

BÖLÜM 6

KARBAPENEMLERE DİRENÇ MEKANİZMALARI

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Giriş

Bakteriyel antimikrobiyal direnç (AMD) 21. yüzyılın önde gelen halk sağlığı tehditlerinden biridir. Doğrudan AMD'ye bağlı ölümlerin sayısının 2019 yılında 1.27 milyon olduğu ve AMD ilişkili ölüm sayıları da eklendiğinde bu sayının 4.95 milyonu bulduğu rapor edilmiştir. Daha önce yapılan tahminler, AMD konusunda önlem alınmazsa, 2050 yılına kadar AMD kaynaklı ölümlerin yılda 10 milyonu bulacağını öngörmüştü. Artık bu sayıya düşündüğümüzden daha yakın olduğumuzu kesin olarak biliyoruz. Günümüzde, şiddetli enfeksiyonların ampirik tedavisinde ilk seçenek ilaçlara karşı gelişen direnç, AMD ilişkili ölümlerin %70'ini oluşturmaktadır (1). Artmış mortalite oranları yanında, AMD, hastanede yatış sürelerinin uzamasına, tedavi başarısızlığına, hastanelerde ve toplumda dirençli bakterilerin yayılmasına, enfeksiyonlarda artışa, ciddi emek ve ekonomik yüke sebep olmaktadır. Anlam ve öneminden dolayı, Dünya Sağlık Örgütü (DSÖ), Birleşmiş Milletler Gıda ve Tarım Örgütü, Dünya Hayvan Sağlığı Örgütü desteği ile, 2015'den bu yana, her yılın 18-24 Kasım haftası "Dünya Antimikrobiyal Farkındalık Haftası" olarak anılmaktadır.

Karbapenemler, bakterilerin hücre duvarı sentezini inhibe ederek etki gösteren β -laktam grubu antibiyotiklerin en geniş spektrumlu üyesi olup, antimikrobiallerin en güvenilir son çare sınıfıdır. Özellikle Gram negatif bakterilerin sebep olduğu enfeksiyonlarda yüksek etkinliğe sahiptir. Bu sebep ile karbapenem kullanımı, geniş spektrumlu β -laktamaz (ESBL) üreten *Enterobacteriaceae* ve diğer üçüncü kuşak sefalosporine dirençli Gram negatif bakterilerin neden olduğu en-

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Kaynaklar

1. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a system analysis. *Lancet*. 2022;399: 629-655. doi: 10.1016/S0140-6736(21)02724-0
2. Tamma PD, Aitken SL, Bonomo RA, et al. Infectious Diseases Society of America 2022 Guidance on the Treatment of Extended-Spectrum β -lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-P. *aeruginosa*). *Clinical Infectious Diseases*. 2022;75(2): 187-212. doi:10.1093/cid/ciac268
3. World Health Organization. WHO publishes list of bacteria for which new antibiotics are urgently needed. Available from: <https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed> (Accessed 17th November 2022).
