BÖLÜM 3

DİRENÇLİ GRAM-POZİTİF BAKTERİLERLE GELİŞEN ENFEKSİYONLARDA KOMBİNASYON TEDAVİSİ

Uzm. Dr. Elif M. SARICAOĞLU

Ankara Şehir Hastanesi Enfeksiyon Hastalıkları
ve Klinik Mikrobiyoloji Kliniği,
Ankara

Giderek artan antibiyotik direnci ile yeni antibiyotik gelişimindeki kısıtlılıklar tüm dünyada önemli bir sağlık sorunu haline gelmiştir (1). Özellikle çoklu ilaç direnci gösteren nozokomiyal *Enterococcus faecium, Staphylococcus aureus, Klebsiella pnemoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* ve *Enterobacter* spp.'lerinin kısaltması olan ESKAPE patojenlerin etken olduğu enfeksiyonların tedavisinde karşılaşılan zorluklar, beraberinde yeni tedavi stratejilerini getirmiştir (2). Adjuvanlar, kombine antimikrobiyal kullanımı, bakteriyofajlar, antimikrobiyal peptidler, nanopartiküller ve fotodinamik ışık tedavileri bunlara örnek olarak verilebilir (2). Enfeksiyon hastalıklarının tedavisinde antibiyotik kombinasyonları, sıklıkla farklı etki mekanizmalarının avantajlarını kullanmak ve/veya toksisiteyi önlemek amacıyla tercih edilmektedir (3). Kombine antimikrobiyal kullanım nedenlerini sıralayacak olursak bunlar; (a) ciddi enfeksiyonların ampirik tedavisi, (b) polimikrobiyal enfeksiyonların tedavisi, (c) bakteriyel direnci önlemek, (d) sinerjistik etki sağlamak, (e) biyofilm oluşturan mikroorganzimalara karşı etkinlik sağlamak, (f) monoterapi ile sağlanamayan hücre/doku penetrasyonunu sağlamak (g) toksin üretimini inhibe etmek (h) enzim üretiminin üstesinden gelmektir (3, 4). Bir diğer taraftan kombinasyon tedavisinin; maliyet artışı, artmış yan etki profili, antagonizma ve süperenfeksiyonlar gibi dezavantajları da bulunmaktadır (3). İki antimikrobiyalin kullanımının sinerjistik etkisini değerlendirmek amacı ile fraksiyonel inhibitör konsantrasyonu/checkerboard, zaman-öldürme eğrisi metodu, agar difüzyon, simule edilmiş farmakodinamik modeller kullanılmaktadır (3,

İnvazif enterokokkal enfeksiyonların tedavisinde tek başına tigesiklin kullanımı düşük serum konsantrasyonları nedeni ile tercih edilmemektedir. Ancak VR*E. faecium* ilişkili bakteriyemi ve endokarditlerin tedavisinde tigesiklin içeren kombinasyonların başarılı sonuçlar verdiği gösterilmiştir (49). Schutt ve arkadaşlarının VR*E.faecium* endokarditi olan bir hastada çeşitli daptomisin kombinasyonları ile tedavi başarısızlığı yaşanırken, yüksek doz daptomisin ve tigesiklin kombinasyonu klinik ve mikrobiyolojik başarı sağlamıştır (62). Deneysel linezolid dirençli *E.faecium* endokardit hayvan modelinde; tigesiklin ile tedavi edildiğinde vejetasyonda 2.8 log10CFU/g mikrobiyal azalma saptanırken, tigesiklin/gentamisin kombinasyonu ile koloni sayısında aritmetik olarak düşüş saptanmıştır (63). Tigesiklinin klinik etkinliği ile kısıtlı veri olması ve yan etki profili nedeni ile kullanımının mutlaka gerekli olacağı vakalar için saklanması uygun bir yaklaşım olarak görülmektedir (49).

3.1.4. Fosfomisin ile Kombinasyon Seçenekleri

Fosfomisin; VRE izolatlarında güçlü in vitro antibakteriyel etkisi ve iyi tolere edilebilirliği nedeni ile yeni tedavi seçenekleri arasında yer almaya başlamıştır. Tang ve ark. tarafından biyofilm ilişkili VRE enfeksiyonlarında fosfomisinli kombinasyonlar in vitro olarak değerlendirilmiştir. Fosfomisin ile özellikle teikoplanin kombinasyonu VR*E.faecalis* izolatlarının %89'unda sinerjistik etki göstermiştir. Fosfomisin ve rifampisin kombinasyonu biyofilm gömülü VR*E.faecalis* ve VR*E. faecium* izolatlarında sırası ile %100 ve %40 sinerji göstermiştir. Ancak fosfomisin ile ampisilin kombinasyonu VR*E.faecalis* izolatlarının 2/3'ünde antagonistik bulunmuştur (64).

