spp.	4	0.3
Citrobacter spp.	3	0.2

Table 4. Resistance profiles of isolates to antibiotics of the carbapenem group

Bacteria		Imipenem resistance		Meropenem resistance		Ertapenem resistance	
	n	n	%	n	%	n	%
Pseudomonas Aeruginosa	452	425	94.0*	412	91.2	0	0*
Acinetobacter Baumannii	335	1	0.3*	335	100*	0	0*
Klebsiella spp.	242	33	13.6*	213	88.0*	234	96.7*
Proteus spp.	23	11	47.8	15	65.2*	16	69.6*
Escherichia Coli	13	3	23.1	4	30.8*	11	84.6*
Enterobacter spp.	4	2	50	3	75	4	100
Citrobacter spp.	3	0	0	0	0	3	100
Total	1072	475	44.3	982	91.6	268	25

* $p<0.01$ (the percentage of antibiotic resistance of the bacteria is significantly different from the average of other bacteria, for marked values)

When resistance rates of P. aeruginosa and A. baumannii to different groups of carbapenem antibiotics were analyzed, ertapenem resistance was significantly lower in P. aeruginosa strains compared with other antibiotics ($p<0.01$). Meropenem resistance was significantly higher in A. baumannii strains when compared to other antibiotics.

DISCUSSION

Despite developments in infectious disease prevention and control programs, the prevalence of carbapenem-resistant Gram-negative bacteria and the infections they cause are increasing, and epidemiological data change frequently.[9] Gram-negative pathogens such as carbapenem-resistant P. aeruginosa, A. baumannii, and the predominant species among Enterobacteriaceae Klebsiella pneumoniae are the major causes of hospital-acquired infections, and account for 40% of hospital-acquired infections in the intensive care units.[10] The majority of antimicrobial-resistant strains isolated from the patients in the intensive care and palliative care units in our study supports this information.

The clinically most important carbapenemases in Enterobacteriaceae are the class A enzymes of the KPC type and class B metallo-β-lactamases (MβLs), represented mainly by the VIM, IMP, and NDM types, and class D carbapenemases of the OXA-48 type.[11]

A rapid and extensive dissemination of KPC-producing K. pneumoniae was first noticed in the United States with low prevalences in Northern and Western European countries. Among three MβL families (VIM, IMP, and NDM) which have international spread, local differences do exist. VIM-positive K. pneumoniae which was first observed in Southern Europe, introduced later to Northern Europe and the United States, being low in isolation rates. Acquisition of IMP MβLs by K. pneumoniae was described primarily in Japan, Taiwan and Singapore. Dissemination of IMP-producing Enterobacteriaceae in the rest of the world appears to be limited. For NDM producers, the epicenter of the epidemic is the Indian subcontinent and also seems to exist in the central Balkans.[11]

OXA-48-producing K. pneumoniae was first detected sporadically in Türkiye in 2001, soon followed by hospital outbreaks. About the same time, OXA-48-positive K. pneumoniae isolates were also identified in other Middle Eastern and North African countries, as well as in Western European countries. In Türkiye, OXA-48-producing K. pneumoniae has reached an endemic level recently.[11]

Among the isolates reported to the National Healthcare Safety Network (NHSN) in 2006-2007, carbapenem resistance was reported to be up to 4.0% for Escherchia coli and 10.8% for K. pneumoniae isolates.[12]

In Türkiye, Türker *et al.* reported carbapenem resistance rates of 60% for K. pneumoniae and 41.2% for P. aeuroginosa in 2021.[13] Akkuş *et al.* reported carbapenem resistance rates between 2019 and 2021 as 74.8%, 91%, and 62.5% for K. pneumoniae, A. baumannii, and P. aeuroginosa isolates, respectively.[14]

National Healthcare-Associated Infections Surveillance Network (NHAI-NET) summary reported the antimicrobial resistance rates in healthcare-associated infections in Türkiye as: carbapenem-resistant A. baumannii (72.60%), carbapenem-resistant P. aeruginosa (34.92%), and carbapenem-resistant K. pneumoniae (44.26%) for 2019. In the same report, analysis of this rate in university hospitals was found as carbapenem-resistant A. baumannii (79.90%), carbapenem-resistant P. aeruginosa (37.37%), and carbapenem-resistant K. pneumoniae (44.97%).[15]

The leading pathogens in our study were P. aeruginosa (42.1%), A. baumannii (31.2%), and Klebsiella spp (22.5%) out of 1072 carbapenem-resistant MDR isolates within our university hospital.