4. World Health Organization Regional Office for Europe/European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2022 – 2020 data. Copenhagen: WHO Regional Office for Europe; 2022. Available from: <https://www.ecdc.europa.eu/en/publications-data/antimicrobial-resistance-surveillance-europe-2022-2020-data> (Accessed 17th November 2022)
5. Aurilio C, Sansone P, Barbarisi M, et al. Mechanisms of Action of Carbapenem Resistance. *Antibiotics*. 2022;11: 421. doi: 10.3390/antibiotics11030421
6. Ghai I, Ghai S. Understanding antibiotic resistance via outer membrane permeability. *Infection and Drug Resistance*. 2018;11: 523-530. doi: 10.2147/IDR.S156995
7. Tenover FC, Nicolaub DP, Gil CM. Carbapenemase-producing *Pseudomonas aeruginosa* –an emerging challenge. *Emerging Microbes & Infections*. 2022; 11: 811-814. doi: 10.1080/22221751.2022.2048972
8. Li XZ, Plésiat P, Nikaido H. The challenge of efflux-mediated antibiotic resistance in Gram-negative bacteria. *Clinical Microbiology Reviews*. 2015;28(2): 337-418. doi: 10.1128/CMR.00117-14
9. Abdi SN, Ghotaslou R, Ganbarov K, et al. Acinetobacter baumannii Efflux Pumps and Antibiotic Resistance. *Infection and Drug Resistance*. 2020;13: 423-434. doi: 10.2147/IDR.S228089
10. AlMatar M, Albarri O, Makky EA, et al. Efflux pump inhibitors: new updates. *Pharmacological Reports*. 2021;73(1): 1-16. doi: 10.1007/s43440-020-00160-9
11. Partridge SR, Kwong SM, Firth N, et al. Mobile Genetic Elements Associated with Antimicrobial Resistance. *Clinical Microbiology Reviews*. 2018;31(4): e00088-17. doi: 10.1128/CMR.00088-17.
12. Aslam B, Rasool M, Muzammil S, et al. (2020). Carbapenem Resistance: Mechanisms and Drivers of Global Menace. In S. Kirmusaoğlu, & S. B. Bhardwaj (Eds.), *Pathogenic Bacteria*. IntechOpen; 2020. Available from; <https://doi.org/10.5772/intechopen.90100> (Accessed 17th November 2022)
13. European Society of Clinical Microbiology and Infectious Diseases. EUCAST guidelines for detection of resistance mechanisms and specific resistances of clinical and/or epidemiological importance. 2017. Available from; https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Resistance_mechanisms/EUCAST_detection_of_resistance_mechanisms_170711.pdf (Accessed 17th November 2022)
14. Codjoe FS, Donkor ES. Carbapenem Resistance: A Review. *Medical Sciences (Basel)*. 2017;21; 6(1):1. doi: 10.3390/medsci6010001
15. Ambler RP. The structure of beta-lactamases. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*. 1980;289(1036): 321-331. doi: 10.1098/rstb.1980.0049
16. Bush K, Jacoby GA. Updated functional classification of beta-lactamases. *Antimicrobial Agents and Chemotherapy*. 2010;54(3): 969-976. doi: 10.1128/AAC.01009-09