KAYNAKLAR

1. Cottarel G, Wierzbowski J. Combination drugs, an emerging option for antibacterial therapy. Trends in biotechnology. 2007;25(12):547-55.
2. Mulani MS, Kamble EE, Kumkar SN, Tawre MS, Pardesi KR. Emerging strategies to combat ESKAPE pathogens in the era of antimicrobial resistance: a review. Frontiers in microbiology. 2019;10.
3. Rybak MJ, McGrath BJ. Combination antimicrobial therapy for bacterial infections. Drugs. 1996;52(3):390-405.
4. Hagihara M, Crandon JL, Nicolau DP. The efficacy and safety of antibiotic combination therapy for infections caused by Gram-positive and Gram-negative organisms. Expert opinion on drug safety. 2012;11(2):221-33.
5. Davis J, van Hal S, Tong S, editors. Combination antibiotic treatment of serious methicillin-resistant Staphylococcus aureus infections. Seminars in respiratory and critical care medicine; 2015: Thieme Medical Publishers.
6. Tagliaferri TL, Jansen M, Horz H-P. Fighting pathogenic bacteria on two fronts: phages and antibiotics as combined strategy. Frontiers in cellular and infection microbiology. 2019;9:22.
7. Hassoun A, Linden PK, Friedman B. Incidence, prevalence, and management of MRSA bacte-

remia across patient populations—a review of recent developments in MRSA management and treatment. Critical care. 2017;21(1):211.
8. Vazquez-Guillamet C, Kollef MH. Treatment of gram-positive infections in critically ill patients. BMC infectious diseases. 2014;14(1):92.
9. Concia E, Viscoli C, Del Bono V, Giannella M, Bassetti M, De Rosa GF, et al. The current role of glycopeptides in the treatment of methicillin-resistant Staphylococcus aureus (MRSA) infections in not neutropenic adults: the viewpoint of a group of Italian experts. Journal of Chemotherapy. 2018;30(3):157-71.
10. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2011;52(3):e18-55.
11. Sakoulas G, Moise-Broder PA, Schentag J, Forrest A, Moellering RC, Eliopoulos GM. Relationship of MIC and bactericidal activity to efficacy of vancomycin for treatment of methicillin-resistant Staphylococcus aureus bacteremia. Journal of clinical microbiology. 2004;42(6):2398-402.
12. Soriano A, Marco F, Martinez JA, Pisos E, Almela M, Dimova VP, et al. Influence of vancomycin minimum inhibitory concentration on the treatment of methicillin-resistant Staphylococcus aureus bacteremia. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2008;46(2):193-200.
13. Lewis PO, Heil EL, Covert KL, Cluck DB. Treatment strategies for persistent methicillin-resistant Staphylococcus aureus bacteraemia. Journal of clinical pharmacy and therapeutics. 2018;43(5):614-25.
14. Tran K-N, Rybak MJ. β-Lactam combinations with vancomycin show synergistic activity against vancomycin-susceptible Staphylococcus aureus, vancomycin-intermediate S. aureus (VISA), and heterogeneous VISA. Antimicrobial agents and chemotherapy. 2018;62(6):e00157-18.
15. Dilworth TJ, Casapao AM, Ibrahim OM, Jacobs DM, Bowers DR, Beyda ND, et al. Adjuvant β-Lactam Therapy Combined with Vancomycin for Methicillin-Resistant Staphylococcus aureus Bacteremia: Does β-Lactam Class Matter? Antimicrobial agents and chemotherapy. 2019;63(3):e02211-18.
16. Navalkele B, Pogue JM, Karino S, Nishan B, Salim M, Solanki S, et al. Risk of acute kidney injury in patients on concomitant vancomycin and piperacillin–tazobactam compared to those on vancomycin and cefepime. Clinical Infectious Diseases. 2017;64(2):116-23.
17. Dilworth TJ, Ibrahim O, Hall P, Sliwinski J, Walraven C, Mercier R-C. β-Lactams enhance vancomycin activity against methicillin-resistant Staphylococcus aureus bacteremia compared to vancomycin alone. Antimicrobial agents and chemotherapy. 2014;58(1):102-9.
18. Truong J, Veillette JJ, Forland SC. Outcomes of vancomycin plus a β-lactam versus vancomycin only for treatment of methicillin-resistant Staphylococcus aureus bacteremia. Antimicrobial agents and chemotherapy. 2018;62(2):e01554-17.
19. Casapao AM, Jacobs DM, Bowers DR, Beyda ND, Dilworth TJ, Group RIS. Early Administration of Adjuvant β-Lactam Therapy in Combination with Vancomycin among Patients with Methicillin-Resistant Staphylococcus aureus Bloodstream Infection: A Retrospective, Multicenter Analysis. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2017;37(11):1347-56.
20. Davis JS, Sud A, O'Sullivan MV, Robinson JO, Ferguson PE, Foo H, et al. Combination of vancomycin and β-lactam therapy for methicillin-resistant Staphylococcus aureus bacteremia: a pilot multicenter randomized controlled trial. Clinical Infectious Diseases. 2016;62(2):173-80.
21. Holland TL, Davis JS. Combination Therapy for MRSA Bacteremia: To ß or Not to ß? Clinical Infectious Diseases. 2019.
22. Davis JS FH LD, Nelson J, O'Sullivan M, Paterson DL, Paul M, Sud A, Yahav D, Tong SYC Combination antibiotic therapy for methicillin-resistant Staphylococcus aureus bacteraemia: the CAMERA2 randomised controlled trial [Abstract L0014]. In: Program and abstracts of the