According to the SENTRY surveillance program, over 20-years worldwide (excluding Africa and the Middle East) carbapenem resistance rates utilizing the Clinical and Laboratory Standards Institute and European Committee on Antimicrobial Susceptibility Testing standards were 17.4 and 10.9%, respectively. Multidrug resistant (MDR) bacteria were most frequently isolated in Latin America (41.1%), followed by Europe (28.4%), North America (18.9%) and the Asia-Pacific region (18.8%). Respiratory samples were also the most frequent source of carbapenem nonsusceptible isolates (35.2%), as we detected in our study.[16]

MDR rates in the SENTRY program were highest in 2005–2008, which later declined. Similarly, in data from Europe in 2017, despite intercountry variation and high carbapenem-resistance rates in Southern and Eastern Europe, a small but significant decrease in carbapenem resistance, which may be associated with the efficient prevention and control programs of the participating countries, was recorded.[16]

A. baumannii is an opportunistic pathogen causing severe nosocomial infections with a global incidence rate of approximately 1 million cases annually. Over the last 30 years A. baumannii has emerged as one of the most troublesome pathogens and its clinical significance has been raised due to its ability to acquire antibiotic resistance which has been reported worldwide. Currently, 45% of all A. baumannii isolates are classified as MDR, and according to surveillance of antimicrobial resistance in Europe, 2017 report, carbapenem resistance and multiple resistance rates are reported to be 80% in countries in Southern and Eastern Europe and high rates in regions such as South America (40-80%) and Asia (40-60%).[17,18]

K. pneumoniae, the most common carbapenemase-producing member of the Enterobacteriaceae worldwide, is solely responsible for the dramatic increase in infectious diseases. According to studies, the prevalence of infections caused by carbapenem-resistant Enterobacteriaceae isolates varies between 0.04-29.5%. Based on the "Survey of Carbapenemase-Producing Enterobacteriaceae" program, the prevalence of carbapenemase-producing Enterobacteriaceae infections was reported to be 1.3 per 10,000 hospital admissions.[19,20]

Studies show that carbapenemase-producing K. pneumoniae isolates are hospital-acquired. Inter-hospital and intra-hospital spread is more common within countries than between countries. Antibiotic use is an important risk factor for these infections. The major problem in hospitalized patients is asymptomatic gastrointestinal carriage of carbapenemase-producing Enterobacteriaceae members, which significantly increases the risk of infections caused by these pathogens.[21,22]

P. aeruginosa is a pathogen causing serious treatment problems associated with higher mortality. Rates of resistance of P. aeruginosa to carbapenems ranged in European countries from 0% to 66%, in the US 10% to 25%, in South American countries 40%, and in Asia-Pacific countries <10–50%. Intrinsic/chromosomal-mediated resistance mechanisms play a major role in carbapenem resistance. Typical resistance mechanisms are low outer membrane permeability, expression of efflux pumps and the production of antibiotic-inactivating enzymes. Acquisition of resistance genes contribute only slightly to resistance.[10,23]

Carbapenems are the most effective broad-spectrum antibiotics against Gram-negative bacteria. However, carbapenem resistance in Gram-negative bacteria leads, decreasing treatment options with prolonged hospital stay, and increasing mortality rates. Increasing carbapenem resistance limits successful therapeutic cure, and antimicrobials such as tigecycline and colistin, which have limited use in some patient populations, need to be added to treatment regimen.[2]

According to the results of the studies of Kizirgil *et al*. in 2005, meropenem, and Yetkin *et al*. in 2006, imipenem, showed 100% activity against the isolates.[24,25] In our study, resistance to meropenem was 91.6%, followed by imipenem (44.3%), and ertapenem (25%). We also detected differences in carbapenem resistance related to isolates. Ertapenem resistance was significantly lower in P. aeruginosa isolates (p<0.01), meropenem resistance was significantly higher in A. baumannii isolates compared to other antibiotics.

In the annual reports of NHAI-NET in Türkiye, resistance rates to antibiotics in the carbapenem group are analyzed under a single heading as carbanemes.[15] Based on the significant differences found between the resistance rates of P. aeruginosa and A. baumannii strains to different members in the carbapenem group in our study, we suggest the antimicrobial resistance surveillance data to be evaluated for each member of the carbapenems separately, as average values under a single topic may not reflect the real ratios.

CONCLUSION

In conclusion, carbapenem-resistant Gram-negative bacilli are spreading rapidly worldwide, and new therapeutic agents need to be developed. To eliminate these pathogens, it is important to conduct prevalence and incidence studies, and detect the reservoirs, control the transmission dynamics, limit the excessive use of antibiotics during treatment which accelerates development of multidrug-resistant strains and know the distribution and present resistance patterns of Gram-negative isolates for each healthcare institution. Antibiotic resistance profiles vary regionally, from hospital to hospital, and even between different units of the same hospital. Therefore, regular monitoring of rates and resistance profiles of infectious agents, especially nosocomial Gram-negative bacteria, will be helpful for empiric treatment.

ACKNOWLEDGMENT

We dedicate this study to the memory of Dr. Aydın Aydınlı who contributed to the collection of data.

*The authors declare that there are no conflicts of interest.