17. Iraz M, Duzgun AO, Cicek AC, et al. Characterization of novel VIM carbapenemase, VIM-38, and first detection of GES-5 carbapenem-hydrolyzing β -lactamases in *Pseudomonas aeruginosa* in Turkey. *Diagnostic Microbiology and Infectious Disease*. 2014;78: 292-294. doi: 10.1016/j.diagmicrobio.2013.12.003
18. Tamma PD, Goodman KE, Harris AD, et al. Comparing the Outcomes of Patients With Carbapenemase-Producing and Non-Carbapenemase-Producing Carbapenem-Resistant Enterobacteriaceae Bacteremia. *Clinical Infectious Diseases*. 2017;64(3): 257–264. doi: 10.1093/cid/ciw741
19. Shields RK, Doi Y. Aztreonam Combination Therapy: An Answer to Metallo- β -Lactamase-Producing Gram-Negative Bacteria? *Clinical Infectious Diseases*. 2020;71(4): 1099-1101. doi: 10.1093/cid/ciz1159
20. Deshpande LM, Jones RN, Fritsche TR, et al. Occurrence and characterization of carbapenemase-producing Enterobacteriaceae: report from the SENTRY Antimicrobial Surveillance Program (2000-2004). *Microbial Drug Resistance*. 2006;12(4): 223-230. doi: 10.1089/mdr.2006.12.223
21. Laurettil L, Riccio ML, Mazzariol A, et al. Cloning and characterization of blaVIM, a new integron-borne metallo-beta-lactamase gene from a *Pseudomonas aeruginosa* clinical isolate. *Antimicrobial Agents and Chemotherapy*. 1999;43(7): 1584-1590. doi: 10.1128/AAC.43.7.1584
22. Riccio ML, Franceschini N, Boschi L, et al. Characterization of the metallo-beta-lactamase determinant of *Acinetobacter baumannii* AC-54/97 reveals the existence of bla(IMP) allelic variants carried by gene cassettes of different phylogeny. *Antimicrobial Agents and Chemotherapy*. 2000;44(5): 1229-1235. doi: 10.1128/AAC.44.5.1229-1235.2000
23. Marra AR, Pereira CA, Gales AC, et al. Bloodstream infections with metallo-beta-lactamase-producing *Pseudomonas aeruginosa*: epidemiology, microbiology, and clinical outcomes. *Antimicrobial Agents and Chemotherapy*. 2006;50(1): 388-390. doi: 10.1128/AAC.50.1.388-390.2006
24. Castanheira M, Toleman MA, Jones RN, et al. Molecular characterization of a beta-lactamase gene, blaGIM-1, encoding a new subclass of metallo-beta-lactamase. *Antimicrobial Agents and Chemotherapy*. 2004;48(12): 4654-4661. doi: 10.1128/AAC.48.12.4654-4661.2004
25. Lee K, Yum JH, Yong D, et al. Novel acquired metallo-beta-lactamase gene, bla(SIM-1), in a class 1 integron from *Acinetobacter baumannii* clinical isolates from Korea. *Antimicrobial Agents and Chemotherapy*. 2005;49(11): 4485-4491. doi: 10.1128/AAC.49.11.4485-4491.2005
26. Nordmann P, Poirel L, Toleman MA, et al. Does broad-spectrum beta-lactam resistance due to NDM-1 herald the end of the antibiotic era for treatment of infections caused by Gram-negative bacteria? *Journal of Antimicrobial Chemotherapy*. 2011;66(4): 689-692. doi: 10.1093/jac/dkq520
27. Khan AU, Nordmann P. Spread of carbapenemase NDM-1 producers: the situation in India and what may be proposed. *Scandinavian Journal of Infectious Diseases*. 2012;44(7): 531-535. doi: 10.3109/00365548.2012.669046
28. Evans BA, Amyes SG. OXA β -lactamases. *Clinical Microbiology Reviews*. 2014;27(2): 241-263. doi: 10.1128/CMR.00117-13
29. Carrër A, Poirel L, Yilmaz M, et al. Spread of OXA-48-encoding plasmid in Turkey and beyond. *Antimicrobial Agents and Chemotherapy*. 2010;54(3): 1369-1373. doi: 10.1128/AAC.01312-09.
30. Ahmed SS, Alp E, Ulu-Kilic A, et al. Spread of carbapenem-resistant international clones of *Acinetobacter baumannii* in Turkey and Azerbaijan: a collaborative study. *European Journal of Clinical Microbiology & Infectious Diseases*. 2016;35(9):1463-1468. doi: 10.1007/s10096-016-2685-x
31. Kong KF, Jayawardena SR, Del Puerto A, et al. Characterization of poxB, a chromosomal-encoded *Pseudomonas aeruginosa* oxacillinase. *Gene*. 2005;358: 82-92. doi: 10.1016/j.gene.2005.05.027
32. Ryan MP, Pembroke JT, Adley CC. *Ralstonia pickettii*: a persistent gram-negative nosocomial infectious organism. *Journal of Hospital Infection*. 2006;62(3): 278-284. doi: 10.1016/j.jhin.2005.08.015.