29th European Congress of Clinical Microbiology & Infectious Diseases Amsterdam, Netherlands 2019.
23. Deresinski S. Vancomycin in combination with other antibiotics for the treatment of serious methicillin-resistant Staphylococcus aureus infections. Clinical Infectious Diseases. 2009;49(7):1072-9.
24. Levine DP, Fromm BS, Reddy BR. Slow response to vancomycin or vancomycin plus rifampin in methicillin-resistant Staphylococcus aureus endocarditis. Annals of internal medicine. 1991;115(9):674-80.
25. Riedel DJ, Weekes E, Forrest GN. Addition of rifampin to standard therapy for treatment of native valve infective endocarditis caused by Staphylococcus aureus. Antimicrobial agents and chemotherapy. 2008;52(7):2463-7.
26. Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, et al. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clinical infectious diseases. 2013;56(1):e1-e25.
27. Choo EJ, Chambers HF. Treatment of methicillin-resistant Staphylococcus aureus bacteremia. Infection & chemotherapy. 2016;48(4):267-73.
28. Dhand A, Sakoulas G. Daptomycin in combination with other antibiotics for the treatment of complicated methicillin-resistant Staphylococcus aureus bacteremia. Clinical therapeutics. 2014;36(10):1303-16.
29. Dhand A, Bayer AS, Pogliano J, Yang S-J, Bolaris M, Nizet V, et al. Use of antistaphylococcal β-lactams to increase daptomycin activity in eradicating persistent bacteremia due to methicillin-resistant Staphylococcus aureus: role of enhanced daptomycin binding. Clinical infectious diseases. 2011;53(2):158-63.
30. Geriak M, Haddad F, Rizvi K, Rose W, Kullar R, LaPlante K, et al. Clinical data on daptomycin plus ceftaroline versus standard of care monotherapy in the treatment of methicillin-resistant Staphylococcus aureus bacteremia. Antimicrobial agents and chemotherapy. 2019;63(5):e02483-18.
31. Jorgensen SCJ, Zasowski EJ, Trinh TD, Lagnf AM, Bhatia S, Sabagha N, et al. Daptomycin Plus β-Lactam Combination Therapy for Methicillin-resistant Staphylococcus aureus Bloodstream Infections: A Retrospective, Comparative Cohort Study. Clinical Infectious Diseases. 2019.
32. Rybak JM, Barber KE, Rybak MJ. Current and prospective treatments for multidrug-resistant gram-positive infections. Expert opinion on pharmacotherapy. 2013;14(14):1919-32.
33. Werth BJ, Sakoulas G, Rose WE, Pogliano J, Tewhey R, Rybak MJ. Ceftaroline increases membrane binding and enhances the activity of daptomycin against daptomycin-nonsusceptible vancomycin-intermediate Staphylococcus aureus in a pharmacokinetic/pharmacodynamic model. Antimicrobial agents and chemotherapy. 2013;57(1):66-73.
34. Barber KE, Werth BJ, Rybak MJ. The combination of ceftaroline plus daptomycin allows for therapeutic de-escalation and daptomycin sparing against MRSA. Journal of Antimicrobial Chemotherapy. 2015;70(2):505-9.
35. Zasowski EJ, Trinh TD, Claeys KC, Casapao AM, Sabagha N, Lagnf AM, et al. Multicenter observational study of ceftaroline fosamil for methicillin-resistant Staphylococcus aureus bloodstream infections. Antimicrobial agents and chemotherapy. 2017;61(2):e02015-16.
36. Miro J, Garcia-de-la-Maria C, Armero Y, Soy D, Moreno A, Del Rio A, et al. Addition of gentamicin or rifampin does not enhance the effectiveness of daptomycin in treatment of experimental endocarditis due to methicillin-resistant Staphylococcus aureus. Antimicrobial agents and chemotherapy. 2009;53(10):4172-7.
37. Claeys KC, Smith JR, Casapao AM, Mynatt RP, Avery L, Shroff A, et al. Impact of the combination of daptomycin and trimethoprim-sulfamethoxazole on clinical outcomes in methicillin-resistant Staphylococcus aureus infections. Antimicrobial agents and chemotherapy. 2015;59(4):1969-76.
38. Werth B, Rahman S, Szeliga A, Rose W, Rybak M, editors. Exploring the mechanism of synergy between daptomycin (DAP) and trimethoprim/sulphamethoxazole (TMP/SMX) against methicillin-resistant Staphylococcus aureus (MRSA). 23rd Annual European Congress of Clinical