REFERENCES

1. Peleg AY, Seifert H, Paterson DL. Acinetobacter baumannii: Emergence of a successful pathogen. Clin Microbiol Rev 2008; 21: 538-582.
2. Sheu CC, Chang YT, Lin SY, Chen YH, Hsueh PR. Infections caused by carbapenem-resistant Enterobacteriaceae: An Update on Therapeutic Options. Front Microbiol 2019; 10: 80.
3. Solomon SL, Oliver KB. Antibiotic resistance threats in the United States: stepping back from the brink. Am Fam Physician 2014; 89: 938-941.
4. Kaye KS, Pogue JM. Infections caused by resistant Gram-negative bacteria: Epidemiology and management. Pharmacotherapy 2015; 35: 949-962.
5. Gur D, Hascelik G, Aydin N, et al. Antimicrobial resistance in Gram-negative hospital isolates: results of the Turkish HITIT-2 Surveillance Study of 2007. J Chemother 2009; 21: 383-389.
6. Pfeifer Y, Cullik A, Witte W. Resistance to cephalosporins and carbapenems in Gram-negative bacterial pathogens. Int J Med Microbiol 2010; 300: 371-379.
7. Willyard C. The drug-resistant bacteria that pose the greatest health threats. Nature 2017; 543: 15.
8. Shrivastava SR, Shrivastava PS, Ramasamy J. World Health Organization releases global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. J Med Soc 2018; 32: 76-77.
9. Bassetti M, Poulakou G, Ruppe E, et al. Antimicrobial resistance in the next 30 years, humankind, bugs and drugs: a visionary approach. Intensive Care Med 2017; 43: 1464-1475.
10. Theuretzbacher U. Global antimicrobial resistance in Gram-negative pathogens and clinical need. Curr Opin Microbiol 2017; 39: 106-112.
11. Tzouvelekis LS, Markogiannakis A, Psichogiou M, Tassios PT, Daikos GL. Carbapenemases in Klebsiella pneumoniae and other Enterobacteriaceae: an evolving crisis of global dimensions. Clin Microbiol Rev 2012; 25: 682-707.
12. Gupta N, Limbago BM, Patel JB, Kallen AJ. Carbapenem-resistant Enterobacteriaceae: epidemiology and prevention. Clin Infect Dis 2011; 53: 60-77.
13. Türker E, Kardan MH, Kul S, et al. Bir üniversite hastanesinde COVID-19 pandemi öncesi ve pandemi sırasında hastane kaynaklı enfeksiyonlar. In: 10. Türkiye EKMUD Bilimsel Kongresi, Antalya, Türkiye, 25-29 May 2022, paper no. PS-387, pp. 402.
14. Akkuş İ, Tuncel B, Şahin Ö, et al. Kırıkkale Üniversitesi Tıp Fakültesi Hastanesinde son üç yılda kan kültürlerinde üretilen bazı etkenler ve direnç durumları. In: 10. Türkiye EKMUD Bilimsel Kongresi, Antalya, Türkiye, 25-29 May 2022, paper no. PS-424, pp.425.
15. Ulusal sağlık hizmeti ilişkili enfeksiyonlar sürveyans ağı özet raporu 2019. [May 2020]. https://www.saglikaktuel.com/d/file/ushesa_ozet_raporu_2019.pdf
16. Shortridge D, Gales AC, Streit JM, et al. Geographic and temporal patterns of antimicrobial resistance in Pseudomonas aeruginosa over 20 years from the SENTRY antimicrobial surveillance program. Open Forum Infect Dis 2019; 6: 63–68.
17. Cavallo I, Oliva A, Pages R, et al. Acinetobacter baumannii in the critically ill: complex infections get complicated. Front Microbiol 2023; 14: 1196774.
18. https://www.ecdc.europa.eu/sites/default/files/documents/AMR-surveillance-EARS-Net-2017.pdf
19. Cassini A, Högberg LD, Plachouras D, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis 2019; 19: 56-66.
20. Grundmann H, Glasner C, Albiger B, et al. Occurrence of carbapenemase-producing Klebsiella pneumoniae and Escherichia coli in the European survey of carbapenemase-producing Enterobacteriaceae (EuSCAPE): a prospective, multinational study. Lancet Infect Dis 2017; 17: 153-163.
21. Tischendorf J, de Avila RA, Safdar N. Risk of infection following colonization with carbapenem-resistant Enterobactericeae: A systematic review. Am J Infect Control 2016; 44: 539-543.
22. Tamma PD, Kazmi A, Bergman Y, et al. The likelihood of developing a carbapenem-resistant Enterobacteriaceae Infection during a hospital stay. Antimicrob Agents Chemother 2019; 63: 757-719.
23. Pang Z, Raudonis R, Glick BR, Lin TJ, Cheng Z. Antibiotic resistance in Pseudomonas aeruginosa: mechanisms and alternative therapeutic strategies. Biotechnol Adv 2019; 37: 177-192.
24. Kizirgil A, Yakupoğulları Y, Şenol FF, Toraman ZA. Kan kültürü örneklerinde genişlemiş spektrumlu beta-laktamaz üreten enterik basillerin prevalansı ve antibiyotik duyarlılıklarının araştırılması. İnfeks Derg 2005; 19: 111-114.
25. Yetkin G, Kuzucu Ç, Çalışkan A, Ay S. Kan kültürlerinde Üreyen Escherichia coli'lerin antibiyotik duyarlılıkları, GSBL oranları ve hastane birimlerine göre dağılımı. J Turgut Ozal Med Cent 2006; 13: 147-150.