33. Ambrose M, Malley RC, Warren SJC, et al. Pandoraea pnomenusa Isolated from an Australian Patient with Cystic Fibrosis. *Frontiers in Microbiology*. 2016;7: 692. doi: 10.3389/fmicb.2016.00692
34. Yahav D, Giske CG, Gramatniece A, et al. New β -lactam- β -lactamase inhibitor combinations. *Clinical Microbiology Reviews*. 2021;34: e00115-20. doi: 10.1128/CMR.00115-20
35. Lupia T, Corcione S, Shbaklo N, et al. Meropenem/Vaborbactam and Cefiderocol as Combination or Monotherapy to Treat Multi-Drug Resistant Gram-Negative Infections: A Regional Cross-Sectional Survey from Piedmont Infectious Disease Unit Network (PIDUN). *Journal of Functional Biomaterials*. 2022;13: 174. doi: 10.3390/jfb13040174
36. Gaibani P, Giani T, Bovo F, et al. Resistance to Ceftazidime/Avibactam, Meropenem/Vaborbactam and Imipenem/Relebactam in Gram-Negative MDR Bacilli: Molecular Mechanisms and Susceptibility Testing. *Antibiotics*. 2022;11: 628. doi: 10.3390/antibiotics11050628
37. Hujer AM, Bethel CR, Taracila MA, et al. Imipenem/Relebactam Resistance in Clinical Isolates of Extensively Drug Resistant Pseudomonas aeruginosa: Inhibitor-Resistant β -Lactamases and Their Increasing Importance. *Antimicrobial Agents and Chemotherapy*. 2022;66(5): e0179021. doi: 10.1128/aac.01790-21
38. Gaibani P, Bianco G, Amadesi S, et al. Increased blaKPC Copy Number and OmpK35 and OmpK36 Porins Disruption Mediated Resistance to Imipenem/Relebactam and Meropenem/Vaborbactam in a KPC-Producing Klebsiella pneumoniae Clinical Isolate. *Antimicrobial Agents and Chemotherapy*. 2022;66(5): e0019122. doi: 10.1128/aac.00191-22
39. Carattoli A, Arcari G, Bibbolino G, et al. Evolutionary Trajectories toward Ceftazidime-Avibactam Resistance in Klebsiella pneumoniae Clinical Isolates. *Antimicrobial Agents and Chemotherapy*. 2021;65(10): e0057421. doi: 10.1128/AAC.00574-21
40. Hernández-García M, Castillo-Polo JA, Cordero DG, et al. Impact of Ceftazidime-Avibactam Treatment in the Emergence of Novel KPC Variants in the ST307-Klebsiella pneumoniae High-Risk Clone and Consequences for Their Routine Detection. *Journal of Clinical Microbiology*. 2022;60(3): e0224521. doi: 10.1128/jcm.02245-21
41. World Health Organization. Surveillance of antimicrobial resistance in Europe, 2021 data. Available from: <https://www.ecdc.europa.eu/en/publications-data/surveillance-antimicrobial-resistance-europe-2021-data> (Accessed 1st December 2022).
42. Organisation for Economic Co-operation and Development. Antimicrobial Resistance Tackling the Burden in the European Union. Available from: <https://www.oecd.org/health/health-systems/AMR-Tackling-the-Burden-in-the-EU-OECD-ECDC-Briefing-Note-2019.pdf> (Accessed 1st December 2022).
43. Gales AC, Seifert H, Gur D, Castanheira M, Jones RN, Sader HS. Antimicrobial susceptibility of Acinetobacter calcoaceticus-Acinetobacter baumannii complex and Stenotrophomonas maltophilia clinical isolates: results from the SENTRY Antimicrobial Surveillance Program (1997–2016). *Open forum infectious diseases*. 2019;6(1): 34–46. doi: 10.1093/ofid/ofy293
44. Nordmann P, Poirel L. Epidemiology and Diagnostics of Carbapenem Resistance in Gram-negative Bacteria. *Clinical Infectious Diseases*. 2019;69(7): 521–528. doi: 10.1093/cid/ciz824
45. World Health Organization. Central Asian and Eastern European Surveillance of Antimicrobial Resistance: Annual report 2016. Available from: https://www.euro.who.int/__data/assets/pdf_file/0009/323568/CAESAR-Annual-report-2016.pdf (Accessed 1st December 2022).
46. World Health Organization. Central Asian and Eastern European Surveillance of Antimicrobial Resistance: Annual report 2018. Available from: <https://apps.who.int/iris/handle/10665/324806> (Accessed 1st December 2022).
47. World Health Organization. Antimicrobial resistance surveillance in Europe 2022 – 2020 data. Available from: <https://apps.who.int/iris/handle/10665/351141> (Accessed 1st December 2022).