Microbiology and Infectious Diseases (ECCMID), Berlin, Germany; 2013.
39. Steed ME, Vidaillac C, Rybak MJ. Novel daptomycin combinations against daptomycin-nonsusceptible methicillin-resistant Staphylococcus aureus in an in vitro model of simulated endocardial vegetations. Antimicrobial agents and chemotherapy. 2010;54(12):5187-92.
40. del Río A, Gasch O, Moreno A, Peña C, Cuquet J, Soy D, et al. Efficacy and safety of fosfomycin plus imipenem as rescue therapy for complicated bacteremia and endocarditis due to methicillin-resistant Staphylococcus aureus: a multicenter clinical trial. Clinical Infectious Diseases. 2014;59(8):1105-12.
41. Gudiol C, Cuervo G, Shaw E, Pujol M, Carratalà J. Pharmacotherapeutic options for treating Staphylococcus aureus bacteremia. Expert opinion on pharmacotherapy. 2017;18(18):1947-63.
42. Del Río A, Garcia-De-La-Maria C, Entenza J, Gasch O, Armero Y, Soy D, et al. Fosfomycin plus β-lactams as synergistic bactericidal combinations for experimental endocarditis due to methicillin-resistant and glycopeptide-intermediate Staphylococcus aureus. Antimicrobial agents and chemotherapy. 2016;60(1):478-86.
43. Coronado-Álvarez NM, Parra D, Parra-Ruiz J. Clinical efficacy of fosfomycin combinations against a variety of gram-positive cocci. Enfermedades infecciosas y microbiologia clinica. 2019;37(1):4-10.
44. Patel JB, Jevitt LA, Hageman J, McDonald LC, Tenover FC. An association between reduced susceptibility to daptomycin and reduced susceptibility to vancomycin in Staphylococcus aureus. Clinical Infectious Diseases. 2006;42(11):1652-3.
45. Parra-Ruiz J, Bravo-Molina A, Pena-Monje A, Hernandez-Quero J. Activity of linezolid and high-dose daptomycin, alone or in combination, in an in vitro model of Staphylococcus aureus biofilm. The Journal of antimicrobial chemotherapy. 2012;67(11):2682-5.
46. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clinical infectious diseases. 2004;39(3):309-17.
47. Bartash R, Nori P. Beta-lactam combination therapy for the treatment of Staphylococcus aureus and Enterococcus species bacteremia: a summary and appraisal of the evidence. International Journal of Infectious Diseases. 2017;63:7-12.
48. Baykara N, Akalın H, Arslantaş MK, Hancı V, Çağlayan Ç, Kahveci F, et al. Epidemiology of sepsis in intensive care units in Turkey: a multicenter, point-prevalence study. Critical Care. 2018;22(1):93.
49. Yim J, Smith JR, Rybak MJ. Role of combination antimicrobial therapy for vancomycin-resistant Enterococcus faecium infections: review of the current evidence. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2017;37(5):579-92.
50. Beganovic M, Luther MK, Rice LB, Arias CA, Rybak MJ, LaPlante KL. A review of combination antimicrobial therapy for Enterococcus faecalis bloodstream infections and infective endocarditis. Clinical Infectious Diseases. 2018;67(2):303-9.
51. Hall AD, Steed ME, Arias CA, Murray BE, Rybak MJ. Evaluation of standard-and high-dose daptomycin versus linezolid against vancomycin-resistant Enterococcus isolates in an in vitro pharmacokinetic/pharmacodynamic model with simulated endocardial vegetations. Antimicrobial agents and chemotherapy. 2012;56(6):3174-80.
52. Smith JR, Barber KE, Raut A, Aboutaleb M, Sakoulas G, Rybak MJ. β-Lactam combinations with daptomycin provide synergy against vancomycin-resistant Enterococcus faecalis and Enterococcus faecium. Journal of Antimicrobial Chemotherapy. 2015;70(6):1738-43.
53. Sakoulas G, Rose W, Nonejuie P, Olson J, Pogliano J, Humphries R, et al. Ceftaroline restores daptomycin activity against daptomycin-nonsusceptible vancomycin-resistant Enterococcus faecium. Antimicrobial agents and chemotherapy. 2014;58(3):1494-500.
54. Chuang Y-C, Chen P-Y, Lin C-Y, Chen Y-C, Wang J-T, Chang S-C. A retrospective clinical comparison of daptomycin vs daptomycin and a beta-lactam antibiotic for treating vancomycin-resistant Enterococcus faecium bloodstream infections. Scientific reports. 2018;8(1):1-9.
55. Avery LM, Kuti JL, Weisser M, Egli A, Rybak MJ, Zasowski EJ, et al. Pharmacodynamics of daptomycin in combination with other antibiotics for the treatment of enterococcal bacteraemia. International journal of antimicrobial agents. 2019;54(3):346-50.