48. Aydın M, Azak E, Bilgin H, et al. Changes in antimicrobial resistance and outcomes of health care-associated infections. *European Journal of Clinical Microbiology & Infectious Diseases*. 2021;40(8): 1737-1742. doi: 10.1007/s10096-020-04140-y
49. Ergönül Ö, Aydın M, Azap A, et al. Healthcare-associated Gram-negative bloodstream infections: antibiotic resistance and predictors of mortality. *The Journal of Hospital Infection*. 2016;94(4): 381-385. doi:10.1016/j.jhin.2016.08.012
50. Ergonul O, Tokca G, Keske Ş, et al. Elimination of healthcare-associated *Acinetobacter baumannii* infection in a highly endemic region. *International Journal of Infectious Diseases*. 2022;114: 11-14. doi: 10.1016/j.ijid.2021.10.011
51. Akkaya Isik S, Yenilmez E, Cetinkaya RA, et al. A meta-analysis of antibiotic resistance rates in *Pseudomonas aeruginosa* isolated in blood cultures in Turkey between 2007 and 2017. *Northern Clinics Of Istanbul*. 2021;8(3): 286-297. doi: 10.14744/nci.2020.93195
52. Agyeman AA, Bergen PJ, Rao GG, et al. Mortality, clinical and microbiological response following antibiotic therapy among patients with carbapenem-resistant *Klebsiella pneumoniae* infections (a meta-analysis dataset). *Data in Brief*. 2020;20: 104907. doi: 10.1016/j.ijantimicag.2019.10.014
53. Vatansever C, Menekse S, Dogan O, et al. Co-existence of OXA-48 and NDM-1 in colistin resistant *Pseudomonas aeruginosa* ST235. *Emerging Microbes & Infections*. 2020;9(1): 152-154. doi: 10.1080/22221751.2020.1713025
54. Boral B, Unaldi Ö, Ergin A. et al. A prospective multicenter study on the evaluation of antimicrobial resistance and molecular epidemiology of multidrug-resistant *Acinetobacter baumannii* infections in intensive care units with clinical and environmental features. *Annals of Clinical Microbiology and Antimicrobials*. 2019;18: 19. doi: 10.1186/s12941-019-0319-8
55. Al-Zahrani İA. Routine detection of carbapenem-resistant gram-negative bacilli in clinical laboratories. *Saudi Medical Journal*. 2018;39 (9): 861-872. doi: 10.15537/smj.2018.9.22840
56. Brolund A, Lagerqvist N, Byfors S, et al. Worsening epidemiological situation of carbapenemase-producing Enterobacteriaceae in Europe, assessment by national experts from 37 countries, July 2018. *Euro Surveillance*. 2019;24(9): pii=1900123. doi: 10.2807/1560-7917.ES.2019.24.9.1900123
57. Ludden C, Lötsch F, Alm E, et al. Cross-border spread of blaNDM-1- and blaOXA-48-positive *Klebsiella pneumoniae*: a European collaborative analysis of whole genome sequencing and epidemiological data, 2014 to 2019. *Euro Surveillance*. 2020;25(20):pii=2000627. doi: org/10.2807/1560-7917.ES.2020.25.20.2000627
58. Neidhöfer C, Buechler C, Neidhöfer G, et al. Global Distribution Patterns of Carbapenemase-Encoding Bacteria in a New Light: Clues on a Role for Ethnicity. *Frontiers in Cellular and Infection Microbiology*. 2021;11: 659753. doi: 10.3389/fcimb.2021.659753
59. Han R, Shi Q, Wu S, et al. Dissemination of Carbapenemases (KPC, NDM, OXA-48, IMP, and VIM) Among Carbapenem-Resistant Enterobacteriaceae Isolated From Adult and Children Patients in China. *Frontiers in Cellular Infection Microbiology*. 2020;10:314. doi: 10.3389/fcimb.2020.00314
60. Karlowsky JA, Bouchillon SK, El Mahdy Kotb R, et al. Carbapenem-resistant Enterobacteriales and *Pseudomonas aeruginosa* causing infection in Africa and the Middle East: a surveillance study from the ATLAS programme (2018-20). *JAC-Antimicrobial Resistance*. 2022;4(3): dlac060. doi: 10.1093/jacamr/dlac060
61. Köle M, Sesli Çetin E, Şirin MC, et al. Seftazidim-Avibaktam, Meropenem ve Kolistinin Tek Başına ve İkili Kombinasyonlarının Çeşitli Klinik Örneklerden İzole Edilen Karbapenem Dirençli *Klebsiella pneumoniae* Suşlarına Karşı In Vitro Etkinliğinin Araştırılması. *Mikrobiyoloji*