56. Descourouez JL, Jorgenson MR, Wergin JE, Rose WE. Fosfomycin synergy in vitro with amoxicillin, daptomycin, and linezolid against vancomycin-resistant Enterococcus faecium from renal transplant patients with infected urinary stents. Antimicrobial agents and chemotherapy. 2013;57(3):1518-20.
57. Snyder ADH, Werth BJ, Nonejuie P, McRoberts JP, Pogliano J, Sakoulas G, et al. Fosfomycin enhances the activity of daptomycin against vancomycin-resistant enterococci in an in vitro pharmacokinetic-pharmacodynamic model. Antimicrobial agents and chemotherapy. 2016;60(10):5716-23.
58. Hachem R, Afif C, Gokaslan Z, Raad I. Successful treatment of vancomycin-resistant Enterococcus meningitis with linezolid. European Journal of Clinical Microbiology and Infectious Diseases. 2001;20(6):432.
59. Luther MK, Arvanitis M, Mylonakis E, LaPlante KL. Activity of daptomycin or linezolid in combination with rifampin or gentamicin against biofilm-forming Enterococcus faecalis or E. faecium in an in vitro pharmacodynamic model using simulated endocardial vegetations and an in vivo survival assay using Galleria mellonella larvae. Antimicrobial agents and chemotherapy. 2014;58(8):4612-20.
60. Zinner SH, Gilbert D, Lubenko IY, Greer K, Firsov AA. Selection of linezolid-resistant Enterococcus faecium in an in vitro dynamic model: protective effect of doxycycline. Journal of Antimicrobial Chemotherapy. 2008;61(3):629-35.
61. Sweeney MT, Zurenko GE. In vitro activities of linezolid combined with other antimicrobial agents against staphylococci, enterococci, pneumococci, and selected gram-negative organisms. Antimicrobial agents and chemotherapy. 2003;47(6):1902-6.
62. Schutt AC, Bohm NM. Multidrug-resistant Enterococcus faecium endocarditis treated with combination tigecycline and high-dose daptomycin. Annals of Pharmacotherapy. 2009;43(12):2108-12.
63. Pontikis K, Pefanis A, Tsaganos T, Tzepi I-M, Carrer D-P, Giamarellou H. Efficacy of tigecycline alone and in combination with gentamicin in the treatment of experimental endocarditis due to linezolid-resistant Enterococcus faecium. Antimicrobial agents and chemotherapy. 2013;57(7):3392-4.
64. Tang H-J, Chen C-C, Zhang C-C, Su B-A, Li C-M, Weng T-C, et al. In vitro efficacy of fosfomycin-based combinations against clinical vancomycin-resistant Enterococcus isolates. Diagnostic microbiology and infectious disease. 2013;77(3):254-7.