Bülteni. 2022;56(2): 230-250. doi: 10.5578/mb.20229804

62. Hortaç İhtar E, Alışkan HE, Göçmen JS. Diverse efficacy of CarbaNP test among OXA-48 carbapenemase producing Enterobacterales in an endemic region. *Acta Microbiologica et Immunologica Hungarica*. 2021;68(1): 34-39. doi: 10.1556/030.2021.01220
63. Süzük Yıldız S, Şimşek H, Bakkaloğlu Z, et al. Türkiye’de 2019 Yılı İçinde İzole Edilen Escherichia coli ve Klebsiella pneumoniae İzolatlarında Karbapenemaz Epidemiyolojisi. *Mikrobiyoloji Bülteni*. 2021;55(1): 1-16. doi: 10.5578/mb.20124
64. Hazırolan G, Karagöz A. Emergence of carbapenemase-producing and colistin resistant Klebsiella pneumoniae ST101 high-risk clone in Turkey. *Acta Microbiologica et Immunologica Hungarica*. 2020;67(4): 216–221. doi: 10.1556/030.2020.01275
65. Sağıroğlu P, Hasdemir U, Altınkanat Gelmez G, et al. Performance of “RESIST-3 O.K.N. K-SeT” immunochromatographic assay for the detection of OXA-48 like, KPC, and NDM carbapenemases in Klebsiella pneumoniae in Turkey. *Brazilian Journal of Microbiology*. 2018;49(4): 885-890. doi: 10.1016/j.bjm.2018.02.002
66. Cizmeci Z, Aktas E, Otlu B, et al. Molecular characterization of carbapenem-resistant Enterobacteriaceae yields increasing rates of NDM-1 carbapenemases and colistin resistance in an OXA-48- endemic area. *Journal of Chemotherapy*. 2017;29(6): 344-350. doi: 10.1080/1120009X.2017.1323149
67. Erdem F, Oncul O, Aktas Z. Characterization of Resistance Genes and Polymerase Chain Reaction-Based Replicon Typing in Carbapenem-Resistant Klebsiella pneumoniae. *Microbial Drug Resistance*. 2019;25(4): 551-557. doi: 10.1089/mdr.2018.0231
68. Çakar A, Akyön Y, Gür D, et al. Türkiye’de 2014 yılı içinde izole edilen karbapenem dirençli Escherichia coli ve Klebsiella pneumoniae izolatlarında karbapenemaz varlığının araştırılması. *Mikrobiyoloji Bülteni*. 2016;50(1): 21-33. doi: 10.5578/mb.10695
69. Alp E, Perçin D, Colakoğlu S, et al. Molecular characterization of carbapenem-resistant Klebsiella pneumoniae in a tertiary university hospital in Turkey. *Journal of Hospital Infections*. 2013;84(2): 178-180. doi: 10.1016/j.jhin.2013.03.002
70. Kutlu HH, Us E, Tekeli A. Bir üniversite hastanesinde 2010-2014 yılları arasında izole edilen Enterobacteriaceae türlerinin karbapenemaz genlerinin araştırılması ve moleküler epidemiyolojisinin belirlenmesi. *Mikrobiyoloji Bülteni*. 2018;52(1): 1-12. doi: 10.5578/mb.66156
71. Gozalan A, Unaldı O, Guldemir D, et al. Molecular Characterization of Carbapenem-Resistant Acinetobacter baumannii Blood Culture Isolates from Three Hospitals in Turkey. *Japanese Journal of Infectious Diseases*. 2021;74(3): 200-208. doi: 10.7883/yoken.JJID.2020.478
72. Davandeh I, Eraç B, Aydemir SŞ. Investigation of class-d beta-lactamases causing carbapenem resistance in clinical Acinetobacter baumannii isolates. *Turkish Journal of Medical Sciences*. 2017;47(5): 1661-1666. doi: 10.3906/sag-1607-91
73. Çekin ZK, Dabos L, Malkoçoğlu G, et al. Carbapenemase -producing Pseudomonas aeruginosa isolates from Turkey: First report of P. aeruginosa high-risk clones with VIM-5- and IMP-7- type carbapenemases in a tertiary hospital. *Diagnostic Microbiology and Infectious Disease*. 2021;99(1): 115174. doi: 10.1016/j.diagmicrobio.2020.115174
74. Malkoçoğlu G, Aktaş E, Bayraktar B, et al. VIM-1, VIM-2, and GES-5 Carbapenemases Among Pseudomonas aeruginosa Isolates at a Tertiary Hospital in Istanbul, Turkey. *Microbial Drug Resistance*. 2017;23(3): 328-334. doi: 10.1089/mdr.2016.0012
75. Çopur Çiçek A, Ertürk A, Ejder N, et al Screening of Antimicrobial Resistance Genes and Epidemiological Features in Hospital and Community-Associated Carbapenem-Resistant Pseudomonas aeruginosa Infections. *Infection and Drug Resistance*. 2021;14: 1517-1526. doi: 10.2147/IDR.S299742